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Programa de Pós-Graduação em Neurociências

Avaliação de biomarcadores periféricos na depressão pós-acidente vascular encefálico isquêmico agudo

Vinicius Sousa Pietra Pedroso

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Tese apresentada ao Programa de Pós-Graduação em Neurociências da Universidade Federal de Minas Gerais, como pré-requisito para a obtenção do título de Doutor em Neurociências.

Orientador: Antônio Lúcio Teixeira Júnior
Co-orientadora: Érica Leandro Marciano Vieira

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Declaro, para os devidos fins, que **Vinicius Sousa Pietra Pedroso** concluiu o **Doutorado** no Programa de Pós-graduação em Neurociências sob a orientação do Professor Antônio Lucio Teixeira Junior, tendo defendido a tese "**Avaliação de biomarcadores periféricos na depressão pós-acidente vascular encefálico isquêmico agudo**", no dia 29 de novembro de 2016. A tese foi aprovada por banca examinadora composta pelos Professores: Antônio Lucio Teixeira Junior (orientador) – UFMG, Érica Leandro Marciano Vieira – UFMG, Aline Silva de Miranda – UFMG, Vandack Alencar Nobre Junior – UFMG, Paulo Pereira Christo – SCMBH, Bruno Cópio Fábregas – UNIVAÇO.

Belo Horizonte, 16 de dezembro de 2016.

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ATA DA DEFESA DE TESE DO ALUNO
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Realizou-se, no dia 29 de novembro de 2016, às 14:00 horas, Sala 107, Ala Sul, 1º Andar, Hospital das Clínicas da UFMG, Av. Prof. Alfredo Balena, 110 - Santa Ef, da Universidade Federal de Minas Gerais, a 45ª defesa de tese, intitulada *Avaliação de biomarcadores periféricos na depressão pós-acidente vascular encefálico isquêmico agudo.*, apresentada por VINICIUS SOUSA PIETRA PEDROSO, número de registro 2011744991, graduado no curso de MEDICINA, como requisito parcial para a obtenção do grau de Doutor em NEUROCIÊNCIAS, à seguinte Comissão Examinadora: Prof(a). Antônio Lucio Teixeira Junior (Orientador) - (UFMG), Prof(a). Érica Leandro Marciano Vieira (Coorientadora) - (UFMG), Prof(a). Aline Silva de Miranda (UFMG), Prof(a). Vandack Alencar Nobre Junior (UFMG), Prof(a). Paulo Pereira Christo (SCMBH), Prof(a). Bruno Cópio Fábregas (UNIVAÇO).

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Finalizados os trabalhos, lavrei a presente ata que, lida e aprovada, vai assinada por mim e pelos membros da Comissão.
Belo Horizonte, 29 de novembro de 2016.

Carlos Magno Machado Dias - Secretário(a)

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O porvir...
Sim, o porvir...

Adiamento – Álvaro de Campos

Um galo sozinho não tece uma manhã:
ele precisará sempre de outros galos.
De um que apanhe esse grito que ele
e o lance a outro; de um outro galo
que apanhe o grito de um galo antes
e o lance a outro; e de outros galos
que com muitos outros galos se cruzem
os fios de sol de seus gritos de galo,
para que a manhã, desde uma teia tênue,
se vá tecendo, entre todos os galos.
E se encorpando em tela, entre todos,
se erguendo tenda, onde entrem todos,
se entretendendo para todos, no toldo
(a manhã) que plana livre de armação.
A manhã, toldo de um tecido tão aéreo
que, tecido, se eleva por si: luz balão.

Tecendo a manhã - João Cabral de Melo Neto

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Resumo

Introdução: o acidente vascular encefálico (AVE) é um grande problema de saúde pública em todo o mundo e determina altas taxas de morbidade e mortalidade. Sequelas neuropsiquiátricas são muito frequentes após um evento cerebrovascular, destacando-se a depressão. Transtornos mentais associados ao AVE impactam negativamente na recuperação, na qualidade de vida e na sobrevida dos pacientes afetados e existem poucos elementos que possam auxiliar no diagnóstico clínico, tais como biomarcadores.
Objetivo: investigar a prevalência de comorbidades psiquiátricas associadas ao AVE isquêmico agudo e procurar biomarcadores periféricos associados ao desenvolvimento de depressão pós-AVE (DPAVE).
Métodos: foram incluídos sessenta pacientes com AVE isquêmico agudo, admitidos na Unidade de AVE do Hospital Municipal Odilon Behrens, em Belo Horizonte, Minas Gerais. Os pacientes foram avaliados por meio de entrevista clínica estruturada (*Mini International Neuroppsychiatric Interview*) e da aplicação do Mini-Exame do Estado Mental (MEEM), da Escala Hospitalar de Ansiedade e Depressão (HADS), da Escala de Choro e Riso Patológico, da Medida de Independência Funcional (MIF), da National Institutes of Health Stroke Scale e da Escala Modificada de Rankin (mRS). Níveis plasmáticos de IL-2, IL-4, IL-6, IL-10, IL-17A, IFNγ, TNF, sTNFR1, sTNFR2, TWEAK, STREM-1, E-Selectina, VCAM, BDNF, GDNF, NGF, Leptina e Adiponectina foram avaliados por meio de ELISA e CBA. Os pacientes foram comparados com 15 indivíduos controles saudáveis e 15 indivíduos com depressão maior, sem comorbidades cerebrovasculares.
Resultados: Observou-se prevalência de algum transtorno mental em 55% dos pacientes afetados por AVE isquêmico agudo, com predomínio de depressão (26,7%) e transtornos de ansiedade (23,3%), além de abuso ou dependência de álcool (11,7%). Os pacientes com DPAVE apresentaram maior incapacidade à admissão aferida pela mRS e pior funcionalidade avaliada pela MIF, além de pior desempenho cognitivo no MEEM. A presença de diabetes aumentou o risco de desenvolvimento de DPAVE em 3 vezes. A HADS apresentou bom desempenho no rastreamento de casos de depressão, sendo encontrado o valor de corte de 6 para a subescala de depressão, atingindo sensibilidade de 100% e especificidade de 99,17%. Na avaliação de biomarcadores, observamos que os indivíduos com DPAVE tenderam a apresentar níveis reduzidos de STREM-1 e GDNF e essas proteínas se correlacionaram inversamente com a intensidade de sintomas depressivos aferidos pela HADS.
Conclusões: o presente estudo fortalece a visão de que o AVE se relaciona ao desenvolvimento de transtornos mentais e sugere que as interrelações entre diabetes, estados inflamatórios crônicos e insulto cerebrovascular agudo podem desencadear a manifestação de sintomas depressivos.

Palavras-chave: acidente vascular encefálico, depressão, fatores neurotróficos, biomarcadores, mecanismos inflamatórios.

Abstract

Introduction: stroke is a major public health problem worldwide and leads to high rates of morbidity and mortality. Neuropsychiatric sequelae are very commom after a cerebrovascular event, with emphasis on depression. Mental disorders associated with stroke negatively impact the recovery, quality of life and survival of affected patients. Unfortunately, there are still few tools that could aid in clinical diagnosis, such as biomarkers.
Objective: to investigate the prevalence of psychiatric comorbidities associated with acute ischemic stroke and to look for peripheral biomarkers associated with de development of post-stroke depression (PSD).
Methods: we evaluated sixty patients with acute ischemic, who were admitted to the stroke unit at the Hospital Municipal Odilon Behrens, in Belo Horizonte, Minas Gerais. Patients were assessed by the use of a structured clinical interview (Mini International Neuroppsychiatric Interview) and the application of the Mini-Mental State Examination (MMSE), the Hospital Anxiety and Depression Scale (HADS), the Pathological Laugh and Crying Scale, the Functional Independence Measure (MIF), the National Institutes of Health Stroke Scale, and the Rankin Modified Scale (mRS). Plasma levels of IL-2, IL-6, IL-10, IL-17A, IFNγ, TNF, sTNFR1, sTNFR2, TWEAK, STREM-1, E-Selectin, VCAM, BDNF, GDNF, NGF, Leptin and Adiponectin were evaluated by ELISA and CBA. Patients were compared with 15 healthy control subjects and 15 individuals with major depression, without cerebrovascular comorbidities.
Results: We found a prevalence of some mental disorder in 55% of the patients affected by acute ischemic stroke, with predominance of depression (26.7%) and anxiety disorders (23.3%), as well as alcohol abuse or dependence (11.7%). Patients with PSD had greater disability at admission, as measured by the mRS, worse functionality assessed by MIF, and worse cognitive performance on the MMSE. The presence of diabetes increased by 3-fold the risk of developing PSD. HADS performed well in tracking cases of depression. We found the cutoff value of 6 for the depression subscale, which reached sensitivity of 100% and specificity of 99.17%. Regarding biomarkers, we observed that individuals with PSD presented reduced levels of STREM-1 and GDNF and that these proteins correlated inversely with the intensity of depressive symptoms, as measured by the HADS.
Conclusions: this study strengthens the view that the stroke is related to the development of mental disorders and suggests that the interrelationships between diabetes, chronic inflammation and acute cerebrovascular insult can trigger the manifestation of depressive symptoms.

Key-words: stroke, depression, neurotrophic factors, biomarkers, inflammatory mechanisms.

Lista de abreviaturas

AVDs	Atividades de vida diárias
AVE	Acidente vascular encefálico
AVEi	Acidente vascular encefálico isquêmico
BDNF	Fator Neurotrófico Derivado do Cérebro
DA	Doença de Alzheimer
DP	Desvio-padrão
DPAVE	Depressão pós-AVE
DSM	*Diagnostic and Statistical Manual of Mental Disorders* da Associação Americana de Psiquiatria
DV	Demência Vascular
ECG	Escala de coma de Glasgow
GDNF	Fator Neurotrófico Derivado da Glia
HADS	Escala Hospitalar de Ansiedade e Depressão
HADS-D	Subescala de Depressão da Escala Hospitalar de Ansiedade e Depressão
HADS-A	Subescala de Ansiedade da Escala Hospitalar de Ansiedade e Depressão
HAS	Hipertensão arterial sistêmica
HOB	Hospital Municipal Odilon Behrens
HMOB	Hospital Municipal Odilon Behrens
IAM	Infarto agudo do miocárdio
IFNγ	Interferon gama
IL-2	Interleucina-2
IL-4	Interleucina-4
IL-6	Interleucina-6
IL-10	Interleucina-10
IL-17A	Interleucina-17A
IMC	Índice de massa corporal
MIF	Medida de independência funcional
MINI-Plus	*Mini International Neuropsychiatric Interview*
MMSE	Mini-Exame do Estado Mental
mRS	Escala de Rankin modificada

NGF	Fator de Crescimento Neural
NIHSS	*National Institutes of Health Stroke Scale*
PLACS	Escala de Choro e Riso Patológico
PSDRS	Escala de Depressão Pós-AVE
QV	Qualidade de Vida
sTNFR1	Receptor Solúvel do Fator de Necrose Tumoral 1
sTNFR2	Receptor Solúvel do Fator de Necrose Tumoral 2
STREM1	Receptor Solúvel Desencadeador Expresso nas Células Mielóides 1
TA	Transtornos de Ansiedade
TAG	Transtorno de Ansiedade Generalizada
TC	Tomografia de Crânio
TCLE	Termo de Consentimento Livre e Esclarecido
TEEI	Transtorno da Expressão Emocional Involuntária
TEPT	Transtorno de Estresse Pós-Traumático
TNF	Fator de Necrose Tumoral
TOAST	*Trial of Org 10172 in Acute Stroke Treatment*
TWEAK	Indutor Fraco de Apoptose Semelhante ao Fator de Necrose Tumoral
UFMG	Universidade Federal de Minas Gerais
VCAM	Molécula de Adesão Celular Vascular

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Sumário

Prefácio

A proposta do presente trabalho é apresentar os resultados obtidos ao longo do desenvolvimento deste projeto, avaliando parâmetros clínicos e biomarcadores periféricos em pacientes com depressão pós-acidente vascular encefálico isquêmico agudo atendidos no Hospital Municipal Odilon Behrens, em Belo Horizonte, Minas Gerais.

Este estudo se justifica pelo fato de que a depressão pós-acidente vascular encefálico (DPAVE) é a complicação neuropsiquiátrica mais frequente em pacientes afetados por eventos cerebrovasculares. Como será apresentado, a presença de DPAVE associa-se a impactos negativos na sobrevida, na capacidade funcional, na reabilitação e, consequentemente, nos gastos de saúde pública gerados pelos pacientes acometidos. No entanto, seu diagnóstico é complexo e seus mecanismos fisiopatológicos ainda permanecem desconhecidos. Neste sentido, diversos esforços têm sido feitos para identificar instrumentos clínicos e biomarcadores que possam guiar o diagnóstico e lançar luz sobre as alterações neurobiológicas relacionadas à DPAVE.

Para a apresentação de seus argumentos, esta tese foi estruturada em três partes principais:

1. *Primeira parte: Revisão de literatura;*
2. *Segunda parte: Objetivos e Métodos;*
3. *Terceira parte: Resultados e Discussão.*

A revisão de literatura que forma a primeira parte é composta por três artigos. O primeiro deles, intitulado "Síndromes neuropsiquiátricas associadas a acidentes vasculares encefálicos: revisão de literatura", publicado no Jornal Brasileiro de Psiquiatria, buscou descrever toda a ampla gama de manifestações psiquiátricas relacionadas aos acidentes vasculares encefálicos (AVE), oferecendo uma visão abrangente sobre a relevância das alterações comportamentais observadas nos indivíduos acometidos (Artigo 1). No segundo artigo, de título "Post-stroke depression: clinics, etiopathogenesis and therapeutics", publicado na revista Archives of Clinical Psychiatry, procurou-se delimitar o objeto de estudo, traçando um recorte detalhado sobre as síndromes depressivas associadas aos AVE, descrevendo suas características clínicas, possíveis implicações fisiopatológicas e intervenções terapêuticas disponíveis (Artigo 2). No terceiro artigo, chamado "Biomarkers

in post-stroke depression", publicado na revista Current Neurovascular Research, foi realizada uma revisão sistemática da literatura, procurando encontrar as evidências disponíveis sobre o uso de biomarcadores na avaliação de pacientes afetados por DPAVE e suas implicações para futuras pesquisas (Artigo 3).

Na terceira parte, foi realizada uma divisão entre os estudos clínicos e os experimentais. Na seção que trata dos dados clínicos, são apresentados dois artigos: o primeiro deles, intitulado "Early psychiatric morbidity in a Brazilian sample of acute ischemic stroke patients", submetido para publicação na revista Behavioural Neurology, investigou-se a ocorrência de síndromes neuropsiquiátricas em uma amostra de pacientes brasileiros hospitalizados em decorrência de AVE isquêmico agudo, descrevendo suas características demográficas, comorbidades e dados clínicos (Artigo 4). No segundo artigo, chamado "Psychopathological evaluation and use of the Hospital Anxiety and Depression Scale in a sample of Brazilian patients with post-stroke depression", submetido para publicação na revista Archives of Clinical Psychiatry, procurou-se investigar as características clínicas e psicopatológicas entre pacientes afetados por AVE isquêmico agudo com e sem depressão e avaliar as propriedades da Escala Hospitalar de Ansiedade e Depressão (HADS) na detecção de casos de DPAVE. Já na seção dedicada aos dados experimentais, os resultados do estudo com biomarcadores são apresentados na forma de texto convencional, com sua respectiva discussão.

O Diagrama 1 apresenta a estrutura do trabalho.

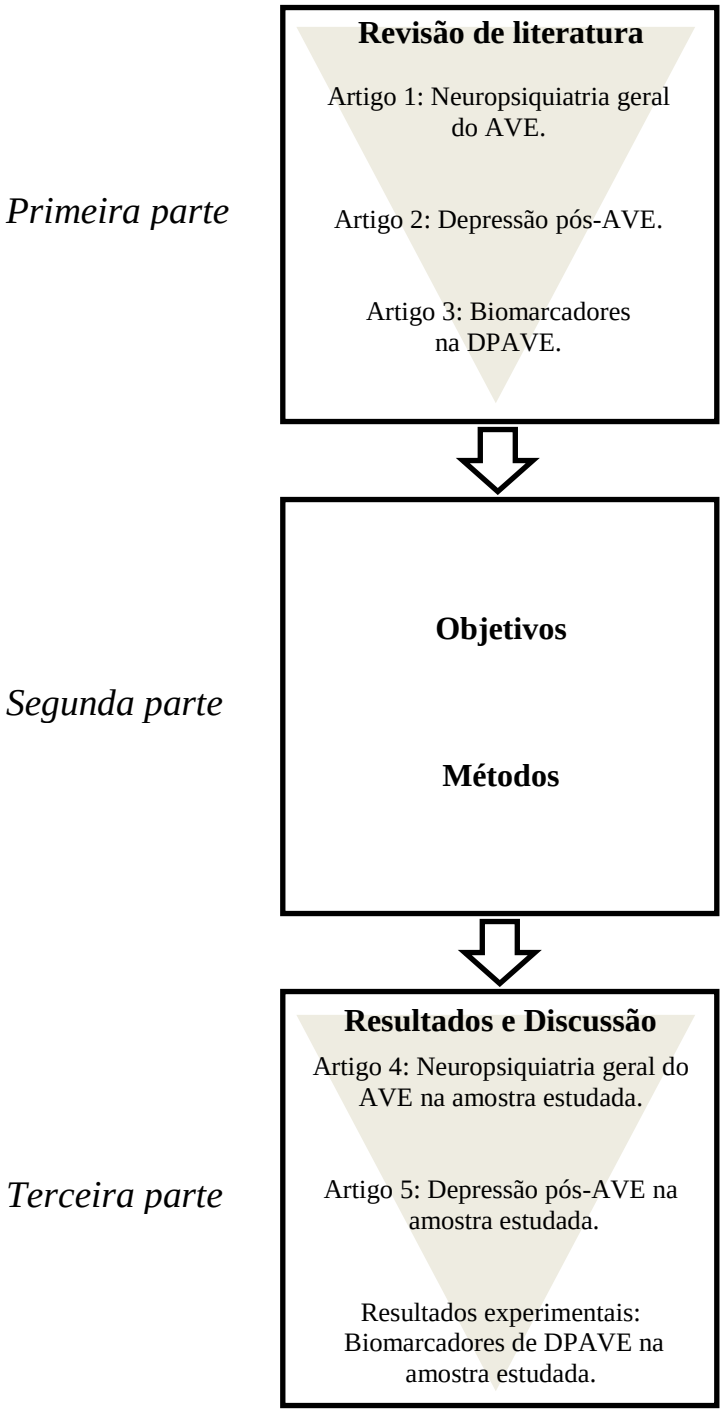

Figura 1: Diagrama de estrutura da tese.

Primeira parte

1. Revisão de literatura

Artigo 1: Síndromes neuropsiquiátricas associadas a acidentes vasculares encefálicos: revisão de literatura.

Vinicius Sousa Pietra Pedroso, Leonardo Cruz de Souza, Antônio Lúcio Teixeira.

J Bras Psiquiatr. 2014; 63(2): 165-76.

ARTIGO DE REVISÃO

Síndromes neuropsiquiátricas associadas a acidentes vasculares encefálicos: revisão de literatura

Neuropsychiatric syndromes associated with stroke: review of the literature

Vinicius Sousa Pietra Pedroso[1], Leonardo Cruz de Souza[1], Antônio Lúcio Teixeira[1]

RESUMO

Objetivo: Revisar as principais síndromes neuropsiquiátricas associadas ao acidente vascular encefálico (AVE), suas características clínicas, impacto sobre a recuperação dos pacientes, tratamento, suas possíveis relações com a fisiopatologia dos AVE e, quando possível, contextualizá-las à realidade brasileira. **Métodos:** Foram realizadas buscas nas bases de dados PubMed/MedLine e SciELO/Lilacs com os termos *"stroke"* e *"cerebrovascular disease"* em combinações com *"neuropsychiatry"*, *"neuropsychiatric disorders"*, *"psychiatry"*, *"psychiatric disorders"*, *"depression"*, *"anxiety"* e *"dementia"*, com ênfase nos últimos dez anos. **Resultados:** Foram revisadas as síndromes neuropsiquiátricas pós-AVE, incluindo depressão, ansiedade, transtorno da expressão emocional involuntária, labilidade emocional, irritabilidade, raiva, reação catastrófica, apatia, demência, mania e psicose, de acordo com os objetivos propostos. **Conclusão:** É notória a escassez de informações sobre o manejo terapêutico das complicações neuropsiquiátricas secundárias aos AVE, especialmente diante do impacto em saúde pública representado pelas doenças cerebrovasculares. Com a evolução da abordagem precoce a esses pacientes e o consequente aumento de sua sobrevida, o aprofundamento do conhecimento sobre o desenvolvimento e o tratamento dos transtornos neuropsiquiátricos parece ter maior potencial para melhorar o desfecho e a qualidade de vida dos indivíduos que sofreram AVE.

Palavras-chave
Acidente vascular encefálico, doença cerebrovascular, neuropsiquiatria, depressão, ansiedade, demência.

ABSTRACT

Objective: To review the main neuropsychiatric syndromes associated with stroke, their clinical features, impact over functional recovery, therapeutics, putative relations to stroke pathophysiology and, when possible, to contextualize them to the Brazilian reality. **Methods:** It was performed a search on PubMed/MedLine and SciELO/Lilacs databases, using the terms "stroke" and "cerebrovascular disease" combined with "neuropsychiatry", "neuropsychiatric disorders", "psychiatry", "psychiatric disorders", "depression", "anxiety" and "dementia". **Results:** According to the proposed objectives, we reviewed the stroke-related syndromes characterized by depression, anxiety, emotional lability, irritability, anger, catastrophic reaction, apathy, dementia, mania and psychosis. **Conclusion:** These findings emphasize the lack of information on the therapeutic management of neuropsychiatric complications secondary to stroke, especially considering the burden on public health represented by cerebrovascular diseases. Following the improvement in the survival rates with the early strategies to stroke, the advancement of knowledge on neuropsychiatric disorders seem to have the greatest potential to improve the quality of life of patients affected by stroke.

Keywords
Stroke, cerebrovascular disease, neuropsychiatry, depression, anxiety, dementia.

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INTRODUÇÃO

O desenvolvimento rápido de alterações neurológicas focais ou globais que duram mais de 24 horas ou levam ao óbito, excluindo-se causas não vasculares, corresponde à definição de acidente vascular encefálico (AVE), de acordo com a Organização Mundial da Saúde[1].

Embora nos últimos 50 anos a incidência de AVE e a mortalidade por causa dele tenham sido reduzidas nos países desenvolvidos, especialmente devido ao avanço na abordagem da isquemia cerebral aguda e à implementação de estratégias para controle de fatores de risco, como hipertensão arterial sistêmica (HAS) e diabetes, os AVE ainda representam um grande problema de saúde pública, sendo a terceira causa de morte no mundo ocidental e a principal causa de incapacidade permanente[2,3].

No Brasil, os dados epidemiológicos disponíveis vêm de poucos estudos desenvolvidos em cidades isoladas e não permitem generalização nacional, especialmente considerando-se as disparidades regionais[4]. No entanto, as informações existentes permitem afirmar que os AVE constituem a principal causa de morte no país e, se há uma tendência de redução da mortalidade similar àquela observada nos países desenvolvidos, esta reflete a realidade das regiões Sul e Sudeste[5].

Entre os indivíduos sobreviventes, cerca de dois terços apresentam algum grau de incapacidade permanente que requer cuidados de reabilitação, e a recorrência de eventos isquêmicos contribui ainda mais para o aumento da morbidade[6]. Acima dos 60 anos de idade, os AVE se destacam como a condição que determina a adoção dos procedimentos mais dispendiosos para o sistema público de saúde e com a maior taxa de óbitos[6,7].

Além das sequelas neurológicas, como déficits motores e sensitivos, as alterações neuropsiquiátricas têm sido reconhecidas como determinantes da recuperação[7]. Há muito se observou que indivíduos acometidos por AVE apresentam maior incidência de transtornos de humor e da cognição em comparação àqueles com outras doenças crônicas[8]. No entanto, nos últimos 20 anos, outras síndromes neuropsiquiátricas, como transtorno de ansiedade generalizada (TAG), apatia, transtornos da expressão emocional, psicose, mania secundária, alterações da personalidade, entre outras, têm sido descritas após AVE. Além de impactar a recuperação neurológica, exercem significativa influência na vida profissional e nas relações interpessoais dos pacientes, de seus familiares e de seus cuidadores, modificando sua autonomia, sua autoestima e sua qualidade de vida (QV) em geral[9].

O presente trabalho tem como objetivo oferecer uma revisão narrativa sobre as principais síndromes neuropsiquiátricas associadas ao AVE, suas características clínicas, impacto sobre a recuperação dos pacientes e possível fisiopatologia.

MÉTODOS

Este trabalho é uma revisão narrativa da literatura que teve como fonte de pesquisa as bases de dados PubMed/MedLine e SciELO/Lilacs. Os termos de busca foram *"stroke"* e *"cerebrovascular disease"* em combinações com *"neuropsychiatry"*, *"neuropsychiatric disorders"*, *"psychiatry"*, *"psychiatric disorders"*, *"depression"*, *"anxiety"* e *"dementia"*, em todos os campos. O período dos últimos dez anos foi utilizado como filtro inicial de busca eletrônica. Foram avaliados artigos nos idiomas português, inglês, espanhol e francês. Consultas às referências dos artigos selecionados, bem como a livros-texto, foram utilizadas como estratégia de busca adicional. Todos os autores participaram da elaboração do texto. Foram selecionados, a critério dos autores e com base na força de evidência e originalidade dos trabalhos, artigos de revisão, revisões sistemáticas, metanálises, artigos originais e relatos de casos para a caracterização de aspectos gerais das síndromes neuropsiquiátricas associadas aos AVE e de questões próprias de cada síndrome em particular, com foco especial em trabalhos realizados no Brasil, de forma a salientar a realidade nacional.

RESULTADOS

A busca no PubMed/MedLine resultou em 11.251 trabalhos, sendo 5.755 publicados nos últimos dez anos e 2.268 artigos de revisão. Já na base de dados SciELO/Lilacs, a busca resultou em 241 trabalhos. Procurou-se priorizar estudos com maior tamanho amostral ou maior nível de evidência, a partir dos quais se definiram os temas a serem abordados na revisão.

Síndromes neuropsiquiátricas pós-AVE: visão geral

Inúmeros autores procuraram determinar a frequência de manifestações neuropsiquiátricas em pacientes com AVE, em momentos diferentes após o evento isquêmico. O quadro 1 apresenta uma distribuição geral de síndromes neuropsiquiátricas em pacientes afetados por AVE de acordo com a literatura.

Angelelli *et al.*[10] procuraram identificar a prevalência de sintomas neuropsiquiátricos entre pacientes com AVE. Observaram uma divisão entre manifestações típicas da fase aguda e da fase crônica, encontrando o ponto de mudança em torno do sexto mês pós-AVE. O perfil "crônico" manteve-se estável por, ao menos, um ano. Assim, na fase aguda, as alterações mais comuns foram agitação, euforia e comportamento motor aberrante. Já na fase crônica, predominaram apatia e transtornos relacionados ao sono, como insônia, hipersonia ou outros comportamentos inadequados, como levantar-se e perambular pela casa à noite. Os sintomas de depressão e de irritabilidade foram frequentes em ambas as fases.

Quadro 1. Características dos estudos que analisaram as principais síndromes neuropsiquiátricas associadas ao AVE

Síndromes e sintomas	Autor (ano)	n	Contexto	Tempo pós-AVE	Prevalência (%)
Depressão	Robinson *et al.* (1983)[11]	103	H	2 semanas	47
	Robinson *et al.* (1984)[12]	61	A	3 meses 6 meses	49 60
	Robinson *et al.* (1987)[13]	65	A	12 meses 24 meses	33 42
	Eastwood *et al.* (1989)[14]	87	UR	1-3 meses	50
	Morris *et al.* (1990)[15]	99	UR/A	2 meses 15 meses	32 12
	House *et al.* (1991)[16]	89	C	Primeiros 12 meses	23
	Astrom *et al.* (1993)[17]	80	H/A	0-3 meses 12 meses 24 meses 36 meses	31 16 19 29
	Burvill *et al.* (1995)[18]	294	C	4 meses	23
	Ng *et al.* (1995)[19]	52	UR	Primeiro mês	55
	Kotila *et al.* (1998)[20]	321	A	3 meses 12 meses	41-54 42-55
	Angelelli *et al.* (2004)[10]	124	H/A	2-12 meses	61,3
	Hackett *et al.* (2005)[21]	51 estudos	Metanálise	0-24 meses	33
	Buijck *et al.* (2012)[22]	145	IEQ	-	33
	Ayerbe *et al.* (2013)[23]	4022	C	Primeiros 15 anos	29-39
	Ayerbe *et al.* (2013)[24]	50 estudos	Metanálise	0-5 anos	29
Irritabilidade e raiva	Angelelli *et al.* (2004)[10]	124	H/A	2-12 meses	33
	Skånér *et al.* (2007)[25]	187	C	3 meses 12 meses	46 34
	Buijck *et al.* (2012)[22]	145	IEQ	-	12
Transtornos alimentares e do apetite	Angelelli *et al.* (2004)[10]	124	H/A	2-12 meses	33
	Skånér *et al.* (2007)[25]	187	C	3 meses 12 meses	34 21
	Buijck *et al.* (2012)[22]	145	IEQ	-	19
Agitação	Angelelli *et al.* (2004)[10]	124	H/A	2-12 meses	28,2
	Buijck *et al.* (2012)[22]	145	IEQ	-	5
Apatia	Starkstein *et al.* (1993)[26]	80	H	Primeiras 2 semanas	11
	Angelelli *et al.* (2004)[10]	124	H/A	2-12 meses	26,6
	Brodaty *et al.* (2005)[27]	167	A	3-6 meses	26,7
	Buijck *et al.* (2012)[22]	145	IEQ	-	9
Ansiedade	Angelelli *et al.* (2004)[10]	124	H/A	2-12 meses	26,6
	Buijck *et al.* (2012)[22]	145	IEQ	-	15
	Burton *et al.* (2013)[28]	44 estudos	Metanálise	Primeiro mês 1-5 meses Após sexto mês	20 23 24
Distúrbios noturnos	Angelelli *et al.* (2004)[10]	124	H/A	2-12 meses	17,7
	Skånér *et al.* (2007)[25]	187	C	3 meses 12 meses	41 31
	Buijck *et al.* (2012)[22]	145	IEQ	-	18
TEEI	Calvert *et al.* (1998)[29] Piamarta *et al.* (2004)[30]	448 33	A H	1 mês 2 semanas	21,5 48,5
Comportamento motor aberrante	Angelelli *et al.* (2004)[10]	124	H/A	2-12 meses	10,5
	Buijck *et al.* (2012)[22]	145	IEQ	-	1
Desinibição	Angelelli *et al.* (2004)[10]	124	H/A	2-12 meses	9,7
	Buijck *et al.* (2012)[22]	145	IEQ	-	1
Delírios	Angelelli *et al.* (2004)[10]	124	H/A	2-12 meses	1,6
	Buijck *et al.* (2012)[22]	145	IEQ	-	3
Alucinações	Angelelli *et al.* (2004)[10]	124	H/A	2-12 meses	0,8
	Buijck *et al.* (2012)[22]	145	IEQ	-	4

A: ambulatorial; C: comunidade; H: hospitalar; IEQ: instalação de enfermagem qualificada; TEEI: transtorno da expressão emocional involuntária; UR: unidade de reabilitação.

Depressão pós-AVE

A investigação sistemática das síndromes depressivas secundárias aos AVE foi desenvolvida principalmente pelo grupo do professor Robert Robinson, da Universidade de Iowa, Estados Unidos[31]. Desde então, foram relatadas prevalências que variam de 18% a 60%, estabelecendo a depressão (maior e menor) como o transtorno neuropsiquiátrico mais comum após AVE. A variabilidade na prevalência deve-se aos diferentes questionários e critérios utilizados para definição diagnóstica, bem como às diferenças entre as populações estudadas e o tempo decorrido após o AVE. De acordo com o DSM-V *(Diagnostic and Statistical Manual of Mental Disorders, fourth edition*), o transtorno depressivo maior corresponde à presença de, ao menos, quatro sintomas acessórios, além de humor deprimido ou anedonia. Já o episódio depressivo menor corresponde a um diagnóstico de pesquisa do DMS-IV, caracterizado pela presença de dois a cinco sintomas depressivos, incluindo humor deprimido ou anedonia. No novo DSM-V, esse construto foi removido dos diagnósticos de pesquisa e aparentemente incorporado à categoria Outros Transtornos Depressivos Especificados: Episódio Depressivo com Sintomas Insuficientes.

A prevalência média de depressão pós-AVE (DPA) entre pacientes hospitalizados em fase aguda gira em torno de 22% para depressão maior e 17% para depressão menor. Em amostras ambulatoriais, é de 23% para depressão maior e de 35% para depressão menor, enquanto amostras comunitárias exibem prevalências médias de 13% e 10%, respectivamente[8]. Uma recente metanálise observou que a prevalência de depressão em qualquer momento após AVE era de 29%[32].

Uma coorte de 4.022 pacientes acompanhados por 15 anos evidenciou a história dinâmica da DPA[33]. Segundo Robinson *et al.*[13], episódios depressivos maiores frequentemente se atenuam, sem remissão completa, um ano após o evento. Na coorte, mais da metade dos pacientes apresentou depressão, com prevalência estável em torno de 30% durante o acompanhamento[33]. A maior parte dos indivíduos apresentou remissão um ano após o AVE, exibindo episódios depressivos de duração relativamente curta. No entanto, o risco de recorrência desses episódios em longo prazo foi elevado, corroborando a relação entre episódios curtos e prevalência estável.

No Brasil, há poucos dados sobre a epidemiologia da DPA. Em Fortaleza, avaliando-se a QV de indivíduos em torno de dois a seis anos pós-AVE, observou-se prevalência de 40% de sintomas depressivos, predominando leves a moderados[32]. A presença dos sintomas depressivos foi o fator mais importante na redução da QV. Similarmente, Souza *et al*. avaliaram pacientes com doença de Chagas e AVE, observando que a QV era mais influenciada pelos sintomas depressivos do que pela incapacidade neurológica[33]. Por sua vez, Carod-Artal *et al.* também demonstraram que depressão, incapacidade e déficit motor eram os principais determinantes da QV relacionada à saúde em pacientes com AVE, sendo depressão o mais forte preditor de redução da QV, especialmente entre mulheres[34]. O quadro 2 reúne trabalhos brasileiros que registraram a frequência de DPA.

Estudos longitudinais sugerem que depressões maior e menor são determinantes de incapacidade, fracasso no retorno ao trabalho, prejuízo no funcionamento interpessoal e mortalidade[39]. A relação entre DPA e comprometimento funcional é complexa. Pacientes afetados por AVE frequentemente sofrem algum grau de incapacidade em longo prazo. Embora a maioria dos indivíduos afetados experimente algum grau de recuperação neurológica, com melhora do desempenho de atividades de vida diária (AVD), tem-se observado que pacientes com DPA apresentam significativamente maior incapacidade para AVD do que pacientes eutímicos e com déficits neurológicos comparáveis[10]. Essas observações sugerem um fenômeno de reciprocidade, no qual a depressão influencia a recuperação das AVD e o comprometimento das AVD influencia a gravidade e a duração de depressão.

Os critérios do DSM-V para diagnóstico de DPA correspondem àqueles para transtorno depressivo devido a uma condição médica, que deve ser diferenciado da desmoralização pós-AVE. Diversos autores buscaram diferenciar depressão e desmoralização[40-44]. De forma geral, a desmoralização estaria ligada ao sentimento de incompetência e de perda

Quadro 2. Estudos brasileiros que registraram a frequência de depressão pós-AVC

Autor (ano)	Local	n	Contexto	Tempo pós-AVE	Instrumento	Frequência (%)
Simis e Nitrini (2006)[35]	Sorocaba (SP)	93	H	2 semanas	HAM-D	59,1†
Carod-Artal *et al*. (2009)[34]	Brasília (DF)	260*	A	20,7 meses (média)	HADS	20,0† (F: 25,0; M: 15,4)
Terroni *et al*. (2009)[36]	São Paulo (SP)	73	H/A	1 semana – 4 meses	HAM-D	28,8‡
Fróes *et al*. (2011)[32]	Fortaleza (CE)	64	PR	< 2 anos: 9,4% 2-6 anos: 50% > 7 anos: 40,7%	BDI	40,0†
Scheffer *et al*. (2011)[37]	Porto Alegre (RS)	19*	A	9-27 meses	BDI	33,3†
Rangel *et al*. (2013)[38]	Maceió (AL)	139*	PR	3-316 meses	BDI	49,7†

A: ambulatorial; BDI: Inventário de Depressão de Beck; F: gênero feminino; H: hospitalar; HADS: Escala Hospitalar de Ansiedade e Depressão; HAM-D: Escala de Depressão de Hamilton; PR: programa de reabilitação; M: gênero masculino.
* O estudo incluiu pacientes com AVE hemorrágico (AVE isquêmico: Carod-Artal *et al.*: 87,7%; Scheffer *et al.*: 84,2%; Rangel *et al.*: 83,5%). † Prevalência. ‡ Incidência em 4 meses.

do autodomínio após fracassos repetidos, ao passo que a depressão se caracterizaria por anedonia e redução da motivação. Shader observou que o indivíduo com desmoralização pode responder favoravelmente a um estímulo positivo e ao alívio dos seus estressores, ao passo que o paciente com depressão não pode se livrar de seu estado negativo de humor, independentemente das mudanças ambientais[45]. O clínico, uma vez que reconheça a presença de desmoralização, deve trabalhar com o paciente para promover o sentimento de capacidade, domínio e retorno da esperança. Encorajamento, suporte e educação são essenciais.

Fedoroff *et al.*[46], avaliando a adequação dos critérios diagnósticos para transtorno depressivo maior no diagnóstico de DPA, observaram que, exceto pela insônia terminal, todos os sintomas de depressão eram mais frequentes em pacientes com AVE e humor deprimido do que nos eutímicos. Contudo, alguns autores apontam para diferenças clínicas entre pacientes com DPA e aqueles com transtorno depressivo maior. Comparados a esses, os pacientes com AVE apresentam sinais mais graves de deterioração cognitiva, flutuações do humor, retardamento psicomotor, ansiedade e sintomas vegetativos e somáticos[47]. No Brasil, Terroni *et al.*[36] chamam a atenção para a importância de sintomas de fadiga e de redução do interesse em geral no diagnóstico de DPA. Como não existem marcadores biológicos específicos, o diagnóstico é clínico e essa tarefa pode se tornar difícil na presença de déficits cognitivos graves, notadamente da linguagem.

A etiopatogênese da DPA é, provavelmente, multifatorial, o que explica a dificuldade de se encontrarem substratos neuroanatômicos precisos[48-51]. Pacientes que apresentam AVE vivenciam evento traumático que abala sua integridade corporal e mental, sua autonomia e sua estima pessoal, assim como suas vidas conjugal e profissional. Mecanismos psicológicos de adaptação, assim como personalidade pré-mórbida, certamente desempenham papel relevante no desenvolvimento da DPA. Além disso, as relações entre depressão e AVE podem ser ainda mais complexas: história de depressão aumenta cerca de 35% o risco para o desenvolvimento de AVE, de maneira provavelmente independente de outros fatores de risco, como HAS e diabetes[52].

Ainda que o debate se encontre aberto, as correlações entre local de lesão e sintomas depressivos são baixas. Os trabalhos de Robinson *et al.* sugerem que lesões anteriores, situadas próximas ao polo frontal esquerdo, estariam mais relacionadas ao desenvolvimento de sintomas depressivos[8]. Outros autores contestam isso[11]. Carson *et al.,* em uma metanálise de 35 trabalhos que avaliaram a relação entre localização de lesões no sistema nervoso central e desenvolvimento de depressão, observaram que o risco para o desenvolvimento de depressão não estava associado com a localização das lesões[49]. Isso se deve possivelmente a vieses de seleção, dificuldade de examinar certos grupos de pacientes e variações metodológicas. Ainda que a influência da lateralidade seja incerta, diversos trabalhos implicam disfunção frontoestriatal, ao menos nos primeiros meses após o AVE[51].

O fator mais fortemente associado com o desenvolvimento de depressão é a gravidade da lesão inicial. Essa associação pode ser influenciada tanto por aspectos psicológicos, como reação afetiva desproporcional à gravidade do déficit, quanto biológicos, já que lesões maiores podem afetar mais circuitos cerebrais. Nesse sentido, Carota *et al.*[53] observaram que a presença de labilidade emocional, especialmente choro, associada à gravidade inicial do déficit, estava entre os fatores preditivos mais relevantes para o desenvolvimento de depressão, até mais que a localização da lesão.

Além disso, pacientes que apresentam afasia não fluente grave, que são conscientes de seus déficits e que apresentam compreensão preservada vivenciam experiência extremamente angustiante. Eles mantêm, com esforço, fala espontânea reduzida, com poucas palavras, frases curtas e deficiências gramaticais. Dessa forma, como têm preservada a consciência de seus déficits, emerge enorme frustração por causa da dificuldade para falar. De fato, a afasia não fluente é considerada fator de risco para o desenvolvimento de depressão nas fases tardias do AVE[54]. Em uma metanálise sobre riscos psicossociais para o desenvolvimento de DPA, Ouimet *et al.* observaram que, além de afasia, história pessoal de depressão ou de tratamentos psiquiátricos, incapacidade funcional, viver sozinho e isolamento social após o AVE se associam com aumento da probabilidade de DPA[55].

Ainda que a patogênese da DPA seja discutida, é consenso que, se não tratada, exerce impacto negativo sobre a recuperação funcional[56]. No entanto, ainda não existem diretrizes para o tratamento e a efetividade das intervenções não está estabelecida. Hackett *et al.* concluíram que o uso de antidepressivos se associa a efeito benéfico pequeno, porém significativo[57]. Segundo Price *et al.,* o uso de antidepressivos pode ser indicado tanto na abordagem da síndrome depressiva maior quanto na da menor[58], porém não existem diretrizes para a escolha específica de fármacos. Os medicamentos mais estudados são os antidepressivos tricíclicos, em especial nortriptilina, e os inibidores seletivos da recaptação de serotonina (ISRS), especialmente fluoxetina, sertralina e citalopram. Existem, ainda, trabalhos avaliando a utilização de trazodona, venlafaxina, reboxetina, mirtazapina, milnaciprano e metilfenidato. De forma geral, Tharwani *et al.* recomendam o uso de nortriptilina, no entanto ressaltam seu perfil indesejável de efeitos colaterais e de interações farmacológicas[59]. Nesse caso, os ISRS surgem como alternativa. Mais polêmica e incerta é a utilização de antidepressivos na prevenção de DPA. Trabalhos isolados mostraram benefícios com nortriptilina, fluoxetina, sertralina, mirtazapina e metilfenidato, porém revisão sistemática da Cochrane não observou efeito significativo de antidepressivos na prevenção de DPA[60].

A abordagem psicoterápica associada ao uso de antidepressivos também parece se mostrar benéfica. Na metanálise de Hackett *et al.,* um pequeno, mas significativo, efeito foi encontrado para a psicoterapia na prevenção da DPA[60].

Ansiedade

Transtornos de ansiedade (TA) são frequentes após AVE, e entre 25% e 50% dos pacientes manifestam TAG nos primeiros meses, com pequena redução da incidência nos três anos seguintes[61]. Burton *et al.* observaram que TA diagnosticados por entrevista estruturada ou sintomas ansiosos mensurados por escalas específicas surgem em 20% a 25% dos pacientes em qualquer momento após AVE[62]. Segundo Angelelli *et al.*[10], TA pós-AVE são observados em cerca de 23% dos indivíduos e aumentam consideravelmente entre pacientes com DPA, sugerindo que compartilhem mecanismos fisiopatológicos.

Os critérios diagnósticos do DSM-V para TA pós-AVE são aqueles do transtorno de ansiedade devido a uma condição médica geral, os quais correspondem aos critérios para pacientes sem lesão cerebral.

A maior parte dos estudos feitos com pacientes afetados por AVE no Brasil ou em outros países não explorou efetivamente a presença de TA. Assim, existem poucos dados sobre categorias específicas, como crises de pânico, agorafobia ou fobias. Segundo Burton *et al.,* transtornos fóbicos e TAG são os tipos mais comuns de TA após um AVE[28]. Deve-se destacar que o TAG pós-AVE se aproxima em muitos aspectos do transtorno de estresse pós-traumático (TEPT), os dois manifestando-se após um evento imprevisível, capaz de ameaçar a vida do paciente. Recentemente, observou-se que o TEPT é relatado em cerca de 10% dos indivíduos afetados por AVE, enquanto a prevalência na população geral é de 1% a 2%[62]. Além disso, são fatores de risco para desenvolvimento de TEPT: reação peritraumática intensa, gênero feminino e morbidade psiquiátrica prévia.

Assim como a DPA, os TA podem estar ligados a fatores psicológicos reacionais. As preocupações com a possibilidade de não controlar reações motoras, perceptivas, cognitivas e emocionais em diversos ambientes são frequentes no discurso dos pacientes com AVE, além do temor da ocorrência de novos eventos isquêmicos[63]. Isso pode se refletir na diminuição da percepção da QV[28]. Segundo Carod-Artal *et al.*, pacientes com AVE mais grave e níveis elevados de ansiedade apresentavam pior QV[34].

Por outro lado, os mecanismos neurobiológicos subjacentes aos fenômenos de ansiedade pós-AVE são pouco conhecidos. Os estudos que observaram a associação de ansiedade com sítio lesional não permitiram uma conclusão definitiva. As regiões cerebrais supostamente envolvidas fazem parte de circuitos frontossubcorticais (lobo frontal, tálamo, núcleos da base), do sistema límbico (amígdala, giro do cíngulo) e do eixo hipotálamo-hipofisário. Alguns estudos relataram associação entre síndromes depressivo-ansiosas e lesões corticais esquerdas, ao passo que pacientes somente com lesões subcorticais apresentavam depressão isolada. A ansiedade como sintoma isolado pareceria mais associada a lesões à direita[64].

Uma revisão sistemática recente, que incluiu dois ensaios clínicos envolvendo 175 pacientes com diagnósticos de ansiedade e depressão pós-AVE comórbidos, encontrou evidências limitadas para o uso de psicofármacos no tratamento dos TA pós-AVE[65]. Os autores concluíram que o uso de paroxetina ou de buspirona pode ser eficaz no tratamento de sintomas ansiosos em pacientes com DPA. No entanto, ainda não há estratégias terapêuticas farmacológicas definitivas, havendo relato do uso de benzodiazepínicos por tempo limitado, de ISRS ou de buspirona[31].

Transtorno da expressão emocional involuntária e labilidade emocional

Normalmente, rir e chorar são comportamentos desencadeados em contextos específicos e apropriados. No entanto, lesões do sistema nervoso central podem perturbar a regulação dessas manifestações emocionais. Após um AVE, elas podem aumentar em frequência, ser desencadeadas sem razões aparentes ou escapar ao controle habitual em contextos sociais, definindo transtornos específicos: o transtorno da expressão emocional involuntária (TEEI), também denominado riso e choro patológicos, afeto pseudobulbar ou riso e choro espasmódicos, que se distingue da labilidade emocional (ou *emotionalism*, em inglês)[66].

TEEI associa-se habitualmente a sinais de comprometimento frontobulbar, como alterações da fala e da deglutição, e manifesta-se com caráter reflexo e espasmódico. Os episódios de choro ou de riso aparecem rapidamente após estímulos comuns ou até mesmo na ausência de contexto afetivo apropriado. Além disso, existe dissociação entre a expressão do afeto e o sentimento do paciente, de forma que ele ri ou chora sem sentir alegria ou tristeza, perdendo o controle de sua expressividade facial[66,67].

Em contraste, os indivíduos com labilidade emocional não possuem o caráter forçado da expressão afetiva. Risos ou choros são provocados por estímulos que, de fato, têm um componente emocional e os sujeitos sentem a emoção apropriada (alegria ou tristeza), mas, tal como ocorre entre os pacientes com TEEI, não conseguem controlar sua expressão, exibindo um fenômeno de incontinência emocional[66,67].

Todos esses comportamentos patológicos se distinguem dos risos e choros "normais" na medida em que são excessivos. No entanto, eles conservam seu componente social, uma vez que são desencadeados mais frequentemente em situações de caráter social do que quando o paciente está desacompanhado[67].

A maioria dos trabalhos sobre TEEI concentrou-se nos comportamentos de choro patológico. Segundo a literatura, ele ocorre em aproximadamente 7% dos casos nos primeiros dias após o AVE. Dois a quatro meses depois, a prevalência sobe para 18% a 34%, mantendo-se em 25% após seis meses. Esses dados indicam que a prevalência tende a aumentar com o tempo, ao menos no que se refere aos seis primeiros meses. Como fatores de risco, foram descritos: AVC do tipo isquêmico, gênero feminino, sequelas motoras graves e disfunção cognitiva[68-70].

Não se sabe se o TEEI e a labilidade emocional implicam disfunções neuronais diferentes. Além disso, essa distinção é frequentemente difícil de ser feita clinicamente, especialmente porque não há critérios definitivos para julgar a adequação emocional ou a frequência excessiva de risos e choros. No entanto, o substrato neuroanatômico parece ser mais claro para o TEEI do que para a labilidade emocional. O papel das estruturas pontinas ou mesencefálicas é sugerido no TEEI pela associação deste com lesões que possuem tal localização, de forma uni ou bilateral, e por relatos de tumores da fossa posterior[66].

É importante considerar também fatores psicológicos que possam estar ligados aos transtornos da regulação afetiva[68]. De fato, a labilidade emocional pode ser manifestação particular de TEPT e poderia ser, além disso, fator predisponente ao desenvolvimento de depressão, como relatado anteriormente. Tais transtornos podem gerar embaraço social e grande desconforto, levando o paciente a evitar interações sociais ou a apresentar ansiedade excessiva por causa da falta de autocontrole.

Em 2010, o *Food and Drug Administration* dos Estados Unidos aprovou o primeiro tratamento farmacológico para o TEEI, uma combinação de dextrometorfano e quinidina, comercializada com o nome comercial de Nuedexta®[71]. Em junho de 2013, essa combinação foi aprovada na União Europeia. No Brasil, essa medicação ainda não se encontra disponível. Como opções, estudos isolados relataram efeitos positivos de ISRS, antidepressivos tricíclicos ou agentes dopaminérgicos. Entre eles, citam-se amitriptilina, nortriptilina, desipramina, fluoxetina, citalopram, paroxetina, sertralina, levodopa e amantadina[66,72,73].

Irritabilidade, raiva e reação catastrófica

Compreende-se raiva como uma emoção formada por componentes cognitivos, como indignação e hostilidade, e comportamentais, como agressividade, violência verbal ou física. Irritabilidade refere-se à condição de ser facilmente levado à raiva. Assim, a raiva apresenta-se como fenômeno complexo e multifatorial, envolvendo aspectos desenvolvimentais, socioculturais e fisiológicos[74].

As relações entre irritabilidade, raiva e AVE são bastante intrincadas. Adler *et al.*[74] observaram que a ocorrência de AVE em homens era frequentemente precedida por estados afetivos negativos, especialmente raiva e desesperança. De forma similar, Gianturco *et al.*[75] relataram que pacientes hospitalizados em decorrência de um AVE apresentavam mais frequentemente história de raiva precedendo a internação, em comparação com aqueles sem AVE.

Everson *et al.*[76] relataram que homens propensos a exteriorizar raiva apresentavam risco duas vezes maior para AVE ou, caso tivessem doença coronariana, seis vezes maior, em comparação com aqueles menos propensos a manifestações de raiva. Williams *et al.*[77] observaram que traços de personalidade raivosos aumentavam o risco de AVE, de forma mais significativa entre indivíduos mais jovens ou com hipercolesterolemia.

Angelelli *et al.*[10] observaram que, no primeiro ano após um AVE, irritabilidade era uma das manifestações comportamentais mais frequentes. Ela se caracterizava mais por redução do limiar de tolerância do que por aumento das manifestações de raiva propriamente ditas. Paradiso *et al.*[78] identificaram os seguintes fatores de risco: menor idade, sintomas depressivos, problemas cognitivos e lesões anteriores no hemisfério esquerdo. Além disso, essas dificuldades poderiam estar ligadas à presença de déficits motores, disartria e labilidade emocional.

Reações catastróficas representam um grau mais grave de comportamento associado à frustração[31]. Designam, no caso de pacientes afásicos, uma reação emocional intensa diante da incapacidade de executar uma tarefa linguística solicitada pelo examinador. O paciente se sente impotente, manifestando-se por meio de choro, gestos e palavras de cólera[46]. Ele geralmente se recusa a prosseguir o exame ou a conversação. Segundo Carota *et al.*[79], cerca de 3,7% dos pacientes apresentam reação catastrófica nos primeiros dias após um AVE. A maioria deles desenvolve labilidade emocional ou DPA nos meses seguintes, o que poderia sugerir uma conexão entre essas síndromes.

Assim como no TEEI, a vivência subjetiva e o comportamento podem estar dissociados. No caso da irritabilidade ou da agressividade, os pacientes frequentemente as banalizam e podem manifestá-las somente em situações específicas. No entanto, esses sintomas podem representar sobrecarga significativa e fonte de estresse para familiares e cuidadores[80]. O impacto pode ser negativo na QV, pois a irritabilidade é um dos sintomas que mais levam os cuidadores a criticarem indivíduos que sofreram um AVE. Assim, é preciso estar atento ao desenvolvimento desses comportamentos.

Há poucos estudos abordando especificamente o tratamento desses sintomas. Carota *et al.* sugerem a utilização de abordagens cognitivo-comportamentais, por meio das quais os pacientes reconheçam sintomas iniciais de agressividade, assim como métodos de relaxamento[79]. Ressaltam, no entanto, que intervenções farmacológicas são frequentemente necessárias. Não há revisões sistemáticas ou metanálises sobre a utilização de psicofármacos nesse contexto.

Chan *et al.* conduziram ensaio clínico para o tratamento de irritabilidade pós-AVE, utilizando fluoxetina e nortriptilina, e observaram que, apesar de a irritabilidade isoladamente não ter respondido, a redução de sintomas depressivos se associou à melhora significativa no comportamento agressivo[80]. De forma geral, as opções incluem antipsicóticos de primeira ou segunda geração, como haloperidol, olanzapina, quetiapina e risperidona; benzodiazepínicos; betabloqueadores; anticonvulsivantes, como carbamazepina e ácido valproico; além de fármacos serotoninérgicos, como ISRS, buspirona e trazodona[80]. Chama-se a atenção para potenciais problemas de interações farmacológicas e para a polêmica utilização de antipsicóticos em pacientes idosos, o que poderia associar-se ao aumento da mortalidade. Como exemplo da complexidade do manejo terapêutico desses casos, sabe-se que pacientes agitados recebem maior quantidade de medicação e tendem a sofrer mais quedas do que pacientes não agitados.

Com relação à abordagem das reações catastróficas, as melhores estratégias são preventivas, resguardando o paciente de situações que o predisponham aos episódios[64], durante os quais o manejo se baseia na abordagem acolhedora e segura, transmitindo tranquilidade até que a exaltação ceda.

Apatia

A apatia é comumente definida como uma síndrome de diminuição de comportamentos, emoções e cognições direcionados a um objetivo[81]. A utilização de questionários padronizados demonstrou prevalências de apatia que variam de 20% a 50% nos primeiros meses após um AVE[26,82]. Nas fases mais agudas, a apatia é frequente entre os pacientes com AVE à direita, em especial no território da artéria cerebral média[63]. Angelelli *et al.*[10], no entanto, relataram que a apatia é um fenômeno que tende a se manifestar especialmente na fase crônica pós-AVE, acometendo cerca de 27% dos casos. Recentemente, Van Dalen *et al.* observaram prevalência média de 34,6%, equiparando-se à ocorrência de depressão ou de síndromes demenciais pós-AVE. Os autores salientam que, enquanto depressão e demência pós-AVE são frequentemente estudadas, a apatia pós-AVE tem sido negligenciada[81].

Do ponto de vista comportamental, são classificados como apáticos os pacientes que apresentam redução da iniciativa verbal ou motora, com diminuição do comportamento voluntário e intencional[81]. De forma mais sutil, eles também manifestam achatamento afetivo, que se associa à perda de motivação e de vontade. A apatia, sem dúvida, pode fazer parte de uma síndrome depressiva, no entanto, no caso de associação com depressão, existe sofrimento subjetivo evidente, com manifestação de outros sintomas, como tristeza, baixa autoestima, culpabilidade, ideação negativa e de morte, e labilidade emocional. Além disso, há na depressão a tendência de interpretar negativamente quaisquer estímulos de conteúdo emocional, sejam eles neutros ou positivos. Com efeito, a apatia secundária ao AVE não se acompanha necessariamente de sofrimento subjetivo ou de ideação negativa sobre si mesmo. Em sua metanálise, Van Dalen *et al.* observaram que depressão estava presente em 40,1% dos pacientes com apatia, confirmando a associação, mas também a independência, das duas síndromes[81].

Em geral, a apatia se associa à idade mais avançada, sendo concomitante a sinais, como perseveração, síndrome de dependência ambiental e liberação de reflexos primitivos[81-83]. Van Dalen *et al.* observaram que a apatia pós-AVE estava associada a pior funcionamento cognitivo[81]. De forma sintética, a apatia associada a lesões cerebrais se manifesta por reatividade afetiva reduzida a qualquer estímulo de conteúdo emocional, seja sua natureza positiva, negativa ou neutra[81].

Todos os estudos clínicos sugerem que a apatia é ligada à disfunção de circuitos frontossubcorticais[83]. Esses incluem a região dorsolateral do lobo frontal, o giro do cíngulo, a área motora suplementar, os núcleos da base e o núcleo dorsomediano do tálamo, entre outros. Os estudos de neuroimagem funcional realizados em pacientes com apatia grave pós-AVE mostraram redução do metabolismo pré-frontal dorsolateral e temporal[82]. Van Dalen *et al.,* no entanto, não observaram associações entre localização ou volume das lesões, nem gravidade inicial do AVE com o desenvolvimento de apatia[81].

Os mecanismos subjacentes à apatia podem ser divididos em três subtipos, com base em distúrbios do processamento emocional, cognitivo ou de autoativação[83], como mostra o quadro 3. O último é responsável pela forma mais grave, chamada síndrome de déficit de autoativação, ou atimormia, caracterizada por "esvaziamento mental". Os pacientes podem apresentar atividade adequada após estimulação repetida, demonstrando a dissociação entre autoativação perturbada e heteroativação intacta. Essa síndrome sugere que lesões diretas da eferência dos núcleos da base (globo pálido interno ou vias estriato-palidais) resultam em perda da amplificação de sinais relevantes, diminuindo-os no córtex frontal.

Diversos pesquisadores propuseram que apatia, abulia e mutismo acinético seriam estados clínicos caracterizados por comportamento reduzido, formando um *continuum* no qual os extremos incluiriam a abulia e o mutismo acinético. Neste, os pacientes podem ser incapazes de iniciar movimentos ou de falar[84]. Eles podem estar incontinentes e comer ou beber somente se estimulados energicamente por um terceiro. Quando falam, é somente por monossílabos e não manifestam nenhuma emoção, mesmo em caso de dor.

De acordo com Van Dalen *et al.,* a heterogeneidade dos trabalhos incluídos em sua revisão sistemática dificultou a avaliação quantitativa da relação entre apatia e recuperação funcional[81]. No entanto, observou-se a tendência de que a apatia possa ter impacto negativo na reabilitação dos pacientes, mesmo moderada.

Quadro 3. Características dos mecanismos subjacentes à apatia

Subtipos de apatia	Características clínicas	Localização
Distúrbios do processamento emocional	Incapacidade de estabelecer as conexões necessárias entre sinais afetivos e o comportamento presente ou futuro	Lesões do córtex pré-frontal orbitomedial ou de regiões límbicas nos núcleos da base (por exemplo, estriado ventral ou globo pálido ventral)
Distúrbios do processamento cognitivo	Dificuldades na elaboração do plano de ações para o comportamento presente ou futuro	Lesões do córtex pré-frontal dorsolateral ou de áreas associativas nos núcleos da base (por exemplo, núcleo caudado dorsal)
Distúrbios da autoativação	Incapacidade de autoativar pensamentos ou autoiniciar ações, contrastando com habilidade relativamente preservada para iniciar comportamentos externamente dirigidos	Lesões bilaterais, afetando territórios associativos e límbicos da porção interna do globo pálido

Até o momento, não foram conduzidos ensaios clínicos sistemáticos e não existem evidências suficientes para indicar qualquer tratamento farmacológico específico. Há relatos de benefícios com alguns fármacos, que talvez mereçam maior investigação. Dentre eles, destacam-se nefiracetam, donepezil, agonistas dopaminérgicos, como a bromocriptina, e metilfenidato. Os ISRS parecem não exercer efeitos significativos. Programas de reabilitação envolvendo terapeutas ocupacionais, neuropsicológos e treinamento de cuidadores, por exemplo, podem ser adaptados de acordo com as necessidades dos pacientes[81].

Demência

A demência vascular (DV) é a segunda causa de demência na população geral, podendo ter sua prevalência subestimada em virtude da frequente associação com doença de Alzheimer (DA)[85]. A prevalência estimada de DV tende a aumentar com a idade, variando entre 1,2% e 4,2% aos 65 anos e entre 3,5% e 5,8% aos 90 anos[86]. A prevalência de DV em um centro terciário de atenção a pacientes com demências, em Ribeirão Preto, foi de 25,8%[87]. Inúmeros estudos investigaram a incidência de comprometimento cognitivo e de demência pós-AVE, encontrando taxas de 6% a 32% em pacientes acompanhados por 20 anos[88,89].

O termo DV engloba diversos processos patológicos, que incluem doenças de pequenos ou de grandes vasos, infartos recorrentes ou, de forma controversa, estratégicos, e hipoperfusão subcortical crônica[86]. Entre os fatores de risco, encontram-se idade avançada, gravidade inicial do evento isquêmico, HAS, obesidade, diabetes, fibrilação atrial, evidências radiológicas de lesões de substância branca ou de atrofia cortical (especialmente no lobo temporal) e hiper-homocisteinemia. Além disso, trabalhos demonstram que déficits cognitivos pré-mórbidos também são fatores de risco, ao passo que altos índices de escolaridade podem diminuir o risco de declínio cognitivo pós-AVE[86].

Em função da heterogeneidade neuropatológica, há também grande diversidade das manifestações clínicas, dependendo da natureza, da localização e da extensão das lesões. Tradicionalmente, reconhecem-se dois padrões clínicos principais: um no qual o comprometimento predominante é cortical e o outro, subcortical. Embora esses padrões ainda sejam internamente heterogêneos, ambos apresentam características clínicas distintas entre si[85].

Na DV cortical, as alterações cognitivas tendem a refletir as áreas corticais afetadas. Em geral, decorrem da oclusão de ramos arteriais corticais, frequentemente causados por fenômenos aterotrombóticos ou tromboembólicos a partir do coração ou de grandes vasos, podendo se expressar clinicamente como AVE. Assim, lesões frontomediais podem cursar com disfunção executiva, abulia ou apatia, além de mutismo acinético no caso de comprometimento bilateral. Lesões do lobo parietal esquerdo podem levar a afasia, apraxia ou agnosia, ao passo que lesões do lobo parietal direito podem cursar com síndrome de heminegligência, confusão mental, agitação psicomotora, déficits visuoespaciais e de habilidades visuoconstrutivas. Lesões da região temporal medial podem levar à amnésia anterógrada. O surgimento da síndrome demencial pode dar-se, então, de forma súbita. Quando a divisão superior da artéria cerebral média não é envolvida, sinais motores focais podem não aparecer e a instalação súbita de alterações cognitivas isoladas talvez não seja óbvia clinicamente. Assim, seu curso pode ser insidioso e não é incomum que o paciente se recupere até o próximo evento isquêmico. O curso é percebido como flutuante ou em degraus. Cerca de 30% dos pacientes com demência multi-infarto experimentam tanto início abrupto quanto progressão em degraus.

Já na DV subcortical, os mecanismos principais se associam a alterações dos pequenos vasos. Dentre eles, destacam-se infartos lacunares e isquemia subcortical crônica, afetando principalmente os núcleos da base e a substância branca, de forma silenciosa. Frequentemente interrompem circuitos frontais e outros circuitos córtico-corticais, levando a manifestações clínicas atribuíveis a áreas cerebrais remotas (distantes) às lesões. As principais características clínicas incluem sinais motores focais, distúrbios da marcha (marcha com pequenos passos ou parkinsoniana, apraxia de marcha), história de desequilíbrio e de quedas frequentes e não provocadas, aumento da frequência urinária, com urgência e outros sintomas urinários não urológicos, alterações de personalidade e de humor, apatia, incontinência emocional, transtorno cognitivo caracterizado por déficit de memória relativamente leve, lentificação psicomotora e disfunção exe-

cutiva. O curso da DV subcortical pode ser gradual ou em degraus, podendo ser também de progressão lenta ou rápida.

A presença de doença cerebrovascular e de fatores de risco vasculares associa-se a aumento de risco e de aceleração da DA[90]. No entanto, sintomas depressivos e labilidade emocional são mais frequentes na DV do que na DA[91]. A descoberta da associação entre o aparecimento de uma síndrome depressiva na população geriátrica e a presença de lesões da substância branca de origem vascular, sobretudo nas regiões frontais, levou à hipótese da existência de uma "depressão vascular", que estaria ligada à microangiopatia.

Não existem tratamentos específicos para o déficit cognitivo da DV[92]. Pacientes com comprometimento cognitivo e evidências de doença cerebrovascular devem ter fatores de risco investigados e tratados, especialmente HAS. As evidências de déficit colinérgico na DV similares àqueles da DA têm levado ao estudo dos inibidores da colinesterase. A resposta a esses fármacos é variável, com alta proporção de indivíduos sem resposta[92]. Naqueles em que houve resposta, seus benefícios cognitivos e funcionais tiveram magnitude similar aos daqueles descritos para a DA, representando um atraso de quatro a seis meses no declínio cognitivo, e isso pode se dever à associação neuropatológica com a DA. A memantina mostrou efeitos benéficos em escalas cognitivas, que não foram traduzidos na impressão clínica global ou no desempenho de AVD em pacientes com DV.

Mania

A ocorrência de episódios maníacos associados a AVE é rara, não chegando a 1% dos casos. Santos *et al.* relataram que, nos últimos 50 anos, apenas 74 de casos de mania pós-AVE foram publicados[93]. Essa baixa prevalência limita a descrição das características clínicas, demográficas e prognósticas dessa síndrome. No entanto, com os dados disponíveis, é possível observar algumas características consistentes.

Predomina no gênero masculino, sem influência da idade, de história pessoal ou familiar de transtorno psiquiátrico ou de atrofia subcortical[93]. Adicionalmente, acompanha-se de sinais neurológicos ou cognitivos ligados à localização da lesão (por exemplo, heminegligência ou síndrome disexecutiva). A maior parte dos relatos associa-se a lesões no hemisfério direito, incluindo lobos frontais ou temporais, tálamo ou núcleo caudado. Nesse sentido, Starkstein *et al.*[94] observaram hipometabolismo da região temporal inferior direita em três pacientes com mania associada a lesões subcorticais. Os autores sugerem, como mecanismo fisiopatológico, disfunção da alça fronto-estriado-tálamo-cortical interconectada ao sistema límbico e ao lobo temporal, principalmente o direito. É interessante notar a oposição entre episódios depressivos secundários a lesões esquerdas e episódios maníacos a lesões direitas.

A maior parte dos casos tende a surgir no primeiro mês, havendo, no entanto, casos iniciados até dois anos pós-AVE[93]. Aproximadamente, 92% dos pacientes apresentam elevação do humor como primeiro sintoma[93]. Cerca de 41% apresentam oscilação entre humor elevado e disforia, e apenas 8%, disforia isolada. Os episódios duram de 1 a 12 semanas, frequentemente sem recorrências ou hipomania residual.

A baixa prevalência dificulta o tratamento baseado em evidências[93]. A literatura mostra que o lítio é eficaz. Outros estabilizadores do humor, como ácido valproico e carbamazepina, também têm sido utilizados. Antipsicóticos vêm sendo usados em casos de mania grave com sintomas psicóticos. Benzodiazepínicos também têm sido usados como adjuvantes no tratamento da hiperatividade e da insônia.

Síndromes psicóticas

Síndromes psicóticas também são complicações raras após AVE. Rabins *et al.*[95] avaliaram, durante nove anos, todos os indivíduos com mais de 60 anos admitidos em um hospital, identificando somente cinco pacientes com psicose pós-AVE em 301 casos (0,02%). Todos eles apresentavam lesões frontoparietais à direita e mostravam grau significativo de atrofia subcortical em comparação com pacientes pareados com AVE, porém sem psicose.

É interessante notar que a maior parte dos relatos de casos de transtornos psicóticos pós-AVE é caracterizada por delírios monotemáticos de identificação, como síndrome de Capgras, síndrome de Fregoli, paramnésia reduplicativa ou intermetamorfose, e associa-se a lesões no hemisfério direito[96-98]. Na paramnésia reduplicativa, já se observaram lesões localizadas nas regiões frontais, parietais, talâmicas ou no lobo temporal médio[99]. Já os casos de síndrome de Capgras pós-AVE mostram predominância de lesões no lobo frontal direito ou na junção parieto-occipital direita[100-102]. Além disso, no trabalho de Rabins *et al.*[95], o desenvolvimento de sintomas psicóticos pareceu associar-se à ocorrência de crises epilépticas. Em geral, os pacientes com sintomas psicóticos respondem ao tratamento com fármacos antipsicóticos[95].

CONCLUSÃO

Tendo em vista a magnitude do problema de saúde pública relacionado ao AVE e sua frequente associação a transtornos neuropsiquiátricos, é notória a escassez de dados sobre seu manejo terapêutico. Uma multiplicidade de alterações comportamentais e afetivas pode associar-se a lesões vasculares do sistema nervoso central e se sobrepõem com frequência a déficits cognitivos, interferindo nos programas de reabilitação e de reinserção social. Além da intervenção precoce para prevenir o infarto cerebral, o aprofundamento do conhecimento sobre os transtornos neuropsiquiátricos parece ter grande potencial para melhorar o prognóstico e a QV de pacientes que sofreram um AVE.

CONTRIBUIÇÕES INDIVIDUAIS

Todos os autores contribuíram efetivamente na concepção do presente trabalho, no levantamento de dados e em sua análise e interpretação. Participaram significativamente na redação do artigo, revisaram criticamente o seu conteúdo e aprovaram a versão final a ser publicada.

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CONFLITOS DE INTERESSES

Os autores declaram não possuir conflitos de interesses.

REFERÊNCIAS

1. World Health Organization. Recommendations on stroke prevention, diagnosis, and therapy: report of the WHO Task Force on Stroke and Other Cerebrovascular Disorders. Stroke. 1989;20(10):1407-31.
2. Broderick JP, Philips SJ, Whisnat JP, O'Fallon WM, Bergstralh EJ. Incidence rates of strokes in the eighties: the decline in stroke. Stroke. 1989;20(5):577-82.
3. Heuschmann PU, Kolominsky-Rabas PL, Misselwitz B, Hermanek P, Leffmann C, Janzen RW, et al. Predictors of in-hospital mortality and attributable risks of death after ischemic stroke: the German stroke registers study group. Arch Intern Med. 2004;164(16):1761-8.
4. de Carvalho JJ, Alves MB, Viana GA, Machado CB, dos Santos BF, Kanamura AH, et al. Stroke epidemiology, patterns of management, and outcomes in Fortaleza, Brazil: a hospital-based multicenter prospective study. Stroke. 2011;42(12):3341-6.
5. Minelli C, Fen LF, Minelli DP. Stroke incidence, prognosis, 30-day, and 1-year case fatality rates in Matão, Brazil: a population-based prospective study. Stroke. 2007;38(11):2906-11.
6. Rabelo DF, Néri AL. Bem-estar subjetivo e senso de ajustamento psicológico em idosos que sofreram acidente vascular cerebral: uma revisão. Estud Psicol (Natal). 2006;11(2):169-77.
7. Mota JF, Nicolato R. Qualidade de vida em sobreviventes de acidente vascular cerebral: instrumentos de avaliação e seus resultados. J Bras Psiquiatr. 2008;57(2):148-56.
8. Chemerinski E, Robinson RG. The neuropsychiatry of stroke. Psychosomatics. 2000;41(1):5-14.
9. Tengs TO, Yu M, Luistro E. Health-related quality of life after stroke – a comprehensive review. Stroke. 2001;32(4):964-72.
10. Angelelli P, Paolucci S, Bivona U, Piccardi L, Ciurli P, Cantagallo A, et al. Development of neuropsychiatric symptoms in poststroke patients: a cross-sectional study. Acta Psychiatr Scand. 2004;110(1):55-63.
11. Robinson RG, Starr LB, Kubos KL, Price TR. A two-year longitudinal study of post-stroke mood disorders: findings during the initial evaluation. Stroke. 1983;14(5):736-41.
12. Robinson RG, Starr LB, Price TR. A two year longitudinal study of mood disorders following stroke. Prevalence and duration at six months follow-up. Br J Psychiatry. 1984;144:256-62.
13. Robinson RG, Bolduc PL, Price TR. Two-year longitudinal study of poststroke mood disorders: diagnosis and outcome at one and two years. Stroke. 1987;18(5):837-43.
14. Eastwood MR, Rifat SL, Nobbs H, Ruderman J. Mood disorder following cerebrovascular accident. Br J Psychiatry. 1989;154:195-200.
15. Morris PLP, Robinson RG, Raphael B. Prevalence and outcome of poststroke depression in hospitalized patients. Int J Psychiatr Med. 1990;20(4):327-42.
16. House A, Dennis M, Mogridge L, Warlow C, Hawton K, Jones L. Mood disorders in the year after stoke. Br J Psychiatry. 1991;158:83-92.
17. Astrom M, Adolfsson R, Asplund K. Major depression in stroke patients: a 3-year longitudinal study. Stroke. 1993;24(7):976-82.
18. Burvill PW, Johnson GA, Jamrozik KD, Anderson CS, Stewart-Wynne EG, Chakera TM. Prevalence of depression after stroke: the Perth Community Stroke Study. Br J Psychiatry. 1995;166(3):320-7.
19. Ng KC, Chan KL, Straughan PT. A study of post-stroke depression in a rehabilitative center. Acta Psych Scand. 1995;92(1):75-9.
20. Kotila M, Numminen H, Waltimo O, Kaste M. Depression after stroke: results of the FINNSTROKE Study. Stroke. 1998;29(2):368-72.
21. Hackett ML, Anderson CS. Predictors of depression after stroke: a systematic review of observational studies. Stroke. 2005;36(10): 2296-301.
22. Buijck BI, Zuidema SU, Spruit-van Eijk M, Geurts AC, Koopmans RT. Neuropsychiatric symptoms in geriatric patients admitted to skilled nursing facilities in nursing homes for rehabilitation after stroke: a longitudinal multicenter study. Int J Geriatr Psychiatry. 2012;27(7):734-41.
23. Ayerbe L, Ayis S, Wolfe CD, Rudd AG. Natural history, predictors and outcomes of depression after stroke: systematic review and meta-analysis. Br J Psychiatry. 2013;202(1):14-21.
24. Ayerbe L, Ayis S, Crichton S, Wolfe CD, Rudd AG. The natural history of depression up to 15 years after stroke: the South London Stroke Register. Stroke. 2013;44(4):1105-10.
25. Skånér Y, Nilsson GH, Sundquist K, Hassler E, Krakau I. Self-rated health, symptoms of depression and general symptoms at 3 and 12 months after a first-ever stroke: a municipality-based study in Sweden. BMC Fam Pract. 2007;8:61.
26. Starkstein SE, Fedoroff JP, Price TR, Leiguarda R, Robinson RG. Apathy following cerebrovascular lesions. Stroke. 1993;24(11):1625-30.
27. Brodaty H, Sachdev PS, Withall A, Altendorf A, Valenzuela MJ, Lorentz L. Frequency and clinical, neuropsychological and neuroimaging correlates of apathy following stroke – the Sydney Stroke Study. Psychol Med. 2005;35(12):1707-16.
28. Campbell Burton CA, Murray J, Holmes J, Astin F, Greenwood D, Knapp P. Frequency of anxiety after stroke: a systematic review and meta-analysis of observational studies. Int J Stroke. 2013;8(7):545-59.
29. Calvert T, Knapp P, House A. Psychological associations with emotionalism after stroke. J Neurol Neurosurg Psychiatry. 1998;65(6):928-9.
30. Piamarta F, Iurlaro S, Isella V, Atzeni L, Grimaldi M, Russo A, et al. Unconventional affective symptoms and executive functions after stroke in the elderly. Arch Gerontol Geriatr Suppl. 2004;(9):315-23.
31. Robinson RG. The clinical neuropsychiatry of stroke. New York: Cambridge University Press; 2006.
32. Fróes KSSO, Valdés MTM, Lopes DPLO, Silva CEP. Factors associated with health-related quality of life for adults with stroke sequelae. Arq Neuropsiquiatr. 2011;69(2B):371-6.
33. Souza AC, Rocha MO, Teixeira AL, Dias Júnior JO, Sousa LA, Nunes MC. Depressive symptoms and disability in chagasic stroke patients: impact on functionality and quality of life. J Neurol Sci. 2013;324(1-2):34-7.
34. Carod-Artal FJ, Trizotto DS, Coral LF, Moreira CM. Determinants of quality of life in Brazilian stroke survivors. J Neurol Sci. 2009;284(1-2):63-8.
35. Simis S, Nitrini R. Cognitive improvement after treatment of depressive symptoms in the acute phase of stroke. Arq Neuropsiquiatr. 2006;64(2B):412-7.
36. Terroni LM, Fráguas R, Lucia M, Tinone G, Mattos P, Iosifescu DV, et al. Importance of retardation and fatigue/interest domains for the diagnosis of major depressive episode after stroke : a four months prospective study. Rev Bras Psiquiatr. 2009;31(3):202-7.
37. Scheffer M, Monteiro JK, de Almeida RMM. Frontal stroke: problem solving, decision making, impulsiveness, and depressive symptoms in men and women. Psychol Neurosci. 2011;4(2):267-78.
38. Rangel ESS, Belasco AGS, Diccini S. Qualidade de vida de pacientes com acidente vascular cerebral em reabilitação. Acta Paul Enferm. 2013;26(2):205-12.
39. Lyketsos CG, Kozauer N, Rabins PV. Psychiatric manifestations of neurologic disease: where are we headed? Dialogues Clin Neurosci. 2007;9(2):111-24.
40. Schildkraut JJ, Klein FD. The classification and treatment of depressive states. In: Shader RI. Manual of psychiatric therapeutics. Boston: Little and Brown; 1975.
41. Figueiredo JM, Frank JD. Subjective incompetence, the clinical hallmark of demoralization. Compr Psychiatry. 1982;23(4):353-63.
42. Figueiredo JM. Some issues in research on the epidemiology of demoralization. Compr Psychiatry. 1983;24(2):154-7.
43. Figueiredo JM. Depression and demoralization: phenomenologic differences and research perspectives. Compr Psychiatry. 1993;34(5):308-11.
44. Clarke DM, Kissane DW. Demoralization: its phenomenology and importance. Aust NZJ Psychiatry. 2002;36(6):733-42.

45. Shader RI. Demoralization revisited. J Clin Psychopharmacology. 2005;25(4):291-2.
46. Fedoroff JP, Starkstein SE, Parikh RM, Price TR, Robinson RG. Are depressive symptoms nonspecific in patients with acute stroke? Am J Psychiatry. 1991;148(9):1172-6.
47. Gainotti G, Azzoni A, Marra C. Frequency, phenomenology and anatomical-clinical correlates of major post-stroke depression. Br J Psychiatry. 1999;175:163-7.
48. Bhogal SK, Teasell R, Foley N, Speechley M. Lesion location and poststroke depression: systematic review of the methodological limitations in the literature. Stroke. 2004;35(3):794-802.
49. Carson AJ, MacHale S, Allen K, Lawrie SM, Dennis M, House A, et al. Depression after stroke and lesion location: a systematic review. Lancet. 2000;356(9224):122-6.
50. MacHale SM, O'Rourke SJ, Wardlaw JM, Dennis MS. Depression and its relation to lesion location after stroke. J Neurol Neurosurg Psychiatry. 1998;64(3):371-4.
51. Shimoda K, Robinson RG. The relationship between poststroke depression and lesion location in long-term follow-up. Biol Psychiatry. 1999;45(2):187-92.
52. Dong JY, Zhang YH, Tong J, Qin LQ. Depression and risk of stroke: a meta-analysis of prospective studies. Stroke. 2012;43(1):32-7.
53. Carota A, Berney A, Aybek S, Iaria G, Staub F, Ghika-Schmid F, et al. A prospective study of predictors of poststroke depression. Neurology. 2005;64(3):428-33.
54. Kauhanen ML, Korpelainen JT, Hiltunen P, Määttä R, Mononen H, Brusin E, et al. Aphasia, depression, and non-verbal cognitive impairment in ischaemic stroke. Cerebrovasc Dis. 2000;10(6):455-61.
55. Ouimet MA, Primeau F, Cole MG. Psychosocial risk factors in poststroke depression: a systematic review. Can J Psychiatry. 2001;46(9):819-28.
56. Ribeiro DS, Cerqueira Filho EA, Losapio MF, Sena EP. Terapia medicamentosa na depressão pós-acidente vascular encefálico. J Bras Psiquiatr. 2009;58(2):135-42.
57. Hackett ML, Anderson CS, House AO, Xia J. Interventions for treating depression after stroke. Stroke. 2009;40:e487-8.
58. Price A, Rayner L, Okon-Rocha E, Evans A, Valsraj K, Higginson IJ, et al. Antidepressants for the treatment of depression in neurological disorders: a systematic review and meta-analysis of randomised controlled trials. J Neurol Neurosurg Psychiatry. 2011;82(8):914-23.
59. Tharwani HM, Yerramsetty P, Mannelli P, Patkar A, Masand P. Recent advances in poststroke depression. Curr Psychiatry Rep. 2007;9(3):225-31.
60. Hackett ML, Anderson CS, House A, Halteh C. Interventions for preventing depression after stroke. Cochrane Database Syst Rev. 2008;(3):CD003689.
61. Astrom M. Generalized anxiety disorder in stroke patients. A 3-year longitudinal study. Stroke. 1996;27(2):270-5.
62. Favrole P, Jehel L, Levy P, Descombes S, Muresan IP, Manifacier MJ, et al. Frequency and predictors of post-traumatic stress disorder after stroke: a pilot study. J Neurol Sci. 2013;327(1-2):35-40.
63. Carota A, Dieguez S, Bogousslavsky J. Psychopathology of stroke. Psychol Neuropsychiatr Vieil. 2005;3(4):235-49.
64. Robinson RG. Neuropsychiatric consequences of stroke. Annu Rev Med. 1997;48:217-29.
65. Burton CAC, Holmes J, Murray J, Gillespie D, Lightbody CE, Watkins CL, et al. Interventions for treating anxiety after stroke. Cochrane Database Syst Rev. 2011;(12):CD008860.
66. Sartori HCS, Barros T, Tavares A. Transtorno da expressão emocional involuntária. Rev. Psiq Clín. 2008;35(1):20-5.
67. Grinblat N, Grinblat E, Grinblat J. Uncontrolled crying: characteristics and differences from normative crying. Gerontology. 2004;50(5):322-9.
68. Kim JS, Choi-Kwon S. Poststroke depression and emotional incontinence: correlation with lesion location. Neurology. 2000;54(9):1805-10.
69. Tang WK, Chan SS, Chiu HF, Ungvari GS, Wong KS, Kwok TC. Emotional incontinence in Chinese stroke patients: diagnosis, frequency, and clinical and radiological correlates. J Neurol. 2004;251(7):865-9.
70. House A, Dennis M, Molyneux A, Warlow C, Hawton K. Emotionalism after stroke. BMJ. 1989;298(6679):991-4.
71. Pioro EP, Brooks BR, Cummings J, Schiffer R, Thisted RA, Wynn D, et al. Dextromethorphan plus ultra low-dose quinidine reduces pseudobulbar affect. Ann Neurol. 2010;68(5):693-702.
72. Robinson RG, Parikh RM, Lipsey JR, Starkstein SE, Price TR. Pathological laughing and crying following stroke: validation of measurement scale and double-blind treatment study. Am J Psychiatry. 1993;150(2):286-93.
73. Andersen G, Vestergaard K, Riis J. Citalopram for post-stroke pathological crying. Lancet. 1993;342(8875):837-9.
74. Adler R, MacRitchie K, Engel GL. Psychologic processes and ischemic stroke (occlusive cerebrovascular disease), I: observations on 32 men with 35 strokes. Psychosom Med. 1971;33(1):1-29.
75. Gianturco DT, Breslin MS, Heyman A, Gentry WD, Jenkins CD, Kaplan B. Personality patterns and life stress in ischemic cerebrovascular disease, I: psychiatric findings. Stroke. 1974;5(4):453-60.
76. Everson SA, Kaplan GA, Goldberg DE, Lakka TA, Sivenius J, Salonen JT. Anger expression and incident stroke: prospective evidence from the Kuopio Ischemic Heart Disease Study. Stroke. 1999;30(3):523-8.
77. Williams JE, Nieto FJ, Sanford CP, Couper DJ, Tyroler HA. The association between trait anger and incident stroke risk: the Atherosclerosis Risk in Communities (ARIC) Study. Stroke. 2002;33(1):13-9.
78. Paradiso S, Robinson RG, Arndt S. Self-reported aggressive behavior in patients with stroke. J Nerv Ment Dis. 1996;184(12):746-53.
79. Carota A, Rossetti AO, Karapanayiotides T, Bogousslavsky J. Catastrophic reaction in acute stroke : a reflex behavior in aphasic patients. Neurology. 2001;57(10):1902-5.
80. Chan KL, Campayo A, Moser DJ, Arndt S, Robinson RG. Aggressive behavior in patients with stroke: association with psychopathology and results of antidepressant treatment on aggression. Arch Phys Med Rehabil. 2006;87(6):793-8.
81. van Dalen JW, Moll van Charante EP, Nederkoorn PJ, van Gool WA, Richard E. Poststroke apathy. Stroke. 2013;44(3):851-60.
82. Okada K, Kobayashi S, Yamagata S, Takahashi K, Yamaguchi S. Poststroke apathy and regional cerebral blood flow. Stroke. 1997;28(12):2437-41.
83. Levy R, Dubois B. Apathy and the functional anatomy of the prefrontal cortex-basal ganglia circuits. Cereb Cortex. 2006;16(7):916-28.
84. Nagaratnam N, Nagaratnam K, Ng K, Diu P. Akinetic mutism following stroke. J Clin Neurosci. 2004;11(1):25-30.
85. Wallin A, Milos V, Sjogren M, Pantoni L, Erkinjuntti T. Classification and subtypes of vascular dementia. Int Psychogeriatr. 2003;15(Suppl 1):27-37.
86. Hébert R, Brayne C. Epidemiology of vascular dementia. Neuroepidemiology. 1995;14(5):240-57.
87. Vale FC, Miranda SJC. Clinical and demographic features of patients with dementia attended in a tertiary outpatient clinic. Arq Neuropsiquiatr. 2002;60(3-A):548-52.
88. Béjot Y, Aboa-Eboulé C, Durier J, Rouaud O, Jacquin A, Ponavoy E, et al. Prevalence of early dementia after first-ever stroke: a 24-year population-based study. Stroke. 2011;42(3):607-12.
89. Ivan CS, Seshadri S, Beiser A, Au R, Kase CS, Kelly-Hayes M, et al. Dementia after stroke: the Framingham Study. Stroke. 2004;35(6):1264-8.
90. Sadowski M, Pankiewicz J, Scholtzova H, Li YS, Quartermain D, Duff K, et al. Links between the pathology of Alzheimer's disease and vascular dementia. Neurochem Res. 2004;29(6):1257-66.
91. Newman SC. The prevalence of depression in Alzheimer's disease and vascular dementia in a population sample. J Affect Disord. 1999;52(1-3):169-76.
92. Kavirajan H, Schneider LS. Efficacy and adverse effects of cholinesterase inhibitors and memantine in vascular dementia: a meta-analysis of randomised controlled trials. Lancet Neurol. 2007;6(9):782-92.
93. Santos CO, Caeiro L, Ferro JM, Figueira ML. Mania and stroke: a systematic review. Cerebrovasc Dis. 2011;32(1):11-21.
94. Starkstein SE, Mayberg HS, Berthier ML, Fedoroff P, Price TR, Dannals RF, et al. Mania after brain injury: neuroradiological and metabolic findings. Ann Neurol. 1990;27(6):652-9.
95. Rabins PV, Starkstein SE, Robinson RG. Risk factors for developing atypical (schizophreniform) psychosis following stroke. J Neuropsychiatry Clin Neurosci. 1991;3(1):6-9.
96. Forstl H, Almeida OP, Owen AM, Burns A, Howard R. Psychiatric, neurological and medical aspects of misidentification syndromes: a review of 260 cases. Psychol Med. 1991;21(4):905-10.
97. Fleminger S, Burns A. The delusional misidentification syndromes in patients with and without evidence of organic cerebral disorder: a structured review of case reports. Biol Psychiatry. 1993;33(1):22-32.
98. Feinberg TE, Shapiro RM. Misidentification: reduplication and the right hemisphere. Neuropsych Neuropsychol Behav Neurol. 1989;2(1):39-48.
99. Patterson MB, Mack JL. Neuropsychological analysis of a case of reduplicative paramnesia. J Clin Exp Neuropsychol. 1985;7(1):111-21.
100. Hudson AJ, Grace GM. Misidentification syndromes related to face specific area in the fusiform gyrus. J Neurol Neurosurg Psychiatry. 2000;69(5):645-8.
101. Signer SF. Localization and lateralization in the delusion of substitution. Capgras symptom and its variants. Psychopathology. 1994;27(3-5):168-76.
102. Ellis HD. The role of the right hemisphere in the Capgras delusion. Psychopathology. 1994;27(3-5):177-85.

Artigo 2: Post stroke depression: clinics, etiopathogenesis and therapeutics.

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Review article

Post stroke depression: clinics, etiopathogenesis and therapeutics

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Abstract

Background: Stroke is a major cause of morbidity and mortality worldwide. Neuropsychiatric disorders are often associated with stroke and, among them, depression is the most prevalent. Post-stroke Depression (PSD) is related to disability, failure in returning to work, impairment in interpersonal functioning and mortality. Its etiopathogenesis is still uncertain, as well as its treatment. In Brazil, there are few data on the impact of PSD. **Objective:** This work is dedicated to conduct a comprehensive review of the concept of PSD, its pathophysiology, morbidity and treatment. **Methods:** PubMed, Medline and Lilacs searches of relevant terms yielded 3,265 papers in the last 10 years. We selected original studies and reviews that addressed the aspects mentioned above. **Results:** We present the history of the notion of PSD and describe its epidemiology, looking to highlight Brazilian studies. Diagnostic criteria and clinical presentation were detailed, with emphasis on cognitive aspects. The four main pathophysiological theories proposed to PSD are presented and we discuss the various treatment strategies, involving psychopharmacologic options, brain stimulation techniques and psychotherapy. **Discussion:** This work provides comprehensive information on PSD, of great utility for clinical practice and research in this topic.

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Keywords: Stroke, cerebrovascular diseases, depression, post-stroke depression, vascular depression.

Introduction

Stroke is a major cause of death and disability worldwide[1]. In the United States (US), there are approximately 610,000 new cases each year[1]. In Brazil, epidemiologic data are scarce. The available information allows stating that stroke is the main cause of death in the country, accounting for approximately 100,000 deaths annually[2]. Nevertheless, over the last decades there has been a global trend of decrease in stroke mortality. This is probably due to the improvement in acute stroke management and to preventive measures, such as arterial hypertension treatment. In Brazil, there is also a decrease in stroke mortality, but restricted to the South and Southeast regions[2]. Currently, an estimated 5 million stroke survivors live in the US[1]. In Brazil, where the highest stroke death rates in Latin America are found, it is estimated that stroke survivors achieve at least half of that sum[2]. As the management of acute stroke continues to improve, the number of survivors will increase even more and, since it often results in major changes in the patient's life, factors associated with morbidity have received increased attention.

Stroke is frequently associated with psychiatric symptoms such as depressed mood, anxiety and apathy[3]. The psychiatric complications of stroke, although recognized for more than one century, have never received the attention that has been devoted to other stroke complications, such as motor impairment, language problems, or cognitive deficits[4].

Depression is the most common neuropsychiatric condition experienced after stroke[4]. More than a hundred years ago, Adolf Meyer postulated that depression should be the consequence of the combined effects of brain injury, affecting mainly the left frontal lobe as well as other lobar convexities, and psychosocial vulnerability, such as past psychiatric history. In the beginning of the XX century, Eugen Bleuler noted that after stroke "melancholic moods lasting for months and sometimes longer appear frequently". Further in this direction, in 1962, after assessing 100 elderly patients with depression, Post remarked that the association of brain ischemia with a first episode of depressive disorder was so common that the causes of atherosclerotic disease and depression should be "etiologically linked". However, although the association of depression with stroke has been clinically recognized for several decades, only in the past 25 years systematic studies have been conducted, with emerging evidence that depression after a stroke is associated with increased disability, increased cognitive impairment and, ultimately, worse rehabilitation outcomes and increased mortality[3,4].

This review aimed to gather information on available epidemiological, pathophysiological, clinical and therapeutic aspects of post-stroke depression (PSD), their impacts in patient's recovery and, when possible, to contextualize them to the Brazilian scenario.

Methods

We conducted a narrative review of the literature through Lilacs, Medline and PubMed electronic databases, using the keywords "stroke", "cerebrovascular diseases", "depression" and "post-stroke depression". When indicated, other bibliographies were consulted from the reference lists of these articles. The search was restricted to articles published in English and Portuguese, in the last ten years. After this step, the titles and abstracts of all articles found were read in order to identify studies that addressed the theme and purpose of this review.

Results

Historical perspective

Isolated studies with patients affected by PSD started to appear in the 1960s[4]. Most of these works adopted a perspective of "empathic understanding". In other words, these researchers explained PSD as a natural and understandable emotional reaction of the individual to a decrease in self-esteem produced by the combination of a life-threatening injury, the associated physical and intellectual disability, and the resulting loss of independence. Adopting such psychological perspective, Guido Gainotti's group, from the Catholic University of Rome, Italy, conducted the first systematic study of neuropsychiatric symptoms in patients with stroke or other brain injuries[4]. His works can be considered one of the main representatives of the idea that the depressive syndromes associated with stroke may not be "true"

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depressions, but a completely different category from Major Depressive Disorder (MDD) that would be associated with the patients' adjustment to changes in their living conditions[14].

In 1977, however, Folstein *et al.* conducted a study comparing the prevalence of mood disorders in patients with stroke or orthopedic problems which all presented comparable functional disability[5]. They observed that patients with stroke exhibited a far greater frequency of depression than orthopedic patients, and concluded that mood disorders would be a complication of stroke that was linked not only to the degree of functional disability. This seminal study led to the development of a biological explanation for PSD, whereby brain changes would lead to depressive symptoms. This line of reasoning was primarily developed in the 1980's by Robert Robinson's group, from the University of Iowa, in opposition to the psychological perspective[3,4]. These opposing perspectives have led to many of the continuing controversies and uncertainties about emotional disorders following stroke.

Epidemiology

Since the first systematic studies, depression (major and minor) has been regarded as the most common neuropsychiatric disorder after stroke, with an estimated prevalence ranging from 18 to 60%[3]. According to DSM-V, MDD corresponds to the presence of at least four accessory symptoms, besides depressed mood or anhedonia. Minor Depressive Episode is a DMS-IV research diagnosis characterized by two to four depressive symptoms, including depressed mood or anhedonia[6]. DSM-V incorporated this syndrome into the category Other Specified Depressive Disorders: Depressive Episode with insufficient symptoms.

The prevalence of PSD among hospitalized patients in the acute phase is around 22% for major depression and 17% for minor depression. In outpatient samples (from 3 months to 10 years after stroke), it is around 23% for major depression and 35% for minor depression, while community samples exhibit mean prevalence rates of 13% and 10%, respectively[4]. A recent meta-analysis showed that the prevalence of depression at any time after stroke was 29%[7].

A cohort of 4,022 patients followed for 15 years showed the dynamic history of PSD[8]. The peak prevalence of MDD occurs 3 to 6 months after the stroke. Most subjects had MDD remission one year after stroke, however showing persistent subsyndromal depressive symptoms and/or short lasting depressive episodes. Also according to Robinson, MDD often subside without complete remission one year after the index event[4].

In Brazil, there are few data on the epidemiology of PSD. A study conducted in Fortaleza, which investigated the quality of life (QoL) of individuals from two to six years post-stroke, reported a 40% prevalence of depressive symptoms (predominantly mild to moderate)[9]. The presence of depressive symptoms was the most important factor in reducing QoL. Similarly, de Souza *et al.* evaluated patients with Chagas disease and stroke, and found that QoL was more influenced by depressive symptoms than neurological disability[10]. Carod-Artal *et al.* also demonstrated that depression, disability and motor deficits were the main determinants of health-related QoL in patients with stroke, and depression was the strongest predictor of reduced QoL, especially among women[11]. Table 1 presents Brazilian studies that reported the frequency of PSD.

Diagnosis and clinical picture

The DSM-V criteria for the diagnosis of PSD match those for Depressive Disorder Due to a Medical Condition[6]. Stroke is one of the few conditions listed in the former DSM-IV and the current DSM-V as "directly" causing depression; therefore PSD is diagnosed differently from depression following, for instance, a myocardial infarction or a hip fracture, and can be named as Depressive Disorder Due to Stroke. One of the following specifiers should be added to the diagnosis: "with depressive features", if full criteria are not met for a major depressive episode; "with major depressive-like episode", if full criteria are met for a major depressive episode (except for criterion C); and "with mixed features", if symptoms of mania or hypomania are also present but do not predominate in the clinical picture.

Table 1. Frequency of post stroke depression in Brazilian studies

Author (year)	City (state)	n	Setting	Time after stroke	Instrument	Frequency (%)
Simis, Nitrini (2006)[12]	Sorocaba (SP)	93	H	2 weeks	HAM-D	59,1†
Carod-Artal *et al.* (2009)[11]	Brasília (DF)	260*	O	20.7 months (mean)	HADS	20,0† (F: 25,0; M: 15,4)
Terroni *et al.* (2009)[13]	São Paulo (SP)	73	H/O	1 week – 4 months	HAM-D	28,8‡
Fróes *et al.* (2011)[9]	Fortaleza (CE)	64	RP	< 2 years: 9.4% 2-6 years: 50% > 7 years: 40.7%	BDI	40,0†
Scheffer *et al.* (2011)[14]	Porto Alegre (RS)	19*	O	9 – 27 months	BDI	33,3†
Rangel *et al.* (2013)[15]	Maceió (AL)	139*	RP	3 – 316 months	BDI	49,7†

BDI: Beck Depression Inventory; F: Female gender; H: Hospital sample; HADS: Hospital Anxiety and Depression Scale; HAM-D: Hamilton Depression Scale; M: Male gender; O: Outpatient sample; RP: Rehabilitation Program sample.
* The study included patients with hemorrhagic stroke (Ischemic stroke: Carod-Artal *et al.*: 87.7%, Scheffer *et al.* 84.2%; Rangel *et al.*: 83.5%).
† Prevalence; ‡ Incidence in 4 months.

PSD should be distinguished from post-stroke demoralization, which can be understood as a type of adjustment disorder. Several authors have attempted to differentiate depression and demoralization[16,17]. This distinction may seem even more complicated when considering the concept of PSD adopted by the psychological perspective described above. Overall, demoralization is related to feelings of incompetence and loss of self-control after repeated failures, whereas depression is marked by anhedonia and decreased motivation. Shader observed that individuals with demoralization may respond favorably to positive stimuli and relief of stressors, while patients with depression cannot get rid of their negative mood state, regardless of environmental changes[17]. Once the presence of demoralization is recognized, the clinician should work with the patient in order to promote a sense of ability, mastery and return of hope. Encouragement, support and education are essential.

According to Spalletta and Robinson[18], although it seems likely that some forms of PSD may be, in part, sustained by reaction to disability, the attempt to differentiate between "reactive" (i.e. demoralization) and "endogenous" forms of depression ceased many years ago because no clear etiopathogenetic or phenomenological distinction has ever been shown to distinguish between them and a mixture of these two forms is present in almost all patients with a diagnosis of depression.

Fedoroff *et al.* assessed the suitability of the diagnostic criteria for MDD in the diagnosis of PSD[19]. They observed that, except for early-morning awakening, all symptoms of depression were more frequent in the stroke patients with depressed mood than in the euthymic ones. Cumming *et al.* also conducted an investigation to determine whether the phenomenology of depression after stroke was different from the phenomenology of depression with no known medical cause[20]. They noted that there were no major differences between the symptom profiles of both groups, except that stroke patients were less likely to report anhedonia than controls. Interestingly stroke patients

were no more likely than controls to report somatic complaints over psychological symptoms. However, some authors point to clinical differences between patients with PSD and those with MDD. Compared to these, stroke patients would have more cognitive impairment, mood fluctuations, psychomotor retardation, anxiety and vegetative and somatic symptoms[21]. Gainotti *et al*. identified depressed mood, anhedonia and suicidal thoughts as more prevalent in non-stroke depressive patients than in patients with PSD[21]. In Brazil, Terroni *et al*. point out the relevance of fatigue symptoms and reduction of general interests in the diagnosis of PSD[13].

Despite these controversies, there is no evidence that the diagnosis of depression after stroke is less valid than the diagnosis of depression in non-stroke populations[18,20]. Since there are no specific biological markers, the diagnosis is based on clinical findings, and this task can become very difficult in the presence of severe cognitive deficits, especially language disorders.

Cognitive impairment in PSD

Cognitive deficits are commonly observed in depressed patients. Executive functions, including concept formation, planning, cognitive control, initiation and psychomotor speed, have been regularly shown to be impaired in depression[22]. Short term and working memory are disturbed in depression, as assessed either by the digit span test or by the digit ordering test. Objective memory deficit is regularly demonstrated in depressed patients, characterized by lower immediate and delayed recall performance in both verbal and visual memory tests, but with a normal cued recall and recognition[22]. This pattern is typically described as a retrieval memory disorder, rather than a storage dysfunction. Language and visuospatial abilities are generally preserved in depression.

A series of papers has specifically investigated cognitive disorders in PSD. Post-stroke depression affects problem solving, verbal and visual memory, language, visuospatial processes, attention and psychomotor speed[22,23]. Moreover, the degree of cognitive impairment is associated with the severity of depressive symptoms[23].

In a cohort of 143 patients who were followed up to 10 months after a stroke, Nys *et al*. found that cognitive impairment at baseline independently predicted long-term depressive symptoms[24]. Moreover, they found that cognitive deficits were related to worse quality of life. Among all cognitive deficits, the QoL was mostly affected by visuospatial and visuo-constructive disorders, while unilateral neglect at baseline assessment was the greatest risk factor for depressive symptoms after 6 months.

Taken together, these data suggest that cognitive deficits may account for PSD and, on the other hand, the degree of depression impacts on cognitive performance. Patients with PSD should undergo a formal neuropsychological evaluation, and therapeutic rehabilitation program adapted according to the cognitive profile of the patient.

Pathophysiology

The polarity between the biological and the psychological perspectives may have hampered the development of a comprehensive approach to PSD prevention and treatment. Table 2 presents the main arguments of each school.

Among the major biological theories on the pathophysiology of PSD, four main hypotheses can be listed: lesion location, biogenic amines, inflammatory cytokines and gene polymorphism hypotheses.

The lesion location hypothesis was formulated by Robinson based on the observation that depression severity was associated with lesions in the left frontal lobe, and that this association was stronger in the first 6 months after stroke[4]. However, this finding has not been consistently replicated by other authors. Carson *et al*., in a meta-analysis of 35 studies, observed that the risk for developing depression was not associated with lesion location[25]. Other authors proposed that strategic or specific location of the ischemic damage might play a role in the development of PSD[26]. Neuroimaging studies found the hippocampus, basal ganglia and frontal areas to be associated with PSD[26]. Although the debate is still open, the correlations between affected areas and depressive symptoms seem to be weak.

The biogenic amines theory can be understood as a pathophysiological sophistication of the lesion location hypothesis. It was first proposed by Robinson and Bloom[27]. They postulated that ischemic lesions might interrupt the biogenic amine-containing axons ascending from the brainstem nuclei to the cerebral cortex, thus decreasing the release of serotonin (5-HT) and norepinephrine (NE)

Table 2. Key features of the biological and psychological hypothesis of post stroke depression (PSD) etiopathogenesis

Biological causation		Psychological causation	
Evidence		Evidence	
For	Against	For	Against
Higher frequency of depression in stroke *versus* other similarly disabling medical illness Temporal relationship between stroke and onset of depression Specific lesions associated with PSD PSD may occur in the context of silent infarcts	Finding not consistently replicated Temporal relationship between psychological stressors (*e.g.* bereavement) and depression Finding not consistently replicated -	PSD symptom profile is not specific and may be a form of "functional" depression Temporal relationship between psychological stressors (*e.g.* bereavement) and depression Risk factors unrelated with stroke predicts occurrence of depression (*e.g.* family history of depression) Disability severity is the most consistent risk factor for PSD and psychosocial factors become increasingly important in later onset PSD	"Functional" depression may have biological underpinnings Temporal relationship between stroke and onset of depression These risk factors may reflect biological predisposition (*e.g.* genetic causes) -
Explanatory theories		Explanatory theories	
Lesion location theory: PSD may be related to the location of the lesions, disturbing specific areas of the brain (*e.g.* left frontal lobes, hippocampus, basal ganglia) Biogenic amines theory: PSD may be related to disruption of monoamines circuitry, through direct or indirect mechanisms Inflammatory cytokines theory: PSD may be related to the production of "depressogenic" cytokines by the inflammatory response to ischemia Genetic polymorphisms theory: PSD may be related to genetic predisposition, especially in the serotoninergic system		Patients with stroke experience a traumatic event that undermines their physical and mental integrity, their autonomy and self-esteem as well as their social lives. Psychological coping mechanisms, as well as premorbid personality, are responsible for the development of PSD	

in the limbic structures of the frontal and temporal lobes as well as in the basal ganglia. According to this hypothesis, lesions located in the anterior portions of the frontal lobes could interrupt the ascending monoaminergic axonal bundles leading to depression. Indeed, the studies of Robinson suggested that anterior lesions, located close to the left frontal pole, would be associated with the development of depressive symptoms[4]. Later it was suggested that dysfunction of cortico-striato-pallido-thalamic-cortical circuits predisposes to PSD, and that these loops could even be disrupted indirectly by secondary degeneration when not included in the primary ischemic lesion by means of anterograde or retrograde degeneration and vasogenic edema. This could explain, at least partly, the great variability described by anatomo-clinic correlational studies. In addition, it was observed that in acute brain lesion, there is decreased monoamine synthesis because of enzyme inhibition during ischemia. Accordingly, significantly lower cerebrospinal fluid (CSF) concentrations of the 5-HT metabolite 5-hydroxy-indoleacetic acid were measured in PSD patients compared to non-depressed stroke survivors[28]. Positron Emission Tomography (PET) findings on 5-HT1a receptor availability after stroke suggest that changes in 5-HT neurotransmission may occur in the early phase of stroke and can be modulated by treatment with Selective Serotonin Reuptake Inhibitors (SSRIs)[29].

Based on the strong association of proinflammatory cytokines, such as interkeukin-1β (IL-1β), tumor necrosis factor-α (TNF-α), IL-6, IL-8 and IL-18, with ischemic brain injury and the evidence of interleukins playing an important role in certain subtypes of depression, Spalletta *et al*. proposed the inflammatory cytokines hypothesis for PSD[30]. In the last two decades, increased blood and CSF concentrations of pro-inflammatory cytokines, including IL-1β, IL-6, Interferon-γ (IFNγ) and TNFα, acute phase proteins, such as C-reactive protein (CRP), and their receptors, chemokines, adhesion molecules and other inflammatory mediators, have been demonstrated in MDD subjects[31]. The long-term exposure to cytokines may be associated with the onset of depression. The best studied example comprises patients receiving IFN-α to treat melanoma and hepatitis C virus infection[32]. In experimental animals, the administration of cytokines, such as IL-6, or cytokine inducers, such as lipopolysaccharide (LPS), have been found to induce depressive-like behaviors[33]. The inflammatory mediators seem to activate the widespread tryptophane catabolizing enzyme indoleamine 2,3-deoxygenase (IDO) leading to decreased synthesis of 5-HT. The importance of the activation of IDO in the pathophysiology of depression is also supported by the evidence that, in mice, the blockade of IDO inhibits the onset of the LPS-related "sickness behavior"[33]. Concerning PSD, experimental studies showed that, in mice, IL-1β and TNF-α can induce post-stroke depressive-like behavior resembling the somatic syndrome of depression in humans[34]. Regarding clinical studies, Jiménez *et al*. reported that serum leptin levels in patients with a first episode of ischemic stroke were associated with PSD at discharge from hospital and at one month after stroke[35]. Yang *et al*. observed that serum IL-18 measured 7 days after hospital admission for stroke was associated with PSD in the acute stage and 6 months after stroke[36]. Recently, Spalletta *et al*. found that that serum IL-6 was increased in patients with depressive disorders after stroke, and that its levels were associated with the severity of apathetic-amotivational and somatic symptoms of depression and of neurological deficits 72 hours after stroke[37]. There are many problems with this theory: several cytokines are involved in post-stroke inflammatory process, and they play different roles in distinct stages after stroke. Furthermore, many studies of cytokines are based on animals, and in patients, only the serum and CSF levels can be tested, while it is impossible to measure cytokines in specific areas of the living human brain. Besides that, molecular cascades after stroke also include a marked induction of anti-inflammatory cytokines, which may counterbalance the "depressiogenic" effect of proinflammatory cytokines. To examine the hypothesis, further researches are needed.

It has been proposed that MDD results from the interaction of predisposing genes and the environment. Nowadays, this relationship emerges as the gene polymorphism hypothesis of PSD. Based on the theory of biogenic amines, the serotonergic system appears as a canor genetic susceptibility to PSD. Few studies have investigated the role of serotonin genes polymorphisms in PSD. For instance, Ramasubbu *et al*. reported that the Serotonin Transporter Gene-Linked Promoter Region (5-HTTLPR) s allele was associated with PSD in a sample of 26 stroke patients with major depression and 25 non-depressed stroke patients, the first genetic study of PSD[38]. Later, Kohen *et al*. replicated this finding with a larger sample of 75 depressive and 75 non-depressive stroke patients categorized by the Geriatric Depression Scale[39]. Kim *et al*. found that 5-HTTLPR s/s genotype was associated with PSD[40]. Besides, they observed that Brain Derived Neurotrophic Factor (BDNF) met/met and 5-HT2a receptor (5-HTR2a) 1438 A/A genotypes were associated with PSD. On the other hand, Zhou *et al*. reported that serum BDNF concentrations were decreased in PSD patients 3 to 6 months after stroke, but this was not associated with BDNF gene Val66Met polymorphisms[41]. Tang *et al*. suggested a possible role for genetic variation in 5-HT2c receptors (HTR2C receptors) in the pathogenesis of PSD[42]. Based on the theory of inflammatory cytokines, Kim *et al*. reported that the IL-4 + 33C/C and the IL-10 −1082A/A genotypes were associated with PSD[43]. All these studies rely on very small samples and need to be replicated consistently in larger populations.

It should be noted that, traditionally, most studies on the pathophysiology of PSD has focused on large vessel disease, without making an explicit mention of lacunes[26]. However, paralleling this debate, the literature on "vascular depression" hypothesis is increasingly emphasizing the role of small vessel and microvascular chronic burden in triggering depressive episodes[26]. According to this hypothesis, cerebrovascular disease could predispose, precipitate or perpetuate some geriatric depressive syndromes. Nevertheless, longitudinal studies in large community-based series of patients with PSD are needed to test the validity of this interesting proposal.

As the evidence supporting the different lines of biological explanations has not pointed to definite conclusions, the psychological school still maintains proposals of psychosocial mechanisms for the pathogenesis of PSD. For instance, Gainotti *et al*. found that the symptom profiles and anatomical–clinical correlates of major PSD were not different in the acute and more chronic stages[21]. He argued that this finding was more consistent with a psychological than a neurobiological model of PSD. Lieberman *et al*. studied 516 hospitalized elderly patients, 221 after stroke and 295 after hip fracture[44]. There were no differences in the symptoms of depression score between the two groups, contradicting the influential work of Folstein *et al*.[5]. Bozikas *et al*. performed a clinicopathological analysis of 95 consecutively autopsied elderly individuals who survived an initial stroke and were followed to record the occurrence of PSD[45]. They observed that the severity of brain vessel arteriosclerosis and the frequency of brain vascular lesions were not significantly different between 21 cases with PSD and 74 cases without depression. No lesion pattern characterized the depression group. Thus, they suggested that psychological rather than neuropathological factors were the main determinants of PSD. In fact, patients who had a stroke experience a traumatic event that undermines their physical and mental integrity, their autonomy and self-esteem as well as their marital and professional lives[21]. Psychological coping mechanisms, as well as premorbid personality, certainly play an important role in the development of PSD. However, these arguments are not sufficient to explain the emergence of depression after silent infarctions or in patients with anosognosia.

Ultimately, this polarity of thought appears unreasonable given the current understanding on the inseparable nature of somatic and psychiatric illness. PSD does not appear to be the result of "pure" biological versus psychological causes, but instead is multifactorial in origin and consistent with the biopsychosocial model of mental illness. At this time, more investigations are needed to clarify the relative contributions of both biological and psychosocial risk factors and their interactions to the development of poststroke psychopathology.

Many factors have been roughly associated with PSD[46,47], as can be seen in figure 1, such as previous history of psychiatric disorders, female gender, family history of depression, and cerebrovascular risk factors, among others. Of those, physical disability, stroke severity and cognitive impairment have been more consistently associated with PSD[48]. Further, it has been suggested that patients who develop PSD just after a stroke have different risk factors than those who present a first episode later on[49]. Accordingly, early PSD would be closely related to biological mechanisms, whereas PSD developed six months after a stroke would be related to psychosocial mechanisms. A better understanding of the influence of these risk factors on the course of PSD and treatment response will lead to better treatment and, possibly, primary prevention interventions.

Treatment

There is consensus that, if PSD is left untreated, it may exert negative impact on functional recovery[4]. Longitudinal studies show that major and minor depressions are determinants of disability, failure in returning to work, impairment in interpersonal functioning and mortality[4].

The relation between PSD and functional impairment is complex. Patients with PSD have significantly higher disability in ADLs than euthymic patients with comparable neurological deficits[3]. PSD negatively impacts on the involvement in rehabilitation programs and is associated with more institutional care and increase in using of health services[3]. These findings suggest a phenomenon of reciprocity, in which depression influences the recovery of ADLs and the impairment of ADLs influences the severity and duration of depression.

Increased mortality is perhaps the ultimate validation of the importance of depression in the prognosis following stroke. PSD appears to be a significant risk factor for increased death as early as 1 year and as late as 7 years following stroke[4]. The mechanism underlying increased death rates is an important issue, which has not been examined in depth. One study showed that PSD is associated with decreased heart rate variability (HRV)[50]. In this line, Tokgozoglu *et al.* reported that patients with decreased HRV, as a result of stroke lesions of the insular cortex, are at risk for sudden death[51], and Makikallio *et al.* found that decreased long-term HRV was the only multivariate predictor of death after adjusting for age[52].

There are no guidelines for PSD treatment and the effectiveness of interventions is not well established. In a systematic review, Hackett *et al.* concluded that the use of antidepressants is associated with a small but significant beneficial effect[53]. According to the meta-analysis conducted by Price *et al.*, the use of antidepressants may be indicated on both major and minor depressive disorders, but there are no specific guidelines for the selection of drugs[54]. The most studied drugs were tricyclic antidepressants, especially nortriptyline, and SSRIs, particularly fluoxetine, sertraline and citalopram. There were also studies evaluating the use of trazodone, venlafaxine, reboxetine, mirtazapine, milnacipran and methylphenidate.

Some authors recommend the use of Nortriptyline as the first line drug, based on the evidence that it has a better efficacy than any other antidepressant available[53]. However, Nortriptyline may determine undesirable side effects and drug interactions, which can be problematic in a population at higher risk of cardiovascular disease. In this scenario, SSRIs are an interesting alternative. The use of antidepressants in the prevention of PSD is even more controversial[55]. Isolated studies have shown benefits with nortriptyline, fluoxetine, sertraline, mirtazapine and methylphenidate. Nevertheless, a Cochrane systematic review found no significant effect of antidepressant use in the prevention of PSD[55].

One very interesting point is that antidepressants, especially SSRIs, have been associated with improvement of motor recovery and dependence after stroke even in patients without depression. Experimental studies reporting neurogenic and neuroprotective effects of SSRIs provide a plausible mechanism of action. The largest study conducted to date has been the "Fluoxetine in motor recovery of patients with acute ischaemic stroke" (FLAME) trial[56]. It was a double-blind, placebo-controlled trial, in which 118 ischemic stroke patients with moderate to severe motor deficits, without PSD, were randomly assigned to a 3-month treatment with Fluoxetine or placebo. The authors reported that, after 90 days, the early prescription of Fluoxetine with physiotherapy enhanced motor recovery. Besides, they noted that the early use of Fluoxetine prevented PSD. In a recent meta-analysis, 52 trials randomizing 4,059 patients to SSRI or control were assessed (28 used fluoxetine, 7 sertraline, 10 paroxetine, 5 citalopram, 1 escitalopram, and 1 either sertraline or fluoxetine)[57]. The authors concluded that the favorable effects of SSRIs on disability, depressive symptoms, and neurological deficit scores were greater in participants who were depressed at randomization, but this may be due to quality bias. Besides, the authors report evidence of benefits of SSRIs in patients without depression, especially fluoxetine, the most studied drug. SSRIs appeared to improve dependence, disability, neurological impairment, anxiety and depression after stroke, despite the heterogeneity of the trials and several methodological limitations. Large, well-designed trials are needed to determine whether SSRIs should be routinely given to patients with stroke.

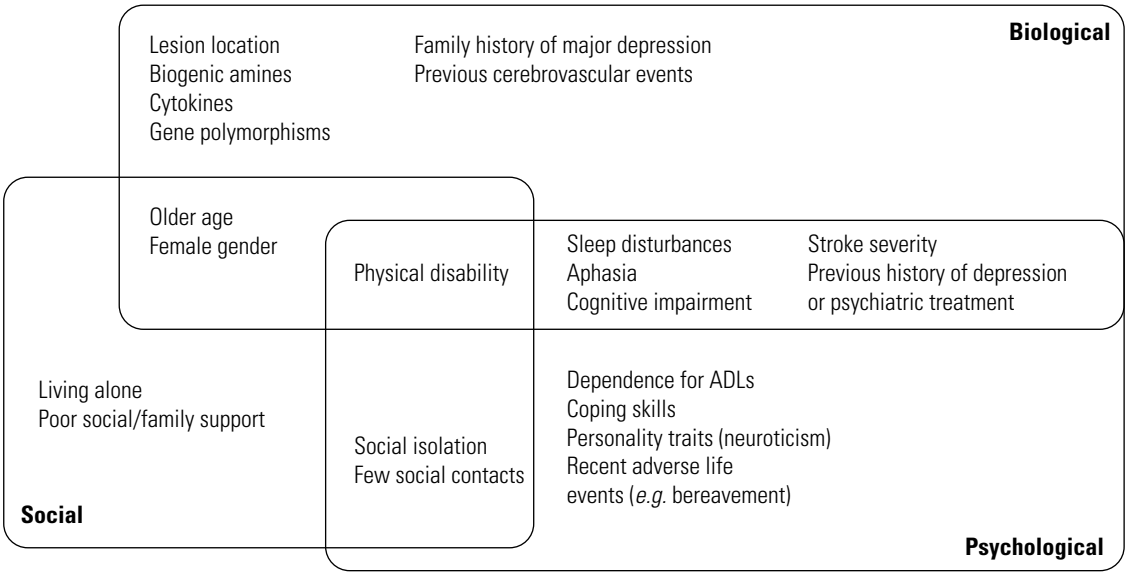

Figure 1. An integrative model of factors involved in post stroke depression pathogenesis. ADLs: activities of daily living.

Although it has not been used in a randomized controlled trial, electroconvulsive therapy has also been reported to be effective in treating PSD[4]. Another emerging technique for the treatment of PSD is non invasive brain stimulation, which encompasses two main techniques: repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS). TMS depolarizes neurons using potent, focal electromagnetic fields that are generated beneath the coil positioned over the patient's head. The electric depolarization, thereafter, induces action potentials. When applied repetitively and for several days, rTMS is able to induce clinical effects in several psychiatric disorders and is already used as a clinical (non-experimental) treatment in several countries, including Brazil. tDCS, in turn, is based on the application of a weak (0.5-2mA), direct electric current in the brain using electrodes placed over the head. Clinical effects are observed in several psychiatric disorders when applied daily for several days. These techniques might be particularly suitable for PSD as their side effects are limited to discomfort over the local of the application of the electrode/coil – i.e., they can induce depression improvement without systemic side effects.

Despite the emerging evidence of these techniques, they are relatively poorly investigated in the context of major depression secondary to clinical disorders, including PSD. For instance, there are only two randomized, double-blinded clinical trials evaluating the efficacy of rTMS in PSD, studying 18 and 20 patients[58,59]. Both studies applied high-frequency (stimulatory) rTMS over the left dorsolateral prefrontal cortex, observing improvement of depressive symptoms. For tDCS, there is only one case report describing a patient with PSD, who showed marked improvement of symptoms after a 10-day course of tDCS[60]. In this context, there is one ongoing large double-blinded, randomized clinical trial enrolling 48 patients with PSD in the University of São Paulo, Brazil, which will provide more evidence regarding the use of tDCS for PSD treatment. This trial is registered at clinicaltrials.gov (NCT01525524).

Finally, psychological treatment in isolation has been found to be no more effective than placebo. Psychotherapeutic approach associated with antidepressant use appears to be of some benefit. In the meta-analysis of Hackett *et al*., a small but significant effect was found for psychotherapy in preventing PSD[55].

Conclusion

A narrative review of the literature was conducted to present a comprehensive panorama on PSD. It should be noted that, due the extent of the addressed theme, we opted to perform a non-systematic search. This method, however, imposes limitations associated with its non-quantitative nature. On the other hand, it was possible to describe in a detailed manner several aspects associated with this complication of stroke.

As discussed above, depression is the most frequent psychiatric complication of cerebrovascular disorder. It is clear that it influences prognosis and functional recovery and its approach must be guaranteed for every stroke patient. Despite its great clinical relevance, there is little insight into its underlying etiological mechanisms and treament. For this reason, research addressed to elucidate the pathophysiological mechanisms of PSD are important. In Brazil, despite the great impact of cerebrovascular diseases, data are scarce even for the implications of PSD, indicating the need for epidemiological surveys to characterize the population affected by poststroke neuropsychiatric syndromes in the country.

A multidimensional approach taking into account biological, psychological and social perspectives is currently the most reasonable to the understanding of depressive symptoms following stroke, and to foster the development of evidence-based therapeutic strategies.

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Disclosure

The authors report no conflicts of interest.

References

1. American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics – 2013 update: a report from the American Heart Association. Circulation. 2013;127(1):e6-e245.
2. de Carvalho JJ, Alves MB, Viana GA, Machado CB, dos Santos BF, Kanamura AH, et al. Stroke epidemiology, patterns of management, and outcomes in Fortaleza, Brazil: a hospital-based multicenter prospective study. Stroke. 2011;42(12):3341-6.
3. Angelelli P, Paolucci S, Bivona U, Piccardi L, Ciurli P, Cantagallo A, et al. Development of neuropsychiatric symptoms in poststroke patients: a cross-sectional study. Acta Psychiatr Scand. 2004;110(1):55-63.
4. Robinson RG. The clinical neuropsychiatry of stroke. New York: Cambridge University Press; 2006.
5. Folstein MF, Maiberger R, McHugh PR. Mood disorder as a specific complication of stroke. J Neurol Neurosurg Psychiatry. 1977;40(10):1018-20.
6. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Arlington: American Psychiatric Publishing; 2013.
7. Ayerbe L, Ayis S, Wolfe CD, Rudd AG. Natural history, predictors and outcomes of depression after stroke: systematic review and meta-analysis. Br J Psychiatry. 2013;202(1):14-21.
8. Ayerbe L, Ayis S, Crichton S, Wolfe CD, Rudd AG. The natural history of depression up to 15 years after stroke: the South London Stroke Register. Stroke. 2013;44(4):1105-10.
9. Fróes KS, Valdés MT, Lopes Dde P, Silva CE. Factors associated with health-related quality of life for adults with stroke sequelae. Arq Neuropsiquiatr. 2011;69(2B):371-6.
10. Souza AC, Rocha MO, Teixeira AL, Dias Júnior JO, Sousa LA, Nunes MC. Depressive symptoms and disability in chagasic stroke patients: impact on functionality and quality of life. J Neurol Sci. 2013;324(1-2):34-7.
11. Carod-Artal FJ, Trizotto DS, Coral LF, Moreira CM. Determinants of quality of life in Brazilian stroke survivors. J Neurol Sci. 2009;284(1-2):63-8.
12. Simis S, Nitrini R. Cognitive improvement after treatment of depressive symptoms in the acute phase of stroke. Arq Neuropsiquiatr. 2006;64(2B):412-7.
13. Terroni LM, Fráguas R, Lucia M, Tinone G, Mattos P, Iosifescu DV, et al. Importance of retardation and fatigue/interest domains for the diagnosis of major depressive episode after stroke: a four months prospective study. Rev Bras Psiquiatr. 2009;31(3):202-7.
14. Scheffer M, Monteiro JK, de Almeida RMM. Frontal stroke: problem solving, decision making, impulsiveness, and depressive symptoms in men and women. Psychol Neurosci. 2011;4(2):267-78.
15. Rangel ESS, Belasco AGS, Diccini S. Qualidade de vida de pacientes com acidente vascular cerebral em reabilitação. Acta Paul Enferm. 2013;26(2):205-12.
16. Clarke DM, Kissane DW. Demoralization: its phenomenology and importance. Aust NZJ Psychiatry. 2002;36(6):733-42.
17. Shader RI. Demoralization revisited. J Clin Psychopharmacology. 2005;25(4):291-2.
18. Spalletta G, Robinson RG. How should depression be diagnosed in patients with stroke? Acta Psychiatr Scand. 2010;121(6):401-3.
19. Fedoroff JP, Starkstein SE, Parikh RM, Price TR, Robinson RG. Are depressive symptoms nonspecific in patients with acute stroke? Am J Psychiatry. 1991;148(9):1172-6.
20. Cumming TB, Churilov L, Skoog I, Blomstrand C, Linden T. Little evidence for different phenomenology in poststroke depression. Acta Psychiatr Scand. 2010;121(6):424-30.
21. Gainotti G, Azzoni A, Marra C. Frequency, phenomenology and anatomical-clinical correlates of major poststroke depression. Br J Psychiatry. 1999;175:163-7.
22. Kauhanen M, Korpelainen JT, Hiltunen P, Brusin E, Mononen H, Määttä R, et al. Poststroke depression correlates with cognitive impairment and neurological deficits. Stroke. 1999;30(9):1875-80.
23. Nys GM, van Zandvoort MJ, van der Worp HB, de Haan EH, de Kort PL, Kappelle LJ. Early depressive symptoms after stroke: neuropsychological correlates and lesion characteristics. J Neurol Sci. 2005;228(1):27-33.
24. Nys GM, van Zandvoort MJ, van der Worp HB, de Haan EH, de Kort PL, Jansen BP, et al. Early cognitive impairment predicts long-term

depressive symptoms and quality of life after stroke. J Neurol Sci. 2006;247(2):149-56.
25. Carson AJ, MacHale S, Allen K, Lawrie SM, Dennis M, House A, et al. Depression after stroke and lesion location: a systematic review. Lancet. 2000;356(9224):122-6.
26. Alexopoulos GS, Meyers BS, Young RC, Campbell S, Silbersweig D, Charlson M. Vascular depression hypothesis. Arch Gen Psychiatry. 1997;54(10):915-22.
27. Robinson RG, Bloom FE. Pharmacological treatment following experimental cerebral infarction: implications for understanding psychological symptoms of human stroke. Biol Psychiatry. 1977;12(5):669-80.
28. Bryer JB, Starkstein SE, Votypka V, Parikh RM, Price TR, Robinson RG. Reduction of CSF monoamine metabolites in poststroke depression: a preliminary report. J Neuropsychiatry Clin Neurosci. 1992;4(4):440-2.
29. Moller M, Andersen G, Gjedde A. Serotonin 5-HT1a receptor availability and pathological crying after stroke. Acta Neurol Scand. 2007;116(2):83-90.
30. Spalletta G, Bossu P, Ciaramella A, Bria P, Caltagirone C, Robinson RG. The etiology of poststroke depression: a review of the literature and a new hypothesis involving inflammatory cytokines. Mol Psychiatry. 2006;11(11):984-91.
31. Mossner R, Mikova O, Koutsilieri E, Saoud M, Ehlis AC, Müller N, et al. Consensus paper of the WFSBP Task Force on Biological Markers: Biological markers in depression. W J Biol Psych. 2007;8(3):141-74.
32. Fábregas BC, Vitorino FD, Rocha DM, Moura AS, Carmo RA, Teixeira AL. Screening inventories to detect depression in chronic hepatitis C patients. Gen Hosp Psychiatry. 2012;34(1):40-5.
33. O'Connor JC, Lawson MA, Andre C, Moreau M, Lestage J, Castanon N, et al. Lipopolysaccharide-induced depressive-like behavior is mediated by indoleamine 2,3-dioxygenase activation in mice. Mol Psychiatry. 2009;14(5):511-22.
34. Craft TK, DeVries AC. Role of IL-1 in poststroke depressive-like behavior in mice. Biol Psychiatry. 2006;15;60(8):812-8.
35. Jiménez I, Sobrino T, Rodríguez-Yáñez M, Pouso M, Cristobo I, Sabucedo M, et al. High serum levels of leptin are associated with post-stroke depression. Psychol Med. 2009;39(7):1201-9.
36. Yang L, Zhang Z, Sun D, Xu Z, Zhang X, Li L. The serum interleukin-18 is a potential marker for development of post-stroke depression. Neurol Res. 2010;32(4):340-6.
37. Spalletta G, Cravello L, Imperiale F, Salani F, Bossù P, Picchetto L, et al. Neuropsychiatric symptoms and interleukin-6 serum levels in acute stroke. J Neuropsychiatry Clin Neurosci. 2013;25(4):255-63.
38. Ramasubbu R, Tobias R, Buchan AM, Bech-Hansen NT. Serotonin transporter gene promoter region polymorphism associated with poststroke major depression. J Neuropsychiatry Clin Neurosci. 2006;18(1):96-9.
39. Kohen R, Cain KC, Buzaitis A, Johnson V, Becker KJ, Teri L, et al. Response to psychosocial treatment in poststroke depression is associated with serotonin transporter polymorphisms. Stroke. 2011;42(7):2068-70.
40. Kim JM, Stewart R, Bae KY, Kim SW, Kang HJ, Shin IS, et al. Serotonergic and BDNF genes and risk of depression after stroke. J Affect Disord. 2012;136(3):833-40.
41. Zhou Z, Lu T, Xu G, Yue X, Zhu W, Ma M, et al. Decreased serum brain--derived neurotrophic factor (BDNF) is associated with post-stroke depression but not with BDNF gene Val66Met polymorphism. Clin Chem Lab Med. 2011;49(2):185-9.
42. Tang WK, Tang N, Liao CD, Liang HJ, Mok VC, Ungvari GS, et al. Serotonin receptor 2C gene polymorphism associated with post-stroke depression in Chinese patients. Genet Mol Res. 2013;12(2):1546-53.
43. Kim JM, Stewart R, Kim SW, Shin IS, Kim JT, Park MS, et al. Associations of cytokine gene polymorphisms with post-stroke depression. World J Biol Psychiatry. 2012;13(8):579-87.
44. Lieberman D, Friger M, Fried V, Grinshpun Y, Mytlis N, Tylis R, et al. Characterization of elderly patients in rehabilitation: stroke versus hip fracture. Disabil Rehabil. 1999;21(12):542-7.
45. Bozikas VP, Gold G, Kovari E, Herrmann F, Karavatos A, Giannakopoulos P, et al. Pathological correlates of poststroke depression in elderly patients. Am J Geriatr Psychiatry. 2005;13(2):166-9.
46. Oldehinkel AJ, Ormel J, Brilman EI, van den Berg MD. Psychosocial and vascular risk factors depression in later life. J Affect Disord. 2003;74(3):237-46.
47. Paolucci S, Gandolfo C, Provinciali L, Torta R, Toso V; DESTRO Study Group. The Italian multicenter observational study on post-stroke depression (DESTRO). J Neurol. 2006;253(5):556-62.
48. Hackett ML, Yapa C, Parag V, Anderson CS. Frequency of depression after stroke: a systematic review of observational studies. Stroke. 2005;36(6):1330-40.
49. Gainotti G, Azzoni A, Marra C. Frequency, phenomenology and anatomical-clinical correlates of major post-stroke depression. Br J Psychiatry. 1999;175:163-7.
50. Robinson RG, Spalletta G, Jorge RE, Bassi A, Colivicchi F, Ripa A, et al. Decreased heart rate variability is associated with poststroke depression. Am J Geriatr Psychiatry. 2008;16(11):867-73.
51. Tokgozoglu SL, Batur MK, Topcuoglu MA, Saribas O, Kes S, Oto A. Effects of stroke localization on cardiac autonomic balance and sudden death. Stroke. 1999;30(7):1307-11.
52. Makikallio AM, Makikallio TH, Korpelainen JT, Sotaniemi KA, Huikuri HV, Myllylä VV. Heart rate dynamics predict poststroke mortality. Neurology. 2004;62(10):1822-6.
53. Hackett ML, Anderson CS, House AO, Xia J. Interventions for treating depression after stroke. Stroke. 2009;40(7):e487-8.
54. Price A, Rayner L, Okon-Rocha E, Evans A, Valsraj K, Higginson IJ, et al. Antidepressants for the treatment of depression in neurological disorders: a systematic review and meta-analysis of randomised controlled trials. J Neurol Neurosurg Psychiatry. 2011;82(8):914-23.
55. Hackett ML, Anderson CS, House A, Halteh C. Interventions for preventing depression after stroke. Cochrane Database Syst Rev. 2008;(3):CD003689.
56. Chollet F, Tardy J, Albucher JF, Thalamas C, Berard E, Lamy C, et al. Fluoxetine for motor recovery after acute ischaemic stroke (FLAME): a randomised placebo-controlled trial. Lancet Neurol. 2011;10(2):123-30.
57. Mead GE, Hsieh CF, Lee R, Kutlubaev M, Claxton A, Hankey GJ, et al. Selective serotonin reuptake inhibitors for stroke recovery: a systematic review and meta-analysis. Stroke. 2013;44(3):844-50.
58. Kim BR, Kim DY, Chun MH, Yi JH, Kwon JS. Effect of repetitive transcranial magnetic stimulation on cognition and mood in stroke patients: a double-blind, sham-controlled trial. Am J Phys Med Rehabil. 2010;89(5):362-8.
59. Jorge RE, Moser DJ, Acion L, Robinson RG. Treatment of vascular depression using repetitive transcranial magnetic stimulation. Arch Gen Psychiatry. 2008;65(3):268-76.
60. Bueno VF, Brunoni AR, Boggio PS, Bensenor IM, Fregni F. Mood and cognitive effects of transcranial direct current stimulation in post-stroke depression. Neurocase. 2011;17(4):318-22.

Artigo 3: Biomarkers in Post-stroke Depression.

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Biomarkers in Post-stroke Depression

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Abstract: Depression is the most frequent neuropsychiatric complication after a stroke. Post-stroke depression has a significant impact on the outcome and prognosis of affected patients. Its diagnosis is complex and currently based only on clinical parameters. In recent years, efforts have been made to find biomarkers related to post-stroke outcomes, including complications such as depression. We carried out a systematic review of the literature looking for studies that investigated biomarkers associated with post-stroke depression (PSD) in Medline, Lilacs and PsycInfo databases. The results of 37 studies are discussed, describing the evidence for each evaluated biomarker. In conclusion, no evidence was found supporting the use of a particular biomarker for PSD. However, several changes were observed in inflammatory balance, oxidative stress, glutamatergic neurotransmission, production of neurotrophic factors, and genetic susceptibility that can be related to PSD. Research in the area of post-stroke biomarkers has the potential to provide personalized approach of stroke patients, also aiding in the diagnosis and understanding of the pathophysiology of this common neuropsychiatric complication.

Keywords: Biomarkers, Depression, Review, Stroke.

1. INTRODUCTION

Stroke is the second leading cause of death and burden of disease in the Western world [1]. Post-stroke depression (PSD) is the most common neuropsychiatric disorder that occurs after stroke, affecting approximately one third of patients [2]. PSD may exacerbate cognitive dysfunction, compromise functional recovery, reduce quality of life, and can increase mortality and risk of stroke recurrence [3]. Patients with PSD show less recovery from functional impairment compared with euthymic patients, and are 3.4 times more likely to die during the first 10 years after stroke [4]. Accordingly, early recognition of depressive symptoms and proper treatment could lead to better outcome. However, signs of depression can be difficult to distinguish from the short and long-term stroke-related cognitive and motor changes [5]. Moreover, the underlying pathophysiology of PSD remains unknown, and is probably associated with multiple mechanisms. In this scenario, the identification of biomarkers could increase the diagnostic accuracy of PSD and assist in the introduction of early intervention.

Biomarkers can be defined as objective indicators found in the blood, other body fluids or tissues that predict physiological or pathological states, increased disease risk, or pharmacological response to therapeutic intervention [6]. Stroke biomarkers could be used for guiding personalized therapy. Indeed, several biomarkers have been evaluated in the context of stroke, investigating different aspects such as early diagnosis, screening high-risk subjects, detection of possible stroke mechanisms and prediction of drug response or outcome [6]. Several biomarkers have also been investigated to assist in the identification of PSD.

The aim of the current manuscript is to report a systematic review of studies that have sought to investigate biomarkers associated with the development of PSD in patients affected by ischemic stroke.

2. METHODS

2.1. Literature Search Strategy

The literature search was performed in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines [7]. The review included articles from English, Portuguese and Spanish languages, utilizing the Medline, PsycInfo and Lilacs databases, without time limits. Searches used the following terms: "biological markers"[MeSH Terms] OR ("biological"[All Fields] AND "markers"[All Fields]) OR "biological markers"[All Fields] OR "biomarkers"[All Fields]) AND ("stroke"[MeSH Terms] OR "stroke"[All Fields]) AND ("depressive disorder"[MeSH Terms] OR ("depressive"[All Fields] AND "disorder"[All Fields]) OR "depressive disorder"[All Fields] OR "depression"[All Fields] OR "depression"[MeSH Terms].

2.2. Inclusion and Exclusion Criteria

Retrieved publications included longitudinal, cross-sectional and animal studies. This review was limited to

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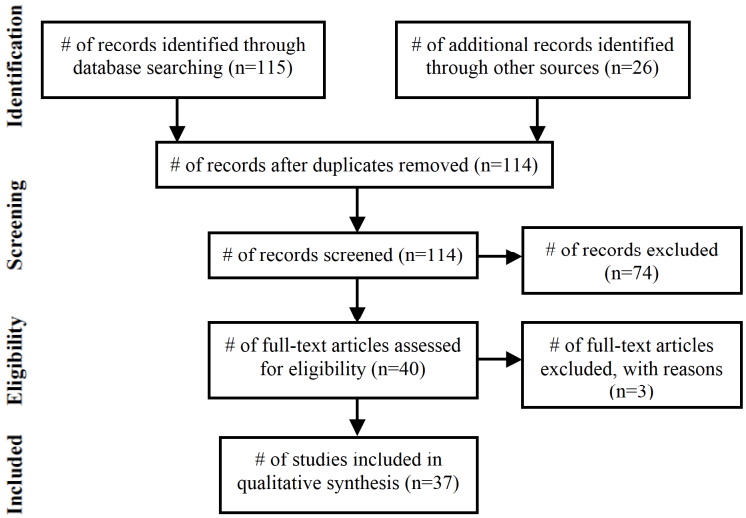

Fig. (1). Flow diagram for the review process of studies on biomarkers and post stroke depression..

studies examining biomarkers of PSD in human patients affected by ischemic stroke. Manuscripts with experimental animals or in which PSD was not assessed were excluded. Fig. (**1**) presents a flow diagram of manuscript selection process.

3. RESULTS

Thirty-seven papers were included in this review, encompassing studies from 1982 to 2015. Table **1** presents information related to the selected studies. The main findings are described below according to the nature of the biomarker.

3.1. Neuroendocrine Markers

3.1.1. Dexamethasone Suppression Test

The first biomarkers investigated for PSD were neuroendocrine markers. From the early 1980s until the mid-1990s, research focused on patient response to dexamethasone suppression test (DST) and the stimulation test with thyrotropin-releasing hormone (TST). In a cross-sectional study with 25 patients, Finklestein *et al.* (1982) found that changes in DST were associated with moderate to severe disorders of mood, sleep and appetite [8]. In 1985, Reding *et al.* observed that response to the DST was associated with depressive symptoms, while Lipsey *et al.* observed that non-suppression in the DST was related with PSD in the first year after stroke [9, 10]. In a cross-sectional study with 62 patients, Olsson *et al.* (1989) found no association between DST response and PSD in the first week after stroke [11]. Dam *et al.* (1991, 1994) also failed to find any association between DST and PSD [12, 13]. In a longitudinal study with 12 patients with stroke, Harney *et al.* (1993) found no cases of PSD, but they observed that patients with higher scores on the Hamilton Depression Rating Scale (HAM-D) were more likely to present abnormalities in the DST [14]. Finally, in a cross-sectional study with 13 patients, Marchesi *et al.* (1996) found association between the response in the DST and PSD in the first year post-stroke [15].

3.1.2. Stimulation Test with Thyrotropin-Releasing Hormone

Dam *et al.* and Marchesi *et al.* found no association between TST and PSD [12, 15].

3.1.3. Prolactin Response to D-Fenfluramine or Buspirone Tests

In a cross-sectional study involving 12 PSD patients, eight stroke patients without depression and 12 control subjects, Ramasubbu *et al*. (1999) used D-Fenfluramine stimulation to evaluate prolactin response [16]. They did not observe any difference in prolactin baseline adjusted changes when comparing PSD patients and controls. However, they found increased prolactin response in depressed patients (who had predominantly right-sided lesions) when compared with non-depressed patients (who had predominantly left-sided lesions), which did not persist after laterality of stroke lesion was taken into account. Sevinçok and Erol (2000) reported blunted prolactin response to Buspirone stimulation in PSD patients compared to healthy controls [17]. However, they did not find any difference between depressed and non-depressed stroke patients. Morris *et al.* (2003) used the D-Fenfluramine test to evaluate prolactin response in nine patients diagnosed with major depression after stroke, 14 patients classified as presenting minor depression after stroke and 38 non-depressed stroke patients, in the sub-acute post stroke period (four to eight weeks) [18]. Patients suffering from major PSD had a blunted prolactin response to D-Fenfluramine, differing from minor PSD and non-depressed patients.

3.2. Serotonergic System and the Kynurenine Pathway

Searching for biomarkers related to other pathophysiological pathways, Rasmussen *et al.* (2003) found no association between the levels of platelet serotonin transporter and the development of PSD in 113 patients with stroke in the acute phase and 116 stroke patients in the chronic phase [19]. In a study with 26 PSD patients and 25 euthymic stroke patients, Ramasubbu *et al*. (2006) found association between

Table 1. Papers which studied biomarkers in post stroke depression.

Authors	Country	Study Type	Number	Age in Years (Means or Ranges)	Gender (Male)	Assessment (Time after Stroke)	Depression Assessment Instruments	Biomarker	Findings
Finklestein *et al*., 1982. [8]	USA	Cross sectional	25 SP* 13 CT	SP: 72 CT: 76	SP: 48% CT: 54%	11 to 111 days	NI	DST.	Changes in STD associated with moderate-severe disorders of mood, sleep and appetite.
Reding *et al*., 1985. [9]	NI	NI	NI	NI	NI	7 weeks	NI	DST.	Changes in DST associated with depressive symptoms.
Lipsey *et al*., 1985. [10]	NI	Cross sectional	65 SP	NI	NI	NI (acute and chronic)	DSM-III	DST.	Non suppression associated with PSD within the first year after stroke
Olsson *et al*., 1989. [11]	Sweden	Cross sectional	62 SP 25 HCT 33 CCT	SP: 74.6 HCT: 76.8 CCT: 80	SP: 60% HCT: 52% CCT: 61%	3 - 7 days	DSM-III	DST.	NA
Dam *et al*., 1991. [12]	Denmark	Cross sectional	76 SP 26 CT	SP: 35-72 CT: 33-79	SP: 59% CT: 58%	NI	NI	DST.	NA
Harney *et al*., 1993. [13]	USA	Longitudinal	12 SP	NI	NI	1†, 3† and 4 weeks	HAM-D	DST.	↑HAM-D associated with changes in DST
Dam *et al*., 1994. [14]	Denmark	Cross sectional	63 SP 23 CT**	SP: 21-72 CT: 33-65	SP: 62% CT: 61%	8- 1280 days	RDC HAM-D BDI	DST, TST.	NA
Marchesi *et al*., 1996. [15]	Italy	Longitudinal	13 HSP 11 HDP 11 CT	HSP: 67.3 HDP: 64.8 CT: 66.5	HSP: 100% HDP: 100% CT: 100%	2 weeks and 1 year	SCID HAM-D	DST, TST.	Non suppression in DST associated with PSD
Ramasubbu *et al*., 1999. [16]	Canada	Cross sectional	12 PSDp 8 nPSD 12 CT	PSDp: 61.8 nPSD: 73 CT: 71.1	PSDp: 33% nPSD: 50% CT: 33%	NI	CES-D HAM-D RDC	Prolactin and cortisol response to D-fenfluramine.	NA
Sevinçok and Erol, 2000. [17]	Turkey	Cross sectional	16 PSDp* 10 nPSD* 10 CT	PSDp: 58.5 nPSD: 62.2 CT: 37.8	PSDp: 69% nPSD: 80% CT: 100%	1 to 6 months	HAM-D DSM-III-R	Prolactin response to Buspirone.	Blunted prolactin response in PSD compared to CT
Morris *et al*., 2003. [18]	Australia	Cross sectional	9 maPSD 14 miPSD 38 nPSD	maPSD: 67.6 miPSD: 68.5 nPSD: 68.4	maPSD: 78% miPSD: 79% nPSD: 68%	4 to 8 weeks	CIDI DSM-III-R MADRS	Prolactin response to D-fenfluramine.	↓prolactin response in maPSD
Rasmussen *et al*., 2003. [19]	Denmark	Longitudinal	113 SPap 56 CT 116 SPcp 45 TIAP 37 MIPcp 154 CT	SPap: 39-89 CT: 39-88 SPcp: 38-80 TIAP: 20-78 MIPcp: 33-82 CT: 38-88	SPap: 47% CT: 46% SPcp: 37% TIAP: 56% MIPcp: 86% CT: 39%	SPap < 28 days SPcp > 1 year	HAM-D	Platelet serotonin transporter.	NA
Glodzik-Sobanska *et al*., 2006. [43]	Poland	Longitudinal	26 FSP 20 CT	FSP: 63.4 CT: 59.7	FSP: 43% CT: 60%	≈ 9 days and 4 months†	DSM-IV HAM-D	MRS (frontal superior gyri)	↑Glx/Cr in contralateral cortex on the first 2 weeks associated with PSD.

Table **1**. contd…

Authors	Country	Study Type	Number	Age in Years (Means or Ranges)	Gender (Male)	Assessment (Time after Stroke)	Depression Assessment Instruments	Biomarker	Findings
Ramasubbu *et al*., 2006. [20]	Canada	Cross sectional	26 PSDp 25 nPSD	PSDp: 59.5 nPSD: 60.4	PSDp: 54% nPSD: 76%	NI	SCID	5-HTTPLR	5-HTTPLR s allele associated with PSD.
Kim *et al.*, 2008. [33]	Republi-cof Korea	Community based prospec-tive study	500 P (53 DP; 13 SP; 7 PSDp)	P: 72.1	P: 43%	NI (follow-up after 2.4 years from baseline)	GMS B3	BDNF gene SNP (val/val; val/met; met/met)	Progressive associa-tion trend between PSD and BDNF SNP from val/val to met/met.
Kohen *et al*., 2008. [22]	USA	Cross sectional	75 PSDp 75 nPSD	PSDp: 56.8 nPSD: 62.6	PSDp: 57% nPSD: 68%	< 4 months.	GDS DISH	5-HTTPLR, rs25531, STin2 VTRN.	5-HTTPLR s, STin2.9 and STin2.12 alleles associated with PSD.
Ramasubbu *et al.*, 2008. [21]	Canada	Cross sectional	26 PSDp 25 nPSD	PSDp: 59.5 nPSD: 60.4	PSDp: 54% nPSD: 76%	NI	SCID	5-HTTPLR, rs25531, STin2 VTRN.	Significant associa-tion between low-expressing alleles and geno-types of 5-HTTLPR polymorphism and PSD
Bossù *et al*., 2009. [31]	Italy	Cross sectional	30 FSP 25 CT	FSP: 66.43 CT: 68.64	FSP: 53% CT: 48%	HA, 3†, 6 and 9 days. PSD con-firmed after 2 weeks.	HAM-D DSM-IV-TR	IL-18.	↓IL-18 correlated with depression severity
Jiménez *et al*., 2009. [26]	Spain	Longitudinal	134 FSP	70,4	67%	HA, HD and 1 month.	GDS	Leptin, IL-1β, TNF-α, IL-6, ICAM-1, CRP, BDNF.	↑Leptin at HD and after 1 month asso-ciated with PSD
Yang *et al*., 2010. [29]	China	Longitudinal	100 SP 50 CT (96 com-pleted follow-up)	PSDp: 69 nPSD: 68 CT: 65	PSDp: 49% nPSD: 59% CT: 44%	HA†, 7†, 14 days and 6 months	HAM-D MADRS DSM-IV	IL-6, IL-18, TNF-α.	↑ IL-18 7 days after stroke associated with PSD 7 days, 2 weeks and 6 months after stroke
Yang *et al*., 2011. [34]	China	Longitudinal	100 SP 50 CT	PSDp: 69 nPSD: 6 CT: 65	PSDp: 49% nPSD: 59% CT: 44%	HA, 7 and 14 days.	HAM-D MADRS	BDNF, tPA.	↓BDNF and ↑tPA on HA associated with PSD after 2 weeks.
Wang *et al*., 2011. [44]	China	Cross sectional	51 FSP 15 CT	FSP: 61.1 CT: 65.3	FSP: 59% CT: 53%	3 months	SCID HAM-D	MRS (ante-rior cingu-late).	↑Glu/Cr associated with PSD.
Pavlovic *et al*., 2011. [37]	Serbia	Cross sectional	23 TIAP 72 SP*** 41 CT	TIAP+SP: 59.8 CT: 57.7	TIAP+SP: 58% CT: 46%	1 - 6 months	HAM-D	Homocys-tein, MTHFR C677T.	NA
Ormstad *et al*., 2012. [27]	Norway	Cross sectional	45 FSP	67.7	60%	3 days†, 6, 12 and 18 months.	BDI	CRP, Glu-cose, Hemo-globin, IL-1β, IL-1ra, IL-2, IL-4, IL-6, IL-8, IL-9, IL-10, IL-12, IL-18, IFN-γ, TNF-α, GRO-α.	Glucose > 126 mg/dL on HA associated with PSD after 12 months.

Table **1**. contd…

Authors	Country	Study Type	Number	Age in Years (Means or Ranges)	Gender (Male)	Assessment (Time after Stroke)	Depression Assessment Instruments	Biomarker	Findings
Su *et al*., 2012. [28]	Taiwan	Longitudinal	104 SP	64.34	68%	HA, 1, 2, 3, 9 and 12 months.	HAM-D DSM-IV	IL-1β, IL-6, IL-10, IFN-γ, TNF- α.	↑ IL-6, IL-10, IFN-γ, TNF- α, IL-6/IL-10 and TNF- α/IL-10 associated with PSD
Pascoe *et al*., 2012. [38]	Sweden	Cross sectional	149 SP	81	35%	< 7 days and 18 months†	DSM-III-R MADRS CPRS	Methylmalonic acid, homocystein.	↑homocysteine and ↑methylmalonic acid associated with PSD
Kim *et al*., 2012. [35]	Republic of Korea	Cross sectional	276 SP	64.3	59%	2 weeks.	MINI	5-HTTPLR, STin2 VTRN, 5-HTR2a 1438A/G, 5-HTR2a 102T/C and BDNF SNPs.	5-HTTLPR s/s and BDNF met/met genotypes associated with PSD (major/minor); 5-HTR2a 1438 A/A genotype associated major PSD; 5-HTR2a 1438 A/G and BDNF val66met SNPs interactively associated with major PSD.
Spalletta *et al*., 2013. [30]	Italy	Cross sectional	48 FSP	68.2	54%	3 days	SCID HAM-D	IL-6.	↑IL-6 associated with PSD
Zhang *et al*., 2013. [41]	China	Cross sectional	67 SP 40 CT	PSDp: 43-76 nPSD: 43-78 CT: 42-78	NI	2 weeks	HAM-D	ApoE mRNA expression in peripheral blood mononuclear cells, ApoE serum levels, event-related potentials.	↑N2 latency, ↑P3 latency, ↓P3 amplitude, ↓ApoE mRNA expression and ↑ serum ApoE associated with PSD
Tang *et al*., 2013. [45]	Hong Kong	Cross sectional	635 SP	PSDp: 66.9 nPSD: 65.6	PSDp: 53% nPSD: 64%	HA† and 3 months.	SCID	Bilirubin, alanine transaminase, alkaline phosphatase.	↑Bilirubin associated with PSD after 3 months.
Li *et al*., 2014. [32]	China	Cross sectional	256 FSP (191 completed follow-up).	68.6	57%	HA† and 3 months	DSM-III-R	Leptin, homocystein, CRP.	↑ Leptin associated with PSD after 3 months.
Li *et al*., 2014. [36]	China	Cross sectional	295 FSP (216 completed follow-up).	66.5	54%	HA† and 3 months	DSM-III-R HAM-D	BDNF, homocystein, CRP, glucose, white cell count.	↓BDNF, ↑ CRP and ↑homocysteine associated with PSD after 3 months.
Ormstad *et al*., 2014. [24]	Norway	Cross sectional	45 FSP	67.7	60%	3 days†, 6, 12 and 18 months	BDI	Serotonin, tryptophan, kynurenine, kynurenic acid, quinolinic acid tyrosine, valine, phenylalanine, leucine, and isoleucine.	NA

Table **1**. contd…

Authors	Country	Study Type	Number	Age in Years (Means or Ranges)	Gender (Male)	Assessment (Time after Stroke)	Depression Assessment Instruments	Biomarker	Findings
Bensimon *et al*., 2014. [25]	Canada	Cross sectional	86 SP	71,7	52%	NI	CES-D	Tryptophan, kynurenin, IL-6, IL-10, IFN-γ, TNF, IL-1β, IL-18	↑IL-1β, ↑ IL-18/IL-10, ↑IL-1β/IL-10 and ↑ IFNγ/IL-10 associated with moderate-severe depressive symptoms.
Yue *et al*., 2014. [42]	China	Cross sectional	322 FSP (244 completed follow-up) 100 CT	CT: 66	CT: 57%	HA† and 6 months	DSM-III-R	25[OH]D	↓25[OH]D associated with PSD after 6 months.
Cheng *et al*., 2014. [39]	China	Cross sectional	209 FSP 120 CT	FSP: 65.8 CT: NI	FSP: 62% CT: NI	HA† and 3 months	HAM-D SCID	Glutamate, GOT, GPT, CRP, homocysteine, glucose, white cell count.	↑Glutamate, ↑CRP, ↑homocysteine, ↓GOT and ↓GPT associated with PSD after 3 months.
Tang *et al*., 2015. [40]	China	Cross sectional	226 FSP	nPSD: 52-70 PSDp: 58-81	nPSD: 62% PSDp: 39%	HA† and 6 months	SCID HAM-D	CRP, Homocysteine.	↑CRP and ↑homocysteine on HA associated with PSD after 6 months

25[OH]D: 25-hydroxyvitamin D; ApoE: apolipoprotein E; BDI: Beck Depression Inventory; CCT: community control; CES-D: Center for Epidemiological Studies Depression Scale; CIDI: Composite International Diagnostic Interview; CRP: C reactive protein; CPRS: Comprehensive Psychopathological Rating Scale; CT: controls; DISH: Depression Interview and Structured Hamilton; DP: depression patients; DSM: Diagnostic and Statistical Manual of Mental Disorders; DST: Dexamethasone suppression test; FSP: first stroke patients; GDS: Yesavage Geriatric Depression Scale; GMS B3: Geriatric Mental State diagnostic schedule; GOT: glutamate oxaloacetate transaminase; GPT: glutamate-pyruvate transaminase ; HA: hospital admission; HAM-D: Hamilton Depression Rating Scale; HCT: hospitalized controls; HD: hospital discharge; HDP: hospitalized depression patients without stroke; HSP: hospitalized stroke patients without depression; MADRS: Montgomery- Åsberg Depression Rating Scale; maPSD: major post stroke depression patients; MINI: Mini International Neuropsychiatric Interview; miPSD: minor post stroke depression patients; MIPcp: myocardial infarction patients in chronic phase; MRS: magnetic resonance spectrometry; MTHFR C677T: methylenetetrahydrofolate reductase C677T genetic polymorphism; NA: no associations found between groups; NI: no information; P: participants; nPSD: patients without post stroke depression; PSD: post stroke depression; PSDp: post stroke depression patients; RDC: Research Diagnostic Criteria; SCID: Structured Clinical Interview for DSM-IV–TR Axis I Disorders; SNP: single nucleotide polymorphism; SP: stroke patients; SP: stroke patients; SPcp: stroke patients in chronic phase; SPap: stroke patients in acute phase; TIAP: transient ischemic attack patients; tPA: tissue plasminogen activator; TST: thyrotropin-releasing hormone stimulation test;

*Study included hemorrhagic stroke patients.
**Controls suffering from prolapsed intervertebral disc.
*** Subcortical stroke.
† Biomarker sampling time in studies in which sampling has not occurred at all time points.

the s allele of the serotonin transporter gene linked promoter region (5-HTTLPR) and the risk of depression. This association was influenced by personal and familial predisposition to mood disorders [20]. Conversely, they observed that homozygosity of the l-allele provided a protective effect. In this same sample, Ramasubbu *et al*. (2008) investigated the serotonin transporter gene (SERT) polymorphisms rs25531 and STin2 VTRN, reporting association between low-expressing alleles (S_A and L_G) and genotypes of 5-HTTLPR and PSD [21]. They did not observe any association between STin2 VTRN and PSD. In a case-control study with 75 PSD and 75 stroke patients without depression, Kohen *et al*. (2008) found that individuals carrying the s allele of the 5-HTTLPR and the STin2.9 and STin2.12 alleles of the SERT had at least 3-fold higher odds of depression compared with individuals with other genotypes [22]. They did not find any association between the rs25531 SERT polymorphism and PSD. Furthermore, they observed evidence of linkage disequilibrium among the 5-HTTLPR s and the STin2.12 alleles, which were more likely to occur in combination. In a cross-sectional study with 276 patients two weeks after stroke, Kim *et al*. (2012) found that (5-HTTLPR) s/s genotype was independently associated with PSD (both minor and major), that serotonin 2a receptor (5-HTR2a) 1438 A/A genotype was independently associated with major PSD, and that 5-HTR2a 1438 A/G and BDNF val66met polymorphisms were interactively associated with major PSD [23]. They did not identify any association between STin2 VTRN or 5-HTR2a 102T/C polymorphisms and PSD.

In a cross-sectional study with 45 patients followed up to 18 months after stroke, Ormstad *et al.* (2014) found no association between PSD and peripheral levels of serotonin, tryptophan, kynurenine, kynurenic acid, quinolinic acid , tyrosine, valine, phenylalanine and isoleucine, obtained 72 hours after stroke [24]. Likewise, Bensimon *et al.* failed to observe any association between the levels of tryptophan and kynurenine and development of depressive symptoms [25].

3.3. Cytokines

Cytokines are the group with the greatest number of different markers investigated to date. The individual molecules evaluated so far are:

3.3.1. IL-1β and IL-1ra

In a longitudinal study involving 134 patients, Jiménez *et al.* (2009) did not find any association between interleukin-1β (IL-1β) levels and PSD in the first month after stroke [26]. Ormstad *et al.* (2012), in a cross-sectional study with 45 patients, found no association between IL-1β levels, as well as interleukin-1 receptor antagonist (IL-1ra), obtained 72 hours post-stroke and the development of PSD up to 18 months of follow-up [27]. Su *et al.* (2012) found no association between IL-1β levels and PSD from hospital admission to one year after hospital discharge [28]. Conversely, in a cross-sectional study with 86 patients assessed in the first month post-stroke, Bensimon *et al*. (2014) reported that increase in IL-1β levels and the IL-1β/interleukin-10 (IL-10) ratio were associated with development of mild to moderate depressive symptoms [25].

3.3.2. IL-6

Jimenez *et al.* (2009) described no association between interleukin-6 (IL-6) levels and PSD in the first month after stroke [26]. In a longitudinal study with 100 patients, Yang *et al.* (2010) found no association between IL-6 levels and PSD up to 6 months of follow-up [29]. Similarly, Ormstad *et al.* (2012) observed no association between the levels of IL-6 obtained 72 hours post-stroke and PSD up to 18 months after stroke [27]. However, Su *et al.* (2012) reported association between the development of PSD and increase in IL-6 levels and in the IL-6/IL-10 ratio in patients who were followed from hospital admission to one year after discharge [28]. Spalletta *et al.* (2013) also found association between increased levels of IL-6 obtained 72 hours post-stroke and the development of PSD. IL-6 levels also correlated with the severity of amotivational, apathetic and somatic symptoms and with the severity of stroke [30]. Bensimon *et al*. (2014), in a cross-sectional study with 86 patients, found no association between IL-6 levels and the development of depressive symptoms [25].

3.3.3. IL-10

Ormstad *et al.* found no association between IL-10 levels and PSD [27]. Su *et al.* (2012) reported a longitudinal study involving 104 patients and found association between PSD and increase in IL-10 levels and in the IL-6/IL-10 and tumor necrosis factor-α (TNF-α)/IL-10 ratios in patients followed since hospital admission up to one year after discharge [28]. Accordingly, Bensimon *et al.* (2014) detected association between increase in interleukin-18 (IL-18)/IL-10 ratios, IL-1β/IL-10 and interferon-γ (IFN-γ)/IL-10 ratios and the development of mild to moderate depressive symptoms after stroke [25].

3.3.4. IL-18

In a cross-sectional study of 30 patients, Bossù *et al.* (2009) found that IL-18 levels 72 hours after of stroke were negatively correlated with depression severity at hospital discharge (9 days on average), especially regarding somatic symptoms [31]. Conversely, Yang *et al.* (2010) found that increase in IL-18 levels 72 hours after stroke was associated with PSD after 7 days, 2 weeks and 6 months [29]. Ormstad *et al*. (2012) found no association between the levels of IL-18 72 hours after stroke and PSD up to 18 months of follow-up [27]. Bensimon *et al.* (2014) observed that increase in the IL-18/IL-10 ratio was associated with the development of mild to moderate depressive symptoms [25].

3.3.5. IFN-γ

Ormstad *et al.* (2012) found no association between IFN-γ levels 72 hours post-stroke and PSD up to 18 months after stroke [27]. Su *et al.* (2012), in a longitudinal study of 104 patients, reported association between PSD and increased IFN-γ levels in patients followed from hospital admission to one year after discharge [28]. Bensimon *et al.* (2014) also observed association between increase in the IFN-γ/IL-10 ratio and development of mild to moderate depressive symptoms post stroke [25].

3.3.6. TNF-α

Jimenez *et al.* (2009) found no association between TNF-α levels and PSD in the first month post-stroke, while Yang *et al.* (2010) found no association between TNF-α levels and PSD up to six months post-stroke [26, 29]. Ormstad *et al.* (2012) reported no association between the levels of TNF-α 72 hours post-stroke and PSD up to 18 months after stroke [27]. Conversely, Su *et al.* (2012) observed association between PSD and increased TNF-α levels and TNF-α/IL-10 ratio in patients who were followed from hospital admission to one year after discharge [28]. More recently, Bensimon *et al.* (2014) found no association between TNF-α levels and the development of depressive symptoms [25].

3.3.7. Leptin

In a longitudinal study with 134 patients, Jiménez *et al.* (2009) observed association between increased levels of leptin and PSD in the first month post-stroke [26]. Li *et al.* (2014), in a cross-sectional study with 256 patients, also reported association between increased levels of leptin obtained on hospital admission and the development of PSD three months after stroke [32].

3.3.8. IL-2, IL-4, IL-8, IL-9, IL-12, GRO-α and ICAM-1

Ormstad *et al.* (2014) found no association between the levels of interleukin-2 (IL-2), interleukin-4 (IL-4), interleukin-8 (IL-8), interleukin-9 (IL-9), interleukin-12 (IL-12) and growth related oncogene-α (GRO-α) and PSD [27]. Jimenez *et al.* (2009) found no association between levels of intercellular adhesion molecule-1 (ICAM-1) and PSD in the first month post-stroke [26].

3.4. Neurotrophic Factors and Related Molecules

In a secondary analysis of a two-year prospective community-based study, Kim *et al*. (2008) observed a trend toward progressive association between stroke and incident depression stratified by brain-derived neurotrophic factor (BDNF) genotype, from val/val to met/met genotype [33]. In short, they proposed that the strength of association between incident stroke and depression increased incrementally with the number of met alleles, and was strongest in participants

with the met/met genotype. However, the study relied on a small sample of PSD (from 500 participants at baseline, only 20 had stroke and, of these, just seven developed PSD). In addition, the diagnosis of stroke was based on self-report information and temporal relationship between stroke and depression was not established. Kim *et al*. (2012), in a cross-sectional study with 276 patients two weeks after stroke, found that BDNF met/met genotype was independently associated with both major and minor PSD and that 5-HTR2a 1438 A/G and BDNF val66met polymorphisms were interactively associated with major depression [34].

Jimenez *et al.* (2009) did not identify any association between BDNF levels and PSD in the first month post-stroke [26]. However, Yang *et al.* (2011), in a longitudinal study of 100 patients, found that reduced levels of BDNF in the first day post-stroke were related with the development of PSD two weeks after stroke [35]. They also observed a negative correlation between BDNF and tissue plasminogen activator (tPA) levels in the first day post-stroke in patients with PSD. This correlation did not persist after 7 days. BDNF levels below 5.86 ng/mL on the first day predicted the development of depression in the next two weeks with sensitivity and specificity of 81 and 86%, respectively. In a cross-sectional study of 216 patients, Li *et al.* (2014) also found that reduced levels of BDNF at hospital admission were associated with PSD three months after stroke [36]. BDNF levels below 10.2 ng/mL at admission predicted the development of depression at three months with sensitivity and specificity of 80.3 and 81.8%, respectively. Stroke severity was negatively correlated with BDNF levels.

3.5. Homocysteine, Methylmalonic Acid and Genetic Polymorphisms

Pavlovic *et al.* (2011), in a study with 23 patients with transient ischemic attack (TIA), 72 stroke patients and 41 healthy controls, found that stroke patients had higher homocysteine levels than controls, but did not find any association with the development of PSD [37]. There was no association between PSD and frequency of methylenetetrahydrofolate reductase (MTHFR) C677T polymorphism. On the other hand, in a cross-sectional study with 149 patients, Pascoe *et al.* (2012) found association between the levels of homocysteine and methylmalonic acid and the diagnosis of PSD within 18 months post stroke [38]. Li *et al.* (2014) found no association between homocysteine and PSD three months after a stroke [32]. However, in another report in the same year, Li *et al.* found higher homocysteine levels at admission in 216 patients who developed PSD three months after stroke [36]. Cheng *et al.* (2014) reported higher homocysteine levels at admission in 209 patients who developed PSD three months after stroke [39]. Tang *et al.* (2015) found that higher levels of homocysteine at hospital admission correlated with the development of PSD after six months [40].

3.6. C Reactive Protein

Jiménez *et al.* (2009) described no association between C reactive protein (CRP) levels and PSD in the first month post-stroke [26]. Likewise, Ormstad *et al.* (2012) observed no association between CRP and PSD up to 18 months after stroke, and Li *et al.* (2014) did not find any association between CRP and PSD up to 3 months after stroke [27, 32]. However, Li *et al.* and Cheng *et al.*, in 2014, reported that higher levels of CRP at hospital admission were associated with PSD after 3 months [36, 39]. Similarly, Tang *et al.* (2015) found that higher levels of CRP at admission associated with PSD after 6 months [40].

3.7. Apolipoprotein E

In a cross-sectional study with 67 patients, Zhang *et al.* (2013) found that the reduction in apolipoprotein E (ApoE) mRNA expression in peripheral blood mononuclear cells and the increase in ApoE serum levels were associated with PSD two weeks after stroke [41].

3.8. Glucose

Ormstad *et al.* (2012) found association between blood glucose levels above 126 mg/dL obtained 72 hours post-stroke and the presence of PSD 12 months after stroke [27]. However, Li *et al.* and Cheng *et al.*, in 2014, in cross-sectional studies with 216 and 209 patients, respectively, found no association between glucose levels at hospital admission and PSD three months after stroke [36, 39].

3.9. Hemoglobin and Blood White Cell Count.

Ormstad *et al.* (2012) found no association between hemoglobin levels obtained 72 hours after stroke and PSD up to 18 months of follow-up [27]. Li *et al.* and Cheng *et al.*, in 2014, found no association between blood white cell count at hospital admission and PSD three months after stroke [36, 39].

3.10. 25-hydroxyvitamin D

In a cross-sectional study with 244 patients, Yue *et al.* (2014) found that lower levels of 25-hydroxyvitamin D (25[OH]D) at hospital admission were associated with PSD six months after stroke [42]. They also noted that serum level of 25[OH]D was reduced in all stroke patients in comparison with controls and that it correlated negatively with the severity of stroke.

3.11. Glutamate

Glodzik-Sobanska *et al.* (2006) used magnetic resonance spectroscopy to evaluate the superior frontal gyrus of 26 patients followed from hospitalization to four months after discharge [43]. Patients with PSD showed an increased Glx (glutamate, glycine, GABA)/Creatine ratio in the contralesional cortex in the first 2 weeks after stroke. This increase did not persist after 4 months. Wang *et al.* (2011) used the same method to evaluate the anterior cingulate gyrus and found that patients with PSD had increased Glutamate/Creatine ratio, which correlated positively to HAM-D scores. Increase in this ratio was also observed in patients affected by stroke without depression in comparison with controls [44].

Cheng *et al.* (2014) found that higher plasma glutamate levels and reduced glutamate oxaloacetate transaminase (GOT) and glutamate-pyruvate transaminase (GPT) at hospital admission were associated with PSD three months after stroke [39]. Glutamate levels were elevated in all stroke patients in comparison to controls and correlated positively

with stroke severity. They reported that glutamate levels above 205 Um at admission predicted the development of depression at three months with sensitivity and specificity of 80.6 and 84.8%, respectively.

3.12. Bilirubin, Alanine Transaminase and Alkaline Phosphatase

Tang *et al*. (2013), in a cross-sectional study with 635 patients, found that higher levels of bilirubin were associated with PSD three months after stroke [45]. They did not observe any association with alanine transaminase or alkaline phosphatase levels and PSD.

3.13. Event-Related Potential

Zhang *et al.* (2013) reported increase in the latency of N2 and the prolongation of P3, with reduced amplitude in patients with PSD, two weeks after stroke [41].

4. DISCUSSION

In this review, we found 37 studies which account for about three decades of efforts to define potential biomarkers of PSD. From the early 1980s until the early-2000s, eleven studies focused on neuroendocrine tests, especially the DST, which have yielded conflicting results. Five studies found association between changes in suppression response and development of depressive symptoms, while three studies reported no significant association. The TST was not relevant in any work. Prolactin response tests after stimulation with D-Fenfluramine or Bupropione relied on very small samples and also yielded conflicting results.

From the 2000s, the number and diversity of investigated biomarkers increased, while the interest in neuroendocrine tests virtually disappeared. Since then, cytokines are the most studied group of markers. Eight studies evaluated at least one cytokine. The most investigated cytokines were IL-1β, IL-6, IL-10, IL-18, IFN-γ, TNF-α and Leptin. Overall, the studies that found association between cytokines and PSD reported a trend to a pro-inflammatory state, *i.e.* increase in inflammatory cytokines like IL-6 and TNF-α, or imbalance in ratios involving inflammatory cytokines and IL-10, a cytokine traditionally regarded as anti-inflammatory. It is worth mentioning that growing evidence supports the role played by inflammatory mechanisms in the pathophysiology of depression [46, 47]. In the particular case of post-stroke inflammatory response, this is a highly complex and dynamic process. Several inflammatory cytokines are implicated, and they play different roles in distinct stages of the post-stroke period, with rapid and marked changes in their expression pattern. Moreover, to counterbalance inflammatory stimuli, anti-inflammatory and other pro-resolution molecules are released, and this may protect against the "depressiogenic" effect of inflammatory cytokines.

As for the other markers, results were even more heterogeneous. There was association between PSD and increased homocysteine and CRP levels, and reduction in BDNF levels in the early post-stroke period (*i.e.* hospital admission). These findings may implicate enhanced inflammatory response and decreased neurotrophic support in the polymorphisms found evidence of the association between increased risk for PSD and the met allele of the BDNF gene or the s allele of the 5-HTTPLR, which has been reported for major depression [48, 49, 50]. Other biomarkers related to serotonergic and kynurenine pathways had no promising results. Two studies using magnetic resonance spectroscopy showed association between raised glutamate/creatine ratio in regions implicated in mood regulation, possibly indicating enhanced glutamate-mediated excitotoxicity, and depressive symptoms. These neuroimaging studies were corroborated by the finding of increased peripheral glutamate level as predictor of PSD after three months.

Biomarkers sampled at an early stage after stroke (*i.e.* in the first week) seem to point to increased expression of inflammatory cytokines or imbalance between pro- and anti-inflammatory cytokines, increase in oxidative stress markers (such as homocysteine or bilirubin) and glutamatergic transmission, which, coupled to the reduction of neurotrophic factors (e.g. BDNF) or to susceptibility traits (*e.g.* polymorphisms in BDNF or SERT genes), could lead to PSD. In cases in which blood sampling took place much later after stroke, the association between the biomarker and the risk for PSD was generally lost. In this sense, the study of the early changes after the ischemic event must deserve careful attention.

There are several flaws in the studies investigating biomarkers in PSD. A major concern is the great variability in methods. Studied populations, recruitment settings, evaluation time-points and instruments used to measure depressive symptoms were very heterogeneous. In addition, many studies employed only symptom quantification scales, not using structured instruments for diagnosing depression. Most studies performed cross-sectional observations without follow-up or serial biomarker sampling. Several studies were conducted without control subjects or with small sample sizes. These problems are partly explained by the challenges in assessing such patients, especially on extended periods, due to limiting sequelae, comorbidities or negative clinical outcome.

CONCLUSION

To date there is no robust evidence to support the use of a particular biomarker for PSD. The analysis of 37 studies published over three decades of research revealed interesting trends that can guide future research. The study of biomarkers in PSD, including neuroendocrine tests, immune molecules, biochemical markers, among others, revealed imbalance in inflammatory/anti-inflammatory state, increase in oxidative stress and glutamatergic neurotransmission, reduction of neurotrophic factors and presence of genetic susceptibility. These different pathways can play together in the development of PSD. To better understand PSD pathogenesis and ultimately define putative biomarkers, further studies, paying special attention to the early stages of stroke, addressing multiple biomarkers longitudinally and in parallel with clinical parameters are warranted. Modeling biomarker-related pathological mechanisms in experimental models can also contribute to its validation and the development of therapeutic interventions. Despite its great clinical relevance, the underlying pathogenic mechanisms and treatment of PSD

are largely unknown, and the search for biomarkers may contribute to shedding light on its pathophysiology and to personalized treatment.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

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REFERENCES

[1] American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics – 2013 update: a report from the American Heart Association. Circulation. 2013; 127(1):e6-e245.

[2] Pedroso VSP, Souza LC, Brunoni AR, Teixeira AL. Post stroke depression: clinics, etiopathogenesis and therapeutics. Arch Clin Psychiatry 2015; 42(1): 18-24.

[3] Brown C, Hasson H, Thyselius V, Almborg AH. Post-stroke depression and functional independence: a conundrum. Acta Neurol Scand 2012; 126: 45–51.

[4] Hadidi N, Treat-Jacobson DJ, Lindquist R. Poststroke depression and functional outcome: a critical review of literature. Heart Lung 2009; 38: 151-62.

[5] Pedroso VSP, Souza LC, Teixeira AL. Neuropsychiatric syndromes associated with stroke: review of the literature. J Bras Psiquiatr 2014; 63(2): 165-76.

[6] Kim SJ, Moon GJ, Bang OY. Biomarkers for stroke. J Stroke 2013; 15(1):27-37.

[7] Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009; 21; 6: e1000097.

[8] Finklestein S, Benowitz LI, Baldessarini RJ, *et al*. Mood, vegetative disturbance and dexamethasone suppression test after stroke. Ann Neurol 1982; 12: 463-8.

[9] Reding M, Orto L, Willensky P, *et al*. The dexamethasone suppression test: an indicator of depression in stroke but not a predictor of rehabilitation outcome. Arch Neurol 1985; 42: 209-12.

[10] Lipsey JR, Robinson RG, Pearlson GD, Rao K, Price TR. The dexamethasone suppression test and mood following stroke. Am J Psychiatry 1985; 142: 318-23.

[11] Olsson T, Aström M, Eriksson S, Forssell A. (1989) Hypercortisolism revealed by the dexamethasone suppression test in patients with acute ischemic stroke. Stroke 1989; 20: 1685-90.

[12] Dam H, Pedersen HE, Damkjaer M, Ahlgren P. The dexamethasone suppression test in depressive stroke patients. Acta Neurol Stand 1991; 84: 14-7.

[13] Dam H, Pedersen HE, Dige-Petersen H, Ahlgren P. Neuroendocrine tests in depressive stroke patients. Prog Neuropsychopharmacol Biol Psychiatry 1994; 18: 1005-13.

[14] Harney JH, Fulton C, Ross ED, Rush AJ. Dexamethasone suppression test and onset of poststroke depression in patients with ischemic infarction. J Clin Psychiatry 1993; 54: 343-8.

[15] Marchesi C, Silvestrini C, Ponari O, Volpi R, Chiodera P, Coiro V. Unreliability of TRH test but not dexamethasone suppression test as a marker of depression in chronic vasculopathic patients. Biol Psychiatry 1996; 40: 637-41.

[16] Ramasubbu R, Flint A, Brown G, Awad G, Kennedy S. A neuroendocrine study of serotonin function in depressed stroke patients compared to non-depressed stroke patients and healthy controls. J Affect Disord 1999; 52: 121-33.

[17] Sevinçok L, Erol A. The prolactin response to buspirone in post-stroke depression: a preliminary report. J Affect Disord 2000; 59: 169-73.

[18] Morris P, Hopwood M, Maguire K, Norman T, Schweitzer I. Blunted prolactin response to D-fenfluramine in post-stroke major depression. J Affect Disord 2003; 76: 273-8.

[19] Rasmussen A, Christensen J, Clemmensen PM, *et al*. Platelet serotonin transporter in stroke patients. Acta Neurol Scand 2003; 107: 150-3.

[20] Ramasubbu R, Tobias R, Buchan AM, Bech-Hansen NT. Serotonin transporter gene promoter region polymorphism associated with poststroke major depression. J Neuropsychiatry Clin Neurosci 2006; 18: 96-9.

[21] Ramasubbu R, Tobias R, Bech-Hansen NT. Extended evaluation of serotonin transporter gene functional polymorphisms in subjects with post-stroke depression. Can J Psychiatry. 2008; 53: 197-201.

[22] Kohen R, Cain KC, Mitchell PH, *et al*. Association of serotonin transporter gene polymorphisms with poststroke depression. Arch Gen Psychiatry 2008; 65: 1296-302.

[23] Kim JM, Stewart R, Bae KY, *et al*. Serotonergic and BDNF genes and risk of depression after stroke. J Affect Disord 2012; 136: 833-40.

[24] Ormstad H, Verkerk R, Amthor KF, Sandvik L. Activation of the kynurenine pathway in the acute phase of stroke and its role in fatigue and depression following stroke. J Mol Neurosci 2014; 54: 181-7.

[25] Bensimon K, Herrmann N, Swardfager W, *et al.* Kynurenine and depressive symptoms in a poststroke population. Neuropsychiatr Dis Treat 2014; 10: 1827-35.

[26] Jiménez I, Sobrino T, Rodríguez-Yáñez M, *et al*. High serum levels of leptin are associated with post-stroke depression. Psychol Med 2009; 39: 1201-9.

[27] Ormstad H, Aass HC, Amthor KF, Lund-Sørensen N, Sandvik L. Serum levels of cytokines, glucose, and hemoglobin as possible predictors of poststroke depression, and association with poststroke fatigue. Int J Neurosci 2012; 122: 682-90.

[28] Su JA, Chou SY, Tsai CS, Hung TH. Cytokine changes in the pathophysiology of poststroke depression. Gen Hosp Psychiatry 2012; 34: 35-9.

[29] Yang L, Zhang Z, Sun D, Xu Z, Zhang X, Li L. The serum interleukin-18 is a potential marker for development of post-stroke depression. Neurol Res 2010; 32: 340-6.

[30] Spalletta G, Cravello L, Imperiale F, *et al*. Neuropsychiatric symptoms and interleukin-6 serum levels in acute stroke. J Neuropsychiatry Clin Neurosci 2013; 25: 255-63.

[31] Bossù P, Salani F, Cacciari C, *et al*. Disease outcome, alexithymia and depression are differently associated with serum IL-18 levels in acute stroke. Curr Neurovasc Res 2009; 6: 163-70.

[32] Li YT, Zhao Y, Zhang HJ, Zhao WL. The association between serum leptin and post stroke depression: results from a cohort study. PLoS One 2014; 9: e103137.

[33] Kim JM, Stewart R, Kim SW, *et al.* BDNF genotype potentially modifying the association between incident stroke and depression. Neurobiol Aging 2008; 29: 789-92.

[34] Kim JM, Stewart R, Bae KY, *et al*. Serotonergic and BDNF genes and risk of depression after stroke. J Affect Disord 2012; 136: 833-40.

[35] Yang L, Zhang Z, Sun D, *et al*. Low serum BDNF may indicate the development of PSD in patients with acute ischemic stroke. Int J Geriatr Psychiatry 2011; 26: 495-502.

[36] Li J, Zhao YD, Zeng JW, Chen XY, Wang RD, Cheng SY. Serum brain-derived neurotrophic factor levels in post-stroke depression. J Affect Disord 2014; 168: 373-9.

[37] Pavlovic AM, Pekmezovic T, Obrenovic R, *et al*. Increased total homocysteine level is associated with clinical status and severity of white matter changes in symptomatic patients with subcortical small vessel disease. Clin Neurol Neurosurg 2011; 113: 711-5.

[38] Pascoe MC, Crewther SG, Carey LM, Noonan K, Crewther DP, Linden T. Homocysteine as a potential biochemical marker for depression in elderly stroke survivors. Food Nutr Res. 2012; 56: 14973.

[39] Cheng SY, Zhao YD, Li J, Chen XY, Wang RD, Zeng JW. Plasma levels of glutamate during stroke are associated with development of post-stroke depression. Psychoneuroendocrinology 2014; 47: 126-35.

[40] Tang CZ, Zhang YL, Wang WS, Li WG, Shi JP. Serum levels of high-sensitivity C-reactive protein at admission are more strongly associated with poststroke depression in acute ischemic stroke than

homocysteine levels. Mol Neurobiol. 2015 May 5. [Epub ahead of print]

[41] Zhang Z, Mu J, Li J, Li W, Song J. Aberrant apolipoprotein E expression and cognitive dysfunction in patients with poststroke depression. Genet Test Mol Biomarkers 2013; 17: 47-51.

[42] Yue W, Xiang L, Zhang YJ, Ji Y, Li X. Association of serum 25-hydroxyvitamin D with symptoms of depression after 6 months in stroke patients. Neurochem Res 2014; 39: 2218-24.

[43] Glodzik-Sobanska L, Slowik A, McHugh P, *et al*. Single voxel proton magnetic resonance spectroscopy in post-stroke depression. Psychiatry Res 2006; 148: 111-20.

[44] Wang X, Li YH, Li MH, *et al*. Glutamate level detection by magnetic resonance spectroscopy in patients with post-stroke depression. Eur Arch Psychiatry Clin Neurosci 2012; 262: 33-8.

[45] Tang WK, Liang H, Chu WC, Mok V, Ungvari GS, Wong KS. Association between high serum total bilirubin and post-stroke depression. Psychiatry Clin Neurosci 2013; 67: 259-64.

[46] Lopes RP, Grassi-Oliveira R, de Almeida LR, *et al*. Neuroimmunoendocrine interactions in patients with recurrent major depression, increased early life stress and long-standing posttraumatic stress disorder symptoms. Neuroimmunomodulation 2012; 19: 33-42.

[47] Barbosa IG, Bauer ME, Machado-Vieira R, Teixeira AL. Cytokines in bipolar disorder: paving the way for neuroprogression. Neural Plast 2014; 2014: 360481.

[48] Taliaz D, Stall N, Dar DE, Zangen A. Knockdown of brain-derived neurotrophic factor in specific brain sites precipitates behaviors associated with depression and reduces neurogenesis. Mol Psychiatry 2010; 15: 80–92.

[49] Alexopoulos GS, Glatt CE, Hoptman MJ, *et al*. BDNF Val66met polymorphism, white matter abnormalities and remission of geriatric depression. Journal of Affective Disorders 2010; 125: 262–68.

[50] Anguelova M, Benkelfat C, Turecki G. A systematic review of association studies investigating genes coding for serotonin receptors and the serotonin transporter: I. Affective disorders. Molecular Psychiatry 2003; 8: 574-91.

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Segunda parte

2. Objetivos

2.1. Objetivo principal

Investigar a expressão de biomarcadores periféricos possivelmente associados à DPAVE isquêmico agudo em pacientes admitidos na Unidade de AVE do Hospital Municipal Odilon Behrens (HMOB).

2.2. Objetivos secundários

Caracterizar clinicamente a população de pacientes com AVE isquêmico agudo incluídos no presente trabalho.

Identificar as manifestações psiquiátricas presentes em uma amostra de pacientes com AVE isquêmico agudo.

Avaliar a associação entre características clínicas e psicopatológicas e a ocorrência de depressão pós-acidente vascular isquêmico agudo.

Avaliar a capacidade da Escala de Ansiedade e Depressão Hospitalar para o rastreamento de casos de depressão pós-acidente vascular isquêmico agudo.

3. Métodos

3.1. Sujeitos de pesquisa

Foi realizado um estudo transversal em que pacientes de ambos os gêneros com diagnóstico de AVE isquêmico foram submetidos à avaliação neuropsiquiátrica, incluindo anamnese semi-padronizada e aplicação de instrumentos específicos, e coleta de sangue venoso periférico. Todos os pacientes encontravam-se na Unidade de AVE do Hospital Municipal Odilon Behrens (HMOB) da Prefeitura Municipal de Belo Horizonte, centro de referência municipal no atendimento de AVE, que conta com 25 leitos destinados a tal fim. As Unidades de AVE constituem espaços físicos definidos, com leitos monitorados, dentro das unidades de emergência de hospitais gerais, destinados à atenção específica de pacientes com doença cerebrovascular, baseada em protocolos para rápida investigação e tratamento, de forma a permitir a pronta abordagem e a instituição de medidas de reabilitação precoces. Em geral, são destinadas a internações de curta a média permanência.

No trabalho em questão, pacientes admitidos na Unidade de AVE do HMOB foram avaliados no período de novembro de 2013 até abril de 2016. As entrevistas foram realizadas na própria Unidade de AVE, à beira do leito, com ou sem a presença de acompanhantes, de acordo com a disponibilidade dos mesmos. Cada avaliação durou entre uma hora e meia e três horas e meia, dependendo do estado clínico de cada paciente. Foram realizadas, em média, uma ou duas avaliações por dia de trabalho, conforme o número de pacientes disponíveis e o tempo gasto nas avaliações. Todos os pacientes foram avaliados pelo mesmo pesquisador. Após a entrevista clínica, os pacientes foram submetidos à punção venosa periférica, resguardando-se critérios de assepsia, procedimento realizado pelo mesmo pesquisador. O material coletado era levado pelo pesquisador ao Laboratório Interdisciplinar de Investigação Médica, na Faculdade de Medicina da Universidade Federal de Minas Gerais (UFMG), onde o mesmo procedia para imediata separação do plasma e armazenamento das amostras em congelamento a – 80ºC, sob a responsabilidade do orientador da pesquisa, até o momento da análise experimental.

Na anamnese semi-padronizada foram coletados dados sobre as características sócio-demográficas do participante, história prévia de doença cerebrovascular, comorbidades clínicas, uso de trombolítico, medicação em uso, antecedentes psiquiátricos,

história familiar de doenças clínicas ou psiquiátricas, além de serem registrados os exames de neuroimagem, eletrocardiograma e o exame físico (peso, altura, circunferência abdominal, pressão arterial e exame neurológico). Todos os sujeitos foram pesados na mesma balança padronizada e regulada. O índice de massa corporal (IMC) foi calculado dividindo-se o peso em quilogramas pela altura, em metros, elevada à segunda potência (IMC = kg/m^2).

Dois grupos de indivíduos constituíram controles da pesquisa, os quais foram recrutados para outro projeto de pesquisa, mas incluídos neste trabalho apenas como controles nas análises de biomarcadores. O primeiro foi formado por indivíduos com diagnóstico de Depressão Maior e o segundo, por indivíduos controles provenientes da comunidade, todos atendidos no Ambulatório de Psicogeriatria do Hospital das Clínicas da UFMG. Ambos os grupos de indivíduos controles foram submetidos a avaliação pelo MINI-Plus. Foram excluídos aqueles que faziam uso contínuo de medicações anti-inflamatórias e/ou corticóides nas duas últimas semanas, com quadro demencial pré-existente, com evidência clínica ou história de ataque isquêmico transitório ou AVE, com história de outros transtornos psiquiátricos maiores (por exemplo, esquizofrenia ou transtorno afetivo bipolar) ou que se recusaram a assinar o Termo de Consentimento Livre e Esclarecido (TCLE).

Todos os sujeitos de pesquisa assinaram o devido TCLE para a participação neste trabalho. O estudo foi aprovado pelos Comitês de Ética em Pesquisa da UFMG e do HMOB (processo CAAE 02811212.3.0000.5149).

3.2. Critérios de inclusão

Foram incluídos no estudo indivíduos com diagnóstico de AVE isquêmico, maiores de 45 anos e que assinaram o TCLE. A idade de 45 anos foi definida com o intuito de minimizar a possibilidade de incluir indivíduos portadores de doenças inflamatórias ou autoimunes, associadas à ocorrência de AVE em indivíduos mais jovens e que pudessem interferir na avaliação de biomarcadores periféricos.

3.3. Critérios de exclusão

Foram excluídos os indivíduos com AVE hemorrágico, doenças infecto-parasitárias ativas, doenças autoimunes, infarto agudo do miocárdio recente, neurocirurgia, síndrome demencial, rebaixamento do nível de consciência

(Escala de Coma de Glasgow < 14) ou afasia grave**.**

A **Figura 2** apresenta o fluxograma de inclusão dos casos no projeto de pesquisa;

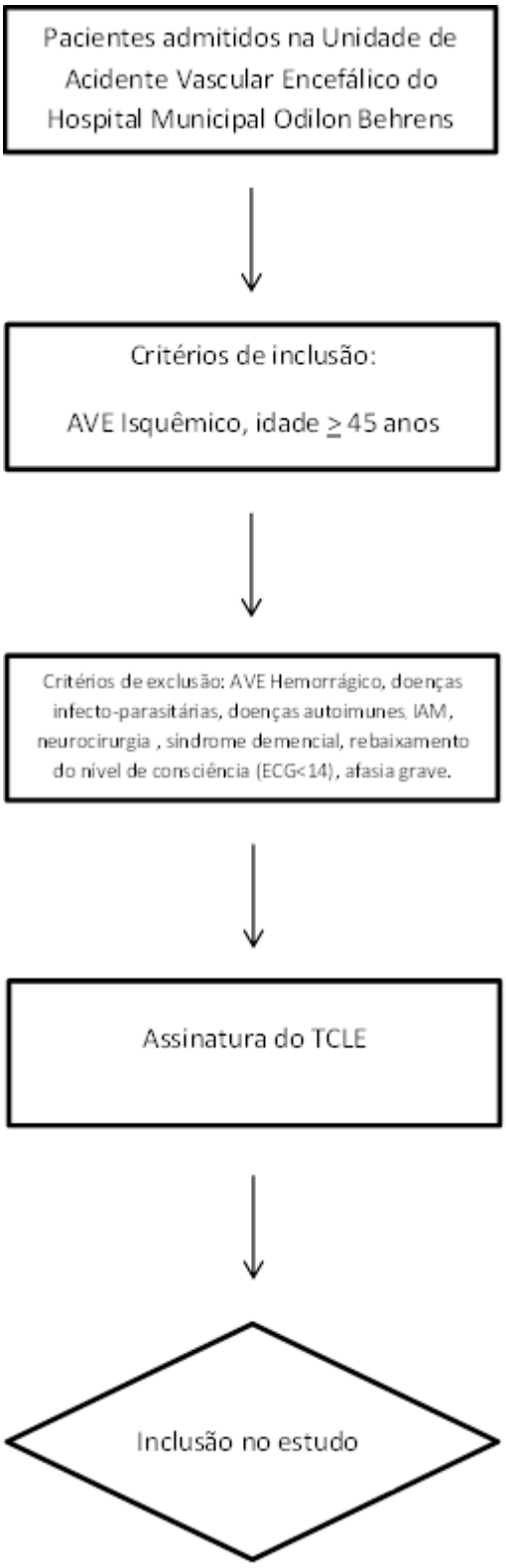

Figura 2: Fluxograma de inclusão dos casos no estudo.

3.4. Instrumentos de avaliação psiquiátrica

Os sujeitos da pesquisa foram examinados por psiquiatra treinado na aplicação de entrevistas e escalas clínicas. Foram empregados os seguintes instrumentos:

- Entrevista clínica estruturada (MINI-Plus - *Mini International Neuropsychiatric Interview – Brazilian, Version 5.0.0*), utilizada para identificar transtornos psiquiátricos do eixo I do *Diagnostic and Statistical Manual of Mental Disorders - Fourth Edition* (DSM-IV) e da Classificação Estatística Internacional de Doenças e de Problemas Relacionados à Saúde (CID-10) (AMORIM, 2000). O MINI-Plus explora sistematicamente todos os critérios de inclusão e de exclusão e a cronologia (data do início, tempo de duração dos transtornos e número de episódios) de 23 categorias diagnósticas do DSM-IV. Este instrumento foi utilizado para o diagnóstico de transtornos psiquiátricos na população em estudo e considerado o padrão-ouro neste trabalho com relação ao diagnóstico de transtornos psiquiátricos do eixo I (DSM-IV). Uma das seções do Mini-Plus é destinada a avaliar risco de suicídio para o qual é dada uma pontuação que varia de 0 a 33. De acordo com a pontuação neste item, o risco de suicídio pode então ser considerado como baixo (1-5), moderado (6-9) e alto (igual ou maior que 10). Duas semanas após a avaliação inicial, os pacientes foram contactados por ligação telefônica a fim de se avaliar a estabilidade do diagnóstico de depressão, utilizando-se a seção do MINI-Plus.

- Mini-Exame do Estado Mental (MMSE), a fim de se avaliar comprometimento cognitivo. Trata-se de um breve questionário composto por 11 itens de avaliação, os quais se agrupam em orientação temporal, orientação espacial, memória de fixação, capacidade de atenção e cálculo, memória de evocação, linguagem e praxia visuoconstrutiva. A pontuação varia entre 0 e 30 pontos, de forma que quanto menor o escore final, pior o desempenho cognitivo (FOLSTEIN *et al*, 1975).

- Escala Hospitalar de Ansiedade e Depressão (HADS), com o intuito de se quantificar sintomas depressivos e ansiosos. Trata-se de um instrumento constituído por 14 itens, sendo sete destes orientados para a avaliação de ansiedade (HADS-A) e os sete

restantes para depressão (HADS-D). Cada item pode ser pontuado de 0 a 3 e a pontuação final, por conseguinte, pode variar entre 0 e 21 pontos, de forma que quanto maior o escore final, maior a intensidade de sintomas (ZIGMOND & SNAITH, 1983).

- Escala do Choro e Riso Patológico (PLACS), a fim de se avaliar a presença de sintomas associados ao Transtorno da expressão emocional involuntária. Trata-se de um questionário composto por 18 perguntas que rastreiam choro e riso patológicos. A frequência de sintomas é mensurada e pontuada de 0 a 3 em ordem crescente de frequência, de modo que o escore final pode variar entre 0 e 54 pontos (ROBINSON, 1993).

- Medida de Independência Funcional (MIF), com o objetivo de se avaliar a capacidade funcional dos participantes. A MIF emprega uma escala que varia de 1 a 7 pontos para avaliar 18 itens em áreas de cuidados pessoais, controle esfincteriano, mobilidade, locomoção, comunicação e cognição social. Esta avaliação foi projetada para mensurar o nível de dependência de pacientes em contexto de internação em enfermaria. Dessa forma, o escore final varia entre 18 e 126, com menores valores indicando maior comprometimento funcional (RIBERTO *et al*, 2004).

- National Institutes of Health Stroke Scale (NIHSS), a fim de se avaliar a gravidade clínica do AVE. Trata-se de um instrumento amplamente utilizado para avaliação da função neurológica de pacientes afetados por AVE. É composta por 11 itens, os quais avaliam nível de consciência, percepção visual, função motora, sensibilidade, negligência e função cerebelar. O escore varia entre 0 e 42, de forma que indivíduos com pontuações mais elevadas apresentam déficit mais importante (BROTT *et al*, 1989).

- Escala modificada de Rankin é uma breve escala de avaliação de incapacidade ou dependência, comumente utilizada em serviços de atendimento a pacientes com AVE. A escala original foi introduzida em 1957 por John Rankin, na Escócia, e modificada posteriormente por um grupo de pesquisa escocês na década de 1980. Consiste em uma

pontuação que varia de 0 a 6, atribuída pelo observador e que obedece aos seguintes parâmetros: 0 – assintomático; 1 – nenhuma deficiência significativa, a despeito de sintomas; 2 – leve deficiência; 3 – deficiência moderada; 4 – deficiência moderadamente grave; 5 – deficiência grave; 6 – óbito (VAN SWIETEN *et al*, 1988).

3.5. Investigação de biomarcadores periféricos

No mesmo dia da avaliação clínica, os sujeitos de pesquisa foram submetidos a coleta de sangue periférico para a avaliação plasmática dos fatores neurotróficos e biomarcadores imunológicos.

3.5.1. Coleta de sangue periférico e separação do plasma

De cada sujeito da pesquisa foi coletada uma amostra de aproximadamente 10 mL de sangue, utilizando-se heparina como anticoagulante. As amostras foram a centrifugadas a 3.000 rpm, a 4 ºC, por 10 minutos para separação do plasma, que foi coletado e armazenado em freezer -70 ºC até o momento das análises.

3.5.2. Análise de biomarcadores inflamatórios e fatores neurotróficos

As amostras de plasma obtidas previamente foram descongeladas para avaliação dos níveis de biomarcadores inflamatórios (citocinas, moléculas de adesão, receptores) e de fatores neurotróficos através de ensaio imunoenzimático sanduíche, do inglês *enzyme-linked immunosorbent assay* (ELISA), utilizando-se kits R&D Systems (Minnesota, EUA) ou do ensaio citométrico de esferas ordenadas, do inglês *cytometric bead array* (CBA), utilizando-se kits BD Bioscience (Califórnia, EUA).

Para a realização do ELISA, de forma breve, a cada poço da placa foram adicionados 100 µL de solução contendo anticorpo monoclonal contra a proteína a ser mensurada (anticorpo de captura) diluídos em tampão fosfato-salino ou, no inglês, *phosphate buffered saline* (PBS). As placas foram incubadas por, pelo menos, 12 horas a 4º C. Os anticorpos não aderidos nas placas foram descartados por inversão e lavagem em PBS–Tween 0,1%. Em seguida, as placas foram bloqueadas com 200 µL/poço de uma solução contendo albumina de soro bovino (BSA) 1%, durante 2 horas, em temperatura

ambiente. Após nova lavagem das placas, foram adicionados 100 µL da amostra ou padrão a cada poço. As placas foram novamente incubadas por pelo menos 12 horas a 4ºC e, em seguida, lavadas. Anticorpos conjugados com biotina e diluídos em BSA 0,1% foram incubados por duas horas em temperatura ambiente.

Em seguida, após nova lavagem, foram acrescentados 100 µL/poço de estreptavidina conjugada com peroxidase às placas, as quais foram incubadas por 30 minutos em temperatura ambiente. Finalmente, após nova lavagem, o cromógeno Ø-fenileno-diamina (OPD) foi aplicado às placas, incubadas na ausência de luz. A reação foi interrompida com solução contendo ácido sulfúrico 1M. A leitura da intensidade de marcação foi realizada em leitor de ELISA no λ de 490 nM (SOFTmax Pro – versão 2.2.1). Por meio do método ELISA, foi realizada dosagem plasmática das seguintes moléculas inflamatórias e fatores neurotróficos:

- Receptor Solúvel do Fator de Necrose Tumoral 1, do inglês *Soluble Tumor Necrosis Factor Receptor 1* (sTNFR1),
- Receptor Solúvel do Fator de Necrose Tumoral 2, do inglês *Soluble Tumor Necrosis Factor Receptor 2* (sTNFR2),
- Indutor Fraco de Apoptose Semelhante ao Fator de Necrose Tumoral, do inglês *Tumor Necrosis Factor-like Weak Inducer of Apoptosis* (TWEAK),
- Receptor Solúvel Desencadeador Expresso nas Células Mielóides 1, do inglês *Soluble Triggering Receptor Expressed on Myeloid Cells 1* (STREM-1),
- E-Selectina,
- Molécula de Adesão Celular Vascular, do inglês *Vascular Cell Adhesion Molecule* (VCAM),
- Fator Neurotrófico Derivado do Cérebro, do inglês *Brain-derived Neurotrophic Factor* (BDNF),
- Fator Neurotrófico Derivado da Glia, do inglês *Glial cell-derived Neurotrophic Factor* (GDNF),
- Fator de Crescimento Neural, do inglês *Neural Growth Factor* (NGF).
- Leptina,
- Adiponectina

Para a realização do CBA, foram utilizados kits Human Th1,Th2, Th17, Becton & Dickinson. De forma breve, esferas de captura para cada proteína foram centrifugadas conjuntamente (200 g, por 5 minutos), ressuspendidas em tampão de enriquecimento plasmático e incubadas por 30 minutos em temperatura ambiente. Posteriormente, 50 µL da solução contendo as esferas de captura foram adicionados aos tubos de ensaio. Soluções-padrão liofilizadas foram reconstituídas (15 minutos em temperatura ambiente) para diluição seriada. Amostras individuais de sujeitos de pesquisa ou dos padrões (50 µL) foram adicionadas aos tubos de ensaio e incubadas por 1 hora. Foram adicionados 50 µL de reagente (*Human PE detection reagent*) aos tubos, os quais foram incubados por 2 horas em temperatura ambiente. Em seguida, 1 mL de solução tampão de lavagem foi adicionado a cada tubo de ensaio, com centrifugação a 200 g por 5 minutos. O sobrenadante foi descartado e 300 µL de solução tampão de lavagem foram adicionados a cada tubo de ensaio novamente, para ressuspender o agregado de esferas. Finalmente, todas as amostras e padrões foram avaliados com citômetro de fluxo (FACS CANTO II, Becton & Dickinson, San Jose, CA, EUA). Os resultados foram analisados por meio do *software* FCAP Array, (Becton & Dickinson, San Jose, CA, EUA). Por meio do método CBA, foi realizada dosagem plasmática das seguintes moléculas inflamatórias:

- Interleucina-2, do inglês *Interleukin-2* (IL-2),
- Interleucina-4, do inglês *Interleukin-4* (IL-4),
- Interleucina-6, do inglês *Interleukin-6* (IL-6),
- Interleucina-10, do inglês *Interleukin-10* (IL-10),
- Interleucina-17A, do inglês *Interleukin-17A* (IL-17A),
- Interferon gama, do inglês *Interferon gamma* (IFNγ),
- Fator de Necrose Tumoral, do inglês *Tumor Necrosis Factor* (TNF).

Todas as análises foram realizadas no Laboratório Interdisciplinar de Investigação Médica (LIIM), da Faculdade de Medicina da UFMG.

3.6. Análise estatística

Na análise descritiva de variáveis categóricas as proporções foram calculadas e apresentadas. Foram verificadas se as variáveis contínuas possuíam distribuição normal através do teste de normalidade de Shapiro-Wilk. Essas variáveis contínuas são apresentadas como médias e desvios-padrão. Para a comparação de variáveis categóricas entre os dois grupos, realizou-se o teste de $\chi 2$ de Pearson. Na comparação de variáveis contínuas entre dois grupos, empregou-se o teste U de Mann-Whitney. Para a comparação de três ou mais grupos, utilizou-se o teste de Kruskal- Wallis com pós-teste de Dunn. Para a realização de correlações, foi utilizado o teste de correlações de Spearman. As análises foram realizadas utilizando-se o programa estatístico SPSS versão 18.0, assim como Graphic Prism 4.0 para Windows. Um valor de p bilateral menor que 0,05 foi adotado como nível de significância estatística para todos os testes. Os gráficos foram construídos utilizando o programa Graphic Prism 4.0 para Windows.

Terceira parte

4. Resultados

4.1. Estudo clínico

Artigo 4: Early psychiatric morbidity in a Brazilian sample of acute ischemic stroke patients.

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Early psychiatric morbidity in a Brazilian sample of acute ischemic stroke patients.

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Abstract

Stroke is a major public health problem worldwide. Its neuropsychiatric sequelae are frequent and disabling. Furthermore, there is evidence that they impair recovery. Brazil has the highest stroke rates in Latin America, but there are few data on the prevalence of neuropsychiatric disorders in these patients. This study aimed to identify mental disorders among inhospital patients with acute ischemic stroke. The Mini International Neuropsychiatric Interview-Plus (MINI-Plus) was applied in 60 patients during the first week of hospitalization. Psychiatric disorders were diagnosed in 55% of patients. A wide range of neuropsychiatric disorders have been identified, mainly mood and anxiety disorders. Specifically, we identified major depression (26.7%), alcohol abuse or dependence (11.7%), specific phobia (8.3%), generalized anxiety disorder (6.7%), psychosis (5.0%), social phobia (3.3%), adjustment disorder (3.3%) and panic disorder (1.7%). Thus, the evaluation of psychiatric comorbidity should be part of the assistance to stroke patients and an aspect carefully observed by physicians.

Keywords: Stroke; Neuropsychiatry; Depression; Anxiety.

Introduction

Stroke is a major cause of death and disability worldwide [1]. Compared to the United States (US), where statistics show 610,000 new cases each year, the epidemiological data are relatively scarce in Brazil. Still, available information allows stating that stroke is the main cause of death in the country, accounting for approximately 100,000 deaths annually [2,3].

Nevertheless, over the last decades there has been a global trend of decrease in stroke mortality. This is probably due to the improvement in acute stroke management and to preventive measures, such as arterial hypertension treatment. In Brazil, there is also a decrease in stroke mortality, but restricted to the South and Southeast regions [2,3]. Currently, an estimated 5 million stroke survivors live in the US. In Brazil, where the highest stroke death rates in Latin America are found, it is estimated that stroke survivors are at least half that many. As the management of acute stroke continues to improve, the number of survivors will increase even more. Since it often results in major changes in patient's life, factors associated with morbidity have received increased attention [2,3].

Stroke is frequently associated with psychiatric symptoms such as depressed mood, anxiety and apathy [4]. The psychiatric complications of stroke, although recognized for more than one century, have never received the attention that has been devoted to other stroke consequences, such as motor impairment, language problems, or cognitive deficits. However, beyond the impact they have on neurological recovery, psychiatric complications exert significant influence on professional life and interpersonal relationships of patients, their families and their caregivers, by modifying their autonomy, self-esteem and quality of life (QOL) in general [5,6].

Despite such importance, there is yet limited information on the profile of neuropsychiatric disorders in patients after acute stroke in the Brazilian literature. Therefore, the aim of this study was to evaluate the occurrence of psychiatric disorders in Brazilian patients affected by acute ischemic stroke.

Methods

This was a cross-sectional study, in which patients with a diagnosis of acute ischemic stroke admitted to the Stroke Unit of the Hospital Municipal Odilon Behrens, Belo Horizonte, Brazil, underwent neuropsychiatric evaluation. We included consecutively encounterd patients of both genders, older than 45 years of age (to exclude stroke in young adults) and who provided written informed consent. Individuals with hemorrhagic stroke, active infectious diseases, autoimmune diseases, acute recent myocardial infarction, dementia, decreased level of consciousness (Glasgow Coma Scale <14), severe aphasia or who underwent recent neurosurgery were excluded.

In a semi-standardized interview, we collected data on sociodemographic characteristics of the participant, previous history of cerebrovascular disease, clinical comorbidities, use of thrombolytic therapy, medication use, as well as neuroimaging results, electrocardiogram and physical examination (weight, height, waist circumference, blood pressure and neurological examination). These variables were used to calculate the Framingham Risk Score for cardiovascular disease [7]. Stroke was classified in accordance with the Bamford [8] and the TOAST [9] classifications. Stroke severity was quantified by using the National Institutes of Health Stroke Scale [10] (NIHSS) and disability was

assessed with the Modified Rankin Scale [11] (mRS) and the Functional Independence Measure [12] (FIM). Subsequently, patients were interviewed by a trained psychiatrist, using the Mini International Neuropsychiatric Interview-Plus (MINI-Plus) - Brazilian version 5.0.0 [13]. Two weeks after the evaluation, patients were contact by phone to ensure the stability of the diagnosis during that period.

The study was approved by the local research ethics committee.

Results

1. Demographic characterization of patients

Sixty patients were enrolled. Table 1 presents the demographic characteristics of the sample. The mean age was 64.3 years. Male participants (70%) of black/brown skin color (87%) predominated. Most patients were living without a partner or spouse (55%). The average educational level was low (5.83 years), reflected in monthly income below three minimum wages in most cases (81.7%). Most of them were not actively working (73.3%). The majority of patients stated some sort of support or religious belief (86.7%).

TABLE 1: Demographic features (n = 60)	
Age (years; mean ± standard deviation)	64.3 (± 8.79)
Gender	
Male	70.0%
Female	30.0%
Skin color	
Black	31.7%
Brown	55.3%
White	13.0%
Marital status	
Single	3.3%
Married	40.0%
Living together	5.0%
Divorced	26.7%
Widower	25.0%
Schooling (mean ± standard deviation)	5.83 (±3.31)
Monthly income	
Without regular income	6.7%
< 3 minimum wages*	75.0%
Between 3 and 10 minimum wages*	18.3%
Current employment status	
Active	26.7%
Unemployed	15.0%
Retired	45.0%
Receiving social assistance	13.3%
Religion	
Catholic	50,0%
Protestant	36,7%
No religion	13,3%

Table 1: Demographic features of a sample of 60 inhospital patients after ischemic acute stroke.
*One minimum wage is the lowest monthly remuneration that employers may legally pay to workers in Brazil. Currently, its value is R$ 880.00 (approximately US$ 270.00).

2. General health data

Table 2 shows general health characteristics of the studied sample. Hypertension and obesity were highly prevalent (95% and 60%, respectively), followed by dyslipidemia (36.8%) and diabetes (30%). Smoking was also frequent. The majority of patients were using antihypertensive drugs (95%), antiplatelet drugs (70%) or statins (65%). Physical assessment yielded a trend toward overweight and high blood pressure. The average Framingham score was 21.7.

TABLE 2: General health features (n=60)	
Clinical comorbidities	
Hypertension	95.0%
Diabetes	30.0%
Obesity	60.0%
Dyslipidemia	36.8%
History of myocardial infarction	6.7%
Congestive heart failure	1.7%
Epilepsy	1.7%
Smoking	
Current	26.7%
Previous	18.3%
Medications in use	
Antihypertensive drugs	95.0%
Statins	65.0%
Hypoglycemic drugs	30.0%
Aspirin or Clopidogrel	70.0%
Psychotropic drugs	1.7%
Clinical data (mean ± standard deviation)	
Body mass index	26.4 kg/m^2 (± 4.49)
Abdominal circumference	97.07 cm (± 13.47)
Systolic blood pressure	141.83 mmHg (± 20.38)
Diastolic blood pressure	88.83 mmHg (± 11.21)
Framingham score (mean ± standard deviation)	21.7 (± 3.28)

Table 2: General health features of a sample of 60 patients after ischemic acute stroke

3. Stroke characteristics

Table 3 shows the characteristics related to stroke in the studied sample. Thrombolytic therapy was used only in 5% of patients. The time elapsed since the ischemic event until our evaluation was 5.4 days on average. All patients underwent computed tomography neuroimaging. According to the classifications of TOAST and Bamford, most cases corresponded to lacunar strokes (53.3%), followed by atherothrombotic ones. Lesion sites were mainly found in the right hemisphere (61.7%), affecting the frontal lobes, the basal ganglia and the internal capsule. The mean NIHSS score at admission was 3.83 and mRS was 2.4. The average FIM score was 113.67.

TABLE 3: Stroke features (n=60)	
Use of thrombolytic therapy	5.0%
Elapsed time since stroke (mean ± standard deviation)	5.4 days (±1.53)
TOAST Classification	
Cardioembolism	8.3%
Large-artey atherosclerosis	38.4%
Small vessel occlusion	53.3%
Bamford Classification	
LACS	53.3%
PACS	38.4%
POCS	8.3%
Affected hemisphere	
Right	61.7%
Left	38.3%
Lesion site	
Frontal lobe	30.0%
Temporal lobe	6.7%
Occipital lobe	8.3%
Parietal lobe	0.0%
Basal ganglia	28.3%
Internal capsule	35.0%
Cerebellum	1.7%
NIHSS	3.83 (± 3.06)
Modified Rankin scale (at admission)	2.4 (± 0.97)
Functional independence measure	113.67 (± 12.44)

Table 3: Features of acute schemic stroke in a sample of 60 patients.

4. MINI-Plus diagnosis

Table 4 shows the results of the assessment using the MINI-Plus. At least one mental disorder was diagnosed in 55% of the sample. Depression was the most frequent disorder, with a prevalence of 26.7%, including one case of depression with psychotic symptoms (mood congruent delusions and auditory hallucinations). Past history of depressive disorders was found in 5% of the cases, but none of them was diagnosed with current major depression. Anxiety disorders as a group were found in 23.3%, especially phobias and generalized anxiety disorder (GAD). Alcohol use disorders were also frequent, found in 11.7% of the cases. Psychosis without other specifications was observed in 5% of the cases.

TABLE 4: Diagnosis by MINI-Plus (n=60)	
MINI-Plus	
Major depression (current)	26.7%
Without psychotic symptoms	25.0%
With psychotic symptoms	1.7%
Depression (past)	5.0%
Anxiety disorders	23.3%
Social phobia	3.3%
Specific phobia	8.3%
Generalized anxiety disorder	6.7%
Adjustment disorder	3.3%
Panic disorder	1.7%
Psychosis (not otherwise specified)	5.0%
Alcohol dependence/abuse	11.7%
No mental disorders	45.0%

Table 4: Psychiatric diagnosis established by the use of MINI-Plus in a sample of 60 patients after ischemic acute stroke.

Discussion

To our knowledge, this is the first study to assess in a systematic and comprehensive way the psychiatric profile of Brazilian patients with acute ischemic stroke. A detailed description of the clinical and demographic characteristics of the sample was performed, followed by a structured psychiatric evaluation using a standardized tool for diagnosis. Sixty patients were evaluated.

The analysis of the sociodemographic characteristics of the sample allows us to trace the profile of patients assisted by a public hospital, considered the local reference center for the care of stroke. Thus, we observed that the sample is composed of older patients, predominantly unemployed, with low income and low education, consisting of patients in social vulnerability.

Patients had a high rate of clinical comorbidities, especially hypertension, obesity, dyslipidemia, diabetes and smoking. A similar profile of medical comorbidity was found in a previous study that investigated the role of Chagas's disease as an independent risk factor for the occurrence of stroke, performed at the same hospital [14]. The observation of mean BMI values above 25 kg/m² and high mean blood pressure values, despite the use of medication, draws attention to the unsatisfactory clinical management of patients prior to admission. The Framingham score for the sample was calculated from the recorded clinical variables. This score was developed based on information collected over 36 years of epidemiological population studies and estimates the probability of stroke from clinical information [7]. The mean score observed was 21.27. This value means that the probability of stroke in 10 years is over 30% for men and 14% for women, and confirms the high risk profile for the development of stroke in the sample.

Interviews took place on average 5.4 days after the ischemic event, in accordance with the purpose of evaluating patients in the acute period after stroke. Most of the observed individuals presented stroke of the lacunar type, with predominance of lesions in

the middle cerebral artery topography of the right hemisphere. The NIHSS, mRS and FIM scales were used to measure the initial severity of the ischemic event and its resulting disability. The mean results found were below 5 for the NIHSS and below 3 for the mRS, indicating a mild stroke impact in the sample. This fact is reflected in the measurement of patient dysfunction obtained by the FIM, a scale which ranges from 18 (worst outcome) to 126 (best outcome) points. The average value of 113.67 found in the sample was compatible with mild functional deficit.

Despite this mild functional impact, assessment through a structured psychiatric interview revealed the presence of mental disorders in approximately 55% of the sample, especially depressive and anxiety disorders. In accordance with other studies, depression was the most frequent psychiatric disorder [15,16]. Chemerinski and Robinson observed that the prevalence of depression among hospitalized patients in the acute phase of stroke is around 22% for major depression and 17% for minor depression [4]. In outpatient samples (from 3 months to 10 years after stroke), it is around 23% for major depression and 35% for minor depression, while community samples exhibit mean prevalence rates of 13% and 10%, respectively. A recent meta-analysis showed that the prevalence of depression at any time after stroke was 29%. We found a similar number, i.e. a prevalence of 26.7% of depression in our sample. Accordingly, a systematic review of Brazilian studies that assessed the prevalence of depression after stroke in different settings found prevalence rates ranging from 20 to 59% [17].

Anxiety disorders are also common after stroke. Between 25% and 50% of the patients develop GAD in the first months after stroke, with a small reduction in incidence in the following three years [18]. Burton et al. reported that anxiety disorders affected 20% to 25% of patients at any time after stroke [19]. However, the majority of studies of patients affected by stroke has not effectively explored the presence of anxiety disorders. Thus, there are scarce data on specific categories, such as panic attacks, agoraphobia or phobias. According to Burton et al., phobic disorders and GAD are the most common types of anxiety disorders after a stroke [19]. In line with this, we found a prevalence of anxiety disorders of 23.3%, especially phobias and GAD.

Considering that mental disorders influence negatively the recovery of patients after stroke and that factors associated with social vulnerability are risk factors that complicate their own treatment, the high prevalence of depression and anxiety disorders calls attention to the possible consequences that may result if they are not properly identified and treated, even in a sample of patients with mild functional impact [20,21]. The relation between depression after stroke and functional impairment is complex. Depressed patients have significantly higher disability in activities of daily living (ADLs) than euthymic patients with comparable neurological deficits [4]. Depression negatively influences engagement in rehabilitation programs and is associated with more institutional care and increase in using of health services. These findings suggest a phenomenon of reciprocity in which depression influences the recovery of ADLs while the impairment of ADLs affects the severity and duration of depression. Increased mortality is perhaps the ultimate criterion of the importance of depression in the prognosis following stroke. Depression appears to be a significant risk factor for increased death as early as 1 year and as late as 7 years following stroke [22].

As with depression, anxiety disorders may be linked to psychological factors after stroke. Concerns about the possibility of failing to control motor, cognitive and emotional reactions in different environments are common in the speech of patients, besides the fear

of occurrence of new stroke events. This may be reflected in decreased perception of QOL. Indeed, patients with severe stroke and high levels of anxiety presented worse QOL [23].

The decreased QOL and negative functional impact caused by mental disorders could further complicate the management of clinical comorbidities and adherece to treatment, contributing to an increase in the overall risk of complications. Thus, the evaluation of psychiatric comorbidity should be part of the assistance to stroke patients and an aspect carefully observed by physicians.

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Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

References

1. American Heart Association Statistics Committee and Stroke Statistics Subcommittee. “Heart disease and stroke statistics – 2013 update: a report from the American Heart Association,” *Circulation*, vol. 127, no. 1, pp. e6-e245, 2013.
2. P.A. Lotufo, A.C. Goulart, T.G. Fernandes and I.M. Benseñor, “A reappraisal of stroke mortality trends in Brazil (1979-2009),” *International Journal of Stroke*, vol. 8, no. 3, pp. 155-63, 2013.
3. J.J. de Carvalho, M.B. Alves, G.A. Viana et al., “Stroke epidemiology, patterns of management, and outcomes in Fortaleza, Brazil: a hospital-based multicenter prospective study,” *Stroke,* vol. 42, no. 12, pp. 3341-6, 2011.
4. E. Chemerinski and R.G. Robinson. “The neuropsychiatry of stroke,” *Psychosomatics*, vol. 41, no. 1, pp. 5-14, 2000.
5. T.O. Tengs, M. Yu and E. Luistro. “Health-related quality of life after stroke – a comprehensive review,” *Stroke*, vol. 32, no. 4, pp. 964-72, 2001.
6. R.F. de Mello, S. Santos Ide, A.P. Alencar, I.M. Benseñor, P.A. Lotufo and A.C. Goulart, “Major Depression as a Predictor of Poor Long-Term Survival in a Brazilian Stroke Cohort (Study of Stroke Mortality and Morbidity in Adults) EMMA study.” *Journal of Stroke and Cerebrovascular Diseases*, vol. 25, no. 3, pp. 618-25, 2016.
7. R.B. D'Agostino, R.S. Vasan, M.J. Pencina, et al., “General cardiovascular risk profile for use in primary care: the Framingham Heart Study,” *Circulation*, vol. 117, no. 6, pp. 743–53, 2008.
8. J. Bamford, P. Sandercock, M. Dennis, J. Burn and C. Warlow, “Classification and natural history of clinical subtypes of cerebral infarction,” *Lancet,* vol. 337, no. 8756 , pp. 1521-26, 1991.
9. H.P. Adams Jr., B.H. Bendixen, L.J. Kappelle, et al., “Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment,” *Stroke*, vol. 24, no. 1, pp. 35-41, 1993.
10. T. Brott, H.P. Adams, C.P. Olinger Jr., et al., “Measurements of acute cerebral infarction: a clinical examination scale,” *Stroke,* vol. 20, no. 7, pp. 864–70, 1989.
11. J. van Swieten, P. Koudstaal, Visser M, et al. “Interobserver agreement for the assessment of handicap in stroke patients,” *Stroke*, vol. 19, no. 5, pp. 604–7, 1988.
12. M. Riberto, M.H. Miyazaki, S.S.H. Jucá, et al., “Validation of the Brazilian version of Functional Independence Measure,” *Acta Fisiatrica*, vol. 11, no. 2, pp. 72-6, 2004.
13. P. Amorim, “Mini International Neuropsychiatric Interview (MINI): validation of a short structured diagnostic psychiatric interview,” *Revista Brasileira de Psiquiatria*, vol. 22, no. 3, pp. 106-115, 2000.
14. L.C. Paixão, A.L. Ribeiro, R.A. Valacio and A.L. Teixeira, “Chagas disease: independent risk factor for stroke,” *Stroke,* vol. 40, no. 12, pp. 3691-4, 2009.
15. P. Angelelli, S. Paolucci, U. Bivona, et al. “Development of neuropsychiatric symptoms in poststroke patients: a cross-sectional study,” *Acta Psychiatrica Scandinavica,* vol. 110, no. 1, pp. 55-63, 2004.
16. B.I. Buijck, S.U. Zuidema, M. Spruit-van Eijk, A.C. Geurts and R.T. Koopmans. “Neuropsychiatric symptoms in geriatric patients admitted to skilled nursing

facilities in nursing homes for rehabilitation after stroke: a longitudinal multicenter study," *International Journal of Geriatric Psychiatry*, vol. 27, no. 7, pp. 734-41, 2012.
17. V.S.P. Pedroso, L. Cruz, A.R. Brunoni and A.L. Teixeira, "Post stroke depression: clinics, etiopathogenesis and therapeutics," *Archives of Clinical Psychiatry (São Paulo)*, vol. 42, no. 1, pp. 18-24, 2015.
18. M. Astrom. "Generalized anxiety disorder in stroke patients. A 3-year longitudinal study," *Stroke*, vol. 27, no. 2, pp. 270-5, 1996.
19. C.A.C. Burton, J. Holmes, J. Murray, et al., "Interventions for treating anxiety after stroke," *Cochrane Database of Systematic Reviews*, vol. 12, CD008860, 2011.
20. A.J. Oldehinkel, J. Ormel, E.I. Brilman and M.D. van den Berg. "Psychosocial and vascular risk factors depression in later life," *Journal of Affective Disorders*, vol.74, no. 3, pp. 237-46, 2003.
21. S. Paolucci, C. Gandolfo, L. Provinciali, R. Torta and V. Toso, "DESTRO Study Group. The Italian multicenter observational study on post-stroke depression (DESTRO)," *Journal of Neurology*, vol. 253, no. 5, pp. 556-62, 2006.
22. V.S.P. Pedroso, L. Cruz and A.L. Teixeira, "Neuropsychiatric syndromes associated with stroke: review of the literature," *Jornal Brasileiro de Psiquiatria*, vol. 63, no. 2, pp. 165-76, 2014.
23. F.J. Carod-Artal, D.S. Trizotto, L.F. Coral and C.M. Moreira, "Determinants of quality of life in Brazilian stroke survivors," *Journal of the neurological sciences*, vol. 284, no. 1-2, pp. 63-8, 2009.

Artigo 5: Psychopathological evaluation and use of the Hospital Anxiety and Depression Scale in a sample of Brazilian patients with post-stroke depression.

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Psychopathological evaluation and use of the Hospital Anxiety and Depression Scale in a sample of Brazilian patients with post-stroke depression.

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Abstract

Background: Depression is the most frequent psychiatric complication of stroke and is often undetected or inadequately treated.
Objectives: This study aimed to characterize psychopathological aspects of Brazilian patients admitted to an acute stroke unit, and to evaluate the performance of the Hospital Anxiety and Depression Scale (HADS) in detecting cases of depression.
Methods: This was a cross-sectional study. Sixty consecutive patients admitted to an acute stroke unit were assessed with the National Institutes of Health Stroke Scale, the Modified Rankin Scale, the Functional Independence Measure, the Mini International Neuropsychiatric Interview-Plus, the HADS, the Mini Mental State Examination (MMSE) and the Pathological Laughing and Crying Scale.
Results: Prevalence of depression was 26.7%. Patients with post-stroke depression were more likely to present diabetes ($p<0.01$) and had greater disability ($p<0.001$) and cognitive impairment ($p<0.001$) in comparison to non-depressed patients. Depressed patients showed worse performance specifically on tasks of attention/calculation and language of the MMSE. ROC curve analysis of HADS provided a cutoff value of 6 for detecting depression (sensitivity: 83.3%; specificity: 83.3%). The depression subscale of HADS (HADS-D) presented sensitivity of 100% and specificity of 99.17%.
Discussion/Conclusion: HADS-D showed good performance in screening for depressive symptoms after acute stroke.

Keywords: Post-stroke depression, Hospital Anxiety and Depression Scale, Mini Mental State Examination, Depression, Acute ischemic stroke.

Introduction

Stroke is a major cause of death and disability worldwide[1]. Mood disorders, especially depression, are commom in stroke-survivors and are associated with morbidity and mortality[2]. A recent meta-analysis showed that the prevalence of depression any time after stroke was 29% and that more than half of stroke survivors will be affected by depression at some point[3,4]. Despite this, mood disorders after stroke are frequently undetected or inadequately treated[5]. Untreated post-stroke depression (PSD) lengthens hospital stays, impairs functional outcome and elevates mortality[6].

Early assessment for possible neuropsychiatric disorders in acute stroke units could allow prompt intervention and provide valuable information for the referral of patients. Stroke survivors often report that their physical needs are prioritised over their psychological ones and this is a relevant issue, since many patients will probably not receive this type of evaluation after discharge[6].

The gold-standard method for psychiatric diagnosing is a standardized clinical interview by an experienced clinician. However, this is time consuming and mostly unavailable on neurological or medical wards. Therefore, there is a need for valid and reliable screening instruments in order to find vulnerable or at risk patients. Hospital Anxiety and Depression Scale (HADS), a simple instrument developed to identify caseness of anxiety and depression among patients in nonpsychiatric hospital clinics, could be potentially useful for screening depressive disorders after stroke[7].

In Brazil, where stroke is the leading cause of death, it is estimated that survivors reach 2.5 million individuals and there is virtually no information on the profile of neuropsychiatric disorders in these patients[8]. Despite limited data on this topic, we recently reviewed Brazilian studies that assessed the prevalence of depression after stroke in different settings and found rates ranging from 20 to 59% [8]. However, there is very limited evidence on the use of screening instruments in this population.

Therefore, the objective of this study was to characterize psychopathological aspects of Brazilian patients admitted to an acute stroke unit, and to evaluate the performance of the HADS in detecting cases of depression in this sample of patients.

Methods

This was a cross-sectional study, in which consecutive patients with a diagnosis of acute ischemic stroke admitted to the Stroke Unit of the Hospital Municipal Odilon Behrens, Belo Horizonte, Brazil, underwent neuropsychiatric evaluation during the first week after stroke. We included patients of both genders, older than 45 years of age and who consented to participate. Individuals with hemorrhagic stroke, active infectious diseases, autoimmune diseases, acute recent myocardial infarction, dementia, decreased level of consciousness (Glasgow Coma Scale <14), severe aphasia or who underwent recent neurosurgery were excluded.

In a semi-standardized interview, we collected data on sociodemographic and clinical characteristics of the participant. These variables were used to calculate the Framingham Risk Score for cardiovascular disease[9]. Stroke severity was quantified by using the National Institutes of Health Stroke Scale (NIHSS)[10] and disability was assessed with the Modified Rankin Scale (mRS)[11] and the Functional Independence Measure (FIM)[12]. Subsequently, patients were interviewed by a trained psychiatrist using the Mini

International Neuropsychiatric Interview-Plus (MINI-Plus) - Brazilian version 5.0.0 to provide formal psychiatric diagnosis[13]. Finally, patients underwent psychopathological evaluation, through the use of HADS[7], Mini Mental State Examination[14] and Pathological Laughing and Crying Scale (PLACS)[15]. Two weeks after the evaluation, patients were contacted by phone to ensure the stability of the diagnosis of depression in that period of time.

Demographic and clinical variables between participants with and without the diagnosis of depression were compared by chi-square test, Mann–Whitney U test and Spearman correlation analysis. Receiver Operating Characteristic (ROC) curve analysis was calculated to identify optimal cut-off values for the diagnosis of depression with the HADS. The level of significance was set at $p = 0.05$.

The study was approved by the local research ethics committee.

Results

1. Sociodemographic and clinical features

Sixty patients were enrolled in the study. Diagnosis of depression made by the use of MINI-Plus reached a prevalence of 26.7%. Diagnosis made in the stroke unit remained stable in all cases after two weeks. Two groups were divided based on the presence of depression, and their demographic and clinical features were compared (Table 1). No differences were observed with respect to age and gender. Depressed patients exhibited higher rate of diabetes, but did not differ in relation to the average values of body mass index (BMI) and waist circumference, as well as to the Framingham risk score. Patients with diabetes had a higher risk for developing depression in the context of stroke (relative risk: 3; odds ratio: 6). There were no differences regarding the presence of other medical comorbidities such as hypertension, dyslipidemia, obesity, myocardial infarction, smoking, heart failure or coronary artery disease (data not shown). Depressed patients showed higher mRS values on admission as well as worse functional performance as assessed by the FIM. A trend of higher score in NIHSS was observed among patients with depression, but this difference did not reach statistical significance (p=0.062).

Sociodemographic and clinical features			
	% or mean (standard deviation)		p value
	Depression (n=16)	No Depression (n=44)	
Age (years)	61.07 (5.7)	65.38 (9.41)	0.069[b]
Gender (% male)	75.00	68.18	0.504[a]
Diabetes (%)	56.25	20.45	<0.01[a]
BMI (kg/m²)	25.43 (3.06)	26.70 (4.87)	0.206[b]
Waist circumference (cm)	95.47 (10.41)	97.60 (14.41)	0.398[b]
Framingham risk score	22 (0.85)	21 (3.80)	0.404[b]
mRS	2.93 (0.88)	2.16 (0.93)	<0.05[b]
NIHSS	5.67 (4.21)	3.22 (2.34)	0.062[b]
FIM	103.67 (14.12)	117.00 (9.93)	<0.001[b]

Table 1: Sociodemographic and clinical features in a sample of 60 patients with acute ischemic stroke.
[a]Chi-square; [b]Mann-Whitney U test.

2. Psychopathological features

Table 2 presents the comparison of psychopathological characteristics between depressed and non-depressed patients. Patients with depression had poorer performance on the MMSE. Specifically, patients with PSD performed worse attention/calculation and language tasks (p=0.001 and 0.049, respectively). Concerning the use of the HADS, depressed patients had higher scores in the total score and in the depression subscale, but did not differ in the anxiety subscale. In the assessment of involuntary emotional expression disorder (IEED) by the PLACS, no differences were observed between the groups, although there was a trend towards higher scoring among depressed patients. There was a positive correlation between the total scores of HADS and the PLACS (rho= 0.322, p = 0.025).

Psychopathological features			
	Mean (standard deviation)		p value
	Depression (n=16)	No Depression (n=44)	
MMSE			
Orientation	8.40 (1.59)	9.31 (0.79)	0.058
Registration	3.00 (0.00)	3.00 (0.00)	1.00
Attention and calculation	1.80 (0.94)	3.33 (1.68)	0.001
Recall	1.93 (0.70)	2.24 (1.09)	0.067
Language	6.87 (1.06)	7.38 (0.89)	0.049
Copying	0.40 (0.51)	0.53 (0.50)	0.375
Total	22.40 (1.96)	25.79 (2.90)	<0.001
HADS			
Total	13.50 (4.23)	5.69 (3.36)	<0.001
HADS Depression	10.08 (2.64)	2.36 (2.10)	<0.001
HADS Anxiety	3.42 (2.15)	3.33 (2.50)	0.744
PLACS			
Total	5.40 (7.06)	1.91 (4.80)	0.059
Crying	2.60 (5.40)	1.16 (3.49)	0.714
Laughing	1.80 (3.75)	0.38 (1.43)	0.105

Table 2: Psychopathological features in a sample of 60 patients with acute ischemic stroke.

3. Receiver Operating Characteristic (ROC) curve analysis

Based on the diagnosis made by MINI Plus and evaluation with the HADS, a ROC curve analysis was made to determine the optimal cutoff point of the scale. Figure 1 shows the resulting ROC curve. The HADS consists of 14 items, of which 7 make up a subscale of depression and 7 make up a subscale of anxiety. The areas under the curve (AUC) were respectively 0.928 and 0.979 for HADS Total and HADS Depression (HADS-D). There was no association between the anxiety subscale and the diagnosis of depression (p=0.748). There was no correlation between the HADS-D and the HADS Anxiety (HADS-A) subscales (p=0.438). The total score and the depression subscale were significantly associated with the diagnosis of depression (p<0.001). The depression subscale exhibited the best performance. The cut-off values chosen based on ROC curve analysis were 10 for the total scale and 6 for the subscale of depression. These cutoffs have led to sensitivity of

83.3% and specificity of 83.3% for the total scale and sensitivity of 100% with specificity of 99.17% for the subscale of depression.

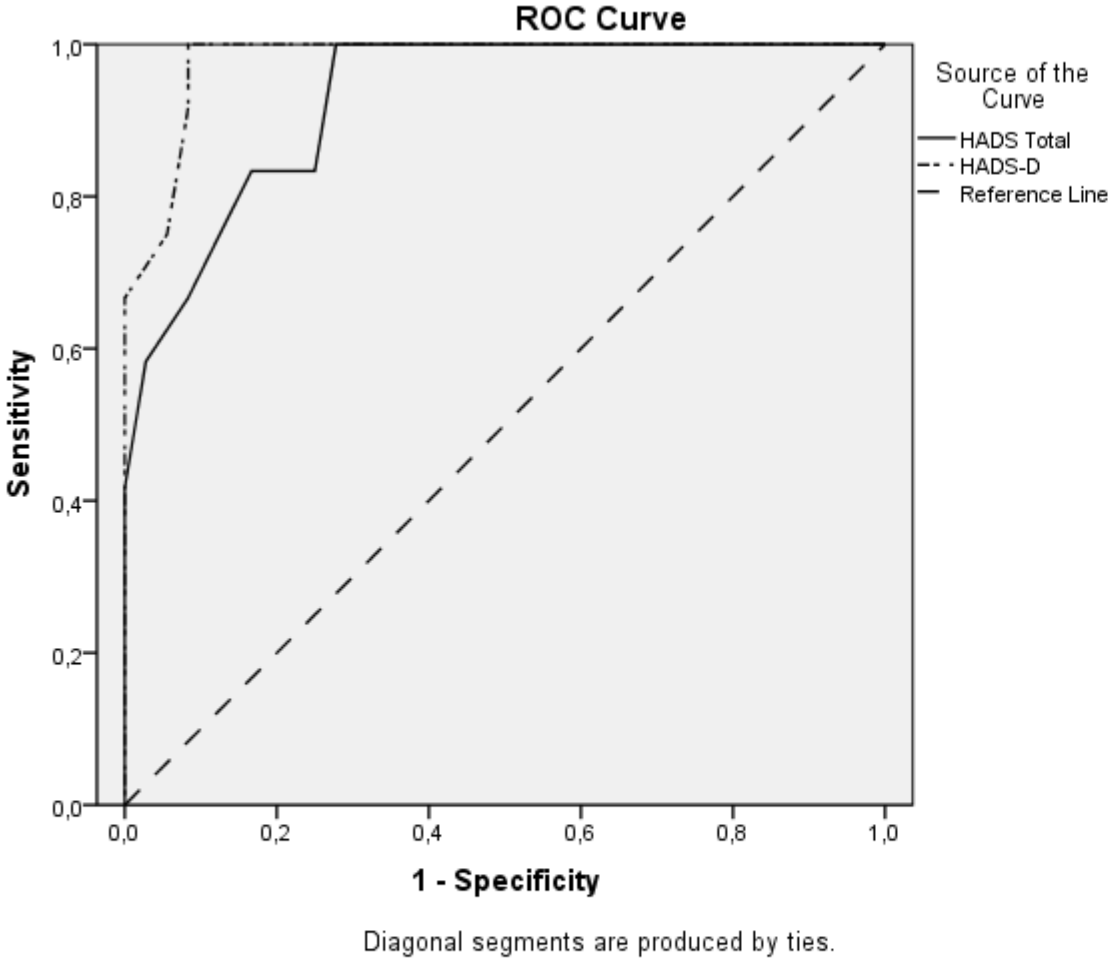

Figure 1: ROC curve analysis of HADS in a sample of 60 patients with acute ischemic stroke.

Discussion

To our knowledge, this is the first study to evaluate the potential of HADS in the screening of PSD in Brazil. We found a prevalence of 26.7% of PSD in the acute phase, which is in agreement with the international literature and confirms the high frequency of mood disorders associated with stroke[16].

Carod-Artal *et al*. found that PSD was the stronger predictor of low health related quality of life in Brazilian stroke survivors[17]. This fact points to the importance of detection

and intervention in such cases. For this reason, we evaluated the use of HADS in screening for PSD. In a review of the literature, the threshold values identified for optimal balance between sensitivity and specificity for HADS showed little variability, and were close to 8, defined as the cut-off for 'possible cases' by the original authors of the scale[18]. This threshold was found for HADS-A and HADS-D in the general population as well as in patients with medical conditions[18]. However, studies evaluating its use in stroke patients suggested that the cutoff values could be lower for PSD detection[19]. In this way, cut-points ranging from 4 through 8 for the HADS-D have been proposed in stroke[20]. In the present study, we found the value of 6 as optimal cutoff point for the depression subscale. This value led to a sensitivity of 100% and a specificity of 99.17%. Wichowicz and Wieczorek found a cutoff value of 7 in a sample of 75 Polish stroke patients, with sensitivity of 90.0% and specificity of 92.2% for the HADS-D[21]. Tang *et al*. also found cutoff values of 6/7 in 100 Chinese patients, though with sensitivity of 88% and specificity of 53%[22].

Patients with depression in our sample tended to be more severely disabled, evidenced by higher scores on the mRS on admission and lower scores on the FIM. Several factors have been associated with PSD, such as previous history of psychiatric disorders, female gender, family history of depression, and cerebrovascular risk factors, among others[8,23]. Among those, physical disability, stroke severity and cognitive impairment have been more consistently associated with PSD. In accordance with these data, we found that patients with PSD had worse performance on the MMSE. Cognitive performance in PSD was assessed by a series of studies, and there is evidence that PSD affects problem solving, verbal and visual memory, language, visuospatial processes, attention and psychomotor speed[8]. For instance, in a cohort of 143 patients who were followed up to 10 months after a stroke, Nys et al. found that early cognitive impairment independently predicted long-term depressive symptoms. Moreover, cognitive deficits were related to worse quality of life[24]. In our sample, patients with PSD presented poorer performance specifically in attention/calculation and language tasks, in accordance with the previous findings mentioned above.

Although PSD patients exhibited higher scores on PLACS, there was no difference in the occurence of IEED between patients with and without depression. This may reinforce the view that PSD and IEED are distinct entities, even though they can present some degree of overlap[25]. Indeed, IEED is regarded as a risk factor for the development of PSD[16,26]. Accordingly, there was a positive correlation between the scores of PLACS and HADS.

Another aspect observed in our sample was the association between diabetes and PSD. Some studies have suggested a bidirectional association between diabetes and PSD, i.e. people with diabetes have increased risk of developing depressive symptoms and people with depression have increased risk of developing diabetes[27,28,29]. Micro and macrovascular complications due to diabetes were strongly related to the occurrence of depression in this group of individuals[30]. In a large cohort of 157,243 Danish patients with stroke, diabetes was found as a risk factor for PSD[31]. The findings of an association between the occurrence of a depressive syndrome in the elderly population and the presence of white matter lesions of vascular origin, particularly in the frontal regions, have led to the hypothesis of the existence of a "vascular depression", which would be linked to microangiopathy[32]. Based on that, one could speculate whether patients with diabetes are more susceptible to the development of depressive symptoms after a major vascular insult superimposed on chronic vascular microlesions.

In conclusion, we observed that HADS-D showed good performance in screening for depressive symptoms after acute stroke. Patients with PSD were more likely to present diabetes, and had greater disability and cognitive impairment in comparison to non-depressed patients. Future studies should focus on the longitudinal assessment of PSD patients to better define the contribution of each variable in the development of depressive symptoms after stroke, with the aim of designing effective interventions for treatment and rehabilitation.

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References

1. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Blaha MJ *et al*. Heart disease and stroke statistics – 2013 update: a report from the American Heart Association. Circulation. 2013; 127 (1): e6-e245.
2. Broomfield NM, Quinn TJ, Abdul-Rahim AH, Walters MR, Evans JJ. Depression and anxiety symptoms post-stroke/TIA: prevalence and associations in cross-sectional data from a regional stroke registry. BMC Neurol. 2014; 14: 198.
3. Ayerbe L, Ayis S, Wolfe CD, Rudd AG. Natural history, predictors and outcomes of depression after stroke: systematic review and meta-analysis. Br J Psychiatry. 2013; 202 (1): 14-21.
4. Ayerbe L, Ayis S, Crichton S, Wolfe CD, Rudd AG. The natural history of depression up to 15 years after stroke: the South London Stroke Register. Stroke. 2013; 44 (4): 1105-10.
5. Sagen U, Vik TG, Moum T, Mørland T, Finset A, Dammen T. Screening for anxiety and depression after stroke: comparison of the hospital anxiety and depression scale and the Montgomery and Asberg depression rating scale. J Psychosom Res. 2009; 67 (4): 325-32.
6. Lees R, Stott DJ, Quinn TJ, Broomfield NM. Feasibility and diagnostic accuracy of early mood screening to diagnose persisting clinical depression/anxiety disorder after stroke. Cerebrovasc Dis. 2014; 37 (5): 323-9.
7. Zigmond AS, Snaith RP. The Hospital Anxiety and Depression Scale. Acta Psychiatr Scand. 1983; 67 (6): 361–70.
8. Pedroso VSP, Souza LC, Brunoni AR, Teixeira AL. Post stroke depression: clinics, etiopathogenesis and therapeutics. Arch Clin Psychiatry (São Paulo). 2015; 42 (1): 18-24.
9. D'Agostino RB Sr, Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, *et al*. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. Circulation. 2008; 117 (6): 743–53.
10. Brott T, Adams HP, Jr, Olinger CP, Marler JR, Barsan WG, Biller J, *et al*. Measurements of acute cerebral infarction: a clinical examination scale. Stroke. 1989; 20 (7): 864–70.
11. van Swieten J, Koudstaal P, Visser M, Schouten HJ, van Gijn J. Interobserver agreement for the assessment of handicap in stroke patients. Stroke. 1988; 19 (5): 604–7.
12. Riberto M, Miyazaki MH, Jucá SSH, Sakamoto H, Pinto PPN, Battistella LR. Validation of the Brazilian version of Functional Independence Measure. Acta Fisiatr. 2004; 11 (2): 72-6.
13. Amorim P. Mini International Neuropsychiatric Interview (MINI): validation of a short structured diagnostic psychiatric interview. Rev Bras Psiquiatr. 2000; 22 (3): 106-115.
14. Folstein MF, Folstein SE, McHugh PR. 1975. Mini-mental state: a practical method for grading the cognitive state of patients for the clinician. J Psychiatric Res. 1975; 12 (3): 189-98.

15. Robinson RG, Parikh RM, Lipsey JR, Starkstein SE, Price TR. Pathological laughing and crying following stroke validation of a measurement scale and a double-blind treatment study. Am J Psychiatry. 1993; 150 (2): 286-93.
16. Chemerinski E, Robinson RG. The neuropsychiatry of stroke. Psychosomatics. 2000; 41 (1): 5-14.
17. Carod-Artal FJ, Trizotto DS, Coral LF, Moreira CM. Determinants of quality of life in Brazilian stroke survivors. J Neurol Sci. 2009; 284 (1-2): 63-8.
18. Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the Hospital Anxiety and Depression Scale. An updated literature review. J Psychosom Res. 2002; 52 (2): 69-77.
19. Tang WK, Wong E, Chiu HF, Ungvari GS. Rasch analysis of the scoring scheme of the HADS Depression subscale in Chinese stroke patients. Psychiatry Res. 2007; 150 (1): 97-103.
20. Prisnie JC, Fiest KM, Coutts SB, Patten SB, Atta CA, Blaikie L, *et al*. Validating screening tools for depression in stroke and transient ischemic attack patients. Int J Psychiatry Med. 2016; 51 (3): 262-77.
21. Wichowicz HM, Wieczorek D. Screening post-stroke depression using the Hospital Anxiety and Depression Scale. Psychiatr Pol. 2011; 45 (4): 505-14.
22. Tang WK, Ungvari GS, Chiu HF, Sze KH, Yu AC, Leung TL. Screening post-stroke depression in Chinese older adults using the hospital anxiety and depression scale. Aging Ment Health. 2004; 8 (5): 397-9.
23. Angelelli P, Paolucci S, Bivona U, Piccardi L, Ciurli P, Cantagallo A, *et al*. Development of neuropsychiatric symptoms in poststroke patients: a cross-sectional study. Acta Psychiatr Scand. 2004; 110 (1): 55-63.
24. Nys GM, van Zandvoort MJ, van der Worp HB, de Haan EH, de Kort PL, Jansen BP, *et al.* Early cognitive impairment predicts long-term depressive symptoms and quality of life after stroke. J Neurol Sci. 2006; 247: 149-56.
25. Pedroso VSP, Souza LC, Teixeira AL. Neuropsychiatric syndromes associated with stroke: review of the literature. J Bras Psiquiatr. 2014; 63 (2): 165-76.
26. Carota A, Dieguez S, Bogousslavsky J. Psychopathology of stroke. Psychol Neuropsychiatr Vieil. 2005; 3(4): 235-49.
27. Golden SH, Lazo M, Carnethon M, Bertoni AG, Schreiner PJ, Diez Roux AV, *et al*. Examining a bidirectional association between depressive symptoms and diabetes. J Am Med Assoc. 2008; 299 (23): 2751-59.
28. Anderson RJ, Freedland KE, Clouse RE, Lustman PJ. The prevalence of comorbid depression in adults with diabetes. Diabetes Care. 2001; 24 (6): 1069–78.
29. Raval A, Dhanaraj E, Bhansali A, Grover S, Tiwari P. Prevalence and determinants of depression in type 2 diabetes patients in a tertiary care centre. Indian J Med Res. 2010; 132: 195-200.
30. Roy T, Lloyd CE. Epidemiology of depression and diabetes: a systematic review. J Affect Disord. 2012; 142 Suppl: S8-21.
31. Jørgensen TS, Wium-Andersen IK, Wium-Andersen MK, Jørgensen MB, Prescott E, Maartensson S, *et al*. Incidence of Depression After Stroke, and Associated Risk Factors and Mortality Outcomes, in a Large Cohort of Danish Patients. JAMA Psychiatry. 2016; 73 (10): 1032-40.
32. Sneed JR, Culang-Reinlieb ME. The vascular depression hypothesis: an update. Am J Geriatr Psychiatry. 2011; 19 (2): 99-103.

4.2. Estudo experimental

4.2.1. Características dos grupos

Para a avaliação de biomarcadores periféricos, além da amostra de pacientes afetados por AVE que se mantiveram eutímicos (AVE) e que desenvolveram depressão (DPAVE), foram incluídos dois grupos controle: o primeiro, composto por indivíduos saudáveis (CT) e o segundo, integrado por indivíduos-controles patológicos (DP), portadores de Depressão Maior, atendidos no Ambulatório de Psicogeriatria do Hospital das Clínicas da UFMG. Ambos os grupos (CT e DP) foram compostos por 15 indivíduos cada. O grupo AVE foi composto por 43 indivíduos e o grupo DPAVE por 15. Não houve diferença significativa entre os quatro grupos no que diz respeito à idade ($p=0,282$). No entanto, houve diferença na distribuição de gêneros, uma vez que ambos os grupos controle foram formados predominantemente por mulheres: 15 mulheres no grupo DEP e 14 no grupo CT ($p<0,001$).

4.2.2. Biomarcadores periféricos: comparação entre pacientes afetados por AVE com e sem depressão

Foram dosados os níveis plasmáticos das citocinas IL-2, IL-4, IL-6, IL-10, IL-17A, IFNγ, TNF e TWEAK; os receptores solúveis sTNFR1 e sTFNR2; as adipocinas Leptina e Adiponectina; os fatores neurotróficos BDNF, GDNF e NGF; as moléculas de adesão VCAM e E-Selectina; e a proteína STREM-1. As Figuras 3, 4 e 5 apresentam os resultados das dosagens, divididas em dois grupos, formados por pacientes afetados por AVE com e sem depressão, respectivamente.

Observou-se que indivíduos acometidos por DPAVE na fase aguda do AVE apresentaram níveis reduzidos de GDNF (Figura 4; $p=0,036$) e de STREM-1 (Figura 3; $p=0,0006$) em relação àqueles que se mantiveram eutímicos. Também foi observada uma

tendência à expressão reduzida de NGF entre pacientes com DPAVE (p=0,0587), porém sem atingir significância estatística.

Não foram observadas diferenças significativas entre pacientes com ou sem DPAVE no que se referiu à expressão das moléculas IL-2, IL-4, IL-6, IL-10, IL-17A, IFNγ, TNF, TWEAK, sTNFR1, sTFNR2, Leptina, Adiponectina, BDNF, VCAM e E-Selectina.

Na Tabela 1 e na Figura 6, apresentam-se os resultados do teste de correlação de Spearman entre os níveis dos biomarcadores avaliados e os escores da HADS. Observaram-se correlações inversas entre os níveis de GDNF, NGF e STREM-1 e os escores da HADS total (p=0,002; p=0,005; p=0,001, respectivamente), entre os níveis de GDNF e STREM-1 e os escores da HADS-D (p=0,011; p=0,014, respectivamente) e entre os níveis de NGF e STREM-1 e os escores da HADS-A (p=0,048; p=0,032, respectivamente). Não houve correlações estatisticamente significativas entre a HADS e os outros biomarcadores avaliados.

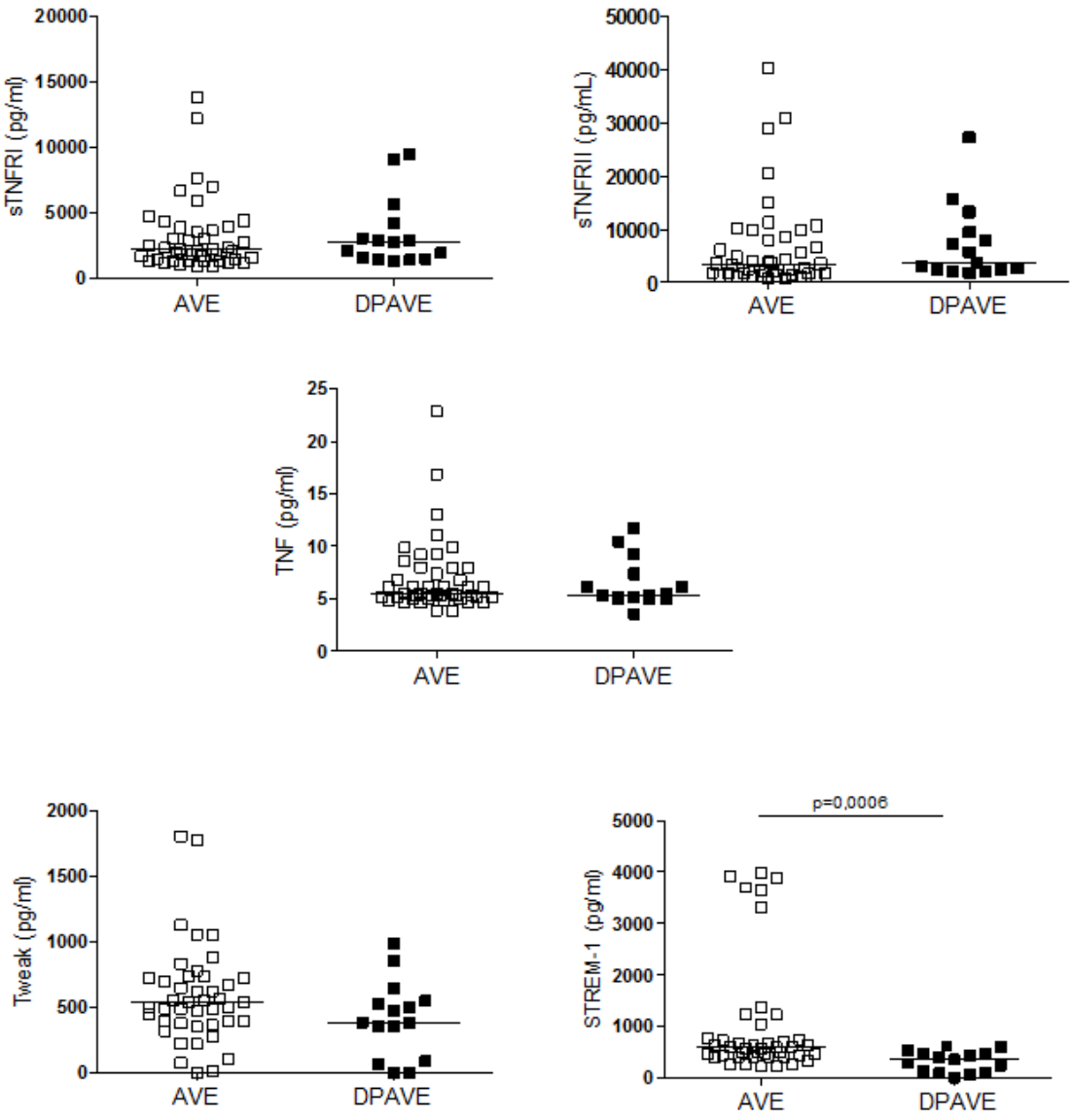

Figura 3: Dosagem plasmática de proteínas da super família do TNF em pacientes eutímicos afetados por acidente vascular encefálico (AVE) e pacientes com depressão pós-acidente vascular encefálico (DPAVE).

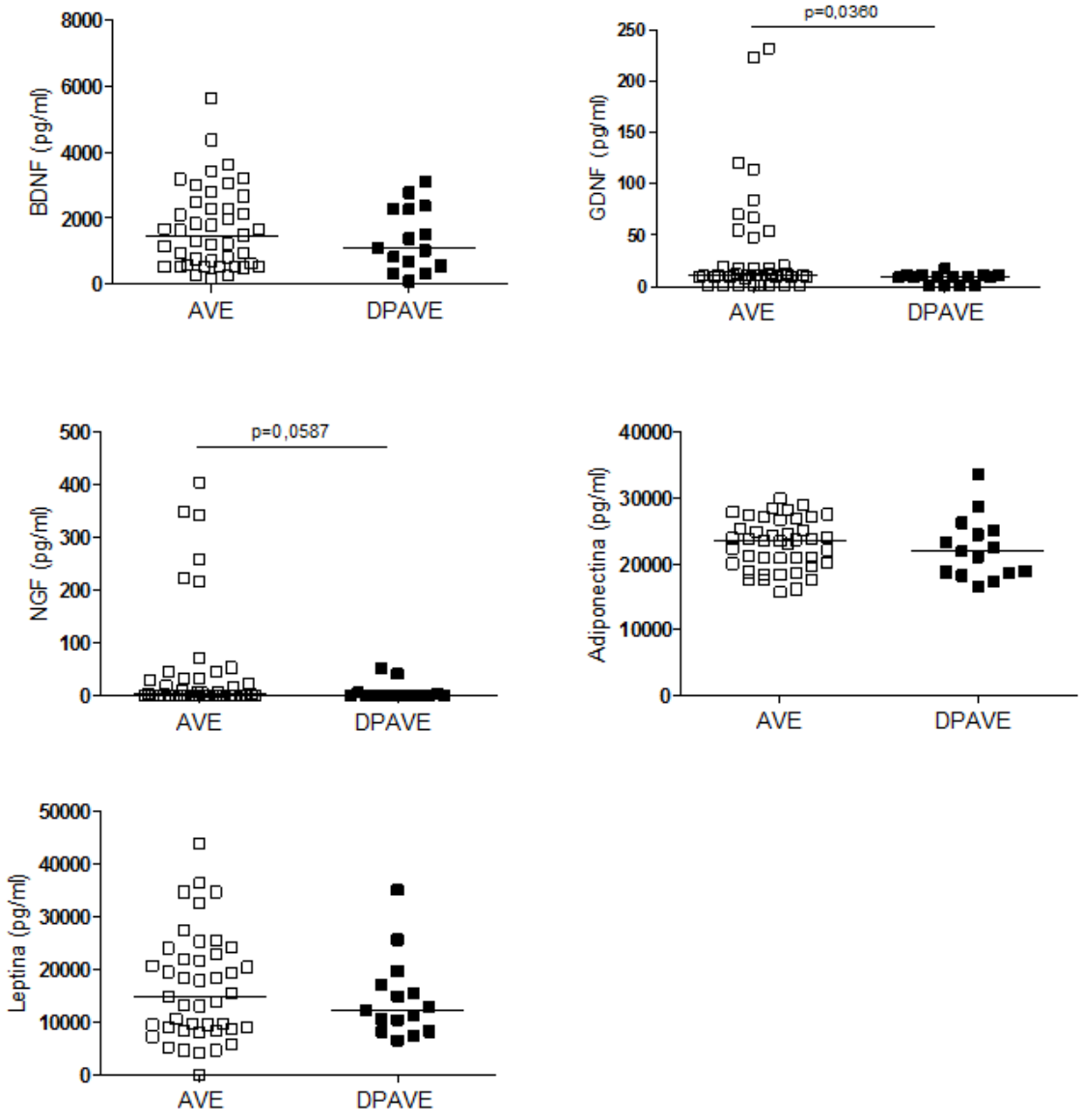

Figura 4: Dosagem plasmática de fatores neurotróficos e adipocinas em pacientes eutímicos afetados por acidente vascular encefálico (AVE) e pacientes com depressão pós-acidente vascular encefálico (DPAVE).

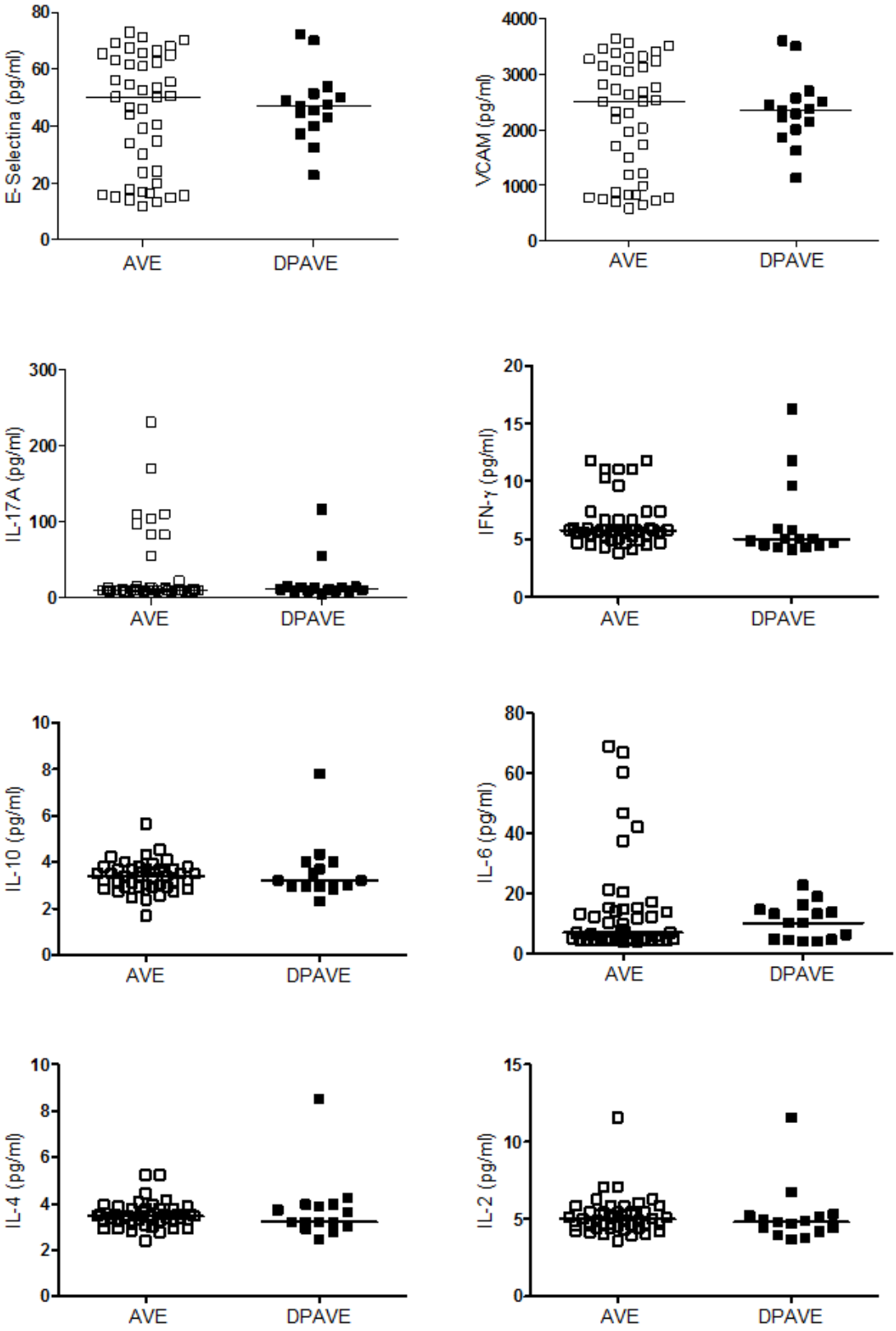

Figura 5: Dosagem plasmática de citocinas e moléculas de adesão solúveis em pacientes eutímicos afetados por acidente vascular encefálico (AVE) e pacientes com depressão pós-acidente vascular encefálico (DPAVE).

		Adiponectina	Leptina	BDNF	GDNF	NGF	sTNFR1	sTNFR2	IL-2	IL-4
HADS	rho	-0,189	0,015	-0,098	-0,434**	-0,395**	0,038	0,045	-0,132	0,083
	p	0,198	0,921	0,508	0,002	0,005	0,796	0,759	0,370	0,573
HADS-D	rho	-0,076	-0,031	-0,071	-0,364*	-0,271	0,116	0,158	-0,094	-0,042
	p	0,608	0,834	0,632	0,011	0,063	0,434	0,284	0,523	0,776
HADS-A	rho	-0,245	0,012	0,027	-0,275	-0,287*	-0,164	-0,225	-0,113	0,274
	p	0,094	0,933	0,853	0,058	0,048	0,265	0,124	0,444	0,060

		IL-6	IL-10	IL-17A	IFNγ	TNF	TWEAK	STREM-1	VCAM	E-Selectina
HADS	rho	-0,092	-0,170	0,045	-0,167	0,064	-0,178	-0,456**	0,016	0,016
	p	0,532	0,249	0,759	0,257	0,667	0,227	0,001	0,913	0,913
HADS-D	rho	-0,110	-0,059	0,005	-0,120	0,136	-0,070	-0,351*	0,099	0,099
	p	0,456	0,689	0,970	0,415	0,356	0,637	0,014	0,505	0,505
HADS-A	rho	-0,118	-0,204	0,025	-0,019	0,054	-0,086	-0,309*	0,030	0,030
	p	0,424	0,164	0,867	0,897	0,717	0,562	0,032	0,841	0,841

Tabela 1: Correlação entre escores da Escala Hospitalar de Ansiedade e Depressão (HADS) e suas subescalas de depressão (HADS-D) e de ansiedade (HADS-A) e os níveis periféricos de biomarcadores. (Teste de correlação de Spearman).

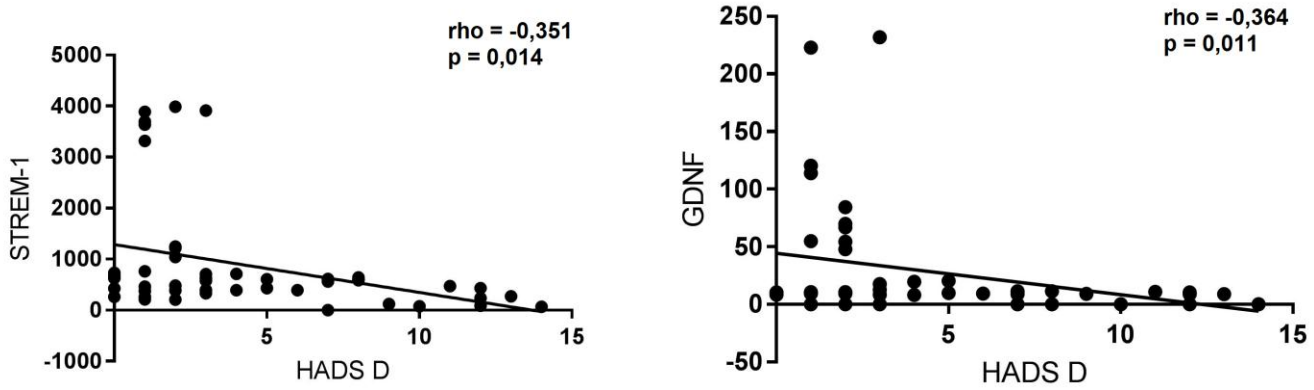

Figura 6: Correlação entre níveis plasmáticos de STREM-1 e pontuação na subescala de depressão da Escala Hospitalar de Ansiedade e Depressão (HADS-D).

4.2.3. Biomarcadores periféricos: comparação entre pacientes afetados por AVE com e sem depressão, pacientes com depressão sem AVE e indivíduos controles saudáveis.

Nas Figuras 7, 8 e 9, apresentam-se os resultados das comparações entre os grupos de pacientes com AVE e controles. Os indivíduos eutímicos afetados por AVE apresentaram níveis mais elevados de sTNFR1 ($p<0,001$), sTNFR2 ($p<0,05$), TWEAK ($p<0,001$), STREM-1 (<0,001), BDNF ($p<0,001$), Adiponectina ($p<0,001$), IL-6 ($p<0,001$) e IL-17A ($p<0,05$) em relação aos controles saudáveis (CT). Quando comparados aos indivíduos com depressão (DEP), os mesmos marcadores se mantiveram elevados ($p<0,001$; $p<0,01$; $p<0,001$; $p<0,01$; $p<0,01$; $p<0,001$; $p<0,001$; respectivamente), exceto por IL-17A. Os indivíduos com DPAVE apresentaram níveis mais elevados de sTNFR1 ($p<0,001$), sTNFR2 ($p<0,01$), BDNF ($p<0,01$), Adiponectina ($p<0,01$), IL-6 ($p<0,01$) e IL-17A ($p<0,05$) em relação aos controles saudáveis (CT), em padrão similar ao observado na comparação entre os grupos AVE e CT, exceto por TWEAK e STREM-1, que não se mantiveram aumentados. Quando comparados aos indivíduos com depressão (DEP), TWEAK voltou a se mostrar aumentado ($p<0,05$), acompanhado pelos mesmos marcadores encontrados na comparação frente ao grupo CT ($p<0,001$; $p<0,001$; $p<0,01$; $p<0,01$; $p<0,001$), exceto por IL-17A. Na comparação entre os grupos AVE e DPAVE, observou-se diminuição nos níveis de STREM-1 entre os indivíduos do último grupo ($p<0,01$), de forma similar ao descrito anteriormente.

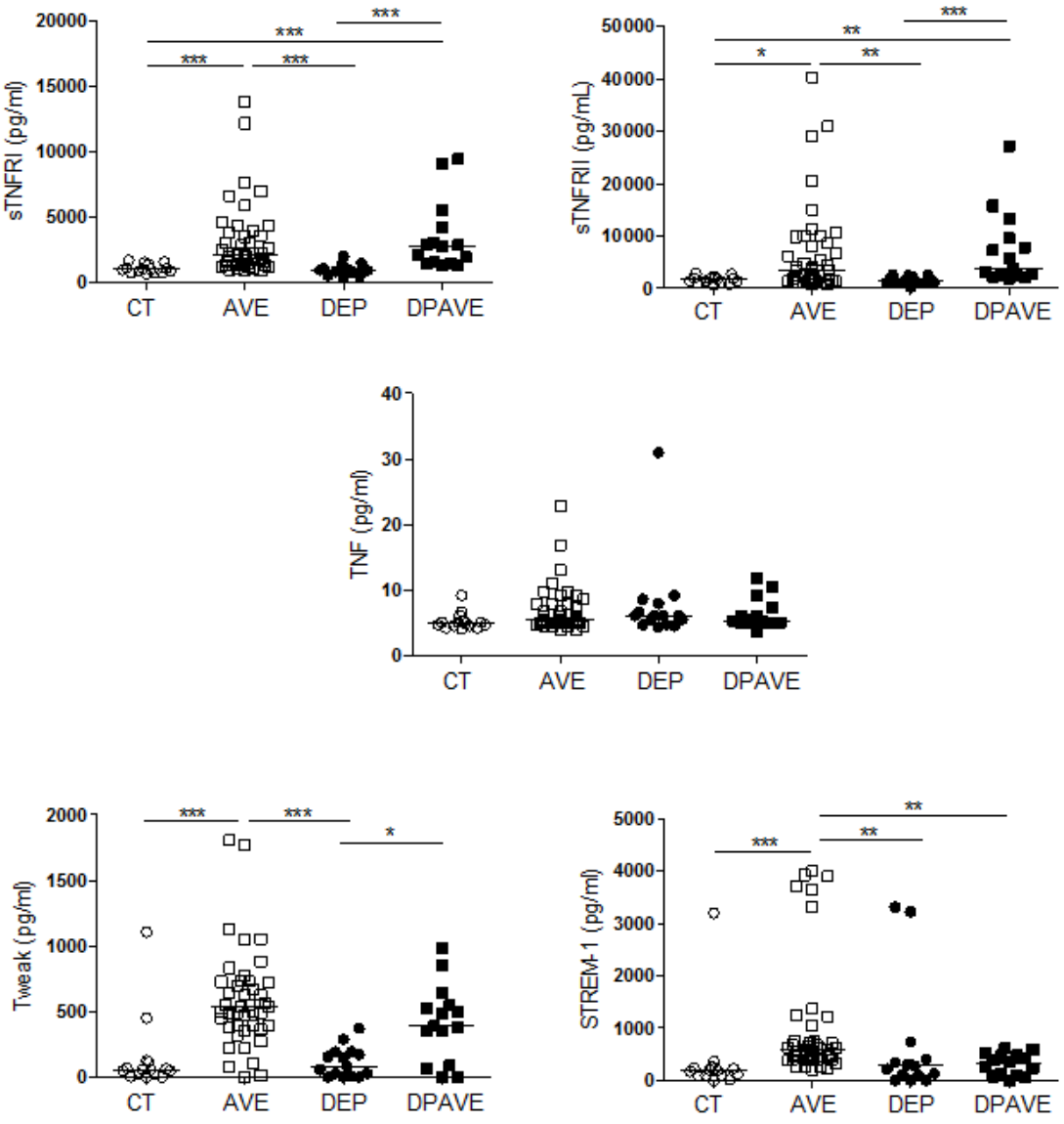

Figura 7: Dosagem plasmática de proteínas da super família do TNF em indivíduos controle eutímicos (CT), pacientes eutímicos afetados por acidente vascular encefálico (AVE), pacientes com depressão maior (DEP) e pacientes com depressão pós-acidente vascular encefálico (DPAVE).

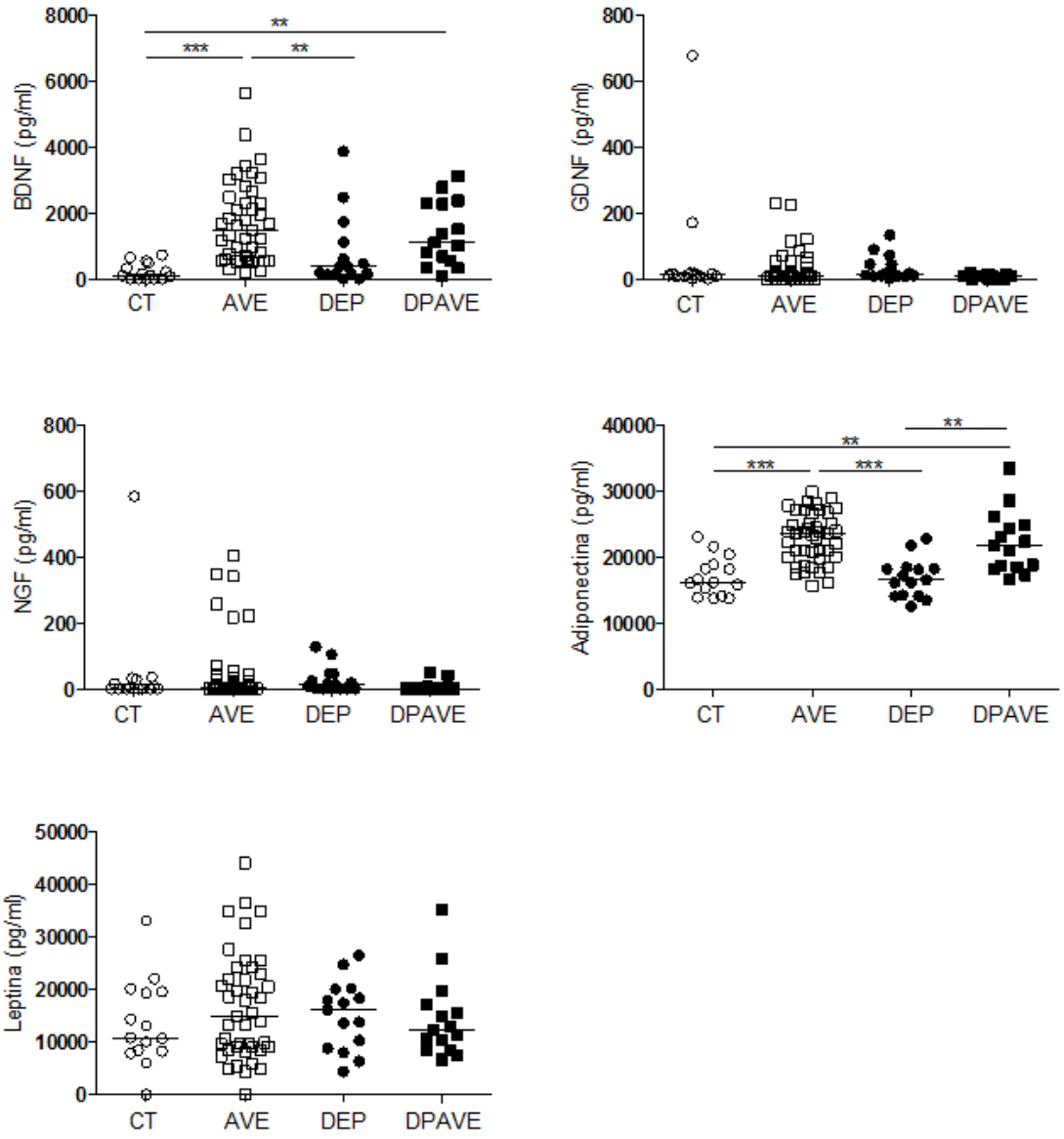

Figura 8: Dosagem plasmática de fatores neurotróficos e adipocinas em indivíduos controle eutímicos (CT), pacientes eutímicos afetados por acidente vascular encefálico (AVE), pacientes com depressão maior (DEP) e pacientes com depressão pós-acidente vascular encefálico (DPAVE).

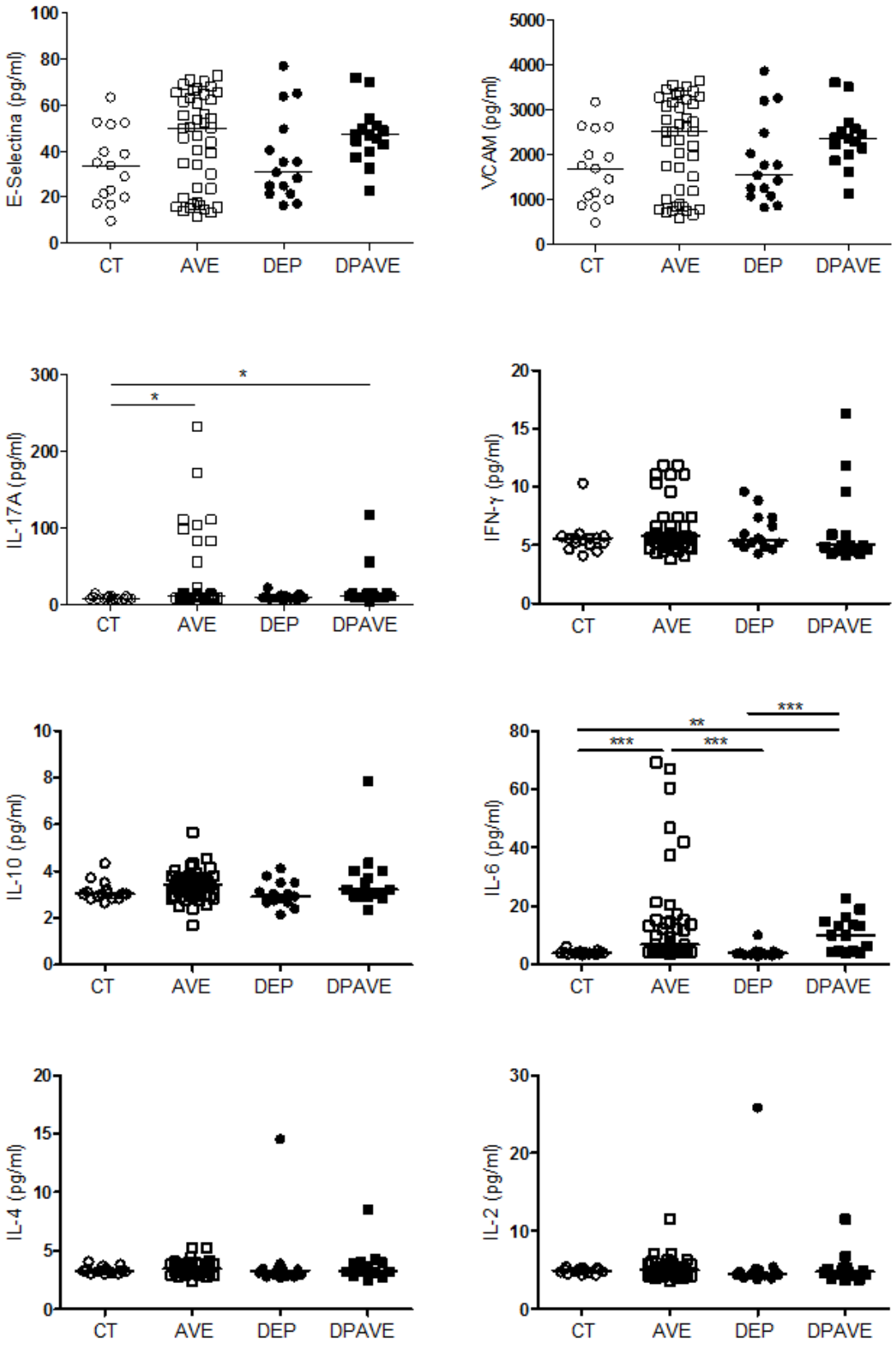

Figura 9: Dosagem plasmática de citocinas e moléculas de adesão solúveis em indivíduos controle eutímicos (CT), pacientes eutímicos afetados por acidente vascular encefálico (AVE), pacientes com depressão maior (DEP) e pacientes com depressão pós-acidente vascular encefálico (DPAVE).

5. Discussão

O presente trabalho envolveu pacientes acometidos por AVE isquêmico agudo, internados em um centro de referência municipal para o tratamento de eventos cerebrovasculares. Foi um estudo transversal, com o objetivo de avaliar a presença de comorbidades psiquiátricas entre esses pacientes e uma possível associação entre o desenvolvimento de depressão e a presença de biomarcadores periféricos.

A opção pela restrição ao estudo de indivíduos acometidos pelo tipo isquêmico de AVE se deu pelo fato de ser essa a forma mais comum, respondendo por mais de 80% dos casos (ANRATHER & IADECOLA, 2016). Nesse sentido, a fim de se buscar a eliminação de um fator de heterogeneidade na amostra, optou-se pela limitação aos casos de AVE isquêmico, com exclusão dos indivíduos afetados por AVE do tipo hemorrágico.

Após a realização de revisão sistemática, apresentada no Artigo 3, observamos que não havia evidências suficientes que indicassem a utilização de um biomarcador específico na avaliação da DPAVE. No entanto, a análise de diversos trabalhos permitiu observar, entre os indivíduos afetados por DPAVE, uma tendência a desequilíbrio pró e anti-inflamatório, redução da expressão de fatores neurotróficos, aumento no estresse oxidativo e na neurotransmissão glutamatérgica, além de fatores genéticos, que se mostrou mais aparente quando analisada nas fases precoces do AVE, especialmente na primeira semana. Nesse sentido, a opção pela avaliação de pacientes admitidos em unidade de AVE, em fase aguda, justificou-se, assim como a pesquisa de biomarcadores inflamatórios e de fatores neurotróficos.

Dessa forma, foram avaliados 60 pacientes, cujas características sócio-demográficas encontram-se discriminadas no Artigo 4. Houve predomínio de indivíduos do gênero masculino (70%), com média de idade de 64,3 anos ($\pm$ 8,79), principalmente pardos e negros (87%), sem companheiro afetivo (55%), fora do mercado de trabalho e com baixas escolaridade e renda mensal, constituindo uma população com vulnerabilidade social significativa para o desenvolvimento de transtornos mentais. A avaliação de comorbidades psiquiátricas nesses indivíduos por meio da aplicação do MINI-Plus revelou prevalência de 55% de algum transtorno mental, principalmente depressão (26,7%) e transtornos ansiosos (23,3%), estes últimos compostos por inúmeros quadros clínicos, incluindo fobias e transtornos ansioso generalizado, de pânico e de ajustamento.

A alta prevalência de comorbidades psiquiátricas entre os pacientes, assim como sua distribuição, com predomínio de quadros depressivos, confirmou os dados apresentados na revisão geral de literatura do Artigo 1. A obtenção desses dados é importante para contribuir com o conhecimento acerca de epidemiologia de transtornos mentais associados ao AVE no Brasil. Além disso, a presença de fatores de risco nessa população, tais como vulnerabilidade social, conforme apresentado no Artigo 2, chama a atenção para a importância da avaliação de depressão nesses pacientes e justifica seu estudo mais aprofundado.

Assim, no Artigo 5, investigamos as características dos indivíduos que desenvolveram DPAVE (grupo DPAVE) em comparação àqueles que permaneceram eutímicos (grupo AVE). Observamos que os indivíduos do grupo DPAVE apresentavam maior incapacidade medida pela mRS à admissão e pior desempenho funcional avaliado pela MIF do que os indivíduos do grupo AVE, dados que vão ao encontro de informações registradas na literatura. Na avaliação com o MEEM, observamos que os pacientes do grupo DPAVE apresentavam pior desempenho cognitivo, especialmente nas tarefas relacionadas à atenção e à linguagem. Em adição, os indivíduos do grupo DPAVE exibiram, com maior frequência, comorbidade com diabetes. O risco relativo para desenvolvimento de depressão no contexto de AVE em pacientes diabéticos foi de 3 (*odds ratio*: 6).

Existem evidências de que a prevalência de depressão é moderadamente aumentada em indivíduos pré-diabéticos e em pacientes diabéticos cujo diagnóstico ainda não foi estabelecido. Já em pacientes sabidamente portadores de diabetes, a prevalência de depressão é marcantemente aumentada em relação a indivíduos não-diabéticos (CHEN *et al*., 2016). As taxas de prevalência de depressão entre portadores de diabetes tipo I e tipo II podem ser, respectivamente, três e duas vezes mais altas do que na população em geral. Por outro lado, a depressão pode aumentar o risco do desenvolvimento de diabetes em 60% MEZUK *et al*., 2008). Dessa forma, parece haver uma associação bidirecional entre depressão e diabetes, em uma complexa relação que pode compartilhar mecanismos fisiopatológicos.

A aplicação da HADS mostrou-se adequada na avaliação de sintomas depressivos, na medida em que pacientes do grupo DPAVE apresentaram escores significativamente

diferentes daqueles do grupo AVE. Dessa forma, foi realizada análise por curva ROC e observamos que a escala apresentou boa capacidade para identificar casos de DPAVE, estabelecendo-se um ponto de corte de 6 para a HADS-D, com sensibilidade de 100% e especificidade de 99,17%. Esse foi o primeiro estudo a determinar um ponto de corte para a HADS em pacientes portadores de DPAVE no Brasil. Conforme discutido no Artigo 5, outros trabalhos internacionais já sugeriram pontos de corte que variam de 4 a 8 para a HADS-D em pacientes com AVE, em consonância com o que foi encontrado neste estudo (TANG *et* al., 2004; WICHOWICZ & WIECZOREK, 2011).

O passo seguinte foi realizar a investigação experimental de biomarcadores periféricos. A partir das análises realizadas, pudemos constatar que a ocorrência de AVE associa-se ao desencadeamento de uma intensa resposta imunológica, caracterizada pelo aumento da expressão de inúmeros marcadores, especialmente IL-6, Adiponectina, TWEAK, STREM-1, sTNFR1, sTNFR2 e BDNF.

Já está bem estabelecido que eventos isquêmicos no tecido nervoso geram processos inflamatórios complexos e dinâmicos, iniciados pela interrupção do fluxo sanguíneo, ativação de leucócitos intravasculares e liberação de mediadores pró-inflamatórios do endotélio isquêmico e do parênquima cerebral, os quais têm o potencial de aumentar a lesão tecidual ou de servir à recuperação da homeostase local. Inicialmente, moléculas de adesão, como E-Selectina ou VCAM, são induzidas rapidamente após a ativação endotelial pela isquemia, desempenhando um papel crucial no recrutamento de leucócitos circulantes, adesão e transmigração. A ativação do sistema complemento promove ruptura da barreira hematoencefálica, contribuindo para a invasão leucocitária do parênquima cerebral. As células necróticas liberam seu conteúdo para o meio extracelular, incluindo padrões moleculares associados ao dano (do inglês *damage-associated molecular patterns* ou DAMP), ou seja, moléculas intracelulares que ativam receptores específicos na micróglia, que passa a expressar mediadores inflamatórios, tais como interleucina-1β (IL-1β) e TNF, induzindo a produção de citocinas e quimiocinas pelos astrócitos e por células endoteliais. Há o desencadeamento de uma resposta imune generalizada, que se caracteriza pelo aumento da produção de diversas citocinas, tais como IL-6, a qual é suplantada, posteriormente, por um estado de imunossupressão sistêmica, associado à ativação do sistema nervoso autônomo simpático, que pode predispor a infecções e que se relaciona à

aumento da mortalidade em pacientes internados por AVE. Dessa forma, o encéfalo isquêmico exerce influência no sistema imunológico periférico, regulando o desenvolvimento e a homeostase das populações de células imunes do baço e da medula óssea, incluindo uma tendência a dirigir a hematopoiese em direção às células da linhagem mielóide, com participação fundamental da eferência simpática nesse processo. Além disso, mediadores com ação anti-inflamatória, tais como o fator transformador de crescimento beta (TGF-β) e a IL-10, também são produzidos por neurônios, astrócitos ou micróglia e o balanço entre estados pró ou anti-inflamatórios dependerá de uma série de fatores, como o contexto fisiológico e bioquímico do sistema nervoso central.

Na presença de depressão, observamos que houve uma alteração no padrão de marcadores associados à ocorrência de AVE, na medida em que os pacientes do grupo DPAVE apresentaram níveis reduzidos de STREM-1 e GDNF em comparação àqueles do grupo AVE. Os pacientes do grupo AVE, quando comparados aos pacientes do grupo controle Depressão Maior sem AVE (grupo DEP), apresentaram níveis mais elevados de IL-6, Adiponectina, TWEAK, STREM-1, sTNFR1, sTNFR2 e BDNF. No entanto, a ocorrência de depressão no contexto de AVE também alterou o padrão de marcadores elevados na comparação dos pacientes do grupo DPAVE com os pacientes do grupo DEP: observou-se aumento limitado a IL-6, Adiponectina, TWEAK,-1, sTNFR1, sTNFR2. Dessa forma, no que diz respeito à avaliação de biomarcadores, os pacientes do grupo DPAVE parecem ter exibido um padrão intermediário de resposta entre os grupos AVE e DEP, caracterizado principalmente por diferenças na expressão de STREM-1 e de neurotrofinas, especialmente GDNF.

A proteína STREM-1 é um membro da superfamília imunoglobulina expressa por neutrófilos, macrófagos e monócitos, que aumenta após estímulos patogênicos, como infecções por bactérias ou fungos. Ela apresenta efeitos pró-inflamatórios, estimulando a liberação de interleucina-8 (IL-8), TNF e IL-1β, enquanto inibe IL-10. Diversos estudos têm investigado a associação entre altos níveis de STREM-1 e aumento de mortalidade em pacientes com quadros infecciosos ou inflamatórios, como sepse, por exemplo. Ravetti e colaboradores (2015) observaram que pacientes com câncer em contexto séptico apresentavam níveis reduzidos de STREM-1 do que pacientes sem doença oncológica, apesar de que níveis mais elevados da proteína se associaram a aumento da mortalidade

entre os pacientes com câncer (RAVETTI *et al*., 2015). Weigelt e colaboradores (2011) observaram aumento na expressão de TREM-1 (a forma não solúvel de STREM-1) em monócitos de pacientes com esquizofrenia e com transtorno bipolar do humor (TBH), mas não nas células de pacientes com depressão maior, sugerindo que os monócitos de pacientes com depressão apresentariam um estado inflamatório distinto daquele de pacientes com esquizofrenia ou TBH (WEIGELT *et al*., 2011). Assim, diferentes estados de ativação do sistema imune, como no caso de pacientes com câncer ou com TBH, poderiam influenciar na expressão de STREM-1.

A proteína TREM-1 é expressa por células gliais (micróglia) e essa relação é interessante, ao considerarmos a redução dos níveis de GDNF observada em nossa amostra (FORD *et al*., 2009). O GDNF é um membro da superfamília do fator de transformação do crescimento-β, distribuído extensivamente pelo cérebro de mamíferos, incluindo o hipotálamo, a substância negra e o tálamo. Promove a diferenciação de neurônios dopaminérgicos e serotoninérgicos e pode estimular o crescimento de neuritos em vários tipos neuronais (SHARMA *et al*., 2016). Além disso, há evidências de que o GDNF pode exercer função protetora contra lesões oxidativas e neuro-inflamatórias para células derivadas de neurônios mesencefálicas, neurônios serotoninérgicos do núcleo da rafe dorsal, neurônios dopaminérgicos mesencefálicos e, por fim, células gliais (UZDENSKY *et al*., 2013)

Dessa forma, os achados, até então, parecem apontar para uma influência da glia no aparecimento de sintomas depressivos pós-AVE. De fato, a ideia de que células do sistema mononuclear poderiam estar envolvidas na fisiopatologia da depressão levou à formulação da "teoria do macrófago da esquizofrenia e da depressão" em 1992, com posterior adaptação em 1995 (SMITH, 1992; SMITH & MAES, 1995). Essa hipótese postula que macrófagos cronicamente ativados (incluindo seus correlatos no sistema nervoso central, ou seja, a micróglia) e células T produzem citocinas e compostos inflamatórios que impactam no desenvolvimento cerebral e predispõem o cérebro de tal forma que influências genéticas ou ambientais tornam-se capazes de precipitar os sintomas de esquizofrenia ou de depressão.

Apesar de que os mecanismos etiológicos da depressão ainda não estejam claros, há evidências de que a desregulação na produção de fatores neurotróficos também

desempenha papel importante na patogênese do transtorno. Neste sentido, já foram relatadas alterações na expressão de diversos tipos de fatores neurotróficos em pacientes com depressão, incluindo BDNF, NGF, neurotrofina-3, fator de crescimento endotelial vascular e fator de crescimento semelhante à insulina-1. Com relação ao GDNF, a literatura apresenta resultados heterogêneos, porém uma meta-análise que incluiu 12 estudos que avaliaram a associação dessa neurotrofina com transtornos de humor encontrou evidências de que há uma tendência à redução dos níveis periféricos de GDNF na depressão (LIN *et al*., 2015). Estudos pré-clínicos indicaram que animais expostos a estresse crônico imprevisível, um modelo experimental de depressão, exibiam comportamento de tipo depressivo e apresentavam redução dos níveis hipocampais de GDNF (SHARMA *et al*., 2016).

A ativação microglial pode ser parte de uma ativação sistêmica do sistema mononuclear fagocitário em geral e existem indícios da ativação de monócitos circulantes em pacientes com diversos transtornos psiquiátricos. Além disso, inúmeras condições clínicas já foram associadas à ativação microglial, tais como hepatite, deficiência de tiamina, privação de sono, e, de forma controversa, diabetes. Apesar de ser uma condição associada à inflamação sistêmica crônica leve, alguns trabalhos falharam em demonstrar ativação microglial no sistema nervoso central associada à diabetes (VAN DER HARG *et al*., 2015), ao passo que outros trabalhos com humanos ou animais demonstraram ativação de micróglia tanto no encéfalo, como na medula espinhal ou na retina (WANG *et al*., 2014; SRODULSKI *et al*., 2014; MADEIRA *et al*., 2015). Em um trabalho com animais não-obesos diabéticos (NOD), um modelo murino de diabetes autoimune, McGuiness e colaboradores (2016) observaram que, após um estímulo imune (injeção de lipopolissacarídeos, LPS), os animais apresentaram aumentos na taxa de proliferação microglial, na inflamação cerebral, redução na produção de neurotrofinas, maior perda de peso corporal e comportamento de doente (*sickness behavior*) mais prolongado (MCGUINESS *et al*., 2016). Por sua vez, Wang e colaboradores (2013) observaram que a inibição da micróglia em ratos correlacionou-se a níveis reduzidos de GDNF, aumento da expressão de TNF e maior déficit funcional sete dias após isquemia cerebral (WANG *et al*., 2013).

Dessa forma, seria possível que indivíduos portadores de diabetes pudessem apresentar alterações inflamatórias crônicas, as quais, por sua vez, induzissem modificações no padrão de ativação microglial que se associariam ao desencadeamento de manifestações depressivas na vigência de um insulto isquêmico cerebral, tornando tais pacientes mais vulneráveis à DPAVE?

Segundo a literatura, diferentes fatores ambientais podem ativar vias fisiopatológicas que, em última instância, acabam por promover depressão e diabetes (BĂDESCU *et al*., 2016). Dentre tais fatores, baixo nível socioeconômico, restrição de sono, inadequação dietética e sedentarismo aparecem frequentemente ligados a ambas as condições. Em conjunto, todos eles parecem se associar à ativação e à perturbação do sistema de estresse. Sabe-se que o estresse crônico associa-se a uma série de eventos, que incluem a ativação do eixo hipotálamo-hipófise-adrenal e do sistema nervoso autônomo simpático, levando ao aumento dos níveis de cortisol e catecolaminas e disfunção do sistema imunológico, estabelecendo um estado pró-inflamatório relacionado a alterações no metabolismo de neurotransmissores, na função neuroendócrina, na plasticidade sináptica e, por fim, no comportamento (MURIACH *et al*., 2014)

Há evidencias de que a diabetes promove uma série de alterações cerebrais estruturais caracterizadas por atrofia difusa e infartos lacunares, com modificações no fluxo sanguíneo associadas tanto a hipo quanto a hiperperfusão. (VAN HARTEN *et al.*, 2006). Reduções volumétricas restritas ao hipocampo já foram relatadas em pacientes diabéticos, ao passo que uma relação inversa entre controle glicêmico e volume hipocampal já foi descrita (GOLD *et al*., 2007). De forma similar, a depressão tem sido associada a processos neurodegenerativos, especialmente nas regiões pré-frontais e hipocampais (SAPOLSKY, 2001).

Enquanto existe ampla evidência de que interações desreguladas entre fagócitos locais aberrantes, células dentríticas e células T formam as bases imunológicas da patogênese de doenças autoimunes, há uma lacuna na compreensão da fisiopatologia dos transtornos de humor. Entretanto, existem evidências crescentes de que a inflamação leve crônica do cérebro pode desempenhar um papel crítico no seu desenvolvimento (BEUMER *et al*., 2012). Neste sentido, já foi estabelecida uma ligação entre ativação pró-inflamatória de monócitos e da micróglia e transtornos de humor, ao menos em um subgrupo de

pacientes. Em nossa amostra, um achado interessante foi a correlação inversa observada entre a intensidade de sintomas depressivos avaliada pela HADS e os níveis periféricos de STREM-1 e GDNF, sugerindo a possibilidade de influência de mecanismos inflamatórios na manifestação de tais sintomas.

Por fim, nosso trabalho apresenta limitações associadas ao fato de ser um estudo transversal, com amostra relativamente pequena. Futuros trabalhos que envolvam o seguimento longitudinal, com aumento no tamanho da amostra e que avaliem de forma mais pormenorizada a função do sistema mononuclear fagocitário podem auxiliar a esclarecer as questões levantadas por este estudo.

6. Conclusões

- Pacientes afetados por acidente vascular encefálico isquêmico agudo apresentam alta prevalência de comorbidades psiquiátricas, especialmente depressão e transtornos ansiosos.
- Pacientes diabéticos têm risco aumentado em três vezes de desenvolver depressão pós-AVE do que indivíduos não diabéticos.
- O ponto de corte igual a 6 na subescala de depressão da Escala Hospitalar de Ansiedade e Depressão (HADS) foi capaz de identificar indivíduos com depressão pós-AVE com sensibilidade de 100% e especificidade de 99,17%.
- Pacientes que desenvolvem depressão pós-AVE apresentam níveis reduzidos de STREM-1 e GDNF em relação aos indivíduos que permanecem eutímicos.
- Os níveis de STREM-1 e GDNF se correlacionaram de forma inversa com a intensidade de sintomas depressivos quantificados pela HADS.

7. Referências

1. ADAMS JR HP, BENDIXEN BH, KAPPELLE LJ, BILLER J, LOVE BB, GORDON DL, MARSH EE 3RD. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. **Stroke**. 1993; vol. 24, 1: 35-41.

2. ADLER R, MACRITCHIE K, ENGEL GL. Psychologic processes and ischemic stroke (occlusive cerebrovascular disease), I: observations on 32 men with 35 strokes. **Psychosom Med.** 1971; 33(1): 1-29.

3. ALEXOPOULOS GS, GLATT CE, HOPTMAN MJ, KANELLOPOULOS D, MURPHY CF, KELLY RE JR, MORIMOTO SS, LIM KO, GUNNING FM. BDNF Val66met polymorphism, white matter abnormalities and remission of geriatric depression. **J Affect Disord.** 2010; 125: 262–68.

4. ALEXOPOULOS GS, MEYERS BS, YOUNG RC, CAMPBELL S, SILBERSWEIG D, CHARLSON M. Vascular depression hypothesis. **Arch Gen Psychiatry.** 1997; 54(10): 915-22.

5. AMERICAN HEART ASSOCIATION STATISTICS COMMITTEE AND STROKE STATISTICS SUBCOMMITTEE. Heart disease and stroke statistics – 2013 update: a report from the American Heart Association. **Circulation.** 2013; 127 (1): e6-e245.

6. AMERICAN PSYCHIATRIC ASSOCIATION. **Diagnostic and statistical manual of mental disorders.** 5ª ed. Arlington: American Psychiatric Publishing, 2013.

7. AMORIM P. Mini International Neuropsychiatric Interview (MINI): validation of a short structured diagnostic psychiatric interview. **Rev Bras Psiquiatr.** 2000; 22 (3): 106-115.

8. ANDERSEN G, VESTERGAARD K, RIIS J. Citalopram for post-stroke pathological crying. **Lancet.** 1993; 342(8875): 837-9.

9. ANDERSON RJ, FREEDLAND KE, CLOUSE RE, LUSTMAN PJ. The prevalence of comorbid depression in adults with diabetes. **Diabetes Care**. 2001; 24 (6): 1069–78.

10. ANGELELLI P, PAOLUCCI S, BIVONA U, PICCARDI L, CIURLI P, CANTAGALLO A, ANTONUCCI G, FASOTTI L, DI SANTANTONIO A, GRASSO MG, PIZZAMIGLIO L. Development of neuropsychiatric symptoms in poststroke patients: a cross-sectional study. **Acta Psychiatr Scand.** 2004; 110 (1): 55-63.

11. ANGUELOVA M, BENKELFAT C, TURECKI G. A systematic review of association studies investigating genes coding for serotonin receptors and the serotonin transporter: I. Affective disorders. **Mol Psychiatry**. 2003; 8: 574-91.

12. ANRATHER J, IADECOLA C. Inflammation and Stroke: An Overview. **Neurotherapeutics**. 2016; 13(4): 661-70.

13. ASTROM M, ADOLFSSON R, ASPLUND K. Major depression in stroke patients: a 3-year longitudinal study. **Stroke.** 1993; 24(7): 976-82.

14. ASTROM M. Generalized anxiety disorder in stroke patients. A 3-year longitudinal study. **Stroke.** 1996; 27(2): 270-5.

15. AYERBE L, AYIS S, CRICHTON S, WOLFE CD, RUDD AG. The natural history of depression up to 15 years after stroke: the South London Stroke Register. **Stroke.** 2013; 44 (4): 1105-10.

16. AYERBE L, AYIS S, WOLFE CD, RUDD AG. Natural history, predictors and outcomes of depression after stroke: systematic review and meta-analysis. **Br J Psychiatry.** 2013; 202 (1): 14-21.

17. BĂDESCU SV, TĂTARU C, KOBYLINSKA L, GEORGESCU EL, ZAHIU DM, ZĂGREAN AM, ZĂGREAN L. The association between Diabetes mellitus and Depression. **J Med Life.** 2016; 9(2): 120-5.

18. BAMFORD J, SANDERCOCK P, DENNIS M, BURN J, WARLOW C. Classification and natural history of clinical subtypes of cerebral infarction. **Lancet.** 1991; 337(8756): 1521-6.

19. BARBOSA IG, BAUER ME, MACHADO-VIEIRA R, TEIXEIRA AL. Cytokines in bipolar disorder: paving the way for neuroprogression. **Neural Plast.** 2014; 2014: 360481.

20. BÉJOT Y, ABOA-EBOULÉ C, DURIER J, ROUAUD O, JACQUIN A, PONAVOY E, RICHARD D, MOREAU T, GIROUD M.. Prevalence of early dementia after first-ever stroke: a 24-year population-based study. **Stroke.** 2011; 42(3): 607-12.

21. BENSIMON K, HERRMANN N, SWARDFAGER W, YI H, BLACK SE, GAO FQ, SNAIDERMAN A, LANCTÔT KL. Kynurenine and depressive symptoms in a poststroke population. **Neuropsychiatr Dis Treat.** 2014; 10: 1827-35.

22. BEUMER W, GIBNEY SM, DREXHAGE RC, PONT-LEZICA L, DOORDUIN J, KLEIN HC, STEINER J, CONNOR TJ, HARKIN A, VERSNEL MA, DREXHAGE HA. The immune theory of psychiatric diseases: a key role for activated microglia and circulating monocytes. **J Leukoc Biol.** 2012; 92(5): 959-75.

23. BHOGAL SK, TEASELL R, FOLEY N, SPEECHLEY M. Lesion location and poststroke depression: systematic review of the methodological limitations in the literature. **Stroke.** 2004; 35(3): 794-802.

24. BJELLAND I, DAHL AA, HAUG TT, NECKELMANN D. The validity of the Hospital Anxiety and Depression Scale. An updated literature review. **J Psychosom Res.** 2002; 52 (2): 69-77.

25. BOSSÙ P, SALANI F, CACCIARI C, PICCHETTO L, CAO M, BIZZONI F, RASURA M, CALTAGIRONE C, ROBINSON RG, ORZI F, SPALLETTA G. Disease outcome, alexithymia and depression are differently associated with serum IL-18 levels in acute stroke. **Curr Neurovasc Res**. 2009; 6: 163-70.

26. BOZIKAS VP, GOLD G, KOVARI E, HERRMANN F, KARAVATOS A, GIANNAKOPOULOS P, BOURAS C. Pathological correlates of poststroke depression in elderly patients. **Am J Geriatr Psychiatry.** 2005; 13(2): 166-9.

27. BRODATY H, SACHDEV PS, WITHALL A, ALTENDORF A, VALENZUELA MJ, LORENTZ L. Frequency and clinical, neuropsychological and neuroimaging correlates of apathy following stroke – the Sydney Stroke Study. **Psychol Med.** 2005; 35(12): 1707-16.

28. BRODERICK JP, PHILIPS SJ, WHISNAT JP, O'FALLON WM, BERGSTRALH EJ. Incidence rates of strokes in the eighties: the decline in stroke. **Stroke.** 1989; 20(5): 577-82.

29. BROOMFIELD NM, QUINN TJ, ABDUL-RAHIM AH, WALTERS MR, EVANS JJ. Depression and anxiety symptoms post-stroke/TIA: prevalence and associations in cross-sectional data from a regional stroke registry. **BMC Neurol.** 2014; 14: 198.

30. BROTT T, ADAMS HP, JR, OLINGER CP, MARLER JR, BARSAN WG, BILLER J, SPILKER J, HOLLERAN R, EBERLE R, HERTZBERG V. Measurements of acute cerebral infarction: a clinical examination scale. **Stroke.** 1989; 20 (7): 864–70.

31. BROWN C, HASSON H, THYSELIUS V, ALMBORG AH. Post-stroke depression and functional independence: a conundrum. **Acta Neurol Scand.** 2012; 126: 45–51.

32. BRYER JB, STARKSTEIN SE, VOTYPKA V, PARIKH RM, PRICE TR, ROBINSON RG. Reduction of CSF monoamine metabolites in poststroke depression: a preliminary report. **J Neuropsychiatry Clin Neurosci.** 1992; 4(4): 440-2.

33. BUENO VF, BRUNONI AR, BOGGIO PS, BENSENOR IM, FREGNI F. Mood and cognitive effects of transcranial direct current stimulation in post-stroke depression. **Neurocase.** 2011; 17(4): 318-22.

34. BUIJCK BI, ZUIDEMA SU, SPRUIT-VAN EIJK M, GEURTS AC, KOOPMANS RT. Neuropsychiatric symptoms in geriatric patients admitted to skilled nursing facilities in nursing homes for rehabilitation after stroke: a longitudinal multicenter study. **Int J Geriatr Psychiatry.** 2012; 27(7): 734-41.

35. BURTON CAC, HOLMES J, MURRAY J, GILLESPIE D, LIGHTBODY CE, WATKINS CL, KNAPP P. Interventions for treating anxiety after stroke. **Cochrane Database Syst Rev**. 2011; (12): CD008860.

36. BURVILL PW, JOHNSON GA, JAMROZIK KD, ANDERSON CS, STEWART-WYNNE EG, CHAKERA TM. Prevalence of depression after stroke: the Perth Community Stroke Study. **Br J Psychiatry.** 1995; 166(3): 320-7.

37. CALVERT T, KNAPP P, HOUSE A. Psychological associations with emotionalism after stroke. **J Neurol Neurosurg Psychiatry.** 1998; 65(6): 928-9.

38. CAMPBELL BURTON CA, MURRAY J, HOLMES J, ASTIN F, GREENWOOD D, KNAPP P. Frequency of anxiety after stroke: a systematic review and meta-analysis of observational studies. **Int J Stroke.** 2013; 8(7): 545-59.

39. CAROD-ARTAL FJ, TRIZOTTO DS, CORAL LF, MOREIRA CM. Determinants of quality of life in Brazilian stroke survivors. **J Neurol Sci.** 2009; 284 (1-2): 63-8.

40. CAROTA A, BERNEY A, AYBEK S, IARIA G, STAUB F, GHIKA-SCHMID F, ANNABLE L, GUEX P, BOGOUSSLAVSKY J. A prospective study of predictors of poststroke depression. **Neurology.** 2005; 64(3): 428-33.

41. CAROTA A, DIEGUEZ S, BOGOUSSLAVSKY J. Psychopathology of stroke. **Psychol Neuropsychiatr Vieil.** 2005; 3(4): 235-49.

42. CAROTA A, ROSSETTI AO, KARAPANAYIOTIDES T, BOGOUSSLAVSKY J. Catastrophic reaction in acute stroke: a reflex behavior in aphasic patients. **Neurology.** 2001; 57(10): 1902-5.

43. CARSON AJ, MACHALE S, ALLEN K, LAWRIE SM, DENNIS M, HOUSE A, et SHARPE M. Depression after stroke and lesion location: a systematic review. **Lancet.** 2000; 356(9224): 122-6.

44. CHAN KL, CAMPAYO A, MOSER DJ, ARNDT S, ROBINSON RG. Aggressive behavior in patients with stroke: association with psychopathology and results of antidepressant treatment on aggression. **Arch Phys Med Rehabil.** 2006; 87(6): 793-8.

45. CHEMERINSKI E, ROBINSON RG. The neuropsychiatry of stroke. **Psychosomatics.** 2000; 41 (1): 5-14.

46. CHEN S, ZHANG Q, DAI G, HU J, ZHU C, SU L, WU X. Association of depression with pre-diabetes, undiagnosed diabetes, and previously diagnosed diabetes: a meta-analysis. **Endocrine.** 2016; 53(1): 35-46.

47. CHENG SY, ZHAO YD, LI J, CHEN XY, WANG RD, ZENG JW. Plasma levels of glutamate during stroke are associated with development of post-stroke depression. **Psychoneuroendocrinology.** 2014; 47: 126-35.

48. CHOLLET F, TARDY J, ALBUCHER JF, THALAMAS C, BERARD E, LAMY C, BEJOT Y, DELTOUR S, JAILLARD A, NICLOT P, GUILLON B, MOULIN T, MARQUE P, PARIENTE J, ARNAUD C, LOUBINOUX I. Fluoxetine for motor recovery after acute ischaemic stroke (FLAME): a randomised placebo-controlled trial**.** **Lancet Neurol.** 2011; 10(2):123-30.

49. CLARKE DM, KISSANE DW. Demoralization: its phenomenology and importance. **Aust NZJ Psychiatry**. 2002; 36(6): 733-42.

50. CRAFT TK, DEVRIES AC. Role of IL-1 in poststroke depressive-like behavior in mice. **Biol Psychiatry.** 2006; 60(8): 812-8.

51. CUMMING TB, CHURILOV L, SKOOG I, BLOMSTRAND C, LINDEN T. Little evidence for different phenomenology in poststroke depression. **Acta Psychiatr Scand.** 2010; 121(6): 424-30.

52. D'Agostino RB Sr, Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, KANNEL WB. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. **Circulation.** 2008; 117 (6): 743–53.

53. DAM H, PEDERSEN HE, DAMKJAER M, AHLGREN P. The dexamethasone suppression test in depressive stroke patients. **Acta Neurol Stand.** 1991; 84: 14-7.

54. DAM H, PEDERSEN HE, DIGE-PETERSEN H, AHLGREN P. Neuroendocrine tests in depressive stroke patients. **Prog Neuropsychopharmacol Biol Psychiatry**. 1994; 18: 1005-13.

55. DE CARVALHO JJ, ALVES MB, VIANA GA, MACHADO CB, DOS SANTOS BF, KANAMURA AH, LOTTENBERG CL, NETO MC, SILVA GS. Stroke epidemiology, patterns of management, and outcomes in Fortaleza, Brazil: a hospital-based multicenter prospective study. **Stroke.** 2011; 42(12): 3341-6.

56. DE MELLO RF, SANTOS IDE S, ALENCAR AP, BENSEÑOR IM, LOTUFO PA, GOULART AC. Major Depression as a Predictor of Poor Long-Term Survival in a Brazilian Stroke Cohort (Study of Stroke Mortality and Morbidity in Adults) EMMA study. **Journal of Stroke and Cerebrovascular Diseases.** 2016; 25(3): 618-25.

57. DONG JY, ZHANG YH, TONG J, QIN LQ. Depression and risk of stroke: a meta-analysis of prospective studies. **Stroke.** 2012; 43(1): 32-7.

58. EASTWOOD MR, RIFAT SL, NOBBS H, RUDERMAN J. Mood disorder following cerebrovascular accident. **Br J Psychiatry.** 1989; 154: 195-200.

59. ELLIS HD. The role of the right hemisphere in the Capgras delusion. **Psychopathology.** 1994; 27(3-5): 177-85.

60. EVERSON SA, KAPLAN GA, GOLDBERG DE, LAKKA TA, SIVENIUS J, SALONEN JT. Anger expression and incident stroke: prospective evidence from the Kuopio Ischemic Heart Disease Study. **Stroke.** 1999; 30(3): 523-8.

61. FÁBREGAS BC, VITORINO FD, ROCHA DM, MOURA AS, CARMO RA, TEIXEIRA AL. Screening inventories to detect depression in chronic hepatitis C patients. **Gen Hosp Psychiatry.** 2012; 34(1):40-5.

62. FAVROLE P, JEHEL L, LEVY P, DESCOMBES S, MURESAN IP, MANIFACIER MJ, ALAMOWITCH S. Frequency and predictors of post-traumatic stress disorder after stroke: a pilot study. **J Neurol Sci.** 2013; 327(1-2): 35-40.

63. FEDOROFF JP, STARKSTEIN SE, PARIKH RM, PRICE TR, ROBINSON RG. Are depressive symptoms nonspecific in patients with acute stroke? **Am J Psychiatry.** 1991; 148(9): 1172-6.

64. FEINBERG TE, SHAPIRO RM. Misidentification: reduplication and the right hemisphere. **Neuropsych Neuropsychol Behav Neurol.** 1989; 2(1): 39-48.

65. FIGUEIREDO JM, FRANK JD. Subjective incompetence, the clinical hallmark of demoralization. **Compr Psychiatry.** 1982; 23(4): 353-63.

66. FIGUEIREDO JM. Depression and demoralization: phenomenologic differences and research perspectives. **Compr Psychiatry.** 1993; 34(5): 308-11.

67. FIGUEIREDO JM. Some issues in research on the epidemiology of demoralization. **Compr Psychiatry.** 1983; 24(2): 154-7.

68. FINKLESTEIN S, BENOWITZ LI, BALDESSARINI RJ, ARANA GW, LEVINE D, WOO E, BEAR D, MOYA K, STOLL AL. Mood, vegetative disturbance and dexamethasone suppression test after stroke. **Ann Neurol.** 1982; 12: 463-8.

69. FLEMINGER S, BURNS A. The delusional misidentification syndromes in patients with and without evidence of organic cerebral disorder: a structured review of case reports. **Biol Psychiatry.** 1993; 33(1): 22-32.

70. FOLSTEIN MF, FOLSTEIN SE, MCHUGH PR. 1975. Mini-mental state: a practical method for grading the cognitive state of patients for the clinician. J **Psychiatric Res.** 1975; 12 (3): 189-98.
71. FOLSTEIN MF, MAIBERGER R, MCHUGH PR. Mood disorder as a specific complication of stroke. **J Neurol Neurosurg Psychiatry.** 1977; 40(10): 1018-20.

72. FORD JW, MCVICAR DW. TREM and TREM-like receptors in inflammation and disease. **Curr Opin Immunol.** 2009; 21(1): 38-46.

73. FORSTL H, ALMEIDA OP, OWEN AM, BURNS A, HOWARD R. Psychiatric, neurological and medical aspects of misidentification syndromes: a review of 260 cases. **Psychol Med.** 1991; 21(4): 905-10.

74. FRÓES KS, VALDÉS MT, LOPES DDE P, SILVA CE. Factors associated with health-related quality of life for adults with stroke sequelae. **Arq Neuropsiquiatr.** 2011; 69(2B): 371-6.

75. GAINOTTI G, AZZONI A, MARRA C. Frequency, phenomenology and anatomical-clinical correlates of major post-stroke depression. **Br J Psychiatry.** 1999; 175: 163-7.

76. GIANTURCO DT, BRESLIN MS, HEYMAN A, GENTRY WD, JENKINS CD, KAPLAN B. Personality patterns and life stress in ischemic cerebrovascular disease, I: psychiatric findings. **Stroke.** 1974; 5(4): 453-60.

77. GLODZIK-SOBANSKA L, SLOWIK A, MCHUGH P, SOBIECKA B, KOZUB J, RICH KE, URBANIK A, SZCZUDLIK A. Single voxel proton magnetic resonance spectroscopy in post-stroke depression. **Psychiatry Res.** 2006; 148: 111-20.

78. GO AS, MOZAFFARIAN D, ROGER VL, BENJAMIN EJ, BERRY JD, BORDEN WB, BRAVATA DM, DAI S, FORD ES, FOX CS, FRANCO S, FULLERTON HJ, GILLESPIE C, HAILPERN SM, HEIT JA, HOWARD VJ, HUFFMAN MD, KISSELA BM, KITTNER SJ, LACKLAND DT, LICHTMAN JH, LISABETH LD,

MAGID D, MARCUS GM, MARELLI A, MATCHAR DB, MCGUIRE DK, MOHLER ER, MOY CS, MUSSOLINO ME, NICHOL G, PAYNTER NP, SCHREINER PJ, SORLIE PD, STEIN J, TURAN TN, VIRANI SS, WONG ND, WOO D, TURNER MB. Heart disease and stroke statistics – 2013 update: a report from the American Heart Association. **Circulation.** 2013; 127 (1): e6-e245.

79. GOLD SM, DZIOBEK I, SWEAT V, TIRSI A, ROGERS K, BRUEHL H, TSUI W, RICHARDSON S, JAVIER E, CONVIT A. Hippocampal damage and memory impairments as possible early brain complications of type 2 diabetes. **Diabetologia.** 2007; 50:711-719.

80. GOLDEN SH, LAZO M, CARNETHON M, BERTONI AG, SCHREINER PJ, DIEZ ROUX AV, LEE HB, LYKETSOS C. Examining a bidirectional association between depressive symptoms and diabetes. **J Am Med Assoc.** 2008; 299 (23): 2751-59.

81. GRINBLAT N, GRINBLAT E, GRINBLAT J. Uncontrolled crying: characteristics and differences from normative crying. **Gerontology.** 2004; 50(5): 322-9.

82. HACKETT ML, ANDERSON CS, HOUSE A, HALTEH C. Interventions for preventing depression after stroke. **Cochrane Database Syst Rev.** 2008; (3):CD003689.

83. HACKETT ML, ANDERSON CS, HOUSE AO, XIA J. Interventions for treating depression after stroke. **Stroke.** 2009; 40(7): e487-8.

84. HACKETT ML, ANDERSON CS. Predictors of depression after stroke: a systematic review of observational studies. **Stroke.** 2005; 36(10): 2296-301.

85. HACKETT ML, YAPA C, PARAG V, ANDERSON CS. Frequency of depression after stroke: a systematic review of observational studies. **Stroke.** 2005; 36(6):1330-40.

86. HADIDI N, TREAT-JACOBSON DJ, LINDQUIST R. Poststroke depression and functional outcome: a critical review of literature. **Heart Lung.** 2009; 38: 151-62.

87. HARNEY JH, FULTON C, ROSS ED, RUSH AJ. Dexamethasone suppression test and onset of poststroke depression in patients with ischemic infarction. **J Clin Psychiatry.** 1993; 54: 343-8.
88. HÉBERT R, BRAYNE C. Epidemiology of vascular dementia. **Neuroepidemiology.** 1995; 14(5):240-57.

89. HEUSCHMANN PU, KOLOMINSKY-RABAS PL, MISSELWITZ B, HERMANEK P, LEFFMANN C, JANZEN RW, ROTHER J, BUECKER-NOTT HJ, BERGER K. Predictors of in-hospital mortality and attributable risks of death after ischemic stroke: the German stroke registers study group. **Arch Intern Med.** 2004; 164(16): 1761-8.

90. HOUSE A, DENNIS M, MOGRIDGE L, WARLOW C, HAWTON K, JONES L. Mood disorders in the year after stoke. **Br J Psychiatry.** 1991; 158 :83-92.

91. HOUSE A, DENNIS M, MOLYNEUX A, WARLOW C, HAWTON K. Emotionalism after stroke. **BMJ.** 1989; 298(6679): 991-4.

92. HUDSON AJ, GRACE GM. Misidentification syndromes related to face specific area in the fusiform gyrus. **J Neurol Neurosurg Psychiatry.** 2000; 69(5):645-8.

93. IVAN CS, SESHADRI S, BEISER A, AU R, KASE CS, KELLY-HAYES M, WOLF PA. Dementia after stroke: the Framingham Study. **Stroke.** 2004; 35(6):1264-8.

94. JIMÉNEZ I, SOBRINO T, RODRÍGUEZ-YÁÑEZ M, POUSO M, CRISTOBO I, SABUCEDO M, BLANCO M, CASTELLANOS M, LEIRA R, CASTILLO J. High serum levels of leptin are associated with post-stroke depression. **Psychol Med.** 2009; 39: 1201-9.

95. JORGE RE, MOSER DJ, ACION L, ROBINSON RG. Treatment of vascular depression using repetitive transcranial magnetic stimulation. **Arch Gen Psychiatry.** 2008; 65(3): 268-76.

96. JØRGENSEN TS, WIUM-ANDERSEN IK, WIUM-ANDERSEN MK, JØRGENSEN MB, PRESCOTT E, MAARTENSSON S, KRAGH-ANDERSEN P, OSLER M. Incidence of Depression After Stroke, and Associated Risk Factors and Mortality Outcomes, in a Large Cohort of Danish Patients. **JAMA Psychiatry.** 2016; 73 (10): 1032-40.

97. KAUHANEN M, KORPELAINEN JT, HILTUNEN P, BRUSIN E, MONONEN H, MÄÄTTÄ R, NIEMINEN P, SOTANIEMI KA, MYLLYLÄ VV. Poststroke depression correlates with cognitive impairment and neurological deficits. **Stroke.** 1999; 30(9):1875-80.

98. KAUHANEN ML, KORPELAINEN JT, HILTUNEN P, MÄÄTTÄ R, MONONEN H, BRUSIN E SOTANIEMI KA, MYLLYLÄ VV. Aphasia, depression, and non-verbal cognitive impairment in ischaemic stroke. **Cerebrovasc Dis.** 2000; 10(6): 455-61.

99. KAVIRAJAN H, SCHNEIDER LS. Efficacy and adverse effects of cholinesterase inhibitors and memantine in vascular dementia: a meta-analysis of randomised controlled trials. **Lancet Neurol.** 2007; 6(9):782-92.

100. KIM BR, KIM DY, CHUN MH, YI JH, KWON JS. Effect of repetitive transcranial magnetic stimulation on cognition and mood in stroke patients: a double-blind, sham-controlled trial. **Am J Phys Med Rehabil.** 2010; 89(5): 362-8.

101. KIM JM, STEWART R, BAE KY, KIM SW, KANG HJ, SHIN IS, KIM JT, PARK MS, KIM MK, PARK SW, KIM YH, KIM JK, CHO KH, YOON JS. Serotonergic and BDNF genes and risk of depression after stroke. **J Affect Disord.** 2012;136(3):833-40.

102. KIM JM, STEWART R, KIM SW, YANG SJ, SHIN IS, KIM YH, YOON JS. BDNF genotype potentially modifying the association between incident stroke and depression. **Neurobiol Aging.** 2008; 29: 789-92.

103. KIM JM, STEWART R, KIM SW, SHIN IS, KIM JT, PARK MS, PARK SW, KIM YH, CHO KH, YOON JS. Associations of cytokine gene polymorphisms with post-stroke depression. **World J Biol Psychiatry.** 2012;13(8):579-87.

104. KIM JS, CHOI-KWON S. Poststroke depression and emotional incontinence: correlation with lesion location. **Neurology.** 2000; 54(9):1805-10.

105. KIM SJ, MOON GJ, BANG OY. Biomarkers for stroke**. J Stroke**. 2013; 15(1): 27-37.

106. KOHEN R, CAIN KC, BUZAITIS A, JOHNSON V, BECKER KJ, TERI L, TIRSCHWELL DL, VEITH RC, MITCHELL PH. Response to psychosocial treatment in poststroke depression is associated with serotonin transporter polymorphisms. **Stroke.** 2011; 42(7): 2068-70.

107. KOHEN R, CAIN KC, MITCHELL PH, BECKER K, BUZAITIS A, MILLARD SP, NAVAJA GP, TERI L, TIRSCHWELL D, VEITH R. Association of serotonin transporter gene polymorphisms with poststroke depression. **Arch Gen Psychiatry.** 2008; 65: 1296-302.

108. KOTILA M, NUMMINEN H, WALTIMO O, KASTE M. Depression after stroke: results of the FINNSTROKE Study. **Stroke.** 1998; 29(2):368-72.

109. LEES R, STOTT DJ, QUINN TJ, BROOMFIELD NM. Feasibility and diagnostic accuracy of early mood screening to diagnose persisting clinical depression/anxiety disorder after stroke. **Cerebrovasc Dis.** 2014; 37 (5): 323-9.

110. LEVY R, DUBOIS B. Apathy and the functional anatomy of the prefrontal cortex-basal ganglia circuits**. Cereb Cortex.** 2006; 16(7): 916-28.

111. LI J, ZHAO YD, ZENG JW, CHEN XY, WANG RD, CHENG SY. Serum brain-derived neurotrophic factor levels in post-stroke depression. **J Affect Disord.** 2014; 168: 373-9.

112. LI YT, ZHAO Y, ZHANG HJ, ZHAO WL. The association between serum leptin and post stroke depression: results from a cohort study**. PLoS One.** 2014; 9: e103137.

113. LIEBERMAN D, FRIGER M, FRIED V, GRINSHPUN Y, MYTLIS N, TYLIS R, GALINSKY D, LIEBERMAN D. Characterization of elderly patients in rehabilitation: stroke versus hip fracture**. Disabil Rehabil.** 1999; 21(12) :542-7.

114. LIN PY, TSENG PT. Decreased glial cell line-derived neurotrophic factor levels in patients with depression: a meta-analytic study. **J Psychiatr Res.** 2015; 63:20-7.

115. LIPSEY JR, ROBINSON RG, PEARLSON GD, RAO K, PRICE TR. The dexamethasone suppression test and mood following stroke. **Am J Psychiatry.** 1985; 142: 318-23.

116. LOPES RP, GRASSI-OLIVEIRA R, DE ALMEIDA LR, STEIN LM, LUZ C, TEIXEIRA AL, BAUER ME. Neuroimmunoendocrine interactions in patients with recurrent major depression, increased early life stress and long-standing posttraumatic stress disorder symptoms. **Neuroimmunomodulation.** 2012; 19: 33-42.

117. LOTUFO PA, GOULART AC, FERNANDES TG, BENSEÑOR IM. A reappraisal of stroke mortality trends in Brazil (1979-2009). **Int J Stroke**. vol. 8, no. 3, pp. 155-63, 2013.

118. LYKETSOS CG, KOZAUER N, RABINS PV. Psychiatric manifestations of neurologic disease: where are we headed? **Dialogues Clin Neurosci.** 2007; 9(2):111-24.

119. MACHALE SM, O'ROURKE SJ, WARDLAW JM, DENNIS MS. Depression and its relation to lesion location after stroke. **J Neurol Neurosurg Psychiatry.** 1998; 64(3):371-4.

120. MADEIRA MH, BOIA R, SANTOS PF, AMBRÓSIO AF, SANTIAGO AR. Contribution of microglia-mediated neuroinflammation to retinal degenerative diseases. **Mediators Inflamm.** 2015; 2015:673090.

121. MAKIKALLIO AM, MAKIKALLIO TH, KORPELAINEN JT, SOTANIEMI KA, HUIKURI HV, MYLLYLÄ VV. Heart rate dynamics predict poststroke mortality. **Neurology.** 2004;62(10):1822-6.

122. MARCHESI C, SILVESTRINI C, PONARI O, VOLPI R, CHIODERA P, COIRO V. Unreliability of TRH test but not dexamethasone suppression test as a marker of depression in chronic vasculopathic patients. **Biol Psychiatry.** 1996; 40: 637-41.

123. MCGUINESS B, GIBNEY SM, BEUMER W, VERSNEL MA, SILLABER I, HARKIN A, DREXHAGE HA. Exaggerated Increases in Microglia Proliferation, Brain Inflammatory Response and Sickness Behaviour upon Lipopolysaccharide Stimulation in Non-Obese Diabetic Mice. **Neuroimmunomodulation.** 2016 Aug 17.

124. MEAD GE, HSIEH CF, LEE R, KUTLUBAEV M, CLAXTON A, HANKEY GJ, HACKETT M. Selective serotonin reuptake inhibitors for stroke recovery: a systematic review and meta-analysis. **Stroke.** 2013; 44(3): 844-50.

125. MEZUK B, EATON WW, ALBRECHT S, GOLDEN SH. Depression and type 2 diabetes over the lifespan: a meta-analysis. **Diabetes Care.** 2008; 31:2383-2390.

126. MINELLI C, FEN LF, MINELLI DP. Stroke incidence, prognosis, 30-day, and 1-year case fatality rates in Matão, Brazil: a population-based prospective study. **Stroke.** 2007; 38(11): 2906-11.

127. MOHER D, LIBERATI A, TETZLAFF J, ALTMAN DG; PRISMA GROUP. Preferred reporting items for systematic reviews and metaanalyses: the PRISMA statement. **PLoS Med.** 2009; 21; 6: e1000097.

128. MOLLER M, ANDERSEN G, GJEDDE A. Serotonin 5-HT1a receptor availability and pathological crying after stroke. **Acta Neurol Scand.** 2007; 116(2):83-90.

129. MORRIS P, HOPWOOD M, MAGUIRE K, NORMAN T, SCHWEITZER I. Blunted prolactin response to D-fenfluramine in post-stroke major depression. **J Affect Disord.** 2003; 76: 273-8.

130. MORRIS PLP, ROBINSON RG, RAPHAEL B. Prevalence and outcome of poststroke depression in hospitalized patients**. Int J Psychiatr Med.** 1990; 20(4):327-42.

131. MOSSNER R, MIKOVA O, KOUTSILIERI E, SAOUD M, EHLIS AC, MÜLLER N, FALLGATTER AJ, RIEDERER P. Consensus paper of the WFSBP Task Force on Biological Markers: Biological markers in depression. **W J Biol Psych.** 2007; 8(3): 141-74.

132. MOTA JF, NICOLATO R. Qualidade de vida em sobreviventes de acidente vascular cerebral: instrumentos de avaliação e seus resultados. **J Bras Psiquiatr.** 2008; 57(2):148-56.

133. MURIACH M, FLORES-BELLVER M, ROMERO FJ, BARCIA JM. Diabetes and the brain: oxidative stress, inflammation, and autophagy. **Oxid Med Cell Longev.** 2014; 2014: 102158.

134. NAGARATNAM N, NAGARATNAM K, NG K, DIU P. Akinetic mutism following stroke. **J Clin Neurosci.** 2004; 11(1): 25-30.

135. NEWMAN SC. The prevalence of depression in Alzheimer's disease and vascular dementia in a population sample. **J Affect Disord.** 1999; 52(1-3): 169-76.

136. NG KC, CHAN KL, STRAUGHAN PT. A study of post-stroke depression in a rehabilitative center. **Acta Psych Scand.** 1995; 92(1):75-9.

137. Nys GM, van Zandvoort MJ, van der Worp HB, de Haan EH, de Kort PL, Jansen BP, KAPPELLE LJ. Early cognitive impairment predicts long-term depressive symptoms and quality of life after stroke**. J Neurol Sci.** 2006; 247: 149-56.

138. NYS GM, VAN ZANDVOORT MJ, VAN DER WORP HB, DE HAAN EH, DE KORT PL, KAPPELLE LJ. Early depressive symptoms after stroke: neuropsychological correlates and lesion characteristics. **J Neurol Sci.** 2005; 228(1): 27-33.

139. O'Connor JC, Lawson MA, Andre C, Moreau M, Lestage J, Castanon N, et al. Lipopolysaccharide-induced depressive-like behavior is mediated by indoleamine 2,3-dioxygenase activation in mice. **Mol Psychiatry.** 2009; 14(5): 511-22.

140. OKADA K, KOBAYASHI S, YAMAGATA S, TAKAHASHI K, YAMAGUCHI S. Poststroke apathy and regional cerebral blood flow. **Stroke.** 1997; 28(12): 2437-41.

141. OLDEHINKEL AJ, ORMEL J, BRILMAN EI, VAN DEN BERG MD. Psychosocial and vascular risk factors depression in later life. **J Affect Disord.** 2003; 74(3): 237-46.

142. OLSSON T, ASTRÖM M, ERIKSSON S, FORSSELL A. Hypercortisolism revealed by the dexamethasone suppression test in patients with acute ischemic stroke. **Stroke.** 1989; 20: 1685-90.

143. ORMSTAD H, AASS HC, AMTHOR KF, LUND-SØRENSEN N, SANDVIK L. Serum levels of cytokines, glucose, and hemoglobin as possible predictors of poststroke depression, and association with poststroke fatigue. **Int J Neurosci.** 2012; 122: 682-90.

144. ORMSTAD H, VERKERK R, AMTHOR KF, SANDVIK L. Activation of the kynurenine pathway in the acute phase of stroke and its role in fatigue and depression following stroke. **J Mol Neurosci.** 2014; 54: 181-7.

145. OUIMET MA, PRIMEAU F, COLE MG. Psychosocial risk factors in poststroke depression: a systematic review**. Can J Psychiatry.** 2001; 46(9):819-28.

146. PAIXÃO LC, RIBEIRO AL, VALACIO AR, TEIXEIRA AL. Chagas disease: independent risk factor for stroke. **Stroke.** 2009; 40(12): 3691-4.

147. PAOLUCCI S, GANDOLFO C, PROVINCIALI L, TORTA R, TOSO V; DESTRO STUDY GROUP. The Italian multicenter observational study on post-stroke depression (DESTRO). **J Neurol.** 2006; 253(5):556-62.

148. PARADISO S, ROBINSON RG, ARNDT S. Self-reported aggressive behavior in patients with stroke. **J Nerv Ment Dis.** 1996; 184(12): 746-53.

149. PASCOE MC, CREWTHER SG, CAREY LM, NOONAN K, CREWTHER DP, LINDEN T. Homocysteine as a potential biochemical marker for depression in elderly stroke survivors. **Food Nutr Res.** 2012; 56: 14973.

150. PATTERSON MB, MACK JL. Neuropsychological analysis of a case of reduplicative paramnesia. **J Clin Exp Neuropsychol.** 1985; 7(1):111-21.

151. PAVLOVIC AM, PEKMEZOVIC T, OBRENOVIC R, NOVAKOVIC I, TOMIC G, MIJAJLOVIC M, STERNIC N. Increased total homocysteine level is associated with clinical status and severity of white matter changes in symptomatic patients with subcortical small vessel disease. **Clin Neurol Neurosurg.** 2011; 113: 711-5.

152. PIAMARTA F, IURLARO S, ISELLA V, ATZENI L, GRIMALDI M, RUSSO A, FORAPANI E, APPOLLONIO I. Unconventional affective symptoms and executive functions after stroke in the elderly. **Arch Gerontol Geriatr Suppl.** 2004; (9):315-23.

153. PIORO EP, BROOKS BR, CUMMINGS J, SCHIFFER R, THISTED RA, WYNN D, HEPNER A, KAYE R. Dextromethorphan plus ultra low-dose quinidine reduces pseudobulbar affect. **Ann Neurol.** 2010; 68(5):693-702.

154. PRICE A, RAYNER L, OKON-ROCHA E, EVANS A, VALSRAJ K, HIGGINSON IJ, HOTOPF M. Antidepressants for the treatment of depression in neurological disorders: a systematic review and metaanalysis of randomised controlled trials**. J Neurol Neurosurg Psychiatry.** 2011; 82(8):914-23.

155. PRISNIE JC, FIEST KM, COUTTS SB, PATTEN SB, ATTA CA, BLAIKIE L, BULLOCH AG, DEMCHUK A, HILL MD, SMITH EE, JETTÉ N. Validating screening tools for depression in stroke and transient ischemic attack patients. **Int J Psychiatry Med.** 2016; 51 (3): 262-77.

156. RABELO DF, NÉRI AL. Bem-estar subjetivo e senso de ajustamento psicológico em idosos que sofreram acidente vascular cerebral: uma revisão. **Estud Psicol (Natal).** 2006; 11(2):169-77.

157. RABINS PV, STARKSTEIN SE, ROBINSON RG. Risk factors for developing atypical (schizophreniform) psychosis following stroke. **J Neuropsychiatry Clin Neurosci.** 1991; 3(1): 6-9.

158. RAMASUBBU R, FLINT A, BROWN G, AWAD G, KENNEDY S. A neuroendocrine study of serotonin function in depressed stroke patients compared to non-depressed stroke patients and healthy controls. **J Affect Disord.** 1999; 52: 121-33.

159. RAMASUBBU R, TOBIAS R, BECH-HANSEN NT. Extended evaluation of serotonin transporter gene functional polymorphisms in subjects with post-stroke depression. **Can J Psychiatry.** 2008; 53: 197-201.

160. RAMASUBBU R, TOBIAS R, BUCHAN AM, BECH-HANSEN NT. Serotonin transporter gene promoter region polymorphism associated with poststroke major depression. **J Neuropsychiatry Clin Neurosci.** 2006; 18(1): 96-9.

161. RANGEL ESS, BELASCO AGS, DICCINI S. Qualidade de vida de pacientes com acidente vascular cerebral em reabilitação. **Acta Paul Enferm.** 2013; 26(2): 205-12.

162. RASMUSSEN A, CHRISTENSEN J, CLEMMENSEN PM, DALSGAARD NJ, DAM H, HINDBERG I, LUNDE M, PLENGE P, MELLERUP E. Platelet serotonin transporter in stroke patients. **Acta Neurol Scand.** 2003; 107: 150-3.

163. RAVAL A, DHANARAJ E, BHANSALI A, GROVER S, TIWARI P. Prevalence and determinants of depression in type 2 diabetes patients in a tertiary care centre. **Indian J Med Res.** 2010; 132: 195-200.

164. RAVETTI CG, MOURA AD2, VIEIRA ÉL, PEDROSO ÊR, TEIXEIRA AL. sTREM-1 predicts intensive care unit and 28-day mortality in cancer patients with severe sepsis and septic shock. **J Crit Care.** 2015; 30(2): 440.e7-13.

165. REDING M, ORTO L, WILLENSKY P, FORTUNA I, DAY N, STEINER SF, GEHR L, MCDOWELL F. The dexamethasone suppression test: an indicator of depression in stroke but not a predictor of rehabilitation outcome. **Arch Neurol.** 1985; 42: 209-12.

166. RIBEIRO DS, CERQUEIRA FILHO EA, LOSAPIO MF, SENA EP. Terapia medicamentosa na depressão pós-acidente vascular encefálico. **J Bras Psiquiatr.** 2009; 58(2): 135-42.

167. RIBERTO M, MIYAZAKI MH, JUCÁ SSH, SAKAMOTO H, PINTO PPN, BATTISTELLA LR. Validation of the Brazilian version of Functional Independence Measure. **Acta Fisiatr.** 2004; 11 (2): 72-6.

168. ROBINSON RG, BLOOM FE. Pharmacological treatment following experimental cerebral infarction: implications for understanding psychological symptoms of human stroke. **Biol Psychiatry.** 1977; 12(5) :669-80.

169. ROBINSON RG, BOLDUC PL, PRICE TR. Two-year longitudinal study of poststroke mood disorders: diagnosis and outcome at one and two years. **Stroke.** 1987; 18(5): 837-43.

170. ROBINSON RG, PARIKH RM, LIPSEY JR, STARKSTEIN SE, PRICE TR. Pathological laughing and crying following stroke validation of a measurement scale and a double-blind treatment study. **Am J Psychiatry.** 1993; 150 (2): 286-93.

171. ROBINSON RG, SPALLETTA G, JORGE RE, BASSI A, COLIVICCHI F, RIPA A, CALTAGIRONE C. Decreased heart rate variability is associated with poststroke depression. **Am J Geriatr Psychiatry.** 2008; 16(11): 867-73.

172. ROBINSON RG, STARR LB, KUBOS KL, PRICE TR. A two-year longitudinal study of post-stroke mood disorders: findings during the initial evaluation. **Stroke.** 1983; 14(5): 736-41.

173. ROBINSON RG, STARR LB, PRICE TR. A two year longitudinal study of mood disorders following stroke. Prevalence and duration at six months follow-up. **Br J Psychiatry.** 1984; 144: 256-62.

174. ROBINSON RG. Neuropsychiatric consequences of stroke. **Annu Rev Med**. 1997; 48: 217-29

175. ROBINSON RG. **The clinical neuropsychiatry of stroke.** New York: Cambridge University Press; 2006.

176. ROY T, LLOYD CE. Epidemiology of depression and diabetes: a systematic review. **J Affect Disord.** 2012; 142 Suppl: S8-21.

177. SADOWSKI M, PANKIEWICZ J, SCHOLTZOVA H, LI YS, QUARTERMAIN D, DUFF K, WISNIEWSKI T. Links between the pathology of Alzheimer's disease and vascular dementia. **Neurochem Res.** 2004; 29(6): 1257-66.

178. SAGEN U, VIK TG, MOUM T, MØRLAND T, FINSET A, DAMMEN T. Screening for anxiety and depression after stroke: comparison of the hospital anxiety and depression scale and the Montgomery and Asberg depression rating scale. **J Psychosom Res.** 2009; 67 (4): 325-32.

179. SANTOS CO, CAEIRO L, FERRO JM, FIGUEIRA ML. Mania and stroke: a systematic review. **Cerebrovasc Dis.** 2011;32(1):11-21.

180. SAPOLSKY RM. Depression, antidepressants, and the shrinking hippocampus. **Proc Natl Acad Sci USA.** 2001; 98: 12320-12322.

181. SARTORI HCS, BARROS T, TAVARES A. Transtorno da expressão emocional involuntária. **Rev. Psiq Clín.** 2008; 35(1): 20-5.

182. SCHEFFER M, MONTEIRO JK, DE ALMEIDA RMM. Frontal stroke: problem solving, decision making, impulsiveness, and depressive symptoms in men and women. **Psychol Neurosci.** 2011; 4(2): 267-78.

183. SCHILDKRAUT JJ, KLEIN FD. The classification and treatment of depressive states. In: SHADER RI. **Manual of psychiatric therapeutics**. Boston: Little and Brown; 1975.

184. SEVINÇOK L, EROL A. The prolactin response to buspirone in poststroke depression: a preliminary report. **J Affect Disord.** 2000; 59: 169-73.

185. SHADER RI. Demoralization revisited. **J Clin Psychopharmacology.** 2005; 25(4) 291-2.

186. SHARMA AN, DA COSTA E SILVA BF, SOARES JC, CARVALHO AF, QUEVEDO J. Role of trophic factors GDNF, IGF-1 and VEGF in major depressive disorder: A comprehensive review of human studies. **J Affect Disord.** 2016; 197: 9-20.

187. SHIMODA K, ROBINSON RG. The relationship between poststroke depression and lesion location in long-term follow-up. **Biol Psychiatry.** 1999; 45(2): 187-92.

188. SIGNER SF. Localization and lateralization in the delusion of substitution. Capgras symptom and its variants. **Psychopathology.** 1994; 27(3-5): 168-76.

189. SIMIS S, NITRINI R. Cognitive improvement after treatment of depressive symptoms in the acute phase of stroke. **Arq Neuropsiquiatr.** 2006; 64(2B): 412-7.

190. SKÅNÉR Y, NILSSON GH, SUNDQUIST K, HASSLER E, KRAKAU I. Self-rated health, symptoms of depression and general symptoms at 3 and 12 months after a first-ever stroke: a municipality- based study in Sweden. **BMC Fam Pract.** 2007; 8 :61.

191. SMITH RS. A comprehensive macrophage-T-lymphocyte theory of schizophrenia. **Med Hypotheses.** 1992; 39: 248–57.

192. SMITH RS, MAES M. The macrophage-T-lymphocyte theory of schizophrenia: additional evidence. **Med Hypotheses.** 1995; 45: 135–141.

193. SNEED JR, CULANG-REINLIEB ME. The vascular depression hypothesis: an update. **Am J Geriatr Psychiatry.** 2011; 19 (2): 99-103.

194. SOUZA AC, ROCHA MO, TEIXEIRA AL, DIAS JÚNIOR JO, SOUSA LA, NUNES MC. Depressive symptoms and disability in chagasic stroke patients: impact on functionality and quality of life. **J Neurol Sci.** 2013; 324(1-2): 34-7.

195. SPALLETTA G, BOSSU P, CIARAMELLA A, BRIA P, CALTAGIRONE C, ROBINSON RG. The etiology of poststroke depression: a review of the literature and a new hypothesis involving inflammatory cytokines. **Mol Psychiatry.** 2006; 11(11): 984-91.

196. SPALLETTA G, CRAVELLO L, IMPERIALE F, SALANI F, BOSSÙ P, PICCHETTO L, CAO M, RASURA M, PAZZELLI F, ORZI F, CALTAGIRONE C, ROBINSON RG, CACCIARI C. Neuropsychiatric symptoms and interleukin-6 serum levels in acute stroke. **J Neuropsychiatry Clin Neurosci.** 2013; 25(4): 255-63.

197. SPALLETTA G, ROBINSON RG. How should depression be diagnosed in patients with stroke? **Acta Psychiatr Scand.** 2010; 121(6): 401-3.

198. SRODULSKI S, SHARMA S, BACHSTETTER AB, BRELSFOARD JM, PASCUAL C, XIE XS, SAATMAN KE, VAN ELDIK LJ, DESPA F. Neuroinflammation and neurologic deficits in diabetes linked to brain accumulation of amylin**. Mol Neurodegener.** 2014; 9: 30.

199. STARKSTEIN SE, FEDOROFF JP, PRICE TR, LEIGUARDA R, ROBINSON RG. Apathy following cerebrovascular lesions. **Stroke.** 1993; 24(11): 1625-30.

200. STARKSTEIN SE, MAYBERG HS, BERTHIER ML, FEDOROFF P, PRICE TR, DANNALS RF WAGNER HN, LEIGUARDA R, ROBINSON RG. Mania after brain injury: neuroradiological and metabolic findings. **Ann Neurol.** 1990; 27(6): 652-9.

201. SU JA, CHOU SY, TSAI CS, HUNG TH. Cytokine changes in the pathophysiology of poststroke depression. **Gen Hosp Psychiatry.** 2012; 34: 35-9.

202. TALIAZ D, STALL N, DAR DE, ZANGEN A. Knockdown of brain-derived neurotrophic factor in specific brain sites precipitates behaviors associated with depression and reduces neurogenesis. **Mol Psychiatry.** 2010; 15: 80–92.

203. TANG CZ, ZHANG YL, WANG WS, LI WG, SHI JP. Serum levels of high-sensitivity C-reactive protein at admission are more strongly associated with poststroke depression in acute ischemic stroke than homocysteine levels. **Mol Neurobiol.** 2016; 53(4) :2152-60.

204. TANG WK, CHAN SS, CHIU HF, UNGVARI GS, WONG KS, KWOK TC. Emotional incontinence in Chinese stroke patients: diagnosis, frequency, and clinical and radiological correlates. **J Neurol.** 2004; 251(7): 865-9.

205. TANG WK, LIANG H, CHU WC, MOK V, UNGVARI GS, WONG KS. Association between high serum total bilirubin and post-stroke depression. **Psychiatry Clin Neurosci.** 2013; 67: 259-64.

206. TANG WK, TANG N, LIAO CD, LIANG HJ, MOK VC, UNGVARI GS, WONG KS. Serotonin receptor 2C gene polymorphism associated with post-stroke depression in Chinese patients. **Genet Mol Res.** 2013; 12(2): 1546-53.

207. TANG WK, UNGVARI GS, CHIU HF, SZE KH, YU AC, LEUNG TL. Screening post-stroke depression in Chinese older adults using the hospital anxiety and depression scale**. Aging Ment Health.** 2004; 8 (5): 397-9.

208. TANG WK, WONG E, CHIU HF, UNGVARI GS. Rasch analysis of the scoring scheme of the HADS Depression subscale in Chinese stroke patients. **Psychiatry Res.** 2007; 150 (1): 97-103.

209. TENGS TO, YU M, LUISTRO E. Health-related quality of life after stroke – a comprehensive review. **Stroke.** 2001; 32(4): 964-72.

210. TERRONI LM, FRÁGUAS R, LUCIA M, TINONE G, MATTOS P, IOSIFESCU DV, SCAF M. Importance of retardation and fatigue/interest domains for the diagnosis of major depressive episode after stroke: a four months prospective study. **Rev Bras Psiquiatr.** 2009; 31(3): 202-7.

211. THARWANI HM, YERRAMSETTY P, MANNELLI P, PATKAR A, MASAND P. Recent advances in poststroke depression. **Curr Psychiatry Rep.** 2007; 9(3): 225-31.

212. TOKGOZOGLU SL, BATUR MK, TOPCUOGLU MA, SARIBAS O, KES S, OTO A. Effects of stroke localization on cardiac autonomic balance and sudden death. **Stroke.** 1999; 30(7): 1307-11.

213. UZDENSKY A, KOMANDIROV M, FEDORENKO G, LOBANOV A. Protection effect of GDNF and neurturin on photosensitized crayfish neurons and glial cells. **J Mol Neurosci.** 2013; 49: 480e90.

214. VALE FC, MIRANDA SJC. Clinical and demographic features of patients with dementia attended in a tertiary outpatient clinic. **Arq Neuropsiquiatr.** 2002; 60(3-A): 548-52.

215. VAN DALEN JW, MOLL VAN CHARANTE EP, NEDERKOORN PJ, VAN GOOL WA, RICHARD E. Poststroke apathy. **Stroke.** 2013; 44(3): 851-60.

216. VAN DER HARG JM, EGGELS L, RUIGROK SR, HOOZEMANS JJ, LA FLEUR SE, SCHEPER W. Neuroinflammation is not a Prerequisite for Diabetes-induced Tau Phosphorylation. **Front Neurosci.** 2015; 9:432.

217. VAN HARTEN B, DE LEEUW FE, WEINSTEIN HC, SCHELTENS P, BIESSELS GJ. Brain imaging in patients with diabetes: a systematic review. **Diabetes Care.** 2006; 29: 2539-2548.

218. VAN SWIETEN J, KOUDSTAAL P, VISSER M, SCHOUTEN HJ, VAN GIJN J. Interobserver agreement for the assessment of handicap in stroke patients. **Stroke**. 1988; 19 (5): 604–7.

219. WALLIN A, MILOS V, SJOGREN M, PANTONI L, ERKINJUNTTI T. Classification and subtypes of vascular dementia. **Int Psychogeriatr.** 2003; 15(Suppl 1): 27-37.

220. WANG D, COUTURE R, HONG Y. Activated microglia in the spinal cord underlies diabetic neuropathic pain. **Eur J Pharmacol.** 2014; 728: 59-66.

221. WANG J, YANG Z, LIU C, ZHAO Y, CHEN Y. Activated microglia provide a neuroprotective role by balancing glial cell-line derived neurotrophic factor and tumor necrosis factor-α secretion after subacute cerebral ischemia. **Int J Mol Med.** 2013; 31(1): 172-8.

222. WANG X, LI YH, LI MH, LU J, ZHAO JG, SUN XJ, ZHANG B, YE JL. Glutamate level detection by magnetic resonance spectroscopy in patients with post-stroke depression. **Eur Arch Psychiatry Clin Neurosci.** 2012; 262: 33-8.

223. WEIGELT K, CARVALHO LA, DREXHAGE RC, WIJKHUIJS A, DE WIT H, VAN BEVEREN NJ, BIRKENHÄGER TK, BERGINK V, DREXHAGE HA. TREM-1 and DAP12 expression in monocytes of patients with severe psychiatric disorders. EGR3, ATF3 and PU.1 as important transcription factors. **Brain Behav Immun.** 2011; 25(6): 1162-9.

224. WICHOWICZ HM, WIECZOREK D. Screening post-stroke depression using the Hospital Anxiety and Depression Scale. **Psychiatr Pol.** 2011; 45 (4): 505-14.

225. WILLIAMS JE, NIETO FJ, SANFORD CP, COUPER DJ, TYROLER HA. The association between trait anger and incident stroke risk: the Atherosclerosis Risk in Communities (ARIC) Study. **Stroke.** 2002; 33(1):13-9.

226. WORLD HEALTH ORGANIZATION. Recommendations on stroke prevention, diagnosis, and therapy: report of the WHO Task Force on Stroke and Other Cerebrovascular Disorders. **Stroke.** 1989; 20(10): 1407-31.

227. YANG L, ZHANG Z, SUN D, XU Z, YUAN Y, ZHANG X, LI L. Low serum BDNF may indicate the development of PSD in patients with acute ischemic stroke. **Int J Geriatr Psychiatry.** 2011; 26: 495-502.

228. YANG L, ZHANG Z, SUN D, XU Z, ZHANG X, LI L. The serum interleukin-18 is a potential marker for development of post-stroke depression. **Neurol Res.** 2010; 32(4): 340-6.

229. YUE W, XIANG L, ZHANG YJ, JI Y, LI X. Association of serum 25-hydroxyvitamin D with symptoms of depression after 6 months in stroke patients. **Neurochem Res.** 2014; 39: 2218-24.

230. ZHANG Z, MU J, LI J, LI W, SONG J. Aberrant apolipoprotein E expression and cognitive dysfunction in patients with poststroke depression. **Genet Test Mol Biomarkers.** 2013; 17: 47-51.

231. ZHOU Z, LU T, XU G, YUE X, ZHU W, MA M, LIU W, ZHU S, LIU X. Decreased serum brain-derived neurotrophic factor (BDNF) is associated with post-stroke depression but not with BDNF gene Val66Met polymorphism. **Clin Chem Lab Med.** 2011; 49(2): 185-9.

232. ZIGMOND AS, SNAITH RP. The Hospital Anxiety and Depression Scale. **Acta Psychiatr Scand.** 1983; 67 (6): 361–70.

Anexos

Anexo A: Termo de aprovação do projeto de pesquisa pelo Comitê de Ética em Pesquisa da Universidade Federal de Minas Gerais.

UNIVERSIDADE FEDERAL DE MINAS GERAIS
COMITÊ DE ÉTICA EM PESQUISA - COEP

Projeto: CAAE – 02811212.3.0000.5149

Interessado(a): Prof. Antonio Lúcio Teixeira Jr.
Departamento de Clínica Médica
Faculdade de Medicina - UFMG

DECISÃO

O Comitê de Ética em Pesquisa da UFMG – COEP aprovou, no dia 27 de junho de 2012, o projeto de pesquisa intitulado **"Investigação do papel de fatores inflamatórios no desenvolvimento de síndromes neuropsiquiátricas pós-acidente vascular encefálico isquêmico"** bem como o Termo de Consentimento Livre e Esclarecido.

O relatório final ou parcial deverá ser encaminhado ao COEP um ano após o início do projeto.

Profa. Maria Teresa Marques Amaral
Coordenadora do COEP-UFMG

Av. Pres. Antonio Carlos, 6627 – Unidade Administrativa II - 2º andar – Sala 2005 – Cep:31270-901 – BH-MG
Telefax: (031) 3409-4592 - e-mail: coep@prpq.ufmg.br

Anexo B: Termo de aprovação do projeto de pesquisa pelo Comitê de Ética em Pesquisa do Hospital Municipal Odilon Behrens.

HOSPITAL MUNICIPAL
ODILON BEHRENS

COMITÊ DE ÉTICA EM PESQUISA

O Comitê de Ética em Pesquisa do Hospital Municipal Odilon Behrens – CEP /HOB, constituído nos Termos da resolução CNS Nº 196/96 e, devidamente registrado na Comissão Nacional de Ética em Pesquisa – CONEP, recebeu, analisou e emitiu parecer sobre a documentação referente ao Protocolo de Pesquisa, conforme abaixo discriminado:

PROTOCOLO DE PESQUISA CEP/HOB

Número do parecer: 039/2013

Título do Projeto: Investigação do papel de fatores inflamatórios no desenvolvimento de síndromes neuropsiquiátricas pós-acidente vascular encefálico isquêmico.

Pesquisador Responsável: Antônio Lucio Teixeira Junior

Data de Recebimento no CEP/HOB: 05/09/2013

Data de apreciação: 12/09/2013

Parecer do CEP/HOB: Aprovado.

Atenciosamente,

Lúcia de Fátima Amorim
Coordenadora do CEP/HOB

Anexo C: Termo de Consentimento Livre e Esclarecido.

TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO

Título do Projeto: Investigação do papel de fatores inflamatórios no desenvolvimento de síndromes neuropsiquiátricas pós-acidente vascular encefálico isquêmico.

Pesquisador Responsável: Vinicius Sousa Pietra Pedroso

Nome do voluntário: _____

Introdução: Você está sendo convidado a participar da pesquisa clínica intitulada "Investigação do Papel de Fatores Inflamatórios no Desenvolvimento de Síndromes Neuropsiquiátricas pós-Acidente Vascular Encefálico Isquêmico". Antes de aceitar participar desta pesquisa clínica, é importante que você leia e compreenda a explicação sobre os procedimentos propostos. Esta declaração descreve o objetivo, os procedimentos, os benefícios e riscos do estudo, e o seu direito de sair do estudo a qualquer momento. Nenhuma garantia ou promessa pode ser feita sobre o resultado do estudo. Estas informações estão sendo dadas para esclarecer quaisquer dúvidas sobre a pesquisa proposta, antes de obter o seu consentimento.

Objetivo: O objetivo deste estudo é avaliar a frequência de transtornos mentais (psiquiátricos) entre os pacientes que sofreram um Acidente Vascular Encefálico (AVE, "derrame") que estão em acompanhamento no Serviço de Neurologia do Hospital das Clínicas da UFMG ou na Unidade de AVE do Hospital Municipal Odilon Behrens e a relação desses transtornos mentais com a inflamação causada pelo derrame.

Resumo: Os AVE são muito frequentes e podem causar grande impacto para os pacientes e seus familiares. Diversas alterações psiquiátricas já foram observadas em decorrência de um AVE, entre eles a depressão, que pode prejudicar muito a qualidade de vida e a reabilitação dos pacientes. O reconhecimento da coexistência dessas alterações do comportamento pode nos auxiliar a compreender melhor a relação entre os AVE e os transtornos mentais, possibilitando o tratamento mais efetivo de ambos e a melhora na qualidade de vida dos pacientes.

Procedimentos: Este estudo irá avaliar pacientes em dois momentos: até 30 dias depois do AVE (período agudo/subagudo) e depois de 6 meses do AVE (período crônico). Se o paciente for entrevistado no período agudo/subagudo, ele será convidado a participar novamente após 6 meses. O estudo vai consistir de uma entrevista para a avaliação da presença ou ausência de transtornos mentais, como ansiedade e depressão, e verificar o impacto na qualidade de vida da pessoa. Além disso, será coletada uma amostra de sangue. A entrevista com o psiquiatra deverá ter duração média de 1 (uma) hora.

Critérios de inclusão: ter sofrido um AVE isquêmico, com idade acima de 45 anos e não ter outras doenças neurológicas, doenças clínicas descompensadas ou ter sido submetido a neurocirurgias prévias.

Benefícios: As informações obtidas nesta pesquisa contribuirão para a melhor compreensão dos AVE e de suas alterações comportamentais. O seu tratamento no Ambulatório de Neurologia não será prejudicado de nenhuma forma. Caso seja identificada alguma alteração clinicamente relevante, com o seu consentimento, seu médico assistente poderá ser informado para que tome as medidas apropriadas.

Riscos: Não há riscos previstos com a sua participação na pesquisa.

Confidencialidade: Os registros de sua participação neste estudo serão mantidos confidencialmente até onde é permitido por lei e todas as informações estarão restritas à equipe responsável pelo projeto. No entanto, o pesquisador e sob certas circunstâncias, o Comitê de Ética em Pesquisa/UFMG, poderão verificar e ter acesso aos dados confidenciais que o identificam pelo nome. É importante informar que qualquer publicação dos dados não o identificará. Ao assinar este formulário de consentimento, você autoriza o pesquisador a fornecer seus registros médicos para o Comitê de Ética em Pesquisa/UFMG.

Desligamento: A sua participação neste estudo é voluntária e sua recusa em participar ou seu desligamento do estudo não envolverá penalidades. Você poderá cessar sua participação a qualquer momento sem afetar seu acompanhamento médico em andamento.

Compensação: Você não receberá qualquer compensação financeira por sua participação no estudo.

Emergência/contato com a Comissão de Ética: Durante o estudo, se você tiver qualquer dúvida ou apresentar qualquer problema médico, contate o Dr. Vinicius Sousa Pietra Pedroso, pelo telefone (31) 9634-0483, ou o Comitê de Ética em Pesquisa da Universidade Federal de Minas Gerais, Av. Antônio Carlos, 6627, Unidade Administrativa II – 2° andar, Campus Pampulha, Belo Horizonte, MG – Brasil, CEP: 31270-901, pelo telefone (31) 3409-4592.

Consentimento: Declaro que li e entendi as informações precedentes. Tive a oportunidade de fazer perguntas e todas as minhas dúvidas foram respondidas a contento. Este formulário está sendo assinado voluntariamente por mim, indicando o meu consentimento para participar do estudo, até que eu decida o contrário.

Belo Horizonte, _____ de _____ de _____.

Assinatura do paciente_____

Assinatura da testemunha _____

Assinatura do pesquisador_____