Journal of Neuroimmunology 336 (2019) 577027

Contents lists available at ScienceDirect

Journal of Neuroimmunology

journal homepage: www.elsevier.com/locate/jneuroim

Short Communication

Microparticles are related to cognitive and functional status from normal aging to dementia

Carolina A. Magalhães[a], Fernanda M. Campos[a], Cristina M.G. Loures[a], Vanessa G. Fraga[a], Leonardo C. de Souza[b], Henrique C. Guimarães[b], Marco T.G. Cintra[b], Maria A. Bicalho[b], Maria G. Carvalho[a], Lirlândia P. Sousa[a], Paulo Caramelli[b], Karina B. Gomes[a,*]

[a] Departamento de Análises Clínicas e Toxicológicas, Faculdade de Farmácia, Universidade Federal de Minas Gerais, Belo Horizonte, Minas Gerais, Brazil
[b] Departamento de Clínica Médica, Faculdade de Medicina, Universidade Federal de Minas Gerais, Belo Horizonte, Minas Gerais, Brazil

ARTICLE INFO

Keywords:
Microparticles
Dementia
Cognition
Functional status

ABSTRACT

Recently, we have shown that microparticles (MPs) levels derived from leukocytes (LMPs), endothelium (EMPs), neurons (NMPs) and those expressing tissue factor (TFMPs) were higher in Alzheimer's Disease (AD) patients when compared to cognitively healthy subjects. Therefore, in this study we proposed to investigate the correlation between MPs levels, cognitive performance and functional status in a sample of elderly individuals. We evaluated MPs derived from platelets (PMPs), LMPs, EMPs, NMPs and TFMPs in 43 participants, of whom 12 with probable dementia due to AD, 16 with mild cognitive impairment (MCI) and 15 with no objective cognitive or functional impairment. PMPs, LMPs and TFMPs, were associated with cognitive impairment in this population. LMPs and NMP, were associated to lower functional performance in the elderly sample. These results suggest that MPs may be involved in the pathophysiology of neurodegenerative disorders.

1. Introduction

Dementia is a general term for the occurrence of cognitive impairment that may be caused by different disorders, being Alzheimer's disease (AD) the most frequent etiology worldwide (Alzheimer's Association, 2017). AD causes a significant and progressive loss of cognitive and functional performance, often accompanied by personality and behavioral changes (Heppner et al., 2015). Mild cognitive impairment (MCI) precedes AD dementia, and refers to a condition in which the subjects are cognitively impaired, but maintain preserved function in daily activities (Petersen et al., 1999). Between normal aging and MCI there is an intermediate state, defined as subjective cognitive decline (SCD), characterized by a self-perceived decline, but without objective evidence.

Microparticles (MPs) are small vesicles, ranging from 0.1 to 1 μm, released from the cell membrane when activated or during apoptosis. MPs are responsible for cell communication, by means of proteins, DNA, mRNA and miRNA transfer (Barile and Vassalli, 2017). Their levels are increased under conditions of vascular injury/dysfunction and inflammation. Moreover, shedding of cellular MPs in the neurovascular system may be linked to the onset and progression of many central diseases, including age-related neurodegenerative disorders (Hosseinzadeh et al., 2018). Cerebrovascular and inflammatory complications are established risk factors for cognitive impairment. Consequently, measurements of plasma levels of MPs in AD patients could help to elucidate the association between circulating MPs and dementia process (Hosseinzadeh et al., 2018).

Recently, we have shown that total MPs, as well as levels of MPs derived from leukocytes (LMPs), endothelium (EMPs), neurons (NMPs) and those expressing tissue factor (TFMPs), were higher in AD patients when compared to cognitively healthy subjects (Magalhães et al., 2019). Therefore, in this study we proposed to investigate the correlation between MPs levels, cognitive performance and functional status in a sample of elderly individuals.

2. Methods

This study was approved by the Ethics Committee of the Federal University of Minas Gerais, Brazil - CAAE 09638212.8.0000.5149 - and all participants or their legal representatives provided written informed consent, according to World Medical Association Declaration of Helsinki.

* Corresponding author at: Faculdade de Farmácia, Universidade Federal de Minas Gerais, Avenida Antônio Carlos, 6627, Pampulha, Belo Horizonte, Minas Gerais, Brazil.
E-mail addresses: karinabgb@gmail.com, karinabgb@ufmg.br (K. B. Gomes).

https://doi.org/10.1016/j.jneuroim.2019.577027
Received 29 January 2019; Received in revised form 15 August 2019; Accepted 20 August 2019

Between June 2014 and December 2016, 43 participants were included in this study, of whom 12 with probable AD, 16 with MCI and 15 SCD individuals with no objective cognitive or functional impairment. All the subjects were recruited among patients attending at the Geriatric and Neurology Outpatient Clinics of the Hospital das Clínicas, Federal University of Minas Gerais (UFMG), in Belo Horizonte, Brazil. The diagnosis of AD was based on clinical evaluation, neuroimaging and CSF biomarkers: Aβ42 < 700 ng/L and total tau (t-tau) > 400 ng/L or phosphorylated tau (p-tau) > 60 ng/L and INNOTEST amyloid tau index (IATI) < 0.8 and index t-tau/Aβ42 > 0.52 (Duits et al., 2014). Clinically, individuals were classified according to the NIA-AA criteria (McKhann et al., 2011) and the MCI according to Petersen et al. (1999).

Cognitive performance was evaluated by Mini-Mental State Examination (MMSE) according to levels of education. The MMSE values were also normalized as z scores, from the standards of performance, according to the four levels of formal educational levels obtained from Caramelli et al. (2007) evaluation (z score negative – cognitive decline when compared to controls; z score = 0 or positive – no cognitive decline or better performance than controls). Patients with no functional impairment were classified as Functional Assessment Staging (FAST) stage 1. Individuals with SDC, but without objective evidence of impairment, were classified as FAST stage 2. FAST stage 3 included MCI patients. Patients with FAST stage 4, 5 and 6 had functional deficits that correspond to mild, moderate and severe dementia, respectively (Shankle et al., 2013). The MPs plasma levels were determined by flow cytometry according to Campos et al. (2010).

Statistical analyses were performed using SPSS 17.0 version. The results are expressed as median (interquartile range) (all non-parametric). The Mann-Whitney test was applied to compare two groups. Correlation was assessed using the Spearman rank correlation test. For all analyses, we considered $p < .05$ statistically significant.

3. Results

The group was composed by 15 (35%) men and 28 (65%) women, with median age (interquartile range) = 72.0 (12.0) years. The frequencies of FAST stages were 1–6 individuals (13.9%); 2–7 (16.3%); 3–18 (41.9%); 4–6 (14.0%); 5–4 (9.3%); and 6–2 individuals (4.6%). We observed 17 individuals (39.5%) with MMSE scores below the education-adjusted cut-off scores. The median MMSE z score was −0,102 (2.970).

We found a negative and significant correlation between PMPs (microparticles derived from platelet), TFMPs, LMPs and EMPs with MMSE z scores (r: −0.542, $p = .002$; $r = -0.501$, $p = .006$; $r = -0.456$, $p = .013$; and $r = -0.485$, $p = .008$, respectively). We also observed a positive and significant correlation between TFMPs, LMPs, EMPs and NMPs with FAST stages ($r = 0.427$, $p = .021$; r: 0.532, $p = .003$; r: 0.589, $p = .001$; and r: 0.655, $p < .001$).

In another analysis, the MMSE scores were reclassified as 1 (z score negative) or 2 (z score = 0 or positive). We observed that in subjects with z score = 1, the PMPs, LMPs and TFMPs levels were higher when compared to subjects with z score = 2 ($p = .016$, $p = .046$ and $p = .023$, respectively) (Table 1).

Similarly, we reclassified FAST groups in 1 (stages 1 and 2) and 2 (stages 3 to 6, MCI and AD dementia). We observed that subjects from Group 2 demonstrated higher levels of LMPs and NMPs when compared to subjects from Group 1 ($p = .024$ and $p = .004$, respectively) (Table 1).

Table 1
Microparticles levels according to MMSE and FAST classification.

Microparticle (MP/μL)	MMSE = 1	MMSE = 2	*P* value
PMPs	206.13 (158.33)	102.43 (109.25)	0.016*
LMPs	84.07 (77.33)	40.33 (68.77)	0.046*
TFMPs	70.60 (61.60)	40.47 (39.08)	0.023*
Microparticle (MP/μL)	FAST = 1	FAST = 2	*P* value
LMPs	40.33 (40.33)	85.87 (83.47)	0.024*
NMPs	39.30 (90.07)	133.87 (486.47)	0.004*

Results expressed as median (interquartile range). Microparticles derived from platelet (PMPs), leukocytes (LMPs), neurons (NMPs) and those expressing tissue factor (TFMPs). MMSE = 1: z score negative; MMSE = 2: z score = 0 or positive; FAST = 1: stages 1 and 2; FAST = 2: stages 3 to 6.
* $P > .05$: significant.

4. Discussion

Our study showed that higher MPs levels, especially PMPs, LMPs, EMPs and TFMPs, were associated with cognitive impairment in this population. PMPs, LMPs, EMPs and TFMPs are related to inflammation, endothelial damage and hemostasis complications (McCarthy et al., 2017). Moreover, these MPs can also stimulate cell release of proinflammatory cytokines, amplifying the systemic inflammatory process (Varon and Shai, 2015). Consequently, the results suggest that the platelet aggregation and inflammation are possible mechanisms associated with cognitive decline.

We also observed that higher MPs levels, mainly LMPs, NMP, TFMPs and EMPs were associated to lower functional performance (FAST stages) in the elderly sample. These findings suggest that inflammation, hemostasis complications and neuronal loss are also associated to dementing process, which compromises the functional capabilities.

Over the last years, inflammation has emerged as a third central feature of AD, as well as a link between Aβ plaques and neurofibrillary tangles, which has been observed in multiple studies of postmortem tissues of AD patient and in animal model. In this context, chronically activated microglia releases a variety of proinflammatory cytokines, as well as reactive oxygen species and nitric oxide. Many studies have pointed to the involvement of neuroinflammation in the progression of the neuropathological changes that are observed in dementia. Neuroinflammation is not thought to be causal, but a result of one or more risk factors associated with AD. Besides, it serves to increase the severity of the disease by exacerbating β-amyloid and tau pathologies (Kinney et al., 2018).

Platelets participate in hemostasis and contribute to inflammation and immune cells response. Recent studies have pointed to a crosstalk between platelets and neuroinflammation. For instance, when the integrity of the blood brain barrier is compromised in dementia process, platelets may be relevant for endothelial inflammation, as well as recruitment and activation of inflammatory cells, thereby potentially contributing to central nervous tissue pathogenesis (Langer and Chavakis, 2013).

The main limitation of our study is the small sample size. However, to our knowledge, this is the first study that investigated the MPs levels according to cognitive and functional stages, from normal aging to MCI to dementia. Our results suggest that MPs related to inflammation, endothelial damage and hemostasis complications might be involved in the pathophysiology of degenerative dementia.

Declaration of Competing Interest

None

Acknowledgements

Fundação de Amparo à Pesquisa de Minas Gerais (FAPEMIG), Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) and Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES). LCS, LPS, MGC, PC and KBG are grateful to CNPq Research Fellowship (PQ).

References

Alzheimer's Association, 2017. Alzheimer's disease facts and figures. Alzheimers Dement. 13, 325–373.

Barile, L., Vassalli, G., 2017. Exosomes: therapy delivery tools and biomarkers of diseases. Pharmacol. Ther. 82, 73–80.

Campos, F.M., Franklin, B.S., Teixeira-Carvalho, A., Filho, A.L., de Paula, S.C., Fontes, C.J., Brito, F.C., Carvalho, L.H., 2010. Augmented plasma microparticles during acute plasmodium vivax infection. Malar. J. 9, 327.

Caramelli, P., Herrera, J.R., Nitrini, R., 2007. Education-adjusted normative values for the mini-mental state examination (MMSE) in a large elderly cohort. Dement. Neuropsychol. 8, 126–131.

Duits, F.H., Teunissen, C.E., Bouwman, F.H., 2014. The cerebrospinal fluid "Alzheimer profile": easily said, but what does it mean? Alzheimers Dement. 10, 713–723.

Heppner, F.L., Ransohoff, R.M., Becher, B., 2015. Immune attack: the role of inflammation in Alzheimer disease. Nat Rev Neurosci. 16, 358–372.

Hosseinzadeh, S., Noroozian, M., Mortaz, E., Mousavizadeh, K., 2018. Plasma microparticles in Alzheimer's disease: the role of vascular dysfunction. Metab. Brain Dis. 33, 293–299.

Kinney, J.W., Bemiller, S.M., Murtishaw, A.S., Leisgang, A.M., Salazar, A.M., Lamb, B.T., 2018. Inflammation as a central mechanism in Alzheimer's disease. Alzheimers Dement. 4, 575–590.

Langer, H.F., Chavakis, T., 2013. Platelets and neurovascular inflammation. Thromb. Haemost. 110, 888–893.

Magalhães, C.A., Campos, F.M., Loures, C.M.G., Fraga, V.G., Oliveira, A.C.R., Chaves, A.C., Rocha, N.P., de Souza, L.C., Maia, R.D., Guimarães, H.C., Cintra, M.T.G., Mateo, E.C.C., Bicalho, M.A.C., Carvalho, M.G., Sousa, L.P., Caramelli, P., Gomes, K.B., 2019. Blood neuron cell-derived microparticles as potential biomarkers in Alzheimer's disease. Clin. Chem. Lab. 57, e77–e88.

McCarthy, E.M., Moreno-Martinez, D., Wilkinson, F.L., McHugh, N.J., Bruce, I.N., Pauling, J.D., Alexander, M.Y., Parker, B., 2017. Microparticle subpopulations are potential markers of disease progression and vascular dysfunction across a spectrum of connective tissue disease. BBA Clin. 7, 16–22.

McKhann, G.M., Knopman, D.S., Chertkow, H., 2011. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement. 7, 263–269.

Petersen, R.C., Smith, G.E., Waring, S.C., Ivnik, R.J., Tangalos, E.G., Kokmen, E., 1999. Mild cognitive impairment - clinical characterization and outcome. Arch. Neurol. 56, 303–308.

Shankle, R.W., Pooley, J.P., Steyvers, M., Hara, J., Mangrola, T., Reisberg, B., et al., 2013. Relating Memory to Functional Performance In Normal Aging to Dementia Using Hierarchical Bayesian Cognitive Processing Models. Alzheimer Dis Assoc Disord. 27, 16–22.

Varon, D., Shai, E., 2015. Platelets and their microparticles as key players in pathophysiological responses. J. Thromb. Haemost. 13, 40–46.