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Rafaela Cabral Gonçalves Fabiano

Análise prognóstica de uma coorte pediátrica em portadores de Nefropatia por IgA, através da Classificação de Oxford.

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RESUMO

A nefropatia por IgA (IgAN) é a doença glomerular mais comum em todo o mundo. A sua evolução clínica apresenta um espectro amplo, que varia desde uma condição benigna até a doença renal crônica terminal, sendo incomum uma evolução de apresentação rapidamente progressiva. Devido ao caráter insidioso, pesquisadores tem buscado a identificação de marcadores prognósticos capazes de predizer o desfecho da IgAN. A função renal basal, a pressão arterial, a proteinúria inicial e a redução da proteinúria durante o acompanhamento representam alguns dos marcadores clínicos identificados. Quanto às características patológicas, vários sistemas de classificação histológica haviam sido propostos para predizer o desfecho da IgAN, mas nenhum foi amplamente aceito, principalmente, devido à carência de estudos de reprodutibilidade. Em 2009, foi publicada a Classificação de Oxford, a qual é baseada na reprodutibilidade dos achados e no poder preditivo das lesões, independente de variáveis clínicas. Na nova Classificação de Oxford, foram identificadas quatro lesões histopatológicas preditoras de evolução da doença renal: hipercelularidade mesangial (M), proliferação endocapilar (E), esclerose segmentar ou adesão (S) e atrofia tubular/fibrose intersticial (T). Todavia, a aplicação dessa classificação em outras populações, principalmente pediátrica, precisa ser validada. Desse modo, este trabalho visa ao estudo da aplicação dessas variáveis como preditoras de risco em uma coorte pediátrica sul-americana.

Neste estudo, foram incluidos 56 pacientes com diagnóstico de IgAN por biópsia renal realizada com menos de 18 anos de idade, entre 1982 a 2010. Variáveis clínicas foram determinadas, tais como proteinuria, pressão arterial e taxa de filtração glomerular. Além das variáveis clínicas, a histologia foi analisada com o objetivo de avaliar a aplicação da classificação de Oxford nesta população. Para cada paciente, o bloco de parafina contendo o fragmento renal obtido por biópsia foi localizado e novos cortes finos foram feitos para a análise histopatológica do material. A Classificação de Oxford foi determinada para cada paciente por um único patologista, cego aos dados de evolução do paciente. Os desfechos principais analisados foram a porcentagem acumulada de pacientes que tiveram redução de 50% da taxa de filtração glomerular

(TFG) e a taxa de declínio da função renal. Durante um tempo de seguimento 88.5±9.4 meses, 8 crianças (14%) tiveram 50% de redução na função renal basal e 5 (9%) evoluíram para doença renal crônica terminal em 109.0±84.7 meses. Na análise por Kaplan Meier, a presença de hipercelularidade endocapilar e atrofia tubular/fibrose intersticial > 25% foram preditores de sobrevida renal. A proteinúria inicial foi igualmente um preditor clínico de má evolução renal. Na análise multivarida por regressão de Cox, após ajuste com proteinúria inicial, hipercelularidade endocapilar (HR 21.6; 95%CI, 2.9 to 160.5; p 0.003) e glomeruloesclerose segmentar (HR 8.2; 95%CI, 1.3 to 51.0; p 0.023) se mostraram marcadores independentes de risco. Na análise por regressão linear múltipla, a atrofia tubular/fibrose intersticial e a hipercelularidade endocapilar também tiveram correlação com a sobrevida renal. A Classificação de Oxford, com exceção da hipercelularidade mesangial, mostrou-se válida para predizer a redução da função renal em pacientes com nefropatia por IgA.

ABSTRACT

IgA nephropathy (IgAN) is the most common glomerulonephritis worldwide. IgAN is characterized by a highly variable course ranging from a totally benign condition to end-stage renal disease (ESRD), although a rapidly progressive course in uncommon. As IgAN disease has an insidious progression, searches look for prognostic markers capable of predicting the IgAN outcome. Baseline renal function, arterial pressure, proteinuria and reduction in proteinuria during follow are some of the identified clinical markers. Several histological classification systems had been proposed to predict the outcome of IgAN; however, none has been widely accepted, especially by the lack of reproducibility studies. In 2009, the new Oxford Classification was published, based on high reproducibility and predictive power of the lesions, independent of clinical variables. The new Oxford Classification identified four histological features, capable of predicting renal outcome (ESKD or 50% reduction in eGFR at baseline): mesangial hypercellularity (M), endocapillary proliferation (E), segmental sclerosis or adhesion (S) and tubular atrophy/interstitial fibrosis (T). However, the application of this classification in other populations, especially paediatric, needs to be validated. This work aims to study the application of these variables as risk predictors in a South American pediatric cohort.

This study included 56 patients with renal biopsy diagnosis of IgAN made with less than 18 years old, from 1982 to 2010. Clinical variables were determined, such as proteinuria, hypertension and glomerular filtration rate. In addition to the clinical features, histology was evaluated in order to address the application of Oxford classification in our population. For each patient, the paraffin block was selected and new thin sections were cut for histopathological analysis of the renal material. The biopsy specimens were classified and standardized according to the Oxford classification, by a pathologist blinded to patient outcome at the time of scoring. The primary endpoint outcomes were the cumulative percentage of patients who had a 50% reduction in glomerular filtration rate (GFR) compared to baseline and the rate of renal decline. Over a follow-up of 88.5 ± 9.4 months, 8 children (14%) had a 50% reduction in baseline renal function and 5 (9%) developed chronic ESRD in 109.0 ± 84.7

months. In Kaplan Meier analysis, the presence of endocapillary hypercellularity and tubular atrophy/interstitial fibrosis > 25% were predictors of renal survival. The initial proteinuria was also a clinical predictor of poor renal outcome. In multivariate analysis by Cox regression, after adjusted for initial proteinuria, endocapillary hypercellularity (HR 21.6, 95% CI, 2.9 to 160.5; p 0.003) and segmental glomerulosclerosis (HR 8.2; 95% CI, 1.3 to 51.0; p 0.023) were shown to be independent risk markers. In multivariate linear regression, tubular atrophy/interstitial fibrosis and also endocapillary hypercellularity were also associated with renal prognosis.

The Oxford classification was showed to be valid to predict reduction in renal function in patients with IgAN, except for mesangial hypercellularity.

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LISTA DE ABREVIATURAS E SIGLAS

ΔT	Intervalo de tempo
C	Hipercelularidade extracapilar
CH	Domínio de cadeia pesada
DRC	Doença renal crônica
DRCT	Doença renal crônica terminal
E	Hipercelularidade endocapilar
eTFG	Taxa de filtração glomerular estimada
Gal	β1,3-galactose
GalNAc	N-acetilgalactosamina
gd-IgA1	IgA1 hipogalactosilada
H:M	Homens:mulheres
IgAN	Nefropatia por IgA
M	Hipercelularidade mesangial
MEST	Acrônimo para as variávies patológicas da classificação de Oxford
MBL	Lecitina ligadora de manose
NA	Não disponível
NeuNac	N-acetilneuramínico
S	Esclerose segmentar
Seg	Seguimento
SRAA	Sistema renina-angiotensina-aldosterona
STn	Antígeno Sialil-Tn
T	Atrofia tubular/infiltrado intersticial
TLRs	*Toll like receptors*

SUMÁRIO

1.0 INTRODUÇÃO

1.1. GENERALIDADES

A nefropatia por IgA (IgAN) é a glomerulopatia mais comum em todo o mundo. A IgAN foi descrita primeiramente por Berger and Hinglais in 1968 ao analisarem biópsias renais de pacientes com hematúria microscópica persistente, com o achado de imunodepósitos de IgA e IgG no mesângio. Sua incidência varia entre regiões do mundo: cerca de 40% das biópsias de rim nativo na Ásia, comparadas com 20% na Europa, 5-10% nos Estados Unidos e menos de 5% na África Central (1). Além de diferenças genéticas, a variabilidade da incidência de IgAN reflete as indicações clínicas para a biópsia renal, haja vista a necessidade de avaliação de espécime renal para o diagnóstico.

A IgAN incide mais em adolescentes e adultos jovens, sendo mais comum no sexo masculino (2 a 3:1 relação homens/mulheres). Os níveis de hematúria e proteinúria são amplos. A hematúria macroscópica é frequente em crianças, após exposição a infecções na mucosa aérea e digestiva, sendo as vezes o primeiro sinal da doença (2). Os adultos geralmente se apresentam com proteinúria, hematúria microscópica ou hipertensão. Síndrome nefrótica é incomum ao diagnóstico (3).

A nefropatia de IgA apresenta evolução clínica variável, desde uma condição benigna (4) até doença renal em estágio terminal (5,6). Uma grande coorte retrospectiva japonesa com 1012 pacientes portadores de IgAN mostrou sobrevida renal de 84,3, 66,6 e 50,3% em 10, 20 e 30 anos, respectivamente (6). Em crianças, uma redução de 50% da eGRF em 5 anos foi observada em cerca de 12-22% dos pacientes pediátricos com IgAN (7,8).

A deposição mesangial de IgA predominante ou co-predominante é o definidor da doença. Codepósitos de IgG e IgM, complemento C3 (9–12) e properdina (13) também são vistos. C4 ou C4d, lecitina ligadora de manose (MBL) e C5b-C9 são frequentemente detectados (14), enquanto C1q está geralmente ausente (10–12,14). Depósitos granulares mesangiais de IgA também foram documentados em população saudável, sem evidência de lesão renal (15) e em pacientes com glomerulonefrite mesangioproliferativa, com urinálise e função renal normais (16). Ainda não está claro

se essas três apresentações de IgAN – sintomática, assintomática e subclínica – dividem os mesmos mecanismos patogênicos (1).

1.2. FISIOPATOLOGIA

A IgA está presente no soro e nas secreções mucosas em dois isotipos distintos, IgA1 e IgA2. Ambos, assim como a IgM, têm a capacidade de formar polímeros. A IgA sérica humana é representada principalmente pela forma monomérica (90-99%), sendo o isotipo IgA1 o predominante (~85% da IgA total), o que condiz com a dominância de células produtoras de IgA1 plasmática na medula óssea, baço e linfonodos (1). Ao contrário da forma monomérica predominante no sangue, a IgA polimérica predomina nas secreções externas (17). Em relação aos subtipos de IgA nas mucosas, a proporção de IgA1 e IgA2 reflete a distribuição das células secretoras de IgA1 e IgA2. Por exemplo, no trato respiratório, nas glândulas salivares e lacrimais e no trato intestinal alto, há mais células produtoras de IgA1, enquanto, há uma leve predominância de células produtoras de IgA2 no colon e trato fenital feminino (18).

As cadeias pesadas da IgA1 e IgA2 apresentam uma homologia marcante na sua estrutura primária (CH2, 99,3% e CH3 98% de homologia). A principal diferença entre os dois subtipos está na região de dobradura entre os domínios 1 e 2 das cadeias pesadas (CH1 e CH2) de cada subtipo. A região de dobradura da IgA1 é mais extensa, com sítios de ligação para O-glicosídeos (19). A dobratura da IgA1 contém nove sítios de O-glicosilação, ricos em resíduos de prolina, serina e treonina. A ligação dos O-glicosídeos consiste em N-acetilgalactosamina (GalNAc) com β1,3-galactose (Gal) e ácido siálico, como ácido N-acetilneuramínico (NeuNac) (20). A composição de carboidratos na IgA1 sérica normal é variável e prevalecem as formas que incluem o dissacarídeo GalNac-Gal (antígeno T), com as formas mono ou dissiálicas. IgA1 sérica normalmente apresenta poucos O-glicosídeos deficientes em galactose (21). Nos pacientes com IgAN, há um aumento de IgA1 circulante com O-glicosídeos compostos de GalNac, sem galactose ligada (antígeno Tn), com ou sem ácido siálico (22,23). Essa estrutura é conhecida como antígeno Sialil-Tn (STn). O antígeno Tn é parte do epítopo reconhecido pelas IgG e IgA, formando os imunocomplexos nefritogênicos (24,25).

O nível de IgG anti-glicosídeo específico está aumentado nos pacientes portadores de IgAN e está relacionado com nível de proteinúria e nível de imunocomplexos IgA1-IgG na urina (26). Além disso, níveis aumentados de IgA1 em imunocomplexos foram observados em episódios agudos de hematúria macroscópica (26). Os imunocomplexos não efetivamente metabolizados pelo fígado são depositados na região mesangial, devido a sua massa elevada, estimulando a proliferação mesangial e aumento de citocinas inflamatórias (27).

A patogênese da IgAN ainda não está completamente elucidada. Pesquisas atuais apontam uma sequência ordenada de quatro "eventos", como fundamentais para a ocorrência da doença (28). Primeiramente, há uma produção anômala de IgA1 hipogalactosilada (gd-IgA1) na região da dobradura. Estímulos genéticos e da resposta imune inata, principalmente via *Toll like receptors* (TLRs), estariam envolvidos neste processo, os quais alterariam também o *crosstalk mucosa-bone marrow*. Os linfócitos B produtores de IgA1 polimérica hipogalactosilada na mucosa são direcionadas para sítios sistêmicos, principalmente a medula óssea, elevando a gd-IgA1 sérica (29). Todavia, apenas a IgA1 sérica aberrante não causa injúria renal. O segundo "evento" na gênese da IgAN é a produção de anticorpos contra a região da dobradiça hipogalactosilada. Esses anticorpos têm ocorrência natural no plasma, mas podem ter sua produção exacerbada, após infecções por bactérias e vírus que expressam N-acetilgalactosamina como antígenos de superfície (30–33). Aconteceria, assim, uma resposta imune cruzada entre os antígenos dos microrganismos e a gd-IgA1. Episódios de hematúria macroscópica, após infecções de mucosa aérea ou intestinal, são descritos como manifestação clínica da IgAN (2). A IgAN portanto é classificada como uma doença autoimune, na qual há a produção de autoanticorpos, tipo IgA e IgG, contra a IgA1 hipogalactosilada. A ligação da IgA aberrante com os anticorpos produzem os imunocomplexos, o terceiro "evento" na patogênese da doença (34). A ligação do anticorpo à dobradiça da IgA1 também difulta o seu reconhecimento da IgA1 pelo fígado e consequentemente reduz o seu clareamento sérico (35). Há evidências de que imunocomplexos maiores são mais indutores de lesão renal do que imunocomplexos menores (25,36). O gatilho para a lesão renal é a deposição dos imunocomplexos no mesângio, definido como o quarto "evento". Há ainda muita discussão acerca do receptor de IgA nas células glomerulares (37), mas sabe-se a

deposição ocorre majoritariamente no mesângio, com pouco depósito tubular e epitelial. Os depósitos de imunocomplexos contendo gd-IgA1 são indutores iniciais de inflamação e, através do *crosstalk mesangio-tubulo-podócito,* induzem inflamação global do glomérulo e injúria tubulointersticial (38).

1.3. MARCADORES DE PROGNÓSTICO

Devido ao caráter insidioso da nefropatia, estudiosos buscam marcadores prognósticos capazes de predizer o desfecho da IgAN, permitindo ajustes na vigilância e tratamento dos pacientes. Além disso, a identificação de marcadores poderia corroborar para o entendimento da patogênese e, consequentemente, o desenvolvimento de novas terapias específicas para a IgAN.

Existem evidências que alguns marcadores clínicos e laboratoriais no momento do diagnóstico são capazes de predizer o risco de uma doença renal crônica progressiva. Função renal basal, pressão arterial, proteinuria (39) e redução da proteinúria durante o acompanhamento (40) são alguns dos marcadores identificados. Atualmente, outros marcadores mais específicos, baseados na teoria de "múltiplos eventos" da fisiopatologia da IgAN, estão sendo estudados, tais como a dosagem sérica de IgA hipogalactosilada, de anticorpos anti-glicano e de complexos imunes contendo IgA (41). Tais marcadores são incipientes por ora, sendo correlacionados principalmente com a atividade da IgAN.

A análise de espécime renal por biópsia, além de obrigatória para o diagnóstico, poderia contribuir com informações prognósticas adicionais às providas por análises clínicas. Vários sistemas de classificação histológica foram propostos, visando predizer a progressão da IgAN (42–46). Todavia, nenhum foi amplamente aceito, principalmente pela carência de estudos de reprodutibilidade. Além disso, os dados longitudinais dos pacientes não foram considerados para a confecção das classificações patológicas prévias. Sabe-se que dados tranversais, como os obtidos por biópsia renal, são raramente preditores de desfecho poderosos, quando comparados com os dados clínicos obtidos ao longo do acompanhamento longitudinal dos pacientes. Isso é particularmente verdadeiro, em glomerulopatias de progressão lenta, como a IgAN (8).

1.4. CLASSIFICAÇÃO DE OXFORD

Em 2009, a Classificação de Oxford foi publicada por um consenso internacional de patologistas, baseada na reprodutibilidade dos achados e no poder preditivo, independente de variáveis clínicas (8,47). Para o estudo, foi utilizada uma coorte retrospectiva de 265 pacientes, distribuídos em 8 países, em 4 continentes. Cerca de 22% (59/265) dos pacientes tinham menos de 18 anos, à data da biópsia. Alguns critérios de inclusão foram: eTFG≥30mL/min/1,73m^2 e proteinúria inicial >0,5g/24h em adultos e ≥0,5g/24h/1,73m^2 em crianças. Na nova Classificação de Oxford, foram identificadas quatro lesões histopatológicas, preditoras de evolução da nefropatia (DRC V ou redução de 50% da eTFG): hipercelularidade mesangial (M), proliferação endocapilar (E), esclerose segmentar ou adesão (S) e atrofia tubular/fibrose intersticial (T). A lesão E não apresentou correlação estatística para o desfecho de sobrevida renal combinado, todavia houve interação significativa entre E e imunossupressão. Nos pacientes que receberam imunossupressão, a presença de E indicou uma menor redução do eGFR/ano, produzindo evidência indireta de que a proliferação endocapilar seria responsiva ao tratamento imunossupressor. Devido ao seu potencial efeito prognóstico em relação ao tratamento, E foi considerada na classificação. MEST se tornou um acrônimo, pelo qual a classificação também é conhecida.

Vários estudos, incluindo o estudo de Oxford original, mostraram diferenças na prevalência das lesões histológicas entre crianças e adultos. Comparadas com adultos, crianças com IgAN apresentam mais hipercelularidade mesangial e endocapilar e menos lesão tubulointersticial (8,48). Contudo, controvérsias sobre a interferência do intervalo de tempo (ΔT) entre o indício de lesão renal e a biópsia sugerem que as lesões proliferativas seriam marcadoras de fase aguda, enquanto a lesão tubulointersticial e a esclerose glomerular, marcadoras de fase crônica (49). Se a maior incidência de lesões proliferativas na criança se deve a uma característica peculiar da IgAN na infância ou a um menor ΔT entre o início de doença e a realização de biópsia renal ainda é desconhecido.

A população original do estudo de Oxford compreendeu pacientes originários de quatro continentes: cinco centros na Ásia, seis na Europa, dois nos Estados Unidos, um na América do Sul e dois serviços multicêntricos (Canadá e EUA). Apesar de racialmente diversa, a ancestralidade foi considerada em subanálise apenas entre caucasianos e asiáticos (sem diferença do poder preditivo das lesões), devido à baixa representação das outras etnias. Portanto, a validação da nova classificação para diferentes populações se faz necessária. Recentemente, vários estudos de validação foram publicados (5,6,50,51), contudo, nenhum na América Latina.

A cerca da população pediátrica, houve três coortes publicadas exclusivamente pediátricas, além de outras duas grandes coortes, que envolveram, além de adultos, crianças. A tabela 1 ilustra comparativamente as diferenças clínicas, patológicas e estatísticas dos diferentes estudos, envolvendo a Classificação de Oxford na população pediátrica. Edström *et. at* constataram que a presença de S não se associava à evolução da IgAN em um coorte 99 crianças suíças (52). Shima *et al* analisaram 161 crianças no Japão e constataram que apenas M e T funcionavam com marcadores prognósticos de IgAN nesta população (53). Na China, a análise de uma coorte de 218 crianças revelou que apenas T servia como marcador de prognóstico, após análise multivariada (7). Herzenberg *et al* estudaram uma população norte-americana de 187 portadores de IgAN, sendo 45 crianças. Concluíram que cada lesão histológica oferecia o mesmo valor preditivo, encontrado no Oxford, exceto o M, que se comportou como preditor mais fraco (54). Recentemente, o estudo europeu VALIGA analisou retrospectivamente 1147 pacientes europeus (97,5% de caucasianos) com IgAN, sendo 174 crianças. M, S e T (e não E) foram identificados como preditivos de desfecho renal nesta coorte (50).

É notável a distinção da atrofia tubular/fibrose intersticial (T) como a única característica patológica capaz de predizer risco de perda de função renal, identificada em todas as coortes. As lesões M e E apresentam variabilidade como marcadores entre os estudos. S não foi identificada nas coortes exclusivamente pediátricas. O achado de T como valor prognóstico corrobora com a teoria que a atrofia tubular/fibrose intersticial é sequela de uma agressão renal prévia. Tal sequela é capaz de perpetuar o processo de deteriorização da função renal, mesmo na ausência do estímulo agressor inicial (55). Além disso, o nosso arsenal terapêutico é limitado para modificar T,

enquanto a terapia hipotensora e imunossupressora teria um potencial de modificar lesões mais agudas, como M e E. T representaria um estágio comum de evolução das glomerulopatias, portanto, inespecífico da nefropatia de IgA. A esclerose segmentar (S) também é considerada um lesão crônica, contudo não foi identificada como marcador prognóstico em nehuma das coortes exclusivamente pediátricas, após análise multivariada. Edström e Shima argumentam que a baixa prevalência da lesão contribuiu para a sua não significância, nas coortes suíça e japonesa, respectivamente (49,52). Para Le, a baixa reprodutibilidade das adesões isoladamente justificaria a diferença de prevalência de S entre as coortes e consequentemente, o seu baixo valor prognóstico (7). A presença de crescentes celulares/fibrocelulares foi estudada em várias coortes de validação de Oxford. Apesar dos crescentes apresentarem correlação estatística na análise univariada, tais lesões não foram significativas, após análise multivariada em todas as coortes citadas.

Em suma, a IgAN é a doença glomerular mais comum em todo o mundo. A publicação de uma classificação patológica com valor prognóstico permite maior atenção e cuidado no seguimento de uma parcela significativa de pacientes com IgAN. A predição de risco fornece também subsídios para o desenvolvimento futuro de novas terapias específicas para a IgAN. A validação da aplicação dessa classificação, a Classificação de Oxford, em nossa população se faz necessária para compartilharmos os benefícios do conhecimento científico em prol de um impacto positivo na história natural da IgAN.

Vale ressaltar que esta dissertação foi organizada em dois artigos científicos, de acordo com as resoluções que regulamentam o formato das teses e dissertações do Programa de Pós-Graduação em Ciências da Saúde - Saúde da Criança e do Adolescente, da Faculdade de Medicina/UFMG. O primeiro artigo é uma revisão da literatura que aborda, resumidamente, diversos aspectos sobre a patogênese e fisiopatologia da IgAN. No segundo artigo, são descritos os resultados obtidos neste trabalho. As referências bibliográficas estão dispostas ao final de cada artigo ou seção, conforme as normas de Vancouver (Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication - www.ICMJE.org).

Table 1 – Características clínicas, patológicas e estatísticas dos estudos envolvendo a Classificação de Oxford em crianças.

	Oxford(8)	Herzenberg(54)	Edstrom Halling(52)	Shima(53)	Le(7)	VALIGA(50)
País	Multi nacional	Canadá/EUA	Suiça	Japão	China	Multi nacional
Etnia						
Caucasiana	66%	69%	NA	-	-	97.5%
Asiática	27%	20%	NA	100%	100%	0.5%
Africana	3%	5%	NA	-	-	0.5%
Outras	4%	4%	NA	-	-	1.5%
Centros[a]	Multi	Multi (4)	Único	Único	Multi (7)	Multi (55)
No. pts	265	187	99	161	218	1147
No. pts - idade < 18 y	59	45	99	161	218	174
% pts - idade < 18 y	22.5	24	100	100	100	15.2
Tempo Seg. (meses)	65	53	156	54	56	56
Idade (anos)	30	34	9.7	11.7	14	36
H:M	2.6:1	1.4:1	1.4:1	1.7:1	1.9:1	2.7:1
Prot. para inclusão (g/d)	>0.5	>0.5	Any	Any	≥0.5	Any
Prot. inicial (g/d)	1.7	1.7	2.0[f]	0.7	1.5	1.3
Prot. Seg. (g/d)	1.1	1.0	1,65[f]	NA	0.6	0.8
TFG para inclusão (mL/min/1,73m^2)	≥30	≥30	Qualquer	≥60	≥30	Qualquer
TFG inicial (mL/min/1,73m^2)	83	82	100	103	134	73
DRC 1/2/3/4/5[b]	36/38/26/0/0	NA	54(1&2)/30/15/2	NA	NA	60(1&2)/28/7/2
Estimativa da TFG	Schwartz (0.55)	Schwartz (0.55)	Depuração de Inulina ou iohexol	Schwartz (0.55 o 0.7)	Schwartz	Schwartz (0.55)
Hipertensão[c] (%)	31	58	NA	NA	NA	65
PAM inicial	98	96	85	79	88	98
PAM Seg.	95	92	84	NA	86	96
Bloqueio do SRAA (%)	74	87	86	NA	61.5	86
Terapia imunossupressora[d] (%)	29	41	43	16	56	46
Desfecho	Redução de 50% da TFG ou DRCT; slope of eGRF	Redução de 50% da TFG ou DRCT; slope of eGRF	Redução de 50% da TFG ou DRCT	DRC estágio 3-5	Redução de 50% da TFG ou DRCT	Redução de 50% da TFG ou DRCT
No. eventos de desfecho	58 (22%)	26 (14%)	18	7	24 (12.4)	183 (16%)
No. eventos de DRCT	34 (13%)	21 (11%)	15	5	NA	135 (12%)
No. patologistas	5, cego	2	1, cego	NA	2	NA
Lesão (%)						
M0/M1	20/80	NA	69/31	36/64	55/45	72/28
E0/E1	58/42	NA	90/10	42/58	77/23	89/11
S0/S1	NA	NA	77/23	92/8	38/62	70/30
T0/T1/T2	NA	NA	84/12/3	99/1/0	93/7/1	79/17.4/3.6
C0/C1	55/45	NA	82/18	48/52	44/56	89/11
A0/A1	NA	NA	NA	NA	NA	72/28
Método estatístico	Regressão linear, regressão logística, regressão de Cox	Regressão linear	Regressão de Cox	Regressão de Cox	Regressão de Cox	Regressão linear, Regressão de Cox
Fatores ajustados	TFG, PAM, proteinúria iniciais e seg.	TFG inicial, PAM e proteinúria seg.	Proteinúria inicial e 1 ano seg.	Proteinúria inicial	TFG, PAM, proteinúria iniciais	TFG inicial, Proteinúria e PAM seg.

Lesões independentes[e]	MST	EST	MET	MT	T	MST
Correlação TFG inicial	EST	-	MESTC	Nenhum	T	MST
Correlação Prot. Inicial	MSC	ES	MC	ME	MESTC	MEST
Correlação PAM inicial		-	-	Nenhum	MST	MST
Correlação uso de ISS	E	E	-	-	-	Nenhum

Nota: os dados nos estudos Oxford, Herzenberg and VALIGA correspondem a toda a coorte (crianças e adultos)

[a] Número de centros

[b] Porcentagem incluída em cada estágio de DRC

[c] Hipertensão ou uso de hipotensores à admissão no estudo.

[d] Uso de esteróides ou outros imunossupressores

[e] Análise multivariada

[f] Albuminúria

Abreviações: DRC, doença renal crônica; DRCT, doença renal crônica terminal; E, hipercelularidade endocapilar; H:M, homens:mulheres; ISS, imunossupressores; M, hipercelularidade mesangial; NA, não disponível; PAM, pressão arterial média; Prot, proteinúria; Pts, pacientes; S, segmental glomerulosclerosis; SRAA, sistema renina-angiotensina-aldosterona; Seg, seguimento; TFG, taxa de filtração glomerular; T, fibrose intersticial/atrofia tubular.

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2.0 ARTIGO DE REVISÃO

Immunoglobulin A Nephropathy: a Pathophysiology View

Rafaela Cabral Gonçalves Fabiano[1], Sérgio Veloso Brant Pinheiro[2], *et al.*

[1] Division of Nephrology, Clinics Hospital, Federal University of Minas Gerais, Belo Horizonte, Brazil.

[2] Unit of Pediatric Nephrology, Federal University of Minas Gerais, Belo Horizonte, Brazil.

*Correspondence to Sergio Veloso Brant Pinheiro, MD, PhD

Rua Antilhas 80, ap 601. Belo Horizonte, MG, Brazil, 30315-480. FAX: + 55-31-34099770, TEL: + 55-31-93024774, e-mail: svbpinheiro@gmail.com

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Abstract

IgA nephropathy is the leading causes of glomerulonephritis worldwide and an important cause of kidney disease in young adults. It has revealed as an autoimmune disease. Current studies indicate an ordered sequence of multi-hits as fundamental to the disease occurrence. Altered glycan structures in the hinge region of the heavy chains of IgA1 molecules act as autoantigens, potentially triggering the production of glycan-specific autoantibodies. Recognition of neoepitopes by IgA and IgG antibodies leads to the formation of immune complexes galactose-deficient IgA1 – anti glycan IgG/IgA. As a result, nephritogenic immune complexes form in the circulation and deposit in mesangium. Deposited pathogenic immune complexes ultimately induce glomerular injury. New insights into the molecular mechanism of this disease could provide the rational bases for developing new biomarkers for diagnosis and monitoring of disease activity and disease-specific therapeutic approaches.

Keywords: IgA nephropathy, IgA1 glycosylation, Anti-glycan antibodies, Galactose deficiency, Glomerulonephritis.

Introduction

The IgA nephropathy (IgAN) was first described by Berger and Hinglais in 1968 while studying the finding of mesangial immunodeposits of immunoglobulin (Ig) A and IgG on renal biopsies of patients with persistent microscopic hematuria. IgAN is one of the leading causes of glomerulonephritis worldwide. It is usually detected among adolescents and young adults and the male-to-female ratio varies from 2:1 to 3:1 in many studies (1). Although there are clear geographical and ethnic variances, IgAN is more common in Asians. IgAN was diagnosed in 40% of native-kidney biopsies in Asia, compared with 20% in Europe, 5-10% in the United States and less than 5% in Central Africa (2). It should be mentioned that differences in indications for renal biopsy might at least in part explain the variability in the prevalence of IgA worldwide.

IgAN typically presents with hematuria and varying degrees of proteinuria. Gross hematuria is common in children after exposure to upper respiratory tract infections and may be the first symptom of the disease (3). Adults usually present with persistent microscopic hematuria, moderate levels of proteinuria or hypertension. Massive proteinuria or nephrotic syndrome is unusual at diagnosis. Moreover, IgAN is characterized by a highly variable course that evolves from a totally benign condition (4) to end-stage renal disease (ESRD) (5,6). According to a Japanese cohort with 1012 IgAN patients, the renal survival was 84.3, 66.6 e 50.3% in 10, 20 and 30 years (6). In children, a reduction of 50% in eGFR was described in 12-18% of patients (7,8). There are several clinical and histologic factors that strongly determined the final outcome of patients with IgAN. Clinical predictors are hypertension, renal function at diagnosis, proteinuria and reduction of proteinuria during follow-up (9). Pathological factors that indicate unfavorable outcomes are: mesangial hypercellularity, segmental glomerulosclerosis, endocapillary hypercellularity and interstitial fibrosis/tubular atrophy; according to the Oxford classification (10,11). Meta-analysis of Oxford validation studies did not confirm the mesangial hypercellularity as a prognostic factor and added the presence of crescents to the other three factors (mesangial hypercellularity, segmental glomerulosclerosis and interstitial fibrosis/tubular atrophy) as determinants of progression to end-stage renal disease (5).

The mesangial deposition of dominant or co-dominant IgA is what defines the disease. Codeposits of IgG and IgM, C3 (12–15) and properdin (16) are also seen. C4 and C4d, mannose-binding lectin (MBL) and C5b-C9 are often detected (17) while C1q is usually absent (13,15,17). These findings suggest activation of the alternate pathway and lectin pathway as well in the pathogenesis of IgAN (18). However, mesangial granular IgA deposits have also been documented in a healthy population with no evidence of renal injury (19) and in patients with mesangioproliferative glomerulonephritis, with normal renal function and urinalysis (20). It is not yet clear whether these three presentations IgAN - symptomatic, asymptomatic and covert - share the same pathogenic mechanisms. The aim of this article is to make an uptodate in the IgAN nephropathy with emphasis in physiopathology.

IgA structure

In humans, IgA surpasses the daily production of all other immunoglobulins (~ 70 mg kg^{-1} day^{-1} versus ~ 22 mg kg^{-1} day^{-1} of IgG and ~ 7 mg kg^{-1} day^{-1} of IgM). The lower plasma level of IgA compared with that of IgG is due to shorter circulatory half-life of IgA (5 days versus 21 days of IgG) and the fact that approximately 2/3 of IgA produced is selectively transport into external secretions (2). IgA is found in the serum and mucosal secretions in two distinct isotypes, IgA1 and IgA2. Both isotypes can form polymers, in which monomers subunit are linked via an additional small polypeptide termed J chain at the C-terminus of α-chains. Human serum IgA is represented mainly by the monomeric form (80-99%). The predominant isotype is IgA1 (~ 85% of total IgA), which is consistent with the dominance of IgA1-producing plasma cells in the bone marrow. On the other hand, polymeric IgA (dimers or tetramers) predominates in external secretions (21). The IgA1/IgA2 ratio reflects differential distribution of IgA1 and IgA2 secreting cells. According to IgA1/IgA2 ratio, IgA1-secreting cells prevails in salivary and lacrimal glands, respiratory tract and upper gastrointestinal tract in comparison to a slight predominance of IgA2-secreting cells in the colon and female reproductive system (22).

The heavy chains of IgA1 and IgA2 show a marked homology in their primary structure (CH2, 99.3% and CH3, 98% homology) (2). The main difference between

these two subtypes is the hinge region (HR) between domains 1 and 2 of the heavy chain (CH1 and CH2) that results in diverse biological properties. In IgA1, there is a duplicated insertion of a stretch of amino acids in the hinge region, while it is absent in IgA2 (23). The extended HR of IgA1 may add sequential flexibility for the Fab fragment and thereby increases the antigen-binding capacity. The IgA1 HR makes them highly susceptible to specific IgA-1 proteases, such as serine proteases, cysteine proteases. Most of these enzymes are specific for human IgA1 HR, given little homology to this region in other vertebrates (2). They are produced by many bacteria, for example, *Haemophilus influenzae, Streptococcus pneumoniae, Neisseria meningitidis, Neisseria gonorrhea, Streptococcus sanguis* and others (23). The antigen specificity is also distinct between the two subtypes. IgA antibodies against proteins and glycoproteins from food or microbial origins are predominantly of IgA1 subtype, whereas IgA antibodies against polysaccharides, lipopolysaccharides and lipoteichoic acid are mainly of IgA2 subtype (24).

The IgA1 HR features a 18 amino-acid insertion, lacking in IgA2, comprising a sequence of amino acids rich in proline, serine and threonine, and is decorated with 3-5, or occasionally 6, O-linked oligosaccharide (25). O-glycosylation is mediated by specific glycosyltransferases in the Golgi apparatus of IgA1-secreting cells (26). The O-glycosides binding regions consist of N-acetylgalactosamine (GalNAc) with β1,3-linked galactose (Gal), with or without attached sialic acid (N-acetylneuraminic acid – NeuNAc) (27). The synthesis of the O-glycoside is initiated via enzymatic addition of GalNAc to serine and threonine residues by *UDP-GalNAc:polypeptide N-acetylgalactosaminyltransferases* (GalNAcTs). Gal is linked to the GalNAc by β1,3-*galactosyltransferase enzyme* (C1GalT1). The stability of C1GalT1 is given by its specific chaperone, *Core 1 β1,3-galactosiltransferase-specific chaperone* (Cosmc). The sialic acid NeuAc is linked to GalNAc by *α2,6-sialyltransferase GalNac I and II* (ST6GalNac I or ST6GalNac II) or linked to Gal by *α2,3 sialyltransferase* (28).

The composition of carbohydrates in normal serum IgA1 varies and most prevalent forms includes GalNAc-Gal disaccharide (T antigen), with mono- and di-sialylated forms. Serum IgA1 usually presents few galactose deficient O-glycosides (Gd-IgA1) (24). In patients with IgAN, there is an increase of circulating IgA1 O-glycosides compounds of GalNAc without galactose (Tn antigen), sialylated or not (29,30). This

structure is known as sialylated Tn antigen (STn).The Tn antigen is part of the epitope recognized by IgG and IgA, forming nephritogenic immune complexes (31,32).

Pathogenesis

The pathogenesis of IgAN is still not completely elucidated. Current studies indicate an ordered sequence of “four hits" as fundamental to the disease occurrence. First, there is an anomalous production of poorly galactosylated IgA1 O-glycoforms. Genetic stimuli and the innate immune response, mainly via Toll-like receptors (TLRs) are involved in this process, which also alter the crosstalk between mucosa and bone marrow. Mucosal B lymphocytes, that produce undergalactosylated IgA1, are displaced to systemic sites, especially the bone marrow, raising the serum Gal-deficient IgA1 (Gd-IgA1). However, only circulating aberrant IgA1 does not cause kidney injury. The “second hit" in the pathogenesis of IgAN is the production of antibodies against the region of the undergalactosylated hinge. These antibodies are naturally occurring in the plasma, but may have exacerbated their production after infection by bacteria and viruses that express N-acetylgalactosamine as surface antigens. A cross-immune response thus happens between antigens of microorganisms and Gd-IgA1. Episodes of gross hematuria after infections of air or intestinal mucosa are described as clinical manifestation of IgAN. The IgAN is therefore classified as an autoimmune disease in which there is a production of autoantibodies, IgG and IgA, against the Gd-IgA1. The binding of glycan-specific IgG and IgA antibodies to aberrant IgA produce the immune complexes, the “third hit" in the pathogenesis of the disease. Antibody binding to the IgA1 hinge also hampers the recognition of IgA1 by the liver and thus reduces their serum clearance. The trigger for the renal injury is the deposition of immune complexes in the mesangium, defined as the “forth hit". There is still much debate about the IgA receptors in glomerular cells, but it is known that deposition occurs mainly in mesangium with little tubular or epithelial deposits. There is evidence that higher immune complexes are more inducers of kidney damage than smaller immune complexes. The immune complexes containing Gd-IgA1 deposition are the initial inducers of inflammation. By activating other glomerular and tubular cells,

the inflammatory process initially restricted to mesangial areas progress to a more severe glomerular and tubulointerstitial injury.

Immune system and mucosa-bone marrow crosstalk

Classically, the immune system is divided into innate and adaptive immunity. The innate response is rapid but nonspecific. It acts through the recognition of pathogen-associated molecular patterns (PAMPs) by macrophages, dendritic cells, leukocytes, and other cells, promoting opsonization and phagocytosis. Receptors of PAMPs are the Toll-like receptors (TLRs). TLRs belong to a family of pattern-recognition receptors that link the innate and the acquired immune system. Activation of TLRs induces the maturation of dendritic cells, cytokine release and recruitment of macrophages and lymphocytes. Mature dendritic cells interact with T cells, activating specific T response and antibody production – the adaptive response (33).

The production of mucosal IgA occurs by activation of follicular B cells in germinal centers. The antigen-presenting cells located below the specialized M cells take up antigens and present them to T helper cells. The interaction through B and T cells through CD40-CD40L binding and cytokines (mainly, TGF-B and IL10) stimulates B cells to undergo class switching from IgM to IgA and somatic hypermutation for affinity maturation(34). However, the stimulation of IgA production occurs also by a T cell-independent pathway. The TLR/MyD88 (TLR2, TLR4, TLR5, TLR9) activated by antigens stimulate antigen-presenting cells in the lamina propria and stromal cells to release innate response signals (as BAFF, APRIL, TNFa, TGFb, retinoic acid), which stimulate the conversion from IgM to IgA in B cells, regardless of T-lymphocytes (28).

It is suggested that immune mucosa dysregulation results in reduced antigen clearance with continuous antigen exposure, which trigger the production of pathogenic IgA (33). In several experimental studies, antigens capable of enhancing serum IgA1 or inducing clinic IgAN were tested, such as *Staphylococcus aureus* (35), *Hemophilus influenza* (36), *Sendai virus* (37,38), gliadin (39). However, no food or viral antigen was consistently found in the mesangial deposits, suggesting a nonspecific dysregulation in IgA production via the innate immune response. The mechanisms behind this dysregulation are still unknown. There is evidence that TLRs are possible

culprits, both in the increased production as in the aberrant glycosylation. TRL9 are hyperexpressed in plasmocytoid dendritic cells in tonsils of patients with IgAN (40). Upregulation of TLR4 was found in patients with IgAN, particularly associated with proteinuria and microscopic hematuria (41). Furthermore, it was noticed a reduction in level of Cosmc, the chaperone involved in galactosylation, promoted by activation of TLR4 by bacterial LPS *in vitro* (42).

Despite the association of respiratory and intestinal infections and IgAN exacerbation, it is well recognized that the circulating undergalactosylated IgA1 antibodies are primarily produced in the bone marrow (43). Some researchers suggest that the B cells have previously encountered the antigen at other sites and then relocated to bone marrow (33). It´s believed there is a defect in the crosstalk between mucosa and bone marrow, induced by cytokines and adhesion molecules. IgA-secreting cells have traffic pattern associated with the production origin. Homing and differentiation of plasma cells in the lamina propria of the small gut is associated with upregulation of integrin α4β7 and CCR9 and CCR10 receptor, whereas the expression of integrin α4β1 and CXCR4 is linked to the homing and differentiation of B cells in the bone marrow (44). One study showed increased expression of α4β1 by CD3T cells in patients with IgAN (45).

Abnormal glycosylation of IgA1

Studies with IgAN patients demonstrated alterations in glycosylation of circulating IgA1 (46,47) and IgA1 from mesangial immunodeposits (48). Typically, the hinge region of IgA1 contains O-glycosides formed by the disaccharide galactose and N-acetylgalactosamine (Gal-GalNAc, also known as T antigen) and their mono- or disyalated forms (ST antigens). Some IgA1 molecules in IgAN patients present O-glycosides with galactose deficiency in the hinge region, which consist of only GalNAc (Tn antigen) or GalNAc terminal with sialylation (sTn antigen). This finding was inferred from the reduction of reactivity of IgA1 in patients with IgAN to specific T lectins antigens, as jacalin (46), and increased reactivity to GalNAc specific lectins, such as that produced by *Helix aspersa* (29).

Using Epstein-Barr virus in circulating B cells that produce IgA, the undergalactosylation was seen only in patients with IgAN, compared to normal controls (49). This change can be basically explained by the expression of key enzymes in the galactosylation pathway. First of all, there are different subtypes of *N-acetylgalactosyltransferases* (GalNAcTs). The GalNAcT2 is ubiquitous and appears to have a predominant role in IgA glycosilation. GalNAc-T2 rarely glycosylates the sites next to GalNAc-attached sites within HR. However, five GalNAc-Ts other then GalNAc-T2 showed very weak and almost negligible activity toward HR, and their specificities were totally different from those of GalNac-T2 (50). A study comparing the transcription of several GalNAcTs in IgAN patients verified that IgA1 Gal deficient-producing cells had significant increase of only GalNAcT14 (2). However, the link between isotypes of GalNAcT and glycosylation defects is still unclear. Secondly, the increased expression and activity of *sialyltransferase* ST6GalNacII result in a premature sialylation. Premature sialylation may inhibit the attachment of galactose to N-acetylgalactosamine in IgA1 Tn antigens. Accordingly, *Suzuki et al* observed an increased expression of ST6GalNacII in B lymphocytes from patients IgAN (29). Thirdly, a reduced expression and activity of *galactosyltranferase* C1GalT1(29) and a decreased expression of C1GalT1-specific chaperone Cosmc (51) have been observed in peripheral B lymphocytes from patients with IgAN.

It should be mentioned that data concerning either intrinsic or extrinsic regulation of glycosylation of IgA1 in B cells are still limited. A previous study comparing the O-glycosylation of serum IgA1 and IgD showed defective O-glycosylation only of IgA1 in patients with IgAN compared to healthy controls (52). Moreover, only a fraction of B lymphocytes produce Gd-IgA1 in patients with IgAN. It is now recognized that glycosylation defects happens in a late stage of B-cell development and maturation as a result of an abnormal immune regulation induced by acquired stimuli. Furthermore, external stimuli and cytokines influence the glycosylation of IgA (28). Increased Th2 response can reduce the glycosylation of IgA (53). IL4 stimulation of B cell lines causes increased production of IgA and significant reduction in the level of Cosmc mRNA and C1GalT1 mRNA level and activity, with consequent defect in hinge region galactosylation (41). Cosmc inhibition was also evidenced by LPS stimulation of B lymphocytes (42). All these evidences point to an

acquired defect of glycosylation whose stimulus comes from an abnormal immune response.

Recently, a new approach to hypogalactosylated structures is being analyzed, based on microheterogeneity studies. This approach includes the direct determination of sites of attachment of the O-glycans as well as characterization of the microheterogeneity of the glycans at each site. For example, in normal individuals, Thr228, Ser230, Ser232 and Thr233 residues are the most common sites attached to glycan; while Thr225 and Thr236 residues are predominantly hypogalactosylated. Indeed, for IgA1 myeloma protein, Thr225, Thr228 and Ser232 were glycosylated predominantly by GalNAc-Gal disaccharide, whereas Gal-deficient GalNac or the absent of glycan was determined at Ser230, Thr233 and Thr236 (26). This microheterogeneity in the hinge structure briefs a new questioning, extrapolated to IgAN. It is highly possible that the shapes of nephritogenic Gd-IgA1 arise not only from galactosylation insufficient, but also from different binding sites of O-glycosides of amino acid residues in the hinge.

Anti-glycan antibodies and immune complexes

As a result of deficiency of galactose, residues of N-acetylgalactosamine in the truncated IgA1 hinges are exposed as neoepitopos. Poorly galactosylated IgA1 *O*-glycoforms may act as autoantigens, potentially triggering the production of glycan-specific autoantibodies. Recognition of neoepitopos by IgA and IgG antibodies leads to the formation of immune complexes Gd-IgA1 IgA and Gd-IgA1 IgG (54). Virtually all serum Gd-IgA1 is complexed with other anti-glycan specific antibody. Antibodies anti-glycosides occur naturally in the plasma. Some bacteria and viruses express N-acetylgalactosamine as surface antigens. An infection by these agents could facilitate the production of anti-glycosides, which might cross-react with Gd-IgA, causing or exacerbating IgAN (55). Urinary abnormalities are often intensified during episodes of upper airway infections.

Moreover, it seems that the anti-glycosides antibodies in patients with IgAN have a peculiarity in its primary structure, which increases its affinity for Gd-IgA1, as shown by *Suzuki M. et al*. This group has cloned EBV-immortalized lymphocytes that

secreted IgG with specificity for Gd-IgA1. Analysis of the sequence of the light (V_L) and heavy (V_H) chain of this IgG showed unique features in complementarity determining 3 region (CDR3) of V_H. Serine was observed in the third position of CDR3 from six of seven patients with IgAN. On the other hand, Alanine was detected in the same position from all six healthy controls. Further, reversing the residue Serine to Alanine through site directed mutagenesis, there was a reduction of the affinity of recombinant IgG for Gd-IgA1(49). Currently, we do not know if this change (Ala to Ser in CDR3) originates from genetic variation or somatic mutation during an active immune response (24).

The complexation of IgA reduces its plasma clearance (56). IgA is catabolized mainly by the liver, through the asialoglycoprotein receptor (ASGP-R), which recognizes disyalated glycoproteins (57,58). In the case of IgA, Gal and terminal GalNac are recognized. However, binding of the anti-GalNAc glycoside specific antibody prevents the recognition of the glycosides in the hinge region by ASGP-R, thereby reducing their catabolism. In addition, immune complexes have difficulty crossing the hepatic fenestrated capillaries up to the space of Disse, reducing their contact with hepatocytes expressing the ASGP-R (2).

Furthermore, the level of specific IgG anti-glycoside is increased in patients with IgAN and is associated with proteinuria level and with IgA1-IgG immune complexes urine level (59). Increased antigen-antibody complexation of IgA1 were observed in acute episodes of gross hematuria (59). Consequently, immune complexes not effectively metabolized by the liver are deposited in the mesangial region, due to its high mass, stimulating the growth of mesangial proliferation and cytokines (60).

Mesangial deposition of immune complexes with Gd-IgA1, cell activation and glomerular injury

The deposition of immune complexes (IC) of Gd-IgA1-specific anti-glycan IgG in the mesangium plays a fundamental role in the pathogenesis of IgAN. They are the triggers of renal response. The isolated deposition of Gd-IgA1 or isolated glycoside antibodies is not sufficient to develop the inflammatory response (32,61). The

deposition is predominantly in the mesangium with limited amount of immune complexes in podocytes and tubular epithelial cells (62).

Studies with cultured human mesangial cells showed that immune complexes (Gd-IgA1 IgG) of high molecular weight (> 800kDa) had a greater impact on mesangial proliferation and cytokine production. In contrast, Gd-IgA1 complexed or non-complexed into smaller immune complex does not induce mesangial proliferation (32,63). Of note is the fact that immune complexes of a similar molecular mass induce further mesangial proliferation in patients with IgAN compared to healthy controls (56). Moreover, immune complexes containing higher amounts of Gd-IgA1 produce a more intense mesangial proliferation (32). Furthermore, no GalNAc epitopes were found in the mesangium, suggesting that specific IgG deposition is not directly targeted to the mesangium, consequently with no formation of immune complexes *in situ* (49). Such findings show how relevant the Gd-IgA1 antigens and the Gd-IgA1 specific IgG or IgA antibodies are to the formation of immune complexes and define the essential role of passive deposition of circulating immune complexes containing Gd-IgA1 in the activation of mesangial cells.

However, some signaling pathways involved in immune responses on kidneys of IgAN patients remains to be clarified. Accordingly, the classic receptors for IgA (ASGP-R, pIgR, Fc-αR (CD89) and Fc-α/μR) are not found in mesangial cells (64). Also, IgA1 receptors in podocytes and tubular epithelial cells are still unknown (62). The transferrin receptor (TfR1/CD71) is the only known mesangial receptor able to bind and internalize pIgA1 and immune complexes containing IgA1(24). Moreover, the binding and internalization trigger a positive feedback loop, inducing higher expression of TfR1/CD71 in mesangial cells (65). Another pathophysiological mechanism involving IgA receptors is the formation of immune complexes with Gd-IgA that induces a change in the interaction between IgA and Fc-αR/CD89. As a result, cleavage of the extracellular domain of CD89 is initiated, leading to the formation of circulating IgA immune complexes bound to CD89. Such compounds are found in mesangial deposits and enrolled in the exacerbation of the inflammatory response and macrophage migration to the kidney. The circulating CD89 also binds to TfR1/CD71 (66). Despite these findings, it is unclear whether the TfR1/CD71 has a direct action in the pathogenesis of IgAN.

Kidney injury begins with the activation of mesangial cells, which alters the profile of cytokines and other mediators released. *Novak et al* demonstrated there are two types of IgA-immune complexes (stimulatory and inhibitory IC) capable of producing distinct patterns of intracellular phosphorylation. The stimulatory IC had higher mass with elevated amounts of Gd-IgA1. These IC exhibited strong stimulatory effect on expression of IL-6 and IL-8 genes (63).

The complement system plays a significant role in the pathogenesis of IgAN. Complement activation occurs in three pathways: [1] Classical pathway, activated primarily by immune complexes with IgG and IgM, but also by necrotic or apoptotic cells and acute phase proteins such as C-reactive protein (67), [2] Alternating pathway, initiated by the spontaneous breaking of the C3 component, but with current evidence of the participation of properdin as initiator, in addition to its role in stabilizing the C3 convertase (68) and [3] Lecithin pathway, which instead of using antibodies to recognize pathogens, uses plasma proteins, mannose binding lecitins (MBL) and ficolins to identify carbohydrate patterns found on the surface of a wide range of microorganisms (67). Regardless of the activation pathway, an amplification cascade is initiated, promoting the formation of soluble proinflammatory molecules and C5b-9 complex, a membrane attack complex (MAC) which promotes osmotic cell lysis. The complement system is highly regulated by the short half-life of their activated factors and endogenous regulatory proteins (69).

Recent studies also indicate the involvement of complement in the pathogenesis of IgA nephropathy. In approximately 90% of IgAN patients, C3 is detected in the glomerulus (12–15). The activation of the alternate complement pathway is also suggested by: [1] the presence of properdin in most renal biopsies, colocated with IgA deposits (16), [2] the absence of C1q (15,13,17) and [3] the elevation of C3 catabolites in serum of patients with IgAN (68). However, recent findings also suggest the involvement of the lecithin pathway in IgA nephropathy. Mesangial deposits of MBL are seen in 25% of patients with IgAN (17). Mesangial deposits of MBL and C4 and/or C4 catabolites are implicated as markers for progression of IgAN. On the contrary, patients with MBL deficiency tend to show better clinical presentation and lower levels of serum creatinine and proteinuria than patients without MBL deficiency. N-glycans on the heavy chains of secretory IgA1

are the candidate ligands for lecithin pathway activation (70). However, further studies will be essential to confirm the ligands for the MBL in the pathogenesis of IgAN.

Activation of mesangial cells by immune system is the initial process involved in the pathogenesis of IgAN inflammation. According to *Kar Neng Lai*, activated mesangial cells could initiate three mechanisms that operate independently or synergistically to develop kidney injury in IgAN patients: [1] tubulointerstitial infiltration by monocytes and macrophages;[2] tubulointerstitial injury secondary to exposure intraluminal to albumin; and [3] glomerulo-podocytic-tubular crosstalk (62). Mesangial cells activated by immune complexes proliferate and release extracellular matrix proteins, chemokines and cytokines. Such proinflammatory and profibrotic agents (TNF, IL-6, angiotensin II, platelet-derived growth factor) modify gene expression of podocyte and stimulate the infiltration of inflammatory cells into the tubulointerstitial compartment. The attracted inflammatory cells in turn release further cytokines that activate tubular epithelial cells, which amplify the inflammatory cascade by releasing more proinflammatory and profibrotic agents. A positive feedback loop is then organized, perpetuating the process. Inflammatory mediators released by mesangial cells also act in podocytes and may change the slit diaphragm and cause proteinuria. Proteinuria by itself stimulates chemotaxis and migration of immune competent cells in various glomerular diseases (71). The mechanisms described above are generic to primary glomerulonephritis, explaining how a glomerular injury prompts response in other compartments and causes loss of podocytes and tubular atrophy and interstitial fibrosis.

Conclusion

IgA nephropathy is defined as autoimmune disease, with a multi-hit kinetics. Anomalous production of IgA hypogalactosylated and recognition by anti-glycan antibodies result in the formation of immune complexes, which were deposited in the mesangium, inducing membranoproliferative glomerular injury. New insights into the molecular mechanism of this disease could provide the rational bases for developing new biomarkers for diagnosis and monitoring of disease activity and disease-specific therapeutic approaches, likely acting in decreasing circulating level of

Gd-IgA1, avoiding formation of immunocomplexes by blocking antigen-sites and preventing activation of mesangial cells.

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3.0 OBJETIVOS DO ESTUDO

O objetivo principal desse trabalho é avaliar o curso clínico e o prognóstico da nefropatia por imunoglobulina A, segundo a classificação de Oxford, em uma coorte de crianças e adolescentes, submetidas à biópsia renal no período de 1982 a 2010, na Unidade de Nefrologia Pediátrica, do Hospital das Clínicas - UFMG.

Como objetivos secundários, podemos listar:

1. Avaliar a correlação entre as variáveis clínicas e laboratoriais e as lesões histopatológicas descritas pela Classificação de Oxford;
2. Analisar a relação entre as variáveis clínicas e laboratoriais e a sobrevida renal;
3. Analisar a relação entre as lesões histopatológicas, descritas pela Classificação de Oxford, e a sobrevida renal.

4.0 ARTIGO ORIGINAL

The Oxford Classification predictors of progressive chronic kidney disease in pediatric patients with IgA nephropathy

Rafaela Cabral Gonçalves Fabiano[1], Sérgio Veloso Brant Pinheiro[2], *et al.*

[1] Division of Nephrology, Clinics Hospital, Federal University of Minas Gerais, Belo Horizonte, Brazil.

[2] Unit of Pediatric Nephrology, Faculty of Medicine, Federal University of Minas Gerais, Belo Horizonte, Brazil.

*Correspondence to Sergio Veloso Brant Pinheiro, MD, PhD

Rua Antilhas 80, ap 601. Belo Horizonte, MG, Brazil, 30315-480. FAX: + 55-31-34099770, TEL: + 55-31-93024774, e-mail: svbpinheiro@gmail.com

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Abstract

Background: The Oxford Classification for IgA nephropathy (IgAN) identified pathological variables predictive of renal failure. However, this classification should be validated in other populations, including pediatric patients. This study aimed to evaluate the Oxford Classification variables as predictors of renal dysfunction in a cohort of children and adolescents with IgAN.

Methods: A total of 56 patients with IgAN biopsied from 1982 to 2010 were assessed. Biopsies were reevaluated and classified according to The Oxford Classification. Multivariate analysis of laboratory and pathological data was performed. The primary outcomes were decline of baseline estimated glomerular filtration rate (eGFR) equal or higher than 50% and the rate of renal function decline.

Results: Median follow-up was 7.4±5.0 years. Median renal survival was 14.0±0.7 years and probability of 50% decline in baseline eGFR was 18% in 10 years. Eight children (14%) had a decline of baseline eGFR equal/higher than 50% and 5 (9%) evolved to End-Stage Renal Disease. Univariate analyses showed that baseline proteinuria, endocapillary hypercellularity and tubular atrophy/interstitial fibrosis were associated with primary outcome. In multivariate analysis, after adjusted for initial proteinuria, endocapillary hypercellularity (HR 21.6, 95% CI, 2.9 to 160.5; p 0.003) and segmental glomerulosclerosis (HR 8.2; 95% CI, 1.3 to 51.0; p 0.023) were shown to be independent risk markers in Cox regression. Tubular atrophy/interstitial fibrosis and also endocapillary hypercellularity were associated with renal prognosis in multivariate linear regression.

Conclusion: The Oxford classification was showed to be valid to predict reduction in renal function in patients with IgAN, except for mesangial hypercellularity.

Keywords: IgA nephropathy, Oxford Classification, Glomerulonephritis, Renal disease, MEST

Introduction

IgA nephropathy (IgAN) is one of the leading causes of glomerulonephritis worldwide. The predominant or co-dominant presence of IgA1 in mesangial immunodeposits is essential to diagnosis (1). IgAN is characterized by a highly variable course that evolves from a totally benign condition (2) to end-stage renal disease (ESRD) (3). The disease usually progresses insidiously and the search for predictors of renal outcome may enable individualized decision-making, early patient care and appropriate treatment with less adverse effects (4–6).

Accordingly, the analysis of renal specimen was suggested to contribute with additional prognostic information. Recently, The Oxford Classification identified four histological features that showed to be independently related to renal outcome in IgAN patients: mesangial hypercellularity (M), endocapillary proliferation (E), segmental sclerosis or adhesion (S) and tubular atrophy/interstitial fibrosis (T)(7,8). The Oxford Classification encompasses analysis of data from patients with a wide range of age. The predictive value of each specific lesion on renal survival was not distinct between children and adults with IgAN in The Oxford Study (9). Some studies had the purpose to assess this system in their pediatric population to valid the classification (5,10,11). Although geographically distinct, none of these studies was made in South America. This study aimed to evaluate the predictive value of clinical, laboratory and pathological variables according to The Oxford Classification on renal dysfunction in a cohort of pediatric patients.

Patients and methods

Patients

The records of 56 patients diagnosed with biopsy-proven IgAN were included in the analysis of this retrospective cohort study. Inclusion criteria were children and adolescents between 2 and 18 years of age with biopsy-proven IgAN who were admitted to the Pediatric Nephrology Unit (PNU), Clinics Hospital, Federal University of Minas Gerais, Brazil, from 1982 to 2010 and had at least 9 months of follow-up. Diagnostic criteria for IgAN were based on the finding of the dominant or codominant

mesangial deposition of IgA on immunohistologic examination of the kidney (13). Our Pediatric Nephrology Unit was established in 1969 and has followed-up several children with IgAN according to a protocol that includes definition of disease etiology and pathology, assessment of clinical course and laboratory alterations, institution of treatment protocols according to clinical and laboratory findings. Pediatric patients admitted to the PNU with estimated creatinine clearance below 45 mL/min/1.73m2 or who had Henoch-Schönlein purpura, liver diseases, diabetes, systemic diseases and any type of secondary IgAN were excluded from the analysis.

Ethical Aspects

The Ethics Committee of the Federal University of Minas Gerais approved the study, according to the Declaration of Helsinki as a statement of ethical principles for medical research involving human (National database approval protocol - CAAE 18196713.4.0000.5149).

Baseline and Follow-up Covariates

For each patient, the date of renal biopsy was established as the baseline point. Follow-up time was considered as the time between renal biopsy and the last outpatient visit, death or 50% reduction in baseline estimated glomerular filtration rate (eGFR). The variables included in the analysis were sex, ethnicity, age at baseline point, eGFR, proteinuria, hypertension, weight-for-age Z score, height-for-age Z score, body mass index (BMI) and serum levels of creatinine. For the variable weight and BMI, it was considered only the dry weight of the patient, thus avoiding that the weight was overestimated in patients with edema. Treatment was also evaluated according to the use of: (1) renin-angiotensin system blockade (RASB), indicating treatment with ACEi (angiotensin-converting enzyme inhibitors) or ARB (angiotensin receptor blockers) or both; and (2) immunosuppressive drugs (corticosteroids, cyclophosphamide or azathioprine). RASB indicates any exposure to angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, regardless the duration. Immunosuppressive treatment is reported as intent to treat, regardless of the type or duration of therapy.

Histologic studies

A renal biopsy was performed in all 56 children from 1982 to 2010. A diagnosis of IgAN was based on the deposition of IgA in the glomeruli. The IgA deposits were predominant or co-dominant. Less than one-third of the cohort (29%) was biopsied before 1990. The biopsies were examined for one pathologist (S.A.P), who was blinded to patient outcome at the time of scoring. The biopsies were analyzed based on 2µg Periodic Acid Schiff-stained sections. No specimens had less than 6 glomeruli.

The biopsy specimens were classified and standardized according to the Oxford classification (MEST) (7,8), in which the number of glomeruli was assessed and their mesangial hypercellularity (M) scored as ≤0.5 or >0,5, if more or less than half of the glomeruli showed hypercellularity defined as >4 mesangial cell/mesangial area, endocapillary hypercellularity (E) (absent or present), segmental glomerulosclerosis (S) (absent or present) and tubular atrophy/interstitial fibrosis (T) (0= 0-25%, 1= 26-50% and 2= >50%). The presence of glomeruli with cellular and fibrocellular crescents and the arterial intimal thickening were also determined.

Definitions

For analysis purposes, the black and intermediate color categories were merged here into a “nonwhite” group. Blood pressure was measured and evaluated according to the recommendations of the Fourth Task Force on Blood Pressure in Children (14) and the 95th percentile was used as the cutoff point. Proteinuria was measured using the 24-hour urine protein per 1,73m^2 or ratio of urine protein/creatinine (uP/Cr). uP/Cr was considered as an estimated of 24-h protein excretion adjusted for body surface area. Proteinuria was considered to be in nephrotic range when it was more than 3g/day per 1,73m^2 or when uP/Cr >3g/g (12). For each year of observation, an average proteinuria was determined. Proteinuria during follow up represents the average of these annual values. Hematuria was diagnosed when 5 or more red blood cells were found in, at least, two urinary sediment exams by high power field (400x) microscopy. Weight-for-age and height-for-age Z scores were used to assess weigh and stature. These measures were calculated using the public-domain software Epi Info (version 3.4.1). Glomerular filtration rate (GFR) was estimated by the formula of Schwartz (15). To avoid sudden artificial

changes in eGFR and to simplify the estimation of renal function, we did not switch from the Schwartz equation to other equations in an individual.

Outcomes

The primary outcomes were the cumulative percentage of patients who had a decline of baseline eGFR equal or higher than 50% and the rate of renal function decline, both through multivariate analysis. Renal survival was measured from the date of renal biopsy to the date of first estimative of GFR 50% lower than baseline eGFR.

Statistical Analyses

Normally distributed values were expressed as mean ± S.D. Categorical variables were described as percentages and analyzed using Chi-square (X^2) test. Student´s t –test (normally distributed variables) and Mann-Whitney or Kruskal-Wallis (nonparametric variables) were used to compared continuous variables. Univariate analyses of continuous prognostic factors were performed using Cox regression, and categorical prognostic factors were analyzed using the Kaplan–Meier and the log-rank methods. Variables at admission examined in univariate analysis included gender, ethnicity, age at baseline point, hypertension and histopathology features. Laboratory tests at baseline were also evaluated: eGFR, serum creatinine and proteinuria. The Cox proportional hazards model was applied to identify variables that were independently associated with 50% decline of baseline eGFR. Only variables that were associated with the event of interest by univariate analysis ($P<0.25$) were included in the Multivariate Cox regression and multiple linear regression models. Multiple linear regression was used to determine independent predictors of the rate of renal function decline. All multivariate models were constructed including one single histological lesion in combination with proteinuria at biopsy.

All reported P values are two sided, and P value < 0.05 was considered statistically significant. Confidence intervals (CI) included 95% of predicted values. SPSS software was used for the analysis.

Results

Clinical and pathological characteristics

A total of 56 patients (32 boys) with IgAN were included in the analysis. The majority of patients were classified as white (51.8%). The median age was 9.7 years (± 3.3 years). At the time of renal biopsy, the median eGFR was 104 mL/min/1.73m^2 (± 31.7 mL/min/1.73m^2). Five patients had a baseline eGRF lower than 60 mL/min/1.73m^2. The median baseline proteinuria was 0.96±1.98 g/day per 1,73m^2. Four patients (7%) were in nephrotic range. Eighteen (32%) patients were hypertensive or were in current antihypertensive therapy at the time of biopsy. Table 1 summarizes clinical characteristics and demographic data at the time of renal biopsy, compared with other pediatric cohorts.

The median follow-up time was 88.5 months (± 9.4 months). Of 56 patients, 8 (14%) developed 50% decline in renal function, with median eGFR of 45.4ml/min per 1.73m^2 (±28.7 ml/min per 1.73 m2). Five patients (9%) developed ERKD in a median time of 109.0 months (± 84.7 months). Survival analysis estimated that the probability of 50% decline in renal function was 7% at 5 years of follow-up and 18% at 10 years after diagnosis. Laboratory evaluation at last visit revealed median eGFR of 104.9 ml/min per 1.73 m2 (±48.2 ml/min per 1.73 m2) for patients who did not progress to the primary outcome.

Pathological analysis detected a median of 23 glomeruli per biopsy (IQ range 11-29). There were 18 patients (32%) with mesangial proliferation (M1), six patients (11%) with endocapillary proliferation (E1), 13 patients (23%) with segmental sclerosis/adhesion lesion (S1), just one patient with moderate tubulointerstitial fibrosis (T1) and another one with severe tubulointerstitial fibrosis (T2). As the low prevalence, we merged T1 and T2 together in the following analyses. The frequency of crescents was low (7%) and vascular lesions were found in just one case (vascular lesions were not used for following analysis).

Association between pathological lesions, baseline clinical features and treatment

The clinicopathological data of the patients at the time of biopsy are shown in Table 2. None of the lesions were significantly associated with eGFR at the time of biopsy. Endocapillary proliferation (absent or present) and tubular atrophy/interstitial fibrosis (<25% or ≥25%) were associated with hypertension and proteinuria at the time

of biopsy. Crescents (absent or present) were also associated with hypertension. Mesangial hypercellularity and segmental glomerulosclerosis were not correlated with any of the clinical features.

According to treatment, the use of renin-angiotensin-system blockade and immunosuppression was assessed in relation to the pathological lesions. There were no significant association between the pathological variables and treatment options during follow up in this cohort.

Correlations between pathological lesions / clinical features and outcome

Univariate survival analysis showed that proteinuria (hazard ratio [HR] of 1.4; 95% CI, 1.13 to 1.82; P 0.003) was found to be an independent predictor of 50% decline in baseline eGFR. No others epidemiological and clinical feature (age at biopsy, gender, race, decade of biopsy, BMI Z-Score, initial blood pressure, initial GFR, use of RASB or immunosuppressive therapy) had independent correlation with the renal survival.

Pathological variables associated with 50% decline in baseline eGFR by Kaplan-Meier analysis were: presence of endocapillary hypercellularity, E1, (HR 18.4; $p<0.001$) and tubular atrophy/interstitial fibrosis greater than 25%, T2, (HR 63.0; $p<0.001$), while mesangial hypercellularity (HR 0.25; $p=0.62$), segmental glomerulosclerosis (HR 3.59; $p=0.058$) and extracapillary hypercellularity (HR 0.65; $p=0.42$) were not. Figure 1 shows the differences in renal survival from the combined event for presence and absent of histological findings.

Two different relevant multivariate models were tested according to the outcomes: cumulative percentage of patients who had a 50% reduction in renal function and rate of renal function decline. All two models were adjusted for initial proteinuria. Univariate analysis was followed by multivariate Cox regression model. When adjusted for initial proteinuria, endocapillary cellularity (HR 21.6; 95%CI, 2.9 to 160.5; p 0.003) and segmental glomerulosclerosis (HR 8.2; 95%CI, 1.3 to 51.0; p 0.023) were significantly related to 50% decline in initial eGFR. When we investigated the relation of pathological lesions with the rate of renal function decline by multiple linear regression, the rate of renal function decline correlated with endocapillary hypercellularity and tubular atrophy/interstitial fibrosis. As mesangial hypercellularity

and extracapillary hypercellularity failed to attain independent significance in univariate analysis, they were not able to be used in multivariate (Table 3).

Discussion

The Oxford Classification aimed to determine pathological criteria that are predictive of renal outcome, independently of clinical variables. The original population of Oxford study comprised patients from four continents: five centers in Asia, six in Europe, two in USA, one in South America and two multi-centers services (Canada and USA). Although racially diverse, the ancestry was addressed in sub-analysis only between Caucasians and Asians (no difference in the predictive power of lesions), due to low representation of other ethnicities (8). Therefore, the validation of the new classification for different populations is needed. Recently, some validation studies were published (2,3,16,17), however, none in South America.

Accordingly, in this retrospective cohort study, we addressed if the pathological variables identified in Oxford study would predict renal outcomes in our population. Up to that time, there have been published only three studies exclusively with pediatric patients, as illustrated also in Table 1. Compared with Chinese (10), Swiss (11) and original Oxford (8) cohorts, our sample is very similar. As expected, high proportions of male (1.3:1) and of white children (51.8%) among IgAN patients were observed. Although there are clear geographical and ethnic differences, IgAN is more common in Asian and in Caucasian children (12). Of note is the fact that our patients presented less severe baseline proteinuria. We also observed that fewer patients presented nephrotic range baseline proteinuria (27%) in comparison to the Oxford cohort. Moreover, the number of patients with no medication during follow up (RASB or immunosuppressive therapy) seemed to be higher in our cohort. These findings suggested that our cohort included milder cases of IgAN than the Oxford study. In agreement, the lower incidence of outcome in our cohort (14% compared to 22% in Oxford Study) might be explained by the occurrence of milder cases than in Oxford cohort.

Regarding pediatric IgA patients, three exclusively pediatric cohorts (10–12) and two other large studies with adults and children (17,18) evaluated the Oxford variables as predictors of renal survival. Edström *et al.* found that the presence of S is not associated to the progression of IgAN in a 99 children Swiss cohort (11). Shima *et al.* analyzed 161 children in Japan and discovered that only mesangial hypercellularity (M) and interstitial fibrosis/tubular atrophy (T) worked as prognostic markers in that population (12). In China, the analysis of a 218 children cohort revealed that only T was able to be a prognostic marker, after multivariate analysis (10). Herzenberg *at al.* studied 187 North American patients, 45 children. They verified that each histological injury offered the same predictive value found in Oxford, except M, which behaved as a weaker predictor (18). Recently, the European study VALIGA retrospectively analyzed 1,147 European patients (97.5% Caucasians), with 174 children. Segmental glomerulosclerosis (S), mesangial hypercellularity (M), tubular atrophy/interstitial fibrosis (T), but not endocapillary hypercellularity (E) were identified as predictive of renal outcome in this cohort (17).

In our study, E and T were significantly related to renal survival, by Kaplan Meier analysis, whereas M, S and extracapillary hypercellularity failed to reach statistical significance. According to multivariate analysis, multiple linear regression showed that the rate of renal function decline correlated with E and T. When the end point of 50% reduction in eGFR was considered as the outcome, the Cox regression showed significant associations for E and S.

The value of mesangial hypercellularity (M) as an independent risk for renal progression is debated. Our study showed no correlation between M and the outcome. A North American group found a lower intraclass correlation coefficient observed for the mesangial hypercellularity score in North America study and discussed it as one of the reasons for error in measurement, leading to a nonsignificant finding (18). However, in large cohorts of Chinese and European patients, mesangial hypercellularity was validated as a significant factor affecting progression (17,19). Hence, we speculated that ethnicities might influence the prediction of mesangial hypercellularity, considering America’s cohorts weren’t able to find the same results as Chinese and European cohorts.

The endocapillary lesion (E) was shown to be a strong predictor in this study, mainly considering the relatively small size sample. In the opposite, in the Oxford classification study, E was not significantly predictive of poor prognosis. It was taken in the classification mainly due to their interaction with the effect of immunosuppressive therapy in IgAN. In a metanalysis with IgA nephropathy cohorts, E wasn't either related to the outcome (3) and also in VALIGA study, that examined 1147 European patients (17). Several studies have demonstrated a benefit on glomerular endocapillary hypercellularity with immunosuppressive therapy in patients with IgAN (18). Shen *et al* showed endocapillary hypercellularity, as crescents and necrosis, could be reversed by immunosuppressive therapy in patients with IgAN. The reversal of these lesions may explain the lack of significant correlation of these lesions with clinical outcomes (20). We found a weak association to treatment in our study, although few patients received immunosuppressive therapy in our cohort.

The segmental glomerulosclerosis (S) was also confirmed in the current study as risk factors for poor prognosis. However, S has not been identified as a prognostic marker in none of exclusively pediatric cohorts, after multivariate analysis. Edström and Shima argued that the low prevalence of that lesion contributed to its non-significance, in the Swiss and the Japanese cohorts, respectively (11,12). For Le, the low reproducibility of adhesions justifies the difference in prevalence between cohorts (10). Although pediatric, our cohort is in agreement with almost all previous validation studies (16,17). Rationally, segmental sclerosis represents a more chronic and late stage of IgAN renal damage.

It should be notice the distinction of interstitial fibrosis/tubular atrophy (T) as the unique pathological feature capable of predicting loss of renal function, identified in all cohorts. The finding of T as a prognostic value corroborates the theory that interstitial fibrosis/tubular atrophy is a sequel of previous renal aggression (21). This sequel is able to perpetuate the deterioration of renal function, even in absence of the initial pathological stimulus. Moreover, our current therapy is limited to modify T compared with the potential that anti-hypertensive and/or immunosuppressive therapy may modify active lesions, as M and E.

As in the Oxford classification study, cellular or fibrocellular crescents were not predictive in our study, due to a low prevalence. Biopsy timing may reflect in the

frequency distribution of pathological variables. As crescents formed early after disease onset and decreased over time, they may be prognostic for acute phase, but not for chronic phase of the disease (22). The median duration from onset to renal biopsy wasn't evaluated in our cohort. Although we believed this timing might not be early, as in other countries (10,12). For example, in Japan, diagnosis and treatment for IgAN are started early in the course of the disease due to a school screening program. We investigate our children only if they have symptoms or have an incidental finding of hematuria. Moreover, we are a tertiary healthy center where pediatric patients with kidney diseases are referenced to after primary care. This could contribute to increase the median time from disease onset to renal biopsy, therefore explaining the low prevalence of crescents in our cohort.

One of the most intriguing finding in our study was that initial eGRF was not associated with the outcome. Initial GFR was studied as a marker of poor prognostic in several studies, with linear correlation. Although, we believe that hyperfiltration must be considered as an ominous feature. We dichotomized initial eGFR in two groups: (1) eGFR≤75 or ≥135mL/Kg/1.73m^2 and (2) eGFR between 75 to 135mL/Kg/1.73m^2. Using Kaplan Meier analysis, the renal survival of patients with extreme eGFR were 11.2±1.3 years, while children with eGFR between 75 to 135mL/Kg/1.73m^2 had 14.9±0.8 months (HR 4.3, p 0.038). A bimodal behavior of eGFR with higher risks in the extremes, ≤75 or ≥135mL/Kg/1.73m^2, might justify why we weren't able to find a linear relation between initial eGFR and the outcome.

For the first time, we addressed a cohort of South America children for the purpose to investigate if the Oxford classification is applicable in our population. Our study has some limitations and several methodological considerations should be taken into account in evaluating our findings. First, it is a retrospective study with limited control over the variables measured. Second, our relatively small sample of pediatric IgAN patients could contribute to the lack of predictive value of some pathological features. Third, we were not able to reliably recover data at the first manifestation of the disease. In addition, we were not able to systematically analyze some time-dependent variables, such as hypertension. However, some features of this study can increase the strength of our findings, such as large set of data collected over many

years and long-term follow-up by the same team with a well-established clinical protocol.

In conclusion, the Oxford classification appears to be valid for predicting renal outcomes in our population, except for mesangial hypercellularity. As well, proteinuria at biopsy was of prognostic significance. Whether Oxford classification has also therapeutic tools for predicting an optimal treatment for our children remains to be clarified.

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Table 1 - Comparing clinical characteristics at the time of biopsy and follow up between pediatric cohorts with IgA nephropathy

	Current study	Le(10)	Shima(12)	Edstrom Halling(11)	Oxford(8)
Country	Brazil	China	Japan	Sweden	Multi country
Ethnicity					
White	51.8%	-	-	NA	66%
Asian	-	100%	100%	NA	27%
African	10.7%	-	-	NA	3%
Other	37.5%	-	-	NA	4%
No. pts	56	218	161	99	265
% pts - age < 18 y	100	100	100	100	22.5
Follow up (months)	88.5±9.4	56	54	156	62[d]
Age (y)	9.7±3.3	14	11.7	9.7	13[d]
M:F	1.3:1	1.9:1	1.7:1	1.4:1	3:1[d]
Prot. initial (g/d)	0.96±1,98	1.5	0.7	2.0[c]	2.0[d]
Prot. F/U (g/d)	0.93±1,68	0.6	NA	1,65[c]	0.9[d]
eGFR initial (mL/min/1,73m^2)	104±31.7	134	103	100	120[d]
HTN[a] (%)	32.1	NA	NA	NA	31
RASB (%)	41.1	61.5	NA	86	56[d]
Immunosuppressive therapy[b] (%)	25	56	16	43	48[d]
End point definition	50% decline in eGFR or ESKD	50% decline in eGFR or ESKD	CKD stages 3-5	50% decline in eGFR or ESKD	50% decline in eGFR or ESKD; slope of eGRF
No. end point events	8 (14%)	24 (12%)	7 (4%)	18 (18%)	58 (22%)
No. of ESKD events	5 (8.9%)	NA	5 (3%)	15 (15%)	34 (13%)

[a] Either presence of hypertension or use of antihypertensive medications at initial evaluation

[b] Either steroids or other immunosuppressive medicine

[c] Albuminuria

[d] Data restricted to children

Abreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ESKD, end stage kidney disease; F/U, follow-up; HTN, hypertension; M:F, male:female; NA, not available; prot, proteinuria; pts, patients; RASB, renin-angiotensin-system blockade.

Table 2 - Clinicopathological data of the patients at the time of biopsy

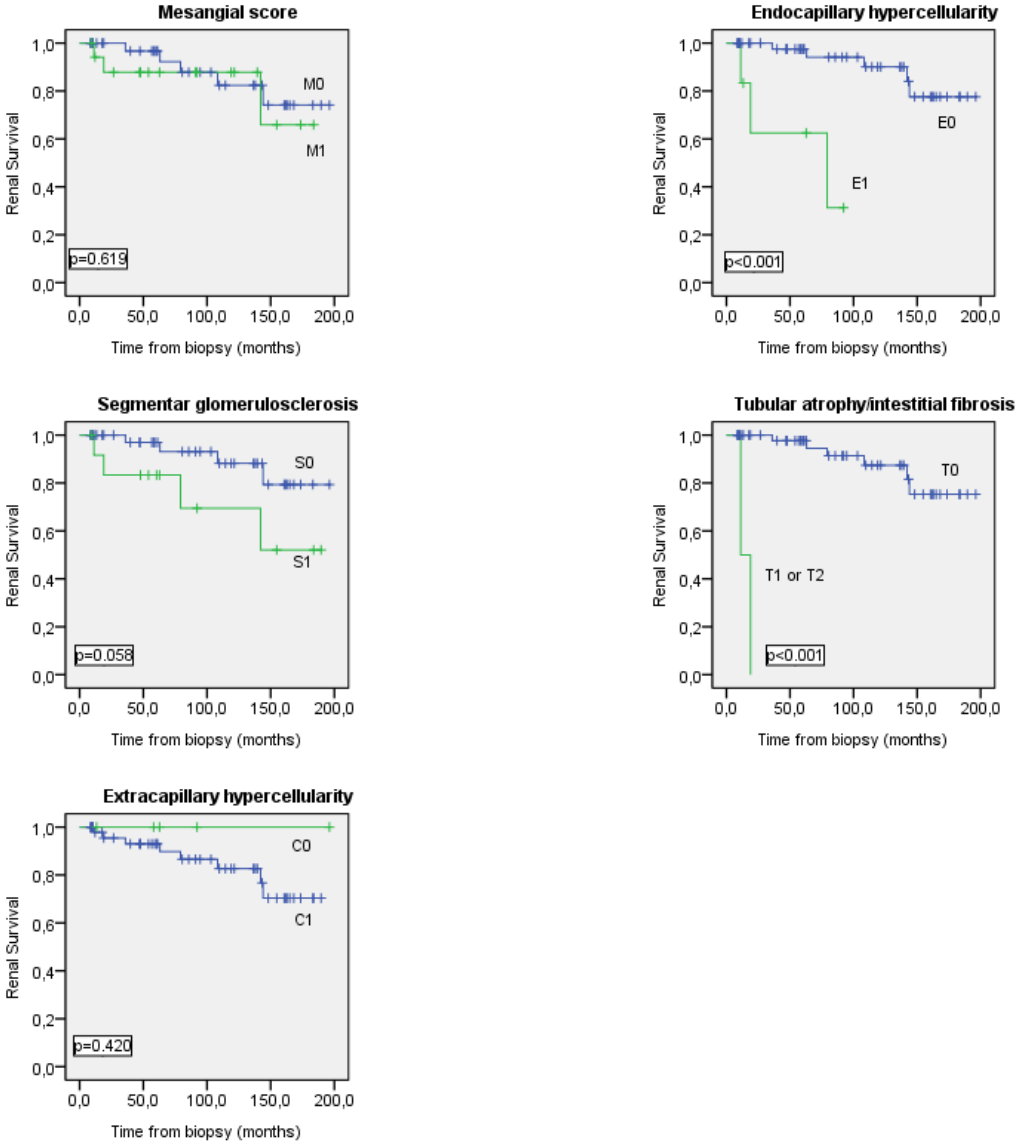
	eGFR	%HTN	%Severe prot.	%RASB	%ISS
Mesangial hypercellularity					
≤0,5	109+-31	23.7	16.7	44.7	26.3
>0,5	92+-30	50	27.8	33.3	22.2
p-value	0.56	0.049	0.339	0.418	0.741
Endocapillary proliferation (E)					
Absent (E0)	107+-31	26	12.5	40	22
Present (E1)	85+-34	83.3	83.3	50	50
p-value	0.127	0.004	<0.001	0.638	0.134
Segmental glomerulosclerosis (S)					
Absent (S0)	106+-32	25.6	17.1	39.5	25.6
Present (S1)	97+-32	53.8	30.8	46.1	23.1
p-value	0.388	0.056	0.285	0.671	0.855
Tubular atrophy/interstitial fibrosis (T)					
0-25% (T0)	105+-31	29.6	17.3	40.7	24.1
≥25% (T1 and T2)	75+-42	100	100	50	50
p-value	0.182	0.036	0.004	0.794	0.406
Crescent (C)					
Absent (C0)	106+-32	27.5	18.4	39.2	23.5
Present (C1)	86+-20	80	40	60	40
p-value	0.184	0.016	0.253	0.367	0.417

Abbreviations: eGFR, estimated glomerular filtration rate; HTN hypertension; Severe prot, proteinuria (>1,0g/day per 1,73m^2 or >1,0g/g), RASB, renin-angiotensin-system blockade; ISS, immunosuppressive therapy.
Values are expressed as mean+-sd for eGFR and as proportion for HTN, Severe prot, RASB and ISS.

Table 3 - Correlations between pathological features and outcomes: univariate and multivariate analysis

	Multivariate		
	%50% decline in GFR	Rate of renal function decline	
	Cox Regression HR (95% CI)	Linear regression B (SD)	
E 0 1	 1 21,6 (2,9-160,5) p 0,003	 1 -18,7 (7,6) p 0,017	 R^2 0,126 F test, with p-value 0,003
S 0 1	 1 8,2 (1.3-51.0) p 0,023	 1 -10,6 (5,2) p 0,048	 R^2 0,096 F test, with p-value 0,073
T 0 1-2	 -	 1 -42,9 (10,8) p<0,001	 R^2 0,250 F test, with p-value < 0,001

Figure 1 - Renal survival related to pathological variables.



UNIVERSIDADE FEDERAL DE MINAS GERAIS

PROGRAMA DE PÓS-GRADUAÇÃO EM CIÊNCIAS DA SAÚDE
SAÚDE DA CRIANÇA E DO ADOLESCENTE

UFMG

ATA DA DEFESA DA DISSERTAÇÃO DA ALUNA
RAFAELA CABRAL GONÇALVES FABIANO

Realizou-se, no dia 04 de maio de 2015, às 09:00 horas, sala 029, andar térreo da Faculdade de Medicina da Universidade Federal de Minas Gerais, a defesa de dissertação, intitulada **"ANÁLISE PROGNÓSTICA DE UMA COORTE PEDIÁTRICA DE PORTADORES DE NEFROPATIA POR IGA, ATRAVÉS DA CLASSIFICAÇÃO DE OXFORD"**, apresentada por **RAFAELA CABRAL GONÇALVES FABIANO**, número de registro 2013652296, graduada no curso de MEDICINA, como requisito parcial para a obtenção do grau de Mestre em Ciências da Saúde - Saúde da Criança e do Adolescente, à seguinte Comissão Examinadora formada pelos Professores Doutores: Sérgio Veloso Brant Pinheiro - Orientador (UFMG), Marlene Antônia dos Reis (UFTM) e Ana Cristina Simões e Silva (UFMG).

A Comissão considerou a dissertação:

(X) Aprovada

( ) Reprovada

Finalizados os trabalhos, lavrei a presente ata que, lida e aprovada, vai assinada por mim e pelos membros da Comissão.
Belo Horizonte, 04 de maio de 2015.

Centro de Pós-Graduação
Faculdade de Medicina / UFMG
Av. Prof. Alfredo Balena, 190 - 5º andar
CEP.: 30130-100 - Funcionários - BH/MG

Prof. Sérgio Veloso Brant Pinheiro (Doutor)

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Faculdade de Medicina - UFMG

Marlene A Reis

Profª. Marlene Antônia dos Reis (Doutora)

Ana Cristina Simões e Silva

Profª. Ana Cristina Simões e Silva (Doutora)

FOLHA DE APROVAÇÃO

ANÁLISE PROGNÓSTICA DE UMA COORTE PEDIÁTRICA DE PORTADORES DE NEFROPATIA POR IGA, ATRAVÉS DA CLASSIFICAÇÃO DE OXFORD

RAFAELA CABRAL GONÇALVES FABIANO

Dissertação submetida à Banca Examinadora designada pelo Colegiado do Programa de Pós-Graduação em Ciências da Saúde - Saúde da Criança e do Adolescente, como requisito para obtenção do grau de Mestre em Ciências da Saúde - Saúde da Criança e do Adolescente, área de concentração em Ciências da Saúde.

Aprovada em 04 de maio de 2015, pela banca constituída pelos membros:

Prof. Sérgio Veloso Brant Pinheiro - Orientador
UFMG

Profª. Marlene Antônia dos Reis
UFTM

Profª. Ana Cristina Simões e Silva
UFMG

Belo Horizonte, 04 de maio de 2015.