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ÁLLAN RAMON SANTOS NASCIMENTO

DOPPLERVELOCIMETRIA ARTERIAL EM PORTADORES DE ANEMIA FALCIFORME: AVALIAÇÃO DOS MEMBROS INFERIORES

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Trabalho de conclusão de curso apresentado ao Departamento de Medicina do Centro de Ciências Biológicas e da Saúde da Universidade Federal de Sergipe como requisito parcial à obtenção do título de bacharel em Medicina.

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Aprovada em: ____/____/____

Orientador: Prof. Thiago de Oliveira Ferrão

Examinador: Prof. Dr. Marco Antônio Prado Nunes

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SUMÁRIO

1 REVISÃO DA LITERATURA

1.1 INTRODUÇÃO

O termo doença falciforme refere-se a um grupo de doenças hematológicas hereditárias autossômicas que apresentam como característica fundamental a presença da forma anômala da hemoglobina S (HbS). Essa anomalia é causada por uma mutação pontual na sexta posição do gene da cadeia globínica beta no cromossomo 11, com a substituição da adenina pela timina, inserindo valina onde deveria estar o ácido glutâmico, com a consequente produção de HbS ao invés de hemoglobina A (HbA) (GLADWIN, 2008).O tipo mais comum de doença falciforme é a Anemia Falciforme (AF) (REES, 2010), que é a expressão da homozigose para HbS (SS). A mutação originou-se em regiões que apresentam malária de forma endêmica, onde os indivíduos heterozigotos apresentam relativa resistência à infecção. Esses indivíduos apresentam o que é chamado traço falciforme, nos quais não se esperam manifestações clínicas, exceto em situações de hipóxia importante (FIGUEIREDO, 2012). Na situação em que o paciente apresenta heterozigose para este gene mutante (HbS), associado a outras hemoglobinas mutantes como hemoglobina C, hemoglobina D ou hemoglobina E, desenvolverá hemoglobinopatias C, D ou E, respectivamente; há ainda a possibilidade de os genótipos heterozigóticos gerarem S/betatalassemia, S/alfatalassemia e outras formas mais raras que compõem a doença falciforme (ZAGO, 2007).

1.2 EPIDEMIOLOGIA

A doença falciforme é a hemoglobinopatia mais comum no mundo, e pode ser encontrada em todos os continentes, principalmente em virtude da migração e tráfico de escravos. Apresenta frequência mais elevada em afrodescendentes (GUIMARÃES, 2009; WOOD, 2008). Estima-se que no mundo, de um total de 332 mil nascidos com hemoglobinopatia, 275 mil apresentam a doençafalciforme (MODELL, 2007).

O complexo do gene da globina beta possui 19 sítios de alteração genética que não se traduzem por alteração proteica e a combinação desses sítios forma padrões denominados haplótipos. Na AF foram identificados 5 haplótipos correlacionados a diferentes regiões do mundo: Senegal, Benin, Banto, Cameroon e Indiano. O estudo desses haplótipos demonstra que a mutação teria sido originada em ao menos três regiões diferentes, independentemente, além de que existem diferenças na apresentação clínica da doença, com os portadores do haplótipo Senegal apresentando quadro clínico mais brando e os Banto mais grave (FIGUEIREDO, 2012; REES, 2010).

No Brasil, a doença foi introduzida pelo tráfico de escravos, e hoje estima-se que existam mais de dois milhões de portadores do gene para a doença, com mais de oito mil portadores de AF. Anualmente nascem por volta de 700 a 1000 novos portadores de anemia falciforme (YANAGUIZAWA, 2008). Em relação à distribuição regional, as regiões Norte e Nordeste apresentam as maiores prevalências de heterozigotos (CANÇADO, 2007).

1.3 FISIOPATOLOGIA

A HbS sofre polimerização em resposta à desoxigenação ou estresse oxidativo, o que leva à deformação da hemácia (que passa a apresentar forma parecida à de uma foice) com consequente prejuízo na circulação microvascular, o que causa hemólise crônica e vasoclusão (BELCHER, 2003; OSAROGIAGBON, 2000), que são as bases das manifestações clínicas da AF.

A hemácia falcizada mantém a capacidade de retornar à forma normal após ser reoxigenada, contudo o processo repetido de polimerização leva a alterações celulares que resultam no aumento da adesividade dos eritrócitos ao endotélio e desencadeia fenômenos inflamatórios, enrijecimento da membrana celular, lesões microvasculares, diminuição do tempo de vida da hemácia, aumento da quantidade de hemoglobina livre (fora da hemácia), o que diminui a biodisponibilidade do óxido nítrico, contribuindo para a vasoconstricção e também para o aumento da adesividade do eritrócito (REITER, 2002; FIGUEIREDO, 2007; ZAGO, 2007).

1.4 MANIFESTAÇÕES CLÍNICAS

A dor decorrente de episódio vasoclusivo é deve-se ao aprisionamento de eritrócitos e leucócitos na microcirculação, com obstrução vascular e isquemia. A interação das hemácias com alteração morfológica com o endotélio da microvasculatura resulta em obstrução e isquemia, seguido de restauração do fluxo sanguíneo, o que restabelece a oferta de oxigênio, mas promove mais dano tissular decorrente da lesão de reperfusão. Ciclos de isquemia e reperfusão causam estresse oxidativo, aumentando a expressão de moléculas de adesão endoteliais, a síntese de citocinas inflamatórias e pode causar leucocitose(FRENETTE, 2002; BELCHER, 2005).

Além disso, a hemólise crônica causa anemia hemolítica que ocasiona o quadro de fadiga e colelitíase, assim como a vasculopatia progressiva que os pacientes com AF apresentam, que se expressa como hipertensão sistêmica e pullmonar, disfunção endotelial e modificações proliferativas na região intimal e de células musculares lisas dos vasos sanguíneos (GLADWIN, 2004; KATO, 2006). Estudos já demonstraram a associação do aumento da hemólise com complicações como colelitíase, úlceras de membros inferiores, priapismo e hipertensão pulmonar (GLADWIN, 2004; KATO, 2007).

Pacientes com baixa concentração de hemoglobina e maior taxa de hemólise apresentam maior risco para desenvolver vasculopatia, enquanto aqueles com maiores níveis de hemoglobina possuem maior tendência a apresentar episódiosde dor aguda (KATO, 2007).

1.5 O PAPEL DA ULTRASSONOGRAFIA NA ANEMIA FALFIFORME

A ultrassonografia doppler (USD) é um método de imagem que pode ser usado para avaliação do fluxo sanguíneo arterial. Através da avaliação da morfologia da onda de pulso e da medição e cálculo da velocidade de pico sistólico (VPS), velocidade diastólica final (VDF), velocidade média (VM), índice de resistência (IR) e índice de pulsatilidade (IP), é possível detectar anormalidades no fluxo sanguíneo; tal recurso tem sido utilizado na avaliação de pacientes portadores de AF.

A principal aplicação da dopplervelocimetria na AF é na prevenção de acidente vascular cerebral (AVC), desde o estudo STOP, no final dos anos 90 (ADAMS, 1998). É sabido que, quando um fluido passa por um tubo, sua velocidade de fluxo é inversamente proporcional à área da secção trasversal do tubo no qual está contido. Em pacientes portadores de AF, com velocidade de fluxo anormal no sistema arterial cerebral, a indicação de transfusão sanguínea diminuiu o risco de AVC (VERLHAC, 2008). Alterações dopplervelocimétricas também foram documentadas em outras artérias, como as oftálmicas (AIKIMBAEV, 2001) e as renais (GUVENC, 2005).

O estudo dopplervelocimétrico arterial de membros inferiores já é utilizado com sucesso na avaliação da Doença Arterial Periférica (EIBERG, 2010) e no acompanhamento pós-operatório em cirurgias de reperfusão (MORAIS FILHO, 2009**)**. Apesar disso, o papel da dopplervelocimetria arterial em membros inferiores de pacientes portadores de AF ainda não foi estabelecido. Busca nos bancos de dados de periódicos (PUBMED, OVID e SCIELO) no dia 04 de novembro de 2013, com o termo “Falciforme” em combinações diferentes com os termos “doppler”, “duplex”, “ultrassom”, “Ultra-som”, “membros inferiores”, “femoral”, “poplítea”, “tibial” em língua portuguesa e inglesa não retornou resultados de trabalhos publicados com a avaliação da circulação arterial dos membros inferiores de indivíduos com AF.

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CRITICAL REVIEWS. Reviews of important and timely subjects can be invited through the editorial board or submitted independently. In the latter case, it is usually helpful for the corresponding author to consult the Editor-in-Chief prior to submission. Reviews should focus on the critical aspects of a subject, linking what is know to what areas remain controversial or unanswered. Historical accounts of important events relating to pediatric hematology/oncology are also acceptable. Reviews should normally be less than 3,500 words, contain an unstructured abstract of 100 words or less, and fewer than 100 references; illustrations and tables should be used only to provide summaries or a synthesis of ideas and/or data not also included in the text. Requests for permission to submit manuscripts of greater length should be emailed to the Editor-in-Chief at arcecro@gmail.com prior to manuscript submission.

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http://www.implementationscience.com/content/pdf/1748-5908-3-45.pdf

MEETING ABSTRACTS

*Abstract text should be 300 words or less. That word count excludes the abstract title, author names and affiliations.

*There should be 4 sections to the abstract: Background/Objectives, Design/Methods, Results, Conclusion. All text should include a single paragraph and contain no lists.

*Abstract text should be written in complete sentences and in correct English.

*There should be a mark of end punctuation at the end of all sentences.

*Tables and figures, only when critical to the content, should be included and must comply in terms of format with PBC Author Guidelines.

*Abstract titles should be in all capital letters, e.g., INDUCTION OUTCOMES IN CHILDREN WITH ALL

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*Author affiliations should be written in upper and lower case letters, e.g., Tata Memorial Centre

*Names of cities and countries with 2 words should be written in upper and lower case letters, e.g., Czech Rep, South Africa, Los Angeles, St. Louis.

*Periods should be used in numbers for decimal points, not commas, e.g., P=0.015, and numbers beginning with a decimal point should be preceded by a zero.

*Disease names should be written without apostrophes, e.g., Hodgkin lymphoma, Non-Hodgkin lymphoma, Burkitt lymphoma, Ewing sarcoma

*The X and Y axis of graphs must be labeled as per PBC Author Guidelines.

*There should be no extraneous writing on radiographic scans, which, for instance, could be patient identifiers.

*Numbers containing more than 3 digits should have a comma, e.g., 3,000.

*Abbreviations should be defined on first usage, then using of abbreviation alone is acceptable: e.g., Wilms Tumor (WT), then referred to as WT in subsequent mention, no quotation marks, however.

*Abstracts need to be corrected for all spelling and grammatical errors.

*Abstracts that do not satisfy publication instructions will not be published.

4 BRIEF REPORT

TITLE PAGE

DOPPLERVELOCIMETRIA ARTERIAL EM PORTADORES DE ANEMIA FALCIFORME: AVALIAÇÃO DOS MEMBROS INFERIORES

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Título Abreviado: Dopplervelocimetria arterial dos membros inferiores em portadores de Anemia falciforme.

Total de Tabelas: 2

Total de palavras do resumo: 98

Total de palavras do artigo: 769

TEXT

RESUMO

O objetivo do presente estudo de avaliar a velocidade de pico sistólico (VPS) em artérias dos membros inferiores de pacientes portadores de anemia falciforme em comparação a um grupo controle. Os valores das médias de VPS das artérias do membro inferior esquerdo e direito dos dois grupos foram comparados. Foram encontradas diferenças estatisticamente significantes entre as médias de falciformes e controles ($p < 0,005$) em todas as artérias estudadas. Esse trabalho demonstrou que o valor do VPS de artérias dos membros inferiores também demonstram diferença em relação à população normal, como já foi demonstrado em estudos de outras artérias.

DESCRITORES: Ultrassonografia Doppler; Extremidade Inferior; Anemia Falciforme.

INTRODUÇÃO

A anemia falciforme, forma homozigótica da doença falciforme, é a hemoglobinopatia hereditária mais frequente no mundo [1]. Ela tem como uma de suas características um grau aumentado de hemólise intravascular, o que leva a lesão endotelial e descompartimentalização da hemoglobina, a qual reage 1000 vezes mais rapido com o óxido nítrico (NO) em comparação com a hemoglobina dentro da hemácia, diminuindo sua biodisponibilidade [2].

A possível diminuição do lúmen vascular decorrente da AF pode levar a um aumento da velocidade de fluxo sanguíneo intravascular em relação à população normal, já que seu valor é inversamente proporcional a área da secção transversal do vaso. O objetivo do presente trabalho foi determinar se havia diferenças na avaliação dopplervelocimétrica arterial em membros inferiores de pacientes portadores de anemia falciforme que não apresentavam complicações agudas da doença no momento do exame.

MÉTODOS

Foram avaliados 103 pacientes, dos quais 71 possuíam diagnóstico de anemia falciforme assintomáticos na época da realização das medições, e 32 pertencentes ao grupo controle. Os pacientes foram agrupados em três faixas etárias: 0-9 anos (31 pacientes), 10-19 anos (39 pacientes) e 20 anos ou mais (33 pacientes). Foram medidas as velocidades de pico sistólico (VPS) das artérias poplítea, tibial anterior e tibial posterior (bilateral) de todos os pacientes, com o aparelho de ultra sonografia modelo LOGIQ P6 com transdutor linear modelo 11L com 11 MHz (GE Healthcare, Fairfield, CT, EUA). Os resultados obtidos no exame de US, idade e categoria (Falciforme ou controle) foram tabulados e calculadas as médias entre os dois membros de cada indivíduo, calculadas suas médias e desvios-padrão (SD) para idade, VPS para todas as faixas etárias. Foi aplicado o teste de Kolmogorov-Smirnov para avaliação do tipo de distribuição das variáveis. As duas categorias foram comparadas usando o teste T-Student ou teste U de Mann-Whitney para a comparação entre as médias de VPS para cada

faixa etária. A análise estatística foi realizada com auxílio do software IBM SPSS STATISTICS 21 (SPSS inc., Chicago, Illinois, EUA). O estudo foi aprovado pelo Comitê de Ética em Pesquisa no sítio da Plataforma Brasil sob número: 05595812.0.0000.0058.

RESULTADOS

A média de idade entre os pacientes portadores de anemia falciforme foi de 14,6 anos (SD= 7,61) e dos controles 15,2 anos (SD= 7,55). Em relação a distribuição etária, os indivíduos de 0-9 anos apresentaram idade média de 6,2 (SD= 2,13), 10-19 anos 13,7 (SD= 2,79), 20 anos ou mais 24,2 (SD= 2,79) (Tabela 1).

Com relação à distribuição amostral, foi possível avaliar pelo teste de Kolmogorov-Smirnov que a VPS apresentou distribuição normal em todas as artérias analisadas, para cada faixa etária, exceto na artéria tibial posterior apenas na faixa de 0-9 anos.

As médias da VPS mostraram uma diferença estatisticamente significativa em todas as artérias analisadas e em todas as faixas etárias (Tabela 2).

DISCUSSÃO

A avaliação dopplervelocimétrica arterial já é uma importante ferramenta no manejo clínico do paciente com AF [3, 4], porém a avaliação de artérias periféricas destes indivíduos ainda não está bem estabelecida, como ocorre, por exemplo, na doença arterial periférica [5] Neste estudo, foram encontradas diferenças significativas na VPS entre pacientes portadores da AF e controles normais nas três artérias analisadas, em todas as faixas-etárias, o que pode ser explicado por fatores próprios da fisiopatologia da AF. É sabido que os portadores da doença possuem taxa aumentada de hemólise, o que diminui o hematócrito, diminuindo a viscosidade sanguínea e aumentando o trabalho cardíaco, além de aumentar a quantidade de hemoglobina livre, levando à diminuição da biodisponibilidade de óxido nítrico [6], com consequente

diminuição da área de secção transversal das artérias, o que diminui fluxo, porém aumenta a velocidade do fluxo sanguíneo em relação à população normal.

Esses achados são compatíveis com estudos anteriores em outros territórios arterais como na artéria cerebral média [3], onde já foi estabelecido que o aumento da velocidade de fluxo está correlacionado a estenose arterial e aumento do risco de acidente vascular encefálico em crianças com anemia falciforme, o que levou a elaboração do estudo STOP.

No presente estudo foram encontradas velocidades de pico sistólico significativamente mais elevadas em pacientes portadores de AF em relação ao grupo controle. Apesar de esperada, a alteração na VPS de artérias dos membros inferiores, como demonstrada nesse estudo, ainda não fora estabelecida empiricamente até o momento de elaboração desse trabalho. Considerando a correlação entre ultra sonografia e a arteriografia já conhecida em estudos sobre doença arterial periférica [5], a VPS pode ajudar a prever quais pacientes se encontram em maior risco de desenvolvimento das complicações da AF, como as úlceras em membros inferiores, cuja fisiopatologia pode estar relacionada à diminuição do suprimento sanguíneo neste segmento corporal [1].

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5 TABELAS

Tabela 1: Distribuição etária da população em estudo.

Faixa Etária (anos)	Média Falciformes	Desvio-Padrão Falciformes	Média Controles	Desvio-Padrão Controles
0-9	6,2	2,25	6,1	1,79
10-19	13,6	2,78	13,8	2,8
20 ou +	24,1	3,09	24,2	2,03

Tabela 2: Comparação das VPS e resultado do teste para comparação de amostras independentes entre Falciformes e grupo Controle.

Faixa Etária (anos)	Poplítea			Tibial Anterior			Tibial Posterior		
	VPS Grupo1[c]	VPS Grupo2[d]	p	VPS Grupo1[c]	VPS Grupo2[d]	p	VPS Grupo1[c]	VPS Grupo2[d]	p
0-9	105,9 ± 21,3	83,4 ± 11,2	0,006[a]	85,5 ± 28,1	52,3 ± 10,6	0,002[a]	87,5 ± 31,8	57,3 ± 9,9	0,001[b]
10-19	106,9 ± 18,9	73,9 ± 12,1	0,000[a]	85,0 ± 27,1	49,4 ± 15,3	0,000[a]	89,4 ± 27,9	49,9 ± 19,2	0,000[a]
20 ou +	99,4 ± 22,8	63,7 ± 19,2	0,000[a]	69,9 ± 15,0	48,4 ± 11,0	0,000[a]	71,7 ± 16,9	48,1 ± 20,8	0,001[a]

a: Aplicado teste t-Student para amostras independentes.

b: Aplicado teste u de Mann-Whitney para amostras independentes

c: Velocidade de pico sisólico em cm/s medida nos pacientes portadores de anemia falciforme e seu desvio-padrão.

d: Velocidade de pico sisólico em cm/s medida nos pacientes do grupo controle e seu desvio-padrão.