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Desvendando a Relação entre Migranea e Alterações Inespecíficas da Substância Branca em estudos de Ressonância Magnética: Uma Revisão Sistemática

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“Nada na vida deve ser temido, apenas compreendido. Este é o momento para se entender mais, para temer menos”

Marie Curie

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Esta dissertação está estruturada de acordo com as normas do Programa de Pós Graduação: Ciências Médicas (PPGCM) da Universidade Federal do Rio Grande do Sul e originou dois artigos que estão apresentados de acordo com as normas do p-PROSPERO e PROSPERO, respectivamente e estão adequados aos padrões de publicação do periódico *Headache Journal of Head and Face Pain*.

RESUMO

Migranea é uma doença altamente prevalente na população geral, e por mais intensas e debilitantes que possam ser as crises de dor, acredita-se ser de natureza benigna. No entanto, frente o aumento de frequência das crises ou mesmo a piora na intensidade da dor, o paciente portador da doença é submetido a investigação por exame de Ressonância Magnética. Em uma parcela considerável desta população, um achado peculiar nestes exames são lesões em substância branca, geralmente em localização profunda, as quais ainda não são completamente compreendidas fisiopatologicamente, e presume-se estarem relacionadas à migranea em si.

Na literatura médica atual, há uma quantidade limitada de estudos investigando a natureza destas anormalidades e existem duas metanálises publicadas previamente que estabelecem uma provável relação causal entre migranea e alterações da substância branca. No entanto, os mecanismos fisiopatológicos por trás deste fenômeno ainda não foram elucidados.

Materiais e Métodos: Nesta revisão sistemática da literatura, for realizada busca de artigos completos em três plataformas digitais de literatura científica médica (Embase, MEDLINE/PubMed e LiLaCs)por meio das palavras chaves "migraine", "MRI scan", "white matter" e termos análogos. A busca foi realizada no dia 31 de Maio de 2020. Os critérios de inclusão compreendiam: estudos publicados em periódicos indexados, realizados entre 1990 e 2020, compreendendo população acima de 18 anos e com exames realizados em equipamento de RM com campo magnético igual ou superior a 1,5 Tesla. Estudos com pacientes portadores de outras doenças do sistema nervoso central, doenças autoimunes ou com desfechos relacionados a alterações cardiovasculares e neurovasculares foram excluídos.

Resultados: Foram selecionados nove artigos entre os 168 artigos originais, satisfazendo os critérios de inclusão e exclusão. Devido a heterogeneidade dos resultados dos artigos selecionados, a análise estatística por metanálise não foi realizada. Dos artigos selecionados, cinco artigos estabeleceram provável relação entre o tempo de doença e a frequência das crises migranosas com a presença de alterações da substância branca em pacientes portadores de migranea.

Os achados reforçam a necessidade de estudos com um número maior de pacientes, onde idealmente a seleção de participantes se dê por meio dos critérios diagnósticos postulados pela International Headache Society (IHS) em sua versão mais recente, com protocolos de aquisição de imagem de RM padronizados e reprodutíveis, softwares validados e se possível com padrão estabelecido para aferição do número de lesões e respectivos volumes, reportando sua localização no

tecido cerebral e nos lobos cerebrais, além de controles pareados e posterior comparação de seguimento após pelo menos 36 meses.

Palavras-chave: Migranea, Substância Branca, Ressonância Magnética.

ABSTRACT

Migraine is a highly prevalent condition among the general population, and as intense and debilitating as the headache crisis may be, it is believed to be benign. However, when there is an increase in crisis frequency or even a worsening in pain intensity, the patient may be submitted to an investigation with a MRI scan. At a considerable parcel of this population, a peculiar finding at their exams are white matter lesions, generally located at the deep white matter, which are not fully comprehended physiopathologicaly, and are presumably related to migraine itself.

At current medical literature, there is a limited quantity of studies investigating the nature of such alterations, and there are two previously published metanalysis that established a probable causal relation between migraine and white matter abnormalities. However, the physiopathological mechanisms behind this phenomena are not yet elucidated.

Materials and Methods: At this systematic review, we searched full text articles at three medical scientific literature online platforms (Embase,MEDLINE/PubMed e LiLaCs) through the keywords "migraine", "MRI scan", "white matter" and their analog terms. This search was performed on May 31st 2020. The inclusion criteria comprehended: studies published in indexed periodics performed between 1990 and 2020, with patients with minimum age of 18 years old and MRI scans performed at equipment with a resolution equal or superior to 1,5 Tesla. Studies with patients bearing other central nerve system pathologies, auto-immune diseases or with outcomes related to cardiovascular or neurovascular alteration were excluded.

Results: Nine among the 168 studies were selected, satisfying the inclusionand exclusion criteria. Due to the heterogeneity of the selected studies findings, statistical analysis through metanalysis was not performed. Five studies among the selected studies established probable relation among time of disease and migraine crises frequency with the presence of white matter abnormalities in patients with migraine.

These findings reinforce the need of studies with a larger number of patients, where ideally the diagnostic criteria established by the International Headache Society (IHS) at the latest version available is used to select the participants, with standardized and reproducible MRI acquisition protocols, validated software for imaging analysis and with a standard pattern for assessed the lesional volume and number, reporting their location in the brain tissue and cerebral lobes, also matched controls and posterior follow-up comparison of at least 36 months.

Keywords: Migraine, Whitte Matter, Magnetic Resonance Imaging

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LISTA DE ABREVIATURAS E SIGLAS

ARIC - Atherosclerosis Risk in Communities

CADASIL - Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy

CAMERA-1 -Cerebral Abnormalities in Migraine, an Epidemiological Risk Analysis

CT - Computed Tomography

ICHD-3 - International Consortium for Headache Diagnostic, 3rd Edition

IHS - International Headache Society

HCPA – Hospital de Clínicas de Porto Alegre

HADS - Hospital Anxiety and Depression Scale

HUNT-MRI - Nord-Trøndelag Health Study

MA - Migranea com Aura

MO - Migranea sem Aura

MS - Multiple Sclerosis (Esclerose Múltipla)

MRI - Magnetic Resonance Imaging

RM - Ressonância Magnética

SNC - Sistema Nervoso Central

T - Tesla

TC - Tomografia Computadorizada

UFRGS – Universidade Federal do Rio Grande do Sul

Unicamp - Universidade Estadual de Campinas

WMH - White matter hyperintensities

SUMÁRIO

1. INTRODUÇÃO

Migranea com ou sem aura é uma doença considerada benigna, de caráter multimodal e flutuante no curso da vida de seus portadores, porém apresenta significativo impacto na qualidade de vida e produtividade destes. (1,2) O diagnóstico de ambas é estabelecido por critérios clínicos bem definidos, elencados e revisados periodicamente através de um consenso entre especialistas, o International Consortium for Headache Diagnostic (ICHD), atualmente em sua terceira edição. (3)

A neuroimagem não é recomendada ou mesmo necessária em pacientes portadores de cefaleias primárias, porém alguns sinais de alarme detectados na avaliação clínica sugerem a necessidade de estudo de imagem, sendo recomendada a Tomografia Computadorizada (TC) em casos de maior urgência e a Ressonância Magnética (RM) em casos que necessitam de avaliação complementar com brevidade. (4)

Quando um paciente portador de migranea apresenta-se com uma ressonância magnética (RM) ambulatorial demonstrando lesões em substância branca, logo existe o ímpeto do neurologista em tranquilizá-lo frente a inespecificidade de tal achado. A realidade é que este é um cenário relativamente comum nesta população, muito embora na literatura a prevalência destas alterações em pacientes portadores de Migranea varie de 12-47%. (5).

A natureza destas alterações inespecíficas da substância branca ainda não foi completamente elucidada, restando apenas algumas postulações e hipóteses ainda a serem comprovadas. Este trabalho visa revisar sistematicamente a literatura para responder a pergunta: Existe associação entre migranea e presença de alterações da substância branca encontradas em exames de RM?

2. REVISÃO DA LITERATURA

2.1. Estratégias para localizar e selecionar as informações

Esta revisão da literatura foi estruturada em uma busca de artigos contemplando aspectos da substância branca avaliada em exames de ressonância magnética de pacientes portadores de migrânea.

A estratégia de busca envolveu a base de dados PubMed e EMBASE, sem restrição de data, com atualização em Novembro de 2020. Foram utilizados os termos *migraine, white matter, magnetic resonance imaging* e suas variações em busca combinada com o auxílio e orientação da equipe de bibliotecárias da Faculdade de Medicina da Universidade Federal do Rio Grande do Sul (FAMED-UFRGS).

A seleção dos artigos a serem incluídos nesta revisão sistemática seguiu critérios estabelecidos antes da busca, dentre eles publicação após 1990, estudos realizados com equipamento de campo magnético igual ou superior a 1.5T, estudos de desenho observacional ou coorte, com participantes sem outras comorbidades neurológicas e que apresentem controle de fatores de risco cerebrovasculares.

A estratégia de busca está inclusa no artigo 1, bem como os critérios de inclusão e seleção das informações e os resultados da seleção e extração dos dados são apresentados no artigo 2.

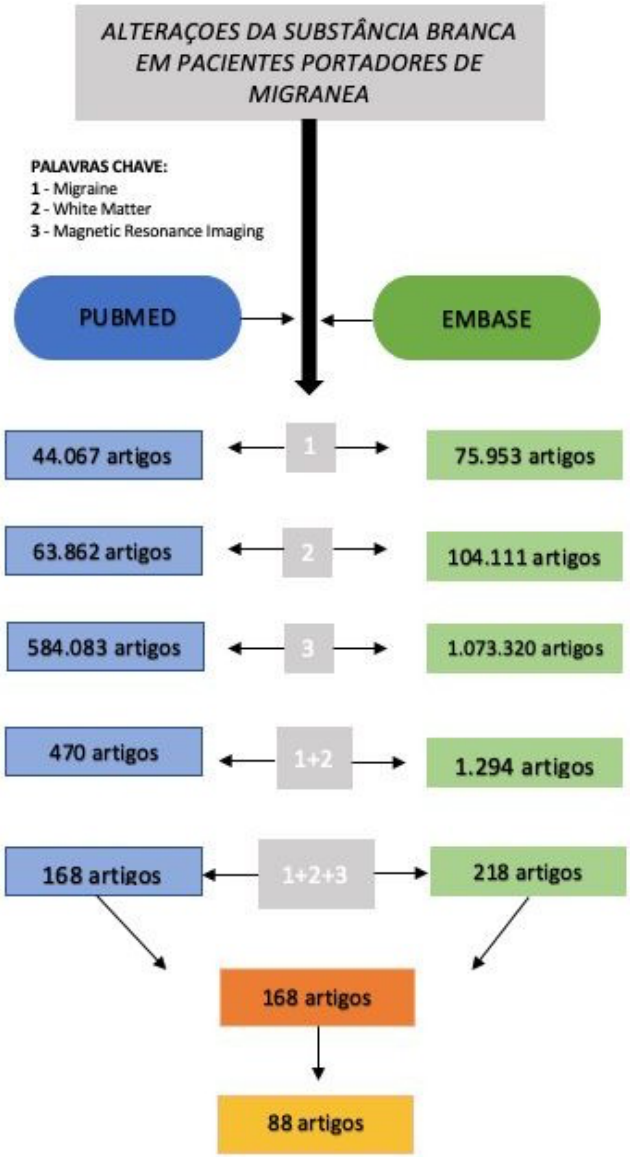

Figura 1 - Estratégia de busca para revisão de literatura contemplando aspectos da substância branca avaliada em RM de pacientes portadores de migranea sobre as bases de dados PubMed e Embase. O quadro em laranja é o número de artigos resultante após fusão dos artigos das respectivas bases de dados e desambiguação manual. O quadro em amarelo é onúmero de artigos para leitura de *abstract* após leitura dos títulos para exclusão de artigos conforme critérios estabelecidos no protocolo da revisão sistemática. Elaborado pela autora (2020)

3. MARCO CONCEITUAL

Cefaleia é uma das queixas mais prevalentes que motivam consultas e avaliações neurológicas. No Brasil, sua prevalência média é de 70,6% e dentre estas, a segunda mais comum é a Migranea, com prevalência média de 15,8% na população brasileira em geral. (11)

A Migranea é uma cefaleia primária caracteristicamente debilitante e recorrente, manifestando-se em crises que podem durar de 4-72 horas. Estas crises apresentam dor geralmente hemicraniana unilateral alternante, de qualidade pulsátil, intensidade moderada a severa, agravada por atividades físicas da rotina (como subir um lance de escadas) e associadas a náuseas/vômitos e/ou fono e fotofobia. Alguns pacientes ainda apresentam sintomas neurológicos complexos antecedendo a crise de dor, a chamada Aura Migranosa. A aura visual é a mais prevalente, seguida pela aura sensitiva e pelas alterações de fala/linguagem bem como a aura hemiplégica ou com sintomas de tronco cerebral. (3). Dada sua alta prevalência na população e seu impacto significativo na funcionalidade e produtividade dos pacientes, a Migranea vem sendo alvo de interesse de pesquisadores, profissionais da saúde em geral e também gestores no mundo inteiro. No Global Burden Of Disease Study de 2016 (1,2), a Migranea foi considerada a terceira causa mais prevalente de incapacidade em homens e mulheres com menos de 50 anos.

A Classificação Internacional de Cefaleias (ICHD-3) não contempla critérios de imagem para o diagnóstico de Migranea. Ou seja, o diagnóstico é essencialmente clínico. Porém muitas vezes nos deparamos com casos onde mesmo com os critérios clínicos para migranea estando presentes, existe a necessidade real de neuroimagem para afastarmos outras doenças potencialmente graves como quando há mudança no padrão da dor, dor progressivamente pior e mesmo aos pacientes refratários aos tratamentos já instituídos.(12)

Um achado comum na Ressonância Magnética de Encéfalo dos pacientes portadores de Migranea são lesões chamadas de alterações inespecíficas da substância branca, que como o nome já revela, ainda não se sabe qual sua relação específica com a doença em si. Em qualquer grupo etário, avaliar lesões focais hiperintensas da substância branca é um desafio, visto que tais alterações podem estar presentes em doenças de etiologias infecciosas, inflamatórias, neoplásicas, desmielinizantes ou mesmo achados inespecíficos relacionados ao envelhecimento ou doenças sistêmicas. Para diferenciar tais lesões devemos levar em conta achados

da história médica pregressa e queixa atual do paciente, bem como compreender a apresentação clínica e fisiopatologia das doenças envolvidas. É fundamental ter uma abordagem de imagem específica para inferir a causa correta destas hiperintensidades, incluindo idade, padrão de distribuição, características do sinal em diversas sequências, padrão de realce pelo contraste e outros achados auxiliares,e ainda assim, muitas vezes a caracterização destas lesões pelo radiologista implica em discussão com o médico assistente e posterior acompanhamento com novaimagem de controle para compreensão diagnóstica adequada. (13)

Hoje em dia, o entendimento que temos da fisiopatologia da migranea evoluiu, e podemos descrevê-la como uma síndrome mediada pelo SNC com evidência de reatividade e ativação microvascular. Em modelos clínicos de migranea como o proposto por Ashina et al, compreendemos o envolvimento de moléculas sinalizadoras na gênese de crises de migranea. Estas moléculas são potentes vasodilatadores e estão distribuídas por todo o sistema trigêmino-vascular, que é o substrato anatômico e fisiopatológico da migranea na compreensão atual da síndrome. Entre elas, figuram o peptídeo relacionado ao gene da calcitonina (CGRp), peptídeo 38 ativador da adenilato ciclase pituitária (PACAP-38) e óxido nítrico (NO). (14)

As alterações de substância branca em alguns pacientes com esta alteração em RM demonstraram ter gliose, desmielinização e perda axonal, o que foi atribuído a dano microvascular. (15) Supõe-se que estes achados podem ser extrapoláveis para pacientes portadores de migranea. (16)

Sendo a migranea uma síndrome recorrente e com apresentação clínica variável, especialmente no tocante à presença ou ausência de aura, a caracterização destas lesões na substância branca de portadores da doença também aparenta ter relação com estes sintomas. Já está bem estabelecida a causalidade de migranea comaura como fator de risco para acidente vascular isquêmico especialmente em mulheres com menos de 45 anos, tabagistas e que usam anticoncepcional hormonal oral. No entanto, não existe na literatura até o momento dados que relacionem com consistência que isto se dá pela presença de alterações de substância branca atribuíveis à migranea. (17)

No entanto, alguns estudos relatam ter encontrado maior incidência de alterações inespecíficas da substância branca em portadores de migranea com aura. Uma explicação possível seria que a oligoemia prolongada e recorrente durante as

crises poderia acometer as pequenas artérias penetrantes profundas, resultando em hipoperfusão local.

As lesões de substância branca que podem ser relacionadas à migrânea são prevalentemente vistas em sequências ponderadas em T2 e FLAIR na RM, localizadas na substância branca profunda (47%) e região periventricular (19%). Lesões em região calosal e subcalosa são muito raras, mas hiperintensidades justacorticais não são incomuns. A maior parte das lesões de substância branca profunda podem ser encontradas nos lobos frontais, seguidas pelos parietais, temporais e occipitais. Estima-se que 63% destes pacientes apresentem lesões múltiplas. (18)

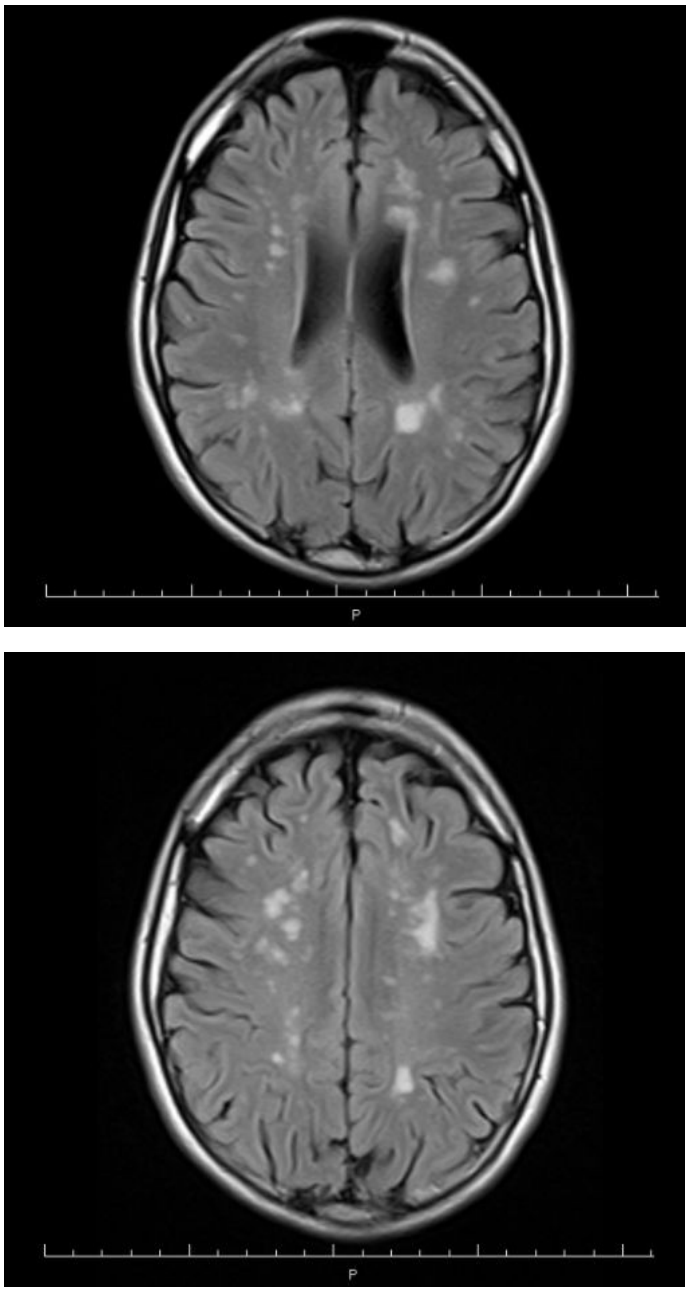

Figura 2 - Lesões hiperintensas na ponderação T2 em RM de paciente feminina de 27 anos, portadora de migrânea crônica. Acervo Pessoal, 2020.

Com o advento de equipamentos mais modernos e a constante aprimoração das técnicas de neuroimagem, possibilitou-se o estudo dos fenômenosfisiopatológicos durante as crises de migranea com e sem aura, bem como o detalhamento estrutural do encéfalo destes pacientes durante as crises e nos períodosinterictais. (19)

Schwedt e Dodick relatam estes achados minuciosamente, mas ainda assim não são o suficiente para determinarmos a natureza das lesões em substância branca,bem como o seu papel exato na fisiopatologia da migranea. O que parece serrelacionável é que, com o passar do tempo e com a cronificação da migranea (ou seja, 15 dias do mês apresentando crises migranosas por pelo menos 3 meses) tende-se a aumentar o número e o tamanho de tais lesões. Embora existam estudos que exploram esta associação, carecem evidências robustas que a consolidem. (20)

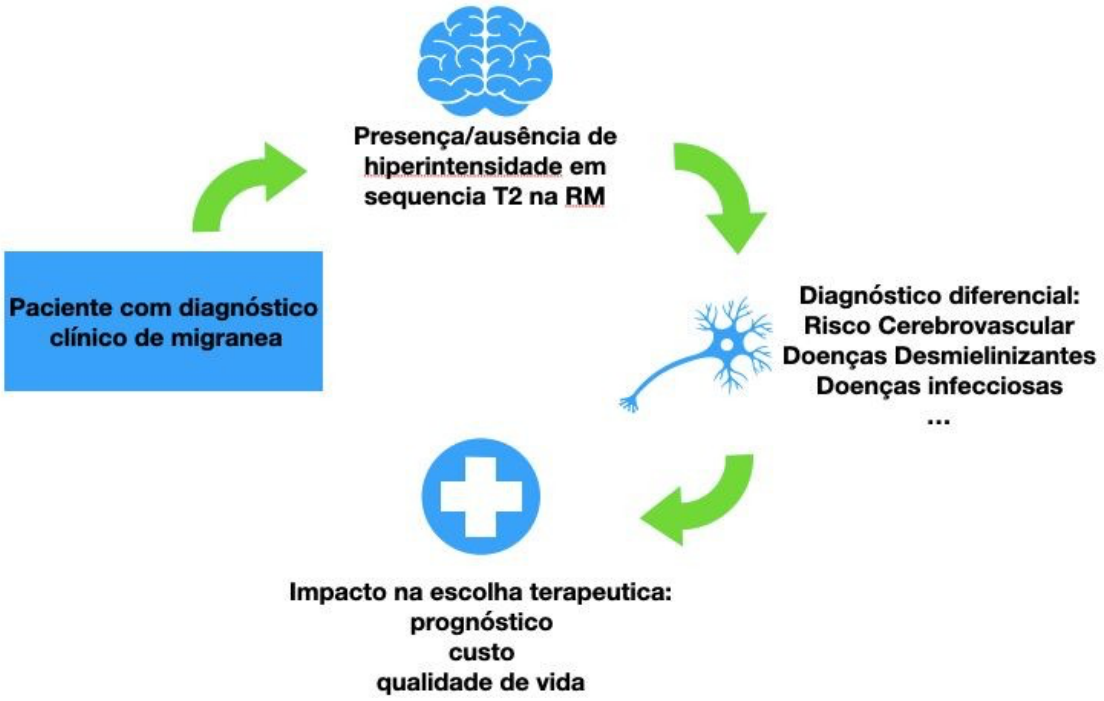

Figura 3 - Marco Conceitual Esquemático

4. JUSTIFICATIVA

Apesar do diagnóstico de migranea com e sem aura ser elementarmente clínico, atualmente com a popularização e consequente maior acesso à exames complementares de neuroimagem complexos como a Ressonância Magnética (RM), o número de pacientes que de fato são submetidos a este exame vem perceptivelmente aumentando nos últimos anos.

Por ser uma síndrome clínica que pode ter apresentações diversas e que tem um impacto funcional significativo na vida de seus portadores, a intensidade da cefaleia das crises migranosas e sua recorrência por vezes assusta o paciente. Se existirem sinais de alarme como mudança no padrão da dor, velocidade de instalação súbita, aumento expressivo na frequência de crises, dor precipitada por esforço físico de qualquer natureza ou mesmo por manobra de valsalva/tosse, dor com piora/alívio frente a mudança de decúbito dentre outros um estudo complementar com neuroimagem é adequado para descartar a presença de cefaleia secundária. (6)

Nestes casos, mesmo com história prévia pessoal e/ou familiar de migranea, a RM está indicada. Em uma parcela considerável dos pacientes portadores de migranea, não encontramos alterações relevantes ao exame. No entanto, não é incomum o achado de lesões hiperintensas em sequências ponderadas em T2 ou FLAIR na RM destes pacientes. (7)

Lesões hiperintensas da substância branca em pacientes com idade de 82 anos são mais frequentes na população geral (entre 64-94%) e são mais comuns e extensas em portadores de fatores de risco cardiovasculares e pacientes com doença cerebrovascular sintomática. Diversos estudos já abordaram a relação destas lesões com acidente vascular cerebral, demência e declínio cognitivo, porém a interpretação destes resultados é dificultada pela heterogeneidade de desenhos de estudos, tipos de imagem, tamanhos de amostra e seguimento. (8)

No entanto, em pacientes portadores de migranea jovens e sem fatores de risco para doença cerebrovascular estabelecido ainda apresentam lesões de natureza semelhante, ainda que de distribuição diversa. (9)

Outro diagnóstico diferencial de relevância e impacto clínico é com pacientes portadores de Esclerose Múltipla. Lesões hiperintensas em substância branca de formato ovalado, especialmente em mulheres jovens, ainda que não realçadas por contraste na RM podem facilmente ser confundidas com doença desmielinizante do sistema nervoso central. (10)

Entendemos que uma revisão da literatura médica atual sistematizada com critérios bem definidos é de alta relevância, visto que os achados em neuroimagem destes pacientes podem ser de difícil caracterização mesmo para radiologistas com alguma experiência. A presente revisão sistemática e seu protocolo serão submetidas para publicação em periódico indexado, visando colaborar com a construção do conhecimento do assunto. O periódico escolhido foi "*Headache Journal of Head and Face Pain",* ISSN: 1526-4610, com fator de impacto 5.887.

5. OBJETIVO

A presente revisão sistemática da literatura visa reportar os achados mais relevantes da literatura médica atual no tocante da relação entre migranea e a presença de alterações da substância branca encontradas em exames de ressonância magnética desta população, bem como explorar possibilidades de fatores associados causais. Desta forma, podemos colaborar com a elaboração de hipótesesnovas e prospeção de estudos com delineamento metodológico o mais próximo doideal para futuras revisões e metanálises referentes a este assunto.

O objetivo primário é determinar se existe na literatura evidências que suportem a associação entre migranea e presença de lesões inespecíficas da substância branca nos pacientes portadores desta doença.

O objetivo secundário é angariar os dados dos estudos selecionados paraanálise de quais variáveis são relevantes para futuros estudos observacionais, bem como quais delineamentos e medidas de controle de viés são aplicáveis para posterior desenho de um estudo com a população dos pacientes portadores de migranea do serviço de Neurologia do HCPA.

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7. ARTIGO 1 - Protocolo para Revisão Sistemática da Literatura

Unraveling the relationship between White Matter Lesions in MRI and Migraine: Protocol for a Systematic Review

First Reviewer: Verena Subtil Viuniski
Team of Reviewers: Debora Gontow
Supervisors: Prof. Dra. Juliana Avila Duarte, Dra. Renata Gomes Londero

1. INTRODUCTION

Migraine is a fairly common condition in the global population, with a personal and financial burden well documented in many countries. The International Headache Society, through a selected committee of worldwide Headache Physicians, stated the ICHD-3 which categorize Migraine with and without Aura, where practitioners can find the criteria for diagnosing their patients. In this last version, the ICHD-3 does not include features of any neuroimage as criteria for Migraine diagnosis. In fact, when a patient has a typical Migraine syndrome, the best practice is not to request a Magnetic Resonance Image (MRI) or a Computed Tomography (CT), given no red flags are present. Moreover, when there is a potential secondary cause to the headache, a brain MRI is very well indicated.

Even so, when submitted to a brain MRI many patients with Chronic Migraine, both with and without aura, present hypointense signal lesions on white matter in the T2 weighted sequence, for which there is no explanation determined to this date. There are many speculations over the matter, but no definitive hypothesis has been settled, so it has been called nonspecific white matter lesions for any purposes. The resemblance between microvascular lesions and Multiple Sclerosis typical lesions with these nonspecific white matter lesions in migraineurs is both intriguing and hopefully a clue to what they might signify.

A few studies in the last two decades aimed to approach such lesions and relate them to a pathophysiological cause that englobes the mechanism behind them and what that might implicate for the patients who present them. Migraine is considered mostly a benign disease; such findings might be a contradiction to that belief.

The aim of this study is to scrutinize the most relevant papers published regarding the relationship between chronic migraine and white matter lesions

visualized in MRI in order to help elaborate new hypotheses and design effective studies for further elucidation on this subject.

1.1 SPECIFIC OBJECTIVES

Our main objective is to clarify the evidence base available around the relationship between chronic migraine with white matter lesions. Such will be made by a systematic review of the evidence base of journals and abstracts in this topic area, looking at all designs of studies, except metanalysis, expert opinions and other systematic reviews.

2. METHODS

2.1 ELIGIBILITY CRITERIA

The inclusion criteria comprehend studies investigating white matter hyperintensities in migraineurs and healthy controls, with MRI imaging studies. The subjects must be older than 18 years old with diagnostic criteria for Migraine with and/or without aura by the ICHD-3 criteria and have not been diagnosed with another neurological syndrome such as stroke, multiple sclerosis, vasculitis and encephalitis. The control groups must be composed by headache-free subjects, and preferably without any other neurological conditions.

For the MRI protocols, our minimum requirement is a 1,5 Tesla scanners, which may provide better resolution on the lesions. Volumetric studies will be accounted for if followed by a standard protocol of acquisition, in order to assess disease progression.

We would be evaluating the outcomes of such studies in regard to the number of individuals with white matter hyperintensities on MRI studies, among them the control groups, if present, and the migraine and migraine with aura. If available, follow up data regarding the absolute number of lesions in every group will be taken, as the total lesional volume both in baseline and follow up imaging studies.

Regarding the studies designs, we expect to include observational and cohort studies rather than randomized control trials, due to the nature of the disease and the whole diagnostic intention of this review.

Studies regarding other primary headache disorders, autoimmune and genetic diseases such as Lupus and CADASIL or sclerodermia, Acute Myocardial Infarction, Stroke, right-to-left shunt and other vascular diseases will be excluded.

2.2 INFORMATION SOURCES AND SEARCH STRATEGY

Database search will be performed with selected keywords (see appendix 1) in Pubmed/Medline, LiLacS and EMBASE in April 2020, regarding indexed papers published after 1990. We established this period of search because of the advances in MRI technology through the last decades, enabling better imaging resolution and definition of the brain tissue. Gray publishing and unpublished studies will not be accounted for.

Reference checking and hand searching, contacting experts in the field and identifying possible data from conference attendees are the other methods to ascertain relevant research.

2.3 STUDY SELECTION

Two independent reviewers will be checking the titles and abstracts of studies identified from the searches. The full text of the potential eligible studies will be independently assessed by the two reviewers, in order to determine which of the studies satisfy the inclusion criteria and methodological quality. Data will be recorded in formularies previously designed in Excel by each investigator, separately.

Posteriorly the results will be compared, and any disagreement will be debated and, if necessary, a third reviewer may be involved for solving the dispute.

2.4 DATA EXTRACTION

Data will be collected from the selected papers and summarized into a data extraction sheet by two independent reviewers. Risk of bias and quality assessment of each eligible study will be independently evaluated by two investigators using the NIH quality assessment tools.

Variables to be extracted are: title of the study; author and year; study design (as stated by the paper); total number of participants; total of female subjects; number of patients in migraine group; number of patients in migraine with aura group (if available); number of control patients; whether the MRI were acquired in a 1.5T or a 3T machine; the absolute number of individuals with white matter hyperintensities (WMH); individuals with WMH in migraine, migraine with aura and control groups both in baseline and follow up (if available); lesional volume at the basal and follow up MRI of the migraine, migraine with aura and control group; overall number of lesions in each localization (if available) Juxtacortical, periventricular, subcortical, deep white matter, callosal and subcallosal; time of diagnose in years in both

migraine and migraine with aura; pain days per month in both migraine and migraine with aura group; time of follow up in each study (if available).

Key findings from each study will be summarized and presented in tables and graphic figures.

2.5 DATA ANALYSIS

Due to the heterogeneity of the studies designs, care contexts and populations, a quantitative synthesis of all the data is probably unattainable. A narrative synthesis will be presented, along with summarized descriptive data of the selected studies, although correlation effect size will be attempted to explore the relationship of the findings regarding absolute number of individuals with WMH in each group and respective lesional burden. The statistical procedures will be described in detail on the research paper, and the analysis of such findings explored and presented in tables.

Challenges associated with integrating heterogeneous data sources, due to for example, differences in interventions studied, methods, outcomes, study population and context are expected. Our effort will be to address these by scrutiny of how relevant are the heterogeneities and how consistent are the findings of included studies.

APPENDIX 1 – SEARCH STRATEGY

PUBMED/MEDLINE:

(White Matter[mh] OR (Brain[mh] AND Nerve Fibers, Myelinated[mh]) OR White Matter[tw]) AND

(Migraine Disorders[mh] OR migraine*[tw])

AND

("Prevalence"[mh] OR prevalen*[tw] OR "Epidemiology"[mh:NoExp] OR epidemiology[sh] OR “surveys and questionnaires”[mh:NoExp] OR "Health Surveys"[mh:NoExp] OR "Health Status Indicators"[mh:NoExp] OR survey*[tw] OR "statistics and numerical data"[sh:NoExp] OR incidence[tw] OR "Epidemiologic Studies"[mh:NoExp] OR "Cohort Studies"[mh] OR "Cross-Sectional Studies"[mh] OR cohort[tw] OR follow-up[tw] OR followup[tw] OR longitudinal[tw] OR prospective[tw] OR retrospective[tw] OR cross-sectional[tw])

AND

(Magnetic Resonance Imaging[mh] OR resonance[tw] OR MRI[tw])

EMBASE:

('migraine'/exp OR 'familial migraine' OR 'headache, migrainous' OR 'migraine' OR 'migraine disorders' OR 'status hemicranicus' OR 'hemicrania') AND ('white matter'/exp OR 'brain white matter' OR 'cerebellar white matter' OR 'cerebellum white matter' OR 'cerebral white matter' OR 'spinal cord white matter' OR 'spinal white matter' OR 'substantia alba' OR 'substantia alba cerebelli' OR 'substantia alba medullae spinalis' OR 'white matter') AND ('prevalence'/exp OR

'prevalence' OR 'prevalence study' OR 'epidemiology'/exp OR 'clinical epidemiology' OR 'cohort effect' OR 'confounding factors (epidemiology)' OR 'confounding factors, epidemiologic' OR 'controlled before after studies' OR 'controlled before and after studies' OR 'controlled before and after study' OR 'controlled before-after studies' OR 'effect modifier, epidemiologic' OR 'effect modifiers (epidemiology)' OR 'effect modifiers (psychology)' OR 'environmental epidemiology' OR 'epidemiologic factors' OR 'epidemiologic methods' OR

'epidemiologic research' OR 'epidemiologic research design' OR 'epidemiologic studies' OR 'epidemiologic study characteristics' OR 'epidemiologic study characteristics as topic' OR 'epidemiologic survey' OR 'epidemiological research' OR 'epidemiology' OR 'epidemiology model' OR 'epidemiometry' OR 'healthy worker effect' OR 'historically controlled study' OR 'interrupted time series analysis' OR 'precipitating factors' OR 'sampling studies') AND ('nuclear magnetic resonance'/exp OR 'nmr' OR 'magnetic resonance' OR 'mr' OR 'nuclear magnetic relaxation dispersion' OR 'nuclear magnetic resonance' OR 'resonance, magnetic')

LILACS:

(mh:("White Matter") OR mh:(Brain AND "Nerve Fibers, Myelinated")) AND (mh:(C10.228.140.546.399.750*) OR tw:("White Matter" OR "Sustancia Blanca" OR "substancia branca") AND tw:(migrain* OR migraine OR migrano* OR enxaqueca*))

(("White Matter") OR (Brain AND "Nerve Fibers, Myelinated")) AND ("White Matter" OR "Sustancia Blanca" OR "substancia branca") AND (migrain* OR migraine OR migrano* OR enxaqueca*))

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8. ARTIGO 2

Unraveling the relationship between White Matter Lesions in MRI and Migraine: A Systematic Review

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ABSTRACT

BACKGROUND: The presence of white matter hyperintensities (WMH) in a MRI scan in patients with intense headache, more commonly in those with migraine, is intriguing and may prompt concern both to the physician who requires the exam and the patient. Even though guidelines in the migraine assessment and diagnosis do not encourage the practitioners to perform neuroimaging studies in patients with ICHD-3 criteria for migraine, it is a fairly common practice. Up to the present moment, there is no consensual or definitive data on the nature of such lesions.

OBJECTIVES: To review the present medical literature concerning white matter hyperintensities found in MRI scans of migraine patients

DATA SOURCES: MEDLINE/PubMed and Embase platforms

RESULTS: We found 196 articles at the above-mentioned platforms after keyword search, and after criteria eligibility was applied, we analyzed the abstracts of 37 selected studies, and found 10 articles that fulfilled all criteria previously established at our protocol. Applying the NIH quality criteria assessment, one study was excluded, and the review was performed with nine original observational studies. Due to the heterogeneity of the extracted data, no statistical method as metanalisis was applied. Among the nine included studies, five concluded that the frequency of migraine episodes and disease duration was significant for the WMH presence and progression.

INTRODUCTION:

As common as Migraine can be in the general population, so are the challenges it proposes to the clinical practitioner and referred neurologist. The imaging diagnostic tools are ever developing, and it is tempting to address a disease through them, especially in a territory where misdiagnosis can lead to permanent impairment.

Usually, when there is clinical evidence of migraine as stated by the IHCD-3 (19) and no new features or neurologic impairment, there is no imperative need of a neuroimaging study to establish a diagnosis. (8) But as many of us who attend outpatient clinics know, the real patient seeks medical attention towards a headache with impending anxiety, and there is a tendency of using these resources (if available) just for excluding other pathologies, even though the clinic is sovereign.

It is indeed a challenge to refuse such practice, especially to the patient, who is concerned and eager for a resolution of the distress. Eventually, some characteristics of the patient pain such as speed of installation, shift of pattern, sudden onset, absence of improvement with therapeutics or even their medical history may compel us to use neuroimaging, and the exam of choice can be determined by the clinical features of each patient. (16)

In Migraine with aura (MA) this is even more challenging, because the differential diagnosis may be a stroke or even a neurodegenerative disease. A retrospective observational study conducted by Vijiaratnam et al in Australia demonstrated that patients bearing MA are more likely to be investigated with computed tomography (CT scan) and MRI than those without Aura. In this study, the abnormal CT Scan did not differ between MA and Migraine without aura. But among those who had an MRI, there was a significant difference between the presence of white matter hyperintensities, more prevalent in patients with MA. (39)

The presence of white matter hyperintensities (WMH) in migraineurs MRI exams is demonstrated in medical literature among many controversies. (7) Such abnormality in a patient exam may concern the clinician and a referral to a neurologist is usual. The significance and repercussion of such findings may only be speculated at this point, for the underlying physiopathology is yet unclear. A few models have been proposed, but larger studies are required for establishment of causal relation. (22)

An urge to establish such causal relation is impending, and other colleagues have attempted to address it in previous revisions and metanalysis (5, 34), but none exclusively focused on the WMH and the course or duration of the disease or

anatomical correlations. This systematic review attempts to provide the required data in medical literature to embase such relation and prompt more investigation on this matter.

METHODS

A protocol has been designed and described in detail on the previous article, and the study is registered in PROSPERO platform under the following registration number: CRD420212665265.

In our literature search we included observational and cohort studies performed between 1990 and 2019 published in indexed periodic investigating WMH in patients with Migraine, both with and without aura, older than 18 years old and with no other neurologic affections who were submitted to at least one brain MRI. The MRI exam must have been performed at a 1.5 Tesla equipment or higher.

We searched such articles at MEDLINE/PubMed, Embase and LiLaCs platforms, using the key words already described in appendix 1 of the previous article, and the last search was in June 2020.

The study selection used the criteria previously described. For the data extraction, two independent reviewers performed the task and posteriorly compared and confronted their results. A third independent reviewer was assigned for resolving any dispute. The missing data on the selected studies were registered and further forwarded to the paper authors for completion. (23)

As for the extracted data, we pursued the absolute number of subjects, female subjects, the mean age of subjects and mean deviation, number of migraine without aura patients, number of migraine with aura patients, absolute number of subjects with WMH in MRI, number of migraine without aura patients with WMH, number of migraine with aura patients with WMH, number of control patients with WMH (if a control group is used), the mean volume in milliliters (mL) of lesions in each of the three groups, disease duration in years, days per month with crises, and if any follow up were performed, the time between the first and last MRI in months and the number of individuals with WMH and the mean volume in mL in each of the three groups. The studies were assessed in quality with the NIH scale for observational and cohort studies (35).

RESULTS

The search at the above-mentioned platforms resulted in 168 papers found at MEDLINE/PubMed, 218 at EMBASE and none at LiLaCs. Using the Mendeley platform for unifying and disambiguating these results, we had 196 studies. Manual evaluation for duplication found a total of 168 original articles. Both independent reviewers analyzed these 168 articles by title, excluding those performed before 1990, specialists' opinions, metanalysis and literature reviews and had 88 studies. Furthermore, we excluded 51 studies that contemplate the pediatric population, and other neurological diseases and some cardiologic conditions, such as left-right shunts, resulting in 37 articles for abstract evaluation. For the abstract evaluation we used the previously cited criteria and excluded 21, concluding with 10 articles. After quality assessment, performed by the two reviewers, one study was excluded, remaining with nine for the review. (image 1 – flow diagram.)

The selected studies characteristics are presented in table 1. These full articles were published between 2011 and 2019 in indexed periodics and data extraction, as previously stated, were performed separately by two investigators, and posteriorly compared and any disputes were solved by a third reviewer.

The strengths and weaknesses of each study can be found at table 2 and will be further discussed. There was a considerable amount of missing data, and we tried to reach the authors of two studies, but in 6 months we had no replies. The heterogeneity of the populations studied, the different machines and imaging methods, and mostly the difference in measuring outcomes such as lesion volume had us realize that performing metanalysis with this data was not the best practice.

Participant Characteristics

The patients included in these studies had ages from 18 to 67 years old, with a mean age of 47.7 years old. The majority of the population was female patients (61,3%). All the included studies assessed the subjects for cardiovascular risk factors such as hypertension, smoking, diabetes, hypercholesterolemia. Two studies (Erdélyi-Bótor et al, Lee et al) only included patients with no comorbidities and one study matched the risk factors of the migraineurs with the control group.

Trauminger et al found that WMH were more frequent in migraineurs with elevated serum cholesterol and uric acid and raised the possibility of endothelial dysfunction contribution on the lesions formation. Subclinical Hyper and Hypothyroidism, was found in more than a half of the patients with WMH, and also elevated serum level of homocysteine, which was not further assessed. Also, in this

study, the WMH frequency did not differ between the smokers and no-smokers migraineurs, but the frequency of headache episodes was higher between smokers.

In their prospective study, Dinia et al found 26 of 41 patients with WMH in their MRI exams. Among them, there were 6 smokers and also 6 with hypertension, one with diabetes, three with hypercholesterolemia, 16 with coagulation disorders and seven with left to right ventricular shunt. For the size sample was limited, there was no correlation established with these findings and the progression of the lesions on the eight patients that developed new lesions.

The Dutch cohort studied by Palm-Mendeirs et al in 2012 was provenient from the CAMERA-1 study and comprehended individuals with well-established migraine and sex matched controls. Low education, Hypertension, diabetes, alcohol consumption and smoking were the comorbidities registered, but no statistical correlation between these data and the presence of WMH was reported.

The ARIC MRI study performed by Hamedani et al analyzed the data from the Atherosclerosis Risk in Communities brain MRI cohort. Being a large populational and ongoing cohort study, the findings relating migraine and the presence of WMH are worthy of scrutiny and reproduction, but in this specific paper there were no statistical analysis of the impact of the comorbidities on these findings. Among the 91 migraine patients eligible at the HUNT-MRI 3, the comorbidities reported were smoking, alcohol consumption, ischemic heart disease, cerebral infarction and depression/anxiety (measured by HADS). This study does not report the number of patients with WMH in each studied group, and no adjustment or statistical procedure regarding the comorbidities is reported as well.

At the longitudinal three-year study performed by Erdélyi-Bótor et al and at the Korean study by Lee et al the selected subjects had no comorbidities, while Arkink et al had matched controls for the comorbidities. These two designs may aid with the bias-control and avoiding type II error for further studies, and we strongly suggest that, if possible.

Selected studies strengths and limitations

Even with the strict criteria established, the selected studies are not bias proof. Even so, it is a good practice to report the strengths and limitations of one's study, and all of the selected studies present such information. Observational studies, as the ones enrolled at our review, are known for having less strength of evidence in science compared to Randomized Clinical Trials, but being the nature of such phenomena as WMH and Migraine is actually the most adequate form to assess the correlation possibility.

Most studies were performed with a small sample of participants, and for that reason their results isolatedly are not applicable for all populations. Only two studies had a large population-based design (18, 20), but their data are also limited for possible selection bias.

Imaging Protocols and Analysis of WMHs

When it comes to MRI acquisition, most protocols are quite accessible, which enable reproduction, and in all selected studies are well described. For the analysis of the MRIs results there are a few limitations to report. First there is the heterogeneity of techniques to describe WMH, and the lack of standardization is understandable for the ever evolving technology in the imaging processing field. Also, three of the nine studies did not evaluate the volume of WMH, and while the other six did, only Palm-Meinders et al and Arkink et al had both control groups and follow-up volumetry. Even though the ARIC study and Eldery-Botor et al had measured the volume on baseline and follow-up, they did not present this data for control groups, and the latter did not differentiate MA from MO. Lee et al presented the volumetric measurement data for both migraine groups and controls, but had no follow-up reported, and the HUNT-MRI despite the large number of participants had not presented volumetric data of controls nor follow-up.

There are interesting details about each study methods of processing and interpreting the participants MRIs. Seneviratne et al opted for the Barkof (4) method, using the concept of time-space dissemination that is usually employed in multiple sclerosis and described the location of WMH accordingly, while Dinia et. al., Éldery-Bótor et al and Trauminger et al considered WMH as hyperintense areas in T2 and Flair weighted scans without hypointensities in T1 weighted scans, up from 2mm and present in 2 consecutive slices, counting these lesions manually with the aid of two (or more) neuroradiologists. Dinia et. al. also divided the lesions based on

the vascular territory. Hamedani et al at the ARIC study used a scale from 0-9 developed especially for this cohort and analysed the brain/lesion volume through both automated and manual volumetry, but there is loss of data in follow-up for multiple reasons, especially because the volumetry was estimated at the follow-up MRI visit. Palm-Meinders et al used results of automatic segmentation of white matter lesions and if necessary, corrected manually and both baseline and follow-up exams were revised by two neuroradiologists while a third senior was assigned to disambiguation for both quantitative and volumetry assessment. Arkink et. al used a similar process and both used the same software (QBrain 1.1). Éldeiry-Bótor et. al. also used a software to aid neuroradiologists on evaluating the images (Volumetry 3D Slicer).

At the HUNT-MRI imaging analysis the chosen scales were semi-quantitative Fazekas (12) and Scheltens (29). While Fazekas was developed for assessing WMH linked to cerebrovascular comorbidities in the whole brain, the scale developed by Scheltens assess periventricular lesions separately from the deep white matter and claims to be more specific, but the first is more commonly used for this purpose. The volumetry in the HUNT-MRI study used a method based on the Statistical Parametric Mapping (SPM) software package, and intracranial volumes were calculated using the adapted reverse and automatic reverse brain-masking techniques.

Lee et al. validated a very promising method called DEWS (25) to automatically quantify the WMH of their participants. DEWS is a fully automated, machine learning–based pipeline for detecting deep WMHs that was developed to be used in nonelderly patients with migraine, with an impressive correlation coefficient between the automated and manually counted WMHs, confirmed by the investigators.

Findings on Migraine Patients White Matter

The main outcomes of the nine included studies were heterogeneous as well, even though the overall aim was similar. Trauminger et al found no difference between migraine with and without aura concerning WMH, and that all lesions were supratentorial and more prevalent in patients with longer course of disease and higher crisis frequency. They also investigated the correlation with a few comorbidities and found that the frequency in WMH did not differ among smokers and non-smokers, but smokers had a higher headache frequency, which was found to increase the risk of developing WMH. Another interesting finding was a significant relation between abnormal homocysteine seric levels and the presence of WMH, and subclinical

hypothyroidism happened more frequently in patients with WMH.

In a population of patients with migraine with aura, Dinia et al found that 63.4% had WMH at the baseline MRI scan and after 33 months 19.5% of these patients developed new WMH. A significant correlation was found between the duration of migraine with aura and the number of new WMH and between the number of attacks with aura per year and the number of new WMH.

Seneviratne et al aimed to emphasize the importance to discern WMH in Migraineurs from the lesions that characterize MS. It was found that 43.2% of the Migraine patients had WMH, of which 9% fulfilled the McDonald criteria for dissemination in space. In the multiple logistic regression analysis only 3 variables emerged as factors associated with WMH in migraine. In multiple logistic regression,increasing headache frequency was highly significant with a p value of 0.004 (OR 1.26, 95% CI 1.08–1.48). Those with a family history of migraine were over 50 timesmore likely to have WMH (OR 52.95, 95% CI 1.94–1442.79, p 0.019) and increasingage was the third association (OR 1.2, 95% CI 1.02–1.41, p 0.031). At the community based cohort study conducted by Palm-Meinders et al, patients and controls had a baseline MRI scan and were followed-up nine years after.The main findings were no difference in baseline and follow-up between men in the migraine group and controls. However, among women deep white matter hyperintensities volume was higher in the migrain group then in controls, both in baseline and follow-up. Also, the incidence of deep white matter hyperintensity progression was highest among women with migraine without aura. In multivariate logistic regression analyses involving only women, migraine was independently associated with deep white matter hyperintensity progression (adjusted odds ratio [OR], 2.1; 95%CI, 1.0–4.1). The increase in total deep white matter hyperintensity volume among women with migraine was related to an increased number of new lesions rather than an increase in the size of the preexisting lesions. Mean size of individual hyperintensities at follow-up did not differ between groups. Similarly, women in the migraine group had a higher incidence of high progression than those in the control group (23%vs 9%; P=.03). The interaction with comorbidities was not significant.

Hamedani et al at the ARIC MRI study followed-up a group of migraine, other headache patients and headache-free patients for 8 to 12 years with MRI scans. The presence of any headache, migraine, or non-migraine headache was not associated with a statistically significant increase in the odds of having a WMH score of 3 or more (at the score that was developed by the researchers) compared to individuals without any headache after adjustment for potential confounders. Migraine with and without aura were subcategorized, and migraine without aura was associated with a significantly increased risk of severe white matter disease (odds ratio [OR] 5 1.87; 95% confidence interval [CI]: 1.04, 3.37), when migraine with aura was not (OR 5 0.55; 95% CI: 0.17, 1.83). However, when migraine with and without aura were compared directly in a distinct model, this difference was not statistically significant (OR 5 0.53; 95% CI: 0.27, 1.01). At the brain MRI visit, individuals with migraine had an average volume of 2.65 cm3 more WMH than those without headache (95% CI: 0.06, 5.24), whereas non-migraine headache was not associated with greater WMH volume (20.77 cm3 WMH; 95% CI: 23.54, 2.10). Compared with the control group, migraine was associated with a significantly greater rate of progression in WMH between the 2 visits in the partially adjusted model but not in the fully adjusted model. Neither migraine with nor without aura were separately associated with greater WMH volume or progression.

In Eldélyi-Bótor longitudinal study, the same group of migraine patients was followed up in three years with MRI scans and analyzed the lesions individually. A significantly higher number of WMHs was detected in the follow-up study than in the baseline study (498 vs 370, $P < .001$). The lesions were found more frequently at the deep white matter, followed by subcortical, periventricular e callosal locations, and concerning the lobar distribution the highest number of hyperintensities in the frontal lobe fol- lowed by the parietal, temporal, and occipital lobes. It was found that 264 lesions, 67.7% of the WMHs observed at baseline, had increased in the follow-up time, and all patients had at least 1 lesion with increased volume. A total of 91 WMHs had a smaller volume at follow-up (23.3%) and all patients had at least one WMH that became smaller. It was not found any correlation between the increase or decrease of the lesions size with age, time of disease or headache frequency.

The WMH findings at the HUNT MRI, a Norwegian population based study performed by Honninsvag at al were assessed by semi-quantitatively using Fazekas and Scheltens scales, and by manual and automated volumetry of MRI. With a standardized questionnaire developed by the researchers, participants were separated between 4 cross-sectional groups: Headache free, tension type headache, migraine and unclassified headache. At this study, no correlation between migraine and WMH was found, however, it was found an association with tension type headache. The main limitation of the study, even more than the semi-quantitative scale use, is that the diagnosis of headache type was not based on the ICHD criteria and self assessed, which can produce a type II error, as previously stated.

Lee et al studied the WMH burden in non-eldery patients with episodic migraine without comorbidities and controls with a single visit MRI scan. Among the studied headache patients, 69.8% had WMH, and the lesional burden was small in most patients, concerning number and volume. Controls had also a small WMH burden, and it was numerically less than patients, but statistical comparison was not performed for the difference in the MRI resolution between the groups. Increased headache frequency was not associated with either deep WMH number or volume, and increased age was the only factor associated with higher deep WMH volume in patients with migraine.

Patients and controls from the CAMERA study were assessed by Arkink at al in a 9 year follow-up with magnetization transfer imaging (MTI) to assess white matter tissue integrity in migraine and analyze deep WMH and volume. Although no statistical correlation was performed with the WMH volume of the patients, we decided to include the study for the consistency and methodologic quality of the data. The control group had a baseline deep WMH volume of 0.04mL (0.00-0.80mL), and at the nine year follow-up of 0.24mL (0.01-1.56mL). At baseline, approximately 23% of the controls had deep WMH. The migraine group had a baseline deep WMH volume of 0.07mL (0.00-0.77mL) and 0.36mL (0.00-4.16mL) at the 9 year follow-up. Close to 36.5% of the migranours had deep WMH at baseline. When it comes to migraine type, patients with migraine with aura had a median lesional volume of 0.06mL (0.00-0.77mL) at baseline and 0.36mL (0.01-4.16mL) at follow-up, while patients with migraine without aura had 0.09mL (0.00-0.55mL) at baseline and 0.36mL (0.00-2.55mL) at follow-up scans. Close to 38% of the patients with migraine with aura and approximately 34.5% of those without aura had deep WMH at baseline.

DISCUSSION

When it comes to designing a study to assess WMH in migraine patients, a few characteristics may be taken in consideration. The mean age of participants is relevant for the increase of vascular comorbidities and natural brain volume decrease present in elder patients may be a confounding factor. The assessment of comorbidities in these patients may be strict as well, for they are well established causes of WMH in the general population. The standardized instrument for migraine and other headaches diagnosis must be the latest version available of ICHD at the investigation moment (19), for its accuracy and consensual criteria among specialists. Finally, the MRI scan protocols and resolution are relevant especially for comparison between patients and controls and further reproductility, as it is currently the best method we have for such investigation.

The lack of large and representative studies in this subject may be explained for the presumed benignity of the disease, but also for the lack of a valid qualitative/quantitative scale to classify these lesions, for the major other causes of WMH have their own. For such a prevalent medical condition with a major impact in quality of life and productivity among affected individuals, it seems imperative for better comprehension of the disease to understand the pathological mechanisms of the WMH in these patients.

Since the physiopathology of migraine episodes is being better understanded with the breakthrough of the calcitonin gene peptide receptor role discovery (3), assumptions on the vascular nature of such lesions are presumible but do not elucidate the whole mechanism. The studies in the present review present a few hints on the nature of the WMH development phenomena: most of them demonstrated that the headache frequency and time of disease are possibly associated with a higher lesional burden, as much as in the number of lesions as in their volume. Another interesting consistent finding is that the patients' comorbidities seem to have no relation with the presence or the progression and development of the WMH found in their MRI scans. (9, 11, 24, 38)

One important point that we had not assessed, nor the majority of the included studies, is the implication of these lesions in the overall cognition and cerebrovascular risk of the migranours. We assume that understanding the pathological involvement of these findings in migraine patients MRI may hint to the consequence of their presence for this population.

CONCLUSION

It is evident that for fully elucidating the WMH in migraine patients more and better designed studies are required. Analysing the strengths of the studies included in this review, we may suggest a few points for enhancing the power of future researches: larger number of subjects, adjustment for comorbidities, matched controls, comparison with other WMH causing diseases, using the latest ICHD criteria available for the diagnostic of migraine patients to be included, well characterized and reproducible MRI scans protocols, standardized softwares and measurement of the assessed lesions as well as individualized analysis of each lesion dimension, volume and location in the brain.

Unraveling the nature of WMH in migraineurs may aid in the ever evolving elucidation of this prevalent and disabling disease, with great impact in the way we classify, diagnose and treat these individuals. Not to mention the possibility to answer more accurately the patients inquiries after their MRI scans results other than the vague term in use, nonspecific migraine white matter alterations, which may prompt more anxiety both in clinicians and affected patients, not to mention the expenses in further scans and the astounding lead to misdiagnosis with a life changing disease such as MS and its variants.

FUNDING

No funding was required or used in this systematic review.

Table 1 - Selected studies general characteristics

Name, author and year of publishing	Study Design*	N total (controls)	MO /MA	Follow-up (months)	WMH (basal / follow-up)
Risk factors of migraine-related brain white matter hyperintensities: an investigation of 186 patients Trauminger et al, 2011	N/A	186	141/45	N/A	MO:42 MA:16 *no control, no follow-up
White Matter Lesions Progression in Migraine with Aura: A Clinical and MRI Longitudinal Study Dinia et al, 2011	Longitudinal Prospective	41	0/41	33.2	MA:26/8 *no control group
Brain white matter hyperintensities in migraine: Clinical and radiological correlates Seneviratne et al, 2012	Retrospective Cohort	44	26/18	N/A	MO: 7 MA: 12 *no control, no follow-up
Structural Brain Changes in Migraine Palm-Meinders et al, 2012	Prospective Cohort	286 (83)	89/114	108	MO: 89/68 MA: 114/84
Migraine and White Matter hyperintensities - The AIRIC Study Hamedani et al, 2013	Prospective Cohort	1028 (936)	59/33	48	MO: 2.72 mL (20.40, 5.82) / 1.13 mL(21.20, 3.46) MA: 2.58mL (21.67, 6.83) / 2.50 mL(20.70, 5.70) *lesional volume
Changes of Migraine-Related White Matter Hyperintensities After 3 Years: A Longitudinal MRI Study Erdélyi-Bótor et al, 2014	Longitudinal	17	10/7	36	MO:10/9 MA:7/7 Lesional volume: 0.896 mL(0.628-2.434) / 1.140 (0.842 -2.666)
White matter hyperintensities and headache: A population-based imaging study (HUNT MRI)	Cohort	862 (551)	29/62	NA	407 patients w/ WMH – 9 w/migraine

Honningsvaˆg et al, 2018					
Cerebrovascular reactivity as a determinant of deep white matter hyperintensities in migraine Lee et al, 2019	N/A	121(35)	71/15	N/A	60 *no control group
Microstructural white matter changes preceding white matter hyperintensities in migraine Arkink et al, 2019	Longitudinal	211(74)	58/79	108	MO: 20/20 MA: 30/29

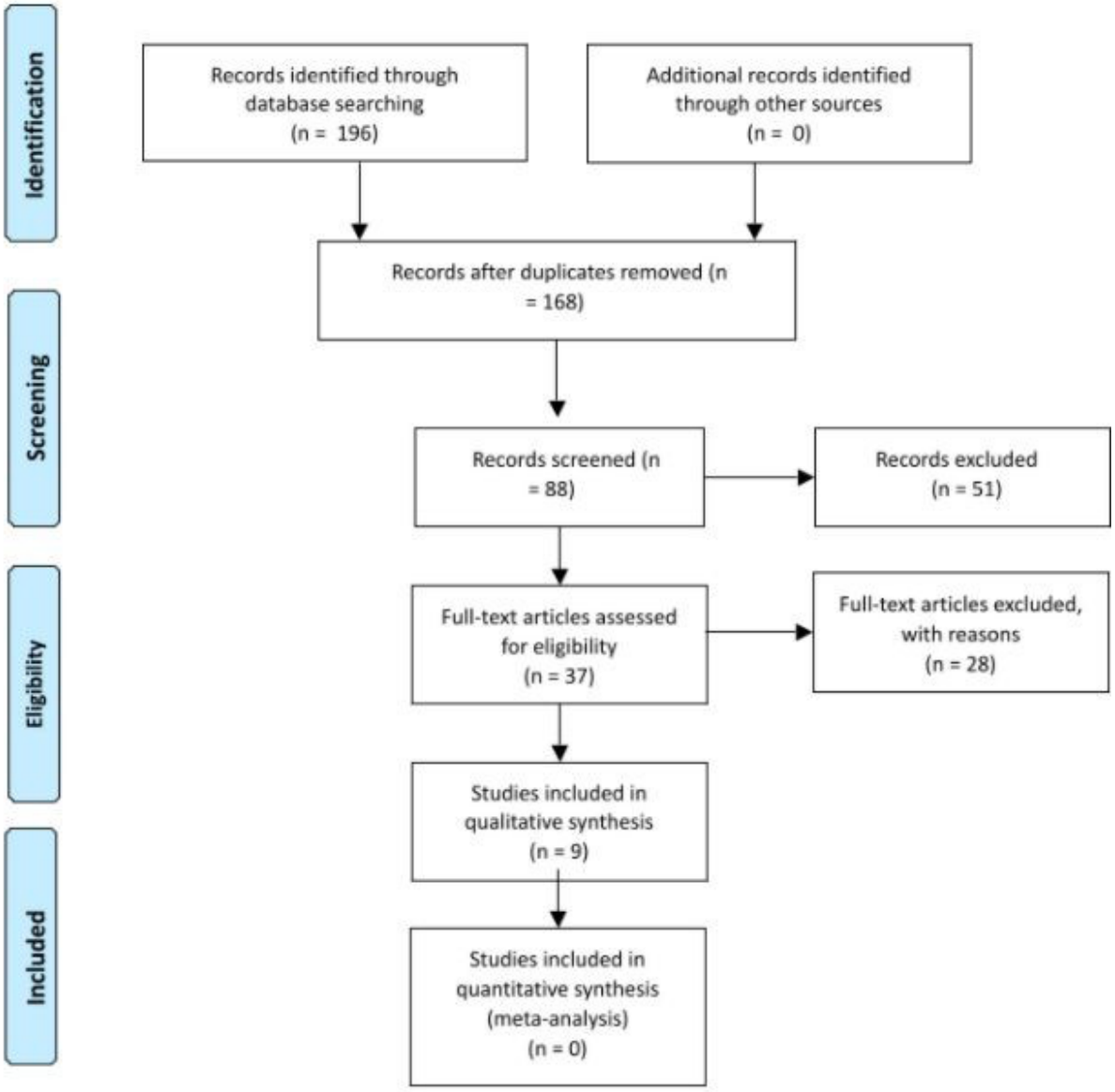
*as reported by the authors

Table 2 - Selected Studies Strenghts and Limitations

	Strengths	Limitations
Trauminger et al, 2011	-Assessment and statistical analysis of risk factors associated with WMH; -Evaluation for WMH in both Migraine with and without aura separately;	-Small sample size; -Few details on MRI acquisition protocol and WMH measurement; -No control group, no follow-up;
Dinia et al, 2011	-Well established MA diagnosis and documented disease course/duration; -Assessment and report of comorbidities; -Longitudinal design allowing follow-up MRI of all the participants;	-Small sample size; -Nongenetic laboratory parameters were only assessed at the baseline; -No volumetric analysis of the WMH; -Did not considered patients with MO -No control group
Seneviratne et al, 2012	-Reported the distribution of WMH load in the brain;	-Small sample size; -No control group
	-Exploited potential for confusion with MS and clues for the distinction with migraine lesions;	-Retrospective design -Possible selection bias (severe and complicated migraine);

Palm-Meinders et al, 2012	-Longitudinal design; -Lenght of follow-up; -Well characterized cohort; -ICHD criteria for migraine diagnosis; -Sensitive and reproductible methods of MRI acquisition;	-Wide C.I.; -Possible selection bias: ⅓ of the original baseline population was not reinvestigated;
Hamedani et al, 2013	-Large, biracial, populational-based cohort; -Standardized headache and WMH assessment;	-Possible selection bias: the brain MRI subcohort was smaller; -Headache assessment was retrospective and did not used ICHD criteria; -Possible dilluition effect: patients were treated for migraine and may be on the migraine-free group; -Lack of information of duration of disease and crisis per year
Erdélyi-Bótor et al, 2014	-Through description of the MRI acquisition protocol; -Volumetric measurement of all lesions -Reported the distribution of the WMH lesions on the brain;	-Small sample size; -Lack of follow-up images of control group;
Honningsva˚g et al, 2017	-Large population-based design; -Assessment of headache status at two times; -Reproducible MRI protocol and manual volumetry;	-Possible Selection bias: participants with lower CV risk; -No gender stratification; -Self assessment of headache (did not used ICHD)
Lee et al, 2019	-Use of a high-sensitivity automated quantification method to detect WMH (DEWS); -Through clinical and neurophysiological assessment of all participants;	-Different protocol for MRI acquisition between patients and controls; -No sex and age matching;
Arkink et al. 2019	-Well documented and reproductible MRI acquisition protocol -Long follow-up -Age,sex and comorbidities adjusted;	-Small sample size; -Possible selection bias: loss of over half of the participants on follow-up;

PRISMA Fluxogram



Adapted from: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta- Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed100009

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9. CONSIDERAÇÕES FINAIS

Por meio desta revisão da literatura, nos deparamos com uma quantidade limitada e heterogênea de dados frente à natureza das lesões de substância branca em pacientes portadores de migranea. As hipóteses que os artigos selecionados aventam são tão heterogêneas quanto os resultados dos mesmos, expondo um nicho importante a ser explorado em estudos observacionais futuros.

Uma dificuldade real que enfrentamos foi a falta de alguns dados e a dificuldade de contato com os autores dos estudos, que em um prazo de 8 meses não retornaram nossas solicitações. A possibilidade de excluir os dois estudos onde não foram apresentados dados importantes foi cogitada, mas como a metanálise já não poderia ser realizada mesmo sem estes, optamos por mantê-los e descrever no texto seus achados.

Mesmo sem a possibilidade de apresentar cálculos e metanálise para a revisão realizada, o estudo prova sua utilidade e reforça o valor das revisões sistemáticas para os avanços em compreendermos patologias específicas e pouco compreendidas até o presente momento justamente por organizar as informações que já foram publicadas e expor a necessidade de elaborarmos com cuidado as próximas investigações.

10. PERSPECTIVAS

O valor real de uma revisão sistemática desta natureza é o de possibilitar um melhor desenvolvimento e desenho de estudos futuros. Esperamos que a publicação dos artigos elaborados para esta dissertação incentive outros grupos de pesquisa a idealizar e publicar investigações com critérios mais homogêneos e reprodutíveis.

Identificada a heterogeneidade dos resultados e métodos de avaliação da neuroimagem dos pacientes portadores de migranea, parece razoável a elaboração de uma classificação quanto ao local, forma, tamanho, distribuição, características de sinal e de realce das lesões da substância branca dos pacientes com migranea. Essa ferramenta teria como objetivo auxiliar radiologistas e clínicos a estreitar o diagnóstico diferencial pela RM de encéfalo com tais alterações, principalmente em relação às lesões de natureza desmielinizante, que podem ser difíceis de diferenciar e são frequentemente confundidas e tratadas erroneamente devido a diagnósticos incorretos, levando a tratamentos clínicos desnecessários, custosos e deletérios aos pacientes.

Posto isso, visamos também concluir um estudo observacional, previamente aprovado pelo GPPG do HCPA e interrompido devido a pandemia de COVID-19, para estudar a coorte dos pacientes portadores de migranea do ambulatório de cefaleia do HCPA frente a prevalência e características destas lesões de substância branca. Idealizamos que este estudo possa apresentar as qualidades necessárias para gerar evidência relevante frente a elucidação da natureza das lesões encontradas em exames de RM na substância branca desta população e futuramente embasar a elaboração da classificação das lesões presentes nos exames de pacientes com migranea supracitada.

11. ANEXOS E/OU APÊNDICES

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	2
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	3
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	3
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	3
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	3
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	3
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	3
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	3
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	3
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	3
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	3

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	3
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	3
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	4
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	4/5
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	4/5
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	5/6
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	5-10
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	6
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	6
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	11
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	11/12
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	12
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	12

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