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VIEW AND REVIEW

Disability and progression in Afro-descendant patients with multiple sclerosis

Incapacidade e progressão em pacientes afrodescendentes com esclerose múltipla

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ABSTRACT

Multiple sclerosis (MS) prevalence is higher in Caucasian (CA) populations, narrowing the analysis of the impact of Afro-descendant (AD) populations in disease outcomes. Even so, recent studies observed that AD patients have a more severe course. The main objective of this study is to confirm and discuss, through a systematic review, that being AD is a risk factor for disability accumulation and/or severe progression in patients with MS. A systematic review of published data in the last eleven years was performed, which evaluated clinical aspects and long term disability in patients with MS. Fourteen studies were included. Of these fourteen articles, thirteen observed a relationship between ancestry and poorer outcome of MS. African ancestry is a condition inherent in the patient and should be considered as an initial clinical characteristic affecting prognosis, and influencing which therapeutic decision to make in initial phases.

Keywords: multiple sclerosis; disease progression; disability, Afro-descent.

RESUMO

A prevalência da esclerose múltipla (EM) é maior em populações caucasianas (CA), o que limita a análise do impacto da Afrodescendencia (AD) nos desfechos da doença. Apesar disto, estudos recentes observaram que a AD determina um curso clínico mais severo. O principal objetivo deste estudo é confirmar e discutir, por meio de uma revisão sistemática, que a afrodescendência é um fator de risco para acúmulo de incapacidade e/ou progressão mais severa em pacientes com EM. Foi realizada uma revisão sistemática de trabalhos publicados nos últimos onze anos que avaliaram aspectos clínicos e incapacidade a longo prazo em pacientes com EM. Quatorze artigos foram incluídos. Entre eles, treze observaram uma relação entre AD e pior prognóstico da EM. AD é uma condição inerente ao paciente e deveria ser considerada, assim como as características clínicas relacionadas ao prognóstico, influenciando a decisão terapêutica a ser tomada nas fases iniciais da doença.

Palavras-chave: esclerose múltipla; progressão da doença; incapacidade, afrodescendente.

Multiple sclerosis (MS) is among the most common causes of nontraumatic neurological disability in young adults[1]. Its natural history has been extensively studied in Caucasian (CA) populations, and prognostic factors have been well recognized: being male, late age at the first symptom, high number of relapses in the onset of the disease, and short interval between initial relapses with poor recovery have been identified as predictive factors of long term disability[2,3,4,5,6,7,8,9,10,11].

While MS is a worldwide disease, its prevalence is higher in populations from western countries in the northern hemisphere compared to those from Africa, Asia and Latin America[12]. Despite this, MS in Afro-descendant (AD) individuals has been described for a long time, mainly in areas where there has been immigration of African natives, such as United States of America, Brazil and the Caribbean region. Recent studies have observed a severe course with higher disability and faster progression in AD patients[13,14,15,16,17], and a worse response to disease modifying drugs[18]. Raising awareness of the prognosis of MS in racially mixed populations in available data in literature highlights the growing therapeutic options of disease modifying drugs that are more effective when administered early. The main objective of this study is to confirm and discuss, through a systematic review, that being of AD heritage is a risk factor for disability accumulation and/or severe progression in patients with MS.

METHODS

A systematic review of published data between January, 2003 and October, 2014, with AD as a risk factor

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for disability accumulation and/or severe progression of MS was performed. It included original articles in English of cross-sectional and cohort studies, prospective and retrospective, that evaluated clinical aspects and long-term disability in patients with MS in the different clinical phenotypes (relapsing-remitting [RR], secondary progressive [SP] and primary progressive [PP]), according to Lublin's and Reingold's definition[19]. Review articles, meta-analyses, editorials and case reports were rejected. Studies with laboratorial and/or image endpoints were also excluded.

The databases MEDLINE, Latin-American and Caribbean Literature in Health Sciences (LILACS), Scientific Electronic Library Online (SciELO) and PubMed were consulted with the following combined descriptors (in English): "multiple sclerosis", "secondary progression", "progression", "primary progression", "African ancestry", "African American", "African descendants", "Black patients", "Negro", "risk factors", "prognostic factors". The abstracts of the selected articles were read independently by two authors (JCKA and CCFV), for inclusion or exclusion from the systematic review. The reviewers reached a consensus on all items. The reviewers evaluated the titles and abstracts of all identified studies and then obtained complete copies of all relevant articles. Any related article's function was used to broaden the search. References of the selected articles were also searched manually. The studies that evaluated the association between AD ethnicity and progression and/or disability accumulation were fully analyzed. The following items were extracted from each study if available: first author's name, publication year, clinical and demographic factors, number of subjects, clinical impairment, time to reach a certain disability level or time to progression, mean of Expanded Disability Status Scale (EDSS) or progression index stratified by ethnicity.

The electronic research identified 184 studies published with the keywords, combined between them, in PubMed and MEDLINE. Initially, 166 articles were excluded for not being relevant. Eighteen articles were selected, of which a further five were excluded because they were about laboratorial or image aspects. Four articles were excluded for being performed only in a pediatric population or related only to treatment outcomes. By manual search we selected a further nine articles, four of which were excluded for having been published in French and/or for not being related to the main endpoint of this review. The remaining articles were fully analyzed and the STROBE checklist for cohort studies was applied. Studies that had the same source of patients, like the New York State Multiple Sclerosis Consortium (NYSMSC)[16,20] and North American Research Committee on Multiple Sclerosis (NARCOMS)[17,21] were only counted once, using the study with the higher number of patients, thus avoiding a duplicate count. Fourteen articles fulfilled the inclusion criteria (Figure).

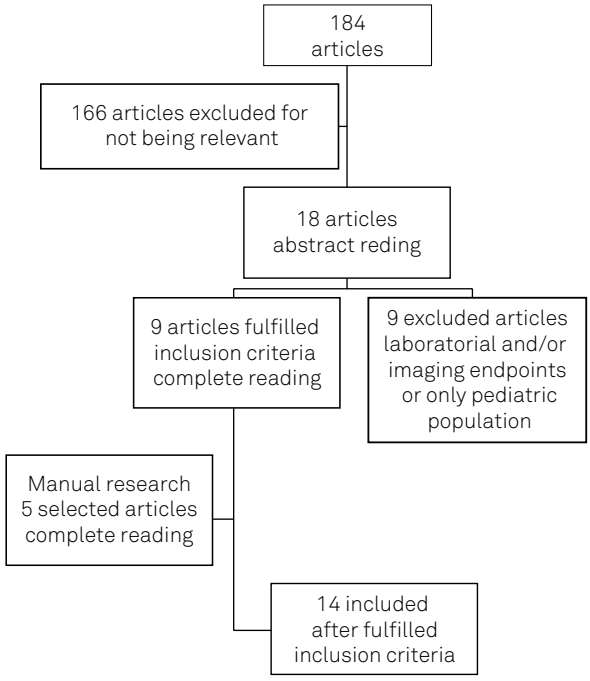

Figure. Flow chart of the search strategy.

RESULTS

Among the 14 articles considered relevant, nine articles are from North America, three articles from Brazil, and two from Europe. Together, they covered a population of 52,470 patients, 4,068 AD (7.8%) and 48,402 CA (92.2%). Eleven studies analyzed the three clinical phenotypes of the disease[15,16,17,20,21,22,23,24,25,26,27], two only evaluated the RR/SP forms[2,28] and one, just the PP form[29].

The clinical and demographic characteristics analyzed in twelve studies were: gender, age, race, MS history (age at onset, age at diagnosis, functional system affected), disability status and treatment[2,15,16,17,20,21,22,23,26,27,28,29]. Six studies also evaluated the progression status[2,15,26,27,28,29].

The ancestry was defined through self-report questionnaires[2,15,16,17,20,21,26,27], by the presence of one black skin relative up to three previous generations[28,29], or by the parents' background[22]. One study did not describe how ethnicity was determined[23].

Different endpoints were adopted: a) the mean or median EDSS at a certain time[16,23,26,28], b) time to reach disability markers by EDSS 0 and 2[16], EDSS 3[16,29], EDSS 4[22,27], EDSS 5[16], EDSS 6[2,15,16,22,23,27,29], EDSS 7[2,15,16,23], and EDSS 8[2,16,27,29], c) EDSS score in the 4th and 6th year of disease and at last follow-up[23], in the 5th and 10th year and at the last follow-up[28], d) time to start of the progressive phase[15,26,27,28,29], e) analysis of benign and malignant courses[2,28]. Besides the EDSS, another three scales were applied for assessing the disability: the Multiple Sclerosis Severity Score (MSSS)[20], Patient Determined Disease Steps (PDDS)[17,21] and ADL Long Form Scale[24,25] (Table 1 and Table 2).

Table 1. Summarizes the studies that have used the Kurtzke Expanded Disability Status Scale (EDSS) to evaluate disability and functional capacity.

Author,y.	AD (n; %) in the cohort	Results concerning AD population (compared to CA)
Kaufman et al. 2003[26]	95; 12.9	Higher EDSS mean after 4 years of disease and shorter time to progression
Cree et al. 2004[15]	375; 46.7	Shorter time to progression and EDSS 6 and 7
Naismith et al. 2006[23]	79; 49.7	Higher EDSS mean at diagnosis and after 4 and 6 years of follow up
Debouverie et al. 2007[22]	211; 6.7	Shorter time to EDSS 4 and 6
Weinstock-Guttman et al. 2008[16]	329; 5.9	Higher EDSS mean after 5, 10, 15 and 20 years of disease
Vasconcelos et al. 2010[29]	23; 35.4	Shorter time to EDSS 3, 6 and 8
Vasconcelos et al. 2012[28]	33; 22.0	Shorter time to progression and higher EDSS median after 5 and 10 years of follow up
Koffman et al. 2013[27]	43; 50.0	Shorter time to EDSS 4, 6, 8 and progression

y: years; AD: afro descendants; CA: Caucasians.

Table 2. Summary of clinical and demographic factors associated with afro descendants patients and the studies that have used other scales to evaluate disability and functional capacity.

Author, y.	AD (n; %) in the cohort	Results concerning AD population (compared to CA)
Kaufman et al. 2003[26]	95; 12.9	Had advanced age at onset and shorter disease duration than CA
Buchanan et al. 2004[24]	1367; 12.8	Were admitted to nursing home younger; more frequency of AD with worse cognitive performance; were less independent in ADL Long Form Scale
Cree et al. 2004[15]	375; 46.7	Were older at onset and had shorter disease duration, had early diagnosis and early treatment and had more polysymptomatic relapses
Buchanan et al. 2006[25]	461; 11.3	Were admitted to nursing home younger; more frequency of AD with worse cognitive performance; were less independent in ADL Long Form Scale
Naismith et al. 2006[23]	79; 49.7	Had a higher frequency of progressive forms, ataxia, tremor and cognitive dysfunction; Lower frequency of benign forms among ADs
Marrie et al. 2006[21]	1017; 4.7	Early diagnosis and shorter disease duration; PDDS median was higher
Debouverie et al. 2007[22]	211; 6.7	Younger age at onset and shorter mean of follow up; had more frequently incomplete recovery from the first relapse, shorter time interval between first and second relapse and higher number of relapses in the first five years of the disease
Weinstock-Guttman et al. 2008[16]	329; 5.9	Were diagnosed younger; cognitive impairment was more frequent
Kister et al. 2010[20]	419; 6.7	Shorter disease duration at diagnose; lower AD frequency of benign form; higher AD frequency of malignant form; higher median MSSS
Vasconcelos et al. 2010[29]	23; 35.4	Men predominant in AD group and ADs had shorter disease duration
Buchanan et al. 2010[17]	1313; 4.6	Mean age at NARCOMS enrolment was lower among AD. ADs had shorter disease duration, had severe gait disability, fatigue, bowel and bladder incontinence, spasticity, visual and cognitive impairment, depression, tremor and loss of coordination than CAs; were more frequent represented at higher PDDS scores
Vasconcelos et al. 2012[28]	33; 22.0	Older at disease onset; more incomplete recovery and higher number of relapses; benign form less frequent in AD; malignant form more frequent in AD
Koffman et al. 2013[27]	43; 50.0	More cognitive impairment; MSSS mean was higher

y: years; CA: caucasians; AD: afro descendants; ADL: activities of daily living; PDDS: patients-determined disease steps; MSSS: multiple sclerosis severity score; NARCOMS: Registry of the North American Research Committee on Multiple Sclerosis.

Progression was considered as the increase of one point in the EDSS scale, not attributed to relapse, maintained for six months or more, without improvement, or for a progressive worsening of symptoms in six articles[2,15,26,27,28,29]. The definition of a benign course was an EDSS score of 3 or less after ten years of disease and a malignant course was defined as an EDSS score of 6 or higher after five years of disease, in two articles[2,28].

DISCUSSION

In 1962, Alter published the research results of MS in Blacks from New York and affirmed that the disease was rare in this group, however without significant differences between Blacks and Whites regarding clinical manifestations[30]. After 33 years, in 1995 the first Brazilian article was published in which a frequency of 31.4% AD among MS patients[31] was described. Unlike that observed by Alter, in the Brazilian study there was a higher frequency of AD women with motor relapses compared to CA women, who had more relapses of visual and cerebellar type. Nowadays it is known that both AD ethnicity and motor impairment are independent predictors of a poorer long-term outcome. Although analyses of the impact of AD ethnicity in disease outcomes are still scarce, in the last ten years, studies with racially mixed populations, such as in North America and

Brazil, have pointed to differences between the disease outcome in CA and AD patients.

Considering that MS is a worldwide disease, studies on the influence of ethnicity have been performed in only four locations, three of them (USA, Brazil and Caribbean region) probably due to the African background during colonization.

The frequency of AD patients in the analyzed studies was not more than half of each cohort. In four studies, self-response questionnaires were used in which the patients classified themselves as CA or AD, a fact that may explain the low frequency of AD observed in them[16,17,20,21]. Despite the lower frequency of AD studies, the majority of them showed a worse outcome in the AD group. It is worth noting that two studies did not exclude patients with the diagnosis of neuromyelitis optica[15,26], a circumstance that may have caused bias, due to neuromyelitis optica being more common in AD than CA patients[32] and having a more severe course.

Diverse risk factors for severe progression have been identified and extensively discussed in the literature; nevertheless, these results are not always consistent between studies, due to different classifications and methods of analysis, and genetic variability of the studied populations. In relation to these prognosis factors, in this systematic review it was observed that AD patients were more likely to be older at onset[26], have incomplete recovery of relapses, shorter inter-attack intervals and more relapses in the first five years of disease[22]. Afro-descendants were younger when they presented for medical care[17,26], probably due to severe relapses, they sought neurological care in a shorter time, and when admitted to nursing homes, had a higher disability score,[24,25] with more motor limitation[23,24] and more severe and rapid cognitive impairment[16,24]. More AD patients were bowel or bladder incontinent than CA patients on admission to nursing homes[25]. Even though the studies adopted different disability markers in the EDSS scale[15,16,22,23,26,27,28,29], it was possible to observe that AD patients reached these markers in shorter times or had higher EDSS mean or median scores after a set time of follow-up. Despite the fact that the complex association between immunogenetic and ethnic factors has not yet been fully elucidated, the worse and faster evolution observed in Afro-Brazilian patients, as well as African-Americans and Afro-Europeans suggests a greater ethnic influence in the progression of multiple sclerosis.

Correlation between AD ethnicity and the endpoints was observed in the majority of the studies, with the exception of the study performed in the city of Campinas[2], in the southeast region of Brazil, where most of the genetic ancestry is European, with AD ethnicity corresponding to 7.4%[33,34]. Forty percent of the patients analyzed presented for less than five years of follow-up, a fact that can cause bias in the analysis of long-term outcomes.

The EDSS scale was the most used in MS studies, and, even when less common scales were used, AD patients had a higher chance of developing severe disability and a poorer outcome.

In studies that analyzed progression[2,15,26,27,28,29], AD patients had an unfavorable disease course, the progressive phase of the disease was reached faster by AD patients[15,28] with a higher progression index[26] and they had a higher risk for malignant MS[28]. Caucasians had a greater risk[28] and a higher frequency[26] of the benign form.

In relation to the clinical phenotype, AD patients had a higher incidence of the PP form and lower incidence of the RR form[23]. With regard to the higher frequency of men in the AD group[29], male gender has been identified as a risk factor for the worst result for the illness, therefore studies with multivariate analysis would clarify whether the two factors together increase the risk. However, considering that for PPMS the female/male ratio is almost 1:1, in the study that only evaluated the PP form, the high number of males in the AD group could be considered as a bias. Furthermore, in this same study[29], even though PPMS had a worse prognosis, AD patients reached disability markers in a shorter time, reinforcing the greater disease severity in those with African ancestry.

Although this systematic review has considered demographic, clinical and evolutive aspects that could lead to long-term disability and progression among AD patients, some studies correlate imaging and immunological aspects in the cerebrospinal fluid among AD patients that could lead to a worse outcome. Howard et al.[14], in 2012, showed that AD patients had higher lesion burden compared to CA patients and showed a more severe disease course. Weinstock-Guttman et al.[35], in 2010 showed that AD patients had increased tissue damage and higher lesion volumes, compared to White Americans. Rinker et al.[36], in 2007, observed that AD patients had a more active immune response in the cerebrospinal fluid compared to CA patients with MS but this did not predict earlier progression, and Gama et al.[37], in 2015, showed that the presence of oligoclonal bands in the cerebrospinal fluid were significantly associated with AD origin, and progressive forms despite ethnicity.

Regarding treatment, Cree et al.[18] in 2005, Jeannin et al.[38] in 2011 and Klineova et al.[39] in 2012, showed that AD patients had a worse response to drug modifying treatment when compared to CA patients.

Although world statistics point to unfavorable socioeconomic conditions among AD individuals, especially on the American continent, it is very important to call attention to the fact that in most of the studies[2,15,16,17,20,21,22,23,24,25,28,29], the access to medical care, diagnosis and treatment was reported to be similar for AD and CA patients. In one of the studies, the mean and median time to diagnosis was shorter in AD patients[17]. These data suggest that socioeconomic factors may not influence the results. This observation lets us infer that AD ethnicity confers higher risk for a worse outcome despite early diagnosis and treatment, however, current accessibility to more effective drugs that are indicated for disease forms with potentially severe evolution could be an option.

FINAL REMARKS

In this systematic review on the influence of AD on the clinical course of MS, it was possible to observe that although the disease is more common in CAs, the AD condition creates a greater risk for adverse outcomes such as disability and earlier progression. In a mixed MS population, as well as well-known prognostic factors, AD ethnicity should be considered at the time of the therapeutic decision.

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