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Original article

Association between demyelinating disease and autoimmune rheumatic disease in a pediatric population☆

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ARTICLE INFO

Article history:
Received 7 January 2016
Accepted 19 August 2016
Available online 25 October 2016

Keywords:
Autoimmune diseases
Rheumatic diseases
Demyelinating diseases
Childhood

ABSTRACT

Introduction: Multiple sclerosis (MS) and neuromyelitis optica (NMO) are demyelinating diseases of the central nervous system. Autoimmunity in patients with demyelinating disease and in their families has been broadly investigated and discussed. Recent studies show a higher incidence of rheumatic autoimmune diseases among adult patients with MS or NMO and their families, but there are no studies in the pediatric population.
Objective: To evaluate an association of MS and NMO with autoimmune rheumatic diseases in pediatric patients.
Method: 22 patients younger than 21 years old with MS or NMO diagnosed before the age of 18 years were evaluated regarding epidemiological data, clinical presentation, association with autoimmune diseases, family history of autoimmune diseases, laboratory findings, imaging studies and presence of auto-antibodies.
Results: Among the patients studied, there was a prevalence of females (68.1%). The mean age of symptoms onset was 8 years and 9 months and the mean current age was 16 years and 4 months. Two patients (9%) had a history of associated autoimmune rheumatic disease: one case of juvenile dermatomyositis in a patient with NMO and another of systemic lupus erythematosus in a patient with MS. Three patients (13%) had a family history of autoimmunity in first-degree relatives. Antinuclear antibody was found positive in 80% of patients with NMO and 52% of patients with MS. About 15% of antinuclear antibody-positive patients were diagnosed with rheumatologic autoimmune diseases.
Conclusion: Among patients with demyelinating diseases diagnosed in childhood included in this study there was a high frequency of antinuclear antibody positivity but a lower association with rheumatologic autoimmune diseases than that observed in studies conducted in adults.

☆ This is a study conducted with the joint collaboration of the Pediatric Rheumatology and Demyelinating Diseases divisions, Universidade Federal de São Paulo, São Paulo, SP, Brazil.

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http://dx.doi.org/10.1016/j.rbre.2016.09.016

Associação entre doença desmielinizante e doença reumática autoimune em uma população pediátrica

Palavras-chave:
Doenças autoimunes
Doenças reumáticas
Doenças desmielinizantes
Infância

RESUMO

Introdução: Esclerose múltipla (EM) e neuromielite óptica (NMO) são doenças desmielinizantes do sistema nervoso central. A autoimunidade entre pacientes com doenças desmielinizantes e seus parentes tem sido amplamente investigada e discutida. Estudos recentes demonstram maior incidência de doenças reumáticas autoimunes entre pacientes adultos com EM e NMO e seus parentes, mas não há estudos na população pediátrica.
Objetivo: Avaliar a associação de EM e NMO com doenças reumáticas autoimunes em pacientes pediátricos.
Método: Foram incluídos 22 pacientes menores de 21 anos com diagnóstico de EM ou NMO antes dos 18 anos e avaliados dados epidemiológicos, clínicos, associação com doenças autoimunes, história familiar de doenças autoimunes, exames laboratoriais, exames de imagem e presença de autoanticorpos.
Resultados: Entre os pacientes estudados, houve prevalência do sexo feminino (68,1%). A média de idade de início dos sintomas foi de oito anos e nove meses e a média de idade dos pacientes na avaliação foi 16 anos e quatro meses. Dois pacientes (9%) apresentaram doença reumática autoimune associada, um caso de dermatomiosite juvenil em paciente com NMO e outro de lúpus eritematoso sistêmico juvenil em paciente com EM. Três pacientes (13%) apresentaram história familiar de autoimunidade em parentes de primeiro grau. Anticorpo antinuclear (ANA) positivo foi encontrado em 80% dos pacientes com NMO e em 52% dos pacientes com EM. Cerca de 15% dos pacientes com ANA positivo apresentaram diagnóstico definitivo de doença autoimune reumática associada.
Conclusão: Entre os pacientes com doenças desmielinizantes diagnosticadas durante a infância incluídos nesta pesquisa houve uma alta frequência de ANA positivo, mas uma menor taxa de associação com doenças reumáticas autoimunes do que a encontrada em trabalhos conduzidos em adultos.

Introduction

The term *demyelinating disorder* refers to a group of diseases that have in common the loss of the myelin sheath, with a relative axonal preservation. Among the various categories, we highlight those of inflammatory origin, in particular, multiple sclerosis (MS), the most disabling neurological disease in young adults, and neuromyelitis optica (NMO). Clinical and pathological aspects of these conditions lead one to believe that these are inflammatory autoimmune diseases, which lead to a progressive deterioration of multiple body functions.[1–4]

MS may involve any part of the CNS at different times of its progression. The most common early symptoms are paresis of one or more members, pyramidal signs (spasticity, hyperreflexia, Babinski sign, and clonus), ataxia, dysarthria, paresthesias, fecal or urinary incontinence or retention, or sexual dysfunction.[5]

NMO, or Devic disease, is characterized by the production of antibodies against the blood–brain barrier. The first symptoms occur between the 3rd and 4th decades of life, in the form of optic neuritis and/or myelitis with longitudinal extension. Optic neuritis is manifested with an acute bilateral loss of visual acuity, with partial recovery. Myelitis is characterized by bilateral motor symptoms, with significant loss of strength, sensory changes and partial recovery after outbreaks.[6]

The autoimmunity that surrounds patients with demyelinating disease and their family members has been widely investigated and discussed. Recent studies show that patients with MS and NMO, as well as their families, are at greater risk of presenting, at some point, an associated diagnosis of an autoimmune rheumatic disease. However, none of these studies was directed to the pediatric population.[7,8]

The aim of this study was to evaluate the association of MS or NMO with autoimmune rheumatic diseases in a pediatric population and their first-degree relatives.

Patients and methods

In this retrospective cross-sectional study we included all patients with a current age up to 21 years, diagnosed with MS according to McDonald criteria, or with NMO according to the 2006 revised criteria, monitored in Demyelinating Disease Unit of the Department of Neurology and Neurosurgery, and in the Pediatric Rheumatology Unit of the Department of Pediatrics, Unifesp/EPM. The diagnosis of juvenile systemic lupus erythematosus (JSLE) and juvenile dermatomyositis (JDM) was established in accordance with published criteria.[6,9–11] All patients were under the age of 18 at diagnosis of demyelinating disease or autoimmune rheumatic disease.

The following information was collected from the clinical records: demographics, current age, age at the onset of

Table 1 – Demographic characteristics of the study population.

	MS $n=17$	NMO $n=5$	Total $n=22$
Female gender	10 (58.8)	5 (100)	15 (68.2)
Current age (months)	223	235	224
Age at the onset of symptoms (months)	150	120	132
Disease duration (months)	12	57	24

MS, multiple sclerosis; NMO, neuromyelitis optica.
Results are expressed as *n* (%) and median (range).

symptoms, and disease duration; signs and symptoms of demyelinating disease, recurrence history, number of outbreaks and intervals between these outbreaks; autoimmune diseases associated; family history of autoimmune disease; laboratory tests and presence of antinuclear antibody (ANA), rheumatoid factor (RF), extractable nuclear antigen (ENA) antibodies, anti-aquaporin, anti-cardiolipin and anti-DNA; cerebrospinal fluid (CSF) analysis, and imaging tests such as brain magnetic resonance imaging (MRI) l and MRI of the spinal column.

The demographic and clinical characteristics were described in absolute and relative frequencies, median, and minimum and maximum values, according to the nature of the variables studied.

Results

Twenty-two patients with a diagnosis of demyelinating disease were selected: 17 patients with MS (77.3%) and five patients with NMO (22.7%). Table 1 summarizes the demographic characteristics of these patients.

The predominant complaints of patients with MS were sight impairment (41%), brainstem impairment (41%), and pyramidal motor impairment (35%). All patients with NMO showed sight impairment at some point in the progression of the disease. Other frequent complaints were pyramidal motor impairment (60%), sensory impairment (40%), and sphincter impairment (40%) (Table 2). Table 2 describes the clinical characteristics of patients with demyelinating diseases.

Fourteen patients with MS had recurrences with an average of 2.5 outbreaks per patient, with a minimum interval of one month and a maximum interval of 108 months between outbreaks. All patients with NMO had a history of recurrence, with a mean of three outbreaks per patient, with a minimum interval of two months and a maximum interval of 29 months between outbreaks.

Among the patients included in this study, only two (9%) had a history of association with an autoimmune rheumatic disease. The first patient had a previous diagnosis of MS, and about a year after the first outbreak, this patient evolved with clinical and laboratory findings compatible with JSLE. The second patient had a diagnosis of JDM, evolving with a diagnosis of NMO about ten years after the onset of symptoms of the autoimmune disease.

Only three (13%) patients had a family history of autoimmunity in first-degree relatives. Two patients with MS (one of them diagnosed with JSLE associated with the demyelinating disease) had a family history of systemic lupus erythematosus. A patient with a diagnosis of NMO had a family history of rheumatoid arthritis.

Among those patients with MS, nine (53%) were ANA-positive subjects, including the patient with JSLE. There was a predominance of a nuclear fine speckled pattern (88%). The patient with an associated diagnosis of JSLE also tested positive for IgM anti-cardiolipin and anti-nucleosome. Among patients with NMO, four (80%) had a positive ANA, including the patient with JDM. There was a predominance of a nuclear fine speckled pattern (75%). The patient with an associated diagnosis of JDM was also positive for anti-cardiolipin IgM. On a subsequent examination, the result for this antibody was negative. Altogether, 15% of ANA-positive patients showed a conclusive diagnosis of autoimmune rheumatic disease associated with a demyelinating disease.

Three of the patients diagnosed with NMO (60%) were positive for anti-aquaporin. Table 3 summarizes the presence of autoantibodies in the study population.

No anti-ENA antibodies, anti-DNA antibodies, or rheumatoid factor were found in these patients. None of the patients in this study had any cytopenia (anemia, leukopenia, thrombocytopenia), a decrease in complement, or kidney function changes.

Only patients diagnosed with MS were subjected to a lumbar puncture. Of these patients, six (35.3%) had oligoclonal bands in cerebrospinal fluid.

Four patients (23.5%) with MS were treated with glatiramer, and nine (52.9%) patients received treatment with interferon beta. Other drugs associated were prednisone (5%) and immunoglobulin (5%). The patient diagnosed with JSLE

Table 2 – Clinical characteristics of the study population.

	MS $n=17$	NMO $n=5$	Total $n=22$
Motor impairment (tetraparesis/hemiparesis/paraparesis)	6 (35.3)	3 (60)	9 (40.1)
Cerebellar impairment (dysmetry and gait ataxia)	3 (17.6)	0	3 (13.6)
Sensory impairment (superficial and deep tactile hypoesthesia/painful hypoesthesia)	4 (23.5)	2 (40)	6 (27.3)
Visual impairment (decrease in visual acuity and afferent pupillary defect)	7 (41.2)	5 (100)	12 (54.5)
Brainstem impairment (diplopia, nystagmus)	7 (41.2)	0	7 (31.8)
Sphincter impairment (bladder/anal)	1 (5.9)	2 (40)	3 (13.6)

MS, multiple sclerosis; NMO, neuromyelitis optica.
Results are expressed as *n* (%).

Table 3 – Presence of autoantibodies in the study population.

		MS $n=17$	NMO $n=5$	Total $n=22$
ANA		9 (52.9)	4 (80)	13 (59.1)
Pattern	NFS	8 (88.9)	3 (75)	11 (84.6)
	Other patterns	1 (11.1)	1 (25)	2 (15.4)
Dilution	1:160	3 (33)	1 (25)	4 (30.8)
	1:320	3 (33)	2 (50)	5 (38.5)
	1:640	1 (11)	0	1 (7.7)
	1:1280	2 (22)	1 (25)	3 (23.1)
aCL	IgM	1 (5.9)	1 (20)	2 (9.1)
	IgG	0	0	0
Other	Anti-aquaporin	[a]	3 (60)	[a]

MS, multiple sclerosis; NMO, neuromyelitis optica; ANA, antinuclear antibody; NFS, nuclear fine speckled pattern; aCL, anticardiolipin. Results are expressed as *n* (%).

[a] The anti-aquaporin antibody was evaluated only in patients with a diagnosis of NMO.

was also treated with acetylsalicylic acid, hydroxychloroquine, and azathioprine, as well as with intravenous methylprednisolone and cyclophosphamide. All NMO patients received treatment with prednisone and azathioprine, and one patient was treated with intravenous immunoglobulin. The patient diagnosed with an associated JDM also received treatment with methotrexate.

Patients diagnosed with MS-JSLE and NMO-JDM had several episodes of outbreaks and remissions throughout their progression and currently are in remission without neurological sequelae.

Discussion

Different studies have shown an association between demyelinating diseases and other autoimmune diseases.[8] The results of a recent systematic review point to systemic lupus erythematosus (SLE) and rheumatoid arthritis as the rheumatic autoimmune diseases most often associated with MS.[8]

In 2000, a case–control study compared MS patients versus controls without demyelinating diseases, mostly adults, regarding the occurrence of autoimmune diseases, which included autoimmune thyroiditis, autoimmune gastritis, Addison's disease, rheumatoid arthritis, pemphigus vulgaris, scleroderma, primary biliary cirrhosis, SLE, and ankylosing spondylitis. Patients with MS had a higher prevalence of these conditions (20%) compared to controls without MS (13%) and their first-degree relatives (45% vs. 27%, respectively).[7] In 2006 a case–control study found similar results that further pointed to the importance of HLA-DR genes in the determination of autoimmunity involving MS patients and their families.[12]

A study on patients (mostly adults) with NMO also showed that about one-third of patients had a diagnosis of another autoimmune disease, such as Sjogren's syndrome, primary sclerosing cholangitis, and immune thrombocytopenic purpura.[13]

On the other hand, a retrospective cohort showed no increased risk of autoimmune rheumatic diseases in patients with MS (RR: 0.9; CI: 0.7–1.03), unlike their relatives, who were at increased risk for such diseases (RR: 1.2; CI: 1.1–1.4).[14] These findings may be related to a possible bias and to the use of different diagnostic criteria for the different autoimmune diseases evaluated.[14]

Two patients (9%) with MS or NMO included in this study had autoimmune rheumatic diseases: JSLE and JDM, respectively. Although SLE has been described in association with demyelinating diseases, in our review of the literature we found only two publications relating these diseases to dermatomyositis.[15,16] The first report refers to a male adult with a previous diagnosis of MS that, after treatment with interferon beta-1a, came to suffer the typical rash of dermatomyositis (Gottron's papules and heliotrope rash) and proximal muscle weakness with a skin biopsy compatible with the diagnosis.[15] The second publication consists of a series of cases of patients with NMO with its onset in childhood and adolescence, in which one of the patients had an associated diagnosis of JDM. In this publication, neither the clinical course nor the treatment received by this patient was detailed; moreover, the family history of autoimmune diseases in patients with NMO has not been evaluated.[16]

The neurologic manifestations of SLE patients can mimic the changes found in patients with MS and NMO, especially in those periods when the disease is more active. Transverse myelitis, for example, although rare, has been described several times as a neurological manifestation of SLE patients, with or without optic neuritis. In these patients, the differentiation between SLE activity, or coexistence of MS or NMO, may be complex.[17]

Szmyrka-Kaczmarek et al. describe in their case–control study the highest prevalence of ANA and anti-phospholipid antibodies in patients with MS – without, however, any correlation with symptoms suggestive of autoimmune rheumatic diseases or thromboembolic events.[18] In the same study, it was possible to correlate the autoantibodies to certain patterns of clinical presentation of MS. Thus, ANA-positive patients, mainly with high titles, suffer from a disease of shorter duration, with little progression to disability. On the other hand, the presence of anti-β2 glycoprotein I was associated with diseases of a more dragged course, with greater limitations.[18]

In their study, Hilario et al. found ANA positivity in 12.6% of healthy children and in 36.2% of children with several autoimmune rheumatic diseases.[19] Studies show that the positivity of ANA in MS patients can vary from 20% to 60%; on the other hand, in patients with NMO this positivity approaches 45%.[18,20,21] The positivity of ANA in patients with demyelinating diseases included in this study was about 59%, of which 15% (2 patients) had a final diagnosis of an associated autoimmune rheumatic disease. It is suggested, therefore, that patients with demyelinating diseases and with ANA positivity receive a more detailed complementary investigation to exclude the possibility of associated autoimmune disorders.

In short, among patients with demyelinating diseases diagnosed in infancy included in this study, we found a high frequency of ANA positivity, but a lower rate of association with autoimmune rheumatic diseases than that found in studies conducted on adults, although significant in the population of this study.

Conflicts of interest

The authors declare no conflicts of interest.

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