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Mielopatias agudas não neoplásicas em idade pediátrica: 11 anos de experiência em revisão

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ACUTE NON-NEOPLASTIC MYELOPATHIES IN PAEDIATRIC AGE: 11 YEARS OF EXPERIENCE IN REVIEW

Artigo Científico

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Abbreviations

AM – acute myelopathy

MRI – magnetic resonance imaging

ATM – acute transverse myelitis

ADEM – acute disseminated encephalomyelitis

NMOSD – neuromyelitis optica spectrum disorders

MOGAD – myelin oligodendrocyte glycoprotein antibody associated disease

MS – multiple sclerosis

RRMS – relapsing-remitting multiple sclerosis

CNS – central nervous system

MOG – myelin oligodendrocyte glycoprotein

AQP4 – aquaporin-4

HSV – Herpes Simplex Virus

LETM – longitudinally extensive transverse myelitis

GD+ – gadolinium enhancement

OCB – oligoclonal bands

Resumo

Introdução: As mielopatias correspondem a lesões na medula espinhal, sendo consideradas agudas quando os sintomas progridem e atingem o nadir no máximo de 21 dias após o seu início. Podem ter distintas etiologias, incluindo inflamatória, degenerativa, infeciosa e vascular, para além de traumática e neoplásica, mesmo em idade pediátrica. O objetivo deste estudo é caracterizar uma coorte de crianças e adolescentes com diagnóstico de mielopatia aguda não neoplásica, comparando as diferentes etiologias, com base na revisão dos seus processos clínicos.

Métodos: Foi realizado um estudo observacional retrospetivo, para o qual se recrutaram crianças com idades compreendidas entre os 0 e 18 anos, com diagnóstico de mielopatia aguda não neoplásica e acompanhadas no nosso centro, nos últimos 11 anos. Foram analisadas as manifestações clínicas apresentadas, os resultados dos exames complementares de diagnóstico efetuados, os tratamentos instituídos e o prognóstico funcional dos doentes.

Resultados: Foram diagnosticados 36 casos de mielopatias agudas não neoplásicas no nosso centro, no período de tempo considerado. A idade média foi 10.8 ± 5.3 anos. Dos 36 casos, 16 (46%) são de etiologia desmielinizante e inflamatória, 13 (37%) são de etiologia vascular, 3 (6%) de causa infeciosa e 4 (11%) de etiologia idiopática. Um dos sintomas iniciais mais comuns foi a fraqueza muscular (68.9%), havendo queixas sensitivas em 48.3% dos casos. A dor, como sintoma inicial, foi reportada em apenas 20%, estando associada a etiologia idiopática ($p=0.05$). Todos os doentes com mielopatia de origem vascular descreveram um início hiperagudo dos sintomas ($p<0.001$) e 75% dos doentes com mielopatia desmielinizante e inflamatória apresentaram um início subagudo. O estudo por ressonância magnética mostrou que a presença concomitante de lesões cerebrais está mais relacionada com a etiologia desmielinizante e inflamatória ($p=0.003$). O estudo da medula espinhal mostrou haver uma relação significativa entre a presença de lesões anteriores em corte axial e a etiologia vascular ($p=0.018$). Relativamente ao prognóstico, verificou-se a existência de uma relação significativa entre uma pior evolução e um início de sintomas hiperagudo ($p=0.024$).

Conclusão: Mielopatias agudas de causas não neoplásicas não são muito comuns em doentes pediátricos. Conhecer as particularidades destas entidades, nesta população, é crucial para estabelecer uma abordagem clínica eficaz, com um potencial impacto positivo na qualidade de vida das crianças, adolescentes e das suas famílias, a curto, médio e longo prazo.

Palavras-chave: mielopatia aguda, crianças, adolescentes.

Abstract

Introduction: Myelopathies correspond to spinal cord injuries, being considered acute when symptoms progress and reach the nadir within a maximum of 21 days after its onset. They can have different etiologies, including inflammatory, degenerative, infectious and vascular, in addition to traumatic and neoplastic, even at paediatric age. The aim of this study is to characterize a cohort of children and adolescents diagnosed with non-neoplastic acute myelopathy, comparing the different aetiologies, based on a review of their clinical files.

Methods: A retrospective observational study was carried out, for which children aged between 0 and 18 years, diagnosed with non-neoplastic acute myelopathy and followed up at our center for the last 11 years, were recruited. The clinical manifestations presented, the results of the complementary diagnostic tests performed, the treatments prescribed, and the functional prognosis of the patients were analyzed.

Results: Thirty-six cases of non-neoplastic acute myelopathies were diagnosed in our center during the period considered. The mean age was 10.8 ± 5.3 years. Of the 36 cases, 16 (46%) are of demyelinating and inflammatory etiology, 13 (37%) are of vascular etiology, 3 (6%) of infectious cause and 4 (11%) of idiopathic etiology. One of the most common initial symptoms was muscle weakness (68.9%), with sensory complaints in 48.3% of cases. Pain, as an initial symptom, was reported in only 20%, being associated with an idiopathic etiology ($p=0.05$). All patients with myelopathy of vascular origin described a hyperacute onset of symptoms ($p<0.001$) and 75% of patients with demyelinating and inflammatory myelopathy had a subacute onset. The magnetic resonance study showed that the concomitant presence of brain lesions is more related to the demyelinating and inflammatory etiology ($p=0.003$). The spinal cord study showed a significant relationship between the presence of anterior lesions in axial section and vascular etiology ($p=0.018$). Regarding prognosis, there was a significant relationship between a worse outcome and a hyperacute onset of symptoms ($p=0.024$).

Conclusion: Acute myelopathies of non-neoplastic causes are not very common in paediatric patients. Knowing the particularities of these entities, in this population, is crucial to establish an effective clinical approach, with a potential positive impact on the quality of life of children, adolescents and their families, in the short, medium and long term.

Keywords: Acute myelopathy, children, adolescents.

Introduction

The term “myelopathy” refers to any disorder leading to neurologic deficits originating from the spinal cord and encompasses a wide spectrum of aetiologies. Intramedullary lesions in children are rare but can result in profound morbidity (1). Myelopathies are generally classified as acute, subacute, or chronic, for which the aetiologies are totally different. The first management step is to categorize it, according to the time it reaches its maximum neurologic deficit and so acute myelopathy (AM) should be considered when symptoms progress and reach the nadir within 21 days of its onset (2)**.**

Diagnostic approach should be based on detailed demographic information, clinical manifestations, thorough physical (not only neurological) examination, imaging and laboratory investigation. Clinical signs that strongly suggest myelopathy include a well-defined sensory level in the trunk, unilateral corticospinal tract signs associated with contralateral spinothalamic tract signs, and sphincter dysfunction (3). After recognizing these clinical signs, contrast spinal Magnetic Resonance Imaging (MRI) plays an important role in characterizing spinal cord injuries, by excluding a compressive cause (4), and guiding the selection of additional exams, to arrive to a specific diagnosis. After compression has been excluded, the main causes of myelopathy are generally divided into the following categories: primary demyelinating, vascular, associated to systemic inflammatory disorders, infectious and idiopathic (2). Nevertheless, the main diagnostic categories can be summarized in two fundamental aetiologies, excluding the neoplastic cause: inflammatory and vascular.

Acute transverse myelitis (ATM) is an inflammatory spinal cord disorder that is an important cause of non-compressive myelopathy (5). Over 20% of all ATM cases belong to paediatric patients, with a reported incidence of around 2 million children/year (6). Within disease-associated ATM, the three main myelopathies are infectious myelitis (e.g., herpes viruses), systemic inflammatory disorders (e.g., systemic lupus erythematosus) and acquired demyelinating conditions, in which ATM may be the first presentation of relapsing acquired demyelination, as seen in multiple sclerosis (MS) (7), acute disseminated encephalomyelitis (ADEM) (8), neuromyelitis optica spectrum disorders (NMOSD) (9) and the progressively recognised myelin oligodendrocyte glycoprotein antibody associated disease (MOGAD) (10) .The existence of concomitant encephalopathy or polyfocal neurological deficits is not characteristic of isolated ATM and should suggest other conditions, such as ADEM or MOGAD (8–10).

Multiple sclerosis (MS) is a demyelinating disorder that affects the brain, the brainstem and the spinal cord, and is characterized by lesions (and their corresponding clinical deficits) that are disseminated in space and time. The number of diagnoses has been increasing, and between 3%-10% of MS cases are identified before 18 years (in paediatric age), with an estimated frequency of approximately 2.5 per 100,000 children (11). The age of the first relapse is 11 to 13 years in most studies (12), and less than 1% have a diagnosis of paediatric MS (PMS) at prepubescent age (11). The most recent diagnostic criteria for PMS are based in part on the revised 2017 McDonald criteria (7). As for the progression of PMS, in 97 to 99 percent of cases the initial form is a relapsing-remitting condition (RRMS) (13).

Another diagnosis associated with manifestations of myelopathy is ADEM, which has an estimated annual incidence of 0.2 to 0.5 per 100,000 children (14). Although it can occur at any age, most cases occur in young children, and the average age of presentation is 5 to 8 years (15)**.** ADEM Is defined as demyelination of the central nervous system (CNS) in which the focal deficits are typically associated to encephalopathy. It is usually characterized as a demyelinating single-phase condition, with multifocal simultaneous neurological deficits (11). In many cases, it is related to an history of previous infection or vaccination (15). Testing the myelin oligodendrocyte glycoprotein (MOG) IgG autoantibody and the aquaporin-4 (AQP4) IgG autoantibody is indicated for patients with suspected ADEM, since this situation is increasingly considered as a kind of umbrella-term, which may correspond to the first manifestation of a different set of diseases, with different pathophysiology. In children with ADEM, seropositivity for MOG antibodies is found in 33 to 66 percent of cases (16), which is substantially different from what is defined for the adult.

Infection of the spinal cord and roots of spinal nerves leading to ATM can be caused by viruses, bacteria, parasites or fungi (17). In children, enteroviruses such as coxsackieviruses A and B, and members of the herpes family (mainly Herpes Simplex Virus-1 [HSV-1]) are the main causes of viral myelitis (18)**.** Historically, acute flaccid paralysis was more often caused by poliovirus, but with eradication efforts, the incidence has significantly decreased, and other viruses were found to cause Polio-like disease, such as Enteroviruses (i.e., Enterovirus 71, 68; Coxsackie viruses) and Flaviviruses. Viral infections may cause acute myelopathy by direct damage of neuronal cells (true infectious myelitis), which is relatively uncommon in developed countries, or by post-infectious mechanisms, because of the host's response to infection (often gastrointestinal or respiratory) (1). In addition to motor and sensory changes that may accompany myelopathy, radiculopathy may be present in some cases of infectious

myelitis, resulting in lower motor neuron signs. The increasing availability of new autoimmune markers, imaging techniques, and microbiological tests, able to define a specific etiology for acute myelopathy, has been decreasing the proportion of idiopathic inflammatory myelitis (19).

Regarding the vascular etiology, it is worth to mention that spinal cord infarct is extremely rare in children. Vascular spinal cord injury is an uncommon cause of acute myelopathy and can be difficult to distinguish from other conditions (20). Patients typically present with acute onset motor weakness, loss of pain/temperature sensations, with relative loss of proprioception and vibratory sensation below the level of the lesion, neurogenic bladder and intestinal dysfunction depending on the level of spinal cord involvement (21). The anterior spinal artery is the most affected vessel, and the thoracolumbar region is the most susceptible topography for ischemia.

Spinal cord ischemia can occur in the context of minor trauma, because of arterial disruption or thrombosis (20). Procedures involving the thoracoabdominal aorta, obstruction of blood flow associated with cardiovascular compromise, can cause a diffuse cord ischemia. Focal spinal infarcts are extremely rare in children and frequently difficult to differentiate from acute foci of inflammatory transverse myelitis. Other described aetiologies of spinal cord ischemia include malformation, iatrogenic, traumatic injury, vasculitis and non-aortic surgeries, being spinal surgery the most frequently associated to this complication (22). Prognosis depends on the level of spinal cord damage, early identification and reversion of ischemia, and follow-up with intensive physiotherapy and medical support.

Studies comparing clinical, imaging and laboratory profiles of acute myelopathy are scarce. The aim of this study is to provide an update on current knowledge about acute myelopathy in paediatric age, comparing the clinical, imaging and laboratory data of patients suffering from different aetiologies of acute myelopathy, admitted to our centre, with previously published studies.

Methods

Study design and oversight

A retrospective observational study was performed at the “Hospital Pediátrico” (“Centro Hospitalar e Universitário de Coimbra”) in collaboration with the Faculty of Medicine of the University of Coimbra (FMUC), Coimbra, Portugal.

Study Population

For this study we retrospectively analysed all the medical records of children aged less than 18 years old, observed at or admitted to our centre in the period between the 1st January 2010 and the 31st December 2021, diagnosed with acute myelopathy. Patients with manifest morphological causes of myelopathy, such as spinal cord compression, intramedullary neoplasms, or not signing the informed consent form were excluded from the study. The inclusion criteria were acute motor and/or sensory symptoms with or without sphincter dysfunction (defined as subjective complaints of urgency, frequency, retention or more severe sphincter compromise), spinal segmental sensory disturbance referable to a well-defined upper limit, occurrence of symptoms over no more than a 3-week period, no imaging evidence of spinal cord compression and no known previous history of cancer.

The study population was divided according to myelopathy aetiologies. The following categories were defined: demyelinating and inflammatory, vascular, infectious and idiopathic. The diagnosis of infectious AM was made only if serological proof of a recent infection (or reinfection) was obtained. An idiopathic aetiology for AM was considered for patients in which all the other diagnostic categories were excluded.

Clinical variables

We collected demographic characteristics (age at clinical onset and sex). Since patients with AM of vascular aetiology caused by scoliosis’s surgery had missing information in the notes regarding signs and symptoms at the onset, we excluded these 7 patients from the subgroup of vascular etiology. For each AM subgroup we analysed and compared: medical history (infection in the last 30 days, vaccination in the last 30 days), clinical presentation (presence of motor, sensory, or bladder/bowel symptoms, back pain as a first symptom), time to reach maximum functional deficit (hyperacute [<6hours], acute [6-24hours], subacute [>24hours-21days]) and clinical outcome. For each AM aetiology we analysed the acute treatment and the outcome. Outcome was

classified using the scale of Paine and Byers (23): “normal” includes full recovery; “good” is defined as an outcome with insignificant sequelae, such as normal gait, mild urinary symptoms, and/or minimal sensory and upper motor neuron signs; “fair” includes significant sequelae, such as mild spasticity, independent (but not normal) ambulation, urgency of urination and/or constipation, with some sensory signs; “poor” includes patients with sequelae interfering with activities of daily living: “severe” gait disturbance, absence of sphincter control and sensory deficit. In the final analysis, Paine and Byers categories of “normal” and “good” were considered as representing a good prognosis.

MRI variables

Spinal and brain MRIs obtained at clinical onset were reviewed. All patients, excluding patients with AM of vascular etiology caused by scoliosis’s surgery, were submitted to an MRI. Imaging characteristics were recorded and compared between different AM aetiologies. We analysed anatomic regions involved (which were divided in cervical, thoracic, lumbar, and distal cord/conus lesions), axial lesion topography (defined as anterior, posterior/lateral or central), the extension of lesions (one segment was considered as one vertebra body height and lesions with more than 3 vertebral segments on sagittal T2-weighted images were defined as longitudinal extensive transverse myelitis [LETM]), the presence of cranioencephalic lesions, and the evidence of gadolinium enhancement (Gd+).

Laboratory variables

All patients except those diagnosed with vascular causes were submitted to lumbar puncture and the results, including pleocytosis (> 20 cells/μl), glucose > 70 mg/dl, protein > 40 mg/dl, IgG index (positive if > 0.77) and presence of oligoclonal bands (OCB) tested by isoelectric focusing, were compared among the various aetiologies.

As the study crosses 11 years, there was some variability in the availability of data on serum antibodies (this is a situation that results from the technological advances that have taken place). Serum anti-MOG and anti-AQP4, only considered in recent years, were tested in 12 out of 36 patients.

Statistical analyses

IBM SPSS® 23 was used for data analysis. Qualitative variables were described by means of observed absolute (n) and relative (%) frequencies, while continuous

variables were presented by their mean ± standard deviation. Chi-square, Anova and Kruskal Wallis tests were used, when appropriate, for inferential analysis. Statistical significance was considered for $p < 0.05$.

Ethical approval

This study was approved by the local Ethics Committee. All participants (or caregivers) gave their consent (and assent, when necessary) to participate in the study.

Results

Study population

In the period selected for the study, 36 cases of AM were diagnosed in our centre, of which 18 were boys and 18 were girls, (1:1 male-female ratio). The mean (±SD) age was 10.8 ± 5.3 years (range 1-17 years) at the onset of symptoms. The age of the patients was not statistically different, considering the different aetiologies that were found (p=0.297). Figure 1 represents the age distribution of the cases identified.

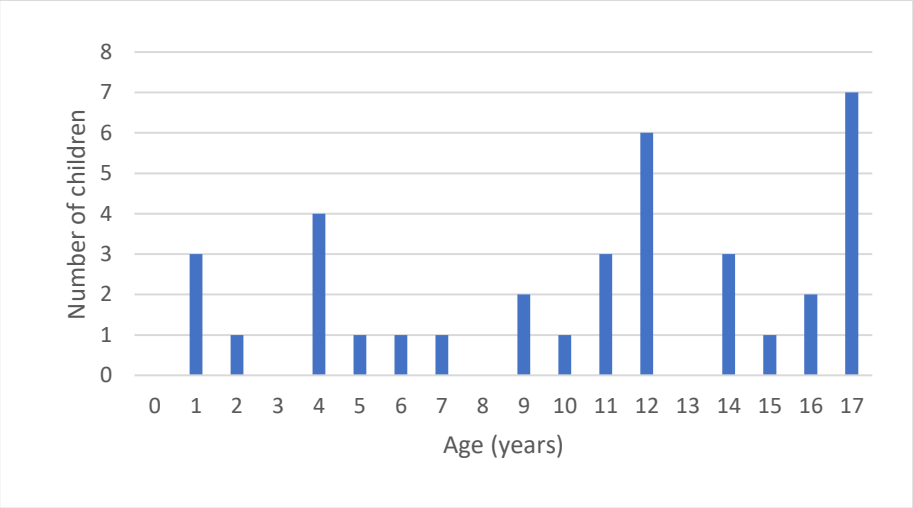

Figure 1. Age distribution of patients diagnosed with AM in the 11-year period considered for the study.

Aetiologies

Demyelinating and inflammatory myelopathies (n=16; 46%) were the most prevalent entities in our cohort. The differential diagnosis included MS (n=11), ADEM (n=4) (diagnosis based on International Paediatric Multiple Sclerosis Study Group – IPMSSG – criteria for paediatric MS and immune-mediated CNS demyelinating disorders criteria, 2013 revision and McDonald criteria, 2017 revision) and Fisher's inflammatory myeloradiculitis with anti-GQ1b antibody (n=1). Thirteen patients (n=13; 37%) were diagnosed with AM of vascular aetiology: 7 of them due to scoliosis surgery, 2 as consequence of minor trauma, 1 has Chiari type 1 malformation, 1 case due to renovascular hypertension (HTA) and 2 were considered of idiopathic nature. Infectious AM was reported in 3 patients (6%). The diagnosis was assumed with a positive serological result for HSV1, *Mycoplasma pneumoniae* and Coxsackievirus. Four patients

(11%) had a diagnosis of idiopathic AM, after all the aforementioned aetiologies have been excluded.

Figure 2 shows the distribution of identified aetiologies.

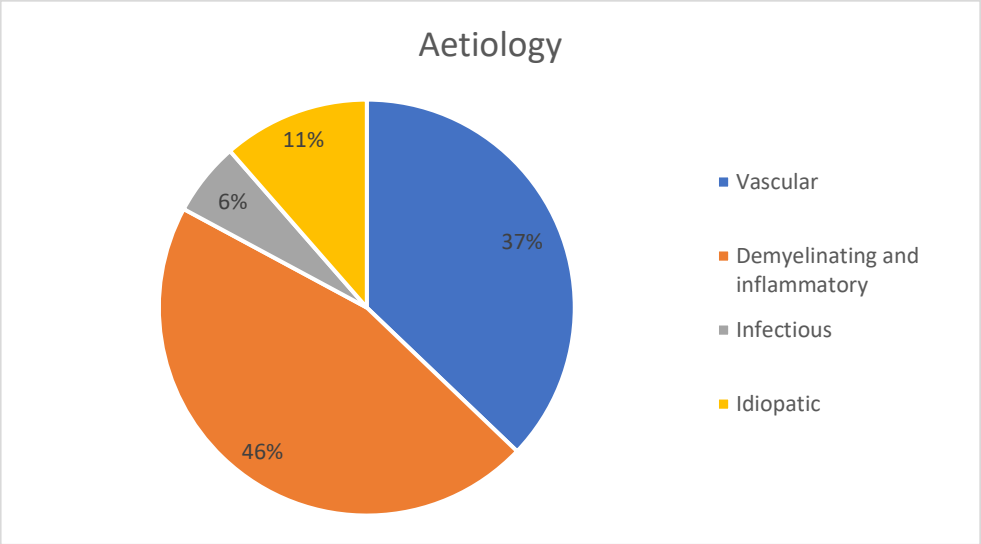

Figure 2. Distribution of different aetiologies identified in the cohort of patients included in the study.

Clinical characteristics

The main clinical symptoms and signs at presentation in 29 patients (7 patients with iatrogenic vascular myelopathy related to scoliosis surgery were excluded) were motor impairment in 20 (68.9%), sensory disturbance in 14 (48.3%), sphincter dysfunction in 8 (27.6%); and 4 patients (13.8%) reported back pain as their initial manifestation. Six patients (20.7%) reported isolated motor involvement at clinical debut, 3 (10.3%) had exclusive sensory involvement, 6 (20.7%) had motor and sensory involvement and none of the patients experienced isolated loss of bowel or bladder control. None of the children in our series reported vaccination within 1 month of AM onset and 5 (17.2%) patients had a history of infection in the previous 30 days.

Sixteen (55.2%) patients had a subacute onset of symptoms, 7 (24.1%) reported an acute presentation and 6 (20.7%) patients presented a hyperacute disease. The main clinical characteristics of the cases included in the study are summarized in Figure 3.

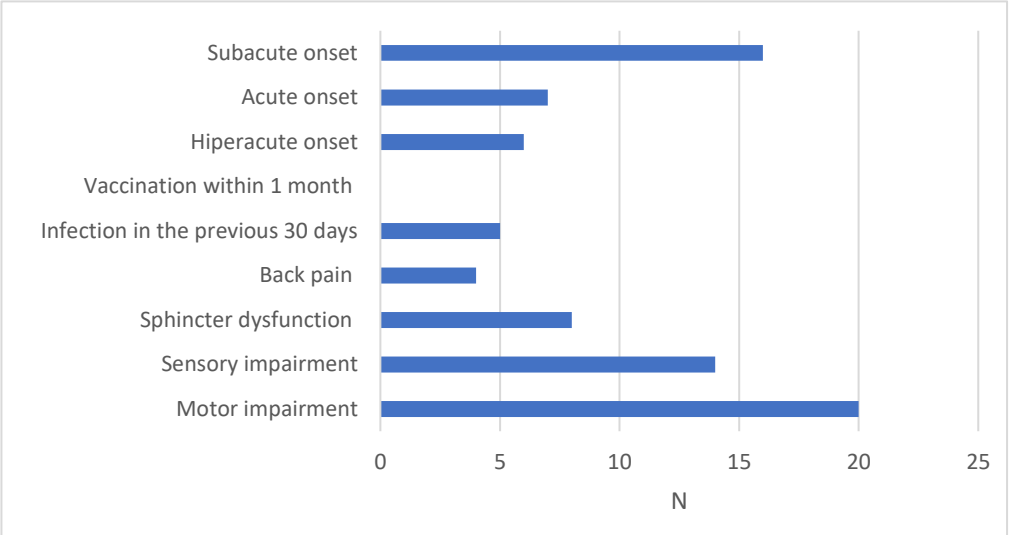

Figure 3. Clinical findings at presentation of AM. Time to reach maximum deficit was defined as hyperacute (< 6 hours), acute (6-24 hours) and subacute (>24 hours – 21 days).

MRI characteristics

MRI of all patients with initial symptoms of AM were analyzed (again, 7 patients with iatrogenic vascular myelopathy related to scoliosis surgery were excluded, because it was not possible to identify the moment when the deficits were installed), in a total of 29 patients. Eighteen patients (62.1%) also presented brain lesions. Considering the topography of the lesions, 20 (68.9%) patients had cervical lesions, 18 (62.1%) had dorsal lesions, 1 patient had lumbar lesions and 6 (20.7%) patients presented distal cord/conus lesions. The central medullar pattern (Figure 4) was presented in 10 patients, 14 had posterior/lateral lesions and 5 patients had anterior lesions.

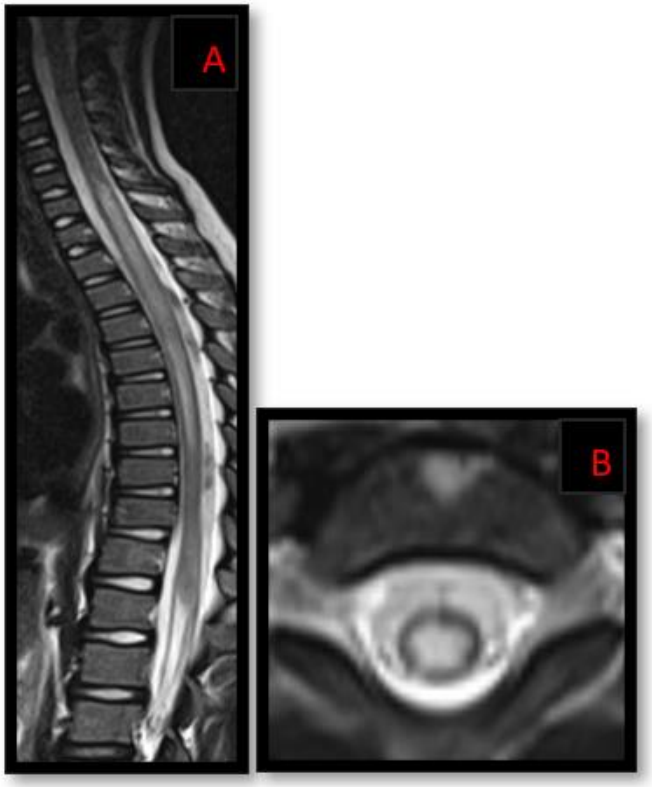

Figure 4. (**A**)Spinal cord MRI of a 7 year-old patient with infectious myelitis secondary to *Mycoplasma pneumoniae* infection.T2-Weighted sequence. Extended hipersignal with a swelling of the cervical and dorsal cord (C7-D9). (**B**) Lesion localized in the centromedullary territory.

Acute treatment

The medication of choice in acute treatment of all patients was intravenous methylprednisolone, at the dosage of 30 mg/kg/dose, for 3–5 days. The combination of antibiotics or antiviral drugs was only made in high-risk patients, with evidence of infection.

Subgroup comparisons:

Clinical manifestations and aetiology

The presence of acute back pain at onset was more associated with idiopathic myelopathy, comparing to other aetiologies (p=0.05). While weakness was present in all patients with idiopathic, infectious and vascular AM, a lower frequency was seen in the inflammatory and demyelinating group (43.8%), which was statically significant (p=0.017). Patients with demyelinating and vascular aetiology (18.8% and 16.7%,

respectively) were less likely to have compromised sphincters, in comparison with those with an infectious aetiology (66.7%) and with idiopathic AM (50.0%), but this does not reach statistical significance (p=0.2). Regarding sensory complaints, no statistically significant difference was identified between the various aetiologies (p=0.7).

All patients with vascular etiology had a hyperacute onset (p<0.001) and 75% of patients presenting with subacute onset had demyelinating and inflammatory etiology (p<0.001). The deficit installation time is therefore quite different, in our cohort, depending on the different aetiologies found.

MRI characteristics and aetiology

The results of spinal cord and brain MRI were compared between different aetiologies. Cranioencephalic lesions were present in 18 patients. Of these, 14 had a demyelinating etiology, particularly of ADEM or paediatric MS. No patients with vascular myelopathy presented cranioencephalic lesions (p=0.003).

The location of the lesions in the sagittal plane was more frequently cervicodorsal in all the considered subgroups. Lesions involving the distal cord, or the *conus medullaris* were present in 5 out of 29 patients. Three had a demyelinating aetiology, 1 had an infectious myelopathy and 1 was considered to have an idiopathic myelopathy. In axial sections, there was a clear predominance of images with lesions of anterior topography in the vascular etiology (83.3%), compared to other conditions (p<0.05). In children with MS, the lesions affected more frequently the posterolateral cord. The central pattern could be observed in all aetiologies, except vascular. Although LETM were less frequently observed in children with a final diagnosis of inflammatory or demyelinating disease (31.0% of cases), this was not considered statistically significant, when compared to other aetiologies (p=0.1). Gadolinium enhancement (Gd+) was found in 8 patients, 6 of them fulfilling the McDonald criteria for paediatric MS. Other aetiologies were less likely to have Gd+ lesions. Figures 5 and 6 show different topographies of lesions, depending on the etiological diagnosis.

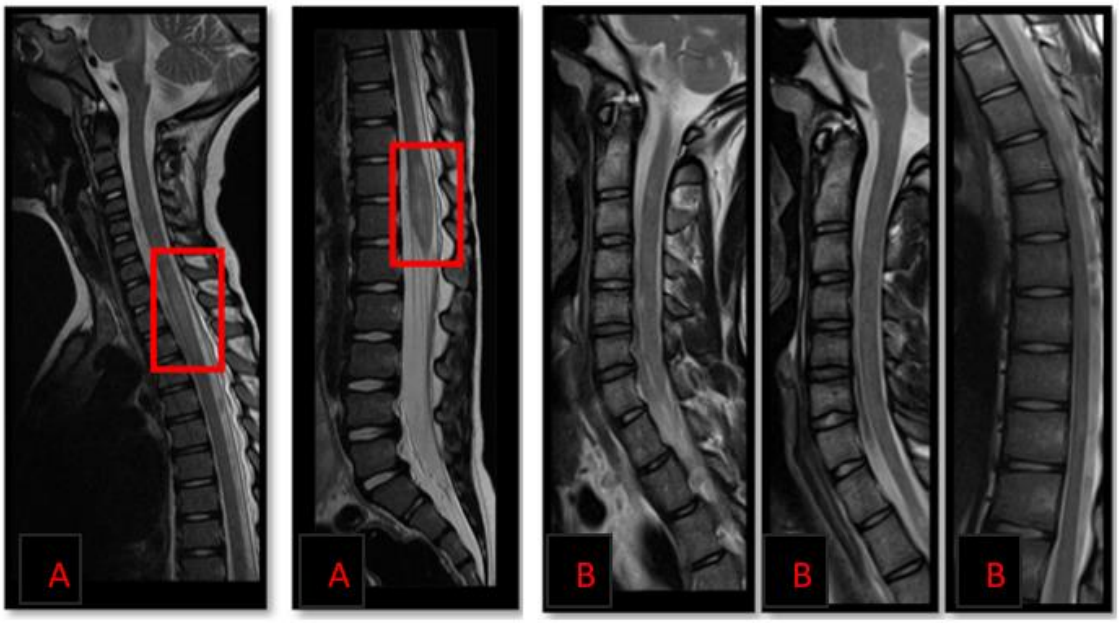

Figure 5. Paediatric myelopathies secondary to demyelinating diseases. (**A**) ADEM. 4 years old patient presenting with encephalopathy and showing extensive spinal cord signal change throughout, affecting C7-D4 central medullar lesion and conus cord. (**B**) MS. 16 years old patient with motor and sensory impairment. Typical multiple, small, and short segment cord (less than 3 vertebral segments) at C5 cervical level; and at the dorsal level: D2-D3, D5-D6, D9-D10.

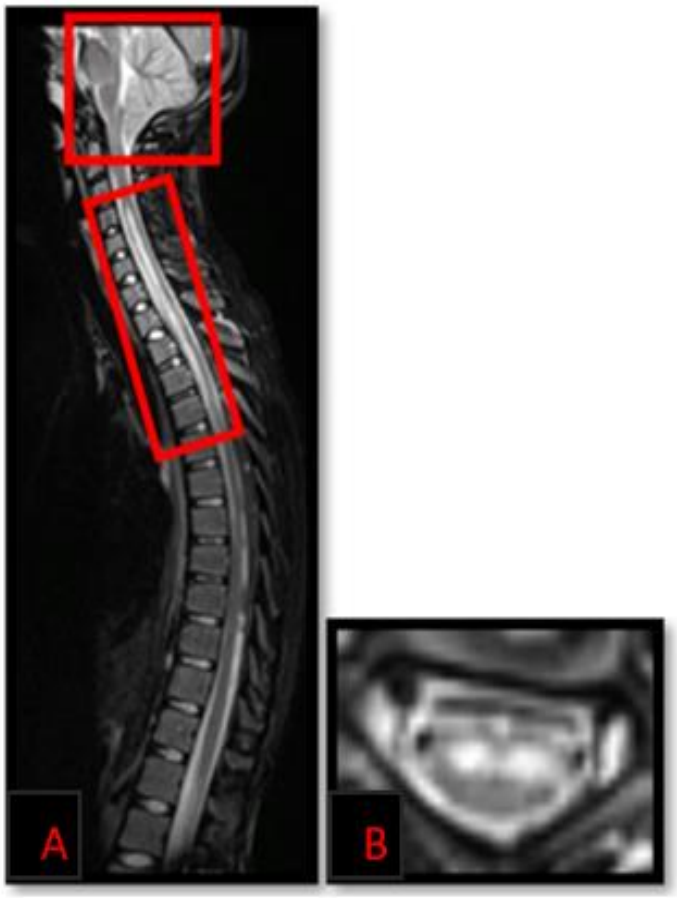

Figura 6. Spinal cord MRI of a 11 years old patient with a Chiari malformation type I. T2-weighted sequence. (**A**) Caudal desplacement of the cerebellar tonsils more than 5mm. Extended hipersignal with a swelling of the cervical and dorsal cord (C4-D8). (**B**) Lesions affecting principally the anterior horn.

CSF profile and aetiology

The profile of initial CSF samples obtained after the onset of symptoms was available for 23 patients. Considering patients with demyelinating conditions (n=16), among the 4 patients with ADEM, 1 of them had an increase in CSF proteins (> 40 mg/dl), and another did not present any abnormal value. The remaining 2 presented pleocytosis and increased proteins. Of the 11 patients diagnosed with paediatric MS, 8 (72.72%) had oligoclonal bands detected by isoelectric focusing and less than 20% presented pleocytosis and increased proteins. The patient with Fisher myelorradiculitis presented pleocytosis and proteins higher than 40 mg/dl. Within patients with infectious myelopathy (n=3) 1 of them presented pleocytosis and increased proteins CSF, 1 patient had only increased IgG index and another patient had no CSF changes. The 4 patients with myelopathy of undetermined caused (n=4), 3 (75%) had protein increased levels, 2

patients presented oligoclonal bands and pleocytosis. However, when comparing the considered aetiologies and the CSF results, no statistically significant differences were found.

Serum antibodies and aetiology

Anti-AQP4 and anti-MOG antibodies were tested in 12 patients, 1 patient with infectious myelopathy, 3 with idiopathic etiology and in 8 patients of demyelinating conditions. All tested negative for anti-AQP4, only 3 patients tested positive for anti-MOG and all these patients were diagnosed with ADEM.

Outcome and aetiology

The outcome was compared with different aetiologies of AM and the main results are summarized in Table1. Approximately 50% of our paediatric patients with AM experienced complete recovery. The outcome was good in 14 (87.5%) patients with demyelinating or inflammatory conditions. It was poor or fair in 11 (84.6%) patients with vascular aetiology and this difference was considered statistically significant (p=0.003).

Table1. Outcome (*****classified using the scale of Paine and Byers modified) and aetiologies.

Outcome*	Demyelinating and inflammatory (n=16)	Idiopathic (n=4)	Infectious (n=3)	Vascular (n=13)	Total (n=36)
Good	14/16 (87.5%)	2/4 (50.0%)	2/3 (66.7%)	2/13 (15.3%)	20/36 (55.6%)
Fair	1/16 (6.3%)	1/4 (25.0%)	1/3 (33.3%)	6/13 (46.2%)	9/36 (25.0%)
Poor	1/16 (6.3%)	1/4 (25.0%)	0	5/13 (38.5%)	7/36 (19.4%)

Outcome with clinical onset and MRI results

The analyses of outcome groups for each of the clinical and imaging variables found no significant differences. A statistically significant difference (p=0.024) was observed when comparing the prognosis with the onset of symptoms: a subacute presentation is related to a better outcome (Table 2).

Table2. Outcome distributed according to the clinical onset of symptoms.

Clinical onset of symptoms	Poor	Fair	Good
Hyperacute	3 (60.0%)	2 (40.0%)	1 (5.3%)
Acute	1 (20.0%)	2 (40.0%)	6 (31.6%)
Subacute	1 (20.0%)	1 (20.0%)	12 (63.2%)

Discussion

In this case series, we described 36 children with AM and compared their clinical, neuroimaging, laboratory features at onset and their outcome. The present study included 18 boys and 18 girls. Other studies also have shown that the sex ratio was not significantly different, nevertheless transverse myelitis secondary to paediatric MS and other demyelinating causes are more often seen in women (24). Studies in children have suggested a teenage predominance (23,25), like in this cohort, with a mean age of 10.8 ± 5.2 years. However, the study by Pidcock (26) has shown a bimodal distribution of incidence, predominantly affecting children under 5 years and adolescents. This study also showed that a myelopathy is not unusual in young children (the youngest child included in our study was 1 year old, with an inflammatory aetiology).

Lesions in the spinal cord can have effects in motor, sensory and autonomic tracts. Therefore, the clinical manifestations of AM are not necessarily uniform in severity or symmetric across different aetiologies. One of the most common initial symptoms in children, described in our patients, was motor weakness. Other studies besides mentioning motor impairment, reported pain as a frequent symptom, which was not the case in our study, considering that only approximately 14% of patients reported it, in contrast to 60% in other studies (27,28). We observed that back pain seemed to be more associated with idiopathic aetiology (than with the vascular cause itself, where we know that pain complaints are often associated with anterior spinal artery syndrome). Even so, it should be noted that our series is small in size and does not allow very effective conclusions regarding pain complaints.

Timing of symptoms onset and their development can suggest the aetiology of AM. In this study a hyperacute presentation suggested a vascular cause, whilst a subacute onset of symptoms, progressing to a nadir within days to weeks, was more indicative of an inflammatory myelopathy. This data is in accordance with other studies (9,29).

MRI pays a critical role at diagnosis and evaluation of these patients. Once it excludes compressive aetiology, a closer view at the imaging techniques may help in narrowing the differential diagnosis. The radiologic features suggesting diagnosis and prognosis have been widely reported in adults, whereas in children they are scarce (30). Even so, it should be noted that most of the lesions observed in our cohort of patients were in the cervicothoracic region, as reported in the literature (31). This can help to narrow the observation window in imaging studies.

Spinal cord lesions due to paediatric MS can usually be differentiated from those that are related to other demyelinating, idiopathic or infectious aetiologies, since meningeal involvement, vertically extending lesions over several segments and horizontally spreading lesions involving a significant part of the spinal cord are uncommon for paediatric MS.

As previously described (32,33), we observed that paediatric MS lesions were typically less than 3 vertebral segments in length, multifocal, primarily located in the cervical cord and mostly located in the posterior or lateral columns, contrasting with ADEM and other causes of acute myelitis identified in our cohort, in which LETM reached a very high prevalence. According to Alper et al (31), more than 3 segments are involved in 66% to 85% of children with ATM and our sample is in line with these numbers. On the other hand, the MRI pattern of axial involvement in vascular myelopathy is characterized by lesions in the anterior horn, described as ‘‘snake-eyes’’ or ‘‘owl-eyes’’, in the anterior spinal artery territory. It was also possible to identify these lesions in our patients with vascular myelopathies (Figure 6).

Gadolinium enhancement is frequently observed in acute myelopathies, but its absence does not rule out a diagnosis of acute myelitis (26,31). In our cohort, cord enhancement on MRI was found in less than 20% of children, like the 20%-30% rate reported by Alper et al (31). This could eventually be explained by the time elapsed between the onset of symptoms and MRI scanning (30). MRI of the brain should be included in early evaluation, as asymptomatic brain lesions were reported in 40% of children with idiopathic myelitis. They naturally can contribute to a better diagnostic definition, particularly when a primary demyelinating disorder is being considered. In our cohort, a high concomitant prevalence of brain lesions was observed, but this may be biased by the fact that most of our patients had a final diagnosis of demyelinating diseases (32,33). Nevertheless, the presence of brain lesions can be a predictor of subsequent relapses and should be valued (34).

CSF analysis and serum studies are required for evaluation of every patient with suspected myelopathy. In this study, 34.8% had normal protein levels and white blood cell counts. Other studies demonstrated that CSF may be normal in 20%-50% of children with definite acute myelitis (26,28,31). When CSF shows signs of inflammation (pleocytosis, elevated protein concentration, oligoclonal bands or elevated IgG index), the main suspicion should focus on demyelinating, infectious, or other inflammatory causes of acute myelitis. Acute infectious myelitis is usually diagnosed by prominent CSF inflammation (pleocytosis above the usual post-infectious range and markedly elevated protein), presence of systemic infectious symptoms and positive PCR testing

for a specific microorganism in CSF or demonstration of acute and convalescent serum antibody titles providing the best evidence for a direct infection. OCB were present in the CSF of 91.7% of patients with definitive MS and in only 2 patients with idiopathic aetiology. This confirms the relevance of OCB positivity for developing MS.

Of the 12 patients tested for anti-AQP4 and anti-MOG antibodies, only 3 were positive for Anti-MOG (25%). These 3 patients were diagnosed with ADEM. Other studies had already demonstrated a correlation between demyelinating diseases, MOG antibodies and their value in the setting of acute demyelinating syndromes (35), including as an epiphenomenon.

Gender did not influence outcome in our study. Previous series have not found either a preponderance or a gender effect on outcome (6) It is worth to mention that in our cohort a good outcome was reached in more than half of the cases. Several prognostic factors have been previously identified. According to the results of other studies (25,36), in this cohort rapid disease progression from onset to nadir within 6 hours has been associated with a worse prognosis, with only 2 children having a good prognosis in this context. Some studies have described a worse outcome in patients presenting with back pain (23,25), however we did not observe such relationship. In this cohort there was also no association found between the extension of spinal cord involvement and outcome, which is in line with the results of a prospective 2-year study of Goede et al and to a Israeli study (6,30). These authors have related clinical factors such as absence of tetraparesis, prolonged time to nadir and laboratory factors like CSF pleocytosis to be associated with good prognosis, which was not possible to confirm with our study.

The most frequently reported sequelae are sensory disturbances and sphincter dysfunction (15%-50%). Approximately one quarter of patients require walking assistance and 10%-20% never regain mobility or bladder function(9). In our cohort, at the time of data collection, approximately 20% of the patients presented bladder dysfunction, 11% required walking assistance and 14% had a severe motor impairment.

Overall, data suggest that the potential benefit of therapy outweighs the theoretical concerns of treating acute myelitis empirically, with anti-inflammatory drugs. Standard empiric therapy consists of high doses of corticosteroids. Paediatric patients are usually treated with methylprednisolone at the dosage of 30 mg/kg intravenously, once a day, for 3-5 days. Several studies have supported the efficacy and safety of corticosteroids in inflammatory CNS disorders, including acute myelitis (37,38). In this study, all patients, independently of the cause of myelopathy, were treated with intravenous corticosteroids. In case of confirmed infectious aetiology, or when there was

a high clinical, imaging or laboratory suspicion, appropriate antibiotic or antiviral treatments were started, as soon as possible. Naturally, the continuation of the treatment was always adjusted, depending on the results that were obtained in the complementary exams (39) .

It should be noted that this is a study with some limitations. Firstly, the sample included only concerns a single centre, which is why it is not very large and may suffer from some selection bias, which depends on the characteristics of the population served by the centre. Thus, it is not possible to make extrapolations or generalizations to other populations. Due to the retrospective nature of the study, over a 11-year period of time, there was some missing information in the notes regarding signs and symptoms, imaging, serological and other laboratory data. Also, antibody screening was not done uniformly. A prospective study with a larger sample size could be useful to establish clinical and imaging prognostic factors associated to acute myelitis. Despite these limitations, our study is focused on a relevant topic, which is not very common in paediatric age, but that can be a clear limitation of the quality of life of patients and their families. To our knowledge, there are no other studies, at a national level, addressing these same issues in children and adolescents.

Conclusion

Acute myelopathies of non-neoplastic causes are not very common in paediatric patients. Even so, they can be related to different aetiologies, with different clinical, imaging and laboratory characteristics. Knowing the particularities of these entities, especially when they manifest very early in life, is crucial to establish an effective treatment, with a potential positive impact on the quality of life of patients and their families, in the short, medium, and long term.

As this is a single-centre study, it is of great importance for a more assertive approach to the population that most directly relates to us. However, some of the conclusions of a more inferential nature will need to be explored and validated with larger cohorts. More studies are needed in this field to better understand non-neoplastic acute myelopathies in children.

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