Diagnostic Evaluation of Patients with Suspected Atypical Demyelinating Diseases: A Comprehensive Analysis of Differential Diagnoses

NEUROIMUNOLOGIA
Hospital das Clínicas FMUSP

European Charcot Foundation

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Introduction

Atypical demyelinating diseases (ADD) are rare disorders distinct from multiple sclerosis (MS) due to unusual clinical or magnetic resonance imaging (MRI) findings. Patients are frequently referred with suspected neuromyelitis optica spectrum disorder (NMOSD) or myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD). Immunotherapy has improved outcomes in many patients with ADD, while unsuitable treatment can worsen prognosis. A detailed understanding of inflammatory, infectious, or vascular conditions mimicking ADD is essential.

Objective

To characterize the final diagnoses of patients referred with suspected ADD.

Methods

- This cross-sectional study utilized medical records from a tertiary outpatient clinic at the Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo.
- Patients were identified based on appointments scheduled between January 2021 and January 2024, alongside data from a REDCap database (2015–2024).
- Nine patients were excluded due to insufficient data.
- Diagnoses were done based on the established criteria: MS (McDonald 2017), NMOSD (IPND 2015), MOGAD (2023), Optic neuritis (2022), Acute transverse myelitis (2002).

Results

- Among 563 patients, 303 (53.8%) had NMOSD, including 245 AQP4-IgG positive and 58 double-seronegative. MOGAD (9.25%) and MS (8.17%) were also common. Of the remaining 162 patients, inflammatory diagnoses (Table 1) included CRION/RION (19.1%), SION (23.4%), recurrent or isolated longitudinally extensive transverse myelitis (24.6%), short segment myelitis (1.8%), and CNS vasculitis (2.4%). Infectious (Table 2) causes (all myelitis) included HTLV-1 (0.6%), arboviral disease (0.6%), cytomegalovirus (0.6%), schistosomiasis (1.2%), tuberculosis (0.6%), and herpes simplex (0.6%). Vascular (Table 3) causes included ischemic myelopathy (8.6%), spinal cavernoma (0.6%), dural arteriovenous fistula (1.2%), ischemic optic neuropathy (1.8%), and CADASIL (0.6%). Other diagnoses (Table 4) included migraine, optic neuropathy, functional disorders, motor neuron disease, hereditary spastic paraplegia, and CNS lymphoma (all <3%).

Table 1. Autoimmune inflammatory differential diagnosis

Diagnostic	Total = 162
Recurrent optic neuritis – CRION/RION	31 (19.1%)
Single Isolated optic neuritis – SION	37 (22.8%)
Recurrent longitudinally extensive transverse myelitis	9 (5.5%)
Isolated longitudinally extensive transverse myelitis	31 (19.1%)
Short segment myelitis with atypical presentation	3 (1.8%)
Encephalic atypical demyelination (pseudotumoral/brainstem)	3 (1.8%)
Acute disseminated encephalomyelitis (ADEM)	2 (1.2%)
Neurosarcoidosis	2 (1.2%)
Idiopathic hypertrophic pachymeningitis	2 (1.2%)
Central nervous system vasculitis	4 (2.4%)
Autoimmune encephalitis	1 (0.6%)

Table 2. Infectious differential diagnosis

Diagnostic	Total = 162
HTLV-1 associated myelitis	1 (0.6%)
Arbovirus associated myelitis	1 (0.6%)
Cytomegalovirus associated myelitis	1 (0.6%)
Spinal neuroschistosomiasis	2 (1.2%)
Tuberculous myelitis	1 (0.6%)

Table 3. Vascular differential diagnosis

Diagnostic	Total = 162
Ischaemic myelopathy	*14 (8.6%)*
Spinal cavernoma	*1 (0.6%)*
Dural arteriovenous fistula	*2 (1.2%)*
Ischaemic optic neuropathy	*3 (1.8%)*
CADASIL	*1 (0.6%)*

Table 4. Other differential diagnosis

Diagnostic	Total = 162
Migraine	1 (0.6%)
Optic neuropathy	4 (2.4%)
Functional disorders	1 (0.6%)
Motor neuron disease	1 (0.6%)
Hereditary spastic paraplegia	1 (0.6%)
CNS limphoma	1 (0.6%)

Discussion

- The majority of patients referred to the outpatient clinic for atypical demyelination were diagnosed with NMOSD, and 80% of those with NMOSD tested positive for serum anti-AQP4 antibodies, which aligns with current literature[1]
- Studies show that approximately 10% of multiple sclerosis cases begin with atypical lesions. Therefore, long-term follow-up can help clarify the diagnosis.
- The infection most associated with LETM in our population was schistosomiasis. This highlights the need to keep this differential diagnosis in mind even in places not considered endemic of this disease[3].
- Almost 13% of the final diagnoses had a vascular etiology, primarily longitudinally extensive myelitis (8.6%). Consistent with previously described literature[2], the rapid onset and progression serve as an important clinical clue.

Conclusion

- NMOSD is the most frequent ADD, while MS and MOGAD are also relevant etiologies, but there are a significant number of other diagnoses
- Comprehensive diagnostics are crucial for accurate diagnoses and effective treatments.

Literature

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Disclosure

- Authors have nothing to disclose.

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