Rare Neurologic Diseases mimicking a Multiple Sclerosis like phenotype

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Genetic diseases misdiagnosed as multiple sclerosis: Observational study and review of literature

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Background: Adult-onset neurogenetic diseases (NGDs) with white matter abnormalities are rare and often misdiagnosed as Multiple Sclerosis (MS) due to overlapping clinical and radiological features. Misdiagnosis can lead to unnecessary immunosuppressive treatments and delayed genetic counseling. This study combines a retrospective multicenter analysis with a systematic review of the literature to assess the characteristics of patients with NGDs misdiagnosed as MS (Mis-MS) or with coexisting MS (NGD-MS), with the goal of improving diagnostic accuracy.

Results: **The retrospective study included 46 patients (37 Mis-MS, 9 NGD-MS). Common NGDs in Mis-MS were Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL) (22 %), Adult-onset Leukoencephalopathy with Axonal Spheroids and Pigmented Glia (ALSP) (8 %), and Adult-onset Alexander Disease (AOAD) (5 %). NGD-MS cases were primarily mitochondrial disorders (67 %). The median diagnostic delay for NGDs was nine years. Despite 80 % of Mis-MS patients showing atypical MRI features, 41 % met MS dissemination in space and 20 % dissemination in time criteria. CSF oligoclonal bands were absent in 92 % of Mis-MS patients but present in 83 % of NGD-MS patients. Literature review identified 81 Mis- MS and 22 NGD-MS cases, with Fabry disease and CADASIL most frequently involved**.

Diagnosing NGDs that mimic MS is challenging. CADASIL, ALSP, and AOAD were the most commonly misdiagnosed neurogenetic diseases as MS. Vasculopathies like CADASIL are challenging to differentiate from MS due to similar clinical and imaging features, including remitting course and gadolinium enhancement. Recognizing atypical MRI patterns and integrating clinical and genetic evaluations can improve diagnostic accuracy and patient care by preventing unnecessary MS treatment and enabling timely genetic counseling.

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Genetic diseases mimicking multiple sclerosis

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Multiple sclerosis (MS) is an inflammatory neurodegenerative disorder manifesting as gradual or progressive loss of neurological functions. Most patients present with relapsing-remitting disease courses. Extensive research over recent decades has expounded our insights into the presentations and diagnostic features of MS. Groups of genetic diseases, CADASIL and leukodystrophies, for example, have been frequently misdiagnosed with MS due to some overlapping clinical and radiological features. The delayed identification of these diseases in late adulthood can lead to severe neurological complications. Herein we discuss genetic diseases that have the potential to mimic multiple sclerosis, with highlights on clinical identification and practicing pearls that may aid physicians in recognizing MS-mimics with genetic background in clinical settings.

We will describe several cases with misdiagnosis in the following genetic conditions:

- Adrenoleucodystrophy and Adrenomyeloneuropathy
- Metacromatic leucodystrophy
- Krabbe disease
- Paelizaeus Merzbacker disease
- CADASIL and CARASIL
- Hereditary Leucoencephalopathy with axonal spheroid
- Vanishing White matter diseases and other vacuolating leucoencephalopaties
- Mitochondrial diseases with particular regards with Leber's hereditary Optic Neuropathy and misdiagnosis with optic neuritis

Rare Neurologic Diseases mimicking a Multiple Sclerosis like phenotype

- Since for many of these reported cases an appropriate diagnosis and early recognition give the possibility of early treatments (ADL,ADM,MLD) with gene therapy or recombinant enzyme substitution, with good impact on the clinical evolution of the disorders, it is mandatory to have informations on these topics..
- When therapy does not yet exist, genetic counselling and prenatal diagnosis will be done in family members at risk.
- Finally the knowledge of these atypical phenotypes will increase our attention of the existence of rare neurologic disorders and to develop appropriate standards to early diagnosis and prevention in all countries, collaborating with Reference Centers expert in Diagnosis of Rare Neurologic Diseases.
- The WFN are trying to increase the informations on this topic.