Hereditary Disorders Mimicking Progressive Multiple Sclerosis

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Multiple sclerosis (MS) is a chronic demyelinating disease of central nervous system that affects mostly young adults. While the main clinical characteristic of disease is a relapsing and remitting course, 10-15% of the patients present with a progressive form from onset, termed primary progressive multiple sclerosis (PPMS). Clinical features of PPMS often vary from acute MS relapses. Optic neuritis, brainstem syndromes and partial spinal cord syndromes are the most common forms of MS relapses. By contrast PPMS usually presents with progressive spastic paraparesis usually with no clear sensory contribution and less often with progressive cerebellar ataxia, cognitive dysfunction, brainstem or visual symptoms. The typical acute neurological deterioration that last longer than 24 hours and followed by a recovery period might easily suggest diagnosis of MS in a young adult patient but in the case of PPMS, the diagnosis could be a challenge. Differential diagnosis spectrum is broad and includes hereditary, metabolic, inflammatory, degenerative, paraneoplastic, toxic diseases and certain infections that present with lower extremity dysfunction regardless of patient age, concomitant diseases, family history and geographic location (1)

In cases with positive family history, the list of differential diagnosis could be narrowed to hereditary disorders. Hereditary spastic paraparesis (HSP) defines genetically and clinically heterogeneous group of disorders which is mainly characterized by progressive weakness of lower limbs and spasticity. In complicated forms of HSP, spastic paraparesis is accompanied by additional clinical features like mental retardation, peripheral neuropathy and retinal changes and this clinical presentation is easily distinguishable from MS. However, pure forms of HSP may lead to misdiagnosis of PPMS particularly if family history is unremarkable. HSP symptoms may start from infancy and, different from MS, those early-onset forms show relative preservation of muscle strength despite prominent increase in muscle tone in legs (2). Lack of magnetic resonance imaging (MRI) findings and cerebrospinal fluid (CSF) abnormalities attributable to MS are distinctive features of HSP from MS (3).

Hereditary leukodystrophies are prototype of dysmyelinating disorders and adult onset forms may resemble progressive MS. X-linked adrenoleukodystrophy (ALD) is a peroxisomal disorder that affects both central nervous system and adrenal cortex and shows a wide range of clinical spectrum. The most common form is slowly progressive myelopathy that begins at second or third decade of life. Cranial MRI shows cerebral demyelination but spinal MRI usually does not show significant inflammatory changes in contrast to MS (4). Additional features that suggest adrenal insufficiency, absence of oligoclonal bands in CSF should prompt to investigate very long chain fatty acids for ALD diagnosis (5). Adult-onset autosomal dominant leukodystrophy (ADLD) is a slowly progressive disorder presents with pyramidocerebellar syndrome. Autonomic dysfunction is a distinctive feature of the disease and helps distinguish ADLD from progressive MS (6). Metachromatic leukodystrophy (MLD) and Krabbe's disease are autosomal recessive disorders caused by lysosomal enzyme deficiency. Prominent cognitive decline that usually evolves into severe dementia, optic atrophy, nystagmus, spastic weakness and peripheral nervous system involvement are characteristic features of MLD. Atypical late-onset forms of Krabbe's disease may present with spastic paraparesis, ataxia, tremor, nystagmus, bulbar signs, cognitive dysfunction and less prominent peripheral nerve disturbances. Electrophysiological studies to reveal peripheral neuropathy and a search for leucocyte enzyme abnormalities should take place in diagnostic work-up if lysosomal disorders are suspected (5, 7).

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Freidreich's ataxia, other hereditary ataxias and olivopontocerebellar atrophies should be taken into consideration in cases with significant ataxia. Positive family history, lack of inflammatory changes in cranial MRI and the presence of additional findings that are uncommon for MS like cardiomyopathy, diabetes, hearing loss and extrapyramidal signs should direct the physician to search for etiological causes of progressive ataxia syndromes other than MS (8)

Wilson's disease is an autosomal recessive disorder associated with copper metabolism and clinical findings arise from the damage that copper deposits cause at certain tissues like brain, liver and eyes. The age of onset is similar with MS and in the case of progressive cerebellar syndrome, diagnosis of Wilson's disease should be considered especially because it is a treatable disease (8).

In conclusion, differential diagnosis of PPMS could be confusing considering the overlap of symptoms with other hereditary disorders. In the presence of positive family history, neurological findings uncommon for MS, additional systemic manifestations, normal results in MRI and CSF studies and abnormal electrophysiological study findings, the clinician should be alert for an alternative diagnosis.

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