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Case Report

Comorbid Multiple Sclerosis and Huntington's Disease

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Abstract

Huntington's disease (HD) and multiple sclerosis (MS) are two neurodegenerative diseases for which different pathologies and limited commonalities have been described. Here, we report the second case in the literature of comorbid MS and HD. When comorbidity occurs between rare diseases, shared pathological pathways may be suspected and common genetic or environmental triggers can be hypothesized to ultimately advance the understanding of the two diseases.

Keywords: Multiple Sclerosis; Huntington's Disease; Commonalities; Toxin Exposure; Case Report

Abbreviations

HD: Huntington's Disease; MS: Multiple Sclerosis; HTT: Huntingtin

Introduction

Huntington's disease (HD) and multiple sclerosis (MS) are both chronic, progressive, neurodegenerative diseases of the central nervous system. HD is a genetic disorder caused by expanded CAG trinucleotide repeats in the huntingtin (HTT) gene [1]. Conversely, the cause of MS is unknown, and possibly a result of an environmental trigger in a genetically susceptible host [2]. Although other neurodegenerative diseases have been described in association with MS, to our knowledge our report is the second case in the literature of comorbid MS and HD [3]. Case series of rare disease comorbidity can unveil pathological pathways involved in the diseases. As such, this case may help in hypothesizing potential etiologic commonalities between MS and HD.

Case Presentation

Our patient is a 47-year-old United States veteran, who was referred to the neurology clinic for subacute onset of left extremities weakness, and occasional left-hand numbness. Past medical history was significant for Attention-Deficit/Hyperactivity Disorder treated with methylphenidate since his childhood and one episode of retrobulbar optic neuritis which resolved after a course of intravenous steroids at the age of 23 years. His presenting symptoms prompted an MRI of the brain which revealed supratentorial, subcortical and callosal T2 hyperintensities. Cerebrospinal fluid revealed 40 mg/dL of protein, positive oligoclonal bands, and negative myelin basic protein. The patient was eventually diagnosed with relapsing-remitting MS and subsequently followed in the MS outpatient clinic. The patient was initially treated with glatiramer acetate for three years, and then switched to ocrelizumab infusion for recrudescence of the symptoms and a new lesion on the MRI (Figure 1A). During this time, the patient's main complaints included some cognitive "clouding" and mild weakness of the left extremities. The neurologic examination was remarkable for weakness graded 4/5 on the Medical Research Council's scale affecting knee extension and plantarflexion and dorsiflexion of the left ankle. Patellar and ankle hyperreflexia bilaterally with left ankle clonus and left Babinski sign were also present. The patient was stable on ocrelizumab for the following two years when he developed nonrhythmic choreiform involuntary movements of his head and athetosis affecting the left upper extremity. In one year, at the age of 52, these hyperkinetic movements progressed to the right upper and lower extremities and eventually to the face and neck. The patient continued to complain of cognitive "clouding" and re-

ported occasional abrupt laughter and emotional incontinence, but no history of depression or other psychiatric symptoms. An MRI at that time showed mild caudate atrophy (frontal horn width to inter-caudate ratio = 1.3 (references values = 2.2 - 2.6)) in a setting of diffuse brain parenchymal volume loss (Figure 1B). Diagnostic considerations included HD, pharmacologic side effects, and MS progression. Other causes such as autoimmunity, copper and iron abnormalities, and endocrinopathies were excluded (Table 1). Genetic testing ultimately revealed 44 repeats (normal < 35) in the HTT gene which is consistent with the diagnosis of HD. His family history was unknown for paternal ancestry, and noncontributory for maternal ancestry which was of European descent. Written consent was obtained from the patient.

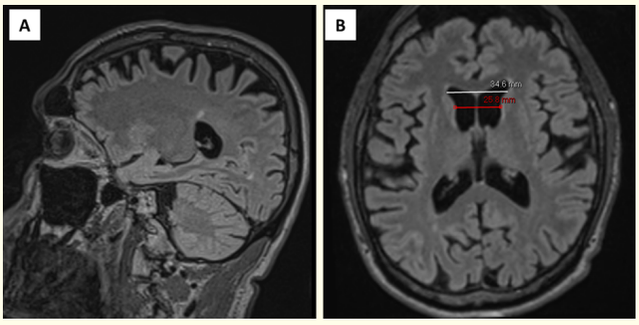

Figure 1: (A) Sagittal FLAIR MRI showing pericallosal and white matter hyperintensities and (B) axial FLAIR showing bilateral caudate head atrophy. Frontal horn width to inter-caudate ratio (FH:CC) is low 1.3 (normal = 2.2-2.6).

Blood test	Result	Reference range
Blood smear	No abnormalities detected	
TSH	1.07 mU/L	0.35-5.00 mU/L
Urea Nitrogen	17 mg/dL	7-25 mg/dL
Creatinine	0.74 mg/dL	0.5-1.5 mg/dL
Copper plasma levels	104 mcg/dL	70-175 mcg/dL
Ferritin	29.5 ng/mL	20-300 ng/mL
Hemoglobin A1C	5.3 %	4-6 %
Vitamin B12	348 pg/mL	200-900 pg/mL
Vitamin D total	21.7 ng/mL	20-50 ng/mL
Cardiolipin IgG	<14 GLP	<14 GLP
Cardiolipin IgM	<12 GLP	<12 GLP
Antinuclear antibody	Positive 1:80 speckled	Neg <1:40
Lupus anticoagulant	Negative	Negative
B2 glycoprotein IgG	<9 SGU	<9 SGU
B2 glycoprotein IgM	<9 SMU	<9 SMU
Anti-streptolysin O	89 IU/ML	0-200
Lyme antibody index IgG and IgM	Negative	Negative
Hepatitis C Ab	Negative	Negative
Hepatitis B surface antigen	Negative	Negative
Hepatitis B core antibody	Negative	Negative
Syphilis serology	Negative	Negative

Table 1: Results of the diagnostic work-up of choreoathetosis.

Discussion and Conclusion

Our case offers some reflection points which neurologists and researchers may benefit from. MS is a polymorphic disease with many clinical manifestations. Together with sensory and motor symptoms, new compelling evidence shows that psychiatric and cognitive symptoms are also highly prevalent in patients with MS [4]. Major depressive disorder is the most common, but pseudobulbar affect has been described in 10% of patients with MS [4]. Additionally, some degree of deficit in memory, complex attention, and executive functions have been described in up to 30% of MS patients [5]. Therefore, attributing new cognitive deficits and psy-

chiatric symptoms to causes other than MS progression may be particularly challenging. However, this case serves as a reminder that a differential diagnosis is always warranted for new symptoms, especially for genetic diseases which have implications for future generations. A formal and extended cognitive evaluation can help in highlighting impairments with patterns more consistent with other neurodegenerative diseases. In this case, HD cognitive symptoms could have been identified through tests such as the word reading component of the Stroop test, multi-tasking evaluations, and tests of executive contribution to memory failures [5].

Additionally, this case prompts discussion regarding the pathogenesis of the two diseases. HD is a genetic disease, whereas MS etiology is believed to be only in part genetic. Familial MS constitutes around 20% of all cases [6], and genetic studies of sporadic MS revealed that as many as 200 genes may be involved in MS pathology [2,7]. However, no common variants which have been found to increase the risk of sporadic MS seem to interact with the 4p16.3 locus, where the HTT gene maps. As such, if a genetic signature plays a pivotal role in both diseases, a shared genetic pathway has not yet been established.

To our knowledge, only one additional case has been reported with the co-existence of MS with HD. Interestingly, the other described patient was also a US Army officer [3]. Not infrequently, neurodegenerative diseases are triggered by an environmental exposure. For MS, previous literature suggests that organic solvent exposure may be implicated in the development of the disease [8]. Toxins are less often associated with HD, but environmental exposure can increase mutations throughout the genome. Genes modifiers and transcriptional regulators are being explored in relation to HD age of onset, suggesting an avenue by which environmental exposure could contribute to development of HD [9,10]. Given the occupational similarity between the cases, the hypothesis of occupational toxin exposure may be entertained. Our patient was deployed to Southeast Asia. Environmental hazards may have included exposure to smoke and particles from oil well fires, pesticides and insecticides, and various solvents. Unfortunately, we do not know any details of toxic exposure for the other reported case. Since only two cases have been reported, this hypothesis remains speculative.

Further descriptions of the commonalities between neurodegenerative diseases can identify shared genetic pathways or shared environmental risk factors, hence increase the understanding of the pathological pathways underlying the diseases.

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Conflict of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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