Case Report

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Diagnosing Hereditary Ataxias: A Case-Based Step-By-Step Approach

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Introduction

Diagnosing ataxias can be challenging. The differential diagnosis for both acquired and hereditary ataxias is vast and expansive, obligating the neurologist to first rule out all potential treatable causes of ataxia prior to considering the possibility of hereditary ataxias. Family history is important, but more often than not family history is lacking, and sporadic cases are not uncommon. Not uncommonly an extensive workup might be unrewarding, which could be due to the variability of phenotypes, lack of commercially-available genetic testing, or perhaps more significantly, cost.

Here we encountered a case which strongly suggested an autosomal dominant hereditary ataxia, but presented with limitations in obtaining a history and performing a neurological exam due to the patient's bedridden state, whichrequired in-depth knowledge of salientclinical features for differentiating various forms of hereditary ataxias, and ordering cut-to-the-chase genetic testing in a cost-efficient manner.

Case Presentation

A 51 year-old African-American male was admitted to an outside hospital for generalized weakness and hypoxia. He experienced recurrent aspiration pneumonia due to dysphagia status-post PEG tube placement, which resulted in sepsis. He was then transferred to our long-term acute care facility for further management. His mother reported that pregnancy and delivery were all normal. There was no history of developmental delay.

He started having episodes of stumbling and unsteadiness in his twenties. When he became 31 years of age his gait worsened even further; he stood with his feet wide apart to maintain his balance and his legs had become very stiff. Eventually he had to stop working in stocking merchandise.

He had been using a cane up till age 40 and then had to transition to a walker.He has had nasal dysarthria since at least age 40. At age 50 he was able to speak only in simple words, such as yes or no; he could not carry on a conversation. His mother noticed that his eyes 'would not move normally' since his 30s. He has had bladder frequency since age 42.

There was no history of high-arched feet or cardiac disorders. His mother denied any cognitive decline. He was very social, optimistic, and talkative. At age 35 he was first diagnosed with hereditary cerebellar ataxia and was placed on disability but never had genetic testing. His mother wished to find out what type of ataxia he has and requested for genetic testing. His head CT at the outside hospital reported global, cerebellar more than cerebral atrophy (images not available). He was transferred to our hospital, a long-term acute care facility, for further management.

Past medical history was significant for diabetes, hypertension and asthma. He had a 50-year-old brother who has had gait ataxia since his late 40s and a 46-year-old healthy sister. His step-brother also had gait ataxia.His father had gait ataxia since his late 40s and his paternal grandmother since her 60s. Fourteen out of the 17 siblings of his father were also affected, as well as the children of the affected siblings; the exact numbers were unclear as his mother had divorced him and was estranged from them. His father had been genetically tested but had already died; unfortunately, his second wife did not have the results with her either. There was no history of smoking or drinking alcohol. He was single without any children, living with his mother and bed-bound. He had no allergies.

Blood pressure was 132/90, heart rate 86, respiratory rate 14 and temperature 98.8°F. Exam revealed an emaciated young male in no acute distress. He was on a ventilator via tracheostomy and had a feeding tube placed. He was awake with occasional eye contact but was unable to mouth words or follow any commands, in part due to being sedated for anxiety while on the ventilator. Pupils were equally round and reactive. There was ophthalmoparesis with divergent gaze, spastic quadriparesis with hyperreflexia and ankle clonus. There was right thumb-in-palm and left Babinski sign. Cerebellar exam could not be performed due to sedation (**Fig 1**).

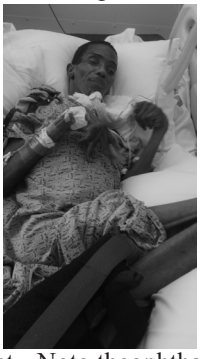

Figure 1: The patient. Note theophthalmoparesis with divergent gaze, spastic quadriparesis with hyperreflexia and ankle clonus. He was non-verbal and could not follow commands.

Laboratory data revealed an elevated ferritin level of 305, WBC count 10.2, hemoglobin 9.4 and platelets 135, sodium 143, potassium 3.9, creatinine 0.7, glucose 93.

Diagnostic approach

Given the limited exam and lack of previous records/objective data we decided to implement a logical, step-by-step process to arrive at the diagnosis.

1. What are the most common causes of acquired ataxia?

The most common causes of acquired ataxia are stroke, alcoholism, multiple sclerosis, malignancy, and vitamin deficiencies [1]. The clinical presentation was not suggestive of any of these conditions.

2. What are the most common causes of hereditary ataxia?

The prevalence of the autosomal dominant cerebellar ataxias (ADCAs) is estimated to be approximately 1-5 in100,000 [2,3]. Among the autosomal dominant ataxias, SCA3 is the most common worldwide, followed by SCA1, 2, 6, and 7 [1]. Spinocerebellar ataxia is estimated to affect approximately 150,000 individuals in the US.

Autosomal recessive types of hereditary ataxia account for approximately 3 in 100,000 [3], with Friedreich ataxia, ataxia-telangiectasia, and ataxia oculomotor apraxia (AOA types 1 and 2) being most common. The most common type of hereditary ataxia is Friedreich's ataxia, with a prevalence between 2-4/100,000 and a carrier frequency of 1:60-1:100. The hyperreflexia and absence of pes cavus made this condition less likely.

3. What mode of inheritance can be inferred based on the history?

There was a strong family history of ataxia, involving his biological father, his younger brother, his step-brother and more than half of his father's siblings, with both males and females affected. This clearly represents an autosomal dominant mode of inheritance. The onset was adulthood, not childhood, which would also favor an autosomal dominant hereditary ataxia [4].

4. What does his neurological exam tell us?

His exam tells us that not only does he have cerebellar but also pyramidal tract involvement, ruling out pure autosomal dominant cerebellar ataxias, such as SCA 7. The ophthalmoparesis is also a distinguishing feature, which can be seen in SCA 3. Due to sedation it was unclear as to whether he truly had parkinsonian features or not, which are commonly seen in SCA 3.

5. Based on the history and exam which types of hereditary ataxias would be on the top of your list of differential diagnosis?

The history and exam was clearly suggestive of an autosomal dominant hereditary ataxia with extra-cerebellar features of ophthalmoparesis, spasticity, and hyperreflexia. Pure cerebellar ataxias such as SCA 6 would be less likely. Therefore at this point the main differential diagnosis would be SCA types 1, 2 and 3.

SCA1, which is due to CAG repeat expansions in ataxin (ATXN) 1, manifests with pyramidal signs, peripheral neuropathy, and in some cases cognitive decline. SCA2 is due to CAG repeat expansions in the ATXN2 gene, demonstrating slow saccadic eye movements, peripheral neuropathy, decreased deep tendon reflexes, and dementia. A large Cuban founder population has been associated with SCA 2. SCA3, otherwise known as Machado-Joseph disease, with a large Portuguese(especially the Azores Islands) founder population, is due to CAG repeat expansions in the ATXN3 gene, demonstrating Parkinsonian-like extrapyramidal signs such as masked facies, bulging eyes, bradykinesia, with pyramidal signs. Lid retraction, nystagmus, decreased saccade velocity, amyotrophy, fasciculations, and sensory loss have been reported [1].

6. Which test would you order first, given that this is an inpatient on a ventilator and you want to diagnose as quick as possible?

An MRI could not be performed as the patient was on a ventilator; MRIs in general do not provide clear differentiating features specific to a particular type of ataxia. In order to arrive to a definitive diagnosis in a cost-effective manner, we decided to perform genetic testing. Genetic counseling was provided to his mother prior to testing. We tested for SCA 1, 2, 3 and 6 (although clinical suspicion was much less for SCA6 as this was not a pure cerebellar ataxia), which are the most common forms of autosomal dominant cerebellar ataxia. 53 CAG repeats on allele 2 of the ATXN 1 were detected, which was well-beyond normal (4-39 CAG repeats), clinching the diagnosis of SCA1. He tested negative for SCA 2, 3 and 6.

7. What is the treatment for SCA 1?

The treatment for SCA 1 at this point is supportive. However, pharmacological enhancement of metabotropic mGlu1 receptors demonstrated a robust and sustained motor improvement in SCA1 heterozygous transgenic mice [5]. Biohaven's lead drug candidate BHV-4157, a glutamate modulator, has been designated orphan drug status by the FDA in May 2016, and entering phase 3 trials.

Conclusions

Diagnosing hereditary ataxias are challenging, but by obtaining a detailed history, the mode of inheritance, and identifying differentiating key features on the exam one can narrow the differential diagnosis and order a more focused genetic panel to establish a definitive diagnosis. Diagnosing hereditary ataxias is imperative as novel therapies are approaching our horizon of medicine.

Refererences

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