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Genetics of Ataxias: Hereditary Forms

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ABBREVIATION: SCA = spinocerebellar ataxia

WHAT ARE HEREDITARY ATAXIAS?

Ataxia is a neurologic disorder in which there is loss of coordination of movement. It can result from dysfunction of the cerebellum and brain stem and their afferent or efferent pathways. The etiology of ataxia can be divided into 3 main categories: acquired, sporadic, and hereditary.[1,2] Hereditary ataxias are one of the largest groups of hereditary progressive neurodegenerative diseases with an estimated prevalence for all ataxias of 3–4 per 20,000.[2,3] Although there is no present curative therapy for hereditary ataxias, novel treatments aim to impact the disease process at the molecular level. Neuroimaging, particularly MR imaging, should be performed in all patients with suspected hereditary ataxias. Neuroimaging can help to make the correct diagnosis, identify treatable causes, monitor disease progression, and exclude secondary causes. The objective of this vignette is to describe the heterogeneous group of hereditary ataxias and to discuss their diverse clinical presentations, imaging characteristics, and diagnostic challenges.

WHAT ARE THE MODES OF INHERITANCE OF HEREDITARY ATAXIA?

There are multiple modes of inheritance of hereditary ataxia: These include autosomal recessive, autosomal dominant, X-linked (paternal), mitochondrial forms (maternal), and incomplete penetrance.

AUTOSOMAL DOMINANT MODE OF INHERITANCE

Classification of autosomal dominant spinocerebellar ataxias (SCAs) is traditionally described by using the Harding classification, which is based on clinical presentation.[4] However, given the

significant overlap of clinical symptoms, a genetic classification is now favored and subtypes of SCAs are now largely established via genetic testing. To date, there are more than 30 types of SCAs that have been identified (SCA1-SCA36). The pathophysiology of nearly half of the autosomal dominant ataxias is secondary to trinucleotide or codon repeat expansions.[5] The most common trinucleotide repeat expansions are associated with polyglutamine repeats (SCA1, SCA2, SCA3, SCA6, and SCA7). However, polyglutamine repeats are not unique to SCAs and can also be seen with Huntington disease and dentatorubral-pallidoluysian atrophy. It is hypothesized that the large number of polyglutamine repeats can lead to misfolding of mutant protein, cellular dysfunction, and eventually cell death.[1] Larger numbers of expanded alleles can also precipitate earlier disease onset and worsen the clinical course. In addition, germline expansion or instability can cause an anticipation effect with progressive worsening of disease in subsequent generations. Intermediate expansion of trinucleotides may not express phenotypes in tested individuals but may lead to disease in their offspring. Anticipation may be more pronounced in males (eg, fragile X) secondary to the high number of cell divisions during spermatogenesis.[6] Other type of mutations occurring in autosomal dominant spinocerebellar ataxia include missense (SCA5, SCA13, SCA14, SCA23, SCA27, SCA28, and SCA35), frameshift (SCA11), and deletion (SCA15 and SCA16) mutations.[7]

AUTOSOMAL RECESSIVE MODE OF INHERITANCE

Autosomal recessive ataxias are another diverse group of diseases that can be broadly categorized into the following 4 groups: 1) degenerative such as Friedreich ataxia, CoQ10 deficiency, and Charlevoix-Saguenay spastic ataxia; 2) congenital such as Joubert syndrome subtypes 1–5 and Cayman ataxia; 3) metabolic such as ataxia associated with vitamin E deficiency, abetalipoproteinemia, Tay-Sachs disease, and Wilson disease; and 4) ataxias with DNA repair defects such as ataxia telangiectasia, ataxia with oculomotor apraxia subtypes 1 and 2, and spinocerebellar ataxia with neuropathy.[1] The most common autosomal recessive cerebellar

ataxia is Friedreich ataxia, which is secondary to *GAA* trinucleotide repeat expansions.[1,5] In Friedreich ataxia, the mutant proteins cause loss of function of frataxin, an iron storage or chaperone protein in the mitochondria, resulting in iron overload and cellular oxidative damage.[3,8] Patients with Friedreich ataxia can have non-neurologic manifestations such as cardiomyopathy and diabetes,[5] in addition to ataxia.

DIAGNOSING HEREDITARY ATAXIA

Once hereditary ataxia is suspected, a detailed medical history should be obtained before genetic testing and imaging studies.[9] This should include a physical examination, a neurologic examination, and at least a 3-generation family history to exclude secondary causes of ataxia.[9] However, a lack of family history does not preclude a diagnosis of hereditary ataxia because patients with autosomal recessive ataxia, incomplete penetrance, or trinucleotide repeat expansion may have a negative family history. The age of onset can also be important because autosomal dominant ataxias are associated with later ages of onset compared with autosomal recessive ataxias, the former occurring between the third and fourth decades and the latter in the second decade, though findings can vary markedly.[1,2]

LABORATORY AND GENETIC TESTING

Specific genetic tests are available for SCA1, SCA2, SCA3, SCA6, SCA8, SCA10, SCA12, SCA17, dentatorubral-pallidoluysian atrophy ataxias, and fragile X-associated tremor ataxia syndrome, all of which are trinucleotide repeat disorders. However, with the exception of fragile X-associated tremor ataxia syndrome, there is no established consensus on the normal range for the number of repeats.[8] Patients with negative findings on genetic testing who have idiopathic sporadic cerebellar ataxias, mutations associated with many SCAs, and Friedreich ataxias account for nearly 20% of cases; but whether this percentage is secondary to insufficient medical and family history, incomplete phenotypic penetrance, or de novo mutations is unclear.[5] Despite the critical role of genetic testing in making an accurate diagnosis, only 60%–75% of SCAs have identifiable foci.[1,2,5] Nongenetic laboratory tests are also available but are much less specific. For instance, elevated α-fetoprotein is associated with ataxia-telangiectasia and ataxia with oculomotor apraxia type 2.[1,5,9]

ROLE OF NEUROIMAGING

Neuroimaging, particularly MR imaging, should be performed in all patients with suspected hereditary ataxias. Neuroimaging can help make the correct diagnosis, identify treatable causes, monitor disease progression, and exclude secondary causes of ataxia such as tumor or infarct.

In patients with advanced hereditary ataxias, there can be atrophy of the cerebellum and pons and involvement of the basal ganglia nuclei, pyramidal tracts, and cortex.[9,10] Imaging techniques such as diffusion tensor imaging, quantitative 3D volumetric analysis, and spectroscopy can provide valuable additional information.[3,11-13] Studies using voxel-based morphometry and quantitative 3D volumetric analysis suggest that SCA1 ataxias display prominent pontine atrophy, while SCA6 ataxias predominantly show cerebellar atrophy and gray matter involvement.[11,13]

N-acetylaspartate is considered a marker for neuronal integrity and has been shown to correlate with the degree of atrophy and clinical dysfunction in the pons and cerebellum in SCA1 but not in SCA2.[12] Abnormal signal in the basal ganglia and putamen has also been associated with SCAs.[11,13] The degeneration of pontocerebellar fibers (the hot cross bun sign), which is considered pathognomonic for multiple system atrophy of the cerebellum, can also be observed with some SCA subtypes and with idiopathic cerebellar ataxias.[13] The relationship between the degree of atrophy and the number of trinucleotide repeats is difficult to assess from imaging because findings can be influenced by other factors such as the degree of disease progression and the age of onset.[3,13]

TREATMENT

Presently, there is no curative therapy for hereditary ataxia. Most current therapies only provide symptomatic relief. In patients with Friedreich ataxias, high-dose β-blockers and idebenone can yield some benefit in those with cardiomyopathy, though idebenone has failed to show efficacy in phase 3 trials.[1,3] Erythropoietin has also been shown to increase the level of frataxin proteins.[1,3] In SCAs, patients are often treated with acetazolamide for episodic ataxia and baclofen/tizanidine for spasticity.[14] Many novel treatments presently under investigation aim to impact the disease process at the molecular level or inhibit polyglutamine expansions. These include modulation of phosphorylation to reduce toxicity and silencing or down-regulating gene expression via RNA interference.[5,14]

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