

DEGENERATIVE ATAXIAS: CLASSIFICATION, DIAGNOSIS AND DOMINANT FORMS

Stefan Pulst, MD, Dr med, FAAN
University of Utah Medical School
Salt Lake City, UT

This seminar will focus on chronic progressive ataxias that are neurodegenerative in nature. The presentations will follow a genetic classification, first examining the dominant ataxias, then the recessive ones. At the end, we will discuss causes of sporadic ataxias including genetic etiologies.

Definition Degenerative Ataxias

Degenerative ataxias are a group of disorders characterized by slowly progressive incoordination of gait and often associated with poor coordination of hands, speech, and eye movements. Atrophy of the cerebellum is virtually always visible except for the first few months after onset.

Prevalence

Relatively little is known about population-based prevalence of ataxias. Estimates about the relative proportion of sporadic and hereditary ataxias (dominant & recessive) vary widely. Using a Japanese registry, Tsuji estimated prevalence of all ataxias including the cerebellar form of multiple system atrophy (MSAc) at 18 per 100,000 (Tsuji 2009). Prevalence of the autosomal dominant cerebellar ataxias (ADCAs) in the Netherlands is estimated to be at least 3 in 100,000 population [van de Warrenburg et al 2002]. In caucasians, the frequency of the Friedreich ataxia allele is 1 in 90-100 resulting in a disease prevalence of 1 in 10,000.

Dominant Ataxias (ADCA)

Synonyms for ADCA used prior to the identification of the molecular genetic basis of these disorders were Marie's ataxia, inherited olivopontocerebellar atrophy, cerebello-olivary atrophy, or the more generic term, spinocerebellar degeneration. "SCA" is usually reserved for an autosomal dominant ataxia and the term is generally not used for sporadically occurring degenerative ataxias. This distinction is of course artificial as mendelian mutations do arise sporadically. Close to 40 SCA genes have already been identified.

Worldwide, the most common SCAs are those caused by expansion of a coding CAG repeat. Although individual frequencies show great regional variation, often even within a given country, SCA6 and SCA3 are the most common, followed by SCA2, SCA1, SCA7 and SCA17. Many of the "double-digit" SCAs are rare. For example, KCNC3 (Kv3.3) mutations causing SCA13 made up <1% in a large analysis of American and European ataxia samples (Figuroa et al, 2010).

Phenotype

SCA phenotypes can range from pure cerebellar ataxia to other associated movement disorders such as myoclonus and dystonia. Although there are certain phenotypic characteristics that are overrepresented within a given SCA, it is very difficult- even for the expert- to predict the precise SCA type in an individual patient.

SCA phenotypes can range from pure cerebellar ataxia to other associated movement disorders such as myoclonus and dystonia. Many SCAs show involvement of CNS systems in addition to the cerebellar pathways, although in most cases cerebellar dysfunction is the presenting complaint.

However, in occasional patients or even in rare pedigrees, cerebellar symptomatology can be minor or even absent. A Huntington-like phenotype can be seen in SCA17 and DRPLA, PD-like phenotypes in SCA2 and SCA3 (reviewed in van Gaalen et al 2011). In some SCA2 pedigrees, an L-DOPA responsive PD phenotype or an ALS-like phenotype appear to "breed true." In a few SCAs, a pure cerebellar phenotype (without significant long tract or basal ganglia findings) is typical such as in SCA6 and SCA14. Caution has to be exercised for the rarer SCAs in which the phenotype has only been observed in a few pedigrees.

In summary, a significant amount of overlap in phenotypes can be discerned and provides the rationale for genetic testing. Phenotypes do not only depend on the mutated gene, but on the precise nature of the mutation such as length of an abnormal CAG repeat and the duration of the illness.

Anticipation

Anticipation denotes a phenotypic phenomenon and describes the on average earlier onset of a disease in subsequent generations. In autosomal dominant neurodegenerative disease, it may be difficult to distinguish large variability of age of onset around a mean from anticipation, especially as age of onset can be right-truncated in the youngest generation. New methods for statistical analysis of data for anticipation have been suggested.

In the SCAs, anticipation is related to DNA repeat instability. Especially upon passage through the paternal germline, DNA repeats tend to increase. As repeat length is inversely correlated with age of onset, this results on average in earlier onset of disease in subsequent generations.

Pathogenesis

Although cerebellar Purkinje cells are affected in many SCAs, deep cerebellar neurons can be predominantly affected (e.g. SCA3). In many SCAs, other neuronal groups such as brain stem, basal ganglia and motor neurons are involved.

For the polyglutamine ataxias, multiple pathogenetic mechanisms have been proposed. These include toxicity mediated by toxic misfolded proteins, transcriptional dysregulation, gain of normal function, and partial loss of function. For non-polyQ ataxias, channel dysfunction, abnormal calcium handling, and mitochondrial dysfunction appear to be common themes.

Animal Models

Many insights into pathogenic pathways and roads towards therapies have been gained by animal models of ataxias. Features of the dominant ataxias have been recapitulated in mice by expressing cDNA constructs containing the human mutation with a variety of promoters, by knocking-in a mutation into one or both mouse alleles, or by using bacterial or yeast artificial chromosomes (BACs or YACs) to express an entire human gene bearing the mutation. Many models have targeted expression specifically to Purkinje cells using the *Pcp2* promoter.

Evaluation of mouse models has included testing motor behaviors as well as morphologic, biochemical, and recently also physiological approaches. A mainstay of motor testing has been the rotarod, in which mice are placed on a rotating rod, which accelerates from about 4 to 40 RPM. In addition beam walking assays have been used. Therapy trials in rodents have employed lithium, dantrolene as well as a variety of approaches targeting RNA degradation such as the use of viruses or antisense oligonucleotides.

DNA Testing

Most DNA testing for ataxias is performed for symptomatic individuals and more rarely for predictive or prenatal testing. The major benefit of testing is the establishment of a diagnosis minimizing future additional diagnostic tests. It also allows more precise estimates regarding recurrence risk (50% for a dominant SCA). It may also permit more precise prognosis and may direct the patient towards a specific therapy.

Molecular genetic testing for CAG repeat length is a highly specific and highly sensitive diagnostic test. The sizes of the normal CAG repeat allele and of the disease-causing (full-penetrance) CAG repeat expansion vary among the disorders (see individual *GeneReview* for each disorder).

For DNA diagnosis of other SCAs, sequence analysis of the entire gene or targeted sequencing of specific exons is offered commercially. Deletion of entire exons or even an entire gene may not be detectable by routine sequence analysis. Variants of unknown significance may provide a major challenge for interpretation.

Next generation sequencing will result in rapidly decreasing costs for sequence analysis of ataxia genes. Thus, it will be possible to analyze exonic mutations for all SCAs caused by missense/nonsense mutations or small indel mutations with a single whole exome sequencing approach. At current levels of sequencing technology, longer DNA repeats cannot yet be detected in a reliable fashion and will need to be analyzed by conventional methods.

Sporadic Ataxias

The sporadic ataxia patient remains a frustrating challenge. “Sporadic” patients include those who have a truly negative family history with parental longevity, large sibships and three to four generation pedigrees with known medical records and those patients with a non-contributory family history as a result of adoption or premature unrelated death of a parent. Meiotic expansion of a DNA repeat upon transmission from a parent to child may also contribute resulting in later disease onset in a parent.

After imaging has excluded other causes, we usually check for carefully for signs suggesting MSA (orthostasis, parkinsonism, sphincter disturbances) and try to elicit a history of remote or on-going alcohol abuse. With the exception of GAD antibodies, paraneoplastic antibody-mediated syndromes usually do not factor into the differential as these diseases present with a subacute onset, typically resulting in severe ataxia within 3-5 months. Ataxia mediated by anti-GAD antibodies is a rare, but an interesting and under-recognized entity. As serum GAD antibodies are found in diabetics, it is important to determine GAD-Ab levels in the CSF to strengthen a causative etiology.

Testing for recessive and dominant ataxias may reveal mutations in up to 10% of patients without a positive family history (Moseley et al 1998; Abele et al 2002). Although direct percentages vary by ethnicity and geographic region, about 5% are due to recessive mutations (usually FRDA in caucasians) and 5% due to SCA mutations.

Progression

Several large consortia have examined the best ways to measure progression and to provide estimates of progression for individual SCAs. In Europe, this effort has been led by EURO-SCA (Jacoby et al, 2011). In the United States, a similar more recent effort was funded by the NIH SCA-Clinical Research Consortium (Ashizawa et al, 2013). Both research groups were multi-center and used rating scales as well as quantifiable tools such as the 9-hole peg board or the 25 ft. walk. The rating instrument used was the Scale for the Assessment and Rating of Ataxia (SARA).

Of the polyglutamine ataxias, SCA1 progressed most rapidly, followed by SCA2 and SCA3. SCA6 progression was much slower.

Treatment

Although no disease-modifying therapies are currently available for individuals with ataxia, symptomatic treatments can be of great help. We recommend physical and speech therapy to all of our patients, although most insurance plans impose significant limitations on the use of these services.

There is evidence in a number of animal models that exercise may delay neurodegeneration. We recommend exercise to all of our patients as long as it can be conducted in a safe fashion. Stationary bikes can be used for aerobic exercise and some patients have purchased industrial tricycles to exercise outdoors with a partner or friend. Parkinsonian symptoms may respond to dopaminergic therapy, spasticity can be managed with baclofen. Bladder dysfunction especially spastic bladder can be treated with intermittent catheterization, alpha-blockers, anticholinergics, oxybutynin chloride, or tricyclics. Of major importance are fall prevention and fall-proofing of the home or apartment. Screening for osteoporosis is part of this process as is designing exercises with light weights in a safe environment.

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