PRIMEVIEW

SPINOCEREBELLAR ATAXIA

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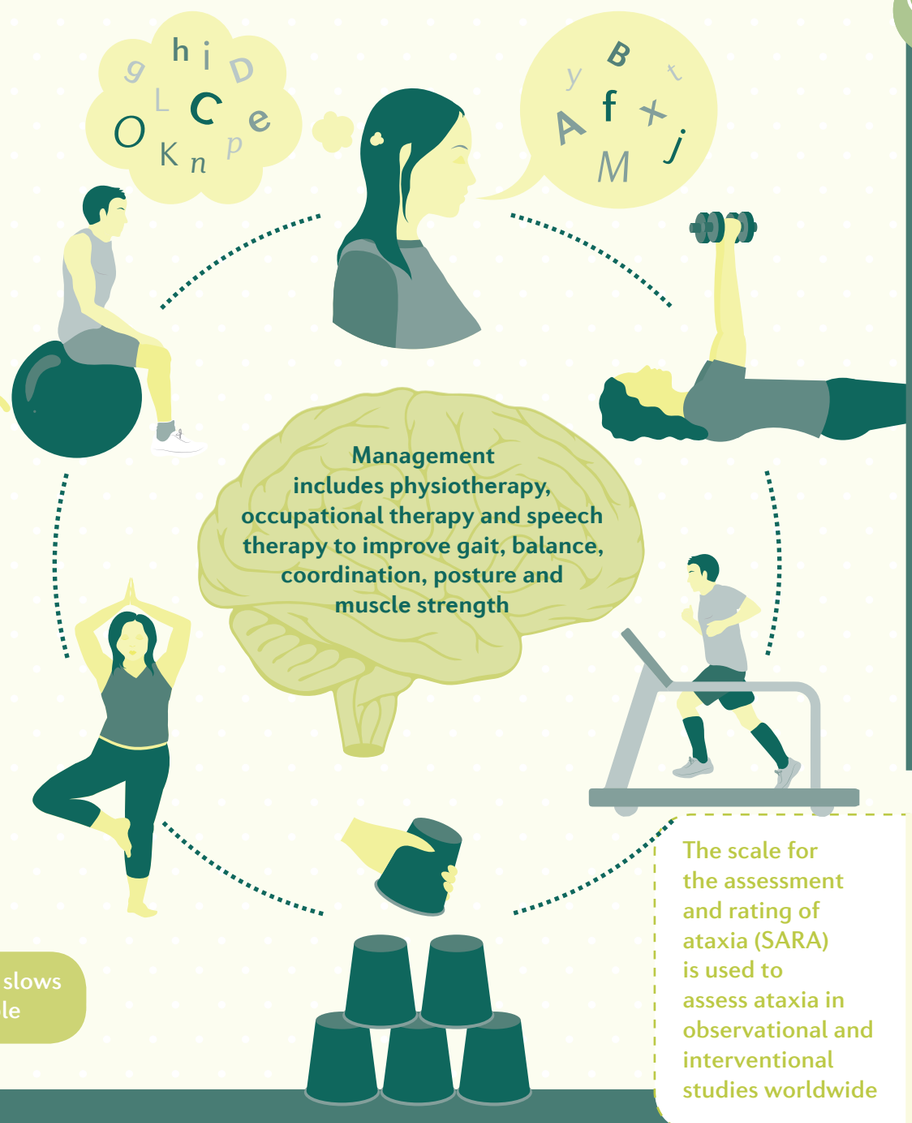
The spinocerebellar ataxias (SCAs) are a group of rare autosomal dominant progressive disorders characterized by loss of balance and coordination, and by slurred speech. As each SCA has a distinct genetic cause, the pathophysiology is heterogeneous.

MECHANISMS

There are >40 genetically distinct SCA subtypes, which are classified either as repeat expansion SCAs or as SCAs that are caused by conventional mutations. One key mechanism underscoring SCAs is polyglutamine (polyQ) repeat expansion. PolyQ repeat expansions cause proteins to have altered conformations, which alters their function, alters their interactions with other proteins, can cause them to oligomerize and can lead to the formation of intranuclear inclusions; these events cause proteotoxicity. SCA-causing proteins without polyQ expansions may also have altered conformations that cause proteotoxicity. Some SCAs are caused by non-protein coding repeat expansions that sequester RNA-binding proteins; other nuclear events that may contribute to the pathogenesis of SCAs are DNA damage, altered chromatin acetylation and changes in transcription. In the cytoplasm, repeat expansions in SCA disease proteins can also cause non-canonical translation, leading to aggregate-prone polypeptides; some SCA-causing mutations directly or indirectly cause ion channel dysfunction, and multiple SCA disease proteins indirectly impair mitochondrial function.

MANAGEMENT

Most SCA-causing mutations result in damage to cerebellar Purkinje neurons; basal ganglia and pontine nuclei in the brainstem may also be involved



Management includes physiotherapy, occupational therapy and speech therapy to improve gait, balance, coordination, posture and muscle strength

Currently no drug that slows or halts SCAs is available

The scale for the assessment and rating of ataxia (SARA) is used to assess ataxia in observational and interventional studies worldwide

EPIDEMIOLOGY

Determining the prevalence of SCAs is challenging owing to the limited number of population-based epidemiological studies and the high number of SCA-causing genes. PolyQ SCAs are the most frequent; of these, SCA3 (also known as Machado-Joseph disease) is the most common SCA worldwide (20–50% of families with a dominant ataxia), followed by SCA2 (13–18% of families with SCA) and SCA6 (13–15% of families with SCA). Founder effects explain the presence of high-frequency rare Mendelian diseases in some populations. As the genetic defect is unidentified in 30–48% of patients with SCA, new causative genes will likely be discovered.

DIAGNOSIS

For most patients with SCA, the onset of ataxia occurs in the third or fourth decade of life and is equated with the time the patient first noticed unsteadiness of gait. However, symptoms likely begin several years before manifest ataxia in a pre-ataxia stage. Other symptoms include the loss of fine motor skills, speech and swallowing problems, oculomotor abnormalities and non-ataxia symptoms. If there is clinical evidence for a diagnosis of SCA, molecular genetic testing is initiated. A targeted genetic test is recommended if a known SCA genotype is in the family, if the phenotype is suggestive of a specific SCA or if a SCA is prevalent in the population. Otherwise, and also when targeted tests are negative, a step-by-step approach to diagnosis, starting with tests for mutations that cause polyQ SCAs, is recommended.

OUTLOOK

Progress in the development of therapies for SCAs is limited; riluzole, valproic acid, varenicline and lithium carbonate gave encouraging results in clinical studies, but no clear evidence of benefit was established. Our increasing understanding of the mechanisms underlying SCAs should help to identify targets for symptom-modifying and disease-modifying therapies, as well as biomarkers for assessing disease progression and treatment efficacy. Treatment in the pre-ataxia stage, before irreversible brain degeneration occurs, is desirable. Finally, the decreasing cost of genetic tests (including whole-exome sequencing), and the availability of new tests (such as long-read whole-genome sequencing), should aid the diagnosis of SCAs and further inform epidemiology.

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