

Progression of spinocerebellar ataxia type 2. What do we need to know?

Progressão da ataxia espinocerebelar tipo 2. O que precisamos saber?

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Spinocerebellar ataxia type 2 (SCA2) is one of the most common autosomal dominant cerebellar ataxias, accounting for 15% of cases within families¹. It is caused by abnormal CAG expansions in the ATXN2 gene and may affect individuals worldwide. Symptomatology is a consequence of both cerebellar and extra-cerebellar structure degenerations including pons, basal ganglia and cerebral cortex. It is a progressive disorder leading mainly to motor symptoms involving abnormal cerebellar function. It can also produce Parkinsonism, oculomotor disturbances, pyramidal signs, lower motor neuron involvement, cognitive decline and muscular cramps².

Despite being an incurable condition, some of the clinical features may be controlled with antiparkinsonian drugs, baclofen (spasticity), mexiletine and magnesium (cramps), among others. Physiotherapy and speech therapy could also help improve the motor symptoms and dysphagia². Future neuroprotective drugs are in the horizon, but until now no proven efficacious therapy is available. A reduction of ataxin-2 expression by the anti-sense oligonucleotide (ASO) therapy can be a promising future therapeutic approach for the disease. This ASO has been tested in SCA2 mouse models and improved motor performance and Purkinje cells firing rate of the animals³. In recent years, many therapeutic attempts have been developed to repair or replace the abnormal protein generated by the genetic mutation. However, few of them were actually successful. We do not know yet whether gene therapy or drugs acting on molecular mechanisms will be the mainstream treatment of neurogenetic diseases in the future.

Researchers need to know the rate of progression of SCA2 and all the other degenerative ataxias to reliably test some of the emerging future treatments. Amarante et al., in the current issue of *Arquivos de Neuro-Psiquiatria*, analyze 16 SCA2 Brazilian patients, correlating disease duration with severity of motor symptoms, balance impairment and functionality⁴. As expected for progressive diseases, they found that the longer the duration of the disease the greater the severity of symptoms and the impairment of balance and functionality of the patients. For instance, the one-year duration of the disease corresponded to a 0.8 increase in the severity scale, a 1.38 decrease in the functionality scale, and a 2.30 decrease in the Berg balance scale⁴. Unfortunately, Amarante et al.⁴ did not design a prospective study to evaluate the progression of the disease. This could have helped to have a more accurate understanding of how SCA2 progresses and what we could expect of a future protective treatment.

We are still waiting for effective treatments for most of the degenerative neurological diseases, including all genetic ataxias. However, first we need to know how these diseases progress. On the other hand, only a large number of subjects and a longer period of treatment will allow the recognition of the real benefit of forthcoming therapies. As an alternative to clinical measures, advanced MRI techniques may be a reliable biomarker to track disease progression from the preclinical phase to the onset of ataxia⁵.

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