Filling a Knowledge Gap: Prevalence of Ataxia and Spastic Paraplegia in Eastern Quebec

In the current issue of the Journal an article "Genetic and epidemiologic study of adult ataxia and spastic paraparesis in eastern Quebec" by Haj Salem et al. describes the prevalence and genetic composition of hereditary ataxias (HA) and hereditary spastic paraplegias (HSP) in the eastern Quebec population.[1] There is remarkably little known about the prevalence of these disorders in Canada. The only previous Canadian publications include a cross-sectional study of HSP prevalence in three provinces[2] published in 2016 and a single-center study on the prevalence of adult-onset ataxia[3] published in 2005, before the advent of next generation sequencing (NGS). This paper begins to fill this Canadian knowledge gap and highlights the opportunity to examine the prevalence of these conditions across Canada.

The prevalence reported in the paper for both HA and HSP conditions combined is over 10/100,000. Although this is relatively low compared to other chronic conditions, it is important to recognize that these are progressive disorders which often cause disability, under/unemployment, and lack specific treatments or even symptomatic therapies. As the authors note, this may be an underestimation of the actual prevalence due to the presence of individuals with mild or asymptomatic disease (and who would therefore not come to medical attention) and the inability to reach all affected patients including affected family members of patients.

Thirty-two different genetic diagnoses for the combined HSP and HA cohorts were reported in this study highlighting the rarity of each individual diagnosis. Biallelic mutations in *SPG7* was the most prevalent autosomal recessive cause of HSP but was also associated with one case of HA demonstrating the phenotypic heterogeneity of this gene.[4] Since mutation in multiple other genes have also been linked to both HSP and HA clinical presentations,[5] it is notable that *SPG7* was the only gene discovered to be causative for both clinical presentations in this cohort. This may be a limitation of the approach in this study, in which patients with HSP clinically were only tested with an HSP panel and patients with HA were only tested for repeat disorders and with an ataxia panel. It may be interesting to see if the diagnostic yield increased if the "unidentified" group from each cohort were tested with the opposing genetic panel. Other notable findings were that many of the autosomal recessive causes of HA in this adult-onset study were genes previously believed to cause childhood onset disorders (e.g., autosomal recessive spastic ataxia of Charlevoix-Saguenay, Friedreich's Ataxia) and should therefore be considered in the differential diagnosis of adult-onset populations. Founder effect may have contributed to the finding that ARCA1 was the most common cause of HA in this population and founder effect was likely the cause of the very surprising lack of SCA3, which in many populations is the most common cause of autosomal dominant HA.[6]

The genetic diagnosis of patients with HA and HSP is challenging and patients often continue on a diagnostic odyssey of many years. The advent of NGS and the commercial availability of affordable genetic panels have improved diagnostic yield for these disorders. This paper outlines a useful algorithm for the genetic work-up of these individuals. Despite the use of large genetic panels in this study (e.g., an ataxia panel with 362 genes plus mitochondrial DNA) a molecular diagnosis was determined in less than 50% of the HA cohort (104/241) and slightly more than 50% of the HSP cohort (67/115). This is a similar diagnostic yield to those reported in other studies,[7] suggesting either a number of yet to be discovered genetic associations and/or non-genetic etiologies. This also highlights a limitation of this study and other studies using genetic panels for diagnoses since panels lag genetic discovery. While most newly discovered variants are exceedingly rare and their addition would not significantly affect the diagnostic yield of large panels, in the past 18 months, for example, biallelic expansion in *RFC1* is proposed to be a common cause of adult-onset HA[8] and was not included in the panels used in this study.

We have entered the era of genetic therapeutics. Antisense oligonucleotide (ASO) therapies have been approved by the Federal Drug Administration in the US in at least three genetic neurological disorders (Spinal Muscular Atrophy, Duchenne Muscular Dystrophy and Familial Amyloid Polyneuropathy)[9] and there are preclinical studies of ASOs for SCA2[10] and SCA3.[11] Other molecular therapeutics are being studied in preclinical trials in related genetic disorders.[12] It will be increasingly important to identify and diagnose rare genetic disorders in order to allow individuals with these conditions the opportunity to take part in future clinical trials. Given the rarity of each diagnosis, recruitment of a sufficient number of subjects for any specific trial will require national and international collaborations and disease registries. Global initiatives have been formed including Ataxia Global Initiative[13] in order to initiate and maintain disease registries and to link patients with clinical trials and eventually future therapeutics.

DISCLOSURES

The author has no conflicts of interest to declare.

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REFERENCES

1. Haj Salem I, Beaudin M, Stumpf M, et al. Genetic and epidemio-logic study of adult ataxia and spastic paraparesis in eastern Quebec. Can J Neurol Sci. 2021;5:1–33.
2. Christian N, Dupré N, Gan-Or Z, et al. Clinical and genetic heterogeneity of hereditary spastic paraplegia in Canada. Neurol Genet. 2016;3:e122.
3. Kraft S, Furtado S, Ranawaya R, et al. Adult onset spinocerebellar ataxia in a Canadian movement disorder clinic. Can J Neurol Sci. 2005;32:450–58.
4. Hewamadduma CA, Hoggard N, O'Malley R, et al. Novel geno-type-phenotype and MRI correlations in a large cohort of patients with SPG7 mutations. Neurol Genet. 2018;4:e279.
5. Bereznyakova O, Dupré N. Spastic ataxias. Handb Clin Neurol. 2018;155:191–203.
6. Teive HAG, Meira AT, Camargo CHF, Munhoz RP. The geograph-ic diversity of Spinocerebellar Ataxias (SCAs) in the Americas: a systematic review. Mov Disord Clin Pract. 2019;6:531–40.
7. Elert-Dobkowska E, Stepniak I, Krysa W, et al. Next-generation sequencing study reveals the broader variant spectrum of heredi-tary spastic paraplegia and related phenotypes. Neurogenetics. 2019;20:27–38.
8. Cortese A, Simone R, Sullivan R, et al. Biallelic expansion of an intronic repeat in RFC1 is a common cause of late-onset ataxia. Nat Genet. 2019;51:649–58.
9. Scoles D, Minikel E, Pulst, S. Antisense oligonucleotides: a primer. Neurol Genet. 2019;5:e323.
10. Scoles DR, Meera P, Schneider MD, et al. Antisense oligonucleotide therapy for spinocerebellar ataxia type 2. Nature. 2017;544:362–66.
11. McLoughlin HS, Moore LR, Chopra R, et al. Oligonucleotide therapy mitigates disease in spinocerebellar ataxia type 3 mice. Ann Neurol. 2018;84:64–77.
12. Tabrizi SJ, Ghosh R, Leavitt BR. Huntingtin lowering strategies for disease modification in Huntington's disease. Neuron. 2019;101:801–19.
13. http://ataxia-global-initiatives.net