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Spinocerebellar Degenerations in Japan New Insights from an Epidemiological Study

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Spinocerebellar degenerations (SCD) comprise a group of heterogeneous progressive neurodegenerative disorders, which affect the cerebellum and its afferent and efferent connections. SCD can be divided into: autosomal-dominant cerebellar ataxias (ADCA), currently designed as spinocerebellar ataxias (SCA); autosomal-recessive cerebellar ataxias (ARCA); X-linked cerebellar ataxias; mitochondrially inherited ataxias; and non-genetic ataxias (sporadic idiopathic cerebellar ataxias); including the cerebellar form of multiple system atrophy (MSA), with olivopontocerebellar atrophy; and idiopathic late onset cerebellar ataxias (also known as idiopathic sporadic cerebellar ataxia or sporadic adult-onset ataxia of unknown etiology), encompassing sporadic cortical cerebellar atrophy [1–5].

Differences in frequency of SCD have been reported around the world, particularly in Japan, where MSA accounts for 40% and SCA and ARCA (together) for 30% of the cases [6]. These findings have been confirmed in epidemiological studies from Japan, showing that MSA is the most common type of sporadic cerebellar ataxia [7]. In 2007, Basri et al. [8] studied the prevalence of ADCA subtypes in Hokkaido (the northern island of Japan) in 113 Japanese families, and showed that 31% of the cases had a molecular diagnosis of SCA type 6, followed by 27% with SCA type 3 (Machado-Joseph disease), 10% with SCA type 1 and 9% with 16q-ADCA. The other subtypes were dentatorubral pallidoluysian atrophy (4%), SCA 2 (4%) and SCA 14 (1%). The remaining 14% had negative findings and were labeled 'ADCA of unknown etiology'.

From a wider perspective, in 2004 Schöls et al. [9] published a seminal paper where SCA type 3 was found to be the commonest ADCA subtype worldwide. The other SCA, including types 1, 2, 6, 7 and 8, have a prevalence of around 2%, and the remaining SCA account for less than 1%.

In this issue of *Neuroepidemiology*, Shibata-Hamaguchi et al. [10] published a very interesting study regarding the prevalence of SCD in the Hokuriku district, Japan.

The authors found that ADCA represented 40.4% of all cases, MSA 24.7%, cortical cerebellar atrophy 13.3% and ARCA only 0.3% of the cases. Among ADCA, SCA type 3 was found in 63.3%,

SCA type 6 in 20.0%, ADCA linked to chromosome 16q22.1 in 10.0%, dentatorubral pallidoluysian atrophy in 4.4%, SCA type 1 in 1.1% and SCA type 2 in 1.1%. SCA type 3 was highly prevalent in the Toyama prefecture of the Hokuriku district, particularly in the Gosei area (the western part of Toyama prefecture), with a prevalence of 19.1 per 100,000 people [10], which is very similar to the prevalence in the Azorean islands, Portugal (27.8 per 100,000 people) [11].

Several insights might be offered by this study. First, SCA 3 or Machado-Joseph disease is the most common type of SCA worldwide, and Japan and Portugal are no exceptions. This finding can be partially accounted for by historical events, as a result of the Portuguese emigration during the navigation era. However, in 2007 Martins et al. [12] studied the worldwide-spread mutational event in SCA type 3, and concluded that the worldwide-spread mutation may have first occurred in Asia, later extending to Europe, beginning in Portugal. A more recent SCA 3 lineage would be explained by later Portuguese emigration. Further haplotype studies could probably help to explain the high prevalence of SCA 3 in the Gosei area in Japan.

Another important piece of information from the study of Shibata-Hamaguchi et al. [10] is the high prevalence of MSA in Japan, which in this study was the second most common form of SCD. MSA is considered to be an adult-onset sporadic progressive neurodegenerative disease, and neuropathologically is termed as an alpha-synucleinopathy [13]. In MSA, a family history of ataxia or parkinsonism is defined as a non-supporting feature or 'red flag' for alternative diagnoses [13]. This subject has recently been put into question after Hara et al. [14] reported 4 multiplex families with typical MSA, findings suggestive of the presence of the familial form of MSA with autosomal-recessive inheritance. This is an interesting new thought about the molecular pathways leading to degeneration in MSA, and the findings of Shibata-Hamaguchi [10] could shed further light onto this issue.

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