Machado-Joseph disease in Brazil: from the first descriptions to the emergence as the most common spinocerebellar ataxia

Doença de Machado-Joseph no Brasil: das primeiras descrições até a emergência como a ataxia espinocerebelar mais comum

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ABSTRACT

Machado-Joseph disease is an autosomal dominant inherited disorder of Azorean ancestry firstly described in 1972. Since then, several Brazilian researchers have studied clinical and genetic issues related to the disease. Nowadays, Machado-Joseph disease is considered the most common spinocerebellar ataxia worldwide. Machado-Joseph disease still has no specific therapy to arrest progression, but the unclear pathophysiological mechanism, features related to genetic characteristics, phenotype variability, apparently global involvement of the nervous system in the disease and the therapeutic challenges continue to attract investigators in the field of spinocerebellar ataxias. Brazilian researchers have distinguished themselves in the ongoing investigation seeking new knowledge about Machado-Joseph disease.

Key words: Machado-Joseph disease, spinocerebellar ataxias.

RESUMO

A doença de Machado-Joseph é uma enfermidade autossômica dominante de origem açoriana primeiramente descrita em 1972. Desde então, vários pesquisadores brasileiros têm estudado as implicações clínicas e genéticas relacionadas com a doença. Atualmente, a doença de Machado-Joseph é considerada a ataxia espinocerebelar mais frequente em todo o mundo. Ainda não há terapia específica para interromper a progressão da doença de Machado-Joseph. Mas o mecanismo fisiopatológico complexo, as características relacionadas às questões genéticas, a variabilidade fenotípica, o envolvimento global do sistema nervoso e os desafios terapêuticos continuam a atrair investigadores no campo das ataxias espinocerebelares. Pesquisadores brasileiros têm se destacado na investigação e na busca de novos conhecimentos sobre a doença Machado-Joseph.

Palavras-Chave: doença de Machado-Joseph, ataxias espinocerebelares.

In 1972, two autosomal dominant diseases of Azorean ancestry in Massachussets were described. Progressive ataxia, nystagmus, dysarthria, distal muscle atrophy, brisk reflexes and ophthalmoplegia were common features of the so-called Machado disease[1,2]. Besides neurological signs described in the first report, extrapyramidal signs were also presented in the second report and started at variables ages, ranging from 17 to 46 year old[2]. In 1976, Joseph disease was described as a "new genetic entity" also in a family of Azorean ancestry in California with dystonia associated to the other previously reported signs[3]. Through autopsy studies in two other patients with phenotypic variability similar to the previous three reports, in 1977, Romanul et al. described a family in Massachussets as Azorean disease and suggested that the three reports described until then might all represent a single genetic entity with variable clinical expression[4].

In 1978, Coutinho and Andrade studied 40 patients in 15 families from the Portuguese Azores Islands, with autosomal dominant inheritance ataxia syndrome, associated to ophthalmoplegia, pyramidal signs, dystonia, rigidity, and distal atrophy as the major clinical findings. Evidence also suggested that this was a single genetic disease with variable clinical phenotypes[5]. In the ensuing years, apparently the same disease had been repeatedly described in other countries, in non-Azorean ancestry patients. In the late 1980's, the eponym "Machado-Joseph disease" (MJD) was recommended to honor the first and the largest families described until then.

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The first description of MJD in Brazil was carried out by Radvany et al. through the evaluation of two families[6]. In subsequent years, new reports of the disease from Brazilian authors began to emerge. In 1991, Teive et al. reported the clinical and laboratorial findings of five affected members of a family with MJD. In this article, the authors already pointed out parkinsonian features and peripheral nerve involvement in the disease[7]. In 1993, Radvany et al. reported the largest family tree described until now, from the state of Santa Catarina (therefore Catarina kindred), Brazil, and studied neuroimaging, psychiatric and neuropsychological findings. At that moment, the Catarina family tree contained 622 individuals, distributed in nine generations. Two hundred and thirty six persons were examined, and of these 37 were found by two examiners to have the disease[8].

An attempt was made to define the chromosomal abnormality of this family at the University of Montreal, but the identification of the gene defect on the long arm of chromosome 14 came from Japan in 1993[9]. In 1994, Kawaguchi et al. showed that an expansion of a CAG repeat at the MJD1 or ATXN3 gene was present in all affected individuals from the study of multiple small affected families along the south-north commercial road from the port of Niigata which had been used by the Portuguese[10]. Genetic testing then confirmed the presence of this genetic abnormality in the previous families diagnosed as MJD with or without known Portuguese ancestry.

Aiming to verify the proportion of Brazilian families with different mutations causing spinocerebellar ataxia (SCA), in 1997, Lopes-Cendes et al. investigated the frequency of SCA1, SCA2, MJD and DRPLA mutations in 328 Brazilian patients with SCA, belonging to 90 unrelated families with various patterns of inheritance and originating in different geographic regions of Brazil. The MJD mutation was the most common, and it was detected in 30% of all patients[11]. In the following year, Iughetti et al. evaluated 38 affected and 155 clinically normal individuals, and found that 68% of the SCA cases in this sample had an expanded trinucleotide repeat for MJD[12]. Nowadays, MJD is worldwide recognized as the most common autosomal dominant spinocerebellar ataxia.

Phenotypic variability had often been reported before genetic testing in several diseases and contributed to many family descriptions not classifiable today. However, the diagnosis of entire families known to be affected for many generations became suddenly available. The most notable case is the Drew family of Walworth, whose clinical profile comprised progressive ataxia, dysarthria, ophthalmoparesis, nystagmus, eyelid retraction, pyramidal signs and extrapyramidal manifestations. Members of Drew family lived in the 19th century and were extensively examined by renowned neurologists, such as Gowers, Collier, Turner, Ferguson and others. Finally, in 1995, Anita Harding found abnormal trinucleotide repeat expansion for MJD in members of the Drew family[13].

Since the first descriptions, MJD phenotypic variability is a central clinical issue. According to the age of onset and clinical manifestations, a division in five subtypes of MJD has been suggested. A correlation between disease duration, clinical subtypes and CAG has been demonstrated[14]. Some clinical data have demonstrated high incidence of non-motor symptoms in MJD, which include cognitive impairment, psychiatry disturbances, olfactory dysfunction and sleep disorders, besides cramps, fatigue and myalgia[15-18]. Moreover, sporadic case reports have demonstrated unusual motor symptoms in MJD, such as stiff person syndrome, camptocormia, restless legs syndrome and akathisia[19].

MJD still has no specific therapy to arrest progression, but the unclear pathophysiological mechanism, features related to genetic characteristics, phenotype variability, apparently global involvement of the nervous system in the disease and the therapeutic challenges continue to attract investigators in the field of spinocerebellar ataxias[20]. Brazilian researchers have distinguished themselves in the ongoing investigation seeking new knowledge about MJD.

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