DOI: 10.1590/0004-282X20130115

Wilson's disease

Doença de Wilson

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Conflict of interest
There is no conflict of interest to declare.

Received 12 July 2013

Accepted 19 July 2013

Progressive lenticular degeneration, or Wilson's disease (WD), even though being a rare condition, has major relevance in the field of movement disorders for it constitutes the first example of progressive neurologic deterioration caused by a toxic mechanism as a result of biochemical abnormality[1]. In 1912, the British neurologist S. A. Kinnier Wilson described the main clinical and pathological features of the disease that now bears his name. Clinical manifestations generally begin in the second or the third decade of life, but the onset may occur later in life. Liver involvement is always present, but often asymptomatic. Neurologic manifestations are found in approximately half of the cases, and clinical-pathological correlation relating movement abnormalities and basal ganglia involvement has long been established since Wilson's first description. Clinical features include movement disorders (dystonia, chorea, tremor), dysarthria and rigidity, among others. Clinical manifestations can be heterogeneous and often misleading, thus making WD a condition of paramount importance in the differential diagnosis of several conditions presenting movement disorders.

WD is inherited as an autosomal recessive disease and gene penetrance is virtually complete. Over the past two decades, linkage analysis studies have identified one single locus situated in chromosome 13 (13q.14.3), and a mutation in the ATP7B gene[2,3]. The protein product of this gene is a copper and membrane-bound ATPase and plays a key role in the transportation and distribution of copper in the hepatocytes, synthesis of ceruloplasmin and biliary excretion of copper. A defect in ATB7B results in progressive copper accumulation in the liver, central nervous system, kidneys and cornea. To the present day, more then 400 mutations in the ATP7B have been identified, but only a few have been found to be more prevalent and, importantly, variations have been observed according to ethnic background[4-6]. The study of frequency mutations is more challenging in countries with highly mixed populations, like the USA and Brazil.

The article by Bem, Raskin, Muzzilo et al. (Wilson's disease in Southern Brazil: genotype-phenotype correlation and description of two novel mutations in ATP7B gene) in this issue addresses the frequency of mutations in Southern Brazil in which a population of European ancestry predominates[7]. A total of 36 subjects with clinical diagnosis of WD were studied and followed-up at Clinical Hospital of the Federal University of Paraná, in Curitiba, Brazil. In 23 subjects, mutations in the ATP7B gene were studied. Fourteen distinct mutations were detected in at least one of the alleles in 23 out of the 36 WD patients. The c.3207C>A substitution at exon 14 was the most common mutation, with an allelic frequency of 37.1%, followed by the c.3402delC at exon 15, with an allelic frequency of 11.4%. These two different mutations account for 48.5% of the alleles studied, thereby indicating that these exons are important regions for detecting mutations in Southern Brazilian patients. The c.3207C>A is the most common mutation described in Europe and the c.3402delC is the most common mutation described for the general Brazilian population, with an allelic frequency of 30.8%. According to the authors, two mutations identified in this sample, c.2018-2030del13 at exon 7 and c.4093InsT at exon 20, are being reported for the first time. These two novel mutations might be pathogenic, as both of them result in a deviation in transcription and, thereafter, lead to a complete stop in the transcription with the consequent formation of a truncated protein.

As aforementioned, findings related to frequency of mutations in the ATP7B are subjected to variations among different regions and ethnic background. In a previous study, Deguti et al. found that the c.3402delC was the most common mutation, with an allelic frequency of 30.8%. The second most frequent mutation was the c.2123T>C, with an allelic frequency of 14.1%, whereas the c.3207C>A, the most common mutation found in the study by Bem et al., was absent in that population[7,8].

Testing for the ATP7B gene can be useful to augment clinical diagnosis of WD. Diagnosis of WD by gene markers can lack other diagnostic tools, and the early recognition at a presymptomatic stage is a goal to be achieved in order to allow early initiation of therapy before the occurrence of tissue damage. One limiting factor of genetic testing as a diagnostic tool is the massive diversity of mutations known to exist. Furthermore, analysis of mutation frequencies in countries like Brazil and others, characterized by highly inhomogeneous immigration pattern, is challenging. Thus, it is highly necessary that the regional distribution of mutation frequencies and correlation with different ethnic background be further enlightened, and the study published in the present issue provides a definite contribution to the subject.

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