

MACHADO-JOSEPH DISEASE: ESSAY OF DEFINITION (Abstract)*. Thesis. Porto, 1992.**PAULA COUTINHO****

A 15 years' experience with Machado-Joseph disease (MJD), including 144 Portuguese cases belonging to 47 large families, is reviewed. The statistical analysis of clinical data aimed at establishing the clinical pattern of the disease and its factors of variation, in terms of age of onset, years of evolution and age of the patient.

The following diagnostic criteria were defined: 1. Autosomal dominant mode of transmission. 2. Adult onset (mean: 40.2 years). 3. Association of cerebellar ataxia and progressive external ophthalmoplegia (PEO) in all patients, after 5 years of evolution. 4. Frequent pyramidal, extrapyramidal (dystonia) and peripheral (distal amyotrophies and weakness) signs depending on the age of onset: the first two in younger patients, the latter in older patients. 5. Minor but very suggestive signs, such as contraction fasciculations of the face and lid retraction. 6. Absence of mental deterioration. 7. Mean survival of 21.4 years.

The identity of the three modes of presentation previously defined was confirmed: type 1 has an earlier onset and a more severe evolution, with predominant extrapyramidal and pyramidal signs; type 3 has a later onset and predominant peripheral signs; type 2, in spite of an intermediate onset, has a more benign clinical picture, limited to the association of cerebellar ataxia and PEO. The causes of the extreme variation in the expression of the disease are discussed: modifier genes may be responsible for the modulation of the age of onset, the neurologic expression being explained by a selective vulnerability of target structures according to the age of the patient.

The neuropathological study of one possible homozygous case and a review of 17 postmortem reports led to the definition of the pathological pattern: 1. Involvement of the following structures: substantia nigra and subthalamic body, red nucleus, pontine and dentate nuclei, vestibular and motor cranial nerve nuclei, anterior horn cells, Clarke's columns and posterior root ganglia. 2. Sparing of the following structures: cerebral and cerebellar cortex, striatum, bulbar olives and corticospinal tracts. The involvement of globus pallidus and locus coeruleus is still controversial.

The nosological position of MJD is therefore defined as a multisystem degeneration, and the clinical and pathological differential diagnoses with olivopontocerebellar atrophy and dentatorubral-pallidolusian atrophy is established.

The geographic distribution of MJD - 224 affected families in mainland Portugal and the Azores, Azorean communities of North America, Brazil, India, China, Japan and Australia - suggests a Portuguese origin of the mutation. MJD might be, as familial amyloid neuropathy, a marker of Portuguese travels around the world since the 15th century.

The identification of a genetic marker for the disease, and the chromosomal mapping of the mutant gene will certainly be the next step in the understanding of MJD, and should rise new issues in its investigation.

KEY WORDS: Machado-Joseph disease, definition, genetics, diagnostic criteria, presentation modes, neuropathological findings, nosological position, geographic distribution.

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