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The Jalisco Mutation: Familiar Alzheimer's Disease in México

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Editorial

Before the age of 65, people with mutations in the genes for Presenilin 1 (PSEN1), Presenilin 2 (PSEN2), and the amyloid precursor protein (APP) experience familial Alzheimer's disease (FAD). The sporadic type of Alzheimer's disease (AD) is multifactorial and associated with the Apolipoprotein E ε4 allele (APOE ε4), which can up to 12 times increase the risk of getting the condition [1].

The PSEN1 gene has at least 253 documented mutations, making it the most frequently affected gene in FAD [2]. The Jalisco mutation (PSEN1, A431E) in people with Mexican ancestry is one of the most prevalent in FAD patients. PSEN1 and especially the A431E mutations lead to heterogeneity in the clinical profile of the individual carrier, who may also have other conditions such as parkinsonism, myoclonus, epileptic seizures, behavioral changes resembling frontotemporal dementia, aphasia, and cerebellar ataxia, as well as spastic paraparesis (SP), in addition to or instead of the "typical" symptoms of AD [2,3].

The types and numbers of mutations that cause FAD in carriers are still poorly understood.

Many individuals with early dementia, mostly from Jalisco, with an average age of 58.11 years, have the mutation that causes a substitution in the amino acid alanine for glutamic acid at position 431 in exon 12 of the PSEN1 gene. In 2001, Rogaeva et al. [4] made the discovery.

Years later, it was discovered that 9 of the 13 unrelated Mexican families with autosomal dominant early-onset AD contained the A431E mutation, indicating that the mutation may have a common ancestor. Thirteen members of these nine families had clinical AD diagnoses. Cortical and subcortical atrophy was seen in mutant carriers' brain images. The family tree (pedigree) examination revealed that the condition had subcortical atrophy and was transmitted in an autosomal dominant way through at least three generations. The analysis of two polymorphic satellites upstream of the gene PSEN1 revealed joint segregation, and haplotype analysis suggested that these individuals share a common ancestor, suggesting a founder effect [5]. Carriers of this mutation may share epigenetic mechanisms to maintain genomic stability and gene expression [6]. 20 additional patients from 15 families with the A431E mutation were found by Murrell and coworkers in 2006 [7]. 14 of the 15 families had Mexican mestizo ancestry and could be traced back to the state of Jalisco; interestingly, 9 of the 20 patients had SP, and after presented cognitive issues characterized by memory loss and, as reported by Ringman et al. [8], psychological changes especially depression. Of the 15 families, two were from Guadalajara, 12 were from Southern California, and one was from Chicago.

Amyloid beta peptide (βA) in plasma or cerebrospinal fluid (CSF) is a significant indicator of AD. There were no discernible changes between these individuals and control patients in terms of the amounts of 42 or 40 amino acids (βA_{42} and βA_{40}) in plasma or CSF [9]. However, the βA_{42}/ βA_{40} ratio was higher in patients with the mutation, indicating that the PSEN1 gene mutation (A431E) may affect where γ-secretase cleaves APP [10]. However, pre-symptomatic people had higher quantities of Tau protein, the other crucial protein in AD, and the hyperphosphorylated state of this protein.

When comparing men with SP caused by the A431E mutation to women who had different PSEN1 mutations (including

A431E) but did not exhibit SP, they found decreased extensive areas of white matter underlying the motor cortex. On the other hand, they discovered that microhemorrhages could be seen in all people with SP, although they did not detect any substantial changes in the volumes of brain structures. The sensorimotor cortex's βA-peptide deposits were determined to be unaffected, and the gray matter volumes were similarly unchanged. This implies that the motor deficits seen in these patients were caused by a variety of substrates, not simply the exclusive metabolism of APP and that the atrophy of the motor cortex's white matter may also be responsible [11].

Since they have identified the A431E mutation in nearly 75% (29/39) of the cases diagnosed with Early Onset Familial Dementia at the Centro Médico Nacional de Occidente-IMSS, Dr. Figuera's group [12] has made the most significant contribution to the identification of people carrying the mutation. Through genealogical research, they have identified 147 affected people, 304 relatives under the age of 48 who are thought to be at risk, and 233 patients' descendants who may be at risk. Although they do not specifically mention the clinical manifestations that mutation carriers exhibit, they report that this mutation results in variability in the presentation of symptoms as well as the absence of a pre-symptomatic diagnosis for adults at risk. This invites us to the clinical and molecular characterization of these patients given the implications of the diagnosis time. The average age at which symptoms first appear is 42.5 years, the disease takes 7.5 years to develop, and the average age of death is 48.9 years.

The only described case of a homozygous A431E mutation state appears to confer an anticipatory phenotype, with earlier clinical onset (28 years) and more rapid progression of neurodegeneration with the presence of atrophy disproportionate to age, chronic microhemorrhages within the bilateral occipital, temporal, and right frontal lobes, and pseudobulbar involvement. It should be noted that with a previously exceptional case, only heterozygous cases for this mutation had been reported [13].

In people with the A431E mutation who displayed atypical non-amnestic moderate cognitive impairment with visuospatial deficits, olfactory abnormalities, and considerable occipital-parietes brain atrophy, our research team has published the most detailed clinical characterization. High demyelination and mental symptoms are reported in other studies, and affected people frequently include SP in their clinical symptoms [11,14] as well as several periventricular white matter hyperintensities whose pattern of progression and location correlated with his motor impairment due to profound cortical atrophy [15], and lack of improvement with optimal medical treatment. A patient mutation carrier of 35-year-old was diagnosed with catatonia after presenting with mutism, lack of spontaneous movement, and refusal to eat [16]. A potential molecular basis for the disease's development has been proposed [15].

Alanine 431 is opposed to the β-strand of APP, a portion of a hybrid, three-stranded β-sheet necessary for cleavage, according to a study of the atomic structure of γ-secretase bound to an APP fragment using cryo-electron microscopy [19]. In mouse embryonic fibroblasts expressing A431E in a PSEN null background and transduced with human APP-C99, this variation was discovered to significantly raise toxic βA43 levels and decrease the A (37 + 38 + 40) / (42 + 43) ratio [17]. This ratio was reported to perform better than the βA42/ βA40 ratio as an indication of AD pathogenicity and linked with the age of AD onset based on investigations of various PSEN mutants. *In vitro* experiments using APP-C99 as a substrate showed that mutation increases the A42/A40 ratio while decreasing the synthesis of both A40 and A42 [18].

Beyond APP processing, the A431E mutation might also impact cellular processes. For instance, the increased monoamine oxidase-A (MAO-A) activity seen in hippocampus HT-22 cells expressing PSEN1 A431E suggests that it may change MAO-A activity [20]. This effect may contribute to the commonly observed depression in patients with the mutation. Additionally, A431E has been shown to cause oxidative stress, promote the production of mitochondria-associated endoplasmic reticulum membranes (MAMs), and impair mitochondrial function [21].

According to these results, the A431E mutation that causes FAD results in a divergent neurological illness that includes early glial and vascular pathological alterations, in which cognitive impairment is clinically outweighed by motor impairment. However, if some patients do not exhibit memory issues, we could say they have AD.

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