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Why does depression worsen progression and treatment response in the most frequent neurological disorders? Implications for clinical practice☆

¿Por qué la depresión empeora el curso y la respuesta al tratamiento en los trastornos neurológicos más frecuentes? Implicaciones en la práctica clínica

Dear Editor:

It was with great interest that we read the recently published study by Robles Bayón and Gude Sampedro[1] on the prevalence of behavioural and psychiatric symptoms, particularly anxiety and depression, in patients from a cognitive neurology clinic. Approximately one in every 2 to 3 patients with the most frequent neurological disorders presents depression at some point over the course of the disease.[2] However, numerous studies suggest that depression may also precede neurological disease and even affect its progression, including the response to pharmacological treatment.

In the case of epilepsy, 3 population studies have shown that patients with primary depression are 2 to 7 times more likely to develop epilepsy, and that those with epilepsy are 3 to 5 times more likely to develop depression.[3] Likewise, presenting depression (alone or combined with other psychiatric disorders) before epilepsy onset influences disease severity and treatment: patients with depression are twice as likely to develop drug-resistant epilepsy,[4] and are at greater risk of presenting seizures at one year[5]; they even show poorer response to surgical treatment for refractory temporal lobe epilepsy.[6]

High depression scores may be expected in patients with migraine, although an inverse correlation has also been observed. In a cohort study including nearly 1200 patients with migraine, patients with severe headache, and controls, presence of major depression during a 2-year follow-up period predicted the first-onset migraine (OR = 3.4; 95% CI, 1.4-8.7), but not other types of headache.[7]

Regarding cerebrovascular accidents, a meta-analysis of 28 prospective studies of a total of 320 000 individuals, including 8478 patients with stroke, showed that a history of depression was associated with increased risk of stroke (adjusted hazard ratio [HR] = 1.45; 95% CI, 1.29-1.63).[8]

A similar bidirectional relationship has also been observed in dementia. In a meta-analysis of 20 studies including approximately 100 000 individuals, 19 studies reported increased risk of Alzheimer disease among individuals with a history of depression; the risk also increased

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in patients with history of chronic depression.[9] However, depression is not simply a premonitory symptom of neurological disease; as with stroke, the association between depression and dementia has been linked to greater difficulties with the activities of daily living, more severe cognitive impairment, and earlier institutionalisation.[10]

History of depression also triples the risk of developing Parkinson's disease, according to a retrospective cohort study evaluating over 68 000 patients in the Netherlands.[11] Furthermore, presence of depression in patients diagnosed with Parkinson's disease has been associated with cognitive impairment at different levels and with poorer motor function.[12]

The trends discussed above suggest that neurological diseases may share a number of pathogenic mechanisms with mood disorders, which may present when several factors are met.

In the case of the association between depression and epilepsy, the hypothesis of a common pathogenic mechanism may be explained as follows: when a person with depression presents another pathogenic factor (e.g., head trauma or genetic predisposition), the epileptogenic process will encounter a damaged brain. This may explain why these patients are more likely to develop refractory epilepsy. Furthermore, studies in animals and in patients with epilepsy have shown a neurochemical link between both types of disorders. For example, patients with temporal lobe epilepsy and those with major depression have shown similarly reduced serotonin 5-HT_{1A} receptor binding in the hippocampus and other brain structures.[13] Another potential link between depression and epilepsy is the high concentration of glutamate seen in the plasma, CSF, and cerebral cortex of patients with depression; increased glutamatergic tone plays an essential role in the development of epileptic foci.[14]

Other studies suggest common neuropathological manifestations. In a 2010 study conducted in Brazil, which evaluated 48 patients with refractory mesial temporal lobe epilepsy, the 24 patients with concomitant depression showed more marked grey matter volume loss.[15]

Depression not only affects these patients' quality of life but can also modify the progression and severity of neurological disease. Neurological symptoms increase the risk of presenting psychiatric disorders, and the opposite may also occur.

The consequences of these findings are of great significance. If we do not screen for history of depression (the most frequent comorbidity) in patients with epilepsy, Parkinson's disease, or dementia, our evaluation would be incomplete and we would lack important data for choosing the most appropriate drug treatment. Certain antiepileptic drugs (levetiracetam, topiramate, vigabatrin, etc.) should be considered the third or fourth line of treatment in patients with depression; the same is true for Parkinson's disease. If we disregard the impact of history of depression on the progression of motor symptoms, how can we be certain that a lack of response is due to ineffectiveness of the drug?

In conclusion, depression may constitute an aspect of the neurological disease rather than an independent sign; its impact on patients' quality of life is such that it should become a treatment priority in neurological patients. However, the million-dollar question is whether effective management of depression can prevent or modify the progression of neurological disease. Although the available evidence suggests that it may, further research is needed. While we await more conclusive evidence, the psychiatric component of neurological disease should always be evaluated.

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A novel pathogenic variant of the *SPAST* gene in a Spanish family with hereditary spastic paraplegia☆

Nueva variante patogénica en el gen *SPAST* en una familia española afecta de paraplejía espástica hereditaria

Dear Editor:

Autosomal dominant hereditary spastic paraplegia (AD-HSP) is a group of neurodegenerative diseases of genetic origin that cause progressive spasticity and weakness in the lower limbs due to degeneration of the corticospinal tract.[1] Seventy-nine loci and more than 70 pathogenic variants causing HSP have been described.[2] Forty percent of all families with AD-HSP present pathogenic variants of the *SPAST* gene, located at 2p22.3. This gene, also known as *SPG4*, contains 17 exons and codes for the protein spastin. Spastin is an ATPase associated with several cellular activities, such as proteolysis, the cell cycle, vesicular transport, peroxisome biogenesis, and mitochondrial functions.[3]

More than 250 pathogenic variants of different types (deletions, insertions, and base substitutions) have been described in the *SPAST* gene, and the majority of families described show private mutations. Some of these variants seem to lead to certain peculiarities, such as earlier onset and greater severity in men, cognitive and bladder impairment, or late onset.

The clinical phenotype is indistinguishable between the different mutation mechanisms (nonsense, deletion, reordering, etc.), with haploinsufficiency being the molecular basis of this variant.[4]

When symptoms manifest during childhood, other diagnoses should be considered, including structural lesions, infections, and metabolic diseases. The pathogenic variants causing HSP of childhood onset occur most frequently in the *ATL1* (*SPG3A*) gene, followed by the *SPAST* gene.[5]

We present a new pathogenic variant of the *SPAST* gene in 3 members of a Spanish family with AD-HSP (Fig. 1).

Patient II:2 (the proband) is a 41-year-old woman presenting only hyperreflexia and mild spasticity in the lower limbs. Patient I:2 is the father of the index case, and started to develop symptoms at the age of 73, manifesting with progressive weakness and spasticity in the lower limbs, making him unable to walk independently for a period of 3 years. Brain and spinal neuroimaging, cerebrospinal fluid study, and microbiological studies (HIV, syphilis, and HTLV1) revealed no alterations. Finally, patient III:1 is a 4-year-old boy, the son of the index case, who presented patellar tendon hyperreflexia and toe-walking (with no Babinski sign or clonus), which improved with physiotherapy.

As we suspected the possibility of an HSP with a dominant inheritance pattern, we decided to perform sequencing of the *SPAST* gene. All 3 patients gave informed consent for blood samples to be taken for the genetic study. The 17 exons and adjacent regions of the *SPAST* gene were amplified by polymerase chain reaction and analysed using single-strand conformation polymorphism analysis by capillary electrophoresis. Sequencing identified a deletion of 4 nucleotides (c.1457_1460del:TGTC) in heterozygosis, causing the substitution of a threonine with an isoleucine and the appearance of a premature stop codon 43 amino acids later (Thr486Ilefs*43) (Fig. 1B). We identified this to be a new variant, classified as pathogenic according to the interpretation guidelines from the American College of Medical Genetics and Genomics,[6] as it causes a reading frame shift and codes for a truncated and dysfunctional spastin. This pathogenic variant has not been described in the literature or in the data bases consulted (Exome Aggregation Consortium, Single Nucleotide Polymorphism, and NHLBI Exome Sequencing Project).

In summary, we have identified a new pathogenic variant of the *SPAST* gene, c.1457_1460del (Thr486Ilefs*43), which is associated with AD-HSP. It is important to highlight, firstly, that while patients may present the same pathogenic variant, phenotype may be heterogeneous, and the absence of symptoms does not rule out the disease; therefore, it should be considered in genetic counselling. Secondly, we should mention the anticipation phenomenon observed in patients II:2 and III:1.

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