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Changes in butyrylcholinesterase activity in patients with Alzheimer disease treated with acetylcholinesterase inhibitors

Alteración de la actividad de la butirilcolinesterasa en pacientes con enfermedad de Alzheimer tratados con inhibidores de la acetylcolinesterasa

Dear Editor:

One of the therapies used to treat patients with Alzheimer disease (AD) is acetylcholinesterase inhibitors (AChEI), such as donepezil, galantamine, and rivastigmine.[1] These drugs act by incrementing cholinergic activity in the brain. When a person undergoes general anaesthesia, the effects of non-depolarizing muscle blockers such as atracurium are antagonized with neostigmine, an AChEI that does not cross the blood-brain barrier and that acts by increasing acetylcholine in the synaptic cleft of the muscle plate. Therefore, if that patient suffers from AD and is on treatment with another AChEI such as donepezil, he/she may exhibit a resistance to the action of this type of muscle blocker.[2,3] However, in addition, neostigmine acts by inhibiting the activity of plasma cholinesterase,[4,5] pseudocholinesterase, or butyrylcholinesterase (BuChE), which also hydrolyzes acetylcholine (even though not specifically used for this process). Likewise, BuChE is active for the hydrolysis of succinylcholine (a depolarizing muscle blocker) and scant or no activity of BuChE, whether due to a genetic or hepatic abnormality or secondary to drug therapy, may cause prolonged apnoea processes. Donepezil also prolongs the action of succinylcholine[6] by decreasing BuChE activity.[2] Rivastigmine[1,7] also reduces BuChE activity. AD is currently being treated with BuChE inhibitors (BuChEI), such as cymserine.[7]

After the case report in Article 2, we have observed another 10 patients with AD who did not suffer any genetic alterations or liver disease and who were being treated with an AChEI. BuChE activity was determined in both a routine pre-operative work-up, as well as after surgery under general anaesthesia during which the two types of muscle blocking agents were administered. The figures corresponding to BuChE activity were as follows: 1,416 U/L (this patient had been on therapy with galantamine for 10 months); 1,761 U/L (donepezil); 2,606 U/L (rivastigmine, 18 months); 2,767 U/L (donepezil, 2 years); 2,927 U/L (donepezil, 1 year); 4,023 U/L (donepezil, 5 years); 4,279 (rivastigmine); 6,064 U/L (donepezil, 4 months); 7,048 U/L (galantamine), and 8,215 U/L (donepezil) (normal BuChE values range from 3,500 to 8,500 U/L). Only two of the individuals had a prior BuChE determination; in one, the figure had fallen from 14,102 U/L 5 years earlier to 4,023 U/L, and in the other case, it had gone from 4,342 U/L 2 years previously down to 2,767 U/L. It is evident that not all patients had low values for this enzyme, despite treatment with AChEI.

Nevertheless, in the patients who presented low BuChE values after treatment with these drugs, the response to succinylcholine was prolonged; thus, the mean duration of muscle block after administration of this medication in the first five patients (BuChE < 3,500 U/L) was 10 minutes, whereas in the latter five (normal BuChE figures) it was 4 minutes. Moreover, at normal dosages of atracurium, they did not present adequate muscle relaxation and the dosage of the drug had to be raised. The mean dose of atracurium administered in the first five patients (BuChE < 3,500 U/L) was 52 mg and the mean dose in the other five (BuChE > 3,500 U/L) was 31 mg. Only those patients in whom BuChE figures were normal displayed adequate response to the two types of muscle blockers.

In a study conducted in rats, Ibebunjo et al.[8] observed that chronic treatment with an AChEI, such as tacrine, tended to decrease the effect of resistance to relaxation due to d-tubocurarine (a non-depolarizing blocker). Although it may not be possible to extrapolate this to humans, it might be one of the reasons why not all patients being treated with these drugs respond appropriately to muscle blockers.

Moreover, it is known that between 15% and 20% of the AD population do not metabolize AChEI normally;[9] half this group metabolize them very quickly and, hence require high treatment doses, whereas the other half are poor AChEI metabolizers and may suffer adverse effects even at low doses. We do not know if the slow AChEI metabolizers are the same ones that present altered BuChE activity and present an abnormal response to muscle blockers, nor what their treatment action and side effects are.

Given that the case series is small, it is not possible to draw any conclusions, but it is possible for the AChEI currently used for the treatment of AD to alter BuChE activity, although we do not know why this alteration appears in only some of the patients in our study and not in all of them. Despite these limitations, we believe that it is important to determine the activity of this enzyme not only in those people being treated with these drugs who are going to have surgery under general anaesthesia, but it would also be of interest to quantify it in AD patients during

the time that they are being treated with AChEI or even with BuChEI, since we presume that this simple test might be useful to reveal the possible association between the activity of this enzyme and the therapeutic effects and side effects of these drugs.

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Hyperinsulinism and hyperammonaemia syndrome and severe myoclonic epilepsy of infancy

Síndrome de hiperinsulinismo-hiperamoniemia y epilepsia mioclónica grave de la infancia

Dear Editor:

Hyperinsulinism-hyperammonaemia syndrome (HI-HA) is a rare cause of congenital hyperinsulinism.[1] The association of hypoglycaemia and hyperammonaemia in a neonate is highly suggestive of the disease. This syndrome is an inborn metabolic error caused by mutations in the GLUD1 gene, a gene that is located on chromosome 10q23.3 and that codes for the glutamate dehydrogenase (GDH) enzyme. The GLUD1 gene contains 13 exons which code for the 505 amino acids comprising GDH.[1] These mutations end up by causing hyperactivity of the GDH enzyme.[1,2] The mutations that cause HI-HA syndrome have been detected in exons 11 and 12, which code for the antenna region of the GDH enzyme, and in exons 6 and 7, which participate in coding for the binding site of GDH to guanosine triphosphate (GTP).[3,4] The mutations can occur de novo or in association with an autosomal dominant inheritance pattern.

The clinical picture in this condition is made up of recurrent symptomatic hypoglycaemias during childhood that are brought about by fasting or a high protein intake. The hyperammonaemia is typically moderate and, unlike disorders secondary to disturbances in the urea cycle, asymptomatic (that is, without episodes of lethargy, vomiting, or headaches).[5] HI-HA syndrome is associated with epilepsy,[6] characteristically a generalized epileptic syndrome consisting of atypical and myoclonic absences,[7] often accompanied by photosensitivity. It is not unusual for the epilepsy to be refractory to anti-epileptic medication. Moreover, the syndrome is completed with other neurological complications such as learning disorders, mental retardation, or dystonia.[6,8] We report here a new case of HI-HA syndrome due to a mutation of the GLUD1 gene. We would like to underscore the description of the phenotypical characteristics of the epileptic syndrome in our case with myoclonic absences triggered by hyperventilation, as well as to highlight the importance of recognizing this rare syndrome, so as to establish an accurate and early diagnosis that can avoid unnecessary studies.

Sixteen-year old female; among her family history of interest, we would point out a maternal cousin with epilepsy, not otherwise specified, and psychomadurational delay. In her personal history: she was born at term without complications, by scheduled Caesarean section due to podalic presentation, and with a birth weight of 3.200 kg; APGAR score of 9. At the age of one month, she was admitted to the ICU due to severe apnoeic episodes secondary to hypoglycaemias requiring prolonged hospitalization for proper control. What at the time constituted a comprehensive aetiological study was conducted, without arriving at any conclusive diagnosis, although the existence of hyperammonaemia was detected at that time and treatment was initiated to control the hypoglycaemia with diazoxide. At the age of 4 years, she debuted with myoclonic and absence seizures, reported as erratic, multifocal, axial shaking of the hands, eyelids, and limbs, associated or not with momentary alteration of consciousness, lasting for several seconds, and occurring spontaneously, both while awake and while sleeping, and clearly precipitated by photostimulation, and eating. At the age of 14, she