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. 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. These mutations end up by causing hyperactivity of the GDH enzyme. 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). 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). HI-HA syndrome is associated with epilepsy, characteristically a generalized epileptic syndrome consisting of atypical and myoclonic absences, 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. 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...
presented several generalized, tonic-clonic crises clustered over a few days. The seizures had been refractory to anti-epileptic medication during childhood and adolescence, despite the different pharmacological strategies used (CZP, CZP+LTG, CZP+LTG+ESM, CZP+VGB, CZP+VGB+LEV, CZP+LEV, CZP+LEV+LTG, LEV+LTG+CLB). VPA could not be prescribed due to the possibility of worsening the hyperammonaemia and the appearance of encephalopathy associated with it. From the age of 16 years onward, under treatment with the latest triple-therapy drug strategy of LEV+LTG+CLB, the patient's seizures are reasonably well controlled (without GTCS and very occasionally non-disabling myoclonias). From a cognitive point of view, she has developed borderline mental retardation, with learning difficulties that require extra classes, with social integration issues, low self-esteem, and affective instability. At a motor level, of interest is a slight gait dystaxia. Upon studying the complementary testing procedures carried out, the only finding of interest in the blood test is a persistent hyperammonaemia with mean values of around 170 micromol/L (range 20-57). On the waking EEG, the predominant finding is slightly slowed activity, together with frequent epileptiform abnormalities consisting of generalized point-poly point waves at 3.5-4 Hz, that are irregular and brief, lasting from 1 to 3 seconds. This pattern is recorded both spontaneously, as well as induced or facilitated by hyperventilation and photostimulation manoeuvres with a generalized photoparoxysmal response. This firing occasionally coincides with palpebral or massive myoclonic activity, that apparently does not affect consciousness (figs. 1 and 2). Cranial NMRI did not reveal any alterations of note.

When re-evaluating the case in the light of the clinical suspicion of HI-HA syndrome, a molecular study of the GLUD1 gene was recently conducted and a mutation detected in exon 11 (p.Ser498Leu), diagnostic for the disease. A genetic study was later performed on the parents that was negative; it is, hence, a de novo mutation. Our case, therefore, corresponds to a HI-HA syndrome due to mutation in exon 11 of the GLUD1 gene. HI-HA syndrome due to mutation of the GLUD1 gene is a rare cause of congenital hyperinsulinism characterized by recurrent hypoglycaemic episodes during childhood and hyperammonaemia. In most cases, the illness debuts during the first year of life as either a symptomatic convulsive seizure due to hypoglycaemia or a hypotonic infant. It can take up to a mean of 12 months to control the hypoglycaemias and the diagnosis make take as long as 5 years to establish.
LETTERS TO THE EDITOR

The treatment of choice for the hypoglycaemias is diazoxide and protein restriction. Diazoxide acts by keeping the ATP-dependent K+ channels from closing, hindering depolarization of the beta cells and with that, the release of insulin. Our patient began during the neonatal period with apnoic crises secondary to severe hypoglycaemias and has been treated since then with diazoxide; she required hospitalization for a period of several months to control her symptoms. The pathophysiological mechanism provoking hyperinsulinism and hyperammonaemia has been described. GDH is an enzyme that mediates the reversible action of glutamate to alpha-ketoglutarate in the interior of the mitochondrial matrix. This action is positively regulated by adenosine diphosphate (ADP) and leucine and negatively by guanosine triphosphate (GTP). In HI-HA syndrome, there would be increased GDH enzymatic activity due to interference with the inhibitory effect of GTP, thereby increasing the production of alpha-ketoglutarate, which would increase the production of adenosine triphosphate (ATP) through the Krebs cycle. Increase in the ATP/ADP ratio would provoke increased release of insulin. On the other hand, in the liver, the increase in the activity of GDH would increment net production of ammonium. GDH is a hexamer consisting of 6 identical subunits comprising 3 domains. In patients with HI-HA syndrome, there would be a mixture of heterohexamers that would contain an equal number of mutant and normal subunits. The most common mutations are located in exons 11 and 12. In our patient, the mutation is located in exon 11. Mutations in exons 6 and 7 have also been reported and there have been odd reports of mutations in exon 10. Some authors estimate that mutations in exons 6 and 7, which encode for the GDH to GTP binding site, are associated more often with epilepsy. In the short HI-HA syndrome case series published, this syndrome (as well as symptomatic hypoglycaemias in neonates) have been proven to be accompanied in large part by neurological manifestations, highlighting in particular the existence of epilepsy in 46-64% of the cases, mental retardation, and learning disorders (51-77%, depending on the series), whereas other manifestations such as pyramidalism, ataxia, or dystonia are less frequent. The classical epileptic phenotype reported is that of epilepsy that debuts months after the onset of illness, during the first few years of life (although there have been reports of onset at up to 12 years of age). The epileptic seizures consist of atypical absences and palpebral and generalized myoclonic seizures, although other types of crisis may also present, in the form of either

Figure 2 Waking EEG. Superficial electrodes. International 10-20 System. Sensitivity: 30 microvolt/mm. Paper speed: 1 page/10 seconds. High frequency cut-off: 50 Hz. Low frequency cut-off: 0.53 Hz. Monopolar montage referenced at Cz. Brief, multispired firing and slow hypervolted waves are seen during hyperventilation, on top of a slightly slowed baseline activity that coincides with a clinical seizure consisting of a disconnect from her surroundings and palpebral and perioral myoclonia.
given the possibility of provoking insulin resistance and worsening the ammonaemia.

The course of illness in our patient has been typical, if such can be said, of HI-HA syndrome. She has developed a predominantly myoclonic form of epilepsy, with absences as well. The seizures characteristically present as palpebral, perioral myoclonic seizures, either massive or generalized, that appear spontaneously, though they can also be triggered by hyperventilation and photostimulation. As a unique datum found in our case, together with the photoparoxysmal response, she presents myoclonic activation with hyperventilation, a finding more rarely reported in the literature consulted. During childhood, the crises were seen to be precipitated by eating, a circumstance that we have been unable to observe at present. The epilepsy she developed during childhood and adolescence was resistant to treatment with anti-epileptic medication, despite the various different regimes tried with drugs at optimal, efficacious doses, for both the absences, as well as the myoclonic seizures; subsequently, from 15-16 years of age, she has displayed an improvement in seizure control, although she currently requires triple therapy. We believe that this improvement has to do with the natural course of the illness (more severe during childhood, tending toward stabilization during youth and adulthood), more than to any specific or appropriate anti-epileptic therapy in particular. Likewise, it is worth noting that the patient is able to maintain adequate control of her myoclonic crises, despite the use of LTG, which could theoretically have made myoclonic activity worse; indeed, when an attempt was made to withdraw the drug, she suffered a worsening of this type of seizure. In recent years, new AEDs have come on board for (zonisamide, rufinamide) that may be of use in this type of seizure. In recent years, new AEDs have come on board for (zonisamide, rufinamide) that may be of use in this type of seizure.

On the other hand, no association has been conclusively proven to exist between the levels of hyperammonaemia/ hypoglycaemia and neurological impairment or epilepsy. The pathophysiological mechanism of the brain damage associated to HI-HA syndrome is not well known and may possibly be complex and multifactorial. It does not appear to be due to a direct injury of the hypoglycaemia itself. Were that the case, we would expect to find focal deficits or epilepsy with predominantly focal crises. The normal cranial NMRI, without any focal lesions, supports this observation. It appears that the hyperammonaemia does not play any major role either. In short, why the epilepsy occurs is unclear, although some authors postulate that mutation of the GDH gene in the congenital hyperinsulinism-hyperammonaemia syndrome: a synopsis. Mol Gene Metab. 2005;84:101-3.


References


Servicio de Neurología, Hospital Universitario Virgen de la Victoria, Málaga, Spain

* Corresponding author.
E-mail: pacoerrazquin@hotmail.com (F. Pérez Errazquin).