Paroxysmal awakenings and seizures in congenital hyperinsulinism: a late diagnosis

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Abstract

We describe the case of a 16-month-old girl with congenital hyperinsulinism diagnosed at the age of 11 months, after a history of a single convulsive seizure at 4 months of age, followed by frequent unexplained paroxysmal events related to sleep. The diagnosis was made when a second convulsive seizure occurred and a severe hypoglycemia was detected. Since the treatment with diazoxide was started, both seizures and sleep disorder disappeared. This case support the recommendations of the literature to consider a congenital hyperinsulinism even in cases of infantile convulsions apparently “benign” and/or in the evaluation of atypical motor or behavioral paroxysmal manifestations of uncertain origin; in this field, the correlation of hypoglycemia with sleep is a current topic of discussion and remains to be clarified.

KEY WORDS: hyperinsulinism, seizures, sleep, paroxysmal awakenings.

Introduction

Congenital hyperinsulinism (CHI) comprises a group of different genetic disorders with the common finding of recurrent episodes of hyperinsulinemic hypoglycemias due to an inappropriate secretion of insulin by the pancreatic β-cells (1). Despite recent advances, the genetic basis of CHI is still unknown in about 50% of patients. To date, the molecular basis of congenital CHI involves defects in nine key genes (ABCC8, KCNJ11, GLUD1, GCK, HADH, SLC16A1, HNF4A, HNF1A and UCP2), the products of which are involved in regulating insulin secretion (3-13). CHI is considered to be the most frequent cause of persistent recurrent hypoglycemia in newborns and infants (1, 2).

Hypoglycaemic seizures during the neonatal period are the main presentation of CHI and are usually recognized. However, a misdiagnosis of epilepsy can be made in cases of seizures appearing later so delaying the recognition and the management of recurrent hypoglycemias which can cause complications and irreversible secondary brain damage (3-5).

Clinical case

This girl came to our attention at the age of 11 months for the diagnostic interpretation of paroxysmal events during sleep associated with interictal EEG abnormalities. She was born from an uneventful pregnancy, the perinatal period was normal, the developmental milestones were adequate for age. A first non febrile seizure had occurred during sleep at the age of 4 months. A mild (74 mg/dL) hypoglycemia was observed after episode and attributed to fasting. The neurological examination and MRI were normal. The EEG showed interictal paroxysmal sequences of bilateral synchronous diffuse irregular slow waves. The girl was dismissed from the hospital with the prescription of endorectal diazepam to stop seizures.

In the following months “strange” paroxysmal episodes appeared, initially occurring every 10-15 days, then many times in a week. They occurred only in the afternoon sleep, at a set time (between 11 a.m. and 2 p.m.). The episodes began with awakening, the child cried “like for a colicky pain”, with eyes wide open, sometimes looking down; muscle tone didn’t change, sometimes drooling and a flushing face were described. She appeared uncomfortable, therefore her mother stopped episodes lasting more than 3-5 minutes with endorectal diazepam, in the hypothesis of seizures.

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Both episodes were recorded with a video EEG (Video 1-2). The differential diagnosis between seizures and parasomnias was initially kept due to the atypical pre-
presentation of the episodes and the lack of a clear correlation with the EEG paroxysmal activity. During a second video EEG, the girl had a seizure with focal motor signs which rapidly generalized (Video 3). The first-level metabolic investigation showed a severe hypoglycemia (28 mg/dl). Subsequent investigations lead to the diagnosis of congenital hyperinsulinism (absence of urinary ketones, normal ammonia, profile of acylcarnitines, plasma amino acids and lactic acid, high insulin level). The genetic investigation was normal (the main genes were analyzed: ABCC8, KCNJ11, GLUD1, HNF4A, GCK, HADH).

A treatment with diazoxide was started, with blood glucose normalization, seizure control and normalization of EEG; the episodes during sleep disappeared. At the control of 16 months of age the psychomotor development progressed normally and the EEG was normal.

Discussion

Typical presentation of CHI are neonatal seizures occurring during hypoglycemia and this usually leads to prompt diagnosis. When treatment resolves both hypoglycemia and seizures, CHI has a favorable evolution but in other conditions the disorder can evolve toward more complex situations. In infancy, seizures can even show specific electro-clinical features fitting with epileptic syndromes such as West syndrome and infantile spasms not always associated with neuroradiological evidence of brain damage (6).

Atypical presentations of CHI are neurologic and psychiatric symptoms appearing with varying latency during life. When paroxysmal episodes appear in a child with a regular psychomotor development, a diagnosis of an idiopathic form of epilepsy can be erroneously made. Yoshikawa et al. reported the case of a persistent hyperinsulinemic hypoglycemia interpreted as benign infantile convulsion. The Author described an 18-month-old boy with a normal psychomotor development and a normal EEG who developed seizures at 3 months of age. At that time, the exams showed a normal blood sugar level and the diagnosis of benign infantile convolution was made. When seizures reappeared at 7 months of age hypoglycemia associated with hyperinsulinism was disclosed (7).

The possibility of misdiagnosis of critical events during hypoglycemia is well known and described in cases of insulinoma, a pathology of adults rarely described in children. One study documented that 64% of patients with insulinomas were diagnosed as having neurologic disorders, with 12% being treated with anticonvulsant drugs (8). Less than 30 cases of insulinoma at young age have been published, and this rarity makes a timely and accurate diagnosis even more difficult (9). Vague and insidious symptoms like faintness, myalgias, paraesthesias, unexplained irritability, decrease in school performance, the combination of seizures and episodic confusional states, seizures unresponsive to anticonvulsant treatment are described. The literature underlines the importance of fatigue and fasting. In particular, early morning behavioural changes are emphasized (10). The juvenile age and the time locked appearance of symptoms, in particular of early morning seizures, can be elements relevant for the diagnostic classification of a specific well known epileptic syndrome. In the two cases described in the literature, myoclonic and generalized seizures occurring early in the morning were diagnosed as juvenile myoclonic epilepsy; the refractoriness of the seizures and other signs of neuroglycopenia lead to discover severe hypoglycemias and an insulinoma (11, 12).

Suzuki et al. describe abnormal nocturnal and early morning behavior interpreted as Rapid Eye Movement Sleep Behavior Disorder in three adult cases (13).
Complex mechanisms by which sleep may affect glucose regulation and hypoglycemia may interfere with sleep are interesting topics still debated in the literature (14). In our case, episodes appeared only during a paroxysmal awakening, particularly during postprandial naps. It can be hypothesized that after a particularly high carbohydrate containing lunch, a hyperinsulinemic response occurred provoking paroxysmal non epileptic episodes and rare epileptic seizures. EEG interictal changes are consistent with the diagnosis, considering that hypoglycemia can activate both slow activities and epileptiform abnormalities (15).

The diagnosis was initially difficult due to the atypical presentation of the episodes, the absence of signs usually associated with hypoglycemia (paleness, tremors, sweating) and the lack of a clear correlation with the EEG paroxysmal activity. In conclusion, the literature recommends to consider hyperinsulinism in all patients with vague and insidious symptoms, “funny turns”, atypical neurological signs, complex behavioral manifestation, seizures associated with deterioration of school performances and behavior not responding to standard anticonvulsant treatment.

A red flag is considered a low/normal blood glucose levels at the time of event. Taking a full history and clinical attention are essential to recognize a treatable disorder and prevent neurological sequelae.

References


Video 1-2 - Video EEG sequences of paroxysmal events occurring during sleep in a 11-month girl with normal psychomotor development and previous convulsive seizure at 4 month of age. The episodes occurred only in the afternoon sleep, at a set time (between 11 a.m. and 2 p.m.), initially every 10-15 days, then many times a week. In the two videos the episodes begin with awakening, the child crying and appearing uncomfortable; the child is seated, presenting several episodes of rolling or dropping head. The EEG is rich of movement artifacts and shows diffuse slow activities, sometimes presenting in sequences of diffuse slow waves not specifically correlated with head movements. The record was considered insufficient for a definite diagnosis and video EEG recording was requested.

(EEG, ECG = EKG, PNG, EMG 1 = left deltoid muscle, EMG 2 = right deltoid muscle).

Video 3 - Video EEG recorded the day after showed a seizure with focal motor signs and rapid diffusion. The discoloring of a severe hypoglycemia lead to the diagnosis of congenital hyperinsulinism (EEG, EKG, PNG, EMG 1 = left deltoid muscle, EMG 2 = right deltoid muscle).