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INTERACTIVE CASE

Two patients of different age groups presented convulsions. What is the diagnosis? Part I

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A female patient aged 2 months

A history of seizures in the neonatal period. The patient was hospitalized in the intensive care unit (ICU) for 27 days and had two episodes of urinary tract infection and sepsis. Three days after hospital discharge, the patient was re-admitted to the ICU because of drowsiness and remained hospitalized for 32 days.

The mother had a history of three pregnancies and three births. Prenatal care was performed with eight visits to the Family Clinic, starting the first month of gestation. Maternal serology was negative (SIC). Urinary tract infection reported in the second trimester, and preeclampsia occurred in the last month of gestation. The patient did not smoke and drink alcohol during the gestational period.

The child was born of cesarean at term (40 weeks). APGAR 9/10, with a weight at birth of 3,330 g, length of 47 cm, and head circumference of 34 cm.

1- What are the major metabolic disorders responsible for neonatal seizures?

- A) Hypomagnesemia and hypocalcemia
- B) Hyponatremia and hypoglycemia
- C) Hypernatremia and hypomagnesemia
- D) Hypernatremia and pyridoxine deficiency
- E) Hypoglycemia and hypocalcemia

- In the child, convulsions are more common in the neonatal period.

- Neonatal seizures may have subtle manifestations, such as apnea, sustained gaze deviation, masticatory movements, and pedal movements¹.
- Focal clonic movements are often associated with the underlying structural lesion¹.
- Most cases of neonatal seizures are caused by hypoxic-ischemic encephalopathy, intracranial infections, cerebral congenital malformations, cardiovascular events, and metabolic disorders, particularly hypoglycemia and hypocalcemia¹.
- Other metabolic causes of neonatal seizures are hypomagnesemia and pyridoxine deficiency. Inborn metabolism errors are rare causes. Early diagnosis and treatment is critical to saving lives and improving prognosis¹.

2- What clinical conditions are associated with hypoglycemia?

- A) Severe diarrhea
- B) Sepsis
- C) Malaria
- D) Whooping cough
- E) All the above answers

- Hypoglycemia may occur in infants and children with severe diarrhea. It is rare in previously healthy patients with viral gastroenteritis, except after a period of intense fasting. Hypoglycemia is a risk factor in severely malnourished patients with severe diarrhea,

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including diarrhea caused by cholera or *Shigella* outbreaks.

- In severe malnutrition, hypoglycemia is due to the following conditions:
- Significant reduction of gluconeogenesis substrates such as alanine and lactate
- Decreased glucose production capacity from gluconeogenesis
- Reduced levels of alternative energy sources such as ketones and lactate.
- Hypoglycemia may be a symptom of sepsis, especially in meningococemia. Experimental studies suggest that hyperglycemia occurs in the initial stage of sepsis, followed by hypoglycemia, due to the increased uptake of glucose by multiple organs; in addition, this uptake may be amplified by cytokines such as tumor necrosis factor.
- Hypoglycemia may be associated with severe malaria in approximately 1/3 of children and these cases lead to higher mortality. Insulin levels are reduced whereas the levels of substrates such as ketones, lactate, and alanine are increased, suggesting deficient gluconeogenesis. In addition, antimalarial drugs, especially quinine, may aggravate hypoglycemia due to these drugs' ability to stimulate insulin release².
- Hypoglycemia is common in cases of whooping cough. Evidence from animal studies suggests that hypoglycemia in these cases is caused by hyperinsulinemia and not simply by fasting. Although some studies reported that insulin levels are increased after vaccination, no cases of post-immunization hypoglycemia have been documented Endocrine Diseases in Children and Adolescents section III².

At the time of admission, the mother reported that the infant had at least two episodes per day of hypoglycemia (HGT ranging from 21 mg/dL to 52 mg/dL) for at least one week, and this condition improved after the use of corticosteroids (sic) and feeding (infant formula), the levels reaching 90-135 mg/dL. These episodes became more frequent during the week of admission. She also reported that the infant had no symptoms of hypoglycemia. Glucose levels were checked every 6 hours. The infant had difficulty sucking and was, therefore, fed with a bottle (sic). Blood glucose was measured upon admission to the hospital, and the level was 92 mg/dL.

H. Development: The results of the Guthrie test were unremarkable; auditory screening and eye test were not conducted. The infant was able to smile and sustain the head at age 2 months. The infant presented difficulty in sucking and had a motor deficit in the left hand.

H. Vaccination: The mother had the child's vaccination history. The last consultation occurred 24 days before admission to our hospital and her vaccination status was up to date.

H. Diet: Mixed breastfeeding until the first month of life and exclusive infant formula after that. At present, the child receives 80 mL of Nestogeno I every 2 hours.

H. Family: Parents and two siblings are healthy. Maternal grandmother has diabetes.

H. Social: The child lives with the mother, father, and two brothers in a rented house, with running water and basic sanitation. Quiet family atmosphere. The 35-year-old mother is a homemaker and completed the first year of high school. The 38-year-old father is a painter and completed the eighth year of elementary school.

Physical examination at admission

Anthropometry: Weight of 5,200 g (score Z0), length of 63.5 cm (score Z3), head circumference of 37 cm (score Z-1).

Vital signs: Temperature at 36°C, heart rate of 128 bpm, respiratory rate of 44 incursions per minute, blood pressure was not measured, SatO₂ of 99%.

Ectoscopy: Cushingoid facies, increased facial vascularization, and the presence of rib hump deformity.

Head and neck: Normotensive anterior fontanelle measuring 2 × 2 cm.

Normal cardiac and respiratory auscultation.

Abdomen: Absence of visceromegaly.

Genitalia: Typical of the female sex without abnormalities.

The lymphatic system and locomotor system were unremarkable. The patient presented a scar caused by an incision in right upper limb.

Nervous system and psychological conditions: The infant was attentive to the environment, and her movements were active. She was capable of sustaining the head. Palmar grasp, plantar grasp, and moro reflexes were present. Sucking was weak.

Laboratory tests

| Parameter | 27/01/2015 | 10/02/2015 | Valor de Referência |
|-------------|----------------------|-----------------------|--|
| Blood Cells | 2.88x10 ⁶ | 3.21x 10 ⁶ | 3.50-5.10 x 10 ⁶ /mm ³ |
| Hemoglobin | 9.6g/dl | 10.4g/dl | 9.5-12.5 (g/dl) |
| Hematocrit | 27 | 29.1 | 32-44 (%) |
| Glucose | 28mg/dl | 50mg/dl | 70-99 mg/dl |
| Peptide C | 5.34 | 6.12 | 1.10-4.40 |
| Insulin | 11.1 | 10.2 | 1.9-23.0 |
| Cortisol | 0.4 | 7.5 | 6.7-22.6 |
| Ammonia | - | 48 | 16-53 |
| Lactic acid | 42.1 | 10 | 4.5-19.8 |

Normal urinary sediments

On the night of admission, the infant presented difficulty accepting the diet and HGT was 38 mg/dL, a nasojunal tube was used to maintain adequate nutrition.

Complementary tests were requested for differential diagnosis

Ammonia, lactic acid, galactose-1, uridil transferase phosphate;

T4L and TSH

Growth hormone, cortisol, reducing substances in urine, glycemia, insulin, venous gasometry, glucagon;

Endocrinology, gastroenterology, speech-language, and neurology examinations were also requested.

Transfontanelle ultrasound and abdominal examinations were unremarkable.

Echocardiogram was unremarkable

3- The onset of most cases of hyperinsulinemic hypoglycemia (HH) occurs:

- A) In the neonatal period
- B) In newborns
- C) In preschool children
- D) In school children
- E) In adolescents

- In adults, hyperinsulinemic hypoglycemia is often an acquired disorder due to insulinoma whereas it is usually caused by congenital hyperinsulinism in children. Hyperinsulinism may be transient or persistent/recurrent³.
- Transient hyperinsulinemic hypoglycemia usually resolves spontaneously in days or months. It is often secondary to maternal diabetes mellitus, intrauterine growth retardation, perinatal asphyxia, or maternal use of drugs such as sulfonylureas and intravenous glucose infusion during labor⁴.
- Congenital hyperinsulinism (CI), formerly known as idiopathic hypoglycemia of the infant and nesidioblastosis, is the most frequent cause of persistent hypoglycemia in children. The disease is rare, with an estimated incidence of 1/50,000 live births in the United States, and a higher incidence in countries in which consanguineous marriage is common. Mutations in 11 different genes may cause CI^{3,5-7}.
- Most cases of CI occur in the neonatal period and 60% of cases have manifestations in the first week of life. This complication may occur later in infants and children but is rare in adolescents and adults⁵.
- 4- Hyperinsulinemic hypoglycemia may be associated with syndromes, including:

- A) Sotos syndrome
- B) Kabuki syndrome
- C) Beckwith-Wiedemann syndrome
- D) Turner syndrome
- E) Leprechaunism

- Congenital hyperinsulinism may be associated with various growth-affecting syndromes, including Beckwith-Wiedemann syndrome (BWS), Sotos syndrome, Simpson-Golabi-Behmel syndrome, Costello syndrome, chromosome 13 trisomy, Turner mosaic syndrome, leprechaunism, congenital central hypoventilation syndrome (Ondina syndrome), and congenital glycosylation disorders.
- The most frequent complication is Beckwith-Wiedemann syndrome, which is characterized by macroglossia, omphalocele, visceromegaly, ear lobe abnormalities, and late propensity to malignancies⁸.
- Hyperinsulinemic hypoglycemia occurs in approximately 50% of patients with BWS. The condition is mild and transitory in most cases but can be severe and persistent in approximately 5% of cases^{6,7}.

5- The symptoms of hyperinsulinemic hypoglycemia occur more often:

- A) After vigorous exercise or intense crying
- B) After protein-rich meals
- C) After leucine-rich meals
- D) In the postprandial period
- E) After a period of fasting

- The symptoms usually manifest after a fasting period or when the child is not well.
- In patients with hyperinsulinism syndrome associated with hyperammonemia, the symptoms are triggered by meals rich in proteins, especially leucine. These patients have dominant mutations in the GLUD1 gene, which encodes the mitochondrial enzyme glutamate dehydrogenase. The increased activity of this enzyme induces excessive production of insulin and ammonia.
- Hypoglycemia is triggered by intense exercise in some children. This form of hyperinsulinism is due to a mutation in the SLC16A1 gene encoding the transporter protein involved in the transportation of pyruvate and lactate into β -pancreatic cells. Vigorous exercise causes the accumulation of lactate and pyruvate and increases insulin production.

- Postprandial hypoglycemia (PPH) is a clinical condition that occurs a few hours after a meal and that is caused by inappropriate insulin secretion. The dumping syndrome is an example of PPH observed in children after Nissen fundoplication or gastric bypass. In patients subjected to Nissen fundoplication, the excessive secretion of glucagon-like peptide stimulates insulin hypersecretion. PPH may also be caused by an autoimmune condition in which anti-insulin autoantibodies are found in children who have never used insulin and in patients with leprechaunism (mutations in the insulin receptor gene)⁴.

6- Diazoxide is used as a therapeutic test and assists in the diagnosis in cases of hypoglycemia. The lack of response to this drug increases the suspicion of changes in:

- A) Calcium channels
 - B) Sodium channels
 - C) Magnesium channels
 - D) Potassium channels
 - E) Insulin receptors
- Diazoxide at a dose of 5-15-20 mg/Kg/day is administered for therapeutic and diagnostic purposes. The patient is considered nonresponsive in cases in which, after 5 days at maximum dose, she continues to require venous administration of glucose or fails to maintain normal blood glucose during the adequate feeding period or the overnight fasting period. The absence of response reinforces the suspicion of abnormalities in the ATP-dependent potassium channels (K⁺ATP)⁶.
 - Depolarization of the plasma membrane occurs when the K⁺ATP channels are closed, leading to

insulin secretion. As a K⁺ATP agonist, diazoxide promotes the opening of these channels and causes hyperglycemia, which is a well-known side effect of this drug. Therefore, the absence of response to diazoxide increases the suspicion of abnormalities in these channels⁶.

- Eleven mutations are associated with abnormalities in potassium channels but the two primary mutations are ABCC8 and KCNJ11.

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