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Singularities of the Endocrine Causes of Hypoglycemia in the Pediatric Age

Singularidades de las causas endocrinas de hipoglucemia en la edad pediátrica

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Abstract

Introduction. Investigating endocrine causes of hypoglycemia may be challenging, especially in the first year of life, due to poorly defined cut-off points.

Objective. To detect clinical and biochemical patterns of presentation of endocrine causes of hypoglycemia in the pediatric age.

Methods. Retrospective analysis of patients evaluated in pediatric endocrinology visits, due to hypoglycemia, focusing on those with an identified endocrine cause.

Results. Sample composed of 55 patients, 37 (67.3%) male, 27 (49.1%) with a documented endocrine cause. Hyperinsulinism was found in 19 cases and presented mainly in the neonatal period (n=17), with 9 cases of transient and 8 of persistent hyperinsulinism. Transient hyperinsulinism was associated with lower weight and length at birth, and a higher frequency of small for gestational age (SGA) (p=0.018, 0.041 and 0.029, respectively). The two remaining cases of hyperinsulinism presented at 12 months and 16 years of age. Underlying genetic mutations were identified in 6 hyperinsulinism patients. Deficiency of counterregulatory hormones was diagnosed in 8 patients, 3 with isolated central adrenal insufficiency and 5 with panhypopituitarism. All presented in the first months of life, and 2 out of 6 with Magnetic resonance imaging (MRI) results available had no visible hypothalamic-pituitary abnormalities.

Discussion. Endocrine causes of hypoglycemia tend to present early in life. Hyperinsulinism is the most common endocrine cause and frequently presents in the neonatal period. Lower weight and length at birth and SGA seem to be associated with early resolution. A high rate of suspicion is required for the diagnosis of pituitary insufficiency since it may coexist with an unremarkable MRI.

Key Words: Hypoglycemia, Hyperinsulinism, Hypopituitarism, Endocrine System Diseases

Resumen

Introducción. La investigación de las causas endocrinas de hipoglucemia puede ser un desafío, especialmente en el primer año de vida, debido a los puntos de corte mal definidos.

Objetivo. Detectar patrones clínicos y bioquímicos de presentación de causas endocrinas de hipoglucemia en edad pediátrica.

Métodos. Análisis retrospectivo de pacientes evaluados en consulta de endocrinología pediátrica

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por hipoglucemia, enfocando aquellos con una causa endocrina identificada.

Resultados. Muestra compuesta por 55 pacientes, 37 (67,3%) varones, 25 (45,4%) con causa endocrina documentada. Se detectó hiperinsulinismo en 19 casos, la mayoría en el periodo neonatal (n=17), 9 de los cuales con hiperinsulinismo transitorio y 8 con hiperinsulinismo persistente. El hiperinsulinismo transitorio se asoció a menor peso y longitud al nacer y mayor frecuencia de pequeños para la edad gestacional (PEG) (p = 0,018, 0,041 y 0,029 respectivamente). Los dos casos restantes de hiperinsulinismo se presentaron a los 12 meses y a los 16 años de edad. Se identificaron mutaciones genéticas en 6 pacientes con hiperinsulinismo.

Se diagnosticó deficiencia de hormonas contrarreguladoras en 8 pacientes, 3 con insuficiencia suprarrenal central aislada y 5 con panhipopituitarismo. Todos debutaron en los primeros meses de vida, y 2 de los 6 con resultados de resonancia magnética disponibles no demostraron anomalías hipotalámico-hipofisarias visibles.

Discusión. Las causas endocrinas de hipoglucemia tienden a presentarse temprano en la vida. El hiperinsulinismo es la causa endocrina más común y se presenta con frecuencia en el período neonatal. El menor peso y longitud al nacer y los PEG parecen asociarse con una resolución temprana. Se requiere un alto índice de sospecha para el diagnóstico de insuficiencia hipofisaria, ya que puede coexistir con una resonancia magnética normal.

Palabras clave: Hipoglucemia, Hiperinsulinismo, Hipopituitarismo, Enfermedades del sistema endocrino

Introduction

Clinical hypoglycemia consists in a plasma glucose concentration low enough to cause symptoms and/or signs of altered brain function [1]. The choice of a cut-off point to define hypoglycemia, however, is challenging since signs and symptoms are non-specific [1,2], a low glucose concentration can be an artifact, and prior exposure to hypoglycemia can lead to loss of associated symptoms (tolerance acquired by frequent episodes). The Pediatric Endocrinology Society guidelines suggest that, in children able to report symptoms, the assessment of hypoglycemia should be limited to those with documented Whipple's triad (low blood glucose, symptoms consistent with hypoglycemia, and clinical resolution with normalization of blood glucose). For infants and young children over 48 hours of age, evaluation is suggested for plasma glucose concentrations below 60mg/dL confirmed in a laboratory quality assay [1], although this definition is not universally accepted. For instance, protocols endorsed by the Spanish Society of Pediatric Endocrinology define hypoglycemia as a venous blood glucose value below 50 mg/dL (and 40 mg/dL for neonates) [3].

Glucose is the most important metabolite for the brain, which accounts for more than half of its consumption [1]. The decrease in plasma glucose concentrations to values below 70-110 (physiological post-absorptive range) triggers physiological and behavioral responses [4,5]. At an early stage, there is a decrease in insulin secretion, leading to an increase in hepatic and renal glucose production and a reduction in its use. The first counterregulatory response is an increase in glucagon, and the elevation of epinephrine is the next line of defense [4,6]. These responses raise plasma glucose in minutes. Cortisol and growth hormone (GH) have a slower action, supporting production and limiting glucose use during the subsequent hours [4,5].

Hypoglycemia is a relatively common problem during the pediatric age [7]. The main causes can be divided into several groups: innate metabolism errors, ketotic hypoglycemia, endocrine disorders, and drug-induced and factitious hypoglycemia [8,9].

Endocrine causes of hypoglycemia are the result of abnormalities in the expected hormonal response to hypoglycemia. Hyperinsulinism is a relevant etiology, with hereditary forms found in about 1/50,000 births [10]. Mutations in several genes causing monogenic hyperinsulinism identified to date include: *ABCC8 or KCNJ1I, CGK, GLUD1, HADH, HNF4A/1A, SLC16A1, UCP2*, and *HK*. Some syndromic diseases such as Turner and Beckwith-Wiedemann have also been linked to hyperinsulinism [10,11]. Additionally, the neonatal age represents a period of particular susceptibility to hypoglycemia by cessation of a stable supply of glucose through the placenta, with insulin assuming a central role in glycemic regulation [12]. Insulin above 3 µIU/mL and a C-peptide ≥0.2 nmol/liter during hypoglycemia is a generally accepted criterion for hyperinsulinism in adults [9]. However, in the neonatal period, cut-off points are not so clearly defined and lower insulin values in hypoglycemia may be found in hyperinsulinism [7]. Initial treatment of hypoglycemia requires glucose administration. Diazoxide, which acts by binding to sulfonylurea receptors (SUR1) and opening K-ATP channels, is the first-line pharmacological treatment. Octreotide, a somatostatin analog, is often tried in cases unresponsive to diazoxide. Glucagon is also an option in the acute treatment of severe hypoglycemia caused by hyperinsulinism. Surgery may be necessary in cases of sustained hypoglycemia refractory to medical treatment, sometimes requiring total/subtotal pancreatectomy [2].

Deficiencies in counterregulatory hormones represent rare causes of hypoglycemia, clinically with intolerance to fasting, more often in infants and young children [13]. Cortisol is one of the hormones that contribute to glucose homeostasis. Hypocortisolism may present with hypoglycemia accompanied by symptoms such as fatigue, anorexia, nausea and vomiting, weight loss, abdominal pain, weakness, decreased pubic and axillary hair, hypotension, dehydration, and altered mental status [8]. However, persistent neonatal hypoglycemia may be the only manifestation of hypocortisolism [14]. GH is also a counterregulatory hormone, yet isolated GH deficiency is not so strongly associated with hypoglycemia [15]. The presence of micropenis, cleft palate, cleft lip, other midline defects, or pituitary changes in sellar magnetic resonance are clues pointing to pituitary hormone deficiency [15], but the absence of these abnormalities does not exclude the diagnosis. Cortisol and GH responses to spontaneous hypoglycemia are age-dependent, especially below 6 months of age. During these early months, there is a tendency towards poorer cortisol responses and a more marked elevation of GH in response to hypoglycemia [16]. Dynamic tests to evaluate the hypothalamus-pituitary-adrenal axis or suspected GH deficiency are often necessary [17,18], although it has been suggested that in the early neonatal period a GH value <7ug/dL would be highly sensitive and specific for diagnosis [19]. Glucocorticoid replacement generally corrects hypoglycemia, but GH therapy seems to have less effect [13].

Although some causes of hypoglycemia are relatively benign and transient, there is a risk of associated neurological damage. Patients with congenital hyperinsulinism tend to develop neurological complications more frequently than those with other etiologies of hypoglycemia [7]. Hormonal deficiencies, with particular emphasis on hypocortisolism, are potentially fatal.

Since endocrine causes represent an important group in the etiology of hypoglycemia, we conducted a retrospective study involving patients evaluated in our center in pediatric endocrinology visits, due to hypoglycemia, focusing on those with an identified endocrine cause. Our goal was to detect clinical and biochemical patterns of presentation of hypoglycemia due to endocrine causes in the pediatric age.

Methods

Patient selection

We reviewed the clinical files of patients referred to pediatric endocrinology visits due to hypoglycemic episodes from January 2010 to January 2021. Inclusion criteria were either a glycemia <60mg/dL in infants and young children or a glycemia <60mg/dL with symptoms improving with its correction (Whipple's triad) in patients over 4 years old. These criteria were defined based on the current Pediatric Endocrine Society definition [1]. The age of 4 was considered to be suitable for reporting symptoms since at this age children with adequate neurodevelopment are supposed to have a comprehensible language according to the Mary Sheridan Modified Scale used in our country [20].

Patients with spontaneous resolution of hypoglycemia before they reached 48 hours of age were excluded as this corresponds to a period of transitional glucose regulation (1). Patients that did not fulfill any of the inclusion criteria were also excluded.

Definitions

For the purposes of this study, hyperinsulinism was defined as an inappropriately elevated or measurable insulin concentration during hypoglycemia. Persistent hyperinsulinism was defined as subjects diagnosed with hyperinsulinism that persisted at 4 months of age [21] (or resolved before that period with surgical therapy).

Data collection

Data were collected regarding age and gender, age of onset of hypoglycemic episodes and clinical presentation (symptoms and signs that lead to hypoglycemia being noticed). In cases of neonatal hypoglycemia, anthropometric parameters at birth, gestational age at birth, and maternal diabetes were also registered. Laboratory data were collected including blood glucose value, arterial blood gas test with pH, CO2, and HCO3 evaluation, insulin, lactate, cortisol, GH, C-peptide (when available), point-of-care ketonemia and/or ketonuria. Data on other analytical and imaging studies collected in specific cases was also analyzed, as was information regarding final diagnosis, treatment, and outcome (spontaneous resolution versus long-term persistence).

Statistical analysis

Statistical analysis was performed using the software Statistical Package for the Social Sciences (SPSS) version 23. For continuous variables, the type of distribution was evaluated through standardized asymmetry and homogeneity of variances of variables. Student's t test was preferentially used when the required assumptions were verified. When the distribution was not normal, the Mann-Whitney test was used to establish comparisons between two groups. To find the best cut-off point for a specific biochemical parameter, a receiver operating curve (ROC) was used.

Results

Hypoglycemia was one of the main reasons for evaluation at Pediatric Endocrinology visits in 105 children. Application of the above-mentioned criteria resulted in the exclusion of 3 cases in which hypoglycemia was only documented in the first 48 hours of life, 40 due to failure to fulfill the inclusion criteria (Whipple's triad or glycemia <60mg/dL for infants, and young children) and 7 without a definite diagnosis.

Global Sample Analysis

The analyzed sample consisted of 55 patients, 67.3% (n=37) male and 32.7% (n=18) female. The median age of the first episode was 0.8±2.6 years (minimum 0, maximum 16.1 years), with 26 (47.3%) in the neonatal period, 5 (9.1%) between the 1st month and the 1st year of life, 22 (40%) between the 1st and 10th year, and 2 (3.6%) above 10 years of age.

A baseline study with laboratory blood glucose this part is repeated, please remove it value, arterial blood gas test with pH, CO2, and HCO3 evaluation, insulin, lactate, and counterregulatory hormones (cortisol, GH) was performed in all patients. C-peptide was also ordered in those who presented outside the neonatal period. β hydroxybutyrate measurement has been available at our center since 2014, but point-of-care ketonemia and/or ketonuria was performed instead. All children, except for one immigrant boy, underwent the metabolic neonatal screening recommended in Portugal, which identifies the most common hereditary defects of metabolism. If a diagnosis from this group was considered likely, directed studies were performed. Additional tests were selected on a case-by-case basis.

The initial study generally allowed identification of the underlying cause of hypoglycemia.

The most frequent etiology was ketotic hypoglycemia (n=24) with a median age of 2.6±2.2 years at the appearance of the first symptoms, and with most episodes occurring in the context of acute (n=16, 66.5%) or chronic (n=2, 8.3%) disease. The most frequent symptoms were weakness/prostration (n=19), diaphoresis (n=7), and seizures (n=5), and all episodes were self-limited. Inborn errors of metabolism were detected during the first year of life, with half of the cases manifesting hypoglycemia episodes in the neonatal period. In those who were symptomatic, prostration was commonly described. Endocrine causes were found in 27 patients (hyperinsulinism in 19 and deficiency of counterregulatory hormones in 8 cases) and are further explored in the following section. The main causes identified and the distribution by age is better described in Table 1.

Analysis of endocrine causes of hypoglycemia

Hyperinsulinism

Of the 19 patients diagnosed with hyperinsulinism, 13 (68.4%) were male and 6 (31.6%) female. The majority – 17 (89.5%) – presented in the neonatal period. These neonates had a mean gestational age at birth of 37.7±2.2 weeks with 5 (29.4%) pre-term births. Regarding the type of delivery, 10 (58.8%) were born by vaginal birth and 7 (41.2%) by cesarean section. Anthropometric data analysis revealed an average birth weight of 3063.7±1128.9 grams, length of 47.7±5.2cm, and head circumference of 32.8±3.0cm. Almost one-third (29.4%) were born small for gestational age (SGA) and 17.6% were large for gestational age (LGA). Intrauterine growth restriction was documented in 4 cases (23.5%) and maternal gestational diabetes in 3 (17.6%). Concerning clinical presentation, prostration was reported in 11 cases (64.7%), difficulties in breastfeeding in 9 (52.9%), and seizures in 2 (11.8%). In two cases no signs or symptoms were identified during hypoglycemia. A mean insulin value of 11.0±9.3 µIU/mL was verified in hypoglycemia (mean glycemia of 35.7±8.0 mg/dL). The mean cortisol value in hypoglycemia was 12.3±6.2 ug/dL, ranging from a minimum of 0.9 to a maximum of 22.0 ug/dL. The mean GH value in hypoglycemia was 13.4±9.3 ng/mL. All these patients required glucose infusion with an average rate of 9.6±5.8 mg/kg/min. Diazoxide therapy was started in 9 newborns. In one of them, treatment was stopped during hospitalization at day 8, due to the resolution of hypoglycemia, and in two other cases it was necessary to switch to octreotide at days 2 and 5. Two cases were refractory to medical therapy and since the pancreatic image did not reveal nodules, subtotal pancreatectomy was per-

Table 1. Distribution by ages of the causes of hypoglycemia

	N	Age			
		Neonatal	1M-1A	1-10A	>10 A
Hyperinsulinism	19 (34.5%)	17	1	0	1
Deficiency of counterregulatory hormones	8 (14.5%)	7	1	0	0
Ketotic hypoglycemia	24 (43.6%)	0	1	22	1
Innate errors of metabolism	4 (7.3%)	2	2	0	0

formed. A total of 9 subjects did not require medical therapy at the time of discharge or surgery. The comparison between newborns with persistent hyperinsulinism at discharge (and for ≥4 months) or undergoing pancreatectomy versus those without the need for long-term pharmacological or surgical therapy is presented in Table 2. We found significant differences regarding birth weight (2479.8±1082.9 g in transient vs. 3720.6±800.8 g in persistent hyperinsulinism, p=0.018), birth length (45.0±6.1 cm in transient vs. 50.4±1.7 cm in persistent hyperinsulinism, 0.041), and probability of being small for gestational age (55.6% vs. 0%, p=0.029).

Genetic study was performed in all but one case of persistent hyperinsulinism, which was diagnosed over 20 years ago. Mutations in *ABCC8* were found in two cases, and *ACADS* mutation was found in one case. Composed heterozygosity for *ABCC8* mutations (a nonsense and a missense mutation) was identified in one of the cases submitted to total pancreatectomy. This patient was an appropriate for gestational age (AGA) child, but macrosomic and unresponsive to diazoxide. A missense maternal variant of *ABCC8* was found in an LGA newborn in which a switch to octreotide was required. In one of the cases of diazoxide-responsive hypoglycemia, an AGA newborn girl, a mutation of the *ACADS* gene causing short-chain dehydrogenase deficiency was identified. One child is still waiting for the results of the genetic study, while in the remaining cases no potentially causative mutations were identified. Conducting a genetic study in one of the cases of transient hyperinsulinism was motivated by the presence of other anomalies (microcephaly, facial dysmorphisms, micropenis, interventricular communication, and pulmonary stenosis) and Williams syndrome was diagnosed.

Two cases (10.5%) had the initial episode after the neonatal period. One 11-month-old girl presented with seizures during hypoglycemia. Biochemical studies revealed an insulin level of 10 µUI/mL during spontaneous hypoglycemia (47 mg/dL). Due to recurrent hypoglycemia, diazoxide was started with a good response. The molecular study revealed a de novo heterozygotic mutation in the *GLUD1* gene.

Table 2. Comparison of children with transient versus persistent neonatal hypoglycemia

	Transient HI (n=9)	Persistent HI (n=8)	P-value
Male (%)	55.6	87.5	0.294
Age at birth (weeks)	37.3±2.6 (32 – 41)	38.2±1.8 (35 – 41)	0.420
Prematurity (%)	44.4	12.5	0.294
Birth weight (grams)	2479.8±1082.9 (1145 – 4090)	3720.6±800.8 (2430 – 5040)	0.018*
Length (cm)	45.0±6.1 (37 – 57)	50.4±1.7 (49 - 53)	0.041*
Head circumference (cm)	31.4±3.6 (25 – 36)	34.1±1.5 (31-36)	0.080
Intrauterine growth restriction (%)	44.4	0	0.082
Small for gestational age (%)	55.6	0	0.029*
Large for gestational age (%)	11.1	25.0	0.576
Macrosomics (%)	11.1	37.5	0.294
Caesarean section (%)	44.4	37.5	1.0
Children of diabetic mothers (%)	0.0	37.5	0.082
Insulin in hypoglycemia (µUI/mL)	9.3±7.6 (2.2 – 32.2)	12.4±8.5 (3.1-24.5)	0.463
Ketonemia	Negative	Negative	N/A
Lactate(mmol/L)	3.8±3.0 (1.7 – 7.2)	2.5±1.5 (1.7 – 4.8)	0.466
Cortisol (µg/mL)	10.9±6.1 (1.6 – 18.8)	13.3±6.5 (0.9 – 22.0)	0.503
Growth hormone	12.7±4.8 (5.4 – 19.3)	14.0±12.4 (4.3 – 34.0)	0.814
Maximum glucose infusion rate (g/kg/min)	6.8±4.0 (0 – 12)	11.7±6.2 (4 - 22)	0.118

There was also a case of hyperinsulinism in a 16-year-old boy who presented with altered mental status. The initial study revealed an insulin level of 45 µIU/mL, with that of concomitant blood glucose of 31mg/dL. Further investigation documented pancreatic nodules, suggestive of insulinoma, that were surgically removed. The genetic study detected a heterozygotic mutation in the *MEN1* gene. This patient is under lifelong follow-up, and he has been diagnosed with and treated for primary hyperparathyroidism. A non-functioning pituitary microadenoma has also been identified.

Counterregulatory hormone deficiency

Deficiency of counterregulatory hormones was diagnosed in 8 patients (6 males and 2 females): 3 cases of isolated central adrenal insufficiency (CAI) and 5 of panhypopituitarism.

Gestational age at birth was on average 38.9±2.0 weeks and cesarean section was performed in 3 cases. The average weight was 3535.7±1368.8 g, and the mean length was 48.2±4.2 cm, with 1 SGA and 1 LGA newborns.

All of them presented in the first months of life with episodes of fasting hypoglycemia. Presenting symptoms were seizures (n=4), feeding difficulties (n=3), and/or prostration (n=3). The average glucose infusion rate to maintain euglycemia was 3.3±3.8 mg/kg/min.

The mean cortisol value in hypoglycemia was <2.7±2 ug/dL (median 2.0±1.8 ug/dL, minimum <1 ug/dL, maximum 10.1) and adrenocorticotropic hormone (ACTH) <15.5±13.4 µg/mL. In those with panhypopituitarism, the GH value varied between <0.1-0.7 ng/mL during hypoglycemia.

We had access to the sellar MRI report of 6 patients, which documented pituitary hypoplasia (n=2), septo optic dysplasia (n=1), pituitary hamartoma (n=1), and normal pituitary (n=2). In one of the subjects with an unremarkable MRI, a pathogenic mutation was identified in *TBX19*, causing congenital isolated adrenal insufficiency (CAI). In the remaining patients, the genetic study was inconclusive, although there is a high suspicion of Pallister-Hall syndrome in the child with a pituitary hamartoma.

Analysis of cortisol values in spontaneous hypoglycemia in the first year of life:

Given the difficulty in establishing cut-off points for cortisol levels in the first years of life, we compared children with CAI with those who presented with hypoglycemia in the first year of life. The group with hypocortisolism presented significantly lower cortisol values than the remaining sample (median 2.0±1.8 ug/dL vs. 12.0±11.5; p=0.002), although some overlap was observed (Figure 1). When analyzing the data in a receiver operating curve (ROC), a cortisol value <4.1 µg/mL presented 85.7% sensitivity and 90.0% specificity for the diagnosis of hypocortisolism (area under the curve 89.6, p=0.002) (Figure 2).

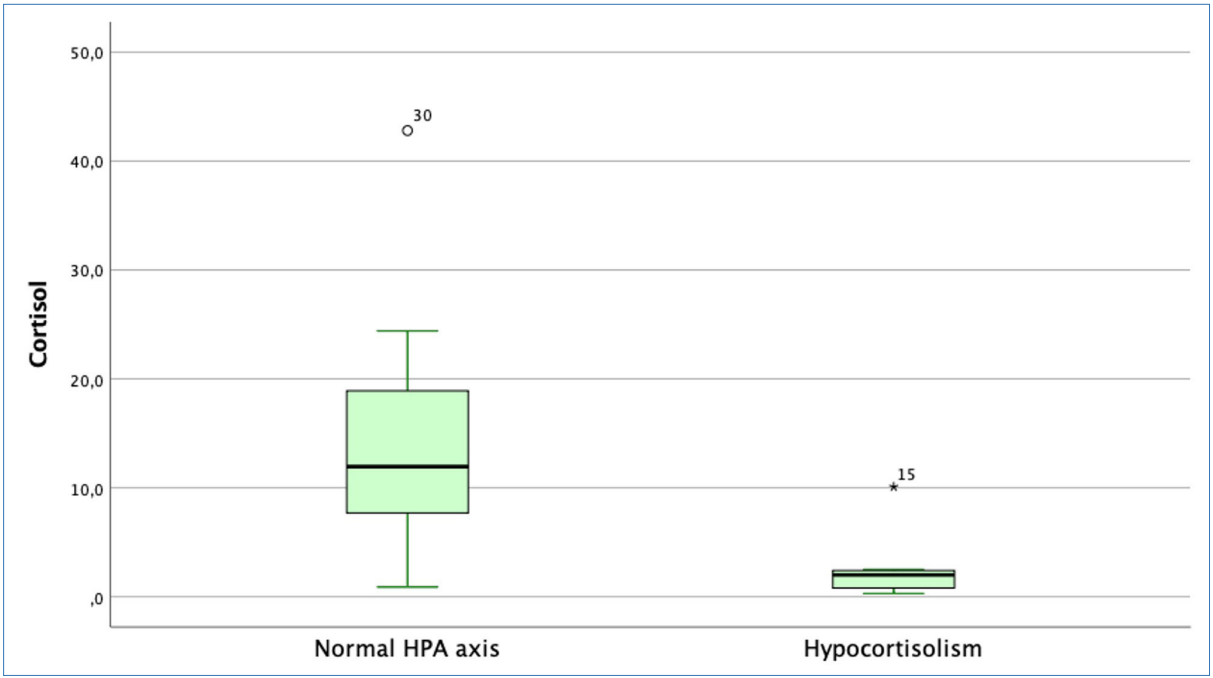

Figure 1. Cortisol values in hypoglycemia in groups with hypocortisolism vs. without hypocortisolism.

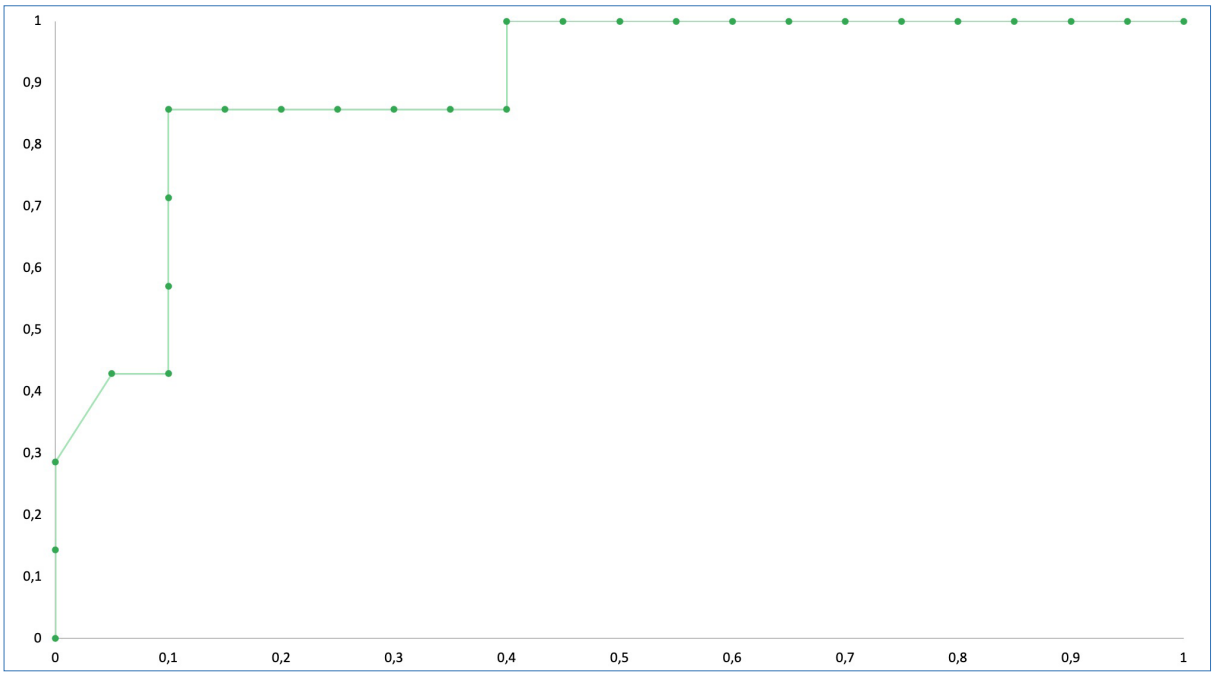

Figure 2. Receiver operating curve (ROC) with analysis of cortisol values in hypoglycemia in the first year of life, for diagnosis of hypocortisolism.

Discussion

Hypoglycemia is a common reason for evaluation in the pediatric age, although not all cases are confirmed in the subsequent investigation. During our initial analysis, we noticed that, in many cases, children referred for evaluation of hypoglycemia suspected by caregivers did not have the criteria for an in-depth study. There were several cases with borderline values measured in glucometers combined with non-specific symptoms. It should be noted that values measured with these devices can be 10-15% lower than those from laboratory quality assays [8]. Additionally, despite this being a sample consisting of children and adolescents sent specifically for Pediatric Endocrinology visits, most cases did not have an endocrine cause. Ketotic hypoglycemia is described as a common cause in the literature [22] and was the most frequently established diagnosis in our sample, after the exclusion of other causes.

The endocrine causes in our sample presented mainly during the first year of life. In the 17 patients with neonatal hyperinsulinism, we found insulin values almost universally higher than 3 µIU/mL (except in a case of transient hyperinsulinism), and high glucose perfusion needs to maintain euglycemia. Those with transient hyperinsulinism had lower birth weight and length and a higher prevalence of SGA, which is consistent with previous data [7]. There was also a tendency towards a higher frequency of intrauterine growth restriction (IUGR), prematurity, and a lower maximum glucose perfusion rate in this group, although without reaching statistical significance. Indeed, characteristics such as prematurity, small for gestational age (SGA), history of IUGR, or maternal diabetes seem to be associated with reduced ability to maintain euglycemia due to lower glycogen storage and transient hyperinsulinism [12]. The newborns with a maternal history of gestational diabetes were restricted to the group of permanent hyperinsulinism. Hypoglycemia in this context tends to resolve in 1-2 days [22]. Since maternal gestational diabetes provides a reasonable explanation for transient neonatal hypoglycemia, it is likely that the only cases referred for further follow-up were the ones that did not have early spontaneous resolution.

Genetic testing was performed essentially in cases of persistent hyperinsulinism. Falzone et al. stated that genetic testing is particularly important in cases unresponsive to diazoxide or in LGA newborns without a maternal diabetes context [21]. In our series, 2 of the 3 cases with persistent hyperinsulinism and documented genetic mutations had a weight exceeding 4000 grams at birth and poor response to diazoxide – a pattern consistent with the *ABCC8* mutation found in these children. Indeed alteration of the genes encoding K-ATP channel subunits (*ABCC8* or *KCNJ1I*) have been associated with hyperinsulinism often unresponsive to diazoxide [10,11]. *SCHAD* mutations cause defects in fatty acid beta-oxidation but have also been associated with hyperinsulinism controllable with diazoxide [23]. In the only patient with transient hyperinsulinism in which a genetic study was performed, other concomitant abnormalities motivated the study and the diagnosis of Williams syndrome.

It should be noted that presentation outside the neonatal period does not exclude a genetic cause for

hyperinsulinism. *GLUD1* mutations are frequently detected after the neonatal period (10), like the case in our sample. In the only adolescent in our series, the presence of an insulinoma motivated further investigation, leading to the diagnosis of multiple endocrine neoplasia, and allowing for adequate posterior surveillance of the patient.

The deficiency of counterregulatory hormones is also an important endocrine cause of hypoglycemia. Our sample included only patients with central adrenal insufficiency (isolated or in the context of panhypopituitarism), without any cases of primary adrenal insufficiency. In fact, hypoglycemia has been associated with secondary more than primary adrenal insufficiency [24]. Even if a low glucose value is present, a clinically wider presentation of primary adrenal insufficiency is likely to lead to the diagnosis, for reasons other than hypoglycemia. Cases of isolated GH deficiency were not found as a cause of hypoglycemia either, as it is more frequently associated with hypoglycemia in the setting of multiple hormone deficiencies [15].

The interpretation of cortisol values during the first year of life can be challenging due to the difficulty in establishing cut-off points. In our study, a cortisol value <4.1 µg/mL presented 85.7% sensitivity and 90.0% specificity for the diagnosis of hypocortisolism. As described by other authors [21], we also found cortisol values inappropriately decreased in some cases of hyperinsulinism. Since the presence of hypocortisolism does not always coexist with other anomalies and 2 of our patients had a normal sellar MRI, close surveillance is recommended in dubious situations and dynamic testing may be essential. Regarding GH, we also found some values that were lower than expected in patients with congenital hyperinsulinism. Posterior evaluations excluded GH deficiency in these patients.

This work has some limitations, namely the retrospective data collection, which led to some missing data and thereby reduced our ability to establish causality between the associations we found. Sample size also interferes with the analysis and conclusions. Finally, because it is a sample specifically referenced for endocrinology consultation, it is not possible to generalize the prevalence of each of the etiologies.

The creation of multicenter databases to better define cut-off points for important biochemical parameters such as insulin, C-peptide, cortisol, and GH during the first years of life might be an important tool to improve diagnostic accuracy and celerity.

To conclude, we would like to stress that in the presence of neonatal hypoglycemia after 48 hours of life, especially in populations submitted to screening for the most frequent inborn errors of metabolism, endocrine causes should be strongly considered. Hyperinsulinism is the most frequent endocrine cause, and we found that even in the neonatal period it is frequently, although not always, associated with insulin values >3 µIU/mL and high glucose perfusion needs to maintain euglycemia. Our results show that, in the neonatal period, lower weight and length at birth and small for gestational age seem to be associated with a higher likelihood of early resolution. Genetic mutations causing hyperinsulinism may be identified beyond the neonatal period and have important clinical implications. Counterregulatory hormone deficiency is a rare but important cause of hypoglycemia in the pediatric age, as adrenal insufficiency is a life-threatening condition. Hypoglycemia may be the only sign of secondary adrenal insufficiency: in our sample a cortisol level <4.1 µg/mL conjugated the best sensitivity and specificity for the diagnosis. Yet, larger studies are necessary to properly define cut-off points at this age.

Conflicts of interest

The authors declare no conflicts of interest related to this article.

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