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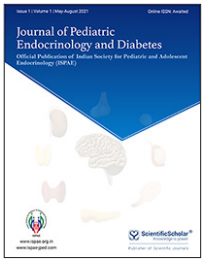

Case Series

Neonatal hypoglycemia: A review with focus on practical challenges and recent updates on management

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ABSTRACT

At birth, a neonate undergoes a transition from the continuous maternal supply of glucose to a variable and intermittent oral glucose intake, which is regulated by the interplay of hormones and metabolic enzyme induction. Because low plasma glucose concentrations are common in the neonatal period, it may be difficult to identify those who have pathologic hypoglycemia. Hence, it is important to formally evaluate such babies by drawing critical samples. Here, we present two cases of neonatal hypoglycemia where the presentation had some similarities, but the comprehensive evaluation revealed a varied etiological spectrum necessitating lifelong management. Through these case studies, authors discuss practical challenges in the diagnosis, management, and follow-up of neonates with endocrine causes of hypoglycemia.

Keywords: Congenital hyperinsulinism of infancy, Hypoglycemia, Neonatal, Hyperinsulinemia, Hypopituitarism

INTRODUCTION

Hypoglycemia is a common metabolic emergency often related to the physiological transition of babies postnatally but rarely attributable to pathological causes, which are often missed. Glucose homeostasis in neonates is mainly dependent on the interplay of insulin, cortisol, and growth hormone (GH). Cortisol deficiency may present with severe hypoglycemia, cholestasis, failure to thrive, hyponatremia without hyperkalemia, fluid imbalance, temperature instability, a lack of thymic involution, and rarely heart failure.[1,2] The most common endocrine causes include congenital hyperinsulinemia, stress-induced hyperinsulinemia, and hypopituitarism.[3] Critical sampling helps in the identification of endocrine disorders, which warrant further confirmation. We describe two cases of severe neonatal hypoglycemia with different etiologies, aiming to review recent literature and discuss practical challenges that arise during diagnosis, management, and monitoring of these infants.

CASE SERIES

Case 1

A 2-day-old baby girl, born of a non-consanguineous union and with a birth weight of 3 kg, presented with hypoglycemic seizures (capillary blood glucose [BG] 26 mg/dL), and treated symptomatically with intravenous (IV) dextrose. In view of the persistent and recurrent

hypoglycemic convulsions, the baby was evaluated in a pediatric endocrine unit, and critical samples revealed BG 28 mg/dL, plasma insulin 18.9 μU/L, serum ketones 0.3 mmol/L, serum cortisol 18.5 μg/dL (normal 2–11 μg/dL), plasma ammonia 54 μmol/L (9–30 μmol/L), and a positive glycemic response to subcutaneous (SC) glucagon injection. The neonate was managed with oral diazoxide (20 mg/kg/d) and octreotide SC injections (11 μg/kg/d), resulting in normalization of BG by 3 weeks. Next-generation sequencing (NGS) revealed a paternally inherited dominant *ABCC8* mutation at exon 36. An 18F-DOPA positron emission tomography/computed tomography (PET/CT) nuclear scan showed a diffusely increased uptake in the pancreas [Figure 1], which was confirmed by a Gallium-68 Dota-Exendin-4 scan [Figure 1]. There was a history of early-onset diabetes mellitus in the father (age of onset 31 years) and paternal grandfather, managed with oral hypoglycemic agents. At the last follow-up, the child was 3 years old, and her growth (weight and height on the 10th percentile on the World Health Organization charts) and development were in normal ranges. The infant remains euglycemic with occasional hypoglycemia on SC octreotide at 8 μg/kg/d in three divided doses.

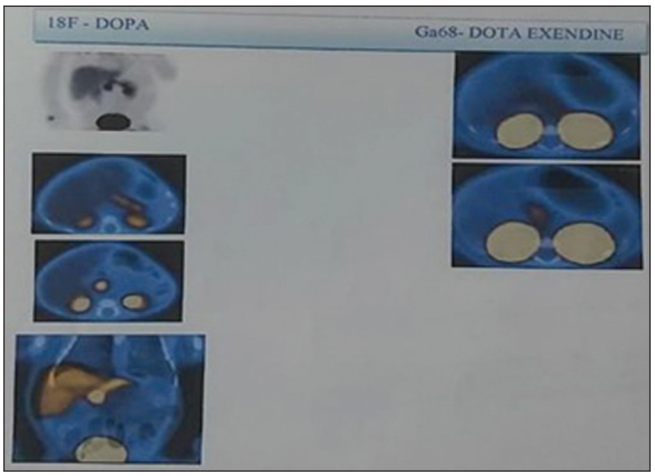

Figure 1: 18F-DOPA positron emission tomography – Diffuse uptake in the pancreas with SUV 20.3. No obvious focal lesion in the pancreas. Gallium-68 Dota Extendin-4 scan – Diffuse uptake seen in the pancreas with SUV 3.7. 18F-DOPA: 18 Fluoro-dihydroxyphenylalanine, SUV: Standardized uptake value.

Case 2

A baby girl born of a non-consanguineous marriage with a birth weight of 2.9 kg and a length of 48 cm by lower-segment cesarean section with a breech presentation developed symptomatic hypoglycemia on day 1 of life and was treated with IV dextrose. The baby did not have further hypoglycemic episodes and received phototherapy for unconjugated hyperbilirubinemia. Cord thyroid-stimulating hormone (TSH) was 0.03 mIU/L; hence, repeated on day 8, it was TSH 0.04 mIU/L with free thyroxine 0.2 ng/dL. The baby was readmitted in the 2nd week of life with hypoglycemia (BG 42 mg/dL) and unconjugated hyperbilirubinemia (17 mg/dL). The critical sample showed cortisol 10 μg/dL, adrenocorticotropic hormone (ACTH) 15 pg/mL, ketones and insulin suppressed, and GH 0.03 ng/mL. She was started on hydrocortisone, and in view of persistent hypoglycemia, the dose was titrated to a maximum of 20 mg/m^2/d in three divided doses, followed by the addition of levothyroxine (LT4), 37.5 μg/d. In spite of optimal replacement of hydrocortisone and LT4, the baby continued to have hypoglycemic episodes for the next 3 days, and GH therapy was started at 0.7 mg/m^2/d, and euglycemia was achieved within 3–4 days after initiation. MRI of the pituitary revealed a cystic lesion of 6.5 × 7.9 × 9.2 mm size within the sella and suprasellar region, significantly compressing the pituitary gland, suggestive of Rathke's cleft cyst with normal posterior pituitary (PP) bright spot [Figure 2]. The ophthalmology evaluation was normal. Neurosurgery advice was conservative management with a repeat imaging after

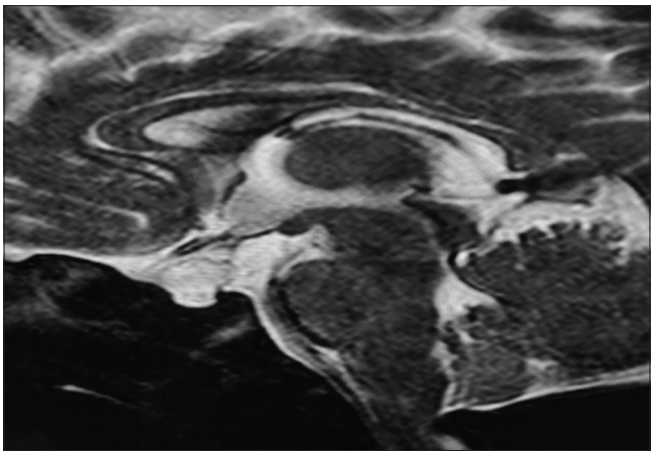

Figure 2: Cystic lesion within the sellar and suprasellar region significantly compressing the pituitary gland.

1 year. NGS revealed a compound heterozygous mutation at exons 4 and 2 of the *LHX3* gene in the index patient. Parental testing revealed an asymptomatic heterozygous missense variation in exon 4 of the *LHX3* gene in the father and heterozygous missense variation in exon 2 of the *LHX3* gene in the mother by Sanger sequencing. At 6 months of life, insulin-like growth factor binding protein-3 was 1.53 μg/mL (normal 0.7–3.6). Follow-up MRI brain at 2 years of age showed resolution of previously seen Rathke's cyst with hypoplastic pituitary (pituitary height 2.8 mm and thin stalk of 1.2 mm). Features of Chiari 1 malformation with peg-like cerebellar tonsils herniating into the posterior cervical spinal canal and indenting the cord were seen without any evidence of edema. At 2 year follow-up, the baby was doing well on GH 0.85 mg/m^2/d, LT4 37.5 μg/d, and hydrocortisone 2.8 mg/m^2/d. It was planned to wean off hydrocortisone with

subsequent adrenal axis evaluation, but unfortunately, the baby succumbed to an intercurrent lung infection. Parents have opted for prenatal genetic testing following counseling.

DISCUSSION

The approach to newborns with hypoglycemia persisting beyond the initial days is depicted in Figure 3. Congenital hyperinsulinism of infancy (CHI) is one of the most common causes of persistent and recurrent hypoglycemia in the newborn. In a resource-limited setting, difficulties pertaining to evaluation are compounded by the high cost and non-availability of medications, unresponsiveness to medical therapy, limited facilities for nuclear imaging, and only a few tertiary centers having surgical expertise in managing the condition.

The approach to CHI in the developed world begins with a rapid analysis of the most frequently implicated (60%) CHI genes, namely, *ABCC8* and *KCNJ11*.[4,5] These genes encode the two subunits of the ATP-sensitive potassium channel (K-ATP), namely, SUR-1 and Kir6.2, respectively, and are located next to each other on chromosome 11p15. The various patterns of inheritance of their mutations and their clinical implications are shown in Table 1. Rapid gene sequencing, with a turnover time of <10 days, confirms the diagnosis along with identification of the possibility of focal pathology (especially those who are diazoxide-unresponsive) and complements the standard NGS, which typically takes 4–6 weeks. This aids in early judicious nuclear imaging and surgical excision and prevents unnecessary prolongation of medical therapy [Table 1].[6] Conversely, an autosomal dominant or biallelic recessive mutation signifies diffuse pancreatic disease, obviating the need for further nuclear imaging.[7] However, due to the limited availability and high cost of rapid gene analysis in the local setting, the approach to a case of CHI rather depends on unresponsiveness to diazoxide therapy, which can indirectly indicate an underlying mutation in the K-ATP channel related genes.

The various pharmacological treatments tried in CHI are shown in Table 2. Diazoxide forms the mainstay of medical therapy, and most responsive patients are well-controlled at a dose of <10 mg/kg/d.[8] Ideally, control of CHI should be ensured by subjecting the patient to safety fast. The duration of the fast varies depending on age, such that a neonate, an infant, and an older child should maintain BG levels >65 mg/dL after a fast of 6–12 h, 12–18 h, and 18 h. respectively.[6] A small percentage of diazoxide-unresponsive (UR) cases may respond to IV or SC octreotide [Table 2]. Children who respond to octreotide can be shifted to long-acting somatostatin analogs such as octreotide long-acting

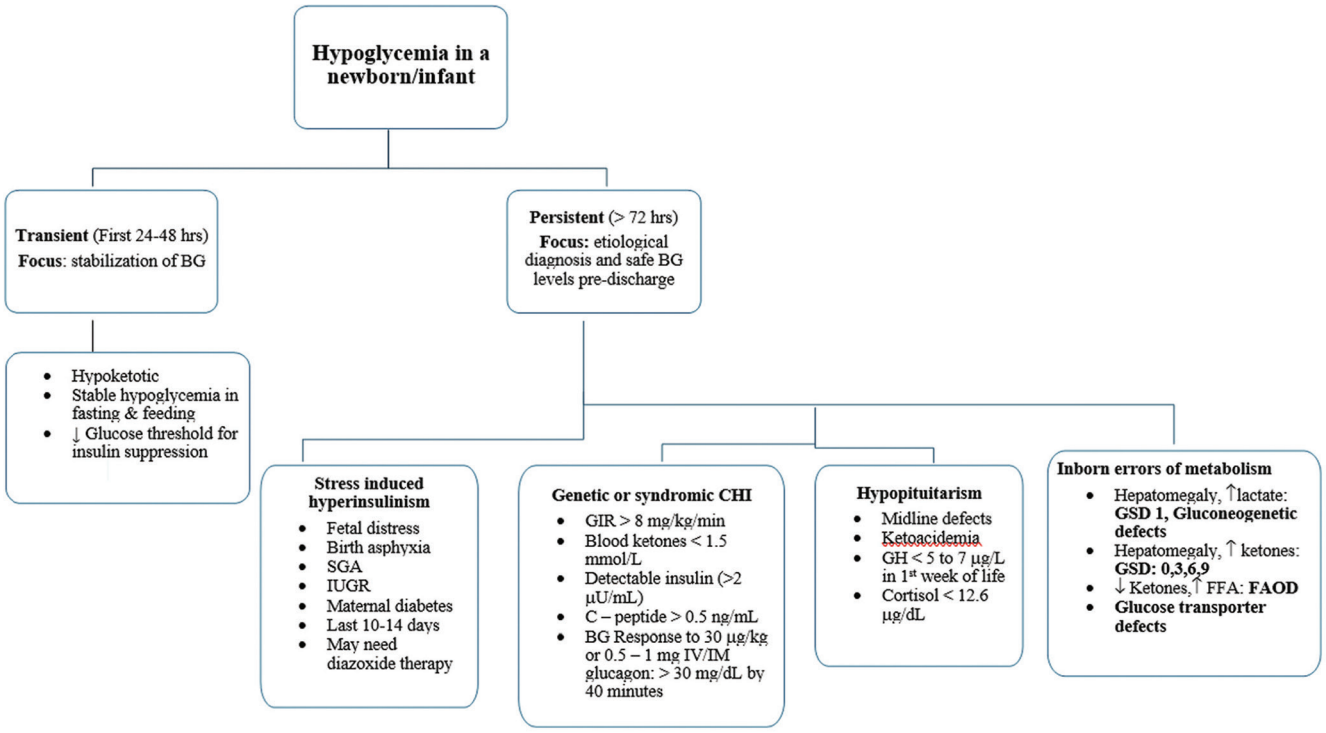

Figure 3: Approach to a newborn/infant with hypoglycemia. BG: Blood glucose, SGA: Small for gestational age, IUGR: Intrauterine growth restriction, CHI: Congenital hyperinsulinism, GIR: Glucose infusion rate; IV: Intravenous, IM: intramuscular, SC: subcutaneous, GH: Growth hormone, GSD: Glycogen storage disease, FFA: Free fatty acids, FAOD: Fatty acid oxidation defect.

Table 1: Various patterns of inheritance of mutations in *ABCC8* and *KCNJ11* genes and their clinical implications.

Pattern of inheritance	Zygosity	Histological type	Diazoxide responsiveness	Comment
AR	Biallelic (homozygous or compound heterozygous)	Diffuse	UR	Most require near total pancreatectomy
	Monoallelic (father)	Focal (rarely diffuse)	UR	*Focal lesions* - Loss of maternal 11p15 gene in a limited area of pancreatic tissue with concomitant paternal isodisomy *Diffuse histology* - Missed mutation in the deep intronic or regulatory region of a maternal gene, missed on routine Sanger sequencing. *Focal lesionectomy* - Curative in almost all patients
	Monoallelic (mother)	Diffuse	UR	Spontaneous resolution with time; near total pancreatectomy can be averted
AD	Heterozygous	Diffuse Atypical or LINE-HI	Milder; usually responsive	*If K-ATP channel activity was completely impaired*– maybe UR to diazoxide, needing octreotide therapy or near total pancreatectomy. *Atypical or LINE-HI* (scattered distribution of abnormal islet cells in the pancreas) can occur in certain AD somatic mutations of *ABCC8, GCK* and *HK1* genes.

ABCC8: ATP-binding cassette subfamily C member 8, AD: autosomal dominant, AR: Autosomal recessive, GCK: Glucokinase, HK1: Hexokinase, K-ATP: Adenosine triphosphate sensitive potassium, LINE-HI: Localized islet nuclear enlargement, UR: Unresponsive

release (LAR) and lanreotide autogel. Although off-label, their use in patients with CHI has reported good control and improved quality of life.[9] Le Quan Sang *et al.* demonstrated a successful switch with octreotide LAR injections by overlapping the first two long-acting injections with daily SC injections.[10] Liver function tests and ultrasound for the appearance of gallstones should be performed periodically in children on long-acting octreotide [Table 2].[11] Trials with sirolimus and nifedipine in diazoxide UR patients have shown variable results.[12-14] At present, such therapy can be considered experimental, with no conclusive evidence advocating its use as standard therapy in patients with diazoxide-UR CHI.[15] In children with persistent hypoglycemia, despite all pharmacological measures and not being candidates for surgical therapy, continuous glucose intake, especially at night, can be provided through a nasogastric or gastrostomy tube. Uncooked cornstarch, a complex carbohydrate with a slow release of glucose, can be tried at 1–2 g/kg/d as a single bedtime dose or in divided doses throughout the day.

In the absence of rapid gene testing, nuclear imaging with 18-F-DOPA PET/CT is performed in children with poor response to medical therapy to rule out focal CHI (indicated by locally high standardised uptake value) with a sensitivity of 85% and positive predictive value of 96%.[16] A newer radiotracer compound, Gallium-68-NODAGA exendine-4 (which is a glucagon-like peptide-1 agonist), is emerging as an alternative to conventional ^{18}F-DOPA PET/CT imaging, which requires a fasting state and encounters more frequent hypoglycemia.[17]

Detection of focal CHI allows lesionectomy and can result in a complete cure of CHI in 97% of cases.[18] However, at times, a lesion in the head of the pancreas, close to the bile duct insertion, may be difficult to excise, necessitating continuation of the conservative therapy. Children with

Table 2: Pharmacotherapeutic options in CHI.

Drug	Mechanism of action	Dose and frequency	Route	Adverse effects	Comments
Diazoxide	Binds to the K-ATP channel to keep it open	Starting dose 5 mg/kg/d; can titrate up to 15 mg/kg/d Every 8–12 h	Oral	*Acute:* Fluid retention, CCF, pericardial effusion, pulmonary hypertension, hyponatremia *Chronic:* Hypertrichosis, coarsening of facies, neutropenia, thrombocytopenia, hyperuricemia	Concomitant hydrochlorothiazide - fluid overload and synergistically improves blood glucose control. CBC, uric acid at initiation and 6 monthly thereafter; baseline 2D-ECHO at initiation and after 1 week
Octreotide	Somatostatin receptor analog	5–20 µg/kg/d; rarely up to 50 µg/kg/d Every 6–8 h	SC or IV	Tachyphylaxis after initial good response. At high doses: Necrotizing enterocolitis, cholelithiasis, and growth failure	An increment in the dose after a couple of days may be required. Growth monitoring, LFT and USG abdomen 6 monthly recommended
Long-acting Octreotide analogs (Octreotide LAR and Lanreotide autogel)	Somatostatin receptor analog	Cumulative dose of daily injections (Octreotide – LAR) or 30–60 mg of lanreotide once in 4–6 weeks	IM	Growth failure, elevated liver enzymes, gallstones	Growth monitoring, LFT and USG abdomen 6 monthly recommended
Glucagon	Glycogenolysis, gluconeogenesis, reduced hepatic uptake of glucose	In acute hypoglycemia: 30 µg/kg as a single dose or 2.5–20 µg/kg/h infusion to maximum dose of 0.5–1 mg	IM, IV or SC	Vomiting, respiratory distress, necrolytic migratory erythema (rare)	IV line set to be changed every 12 hours. Continuous subcutaneous infusions like an insulin pump have been tried but are unreliable due to the precipitation of glucagon and infusion line blockage.
Sirolimus	mTOR inhibitor – beta cell proliferation, insulin secretion and induces insulin resistance	0.5–1 mg/m^2/d; dose can be titrated to achieve serum sirolimus concentration of 5–15 ng/mL; every 24 hours	Oral	Immunosuppression, increased infection and lymphoma risk; pneumonitis; hepatic and renal dysfunction; dyslipidemia	CBC, LFT, RFT, lipid levels. Watch for respiratory symptoms.

CHI: Congenital hyperinsulinism of infancy, 2D-ECHO: 2-dimensional echocardiography, CBC: Complete blood count, CCF: Congestive cardiac failure, IM: Intramuscular, IV: Intravenous, K-ATP: Adenosine triphosphate sensitive potassium, LAR: Long-acting release, LFT: Liver function test, mTOR: Mammalian target of rapamycin, RFT: Renal function test, SC: Subcutaneous, USG: Ultrasonography

diffuse CHI UR to medical therapy may benefit from a near total pancreatectomy in which 98% of the pancreas is removed, leaving a small rim of tissue surrounding the pancreatic and bile ducts. However, there is a growing preference for conservative management over surgical treatment in children with diffuse CHI, relatively euglycemic on medical therapy.[19] Further, a high possibility of post-surgical complications such as persistent hypoglycemia, diabetes mellitus, and exocrine pancreatic deficiency has been reported. Almost all children develop insulin-dependent diabetes by the second decade, and two-thirds require pancreatic enzyme supplementation on follow-up.[8]

Irrespective of diazoxide-responsiveness, a genetic diagnosis can be made in 40–50% of patients with CHI. As per the recent international guidelines, genetic testing is recommended to be performed in all cases of suspected CHI who are diazoxide-responsive but continue to require therapy beyond 12 weeks of age.[7] Other than the K-ATP channel genes as described in Table 1, mutations in *GCK* can sometimes lead to severe diazoxide-UR CHI,[20]whereas mutations in *GLUD1, HNF4A, HNF1A, HADH,* and *SLC16A1* cause diffuse but milder hyperinsulinism, responsive to medical therapy.[21] In those 50–60% of cases in whom no mutation is identified, CHI is usually diffuse, diazoxide-responsive, and

remits with time.[6] In diazoxide UR infants, the chance of finding a positive mutation is almost 90%.[22]

Ambulatory management of CHI includes the timely administration of medications and maintaining a BG log through daily intermittent BG checks. A recent study revealed a diurnal pattern of hypoglycemia in children with CHI, occurring most frequently between 3 a.m. and 6 a.m. and pre-meal.[23] This could provide the basis for evaluating the effectiveness of self-monitoring of BG during specific times in the day when the child is at greatest risk of having a hypoglycemic episode.

Although the use of continuous glucose monitoring systems (CGMS) as a monitoring tool has been increasing, the accuracy of CGMS in patients with CHI has often been questioned. This is due to high variability in the setting of hypoglycemia, poor positive predictive value for low BG readings, and devices not being licensed for use in the very young. However, despite these drawbacks, it has been seen that CGMS aids in the detection of twice as many hypoglycemia events as compared to intermittent checks by glucometer.[24,25] The relationship between time in range (TIR) on a CGMS and neurodevelopmental outcome needs to be established.

The natural history of patients with CHI depends on the setting in which it occurs. Neonates born small for gestational age or with perinatal asphyxia and infants of diabetic mothers may present with transient hyperinsulinemic hypoglycemia. At times, they may require a short duration of diazoxide therapy, which can be tapered and stopped within 1 year of age. Genetic CHI secondary to *HNF4A* and *HNF1A* mutations is diazoxide-responsive and remits with time but causes the development of monogenic diabetes in the young subsequently.[4] Similarly, certain dominant *ABCC8* mutations may also have a dual phenotype of CHI followed by early onset diabetes.[26] The CHI can last for a variable period and may even persist into adulthood. Interestingly, as was demonstrated in our case, adults with such mutations are at risk of developing early-onset diabetes even without features of CHI in the past.[27]

Neurodevelopmental affection in the form of behavioral issues, epilepsy, cognitive impairment, motor delay, learning disabilities, and speech delay has been observed in up to half of all children with CHI.[8] Presentation within the first week of life and the requirement of a high dose of diazoxide, irrespective of underlying genetic etiology and histopathological type, are predictors of adverse neurodevelopment.[28] It has been suggested that an early diagnosis and initiation of treatment can help prevent the development of neurological morbidities.[8]

Neonatal hypoglycemia can sometimes be the only manifestation of congenital hypopituitarism, like in our second case.[29] The incidence of congenital hypopituitarism varies between 1 in 4000 and 10,000.[30] The clinical presentation may vary greatly from no symptoms to non-specific symptoms with or without phenotypic clues.[30] Obvious phenotypical features of midline anomalies such as cleft lip and palate, single central incisor, micropenis, and divarication of the recti and radiological features such as agenesis of the corpus callosum and optic nerve hypoplasia can be pointers to hypopituitarism. Neonates with such phenotypic and radiological features should be evaluated for hypopituitarism despite no clinical features and need to be followed up regularly for evolving pituitary hormone defects.[31,32]

GH deficiency (GHD) is likely to present with neonatal hypoglycemia, especially when associated with multiple pituitary hormone deficiencies (MPHD).[33] GH and cortisol act synergistically to elevate BG, and replacement of both hormones is necessary to maintain euglycemia in children with hypopituitarism.[34] Cortisol and GH are predominantly catabolic hormones that initiate gluconeogenesis and lipolysis and provide substrates for metabolism. TSH deficiency may present as prolonged physiological jaundice and, rarely, hypoglycemia.[35]

A careful and detailed medical history that may predispose the child to congenital, acquired, or syndromic forms of hypopituitarism needs to be noted. Most of the neonates with congenital hypopituitarism are usually born with normal anthropometry at birth. Although up to 52% of patients with hypopituitarism may have postnatal complications such as hypoglycemia, hyponatremia, and recurrent sepsis, the diagnosis is made in the neonatal period in only 23%.[36] The presence of central hypothyroidism is a simple clue to the possibility of an MPHD and underlying malformation of the pituitary gland.[37]

Even though low GH and cortisol levels during hypoglycemia are not diagnostic, they are significant pointers to the possibility of hypopituitarism.[29] Due to the lack of circadian rhythm for cortisol secretion in the initial 6 months, random cortisol assessment may be useful to establish cortisol deficiency. Mehta *et al*., validated that the combination of 8 a.m. serum cortisol >175 nmol/L (6.34 μg/dL) and 30-min cortisol >540 nmol/L (19.56 μg/dL) post-ACTH stimulation test excludes congenital adrenal insufficiency with high specificity (100%) and sensitivity (80%).[36] False-negative results can occur even in infants with ACTH deficiency as placental corticotropin-releasing hormone continues to stimulate adrenals for a few weeks after birth.[29,36] However, cortisol values at either 30 or 60 min below 500 nmol/L (18 μg/dL) can establish adrenal insufficiency.[38]

A random GH concentration of ≤5 ng/mL (5 μg/L) during the first 7 days of life, accompanied by other pituitary hormone deficiencies and/or the MRI abnormality, is sufficient to

diagnose GHD.[39,40] Binder *et al*. suggested that a GH cutoff of 7 μg/L as measured on a neonatal screening card by a highly sensitive polyclonal enzyme-linked immunosorbent assay gave 100% sensitivity and 98% specificity.[41] Physiological elevation of GH levels in the neonatal period, physiological decline in insulin-like growth factor-1 levels in the first 15–18 months of life, inherent risks of GH stimulation tests in the neonatal period, and lack of specificity of low GH with hypoglycemia to diagnose GHD are important diagnostic challenges in the diagnosis of neonatal GHD.[38,39,41]

MRI of brain and pituitary gland is mandatory to look for midline brain abnormalities such as absent or hypoplastic corpus callosum, absent septum pellucidum, schizencephaly, heterotopia, and optic nerve hypoplasia; structural changes such as hypoplastic pituitary gland with ectopic PP or undescended PP, and an interrupted or hypoplastic pituitary stalk and Rathke's cleft cysts.[42]

Several transcription factors have been closely associated with pituitary development and Rathke's cleft cyst, of which IsL1 (Islet-1) deletion has 100% penetrance.[42] *POU1FI (PIT-1), PROP1, HESX1, LHX3, LHX4, SOX2, SOX3, OTX2, TBX19 (T-PIT), DAX-1,* etc., are some of the common genetic mutations associated with congenital hypopituitarism. *LHX3* mutation is associated with deficiencies of GH, TSH, luteinizing hormone, and follicle-stimulating hormone, but rarely ACTH, and the PP is grossly unaffected.[43] Affected individuals have short, rigid cervical spine with limited neck rotation and trunk movement with sensorineural hearing loss. The pituitary morphology may vary from a small to an enlarged anterior pituitary with a lesion suggestive of a microadenoma.[44] Thus, genetic testing complements the clinical, biochemical and radiological diagnosis in children with hypopituitarism and helps to predict the evolution of the disease.[45,46]

Evaluation for cortisol deficiency and cortisol replacement in a dose of 9–12 mg/m^2/d in three divided doses before thyroxine replacement is necessary to prevent adrenal crisis. Subsequently, thyroxine is initiated in a dose of 10–15 μg/kg/d if TSH deficiency exists. In our case, hydrocortisone was initiated, and subsequently, thyroxine was added. Supplementation with cortisol will increase the free water excretion and may unmask diabetes insipidus and should be screened for. GH treatment can be commenced during the neonatal period in neonates with persistent hypoglycemia (despite hydrocortisone supplementation) with daily SC recombinant human GH injections in a dose of 22–35 μg/kg/d in the evening to mimic physiological GH release.[39] Lower doses (10–20 μg/kg/d) can also lead to a comparable response in neonates.[30] A small dose of GH requirement in neonates resulted in challenges with the practical delivery of accurate dosing. Hence, the authors used alternative day GH dosing based on personal experience and preferences. There is a scarcity of data on GH use in neonates.

CONCLUSION

CHI and hypopituitarism are important causes of persistent and recurrent hypoglycemia in newborns, with significant neurological implications in cases of delayed diagnosis and treatment. A systematic focus on clinical, laboratory diagnostic pointers, and genetics would clinch the diagnosis leading to early therapy initiation. Management is challenging in the neonatal age group, and an individualized approach based on the response to medications, underlying genetic etiology, and radiological findings should be adopted. Further, data on optimal dosing and delivery of GH treatment in neonates and better treatment options in diazoxide-UR cases are needed from research and practical experience. With improved accessibility and affordability, appropriate use of genetic analysis tools helps in understanding disease progression, prognosis, precision medication, and finally, genetic counseling where indicated.

Ethical approval

The Institutional Review Board approval is not required.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript, and no images were manipulated using AI.

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