International Journal of Contemporary Pediatrics
Ranabijuli PK et al. Int J Contemp Pediatr. 2025 Dec;12(12):2023-2028
http://www.ijpediatrics.com
pISSN 2349-3283 | eISSN 2349-3291

DOI: https://dx.doi.org/10.18203/2349-3291.ijcp20253787

Case Series

Varied etiologies and management of recurrent hypoglycemia in children: a case series

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Received: 23 October 2025
Accepted: 15 November 2025

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ABSTRACT

Recurrent hypoglycemia in childhood may be caused by various endocrine or metabolic disorders. We present a series of five cases with recurrent episodes of hypoglycemia. The critical blood samples of all the cases were sent for the diagnosis of recurrent episodes of hypoglycemia. Neuroimaging of the brain was done to determine the size and location of the pituitary gland. In our case series, three cases were diagnosed as panhypopituitarism, and the other two were diagnosed by exclusion as idiopathic hyperketotic hypoglycemia. In our case series, no child was detected to have a metabolic cause of hypoglycemia. This case series provides insight for the diagnosis and management of recurrent episodes of hypoglycemia in children beyond infancy.

Keywords: Recurrent hypoglycemia, Critical blood sample, Panhypopituitarism, Idiopathic hyperketotic hypoglycemia

INTRODUCTION

Glucose is an essential substrate for cerebral metabolism and its functioning. Hypoglycemia in children is a plasma glucose concentration low enough to cause signs and symptoms of brain dysfunction. Although a numerical value is difficult to define, a plasma glucose level of less than 50 mg/dl can be associated with neuroglycopenic symptoms. During hypoglycemia, various counter-regulatory mechanisms (glucagon, growth hormone, cortisol, and epinephrine) are activated.[1]

Recurrent episodes of hypoglycemia have serious consequences in children. Hypoglycemia in infancy and childhood represents a treatable cause of mental retardation and seizures. In case of persistent hypoglycemia beyond the neonatal period, one must consider hyperinsulinism, hypopituitarism, hereditary hepatic enzyme deficiencies, and ketotic hypoglycemia.[2,3]

Analysis of "a critical blood sample" at the presentation of spontaneous hypoglycemia or induced hypoglycemia includes serum insulin, cortisol, growth hormone, thyroid-stimulating hormone, thyroxine, IGF-1, free fatty acid, beta-hydroxybutyrate, lactate, uric acid, ammonia, and urine for ketone bodies.[4]

The current WHO recommendations for managing hypoglycemia in children include an initial intravenous bolus of 5 ml/kg of 10% dextrose, as well as oral feed intake, in addition to treating the underlying disease.[5]

Subsequent management of recurrent hypoglycemia depends upon the diagnosis. The management of panhypopituitarism includes hormone replacement therapy with growth hormone therapy, levothyroxine, and hydrocortisone.[6]

Idiopathic hyperketotic hypoglycemia may be diagnosed after ruling out various metabolic and hormonal conditions associated with ketotic hypoglycemia. Sufficient amounts of carbohydrates and proteins, avoidance of prolonged fasting, and increased frequency of food ingestion are the main modes of treating idiopathic ketotic hypoglycemia.[7]

CASE SERIES

Case 1

A 7-year-6-month-old male child, born of a non-consanguineous marriage, 5th by birth order, was brought to the hospital in an unconscious state with a history of fever and vomiting for 2 days. The child was unconscious with a Glasgow coma scale of 7/15; he was febrile with perspiration, had tachycardia, and his blood pressure was less than the 50th centile. He was having tachypnea and SpO_2 of 95 percent in room air. The random blood sugar measured by HGT was 17 mg/dl.

In the emergency room, the intravenous line was secured, and random blood sugar, serum electrolytes, and other blood investigations were sent. A bolus dose of 5 mL/kg of 10% dextrose was administered to the child, and the child was continued with an IV dextrose infusion. The child regained consciousness after bolus dose. Lab value of blood sugar was 20 mg/dl, confirming the diagnosis of hypoglycemia. The critical blood sample was also sent.

There was a history of multiple episodes of altered consciousness associated with generalized tonic-clonic seizures. The first episode occurred at the age of five. The child was seen by a neurologist and was started on oral levetiracetam. The child had recurrent convulsions despite good compliance with anticonvulsants.

Anthropometric examination of child revealed weight of 11 kg and height of 95 cm, which were less than 3rd percentile. X-ray of the wrist showed that bone age was less than height age, which was less than chronological age and was interpreted as likely hypopituitarism.

Critical blood sample investigations revealed TSH of 0.188 micro-IU/ml (0.60-4.84 micro-IU/ml) and free T4 of 0.4 ng/dl (0.92-2.07 ng/dl), which is below normal, and free T3 of 2.3 pg/ml (1.4-4.4), which is suggestive of central hypothyroidism. The fasting insulin was less than 0.4 micro-IU/ml (2.6-24.9 micro-IU/ml), and the C-peptide of 0.01ng/ml (1.1-4.4 ng/ml) ruled out hyperinsulinism. The growth hormone level was 0.1ng/ml (0.6-29 ng/ml), and the IGF-1 level of 31.9ng/ml (55-222 /ml) was below the normal range. The serum cortisol level was 3.8 µg/dl (5-25 µg/dl). The FSH of 0.4 micro-IU/ml (2.5-10), LH of 0.07 micro-IU/ml (2.5-10), and testosterone level of 0.07 ng/ml (4-11) were below the normal range. The vitamin D level of 10.1ng/ml suggested a deficiency. The urine ketones are negative. Urine GC-MS and blood TMS were negative.

MRI brain with contrast was suggestive of hypoplasia of the pituitary gland, which measured in height with an enhancing ectopic posterior pituitary at medial eminence. There was an absence of proximal infundibulum.

The above investigation confirmed the diagnosis of panhypopituitarism.

The child was started on the injection of Growth hormone given subcutaneously at a dose of 0.16 mg/kg/week. A tablet of hydrocortisone 5 mg in three divided doses after food, and a thyroxin tablet of 25 micrograms early morning on an empty stomach.

The child is also advised to avoid fasting and to have regular food intake at appropriate intervals. The parents were counseled in detail regarding the nature of the illness and the subsequent plan of management. Regular growth monitoring of the child has continued to date in the pediatrics OPD. The child had no episodes of hypoglycemia in the last 6 years and is currently thirteen years of age. The anthropometry in the road to health chart reveals height and weight still below 3rd percentile. The management plan for the child is to continue treatment for panhypopituitarism, including a proportionate increase in Inj. growth hormone doses.

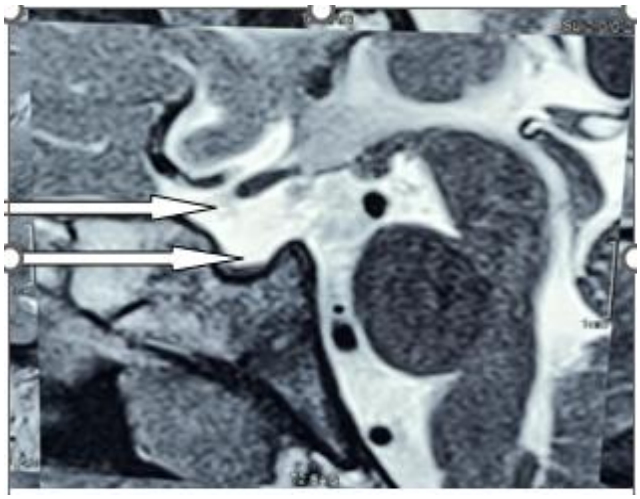

Figure 1: Case 1-Hypoplasia of the pituitary gland.
*Measured 2 mm in height, with an enhancing ectopic posterior pituitary at medial eminence. There was an absence of proximal infundibulum.

Case 2

A 5-year-6-month-old female child born of a non-consanguineous marriage, 3rdby birth order, with a history of four episodes of hypoglycemic seizures at the age of 15 months, 22 months, 4 years 5 months, and 4 years 7 months with a blood sugar of-27 mg/dl, 25 mg/dl, 29 mg/dl and 37 mg/dl, respectively.

The child was referred to our hospital for further management. The anthropometric examination of the child revealed a weight of 11.9 kg and height of 97 cm, which were less than the 3rd centile. The X-ray of the left wrist suggested a bone age of 2 years. The height age was calculated as three years, according to the growth chart. The bone age is less than the height age, which is less than the chronological age. The case is interpreted as likely hypopituitarism.

The critical blood sample revealed a blood sugar of 38 mg/dl. The free T4 level of 0.79 ng/dl (0.92-2.07 ng/dl) and TSH of 4.44 micro-IU/ml (0.60-4.84 micro-IU/ml) were suggestive of central hypothyroidism. The insulin level of<0.5 micro-IU/ml (2.6-24.9 micro IU/ml), C-peptide of 0.05 ng/ml (1.1-4.4) ruled out hyperinsulinism. The growth hormone of 0.380ng/ml (0.6-29 ng/ml), IGF-1 of7.52 ng/ml (55-222 ng/ml), serum cortisol of 0.43 microgram/ml (5-25 µg/dl), and ACTH-1.5 pg/ml (7.2-63.6) were suggestive of panhypopituitarism. The beta-hydroxybutyrate was below 0.01 mmol/L (0.02-0.27 mmol/L), blood ketone and urine ketone were negative, which ruled out ketotic hypoglycemia. The anti-tTg antibody at 0.20 RU/ml (0-10) was negative, ruling out celiac disease. Urine GC-MS and blood TMS were negative. MRI brain is suggestive of a small anterior pituitary gland, ectopic posterior pituitary bright spot, and small pituitary stalk findings suggestive of "pituitary stalk interruption syndrome".

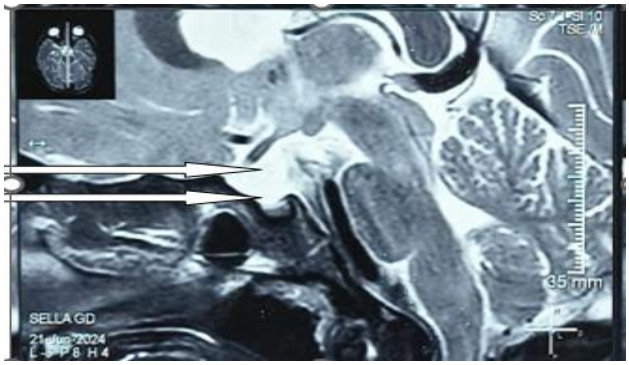

Figure 2: Case 2-Small anterior pituitary gland.
*Ectopic posterior pituitary bright spot, and small pituitary stalk findings are suggestive of "Pituitary stalk interruption syndrome.

Child started on tablet hydrocortisone, tablet thyroxine, and injection of somatropin at 0.9 IU/day subcutaneously.

Table 1: Comparison of case characteristics, laboratory values and MRI findings.

Variables	Case 1	Case 2	Case 3	Case 4	Case 5
Age at presentation	5 years	15 months	8 months	3 years	3 years
Anthropometric examination (weight and height)	Less than the 3rd percentile	Less than the 3rd percentile	Less than the 3rd percentile	Less than the 3rd percentile	Wt-10th to 25th centile Ht-50th to 75th centile
Random blood sugar	17 mg/dl	38 mg/dl	28 mg/dl	17 mg/dl	25 mg/dl
Fasting insulin (2.6-24.9 micro IU/ml)	0.4	<0.5	0.8	0.20	0.82
C-peptide (1.1-4.4ng/ml)	0.01	0.05	0.3	0.22	0.14
Serum cortisol (5-25 µg/dl)	3.8	0.43	3.8	3.8	19.04
IGF-1 (55-222 ng/ml)	31.9	7.52	<15	61.36	89.4
Growth hormone (0.6-29 ng/ml)	0.1	0.380	0.22	2.54	3.31
TSH (0.60-4.84 micro IU/ml)	0.188	4.44	0.01	1.72	1.90
Free T4 (0.92-2.07 ng/dl)	0.4	0.79	6.043	6.34	1.2
Venous blood gas	Normal	Normal	Normal	pH -7.01 (7.35-7.45), HCO_3-10.6 mmol/l (22-28), Lactate-0.7 (0.5-2.2 mmol/l)	pH -7.323 (7.35-7.45) HCO_3-20 mmol/l Lactate-
Urine ketones	Negative	Negative	Negative	Moderate	Moderate
MRI brain with pituitary	Hypoplasia of pituitary gland, which measured 2 mm in height, with an enhancing ectopic posterior pituitary at medial eminence. There was an absence of proximal infundibulum.	Small anterior pituitary gland, ectopic posterior pituitary bright spot, and small pituitary stalk findings are suggestive of "Pituitary stalk interruption syndrome.	The anterior pituitary gland appears smaller in size. The ectopic location of posterior pituitary gland in median eminence.	Pituitary dimensions are small for corresponding age, and no other pituitary lesion is seen.	No significant brain parenchymal abnormality. No evidence of intracranial space-occupying lesions. Pituitary and corpus callosum are normal.

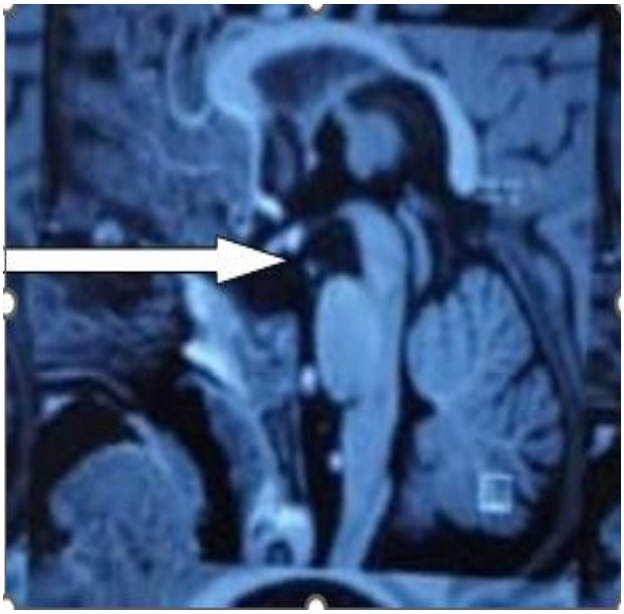

Figure 3: Case 3-The anterior pituitary gland appears smaller in size.

The ectopic location of the posterior pituitary gland in the median eminence.

Case 3

A 5-year-6-month-old male child born of a non-consanguineous marriage. There is a history of multiple episodes of altered consciousness associated with generalized tonic-clonic seizures. The child had documented hypoglycemia in each of the above episodes. The first episode occurred at 8 months, and there were multiple similar episodes every five to six months.

He was treated in the nearby health center for episodes of hypoglycemia and was also started on anticonvulsants.

The anthropometric examination of the child revealed a weight of 8 kg and height of 78 cm, which were less than the 3rd centile.

Critical blood sample revealed blood sugar of 28 mg/dl, serum insulin of 0.8 micro-IU/ml (2.6-24.9 micro-IU/ml), C-peptide of 0.3 ng/ml (1.1-4.4 ng/ml), ruled out hyperinsulinism. The Free T3-5 pmol/l, free T4- 6.043 ng/ml (0.92-2.07 ng/dl), T3-1.21 ng/ml, T4-13 ug/dl, TSH-0.01 micro IU/ml (0.60-4.84 micro IU/ml), IGF- 1-<15 ng/ml (55-222 ng/ml), IGF bp 3-<0.500 ug/ml, growth hormone was 0.22 (0.6-29 ng/ml), serum cortisol-3.8 microgram/dl (5-25 µg/dl), ACTH-4.23 pg/ml, prolactin-9.81 ng/ml, FSH-<0.05 micro IU/ml, LH-<0.01 micro IU/ml. GC-MS urine and blood TMS were negative. The MRI of brain suggested a smaller anterior pituitary gland and ectopic location of the posterior pituitary gland in the median eminence. The child was diagnosed with panhypopituitarism and started on tablet hydrocortisone, thyroxine, and injection somatropin.

Case 4

A 7-year-old male child born of a non-consanguineous marriage with a birth weight of 1.25 kg. The child was brought to the OPD with complaints of not gaining height and weight. There was a history of multiple episodes of convulsions each time early in the morning, while the child was at home in Jabalpur. The child was taken to a nearby hospital, and he was found to have low blood sugar levels and was appropriately treated in the hospital.

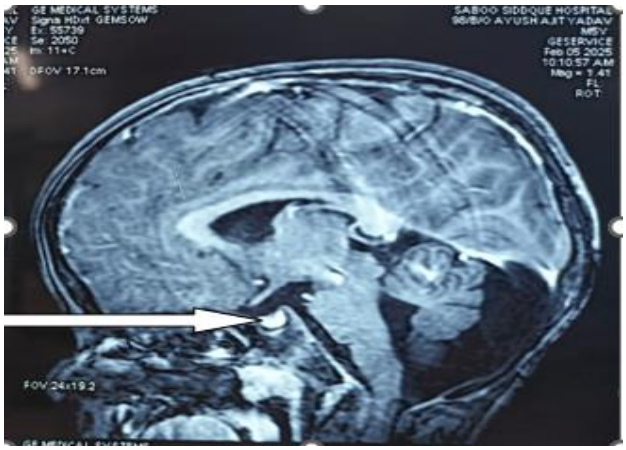

Figure 4: Case 4-Pituitary dimensions are small for the corresponding age.

The anthropometric examination of the child revealed a weight of 12.7 kg and height of 95 cm, which were less than the 3rd centile. The X-ray of the wrist suggested a bone age of 2 years 8 months. The height age as per the growth chart is 2 years 11 months. Hence, the bone age is less than the height age, which is less than the chronological age of 7 years. The interpretation is likely hypopituitarism.

After the child was admitted to our hospital, induced fasting was done for a ‘’critical blood sample”. The critical blood sample revealed a blood sugar of 17 mg/dl. The TSH of 1.72 micro-IU/ml (0.60-4.84 micro-IU/ml), free T3 level of 6.1 pg/ml (5.1-7.4), and free T4 of 6.34 ng/dl (0.92-2.07 ng/dl) were within normal limits. The anti-tTg antibody was negative (<0.2). The fasting insulin level was 0.20 micro IU/ml (2.6-24.9 micro IU/ml), and C-peptide was 0.22 ng/ml, which was low (1.1-4.4 ng/ml), which ruled out hyper insulinemia. The growth hormone level was 2.54 ng/ml, which is within normal limits (0.6-29 ng/ml). The serum cortisol level was 3.8 micrograms/dl, which was normal (5-25 microgram/dl). The serum IGF-1 level was 61.36 ng/ml, which was within normal limits (55-222 ng/ml). There is a vitamin D deficiency with a level of 10.1 ng/ml, the FSH of 0.4 micro-IU/ml (2.5-10), LH of 0.07 micro-IU/ml (2.5-10) and testosterone of less than 0.07 ng/ml (4-11) were below normal range. There were moderate urine ketones. The VBG showed a pH of 7.01(7.35-7.45), HCO_3-10.6 (22-28), lactate-0.7 (0.5-2.2 mmol/l) suggesting severe metabolic acidosis. Clonidine stimulation test was

performed at 0 minutes, 30 minutes, 60 minutes, 90 minutes, and 120 minutes, and results were 5.02 ng/ml, 7.71 ng/ml, 11.71 ng/ml, 10.09 ng/ml, and 7.6 ng/ml, which were within normal limits. Gas chromatography-mass spectrometry of urine revealed an increased excretion of 3-hydroxybutyric acid. Blood tandem mass spectrometry is suggestive of an amino acid and acylcarnitine profile within normal limits. MRI of brain with pituitary study (plain+contrast) suggestive of pituitary dimensions small for corresponding age. Child is diagnosed with idiopathic hyperketotic hypoglycemia with short stature, with a history of small for gestational age, and poor catch-up. The parents were advised to avoid prolonged fasting in the child and to increase the frequency of feeding during stress or illness. The child also started on injection somatropin at 0.24 mg/kg/week.

Case 5

A 5-year-old male child had a history of two episodes of early morning hypoglycemia with altered sensorium at home. The first episode was 2 years ago, and the last episode was five days ago. He was treated for hypoglycemia in a local hospital. The child was brought by their parents to our hospital for further management.

There was a history of hypoglycemia in the neonatal period, for which the child had a NICU admission.

The anthropometric examination of the child revealed a weight of 16 kg, which is observed between the 10th and 25th percentiles, and a height of 113 cm, which is between the 50th and 75th centiles.

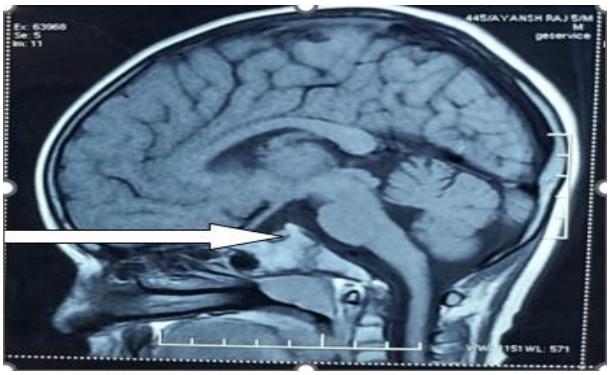

Figure 5: Case 5-Normal pituitary gland and corpus callosum.

The hypoglycemia was induced in the child for a critical blood sample. Investigations revealed a random blood sugar of 25 mg/dl, TSH of 1.90 micro IU/ml (0.60-4.84 micro IU/ml), and free T4 of 1.2 ng/dl (0.92-2.07 ng/dl), within normal limits. Fasting insulin of 0.82 micro IU/ml (2.6-24.9 micro IU/ml), C-peptide of 0.14 ng/ml (1.1-4.4), and USG abdomen and pelvis ruled out hyperinsulinism. The growth hormone levels of 3.31 ng/ml (0.6-29 ng/ml), IGF-89.4 ng/ml (55-222 ng/ml) and cortisol-19.04 microgram/dl (5-25 µg/dl), ruled out hypopituitarism. The serum lactate was 9.39 mg/dl (4.5-19.8 mg/dl). The venous blood gas reveals a pH of 7.323 (7.35-7.45), HCO_3 of 20 mmol/l. Serum beta-hydroxy butyrate-2 mmol/l (0.02-0.27). Moderate urine ketones are present. The GC-MS of urine revealed an increased excretion of 3-hydroxybutyric acid. The blood tandem mass spectrometry is suggestive of an amino acid and acylcarnitine profile within normal limits. The child is diagnosed with idiopathic hyperketotic hypoglycemia. The parents were advised to avoid prolonged fasting in the child and to increase the frequency of feeding during stress or illness.

DISCUSSION

In our case series of five children who presented with recurrent hypoglycemia, additional symptoms such as vomiting, lethargy, convulsions, and altered sensorium were present at the time of presentation. There was clinical improvement with protocol-based management for hypoglycemia.

A detailed clinical examination, including anthropometry, reveals that the height and weight are less than the third percentile, except for case 5, which falls between the 10th and 25th percentiles.

All the children had a history of multiple episodes of hypoglycemia; hence, detailed investigations were done in each case. Critical samples were sent at the time of a hypoglycemic episode in the emergency room in cases 1-3. The critical sample was obtained after induced hypoglycemia for cases 4 and 5.[3]

The critical blood sample investigations revealed that serum fasting insulin and C-peptide in all cases were normal, ruling out hyperinsulinemic hypoglycemia.[8,9]

The levels of free T4, serum cortisol, IGF-1, and growth hormone were low, and TSH was normal or low in cases 1-3, suggesting panhypopituitarism. The above investigations are in the normal range in cases 4 and 5.[10]

In cases 4 and 5, blood TMS was suggestive of amino acid and acylcarnitine profiles within normal limits. In cases 4 and 5, urine GC-MS increased excretion of 3-hydroxybutyric acid, thus ruling out inborn errors of metabolism. Venous blood gas analysis in both cases showed metabolic acidosis, and urine ketones were also moderately positive. The above two cases are suggestive of idiopathic hyperketotic hypoglycemia.[7]

Cases 1-3 commenced on hormone replacement therapy with growth hormone therapy, levothyroxine, and hydrocortisone.[10]

In cases 4 and 5, the management of idiopathic hyperketotic hypoglycemia prevents hypoglycemia, fatty acid oxidation, and protein deficiency by providing sufficient amounts of carbohydrates and protein. It

involves avoiding prolonged fasting, increasing the frequency of feedings, and close monitoring of oral intake, particularly during stressful situations or periods of high activity. The child's bedtime snacks, such as carbohydrates (cornstarch), will help prevent prolonged fasting. The episodes of hypoglycemia resolve spontaneously by 8 to 9 years of age in the idiopathic hyperketotic hypoglycemia cases.[7]

CONCLUSION

Recurrent hypoglycemia in children has various etiologies. A proper diagnosis and management are the cornerstone of an optimal outcome.

In our case series of five children, three children have hypopituitarism, and two were diagnosed as idiopathic hyperketotic hypoglycemia.

Almost all the children with both etiologies in our case series of recurrent hypoglycemia are anthropometrically less than the 3rd centile, suggesting the importance of detailed clinical examination, including anthropometry.

Neuroimaging of the brain and pituitary invariably shows anatomical changes in cases of growth hormone deficiency and panhypopituitarism; however, a small pituitary gland may also be found in idiopathic hyperketotic hypoglycemia, hence detailed endocrionological investigations are mandatory in each case of recurrent hypoglycemia.

Early diagnosis and appropriate hormone replacement therapy in children with panhypopituitarism are essential. The avoidance of fasting in children having idiopathic hyperketotic hypoglycemia and frequent feeding facilitated by parents with high-carbohydrate and high-protein diets will reduce the episodes.

In our case series, we did not encounter alternative etiologies of recurrent hypoglycemia; however, efforts must be made to rule out such cases in appropriate clinical settings.

ACKNOWLEDGEMENTS

The authors would like to thank the children and their parents for their cooperation. The authors would also like to thank the hospital administration of Jagjivan Ram Hospital, Mumbai, and the scientific and ethical committee of the hospital.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Ranabijuli PK, Nazparveen LA, Rajesh T, Ganesh K. Varied etiologies and management of recurrent hypoglycemia in children: a case series. Int J Contemp Pediatr 2025;12:2023-8.