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Case Challenge and Education – Case Report

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Hypoglycaemia in a Child Unmasks a Unique Association

Diksha Shirodkar Shaila Bhattacharyya

Department of Pediatrics, Manipal Hospitals, Bangalore, India

Keywords
Deficient anterior pituitary hormone with common variable immunodeficiency syndrome (DAVID syndrome) · Hypoglycaemia · Isolated secondary adrenal insufficiency · Isolated adrenocorticotropic hormone deficiency · Common variable immunodeficiency

Abstract
Childhood hypoglycaemia results from impairment or defects in glucose homeostasis and has a blood glucose (BG) operational threshold of 60 mg/dL (<3.3 mmol/L) as below this level, neurological symptoms occur, and if the BG falls below 50 mg/dL (2.8 mmol/L), it is highly likely to cause long-term neurological consequences. A 38-month-old previously healthy boy presented with hypoglycaemic seizures (BG: 30 mg/dL [1.7 mmol/L]) after a brief period of being unwell. The sepsis screen was normal. Hypoglycaemia screen detected a low cortisol level (28 nmol/L [83–555]). This was also associated with a low thyroid-stimulating-hormone (0.768 mIU/mL [0.5–5.5]) and a low-normal T4 (5.57 µg/dL [5–12]). Hydrocortisone and levothyroxine replacement was started. Four weeks from the time of discharge, the short synacthen test (SST; generic name: tetracosactide acetate) for adrenal function revealed a low stimulated cortisol (2/1.51/1.52 nmol/L at 0, 30, and 60 min, respectively, post synacthen [normal range: 83–550; peak >420 µg/dL]) and low basal adrenocorticotropic hormone (4.6 pg/mL [10–60]). A rare diagnosis of isolated secondary adrenocortical insufficiency was made, and the neuroimaging demonstrated a reduced pituitary height (3 mm). Three months later, levothyroxine was tapered and omitted as the child was euthyroid, but the SST showed a similar flat response to the synacthen. The genetic testing demonstrated a pathogenic heterozygous mutation in the nuclear factor kappa B subunit 2 (NFKB2) gene responsive for common variable immunodeficiency (CVID), and this entity has been described as deficient anterior pituitary hormone with CVID syndrome (DAVID syndrome). The immunoglobulin profile showed a decrease in three types of immunoglobulin (IgM, IgG, and IgE), meeting the diagnostic criteria for CVID. Till date, less than 35 cases are reported worldwide, and of which, less than 5 of them presented with adrenal insufficiency prior to immunodeficiency, making this case rare and teaching us a lesson to think beyond the usual causes of hypoglycaemia.

Introduction

In childhood, hypoglycaemia is a common metabolic-endocrine emergency with a varied aetiology, which can lead to serious permanent neurological deficits, if not acted upon immediately. It is therefore important to detect and treat these children promptly. In this case report, we describe a young lad who presented with hypoglycaemic seizures, the aetiology of which left us intrigued. Written informed consent was obtained from the parents of the child for publication of the details.

karger@karger.com
www.karger.com/dde

Correspondence to:
Diksha Shirodkar, shirodkardikshas@gmail.com; Diksha.shirodkar@uhbw.nhs.uk

Table 1. Investigations at presentation

Investigations	Results	Normal range
Random BG, mg/dL	**30**	70–110
Insulin, µIU/mL	0.2	(<2)
C peptide, ng/mL	1.87	(0.4–2.2)
Cortisol, nmol/L	**28**	(83–555)
	219 (post IV hydrocortisone)	
GH, ng/mL	14.73	>7
Ammonia, µg/dL	**68**	<50
Lactate, mmol/L	2	(1–2.4)
Bicarbonate, mmol/L	18	22–28
TMS	No fatty acid/urea cycle/amino acid defect	
Urine ketones	**Urine trace proteinuria with 1+ ketones**	
TSH, mIU/L	**0.768**	0.5–5
T4, µg/dL	**5.57**	5–12
T3, ng/mL	**0.84**	0.80–2.0

Case Report

A 38 month-old boy presented with fever, cough, respiratory distress, and diarrhoea for 1 week. He was evaluated in the local hospital and found to have dengue fever (NS1 antigen rapid testing-positive) with bronchopneumonia. He was on antibiotics and due to poor response to therapy, was referred to us. When he presented to us, he was actively seizuring with a blood glucose (BG) = 30 mg/dL (1.7 mmol/L) and poor perfusion. He had a blood pressure of 70/40 (50) mm Hg, a capillary refill time of 4 s, and tachycardia (175 beats/min). Fluid (0.9% saline) resuscitation and 10% glucose bolus (2 mL/kg) was administered, and simultaneously, a hypoglycaemia-screen was done. Prior to this illness, there were not any specific concerns; he was born out of a non-consanguineous marriage at term (only child) having an uneventful neonatal-postnatal period, developmentally normal, without prior hospitalizations. On examination, after initial resuscitation, he weighed 14 kg (25th centile), was 106 cm (97th centile) tall, and had normal prepubertal male genitalia. Baseline investigations demonstrated anaemia, neutrophilic leucocytosis, elevated transaminases; however, despite high C-reactive protein (117 mg/dL [<10]), blood cultures were sterile. Broad spectrum dual antibiotics (vancomycin and meropenem) were commenced; echocardiography performed in view of shock revealed pulmonary hypertension requiring sildenafil. The hypoglycaemia screen (Table 1) showed low cortisol (28 nmol/L [83–555]) and thyroid-stimulating-hormone (TSH) (0.768 mIU/mL [0.5–5.5]), a low-normal T4 (5.57 µg/dL [5–12]), and ketonuria. A stress dose of hydrocortisone was initiated at 50 mg stat followed by 30 mg/m^2/day. After adequate steroid cover for 48 h, 25 µg (once daily) of levothyroxine was initiated. Although sick euthyroid syndrome was a reasonable diagnosis to consider, in view of two anterior pituitary hormones affected, it was prudent to think of a central cause, and hence, a neuroimaging was done which showed a reduced pituitary height of 3 mm with a eutopic bright spot (Fig. 1). There were not any electrolyte disturbances or fluid-balance perturbations after the stress dose of hydrocortisone and the correction of hypoglycaemia. The child improved gradually and was discharged on physiological doses of cortisol and levothyroxine. Review after 4 weeks showed that the free T4 had improved, and hence, levothyroxine was reduced; however, the early morning basal cortisol was still low, and hence, a short synacthen test (SST; generic name: tetracosactide acetate) was performed (Table 2). The response was flat (along with a low adrenocorticotropic hormone [ACTH]), and the provisional diagnosis of isolated secondary adrenocortical insufficiency (ISAI) was performed. Three months later, levothyroxine was stopped as the TSH and free T4 were now normal, but the SST still showed a poor response with low baseline ACTH (Table 2). In the interim, apart from one brief-lasting illness in 3 months (acute otitis media), treated with oral antibiotics (amoxicillin-clavulanic acid) along with a stress dose of hydrocortisone (serum cortisol during illness was 14.6 nmol/L), the growth velocity was unremarkable. There were no other pituitary hormones affected, and we had to investigate the possible genetic aetiology for ISAI. To delineate the aetiology of this rare entity, a clinical exome

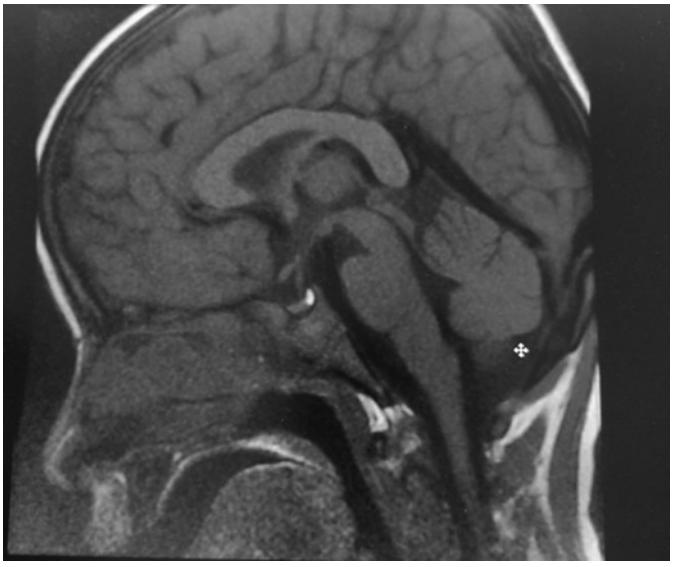

Fig. 1. MRI brain-sagittal T1-weighted images showing the reduced pituitary height for age of 3 mm with a normal posterior pituitary bright spot. The stalk appears normal. Rest of the brain parenchyma reported to be normal.

Table 2. Investigations on follow-up

Investigations	Time duration after discharge		
	4 weeks	10 weeks	3 months
Glucose, mg/dL (70–110)	90	98	110
Free T4, ng/dL (0.8–2.2)	2.5	1.44	1.58
TSH, mIU/L (0.5–5.5)	2.03	3.21	3
Cortisol, nmol/L (83–555)	**2**	**14.66 (unwell)**	**2**
17 OH P, ng/mL (<1.2)	2.40		0.01
Na/K/Cl, mmol/L (135–145/3.5–5.5/90–11)	141/5/101	138/4.2/99	
	0 min	30 min	60 min
SST at 4 weeks from discharge			
Cortisol, nmol/L (peak 420)	2	1.51	1.52
ACTH, pg/mL (10–60)	4.64		
SST at 3 months from discharge			
Cortisol, µg/dL (3–21) peak >15	0.12	0.14	0.16
ACTH, pg/mL (10–60)	2.6		

sequencing was performed which demonstrated a pathogenic heterozygous mutation in nuclear factor kappa B subunit 2 (NFKB2) exon 23, c.2611C>T [P.Gln871Ter] responsible to cause common variable immunodeficiency [CVID]. The literature search for this rare yet unique association unveiled an entity called Deficient Anterior pituitary hormone with CVID (DAVID) syndrome. The immunoglobulin profile showed a decrease in three types of Immunoglobulin (IgM = 8.96 mg/dL [31–208], IgG = 278.90 mg/dL [572–1,474], and IgE<0.10 mg/dL [<90]), satisfying the diagnostic criteria for CVID. DAVID syndrome itself is rare enough, and to add to this, the manifestation of adrenal insufficiency before the clinical manifestation of CVID makes this report unique.

Discussion

ACTH deficiency is a rare cause of secondary adrenocortical insufficiency in children and was first reported in 1968 in a child who presented with severe hypoglycaemia [1, 2]. TPIT (TBX19) is a cell-specific transcription factor needed for the processing of the POMC gene, and the resultant corticotroph differentiation in the anterior pituitary and mutagenic variants in this gene can present with ISAI [3]. However, these mutations present early in the neonatal period with seizures, hypoglycaemia, and failure to thrive [4]. Loss-of-function mutations of the POMC gene presented with red hair, pale skin, and early-onset severe obesity [5]. Other causes of ISAI have been observed as a functional manifestation of lymphocytic hypophysitis (seen more commonly in postpartum women), Prader-Willi, and Kabuki syndrome [6–8]. CVID, although the most common cause primary immunodeficiency, is still a rare condition with an incidence of 1:25,000, characterized by a marked decrease in, at least, two types of Ig (IgG, IgA, and/or IgM) and impaired specific antibody formation after vaccination/infection [9]. CVID is often associated with autoimmune cytopathies. The non-coincidental coexistence of these two conditions was first reported by Tovo et al. [10] and a few years later by Younes et al. [11] in the years 1991 and 2002, respectively, wherein a child who was diagnosed with CVID presented with adrenal crisis and an autoimmune cause for ISAI was hypothesized. The closely knit neuro-endocrine mechanisms (ACTH, POMC peptides, and endorphins along with their receptors being derived from cells of the immune system [12]) for the two conditions was the reason leading to postulations of a genetic defect responsible for this condition. The functional interactions between endocrine and immune systems, although well established, are still partially understood. The bidirectional relation between the pituitary hormones (TSH, prolactin, ACTH, GH) being expressed in the lymphocytes and the cytokines controlling the anterior pituitary hormonal expression/secretion led to the thought of a single gene attributable for this association. The very low incidence of both the conditions, the existence of this combination in a single kindred (familial predisposition), and the interaction between the immune system and the hypothalamo-pituitary-adrenal axis led to further research, and thus, a breakthrough was seen in 2012

wherein the term DAVID came into existence [13]. Although, the NF-κB signalling pathway (pivotal regulator of innate and adaptive immunity controlling B-cell maturation and T-cell differentiation) mutation being responsible for CVID is an established fact, the mechanism by which aberrations of this pathway causes ISAI is yet not clearly deciphered and remains an unsolved mystery. The theory of autoimmunity seems most plausible since circulating autoantibodies against endocrine organs were detected in some, not all, patients [9, 14, 15]. We do not have anti-pituitary antibodies testing easily available in India and hence could not assess these in our patient. Almost all reported patients carrying NF-κB2 pathogenic variants have primary immune deficiency, but only 44% have ACTH deficiency [9]. The common pathogenic variant described in the case of DAVID syndrome was the nonsense NF-κB2 pathogenic variant (c.2557C>T, Arg853Ter), resulting in an abnormal protein [9]. However, there are other NF-κB2 pathogenic variants reported in DAVID syndrome patients, including nonsense, missense, and frameshift mutations in exons 22 and 23 [9]. In our patient, there was a distinctively unique NFKB2 mutation at c.2611C>T (p.Gln871Ter), which was seen in only 1 other patient [9] among the 33 patients reported to have DAVID syndrome (from 27 families). Unlike most reported cases, our patient presented with ACTH deficiency before florid CVID symptoms. A similar picture was seen in only 3 other patients, making this presentation rare [14, 16, 17]. Other concomitant endocrinopathies (growth hormone deficiency, hypothyroidism, and diabetes insipidus) have also been described [11, 13, 18–22], but those were not found in our patient. The hypoplastic pituitary identified in our patient was also reported in 6 other patients [13, 15, 16, 21, 23, 24], but it is not a characteristic feature as the studies in Lym1 mouse models carrying pathogenic mutations in the NF-κB2 gene also show normal pituitary anatomy, hypothesizing that NF-κB2 pathogenic mutations have inconsistent effects on the development of the hypophysis [9]. To summarise, DAVID syndrome widened our approach towards the aetiology of hypoglycaemia and un-curtained this peculiar yet rare association.

Conclusion

Although rare, it is relevant to think of a possibility of CVID if an otherwise-well child presents with an ISAI without an apparent cause. The phenotype of this association is varied and is expanding from an isolated ACTH deficiency to multiple anterior pituitary and posterior pituitary deficiencies. Further studies will be required to delineate the exact phenotype-genotype correlation of the NFKB2 mutation causing DAVID syndrome. The importance of genetic testing and early diagnosis not only would benefit the proband but also the siblings. Considering the clinical heterogeneity of presentation, consequences of undiagnosed life-threatening condition, and the ease of treatment, pre-symptomatic genetic testing of siblings and parents is recommended for these mutations.

Statement of Ethics

Written informed consent was obtained from the parents of the child for publication of the details and any accompanied images. Published research complies with the guidelines for human studies and was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. The Ethics Committee of Manipal Hospitals, Bangalore, has provided a no-objection certificate for the publication of this case report. Official document lies with the authors and the institution (attached as supplementary material).

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

D.S. and S.B. were involved in clinical management of the patient and collecting the clinical data. D.S. wrote the first draft of the manuscript and was revised by S.B., D.S. and S.B. provided intellectual inputs. Both the authors have read and approved the final draft of the manuscript submitted. D.S. will serve as the corresponding author.

Data Availability Statement

All data generated or analysed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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