CASE REPORT

Stress hyperglycaemia as a result of a catecholamine producing tumour in an infant

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SUMMARY

Hyperglycaemia commonly occurs in children presenting at the emergency department. In the absence of diabetic symptoms, this stress-related hyperglycaemia is considered a benign condition. We present a malignant cause of hyperglycaemia in an 11-month-old girl with concomitant symptoms of a neuroendocrine malignancy. One month earlier, she had undergone an episode of stress-related hyperglycaemia concurrent with fever during an upper respiratory tract infection. Current glucose level was 234 mg/dL (13 mmol/L) and the glycosylated haemoglobin level was 44 mmol/mol (6.2%) without metabolic acidosis. We observed periods of hyperglycaemia, sweating, flushing, hypertension and tachypnoea. Urinalysis showed high amounts of catecholamine intermediates. Abdominal ultrasound revealed a mass originating in the right adrenal gland. Histology confirmed the diagnosis of neuroblastoma. Hyperglycaemia in this patient was the first presenting symptom of a metabolically active neuroblastoma.

type 2. At the time, the hyperglycaemia was considered to be secondary to a stress response as a result of infection. Follow-up of blood glucose levels was initiated.

Two weeks later, the patient returned with sweating, flushing and tachypnoea, but no history of polyuria, polydipsia or weight loss. Physical examination revealed no abnormalities besides hypertension (130/85 mm Hg). Her blood glucose level was now elevated in the diabetic range 234 mg/dL (13 mmol/L), and we measured increased levels of glycosylated haemoglobin (HbA1c 44 mmol/mol, 6.2%), indicating longer duration of hyperglycaemia. According to the American Diabetes Association (ADA) guidelines, our patient was, based on HbA1c level, classified as possible 'pre-diabetes'.¹ She was admitted for further evaluation of the glucose metabolism. No insulin therapy was initiated. Besides, the symptoms of catecholamine secretion, suspicious for a neuroendocrine (NE) malignancy, warranted further diagnostic steps, as pointed out below.

BACKGROUND

Hyperglycaemia in the hospital is defined as any blood glucose level ≥ 140 mg/dL (7.8 mmol/L).¹ The prevalence of hyperglycaemia in children presenting to the emergency department is estimated to be 4%.² Stress-related hyperglycaemia is thought of as a benign physiological condition, resulting from complex mechanisms of counter-regulatory hormones. Stress-related hyperglycaemia commonly occurs in children suffering from fever, seizures, trauma, burns, surgery or sepsis. The diagnosis of new-onset diabetes mellitus is usually straightforward in a child with hyperglycaemia and classic symptoms such as polyuria and polydipsia, associated with metabolic acidosis and ketonaemia. In this report, we present a case in which stress hyperglycaemia was the first presentation of a malignant tumour.

CASE PRESENTATION

We present a case of an 11-month-old girl born to non-consanguineous parents of Indian origin. Her medical history was unremarkable. During the past few weeks, the patient had been medically evaluated several times because of intermittent fever. Her symptoms were attributed to recurrent upper respiratory tract infections. At first presentation, peripheral blood leucocyte count and C reactive protein level were unremarkable, but her random blood glucose level was raised 168 mg/dL (9.3 mmol/L). There was no history of intoxication. Family history was positive for diabetes mellitus

INVESTIGATIONS

Normal laboratory findings of insulin (3.4 mE/L) and C-peptide (0.43 nmol/L) ruled out insulin deficiency or resistance. There were no signs of hypercortisolism (cortisol level 169 nmol/L) or hyperthyroidism (free thyroxine 19 pmol/L). Clinically, there were no signs of infection. C reactive protein was normal (<1 mg/L) in concordance with negative serology for various infectious agents.

During 24 h continuous glucose monitoring (CGM, figure 1), periods of sweating, flushing and tachypnoea were observed, coinciding with short episodes of hyperglycaemia. An abdominal ultrasound revealed a mass with a 5 cm diameter in the right adrenal area, more suspect for neuroblastoma than for pheochromocytoma. Twenty-four hour

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Figure 1 Schematic representation of glucose values during 24 h of continuous glucose monitoring system.

Figure 2 Overview of catecholamine metabolism. ADH, alcohol dehydrogenase; MAO, monoamine oxidase; COMT, catechol-O-methyltransferase; DOPEGAL, 3,4-dihydroxyphenylglycolaldehyde; DOPAL, 3,4-dihydroxyphenylacetaldehyde; MHPG, 3-methoxy-4-hydroxyphenylglycol; VMA, vanillylmandelic acid; HVA, homovanillic acid.

urine analysis showed high amounts of catecholamine intermediates homovanillic acid (HVA), vanillylmandelic acid (VMA) and 3-methoxy-4-hydroxyphenylglycol (MHPG; [figure 2](#)).

Nuclear ^{123}I -Metaiodobenzylguanidine (MIBG) scintigraphy demonstrated ^{123}I -MIBG uptake by the local tumour. There were no signs of metastatic disease. A biopsy was performed and histology confirmed the diagnosis of poorly differentiated neuroblastoma, without N-myc amplification.

OUTCOME AND FOLLOW-UP

A primary R0 resection of the tumour was performed after effective preoperative blood pressure treatment with α -adrenergic

Figure 3 Summary of diagnostic process (CRP, C reactive protein; HbA1c, glycosylated haemoglobin; HVA, homovanillic acid; VMA, vanillylmandelic acid).

blocking agents. After resection, glucose levels in our patient normalised.

DISCUSSION

Stress hyperglycaemia is a common entity in the paediatric population. In children, it is documented with an incidence of approximately 5% during acute physiological stress,³ varying from 3.7% to 12.7%.^{4 5} Differences in prevalence might be explained by varying definitions of hyperglycaemia and severity of disease. However, all authors agree that stress induced hyperglycaemia is a common entity, especially in children <6 years of age.^{3 6} The development of stress hyperglycaemia is caused by a highly complex interplay of counter-regulatory hormones such as catecholamines, growth hormone, cortisol and cytokines. High hepatic output of glucose, especially through gluconeogenesis, seems to be the most important contributor to stress hyperglycaemia.⁷ By definition, stress hyperglycaemia is transient. By the time our patient returned 2 weeks later, the fever had resolved but hyperglycaemia persisted, warranting further diagnostic work up. This work up is summarised in [figure 3](#), showing that the focus gradually shifted from the hyperglycaemia to analysis of new alarming symptoms.

During 24 h CGM, symptoms of tachypnoea, sweating, hypertension and flushing came concurrent with periods of hyperglycaemia. The initial symptoms were reminiscent of catecholamine overproduction, as can be seen in patients with NE tumours. However, the age of the patient was not consistent with pheochromocytoma, the most common NE tumour. Neuroblastoma, another NE tumour of the neural crest, is typical for this age group. Indeed, our patient was diagnosed with an adrenal neuroblastoma. However, hypertension, flushing and sweating are uncommon in neuroblastoma and hyperglycaemia has never been described. The difference in symptoms between pheochromocytoma and neuroblastoma can, in part, be explained by differences in maturation of the tumour cells and their enzymatic system for catecholamine production. Neuroblastoma often produces high levels of dopamine and the degrading end product HVA. Pheochromocytoma produces more (nor-)epinephrine and the end product VMA. Therefore, flushing, hypertension and even hyperglycaemia in our patient, are rare symptoms. Metabolically, this patient showed high levels of VMA, HVA and norepinephrine.^{8 9}

Overgrowth of sympathetic neuroblasts led to persisting sympathetic activation with an ongoing surge of catecholamines and glucagon secretion. In healthy people, insulin levels rise after a meal to promote glucose uptake in cells. Glucagon is generally antagonistic to insulin, and prevents hypoglycaemia by stimulating glycogenolysis and gluconeogenesis to increase glucose output. The ongoing surge of catecholamines and persistent high levels of glucagon in our patient may have had synergistic

Learning points

- Stress hyperglycaemia in children is common, and usually has a benign cause.
- Hyperglycaemia as a presenting symptom of neuroblastoma has not been described before, but can occur as a result of increased catecholamine production.
- Awareness of neuroblastoma in the setting of symptoms of catecholamine overproduction should lead to an early diagnosis.

effects so that gluconeogenesis was maintained even in the presence of normal levels of insulin.¹⁰

Stress hyperglycaemia is considered a benign condition. However, in the presence of other symptoms associated with sympathetic stimulation, the presence of a catecholamine-secreting tumour needs to be considered.

Contributors DM initiated presentation of the case together with AMdG, and supervised writing of the manuscript. EPB supervised in the oncological aspects of the case, together with MMvN, who is the treating paediatric oncologist.

Competing interests None declared.

Patient consent Obtained.

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