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Diarrhoea in a 2-year-old boy – thinking beyond the gut

Biegunka u 2-letniego chłopca – etiologia pozajelitowa

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Abstract

We report a male child with an unusual, very rare cause of chronic diarrhoea – WDHA (watery diarrhoea, hypokalaemia, achlorhydria) syndrome. A 2-year-old boy presented with long-term diarrhoea, failure to thrive and a presumed diagnosis of coeliac disease. The failure of a gluten-free diet, permanent hypokalaemia and the progressive worsening of the patient's condition led to the finding of an adrenal tumour (mature ganglioneuroma) with elevation of vasoactive intestinal polypeptide (VIP) – criteria for the diagnosis of WDHA syndrome. Complete symptoms resolution occurred after tumour excision.

Keywords: WDHA, VIP, celiac disease, hypokalaemia

Streszczenie

W niniejszej pracy opisujemy przypadek dziecka z przewlekłą biegunką o niezwykle rzadkiej etiologii, jaką jest zespół WDHA (*watery diarrhoea, hypokalaemia, achlorhydria*), w języku polskim częściej określany jako zespół Vernera–Morrisona. U dwuletniego chłopca występowały przewlekła biegunka oraz niedobór wzrostu i wagi, skutkując domniemanym rozpoznaniem celiakii. W wyniku dalszego postępowania diagnostycznego, wynikającego z braku efektów wprowadzonej diety bezglutenowej oraz utrzymującej się hipokaliemii przy pogarszającym się stanie pacjenta, ujawniono guza nadnerczy (dojrzały *ganglioneuroma*) oraz podwyższone stężenie VIP (*vasoactive intestinal polypeptide*, wazoaktywny peptyd jelitowy), które stanowią kryteria rozpoznania zespołu Vernera–Morrisona. Objawy ustąpiły całkowicie po chirurgicznym usunięciu guza.

Słowa kluczowe: zespół Vernera–Morrisona, VIP, celiakia, hipokaliemia

A 2-year-old boy presented to our general paediatric department with an 8-month history of chronic diarrhoea and failure to thrive. Stool frequency increased from 3 to 7–10 non-bloody, liquid bowel movements per day, he stopped gaining weight and gradually lost the ability to walk independently. There was no fever, vomiting or other associated gastrointestinal symptoms, as well as no surgical, medical or medicinal history. Three months after disease onset, raised IgG antigliadin antibodies were revealed by the primary care physician, and a gluten-free diet was prescribed, but was completely ineffective.

On physical examination, the boy was cachectic [weight – 10 kg (4.4%), height – 84 cm (10%)], mildly dehydrated, with obvious muscle wasting. The boy was afebrile, but tachycardic (120 bpm). His abdomen was distended but nontender and soft. No organomegaly or peripheral lymphadenopathy was noted.

Laboratory tests showed hypochromic anaemia (haemoglobin – 97 g/L) and persistent severe hypokalaemia of 1.8–2.4 mmol/L. Serum chloride and antiendomysium IgA antibodies were normal. Stool culture was negative. Duodenal mucosal biopsy showed villous atrophy. The patient was provisionally diagnosed with a malabsorption syndrome, made nil by mouth, and put on parenteral nutrition, but the voluminous diarrhoea continued and the patient remained persistently hypokalaemic despite aggressive intravenous fluid resuscitation and daily potassium replacement in excess of 4.5 mmol/kg. Therefore, abdominal magnetic resonance imaging (MRI) was performed (Figs. 1, 2). MRI showed an adrenal mass in the right adrenal gland, measuring 6.3 × 3.4 × 4.4 cm. Following surgical excision, there was complete resolution of his diarrhoea and normalisation of serum potassium. His food tolerance quickly improved. Histology was of a benign mature ganglioneuroma.

Our patient's presentation was the most consistent with WDHA (watery diarrhoea, hypokalaemia, achlorhydria) syndrome because he had the typical symptoms of secretory diarrhoea and refractory hypokalaemia. The diagnosis of WDHA syndrome was based on the fast disappearance of all symptoms after the excision of ganglioneuroma, and confirmed by an increased vasoactive intestinal polypeptide (VIP) level. Celiac disease was ruled out by the negative results of IgA – antiendomysial antibodies (which are highly sensitive and specific for celiac disease, whereas IgG antigliadin antibodies are the least specific for it), as well as non-typical histologic findings of the duodenal mucosa and complete inefficiency of the gluten-free diet.

DISCUSSION

This very rare syndrome of WDHA is characterised by oversecretion of VIP from non-beta pancreatic islet cells[1,2]. Because this condition resembles cholera, Matsumoto et al. (1966) suggested an alternative term – "pancreatic cholera"[3]. Only 800 cases have been reported worldwide[4]. In adults, this syndrome is most commonly associated with pancreatic islet cell tumours, but is rarely caused by non-pancreatic tumours, such as bronchogenic carcinoma, medullary thyroid carcinoma, retroperitoneal histiocytoma and adrenal pheochromocytoma[5]. In paediatrics, VIP-producing tumours are more usually neurogenic in the retroperitoneum and mediastinum[6]. Clinical experience is based mainly on case reports[7,8]. 7/10 patients with ganglioneuroblastomas in a series of 62 were children[9]. The majority of VIPomas diagnosed in children are either ganglioneuromas or ganglioneuroblastomas. The incidence of ganglioneuroma is approximately 1 per 100,000 children in the United States[10]. According to the Surveillance, Epidemiology, and End Results (SEER), the incidence of neuroblastoma is approximately 9.5 cases per one million children[11]. Despite the clinical severity, a diagnosis of a VIP-secreting tumour is often delayed. On literature review, we found less than 60 cases of paediatric VIP-secreting tumours[8]. Most of them were either adrenal pheochromocytoma or mixed pheochromocytoma-ganglioneuroma tumours[12].

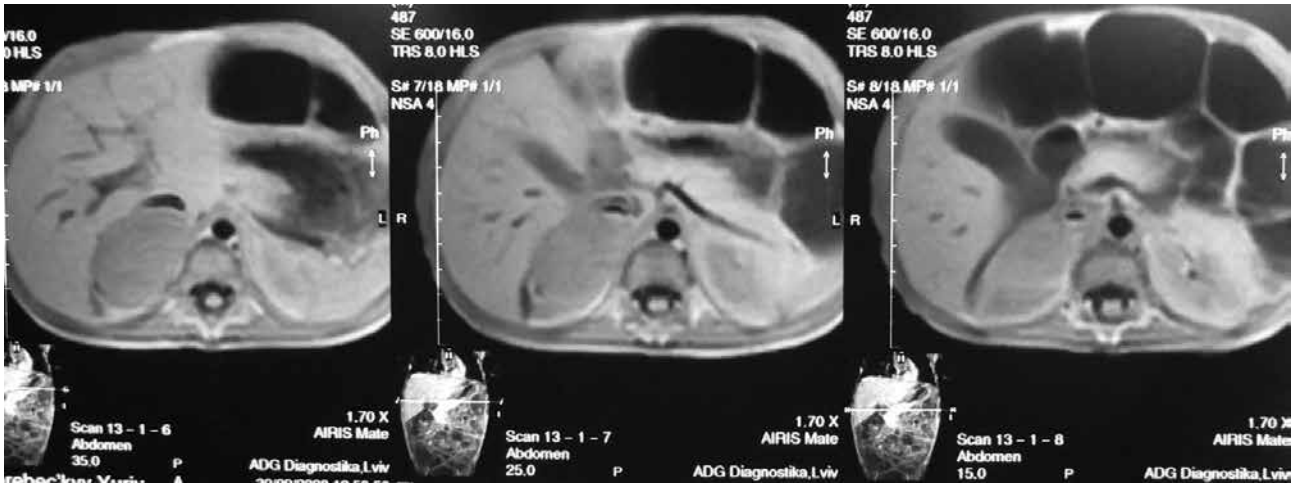

Fig. 1. MRI of the patient's abdomen showing a sub-diaphragm paravertebral tumour

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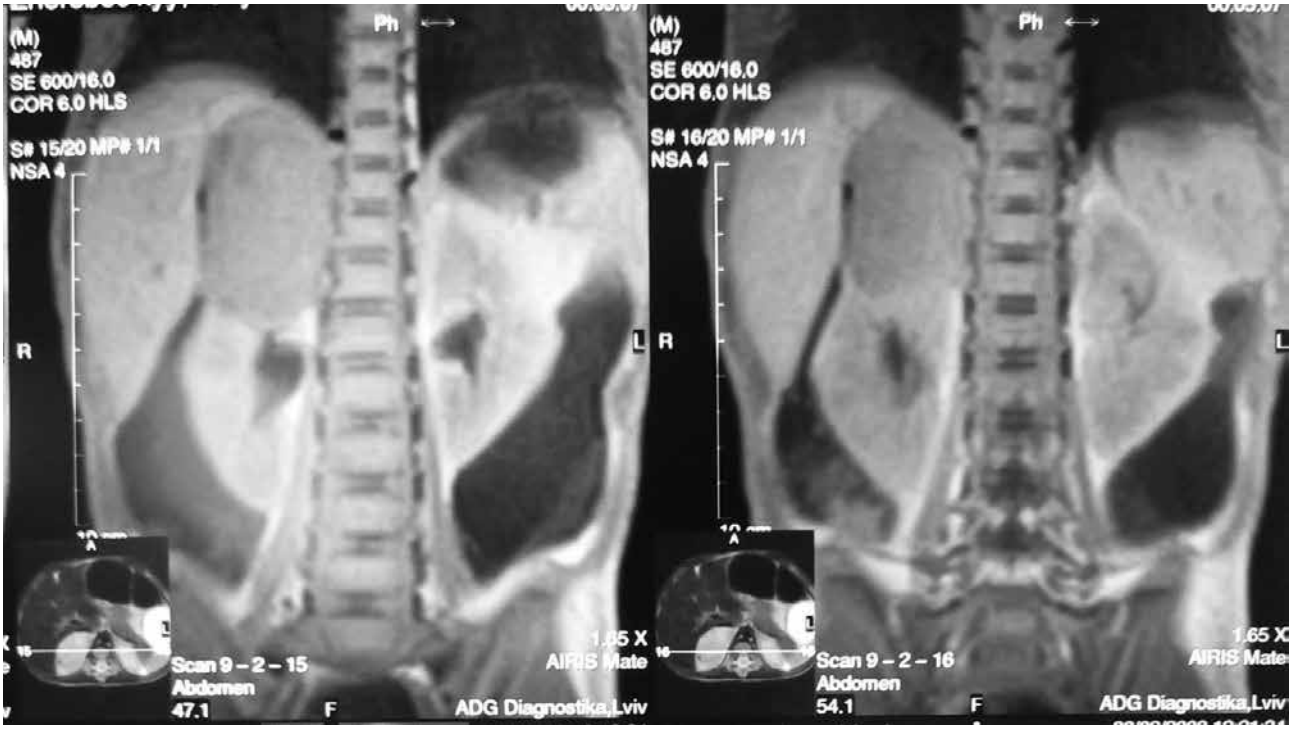

Fig. 2. MRI of the patient's abdomen showed a sub-diaphragm paravertebral tumour 63 × 34 × 44 mm, which shrinks down the right kidney and compresses the inferior vena cava

The most common symptom in WDHA syndrome is chronic refractory diarrhoea, and it occurs in at least 89% of patients. It is secretory in nature and persists with fasting. Abdominal pain is common, occurring in 50% of patients. Weight loss has been reported in 72% of patients, and flushing has been observed in 20%, attributed to the vasodilatory effects of VIP[13]. Physical examination usually reveal signs of volume depletion, malnutrition, and muscle weakness, which may be associated with elevated creatine phosphokinase (CPK) due to hypokalaemic rhabdomyolysis[14].

Hypokalaemia is a universal finding, resulting from faecal loss of potassium and secondary hyperaldosteronism[15], often with coexisting hypomagnesemia, metabolic acidosis, hyperglycaemia and hypercalcemia, also due to VIP effects. Management should be focused on considering the rare diagnosis of WDHA, performing VIP assay, remembering that VIP levels may be normal between episodes of diarrhoea. Conventional imaging studies (transabdominal ultrasound, computed tomography – CT scan, MRI, selective angiography) detect fewer than 60% of primary tumours, and can fail to reveal metastases in more than 30% of cases[16]. Positron emission tomography (PET) scanning may gain greater importance in the future. This modality is more sensitive than CT scanning for tumour localisation, and, when used with 18F-fluorodeoxyglucose, it may allow to predict the presence of malignancy in poorly differentiated tumours. Somatostatin receptor scintigraphy (SRS) using octreotide is the most sensitive modality for identifying a primary tumour or metastatic disease[16].

Treatment is focused on rehydration, electrolyte replacement and the use of the long-acting somatostain analogue octreotide which controls diarrhoea in 87% of cases, as it inhibits the release of VIP. Surgical resection is the only cure[17].

Conflict of interest

The authors do not report any financial or personal connections with other persons or organizations which might negatively affect the content of this publication and/or claim authorship rights thereto.

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