CASE REPORT

Unremitting watery diarrhoea in early childhood period

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SUMMARY

Chronic watery diarrhoea can be a presentation of gastrointestinal disease itself or a less-evident systemic disease. A 17-month-old boy presented with intractable diarrhoea, failure to gain weight, refractory tachycardia and severe hypertension. The ability to recognise and make a quick diagnosis of secretory type of diarrhoea dictated the outcome of patients with this ailment. Catecholamine hypersecretion was considered with the additional clues of refractory tachycardia and hypertension, a well-recognised phenomenon of neuroblastic tumours. A neuroblastic tumour can lead to vasoactive intestinal peptide (VIP) overexpression, which may result in secretory diarrhoea. In this situation, measurements of plasma VIP enabled crucial diagnosis. Imaging studies were used to identify and localise a neuroblastic tumour. Subsequent removal of the tumour was curative and led to the resolution of the symptoms.

BACKGROUND

A syndrome of profuse watery diarrhoea, hypokalaemia and achlorhydria (WDHA or Verner-Morrison syndrome) was first described by Verner and Morrison in 1958 in adult patients with a non-beta islet cell adenoma.¹ In children, such rare endocrine tumour originating in the neural crest includes ganglioneuromas, ganglioneuroblastoma and neurofibroma. These tumours can secrete vasoactive intestinal peptide (VIP) called VIPoma and lead to unremitting secretory diarrhoea.² The rarity of this manifestation (<1%) therefore sometimes results in clinical misdiagnosis and inappropriate management.^{3–5} Here, we describe a child with chronic watery diarrhoea caused by an underlying tumour.

CASE PRESENTATION

A previously healthy 17-month-old boy was referred to our hospital due to unresolved chronic diarrhoea, described as up to 10 times per day for approximately 3 months. There was no history of laxative or other drug use and surgery. Stool was profuse, watery and yellowish in colour, with little mucous and no blood. The patient was admitted twice to a local hospital where he received oral rehydration solution, lactose-free substitute formula and antibiotics. Hypokalaemic metabolic acidosis was corrected by intravenous fluid. Despite these interventions, the profuse watery diarrhoea persisted.

On examination, the following measurements were taken: body weight, 9.6 kg (10th–25th percentile); height, 78 cm (25th percentile); body temperature, 37.5°C; heart rate, 146 beats/min; and blood pressure, 119/66 mm Hg (>99th percentile). Laboratory investigation revealed mild anaemia (haemoglobin 9.3 g/dL), normal white cell count ($9.9 \times 10^9/L$: polymorphonuclear 37%, lymphocyte 47%, eosinophil 5.9% and basophil 0.5%) and platelet count ($389 \times 10^9/L$). Hypokalaemic metabolic acidosis was noted (Na 130, K 2.48, Cl 103 and HCO_3^- 12.7 mmol/L). Thyroid function test was normal. Stool examination was negative for blood cells, reducing substance, parasitic organism and fat globule. Stool pH was 8 and stool Na was 126.6 mmol/L. The calculated stool osmotic gap was 18 mmol/kg. The stool culture was negative for organism. The patient was fasted and received total parenteral nutrition supplement for 48 hours, but the severity of diarrhoea persisted. This led to the possibility that the child had secretory diarrhoea.

INVESTIGATIONS

Panendoscopy did not show any abnormality. Histopathology study did not show villous atrophy. The 24-hour urine vanillylmandelic acid (VMA 65 $\mu\text{mol/day}$, normal range 7–33 $\mu\text{mol/day}$) and serum neuron-specific enolase (NSE 19 ng/mL, normal range 0–15 ng/mL) were elevated. Abdominal ultrasonography revealed a $5.5 \times 4.4 \times 4.0$ cm well-defined left suprarenal mass with heterogeneous echogenicity, internal calcification and vascularity. CT scan of chest and abdomen demonstrated a left adrenal mass measuring $5.6 \times 5.3 \times 4.8$ cm with no abnormal intrathoracic mass (figure 1). The bone scan was negative for evidence of metastasis. Bone marrow aspiration and a biopsy showed no evidence of abnormal cell infiltration.

DIFFERENTIAL DIAGNOSIS

Secretory diarrhoea involving neuroendocrine tumours such as VIPoma, gastrinoma, mastocytosis, carcinoid syndrome and medullary carcinoma of the thyroid.

TREATMENT

The tumour was completely resected, and its histology confirmed neuroblastoma (Schwannian stroma poor, differentiating, low mitosis-karyorrhexis index and favourable histology). No amplification of the N-Myc gene was observed.

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Figure 1 A 5.6×5.3×4.8 cm left adrenal mass showing heterogeneous enhancement and internal punctate calcifications (yellow arrow) with pressure effect in the kidney (K).

The tumour was classified as a low-risk neuroblastoma using the modified International Neuroblastoma Risk Group (INRG) classification according to the Thai Paediatric Oncology Group Neuroblastoma protocol. He completed four cycles of chemotherapy consisting of carboplatin, etoposide, cyclophosphamide and doxorubicin.

OUTCOME AND FOLLOW-UP

On surgical removal of the tumour, the diarrhoea stopped and urine VMA was gradually normalised. No severe chemotherapy-related side effects were noted during treatment. The child remained well without evidence of any residual mass or any metastatic lesion during the time of follow-up (3 years).

DISCUSSION

Chronic diarrhoea in childhood is not uncommon and may result from a wide range of gastrointestinal disorders or rare systemic diseases. The aetiology of chronic diarrhoea in children is primarily osmotic or secretory. A low stool osmotic gap (<50 mmol/kg) and diarrhoea that do not improve while fasting are the hallmarks of secretory diarrhoea. In contrast, a high stool osmotic gap (>100 mmol/kg) with the cessation of diarrhoea after discontinuing food suggests osmotic diarrhoea. The step-by-step approach taken to dissect the cause of chronic diarrhoea can often be time-consuming and cause a significant delay in the management of the true disease. Murphy *et al*⁵ reported a median hospital stay of about 4 weeks in children with VIPoma and the time period from referral to attaining a final diagnosis can range from 1 to 10 months. The late diagnosis delayed treatment of these children (5/6) and they were severely malnourished. In addition, Bourdeaut *et al*³ showed that 20/22 children with VIP-secreting neuroblastic tumours suffered from weight loss and metabolic disturbance. As a result, index of suspicion is crucial to the proper investigation for this group of patients.

Although the overall incidence of neuroblastoma is relatively rare, it disproportionately affects young children especially <2 years of age.^{3–5} Chronic watery diarrhoea despite fasting is

indicative of secretory type of diarrhoea. Clinical observations in the present case including tachycardia and hypertension after corrections of fluid and electrolyte imbalance were telltale signs. Manifestation of secretory diarrhoea, persistent hypokalaemia and metabolic acidosis in very young children should be further assessed with tests such as stool pH, reducing substance and osmotic gap. While expensive and limited in availability, determination of plasma concentration of VIP may reveal a tumour marker for VIPoma, which can provide additional clues to the diagnosis of neuroendocrine tumours. In a resource-limited setting, serum NSE for neural crest-derived tumours and urine VMA can reflect catecholamine overproduction and assist in the neuroblastoma diagnosis and follow-up. Imaging studies such as X-ray, ultrasonography, CT scan or MRI of the chest and abdomen can serve to identify malignant mass and staging. Consistent with a previous report,² all symptoms of the patient of diarrhoea, hypokalaemia and achlorhydria subsided dramatically after tumour removal, suggesting that the root cause of high VIP derived from neuroblastoma.

Learning points

- ▶ Tumours that secrete vasoactive intestinal peptide should be considered in the very young children with unresolved chronic watery diarrhoea, hypokalaemia and metabolic acidosis.
- ▶ Persistent tachycardia and hypertension led to the diagnosis of catecholamine hypersecretion from a neural crest tumour.
- ▶ Awareness that secretory diarrhoea may be caused by underlying conditions other than gastrointestinal disease is important.

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