

# Vasoactive Intestinal Peptide (VIP)-Secreting Neuroblastic Tumors in Children Presenting With Chronic Secretory Diarrhea: A Report of Two Cases

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## Abstract

Vasoactive intestinal peptide (VIP)-secreting neuroblastic tumors are rare pediatric neoplasms that may present with chronic secretory diarrhea prior to tumor detection, posing significant diagnostic and therapeutic challenges. VIP-induced diarrhea is typically profuse, watery, and refractory to standard management, often resulting in dehydration, electrolyte imbalance, weight loss, and failure to thrive. Herein, we report two pediatric patients with neuroblastoma who presented with chronic secretory diarrhea as the initial and predominant symptom. In both cases, the persistent diarrhea remained unexplained by common etiologies and was unresponsive to conventional therapies. After approximately three months of ongoing symptoms accompanied by progressive abdominal distension, radiologic evaluation revealed intra-abdominal masses in both cases. The diagnosis of neuroblastoma was confirmed by tumor biopsy in one patient and bone marrow biopsy in the other. Serum VIP levels were not available in either case; however, the clinical presentation was consistent with VIP-mediated secretory diarrhea. Although surgical resection of VIP-secreting neuroblastic tumors in localized disease is typically associated with resolution of diarrhea and favorable outcomes, delayed diagnosis could result in advanced, metastatic, and inoperable disease. Both of our cases had metastatic, inoperable disease at the time of diagnosis, and proved fatal in one. These cases underscore the importance of considering VIP-secreting neuroblastic tumors in the differential diagnosis of children presenting with unexplained, treatment-resistant secretory diarrhea. Early recognition may facilitate timely diagnosis and improve clinical outcomes.

**Categories:** Oncology, Pediatric Surgery, Gastroenterology

**Keywords:** hypokalemia, neuroblastic tumors, pediatrics, secretory diarrhea, vasoactive intestinal peptide

## Introduction

Neuroblastoma is the most common extracranial solid tumor in children and the most frequently diagnosed malignancy in infants, accounting for approximately 28% of all cancers diagnosed in infants in Europe and the United States [1,2]. The majority of cases are diagnosed in children younger than four years, with a median age at diagnosis of 17-19 months [1,2]. Clinical manifestations vary widely depending on the patient's age, tumor location, size, and the presence of associated paraneoplastic syndromes [1,2]. London et al. demonstrated the prognostic significance of age at diagnosis using a cutoff of 365 days; the four-year event-free survival (EFS) rate was 83% for patients younger than 365 days compared with 45% in those older than 365 days ( $p < 0.0001$ ) [3]. Vasoactive intestinal peptide (VIP)-secreting neuroblastic tumors represent approximately 1% of all neuroblastic tumors [4]. VIP-induced secretory diarrhea was first described in 1958 by Robert H. Verner and Arthur B. Morrison, who linked pancreatic tumors to refractory watery diarrhea, hypokalemia, and achlorhydria - a constellation later termed WDHA syndrome [5]. VIP binds to receptors on intestinal epithelial cells, activating adenylate cyclase and increasing intracellular cyclic adenosine monophosphate (AMP) production. This cascade drives excessive water and electrolyte loss by stimulating chloride secretion and inhibiting sodium absorption [6]. VIP also disrupts potassium homeostasis and suppresses gastric acid secretion [7]. Although uncommon, chronic secretory diarrhea may be the earliest presenting symptom in infants and young children, often preceding tumor detection [4,8,9]. This form of diarrhea is typically refractory to fasting and dietary modifications, and routine diagnostic evaluation frequently fails to identify the underlying cause, leading to delayed diagnosis, more advanced disease at presentation, and poorer outcomes. Prolonged diarrhea can lead to significant complications, including severe dehydration, weight loss, failure to thrive, and serious electrolyte disturbances, particularly hypokalemia and metabolic acidosis [9]. Nevertheless, when diagnosed at a localized stage, VIP-secreting neuroblastic tumors are generally associated with a favorable prognosis [4,9]. Herein, we report two cases of neuroblastoma presenting with persistent secretory diarrhea for three months prior to tumor detection. Although plasma VIP levels were unavailable in both cases, the diagnosis of VIP-mediated secretory diarrhea was clinically supported by characteristic electrolyte disturbances, absence of alternative etiologies, and the therapeutic response to antidiarrheal agents targeting VIP-mediated secretion. At the time of diagnosis, both cases had advanced, metastatic, and inoperable disease - a presentation that may reflect both

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diagnostic delay and inherently aggressive tumor pathology. These cases underscore the importance of considering VIP-secreting neuroblastic tumors in the differential diagnosis of unexplained, persistent secretory diarrhea in young children, as early recognition may improve clinical outcomes.

## Case Presentation

### Case 1

A five-month-old Arab Jordanian female infant, born after an uneventful pregnancy with no family history of genetic or malignant diseases, developed profuse watery diarrhea at two months of age, with approximately 20 episodes of watery diarrhea per day. The diarrhea was persistent and severe, requiring multiple hospitalizations due to severe dehydration and poor weight gain. The initial differential diagnosis included cow's milk protein allergy, cystic fibrosis, infectious diarrhea, and malabsorptive conditions. She was initially diagnosed with cow's milk protein allergy and started on an amino-acid-based formula with no improvement. Prior to referral to King Hussein Cancer Center (KHCC), she underwent an extensive workup, including upper endoscopy, colonoscopy, sweat chloride test, abdominal ultrasound, and stool analysis; however, all results failed to establish a diagnosis. Due to progressive abdominal distension, a repeat abdominal ultrasound was performed three months after the initial one and revealed a retroperitoneal mass, prompting referral to KHCC. At presentation to KHCC, the infant was mildly dehydrated. Vital signs were within normal limits except for elevated blood pressure (119/64 mmHg, >95th percentile for age). Her weight was 5.8 kg (fifth percentile for age). The abdomen was tense and distended. Laboratory results showed anemia (hemoglobin: 7.8 g/dL) with normal serum electrolytes, likely attributable to intravenous fluid resuscitation administered at the referral hospital prior to transfer. Blood gas analysis demonstrated metabolic acidosis with low bicarbonate ( $\text{HCO}_3^-$ : 17.2 mmol/L). A contrast-enhanced abdominal computed tomography (CT) scan revealed a  $7.5 \times 9 \times 8$  cm heterogeneously enhancing retroperitoneal mass with calcifications and necrosis, enlarged para-aortic and mediastinal lymph nodes, a metastatic hepatic lesion, and mild ascites (Figure 1).

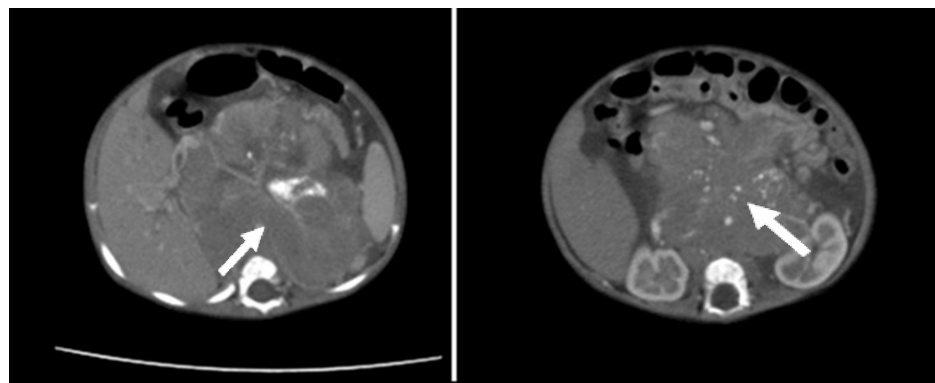


**FIGURE 1: Contrast enhanced CT scan (Case 1) showing large midline retroperitoneal tumor, with heterogeneous enhancement, internal necrosis and calcification (arrows).**

Urinary vanillylmandelic acid (VMA) was elevated at 116  $\mu\text{mol}/24$  hours (normal <35  $\mu\text{mol}/24$  hours), and serum neuron-specific enolase (NSE) was 185 ng/mL (normal <16 ng/mL). Plasma VIP level was not available; however, the combination of refractory secretory diarrhea unresponsive to dietary modification, metabolic acidosis, and the subsequent identification of a retroperitoneal mass with elevated catecholamine metabolites and NSE collectively pointed to a VIP-secreting neuroblastic tumor as the underlying etiology. Biopsy of the mass confirmed poorly differentiated neuroblastoma, with negative MYCN amplification (Figure 2).

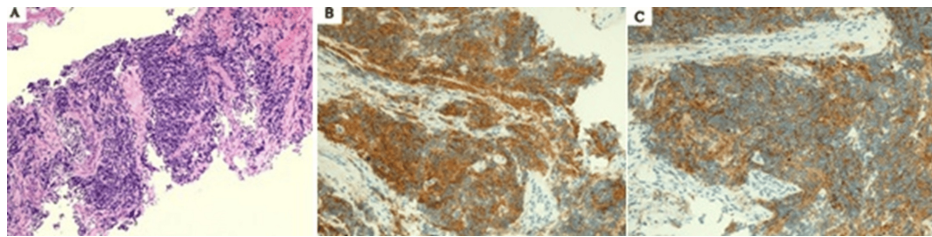


**FIGURE 2: Histopathological and immunohistochemical examination of the abdominal mass (Case 1).**

(A) Hematoxylin and eosin (H&E) staining showing muscle and fibrous tissue infiltrated by poorly differentiated neuroblastoma (H&E; 10×). (B) Positive expression of synaptophysin in tumor cells, confirming neuroendocrine differentiation (synaptophysin; 20×). (C) Positive expression of chromogranin in tumor cells, further supporting the neuroendocrine origin (chromogranin; 20×).

The key diagnostic challenge was the young age of the patient (two months at symptom onset) and the absence of a palpable mass or localizing symptoms during the initial three months, which directed the workup toward common gastrointestinal etiologies and led to delayed tumor identification.

The patient was classified as intermediate-risk metastatic neuroblastoma according to the Children's Oncology Group (COG) protocol [10] and received eight cycles of chemotherapy. Supportive care included intravenous fluids and ongoing electrolyte replacement to correct dehydration and metabolic acidosis. Additionally, loperamide (0.5 mg twice daily) was administered orally for symptomatic control of diarrhea. Loperamide was selected given its oral route of administration and the absence of significant electrolyte disturbances at the time of initiation. Somatostatin analogues were not initiated in this case, as the diarrhea responded to the combination of chemotherapy and loperamide. No changes to the therapeutic regimen were required during the treatment course, as the patient demonstrated progressive clinical improvement: stool volume decreased, and her weight increased. The patient completed all eight planned cycles of chemotherapy without dose modifications or treatment delays.

Imaging at the end of chemotherapy revealed a 60% reduction in primary tumor size. However, the mass remained inoperable due to encasement of major vessels (Figure 3).

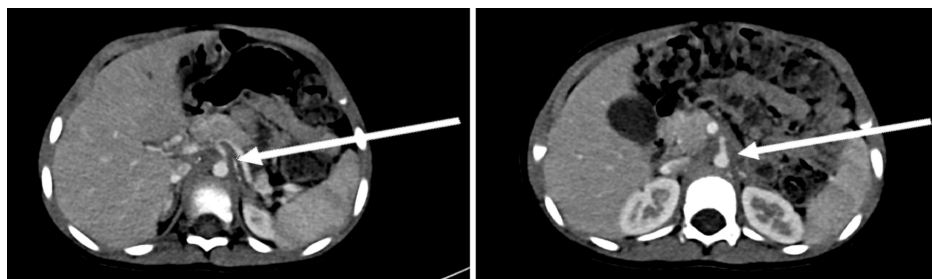


**FIGURE 3: Contrast enhanced CT scan (Case 1) showing persistent complete encasement of the celiac trunk and superior mesenteric arteries and partial encasement of abdominal aorta (arrows).**

At her last follow-up visit, two years after completion of chemotherapy, her weight had increased to 14 kg (70th percentile for age) and her blood pressure had normalized. She continued to grow and develop normally, and the diarrhea had completely resolved. The patient remained under clinical surveillance with no disease progression.

## Case 2

A 27-month-old Arab Jordanian girl, previously healthy with no family history of genetic or malignant diseases, presented with a three-month history of abdominal distension and persistent watery diarrhea, accompanied by fever, decreased appetite, and significant weight loss. There was no prior medical or surgical history. No relevant psychosocial history was identified. The initial differential diagnosis included food allergy and infectious diarrhea. She was initially managed with dietary modification and multiple courses of antibiotics, with no improvement. After three months of refractory diarrhea and progressive abdominal distension, an abdominal CT scan was performed and revealed a retroperitoneal mass, prompting

referral to KHCC for further diagnosis and management.

At presentation to KHCC, the patient appeared ill and cachectic; she was dehydrated with sunken eyes, dry lips, and minimal subcutaneous fat. Vital signs were stable except for elevated blood pressure (120/75 mmHg, >95th percentile for age). Her weight was 12.4 kg (40th percentile for age). Abdominal examination revealed a tense, distended abdomen with a palpable mass in the upper abdomen. The remainder of the physical examination, including assessment of the skin, lymph nodes, and neurological system, was unremarkable.

Laboratory investigations showed mild anemia, hyponatremia, hypokalemia, hypochloremia, and metabolic acidosis (Table 1).

| Parameter            | Patient's value | Normal reference range |
|----------------------|-----------------|------------------------|
| Hemoglobin (g/dL)    | 10.1            | 10.0-16.0              |
| Sodium (mmol/L)      | 131             | 135-145                |
| Potassium (mmol/L)   | 2.5             | 3.6-5.2                |
| Chloride (mmol/L)    | 94              | 98.6-111.0             |
| Bicarbonate (mmol/L) | 11.5            | 21.0-28.0              |

TABLE 1: Laboratory investigations of Case 2 at presentation.

Contrast-enhanced abdominal CT scan revealed a large retroperitoneal mass crossing the midline, invading the left kidney, encasing major retroperitoneal vascular structures, with regional lymphadenopathy and a metastatic lesion in the left iliac bone (Figure 4).

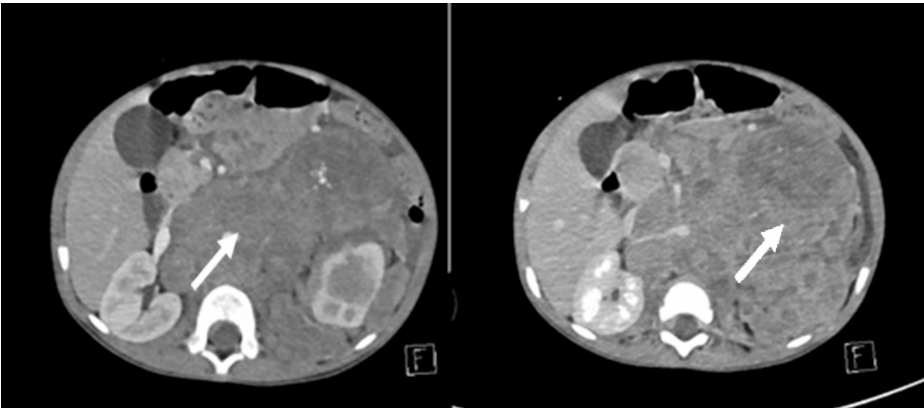


FIGURE 4: Contrast-enhanced CT scan (Case 2) showing a large heterogeneous left retroperitoneal mass, crossing the midline, encasing the abdominal aorta and its major branches, with involvement of the left kidney and extension to the right renal hilum (arrows).

Urinary VMA was elevated at 133 μmol/24 hours, and NSE was markedly elevated at 600 ng/mL. Plasma VIP level was not available; however, the triad of refractory secretory diarrhea, severe electrolyte disturbances (hypokalemia, hypochloremia, and metabolic acidosis), and the identification of a retroperitoneal mass with markedly elevated catecholamine metabolites and NSE strongly supported the diagnosis of a VIP-secreting neuroblastic tumor. Bone marrow biopsy confirmed 70% infiltration by poorly differentiated neuroblastoma (Figure 5).

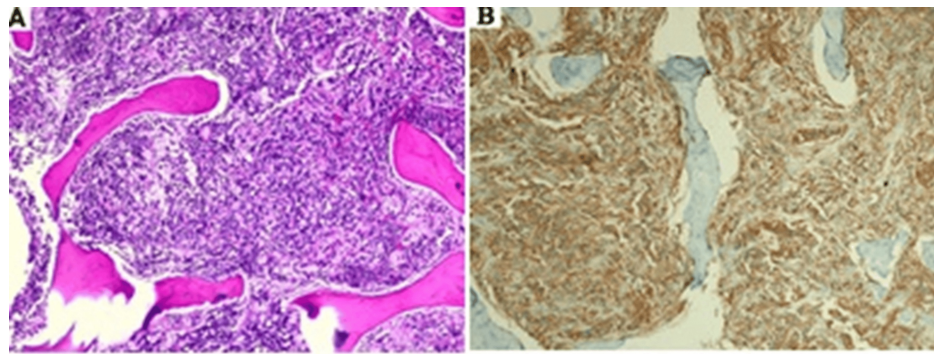


**FIGURE 5: Histopathological and immunohistochemical examination of the bone marrow (Case 2).**

(A) Hematoxylin and eosin staining showing bone marrow almost entirely infiltrated by poorly differentiated tumor cells consistent with neuroblastoma, replacing normal bone marrow elements (H&E; 20×). (B) Positive expression of synaptophysin in tumor cells, confirming neuroendocrine differentiation (synaptophysin; 20×).

The bone scan showed metastatic lesions in the left iliac bone. The diagnostic challenge in this case was a three-month period of persistent diarrhea in the absence of a palpable abdominal mass. The diarrhea was attributed to common pediatric conditions, delaying imaging and tumor detection. The patient was classified as high-risk neuroblastoma and started on chemotherapy according to the COG protocol [11]. Surgery was not feasible due to advanced metastatic disease. Management consisted of intravenous fluid resuscitation, aggressive electrolyte replacement, and intravenous somatostatin analogue (octreotide). The intravenous somatostatin analogue was the antidiarrheal agent chosen, as the child had severe diarrhea accompanied by significant electrolyte disturbances. Nasogastric enteral feeding was initiated due to inadequate oral intake and cachexia. Initially, her disease responded well to chemotherapy, with a 50-60% reduction in tumor size, clearance of bone marrow disease, improvement in diarrhea, normalization of blood pressure, and an increase in weight. Unfortunately, eight months after the initial presentation, she developed disease progression refractory to treatment and subsequently died of progressive disease. No specific adverse events attributed to octreotide or chemotherapy were documented prior to disease progression.

## Discussion

Although an abdominal or neck mass is the presenting symptom in approximately 50% of neuroblastoma cases, secretory diarrhea prior to tumor detection occurs in fewer than 1% [4]. In these rare cases, diarrhea is commonly misdiagnosed as more prevalent pediatric gastrointestinal conditions, including cow's milk protein allergy, malabsorption syndromes, and infectious diarrhea [8,12,13]. While VIP-secreting tumors in adults most commonly originate from pancreatic neuroendocrine neoplasms, in children they more frequently arise from neuroblastic tumors. The interval between diarrhea onset and tumor diagnosis can extend over several months, during which affected children endure dehydration, failure to thrive, and undergo extensive diagnostic investigations. This diagnostic delay may allow disease progression to an advanced stage. In a comprehensive review of all VIP-producing neuroblastic tumors reported between 1975 and 2021, Dornelles et al. found that 83 of 96 patients (86.5%) developed diarrhea prior to tumor detection [9]. The interval from diarrhea onset to diagnosis ranged from 0 to 76 months, with a mean duration of 8.03 months. One of the greatest challenges in achieving early diagnosis is the absence of a palpable abdominal mass or other localizing symptoms that would typically prompt consideration of an underlying tumor. Consistent with previously reported cases, both of our patients had chronic diarrhea for three months before neuroblastoma was diagnosed, as abdominal distension developed only later in the disease course. Uskova et al. similarly reported delayed diagnosis and extensive investigations prior to identifying the tumoral etiology of the diarrhea [14]. Belei et al. described an 11-month-old infant who presented with persistent diarrhea and weight loss and was initially diagnosed with cow's milk allergy; lactose-free and protein hydrolysate formulas failed to alleviate the symptoms [12].

Both of our patients experienced a comparable three-month diagnostic delay, as their diarrhea was initially attributed to common pediatric etiologies such as cow's milk allergy, lactose intolerance, and infectious diarrhea. At the time of diagnosis, both of our cases had advanced, metastatic, and inoperable disease. Such delays, which have been widely reported in the literature, increase morbidity and may adversely affect prognosis, underscoring the importance of early clinical suspicion and timely diagnostic evaluation in children with persistent unexplained diarrhea. To facilitate earlier recognition of VIP-secreting neuroblastic tumors, we propose the following stepwise diagnostic approach that a pediatrician can follow in evaluating a child with persistent, unexplained diarrhea: Step 1: Confirm the secretory nature of the diarrhea. Secretory diarrhea is characterized by persistent watery diarrhea lasting more than 14 days that is unresponsive to standard dietary modifications and antimicrobial therapy, and persists during fasting or with bowel rest,

thereby distinguishing it from osmotic diarrhea. The accompanying electrolyte profile is often characteristic, with hypokalemia, hyponatremia, and metabolic acidosis constituting the well-described watery diarrhea-hypokalemia-achlorhydria (WDHA) pattern. Step 2: Systematically exclude common etiologies of chronic diarrhea in childhood. This includes stool studies comprising cultures, ova and parasites, *Clostridioides difficile* toxin, and rotavirus/norovirus antigen testing, as well as fecal calprotectin to screen for intestinal inflammation. Celiac screening and cow's milk protein allergy evaluation should also be considered based on clinical context. Step 3: Evaluate for an underlying neuroblastic tumor when common etiologies are excluded and secretory diarrhea remains unexplained; clinicians should actively watch for red flags that should prompt evaluation for an underlying neuroblastic tumor, particularly in children aged one to three years. These red flags include abdominal distension or a palpable abdominal mass, unexplained hypertension, episodic flushing or sweating, and failure to thrive despite adequate nutritional support.

The prolonged course of diarrhea, sometimes lasting months, combined with persistent electrolyte abnormalities - especially hypokalemia and metabolic acidosis - should raise suspicion of an underlying malignancy. Significant electrolyte and metabolic disturbances are frequently reported in patients with VIP-secreting neuroblastic tumors, particularly hyponatremia, hypokalemia, and metabolic acidosis [12,15-17]. Hypokalemia is the most consistently observed abnormality, with potassium levels reported as low as 1.42 mmol/L [11]. In the cohort analyzed by Dornelles et al., hypokalemia was present in 59 of 60 patients (98%) [9]. Hyponatremia is likewise common, with sodium levels reported as low as 118 mmol/L [18]. Metabolic acidosis often accompanies these abnormalities and is frequently associated with low serum chloride levels. The life-threatening potential of these disturbances is illustrated by Han and Wang, who reported two deaths attributable to intractable hypokalemia in a series of six patients with diarrheal neuroblastoma [19]. The combination of persistent secretory diarrhea with electrolyte imbalance - particularly hypokalemia and metabolic acidosis - should raise the suspicion of VIP-mediated diarrhea due to excessive gastrointestinal losses and paraneoplastic effects. Both of our patients had metabolic acidosis, and one had significant hypokalemia.

The age at diagnosis of reported VIP-secreting neuroblastic tumors ranges from 5 to 84 months, with a median of 23.5 months [9]. In our first case, diarrhea began at two months of age, and neuroblastoma was diagnosed three months later - younger than the reported median. This early age of onset contributed to diagnostic difficulty and prompted an extensive workup for diarrhea before the underlying tumor was identified. The sex distribution of VIP-secreting neuroblastic tumors varies across published series; some reports suggest a female predominance [9], while others have reported a male predominance [4,19]. Both of our patients were female.

Reported plasma VIP levels vary widely, ranging from mild elevation to markedly high values, typically one to 20 times the upper reference limit. This wide variability complicates diagnosis. VIP levels often correlate with symptom severity, as higher levels are typically associated with more pronounced systemic effects, including chronic diarrhea, hypokalemia, and metabolic acidosis. Beyond its role as a diagnostic marker, VIP also serves as a tool for monitoring treatment response and disease progression [4,9]. Normalization of VIP levels has been consistently reported following surgical tumor resection, often accompanied by resolution of diarrhea and restoration of electrolyte balance. Zhang et al. reported a patient with a markedly elevated VIP level of 830 pmol/L (normal <25 pmol/L) associated with severe profuse watery diarrhea, hypokalemia, and significant weight loss; following surgery, VIP levels normalized with complete resolution of symptoms [17]. Similarly, Thomas et al. described a 17-month-old child with a VIP level of 328.6 pmol/L (normal <25 pmol/L) presenting with intractable diarrhea; following complete surgical resection, VIP decreased to 18.3 pmol/L with full symptom resolution within one month [20]. In our cases, plasma VIP measurements were unavailable, precluding correlation with symptom severity and treatment response.

Among VIP-secreting neuroblastic tumors, ganglioneuroblastoma is the most frequently reported subtype (approximately 50%), followed by neuroblastoma (30%) and ganglioneuromas (20%). The adrenal gland is the most common primary site, followed by the retroperitoneal region [2,9]. Less commonly, tumors arise in the thoracic, mediastinal, presacral, or paravertebral regions. In both of our cases, the tumors were retroperitoneal neuroblastomas.

Management of VIP-secreting neuroblastic tumors requires a multidisciplinary approach involving oncologists, surgeons, gastroenterologists, and supportive care teams. Treatment strategies include surgical resection for localized tumors, neoadjuvant chemotherapy for advanced disease, and targeted supportive care for paraneoplastic syndromes. Nutritional support and fluid-electrolyte management are essential, as prolonged diarrhea can lead to severe dehydration and metabolic derangements [9]. Somatostatin analogs such as octreotide have demonstrated efficacy in reducing diarrhea by inhibiting VIP secretion and improving fluid and electrolyte balance [4,9]. Han and Wang reported on six patients: three underwent surgery alone, and three received surgery plus chemotherapy, with diarrhea resolving in five of six patients [19]. Bourdeaut et al. showed that surgery remains the preferred first-line treatment when feasible, even in cases with potential surgical risk. In all 16 patients with primary VIP-secreting tumors in their series, surgery achieved permanent control of diarrhea within hours, whereas neoadjuvant chemotherapy had no effect on diarrhea in any case; somatostatin was tried in one patient without efficacy [4]. Somatostatin analogues and corticosteroids may also be considered when the tumor remains unidentified or is deemed inoperable. In our first case, a five-month-old girl with an inoperable metastatic tumor and severe

malnutrition was treated with chemotherapy, parenteral fluid replacement, nutritional supplementation, and loperamide. This approach resulted in the resolution of diarrhea, weight gain, and a decrease in tumor size, despite the tumor remaining unresectable. In contrast, the second patient had high-risk inoperable disease that initially showed partial response but ultimately progressed to a fatal outcome. The variable response to somatostatin analogues across reported cases suggests that efficacy may depend on tumor biology, VIP secretion levels, or disease burden. Together, these cases illustrate the diagnostic challenges pediatricians may encounter in children with VIP-mediated secretory diarrhea and the consequences of delayed diagnosis of neuroblastic tumors, and offer practical insights into the diagnosis and management of this entity. The primary diagnostic challenge arises because secretory diarrhea often precedes the detection of a VIP-secreting tumor mass, leading clinicians to initially pursue more common etiologies of chronic diarrhea in children.

This report has several limitations. Its retrospective nature precluded prospective data collection and standardized outcome assessments. Plasma VIP measurements were unavailable in both cases, preventing direct confirmation of VIP hypersecretion and correlation with symptom severity and treatment response. The absence of patient or caregiver perspectives, attributable to the retrospective design, is a further limitation.

## Conclusions

VIP-secreting neuroblastic tumors represent a rare and diagnostically challenging entity that often presents with intractable diarrhea preceding tumor detection. The cases presented here, consistent with prior reports, highlight the detrimental consequences of delayed diagnosis on disease staging, treatment options, and patient outcomes. As evident from the published literature, localized VIP-secreting neuroblastoma carries a favorable prognosis when detected early and treated with surgical resection. However, because diarrhea is an uncommon initial presentation of neuroblastic tumors compared with the far more prevalent etiologies of chronic diarrhea in children, raising pediatricians' awareness of VIP-induced diarrhea as a differential diagnosis remains of paramount importance for early diagnosis and improved outcomes.

## Additional Information

### Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

**Concept and design:** Maha Barbar

**Acquisition, analysis, or interpretation of data:** Maha Barbar, Hadeel Halalsheh, Iyad Sultan, Abdulrahman Alrifai, Ahmad Al-Dabbagh

**Drafting of the manuscript:** Maha Barbar, Hadeel Halalsheh, Iyad Sultan, Abdulrahman Alrifai, Ahmad Al-Dabbagh

**Critical review of the manuscript for important intellectual content:** Maha Barbar, Hadeel Halalsheh, Iyad Sultan

**Supervision:** Maha Barbar

### Disclosures

**Human subjects:** Informed consent for treatment and open access publication was obtained or waived by all participants in this study. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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