Medical and Pediatric Oncology 12:93–96 (1984)

Occult Ganglioneuroma With Diarrhea: Localization by Venous Catecholamines

Andrew J. Schuman, MD, Anthony J. Alario, MD, and Paul A. Pitel, MD

Neural crest tumors can be complicated by secretory diarrhea mediated by vasoactive intestinal peptide (VIP). An eight-month-old male with a several-month history of secretory diarrhea is described. Elevated urine vanillylmandelic adic (VMA), total urine catecholamines, and plasma VIP indicated that a neural crest tumor was responsible for his protracted diarrhea. An extensive search for the tumor including CT scans of his head, neck, thorax, abdomen, and pelvis was unrevealing. A selective vena caval catheterization showed elevated catecholamines in a sample obtained above the renal veins. Subsequent laparotomy disclosed a benign ganglioneuroma arising from the left adrenal; the diarrhea resolved after its removal. Selective venous sampling proved useful in establishing the tumor's location where other techniques had been unsuccessful.

Key words: ganglioneuroma, vasoactive intestinal peptide, catecholamines, secretory diarrhea

INTRODUCTION

Neural crest tumors, including neuroblastomas, ganglioneuroblastomas, and ganglioneuromas, are complicated by secretory diarrhea in less than 10% of reported cases [1]. The mediator of the diarrhea associated with these neoplasms is now known to be vasoactive intestinal peptide (VIP), and not the catecholamines they also produce [2]. Rarely do neural crest tumors escape detection by the conventional methods of tumor localization. The following case details the localization of an occult ganglioneuroma by selective venous sampling of catecholamines.

CASE REPORT

An 8-month-old, male infant was admitted to Rhode Island Hospital with a 5-month history of intractable diarrhea. He was the product of a term pregnancy, born via Cesarean delivery for breech presentation. His postnatal course was uneventful and he thrived on a lactose-based formula. At 3 months of age, he developed frequent, watery, brown stools up to nine times per day. The diarrhea abated minimally and was refractory to treatment with clear fluids, antidiarrheal medication, and formula manipulations. At 7 months of age he had an exacerbation of his diarrhea resulting in hyponatremic dehydration and was admitted to a local hospital. There he was rehydrated intravenously and started on protein hydrolysate and lamb's oil formulas. Multiple laboratory studies and cultures were normal. A quantitative vanillylmandelic acid (VMA) done on a random aliquot of urine was 1 mg/dl, within the normal range for that laboratory. After an 11-day hospitalization, he was transferred to a second hospital where a central venous catheter was inserted for alimentation. Upper gastrointestinal series and barium enema were both unremarkable.

Three weeks later the child was transferred to Rhode Island Hospital. Admission weight was 7.9 kg (25th percentile for age), and height was 73 cm (90th percentile). Vital signs, including blood pressure of 84/50, were normal for age. Physical examination revealed a vigorous child without evidence of chronic malnutrition and was remarkable only for a protuberant abdomen without palpable masses or hepatosplenomegaly. Laboratory data included a hemoglobin of 9.6 gm/dl and hematocrit 27.4% with a normal white blood cell count and differential. Platelet count was 538,000 per mm^3. Repeat serum studies were again normal. Urinalysis was unremarkable.

The child continued on parenteral nutrition exclusively for the first few days and had at least five loose stools daily. Stool volume was approximately 260 cc/day (33 cc/kg/day). Increasing quantities of diluted protein hy-

From the Department of Pediatrics, Rhode Island Hospital, Brown University, Providence.

Address reprint requests to Paul A. Pitel, MD, Dept. of Pediatrics, RIH, Providence, RI 02902.

drolysate formula were offered and tolerated without an increased stool output. Stool pH was 7–8 and tested negative for reducing substances and occult blood. Sudan stain for fat was negative, as were studies for bacterial pathogens and parasites. A duodenal aspirate did not demonstrate Giardia. A diagnosis of secretory diarrhea was established, with twice the sum of the stool sodium and potassium equal to the stool osmolality (Na^+ = 45 mEq/l, K^+ = 98 mEq/l, osmolality = 286 osmol/l).

Ten days into his hospitalization, 24-hour urine collection for VMA and total urine catecholamines and plasma VIP were found to be elevated and continued to be elevated for the next two months (Table I). VMA was measured by a column adsorption technique (Brinkman Instruments, Inc., Westbury, NY), with assays performed while he was on a "VMA diet" (avoiding coffee, chocolate, bananas, and vanilla) and was not receiving drugs known to cause false positive results (aminosalicylic acid, dextroamphetamine sulfate, methyl dopa, and oxytetracycline). Total urine catecholamines were assayed by an automated fluorimetric technique modified from Sobel and Henry [4]. Plasma VIP was assayed by a radioimmunoassay technique modified from Said and Faloona [5]. An extensive search for a neural crest tumor responsible for the child's VIP-mediated diarrhea was undertaken.

The patient underwent intravenous pyelography, abdominal sonography, chest roentgenography, bone marrow aspiration, bone scan, liver-spleen scan, as well as CT scans of his head, neck, thorax, abdomen, and pelvis (GE 7800 Scanner). All studies were unrevealing as to the location of any tumor mass or metastatic disease. The hospitalization was complicated by two episodes of culture-proven bacterial sepsis, felt to be related to the indwelling central venous catheter.

Because of persistent diarrhea and continued nutritional dependence on intravenous alimentation, a selective vena caval catheterization was performed on the 60th hospital day with sampling of blood from the right and left innominate veins, both high and low superior vena cava, the inferior vena cava above and below the renal veins, and the right common iliac vein. A simultaneous abdominal aortogram failed to demonstrate an overt mass. Serum catecholamines were assayed by a radioenzymatic technique modified from Passon and Peuler [6]. As seen in Figure 1 (Table I), elevated levels of epinephrine (E), norepinephrine (NE), and dopamine (DOP) were found in the sample taken from the inferior vena cava just above the renal veins. Unfortunately, matching samples for VIP were lost in transit to a reference laboratory.

On the basis of these findings the patient underwent laparotomy for exploration of both suprarenal areas. A 4.6 × 3.6 × 3.0 cm benign ganglioneuroma arising from the left adrenal was removed en bloc. No neuroblastoma component was found. Many of the ganglion cells could be shown immunohistochemically by the method of Hsu et al [7] to contain abundant VIP (Fig. 2).

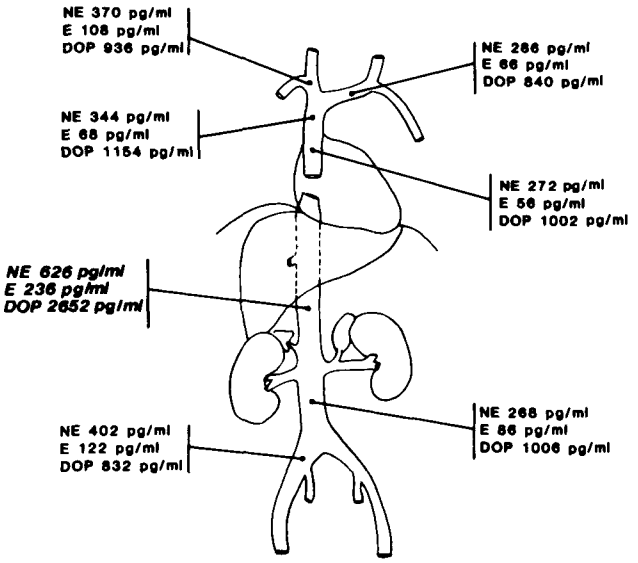

Fig. 1. Plasma catecholamines obtained from several locations in the patient's venous system. Note the elevated values found in the sample obtained just above the renal veins. NE, norepinephrine (normal, less than 450 pg/ml); E, epinephrine (normal, less than 110 pg/ml); DOP, dopamine (normal, less than 140 pg/ml).

TABLE I. Pre- and Postoperative Urine VMA, Total Urine Catecholamines, and Plasma VIP Levels

	Urine VMA (μg/mg creatinine)	Total urine catecholamines (μg/mg creatinine)	Plasma VIP (pg/ml)
Normal range	1.3–8.0	0.038–0.16	< 40
Hospital day 10	35.0	1.0	95.0
Hospital day 50	37.0	0.6	55.0
Hospital day 67		Surgery	
Hospital day 75	19.0	—	6.0
Hospital day 85	5.5	0.1	—

The diarrhea resolved the day of the operation and the postoperative course was uneventful. Plasma VIP returned to normal by the eighth postoperative day and both urine VMA and total urine catecholamine levels were normal by the 18th postoperative day.

DISCUSSION

Hawfield and Daisley [8] first associated chronic childhood diarrhea with neural crest tumors more than 25 years ago. These tumors in children can arise anywhere along the sympathetic chain, frequently presenting

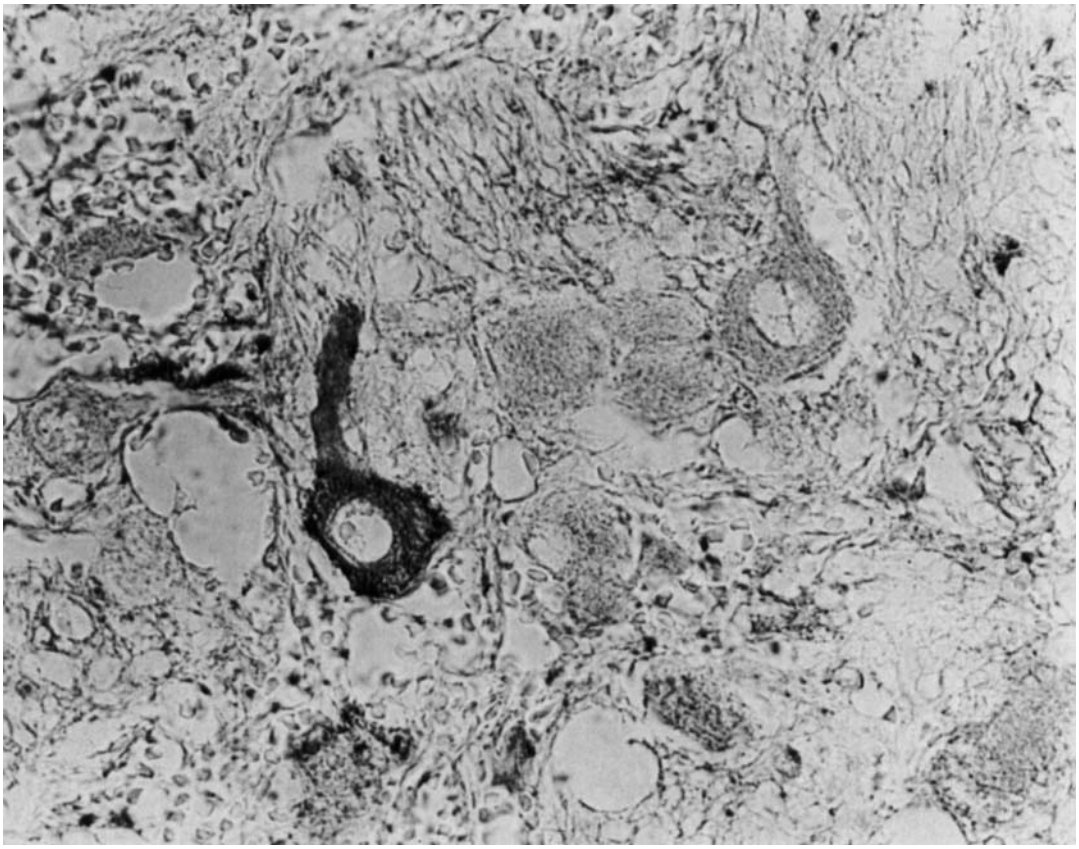

Fig. 2. High power photomicrograph of ganglioneuroma, showing two well-differentiated ganglion cells, one unstained and one very strongly positive for VIP (Avidin–Biotin peroxidase complex stain for VIP, magnification ×400).

as asymptomatic enlarging abdominal, thoracic, or cervical masses. A small number will have secretory diarrhea at presentation, a syndrome demonstrated to be caused by VIP.

VIP was first implicated in the syndrome of watery diarrhea, hypokalemia, and achlorhydria (WDHA), a well-described clinical entity in some adults with pancreatic adenomas, bronchogenic carcinoma, pheochromocytomas, and ganglioneuroblastomas. It is a 28 aminoacid peptide that was isolated from porcine small intestine in 1970 by Said and Mutt [9] and later shown to be elevated in the WDHA syndrome by Bloom et al [10]. VIP inhibits gastric acid secretion, elevates serum calcium and glucose, dilates systemic and splanchnic blood vessels, and has a stimulating effect on small intestinal motility and secretion, causing diarrhea. To date, elevated VIP levels have been found in at least eight infants or children with neurogenic tumors and secretory diarrhea [2]. Elevated urine catecholamines were also found in six of these children. VIP is the mediator of this diarrhea, for diarrhea does not occur in the absence of elevated VIP levels and will cease when they decline to normal in partially resected tumors, despite continued elevated catecholamine levels [11]. Some patients with neuroblastoma may also have mildly elevated VIP levels and no diarrhea [12].

CT scanning may fail to localize a small adrenal tumor and was not helpful with our patient. Jones et al [14] have shown that venous sampling of catecholamines is a useful adjunct to intravenous pyelography and sonography in the localization of pheochromocytomas in adults. They suggest that venous sampling may help direct the surgeon when such tumors are difficult to localize or are multicentric in origin. A recent attempt to obtain transhepatic VIP levels preoperatively in an adult with a VIP-secreting pancreatic tumor was unsuccessful but intraoperative sampling suggested its possible future utility [15]. To our knowledge, our case represents the first use of selective venous sampling to localize a neural crest tumor in a child.

The data obtained served to localize the tumor to the level of the adrenal glands, although no attempt was

made to determine the side of origin. Dopamine levels were extremely elevated at all sample sites, but especially in the suprarenal vena cava. Norepinephrine and epinephrine were elevated in the suprarenal vena cava, but quickly normalized after dilution in the circulation. Although epinephrine and norepinephrine may be elevated above the renal veins, especially after inadvertent adrenal stimulation, the marked elevation of dopamine in the suprarenal region (from 1006 to 2652 pg/ml) is only ascribable to the dopamine-producing ganglioneuroma. Tumors of neural crest origin may also produce elevated levels of norepinephrine and epinephrine. Results of the samples obtained for VIP are unfortunately unavailable but levels probably would also have been elevated in the suprarenal vena cava since immunohistochemical stains of the tumor showed abundant VIP (Fig. 2).

Of note, a spot urine sample for VMA was normal in this patient, although two 24-hour collections showed elevations above the normal range, along with elevation of total urine catecholamines. A random urine sample may not reflect excessive catecholamine excretion and is inadequate to exclude that diagnosis [16].

The VIP-induced diarrhea in our patient necessitated long-term hospitalization and central venous line alimentation that was complicated by two episodes of sepsis. Earlier localization of the tumor might have shortened his hospital course and reduced the associated morbidity. Selective venous sampling for metabolic tumor products helped localize this child's tumor for definitive surgical cure where other techniques were unsuccessful.

ACKNOWLEDGMENTS

The authors wish to thank Drs. Leo Stern and Edwin N. Forman for reviewing the manuscript; Dr. Richard Frates for performing the selective venous catheterization and providing invaluable radiodiagnostic help; Dr. Patricia O'Shea for her assistance in the identification of the tumor and for making the photograph; Dr. Conrad W. Wesselhoeft for performing the surgery; and Ms. Regina Waters for typing the manuscript.

REFERENCES

1. Rosenstein B, Engelman K: Diarrhea in a child with a catecholamine secreting ganglioneuroma. J Pediatr 63:217–226, 1963.
2. Kaplan SJ, Holbrook CT, McDaniel HG, Buntain WL, Crist WM: Vasoactive intestinal peptide secreting tumors of childhood. Am J Dis Child 24:21–24, 1980.
3. Fitzgerald JF, Clark JH: Chronic diarrhea. Pediatr Clin North Am 29:221–231, 1982.
4. Sobel C, Henry RJ: Determination of catecholamines (adrenalin and noradrenalin) in urine and tissue. Am J Clin Pathol 27:240–245, 1957.
5. Said SI, Faloona GR: Elevated plasma and tissue levels and vasoactive intestinal polypeptide in the watery-diarrhea syndrome due to pancreatic, bronchogenic and other tumors. N Engl J Med 293:155–160, 1975.
6. Passon PG, Peuler JD: A simplified radiometric assay for plasma norepinephrine and epinephrine. Anal Biochem 51:618–631, 1973.
7. Hsu SM, Raine L, Fanger H: A comparative study of the peroxidase–antiperoxidase method and an avidin–biotin complex method for studying polypeptide hormones with radioimmunoassay antibodies. Am J Clin Pathol 75:734–738, 1981.
8. Hawfield HH, Daisley GW Jr: A report of a case of a functional adrenal ganglioneuroma. Clin Proc Child Hosp 8:98–105, 1952.
9. Said SI, Mutt V: Polypeptide with broad biological activity isolation from small intestine. Science 169:1217–1218, 1970.
10. Bloom SR, Polak JM, Pearse AGE: Vaso-active intestinal peptide and watery diarrhea syndrome. Lancet 2:14–16, 1973.
11. Swift PGF, Bloom SR, Harris F: Watery diarrhea and ganglioneuroma with secretion of vasoactive intestinal peptide. Arch Dis Child 50:896–899, 1975.
12. Long RG, Tiedemann K, Pritchard J, Bloom SR: Plasma vasoactive intestinal polypeptide and other peptides in children with neurogenic tumors. Gastroenterology 80 (part 2):1217, 1981.
13. Dunnick R, Schanner EG, Doppman JL, Strott CA, Gill JR, Javadpour N: Computed tomography in adrenal tumors. AJR 132:43–46, 1979.
14. Jones DH, Allison DJ, Hamilton CA, Reid JI: Selective venous sampling in the diagnosis and localization of phaeochromocytoma. Clin Endocrin 10:179–186, 1979.
15. Smith FF, Rogers AI: Localization of a vasoactive intestinal peptide-producing tumor with selective venous sampling. Am J Gastroenterol 74:282–284, 1980.
16. Johnsonbaugh RE, Cahill R: Screening procedures for neuroblastoma: false negative results. Pediatrics 56:267–270, 1975.