Neural-Crest Tumor Presenting with Chronic Diarrhea: A Report of Three Cases

Kuo-Ting Tang, Hung-Chang Lee, Der-Cheng Liang, Shu-Huey Chen, Hsi-Che Liu, and Jin-Cherng Shau

Abstract: The association of chronic diarrhea with neural-crest tumors is uncommon. In the past 12 years, we encountered three cases of neural-crest tumors presenting initially as chronic diarrhea. The incidence of chronic diarrhea in patients with neural-crest tumors at our hospital during this period was 3.8%. These patients (two girls and one boy aged between 15 to 28 mo) presented with a 3-week to 6-month history of chronic diarrhea of unknown cause. A posterior mediastinal mass or abdominal mass found on sonography and chest roentgenography eventually led to the diagnosis of neural-crest tumor in these patients. Pathology revealed ganglioneuroblastoma in two cases and neuroblastoma in one. All three patients received chemotherapy and underwent surgery. Diarrhea ceased postoperatively in all three patients. Although one of the patients died of septic shock during chemotherapy, the other two remained free of disease at 30 and 22 months of postoperative follow-up, respectively. A high index of suspicion is needed to identify cases of neural-crest tumor from the presenting symptom of chronic diarrhea.

Case Reports

Case 1
A 28-month-old girl was referred to our hospital because of a 6-month history of watery, non-bloody diarrhea with yellowish stools up to 10 times per day. She had lost 1 kg over the previous 6 months despite a normal diet and good intake. Dietary precautions and anti-diarrheal agents had no effect.

On physical examination, she appeared ill. The eyes were mildly sunken and the skin turgor was fair. The abdomen was somewhat distended with hyperactive bowel sounds; it was tympanic to percussion and soft with no palpable masses. Results of initial laboratory studies included a white blood cell count of 16.3 x 10^3/µL; neutrophils, 84%; lymphocytes, 14%; hemoglobin, 13.5g/dL; platelet count, 630 x 10^3/µL; serum sodium, 133.9 mmol/L; serum potassium, 1.6 mmol/L; and serum chloride, 94 mmol/L. Arterial blood gas analyses were as follows: pH 7.54; PCO₂, 28.2 mmHg; PO₂, 104.9 mmHg; and bicarbonate, 24.5 mmol/L. No enteropathogens were isolated by stool culture, and stool analysis revealed a pH of 6.0 without reducing substance.

A plain abdominal film revealed a posterior mediastinal mass in the lower chest (Fig.1A). Abdominal ultrasound demonstrated a posterior mediastinal mass with calcification. Computerized tomography (CT) showed a posterior mediastinal mass from T5 to T11 with calcification (Fig.1B). Twenty-four hour urinary vanillylmandelic acid (VMA) concentration was elevated at 19.2 mg/day (normal range, 1.0–11.0 mg/day). Surgical exploration was performed with partial removal of a tumor (5 x 5 x 7 cm) found to be a...
ganglioneuroblastoma (stroma-rich, intermixed type by the Shimada classification system). Diarrhea improved postoperatively with the number of watery stool movements decreasing from 10 times a day to five times a day. The patient subsequently received chemotherapy, according to the Taiwan Pediatric Oncology Group N-93-B protocol, containing cisplatin, etoposide, epirubicin and cyclophosphamide. However, the patient died of septic shock due to *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* sepsis about half a month later.

**Case 2**

A 21-month-old boy was referred to our hospital because of a 3-month history of chronic diarrhea. He had frequent, watery, and yellowish stools up to five times per day. The diarrhea abated minimally and was refractory to treatment with anti-diarrheal medication. Serum electrolyte analysis revealed sodium at 142 mmol/L and potassium at 4.3 mmol/L. Abdominal ultrasonography on admission revealed a mass in the lower chest. Chest roentgenography (Fig. 2A) and a CT scan demonstrated a soft-tissue mass with calcification in the posterior mediastinum. Twenty-four hour urinary VMA concentration was 3.8 mg/day. Left thoracotomy was performed with partial excision of a tumor (4 x 3 x 3 cm). Histologic findings revealed a stroma-rich, well-differentiated ganglioneuroblastoma by the Shimada classification system. Diarrhea ceased postoperatively. Subsequently, the patient received chemotherapy with vincristine and cyclophosphamide alternately for 1 year. Near-total excision of the tumor was performed 5 months after starting chemotherapy. On careful follow-up by a pediatric oncologist, there was no evidence of recurrence of ganglioneuroblastoma for 30 months postoperatively.

**Case 3**

A 15-month-old girl was referred to our hospital because of a 3-week history of chronic diarrhea. She had frequent, watery, yellowish stools up to 16 times per day. On physical examination, the abdomen was soft and flat with a palpable mass (5 x 5 cm). Serum electrolyte monitoring revealed sodium at 137 mmol/L, potassium at 4.2 mmol/L, and chloride at 103 mmol/L. Abdominal sonography revealed a right adrenal mass. Twenty-four-hour urinary VMA concentration was elevated at 16.4 mg/day. The patient received chemotherapy, according to the St. Jude 84 disseminated neuroblastoma protocol, containing cyclophosphamide, cisplatin, epirubicin and etoposide. Right adrenalectomy with near-total excision of the tumor was performed 5 months after starting chemotherapy. The diarrhea ceased postoperatively. During careful follow-up by a pediatric oncologist, the patient remained disease-free for 22 months after surgery.

**Discussion**

Neural-crest tumors occur most frequently in the adrenal gland or retroperitoneum, followed by the mediastinum [4]. These tumors reflect the different stages of maturation or differentiation of neural-crest cells [4]. The association between chronic diarrhea and neural-crest tumor was first described in 1952 [5]. Because the diarrhea ceases after tumor removal, it seems likely that a humoral substance secreted by the tumor is responsible. The exact nature of this substance remained unclear until 1973, when Bloom et al [6] provided evidence that vasoactive intestinal polypeptide (VIP) was the causative agent. In 1983, secretory diarrhea was reproduced in normal volunteers by intravenous infusion of VIP, confirming the hormone’s role in diarrhea [7]. The biologic effects of VIP include stimulation of intestinal secretion of water and electrolytes, and inhibition of gastric acid secretion [8]. Mendelsohn et al found VIP to be present in differentiated and mature tumor cells, suggesting that VIP production was a sign of tumor maturation and a better prognosis [9].

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**Fig. 1.** Case 1. A) Abdominal roentgenograph showing a paravertebral mass with soft-tissue density (arrow) in the lower chest. B) Thoracic computerized tomography scan showing a posterior mediastinal mass with calcification (arrow).
The paraneoplastic watery diarrhea hypokalemia-achlorhydria syndrome may occur with a variety of tumors that can secrete VIP. Most pediatric cases are caused by neurogenic tumors, whereas most adult cases are caused by pancreatic islet cell neoplasms [10]. Diarrhea is reported to be more frequently associated with ganglioneuroma and ganglioneuroblastoma than with neuroblastoma [3]. Some neuroblastomas mature and differentiate into ganglioneuroblastomas. This appears to occur predominantly in neuroblastomas in extra-adrenal sites and in a higher proportion of girls than boys. Ganglioneuroma is often found in the posterior mediastinum [11].

Our review of medical records showed that the incidence of chronic diarrhea in neural-crest tumors at our institution was nearly 4%. In the patients in this report, the two ganglioneuroblastomas in the posterior mediastinum and the neuroblastoma in the right adrenal gland were found on either roentgenography or sonography. The defining feature of these three cases was still watery diarrhea, despite nothing administered orally and dietary precautions taken in all cases. This implies that these patients had secretory rather than osmotic-type diarrhea. Because a VIP detection kit was not available in our hospital, we could not examine VIP levels preoperatively and postoperatively. However, diarrhea ceased postoperatively, which supports the association between diarrhea and tumor. Because of the rarity of chronic diarrhea secondary to neural-crest tumor, and the multiplicity of other possible causes, a high index of suspicion is needed to achieve a correct diagnosis. Although the level of VIP can be measured in pediatric patients with chronic diarrhea of unknown cause, simple imaging studies may easily demonstrate a mass, evaluation of which will lead to the diagnosis.

References


