



Vasoactive intestinal peptide releasing tumor which caused to chronic watery diarrhea and hypokalemia

Ali Kanık¹, Maşallah Baran¹, Özlem Çayan¹, Kayı Eliaçık¹, Tunç Özdemir², Mehmet Helvacı¹, Emre Çeçen³

¹Clinic of Pediatrics, Tepecik Training and Research Hospital, İzmir, Turkey

²Clinic of Pediatric Surgery, Tepecik Training and Research Hospital, İzmir, Turkey

³Division of Pediatric Oncology, Adnan Menderes University Faculty of Medicine, Aydın, Turkey

Abstract

Watery diarrhea, hypokalemia and achlorhydria syndrome is a rare cause of chronic secretory diarrhea arising from a vasoactive intestinal peptide releasing tumor. In this article, a 15-month old female patient with watery diarrhea and abdominal distension which lasting four months is presented. In different centers no diagnosis could be made although investigations. The patient was diagnosed with vasoactive intestinal peptide releasing ganglioneuroblastoma localized in the right surrenal gland. (Türk Ped Arş 2014; 49: 160-2)

Key words: Child, ganglioneuroblastoma, secretory diarrhea, vasoactive intestinal peptide

Introduction

Watery diarrhea, hypokalemia and achlorhydria syndrome which was described by Verner and Morrison (1) in 1958 for the first time (WDHA) is a rare cause of chronic secretory diarrhea arising from a vasoactive intestinal peptide (VIP) secreting tumor. In adults, the majority of WDHA syndrome arises from pancreatic islet cell adenoma and hyperplasia (2, 3). In contrast, it mostly arises from VIP secreting tumor originating from the neural crest cells in the adrenal medulla or sympathetic ganglia in children (4). In this article, a 15-month old female patient who could not be diagnosed despite investigations made in different centers because of watery diarrhea, severe malnutrition and abdominal distention which had been lasting for four months and who was later diagnosed with VIP secreting ganglioneuroblastoma localized in the right side was presented.

Case

A 15-month old female baby presented to our hospital because of bulky watery diarrhea approximately 10-12 times a day which had been lasting for four months. She was investigated in two centers before because of chronic diarrhea and no response was obtained with the treatments administered. The patient who had a birth weight and height at the 50th percentile had a weight of 7 080 g (-6,1 SD) and a height of 64 cm (-4,9 SD) at presentation. Her vital findings were within the normal limits. She looked weak and cachectic and had abdominal distension and increased pigmentation on the skin. Other physical examination findings were found to be normal (Figure 1). Laboratory tests were as follows: hemoglobin 9.6 g/dL, WBC 16 100/mm³, platelets 611 000/mm³, serum sodium 130 mmol/L, potassium 2.3 mmol/L, Chlorine 104 mmol/L. Blood gas analysis revealed metabolic acidosis. Stool osmotic gap was found to be 32 mosm/L (secretory diarrhea) and reducing substance and fat were found to be negative in stool. Stool culture and parasite examination were found to be negative. Serum glucose, renal and hepatic function

Address for Correspondence: Ali Kanık, Clinic of Pediatrics, Tepecik Training and Research Hospital, İzmir, Turkey.

E-mail: dralikanik@hotmail.com

Received: 14.06.2012 **Accepted:** 10.09.2012

©Copyright 2014 by Turkish Pediatric Association - Available online at www.turkpediatriarsivi.com

DOI:10.5152/tpa.2014.1054



Figure 1. General appearance of the patient



Figure 2. A solid tissue lesion with a diameter of 4 cm compressing the right kidney in the right surrenal region

tests, immunoglobulin levels were at normal levels. Celiac antibodies and sweat test were found to be negative. Upper gastrointestinal system endoscopy and biopsy performed in the previous center were found to be normal. Since diarrhea with the same frequency and ion gap continued despite treat-

ment, treatment resistant secretory diarrhea was considered and further investigations in terms of hormone- secreting tumors was planned. On abdominal ultrasonography (USG) and computerized tomography (CT), a mass-like hypoechoic lesion with dimensions of 41x36 mm was observed in the right surrenal region. On upper abdominal magnetic resonance imaging (MRI), a mass with a dimension of 4 cm was found in the right surrenal gland which suggested primarily neuroblastoma or ganglioneuroma (Figure 2). Serum VIP, urinary metanephrine and urinary vanilylmandelic acid levels were found to be high (247 ng/L [23-63], 62.1 µg/g [6.7-52.0], 4.3 mg/g [0.5-2.5], respectively). A mass with dimensions of 4.5x4x4 cm and a weight of 35 g was removed from the patient who was operated because of right surrenal mass. Histopathological examination was found to be compatible with ganglioneuroblastoma. No tumor involvement was found on bone marrow aspiration and biopsy performed from bilateral iliac bones with the objective of metastatic evaluation. No additional treatment was given to the patient who was considered Stage 1 (International Neuroblastoma Staging System [INSS]). Follow-up urinary vanilylmandelic acid (VMA) level was found to be normal. The patient whose diarrhea stopped completely and laboratory findings improved in the follow-up after the operation is being followed up without any problem over a one year period of time.

Discussion

Vasoactive intestinal peptide is a polypeptide hormone which has widespread effects especially on the gastrointestinal system. It leads to secretory diarrhea, water and weight loss by preventing sodium, chlorine and water absorption in the intestines. It leads to hypokalemia by inducing potassium secretion in the intestines. It may cause to hypochlorhydria with inhibition of gastric acid secretion (4, 5). In addition to these effects, it may cause to hypercalcemia by increasing bone resorption, flushing on the face by dilating blood vessels and hyperglycemia by way of hepatic glycogenolysis (2).

Patients with this syndrome specifically present with intensive secretory diarrhea and water and weight loss. Since the year of 1975 when the syndrome was described for the first time less than 70 pediatric cases have been defined. Ganglioneuroblastoma and ganglioneuroma have been found in most patients and neuroblastoma and neurofibroma have been found in a small number of cases. Vasoactive intestinal peptide-secreting tumors occur most frequently at the age of 1-3 years. The most common localization is the retroperitoneal area. This is followed by adrenal, thoracic, intestinal, paravertebral, sacral and cervical regions respectively (6). Our patient was 15 months old and the tumor originated from the adrenal medulla. In patients with unstoppable and unexplained secretory diarrhea, examination with USG which is a non-invasive method should be performed in terms of mass. In our patient, a mass was found in the right surrenal

gland on abdominal USG. In VIP-secreting tumors which can not be determined by ultrasonographic examination, serum VIP levels should be evaluated primarily before performing detailed imaging procedures. In cases where the level of vasoactive intestinal peptide levels are high and the diagnosis can not be made by USG, the localization of the tumor can be determined by CT, MRI and angiography performed with the aim of screening (7). In addition, an increase in urinary catecholamine levels can be observed (8). In our patient, catecholamine levels were found to be higher than normal.

This syndrome is a paraneoplastic syndrome which can be observed in neuroblastic tumors. Generally, differentiated tumors are associated with localized disease and a good prognosis (4, 9). The definite treatment for watery diarrhea, hypokalemia and achlorhydria syndrome is removal of the tumor, if possible. If therapeutic operation is not possible, tumor reduction surgery may alleviate the symptoms. In advanced cases, variable success can be obtained with somatostatin analogues and chemotherapy (10). In our patient, the complaint of diarrhea regressed completely with full removal of the tumor.

Conclusively, childhood WDHA syndrome is a picture of secretory diarrhea, hypokalemia and hypochloremia. It may result in severe water loss, electrolyte and acid-base changes and chronic renal failure and mortality, if not treated. In presence of bulky, secretory diarrhea resistant to nonspecific treatment, plasma VIP levels should be investigated.

Informed Consent: Written informed consent was obtained from the parents of the patient who participated in this case.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - A.K., M.B., Ö.Ç., K.E., T.Ö., M.H., E.Ç.; Design - A.K., M.B., Ö.Ç., K.E., T.Ö., M.H., E.Ç.; Supervision - A.K., M.B., Ö.Ç., K.E., T.Ö., M.H., E.Ç.; Funding - A.K., M.B., Ö.Ç., K.E.; Materials - A.K., M.B., Ö.Ç., K.E.; Data Collection and/or Processing - A.K., M.B., Ö.Ç., K.E., T.Ö., M.H.; Analysis and/or Interpretation -

A.K., M.B., Ö.Ç., K.E., T.Ö., M.H.; Literature Review - A.K., M.B., Ö.Ç., K.E., T.Ö., M.H., E.Ç.; Writer - A.K., M.B., Ö.Ç., K.E., T.Ö., M.H., E.Ç.; Critical Review - A.K., M.B., Ö.Ç., K.E., T.Ö., M.H., E.Ç.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Verner JV, Morrison A. Islet cell tumour and a syndrome of refractory watery diarrhea and hypokalemia. *Am J Med* 1958; 29: 529.
2. Petersom HD, Collins OD. Chronic diarrhea and failure to thrive secondary to ganglioneuroma. *Arch Surg* 1967; 6: 934-6. [\[CrossRef\]](#)
3. Marks IN, Bank S, Louw JH, Farman J. Islet cell tumor of the pancreas with reversible watery diarrhoea and achlorhydria. *Gastroenterology* 1967; 52: 695-708.
4. Murphy MS, Sibal A, Mann JR. Persistent diarrhea and occult vipomas in children. *Br Med J* 2000; 320: 1524-6. [\[CrossRef\]](#)
5. Forte LR, Thorne PK, Eber SL, et al. Stimulation of intestinal Cl-transport by heat-stable enterotoxin: activation of cAMP-dependent protein kinase by cGMP. *Am J Physiol* 1992; 263: C607-15.
6. Zhang WQ, Liu JF, Zhao J, Zhao SY, Xue Y. Tumor with watery diarrhoea, hypokalaemia in a 3-year-old girl. *Eur J Pediatr* 2009; 168: 859-62. [\[CrossRef\]](#)
7. Modlin IM, Oberg K, Chung DC, et al. Gastroenteropancreatic neuroendocrine tumours. *Lancet Oncol* 2008; 9: 61-72. [\[CrossRef\]](#)
8. Quak SH, Prabhakaran K, Kwok R, O'Reilly AP. Vasoactive intestinal peptide secreting tumours in children: a case report with literature review. *Aust Pediatr J* 1988; 24: 55-8.
9. Yamaguchi K, Abe K, Otsubo K, et al. The WDHA syndrome: Clinical and laboratory data on 28 Japanese cases. *Peptides* 1984; 5: 415-21. [\[CrossRef\]](#)
10. Melen-Mucha G, Lawnicka H, Kierszniewska-Stepien D, Komorowski J, Stepień H. The place of somatostatin analogs in the diagnosis and treatment of the neuroendocrine glands tumors. *Recent Patents Anticancer Drug Discov* 2006; 2: 237-54. [\[CrossRef\]](#)