Case report

Watery Diarrhea Hypochloremia Achlorhydria Syndrome in an 18-Month-Old Thai Girl with Chronic Secretory Diarrhea

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Abstract:

Watery diarrhea, associated with hypokalemia and achlorhydria (WDHA) syndrome, is caused by a hypersecretory state of the vasoactive intestinal peptide (VIP). The most usual cause of this condition involves VIP-producing tumors and a rare cause of persistent diarrhea in the pediatric age group. We reported a case of an 18-month-old girl who presented profound chronic secretory diarrhea along with severe fluid-electrolyte imbalance. Physical examination revealed severe dehydration and an abdominal mass palpated at the left upper part of the abdomen. Low stool osmotic gap, hypokalemia, and metabolic acidosis were revealed. Abdominal ultrasonography and computerized tomography further documented a retroperitoneal mass at the left suprarenal area. Octreotide and chemotherapy were provided without clinical response; thus, surgical exploration for tumor removal was performed 2 months later. The histologic report identified the mass as ganglioneuroma. Additionally, the stool output and fluid electrolyte disturbance were greatly reduced after the surgical operation. WDHA syndrome is rarely prevalent among children; however, precise physical examination and imaging are important parts of the diagnosis. Tumor removal is also the treatment of choice for this condition.

Keywords: ● *WDHA* ● *Chronic diarrhea* ● *Ganglioneuroma* ● *Childhood*

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รายงานผู้ป่วย

กลุ่มอาการ Watery Diarrhea Hypokalemia and Achlorhydria (WDHA) ในเด็กหญิงไทยอายุ 18 เดือน ที่เข้ารับการรักษาด้วยอาการท้องร่วงชนิดขับสารน้ำเรื้อรัง

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บทคัดย่อ

กลุ่มอาการ WDHA คือกลุ่มอาการที่ผู้ป่วยมีอาการท้องร่วง ระดับโปแตสเซียมในเลือดต่ำ และมีภาวะไร้กรดในกระเพาะอาหาร (achlorhydria) กลไกการเกิดภาวะนี้พบว่าเกิดจากการหลั่ง vasoactive-intestinal peptide (VIP) มากเกินปกติ ซึ่งสาเหตุที่พบบ่อยเป็นการหลั่งจากก้อนเนื้องอกที่สร้าง VIP ในผู้ป่วยเด็กพบกลุ่มอาการนี้เป็นสาเหตุของภาวะท้องร่วงเรื้อรังได้น้อยมาก บทความนี้รายงานผู้ป่วยเด็กหญิงอายุ 18 เดือนที่มีอาการท้องร่วงชนิดขับสารน้ำ (secretory) ร่วมกับมีอาการขาดน้ำและเสียสมดุลของเกลือแร่อย่างรุนแรง การตรวจร่างกายพบอาการขาดน้ำที่รุนแรง (severe dehydration) และพบก้อนในช่องท้องด้านบนซ้าย การตรวจทางห้องปฏิบัติการพบ stool osmotic gap แคบ โปแตสเซียมในเลือดต่ำ และความเป็นกรดในเลือด (metabolic acidosis) มากขึ้น นอกจากนี้การตรวจคลื่นเสียงสะท้อนและการตรวจเอกซเรย์คอมพิวเตอร์ของช่องท้องยืนยันการพบก้อนเนื้อภายในช่องท้องด้านซ้ายบริเวณ retroperitoneum ผู้ป่วยได้รับการรักษาเบื้องต้นโดยใช้ octreotide และยาเคมีบำบัด แต่ไม่พบการตอบสนองต่อการรักษานี้ หลังจากนั้นจึงพิจารณาการรักษาทางศัลยกรรมเพื่อผ่าตัดนำก้อนเนื้องอกออกในอีก 2 เดือนต่อมา ผลการตรวจชิ้นเนื้อรายงานพบเนื้องอกชนิด ganglioneuroma หลังจากการผ่าตัดพบว่าปริมาณอุจจาระ ภาวะการขาดน้ำและภาวะเสียสมดุลของเกลือแร่ในร่างกายดีขึ้นอย่างชัดเจน ภาวะ WDHA เป็นภาวะที่พบได้ไม่บ่อยในเด็ก การตรวจร่างกายอย่างพิถีพิถันและการตรวจเพิ่มเติมทางรังสีวินิจฉัยมีความสำคัญเพื่อให้ได้การวินิจฉัยอย่างแม่นยำ การรักษาทางศัลยกรรมเพื่อนำก้อนเนื้อออกยังเป็นการรักษาหลักที่ใช้ในภาวะนี้

คำสำคัญ: ● *กลุ่มอาการ WDHA* ● *ภาวะท้องร่วงเรื้อรัง* ● *เนื้องอกชนิด ganglioneuroma* ● *วัยเด็ก*

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Introduction

Watery diarrhea associated with hypokalemia and achlorhydria (WDHA) syndrome is caused by a hypersecretory state of the vasoactive intestinal peptide (VIP)[1]. The usual cause of this syndrome is a VIP-producing tumor and the most common site of the tumor is of neural crest origin[2]. This syndrome was first described by Verner and Morrison in 1958[3] and is also described as Verner-Morrison syndrome[4]. A report focusing on a children's age group was first published in 1975 by Swift PGF et al.[5] WDHA has been infrequently reported in the pediatric age group; moreover, a high level for an index of suspicion was the most important part for confirming a diagnosis of this situation.

Case report

An 18 month-old-girl, previously healthy, presented chronic watery diarrhea and weight loss from 11 to 9 kg within two months. Previous treatment with intravenous fluid, antidiarrheal agents, and empirical antibiotics were given without clinical improvement, then she was transferred to Phramongkutklao Hospital. Physical examination showed severe dehydration and abdominal distention with palpable mass at the left upper part of the abdomen. Investigations showed CBC: Hct 38%, Hb 13.1 g/dL, WBC 8,600 (P 55, L 38, M 5, B 2), and Plt 475,000/mm^3. Serum electrolyte was Na 127, K 2.2, Cl 100, HCO3 10 mEq/L, BUN 9, and Cr 0.4 mg/dL. Albumin was 5.7 g/dL, TB/DB 0.2/0.1 mg/dL, and AST/ALT 151/182 U/L. AFP and Beta-hCG were normal. Investigations of stool for enteric pathogens were negative and stool electrolyte revealed secretory diarrhea with stool Na 132, K 12, and Cl 99 mEq/L. Urine vanillylmandelic acid (VMA) was 39.8 mg/day (1-11), urine catecholamine 0.1 g/day (0.7-1.5), and neuron specific enolase (NSE) 102.7 ng/mL (0-15). However, plasma VIP level was not determined in this case because the test was unavailable. Abdominal ultrasonogram and CT revealed an ill-defined heterogenous retroperitoneal mass at the left suprarenal area. The size of the tumor was about 4.5 x 7.5 x 6.7 cm with pressure effect to adjacent organs, and internal calcification was detected (Figure 1). At the first operation, exploratory laparotomy for excisional biopsy was performed and histology was reported as ganglioneuroblastoma. Chemotherapy (carboplatin and etoposide) and continuous subcutaneous octreotide were provided without clinical response or significant change of the tumor size on follow-up imaging. The second

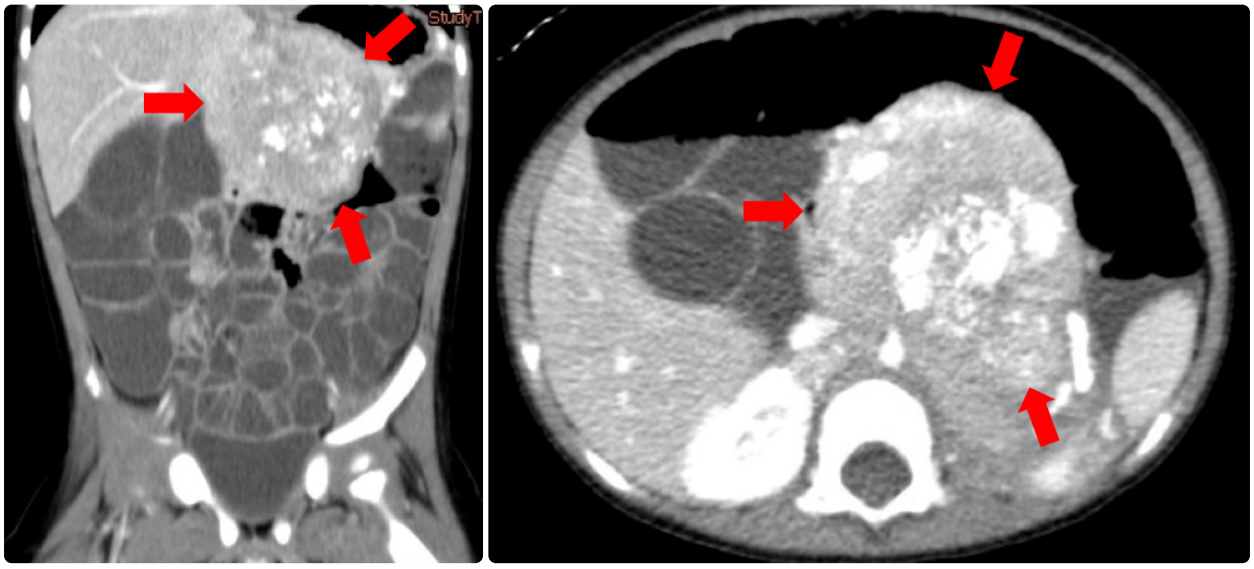

Figure 1 Ill-defined heterogenous retroperitoneal mass at the left suprarenal area (red arrow)

surgical operation for tumor removal was performed revealing a left supra-renal mass 8 cm in diameter (Figure 2) and the pathology report identified the mass as a mature type ganglioneuroma (Figure 3). After the operation, her diarrheal symptoms exhibited marked improvement and stool output decreased from 1,200 to 70 mL daily. However, she developed a fever with a productive cough in the first week after the procedure, and finally, died two weeks post-operation. The cause of death was severe pneumonia from the metapneumovirus with respiratory failure.

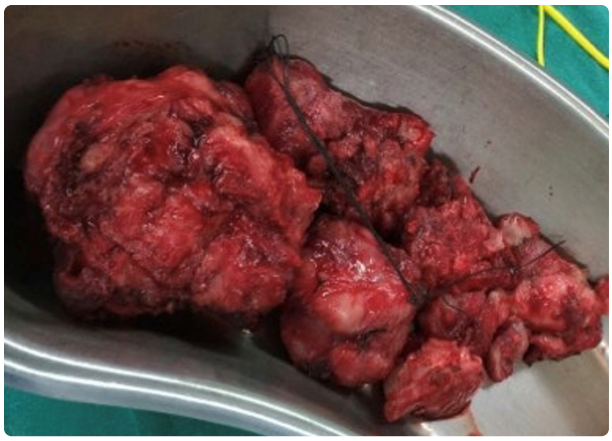

Figure 2 Retroperitoneal mass about 8 cm, attached to the superior mesenteric and celiac artery

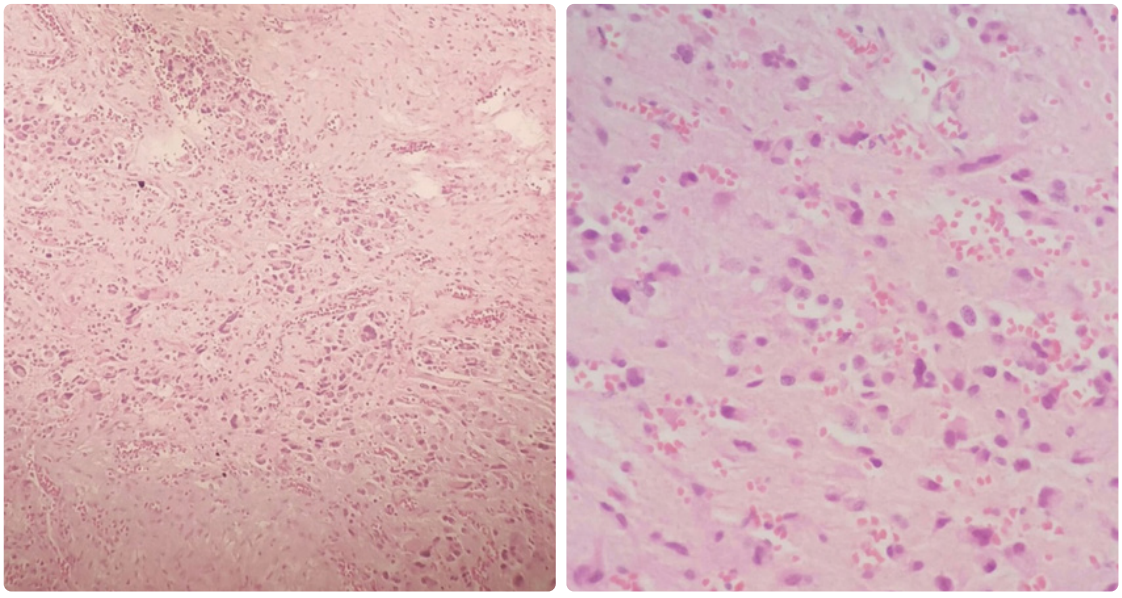

Figure 3 Histopathological finding revealed ganglioneuroma. HE staining showed mature ganglion cells

Discussion

VIP is a gastrointestinal polypeptide affecting various biologic systems including gastro-intestinal (GI), cardiovascular, and respiratory system. The actions of VIP in the GI tract are adenyl cyclase activator, increased fluid-electrolyte secretion in the intestinal lumen and splanchnic or systemic vasodilatation. Moreover, the action inhibits gastric acid secretion causing achlorhydria. These physiologic actions induce specific characteristics of WDHA syndrome comprising intractable secretory diarrhea, hypokalemia, achlorhydria, and metabolic acidosis. Hyperglycemia is often documented and the possible mechanism is increasing hepatic glycogenolytic by VIP[6-8]. Common locations of VIP-producing tumors are typically along the sympathetic ganglion such as intra-abdominal, intrathoracic, and cervical regions. Among children, the most common sites of VIP-producing tumors are the retroperitoneum and mediastinum, while the usual site among adults is pancreatic the islet cell in origin. This tumor and clinical presentations are also described as pancreatic cholera[10,11]. A systematic review of sixty-five adults revealed median age of 54 years (range 18-75 years), female gender of 54% and 42% presented with the classical triad of WDHA (watery diarrhea, hypokalemia

and achlorhydria). The most common location of tumor was determined in the pancreatic tail, which is 54% of cases. Moreover, hepatic metastasis was discovered in 48% of patients[12]. Yeh PJ, et al.[13] reviewed the literature of 45 cases of pediatric VIPomas (average age 3.3 years old) and reported a 1:2.4 male and female ratio, of which, 46.7% presented an adrenal or suprarenal tumor, 15.6% presented a paravertebral or prevertebral tumor, while mediastinum and pancreatic regions demonstrated 13.3% and 4.4%, respectively.

Additionally, watery diarrhea was the most frequent presenting symptom in this series; hypokalemia was identified in 84%, skin flushing in 17% while achlorhydria and acidosis were shown in 27 and 16% of cases, respectively. Moreover, various reports revealed no abdominal mass on physical examination at time of diagnosis[8,14,15].

The differential diagnosis of this condition was considered from a clinical of protracted watery diarrhea and presence of abdominal mass, which is gastrointestinal neuroendocrine tumor including ganglioneuromas, ganglioneuroblastoma as well as neuroblastoma. The common histology in pediatric WDHA syndrome included ganglioneuromas and ganglioneuroblastomas originating from the sympathetic ganglion and the adrenal medulla. Ganglioneuromas are mature cells and also have a benign matured ganglion cell. However, ganglioneuroblastomas have less mature ganglion cells and young children have the potential to develop mature ganglioneuromas or experience tumor regression. Neuroblastomas are neuroblastic tumors originating from the neural crest that also increase VIP-production[4]. Zhang WQ, et al. collected data from 63 cases of WDHA among children revealing 55.6% ganglioneuroblastoma, 31.7% ganglioneuroma, 7.9% neuroblastoma, and 1.6% neurofibroma and neurofibromatosis cases[14]. For this case, the final report of histological examination was compatible with the most common histological finding as "mature-type ganglioneuroma".

Plasma VIP level is typically at marked elevation in WHDA syndrome from the normal range of VIP concentration (0 to 100 pg/mL). Yamaguchi K, et al.[16] reported VIP level in 20 cases of this syndrome with mean plasma VIP level at 2,091 (range 200 to 7,500) (median 1,550; IQR 890, 2,800) pg/mL. The false-negative of single plasma VIP sampling was demonstrated in specific cases with profound watery diarrhea, however, rising of VIP level was demonstrated in bowel ischemia typically found with severe dehydration and hemodynamic compromised status. Thus, repeated blood sampling is necessary to confirm diagnosis in some situations. Additionally, rapidly decreasing serum VIP to normal levels and a brisk decrease in the volume of stool output were common findings after tumor removal[15]. Our report was compatible regarding the clinical outcome of rapidly decreased stool output after the final operation, even when serum VIP was unconfirmed in this case.

Concerning neuroblastoma producing-VIP, rising VMA, homomandelic, and catecholamine levels are common findings. NSE is also elevated in neural crest-origin tumors and can be detected in serum and cerebrospinal fluid as we detected in this case. Imaging is an essential assessment in the investigation plan to diagnose WDHA syndrome after physical examinations. Ultrasonography is typically a first step investigation without radiation exposure and deep sedation. CT and magnetic resonance imaging are the investigations of choice to accurately diagnose and planning for the operation.

The first step of management is a correction of dehydration status, electrolyte imbalance, and improved nutritional status. A somatostatin or somatostatin analog were variable responses of the secretory state and was also used in supportive and pre-operative treatment[18,19]. Thus, tumor resection or debulking is also a satisfactory treatment for VIP-producing tumors due to a lack of

response from chemotherapy[20]. Typically, ganglioneuromas and neuroblastomas are more favorable outcomes[21,22] and recurrence of the tumor has been reported while surveillance remains needed for long-term care. Complete remission was reported at 82% from the total of 45 cases and 11% of mortality was described. The causes of death in this series included sepsis, peritonitis, intestinal perforation, profound diarrhea, and severe hypokalemia[13].

We reported this case for the reason that it constitutes an unusual cause of persistent diarrhea among children and it is the first case documented at Phramongkutklao Hospital. The clinical manifestations and physical findings were typical for this syndrome. Regarding treatment response, continuous octreotide and chemotherapy were not the main therapeutic plans for WDHA syndrome or played an important role for surgical intervention.

Conclusion

WDHA syndrome is rarely prevalent among children, however, an awareness of this condition among patients with chronic diarrhea is needed, especially for considering secretory patterns and unknown possible causes of symptoms. The important part in making a diagnosis is a precise physical examination and consideration for imaging in the possible locations, although no abdominal mass was detected. Tumor removal is also the treatment of choice for this condition.

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