Etiology, Assessment, and management of WDHA (watery diarrhea, hypokalemia, and achlorhydria) and VIPoma

Abstract:

The syndrome of watery diarrhoea, hypokalemia, and achlorhydria (WDHA syndrome) is an uncommon disorder marked by severe, watery diarrhoea caused by non–beta pancreatic islet cell oversecretion of vasoactive intestinal peptide (VIP). The onset of the disease is gradual, and diagnosis is often months or years later. Long-term dehydration, electrolyte and acid-base abnormalities, and chronic renal failure are all linked to morbidity. Pancreatic endocrine tumours are extremely rare, with less than 10 incidences per million people. VIPomas are uncommon tumours that affect between 0.05 and 2.0 percent of people. The most prevalent symptom is diarrhoea, which affects at least 89 percent of patients. VIPoma is treated with a combination of medicine and surgery The goal of first medical treatment is to reduce symptoms and restore fluids and electrolytes as quickly as possible

Introduction:

The syndrome of watery diarrhoea, hypokalemia, and achlorhydria (WDHA syndrome) is an uncommon disorder marked by severe, watery diarrhoea caused by non–beta pancreatic islet cell oversecretion of vasoactive intestinal peptide (VIP). Patients with high VIP levels and a history of dehydration and/or hypokalemia frequently visit the hospital. Matsumoto and colleagues (1966) used the name pancreatic cholera to describe this condition's resemblance to cholera. Hypercalcemia, hyperglycemia, hypochlorhydria, and flushing occur in a small number of people with WDHA syndrome. A small percentage of individuals with hypercalcemia and WDHA syndrome have multiple endocrine neoplasia type 1 (MEN-1) syndrome (ie, Wermer syndrome). [1] The onset of the disease is gradual, and diagnosis is often months or years later. Long-term dehydration, electrolyte and acid-base abnormalities, and chronic renal failure are all linked to morbidity and death in untreated WDHA syndrome. Large quantities of secretory diarrhoea, increased serum VIP levels, and localisation of the VIP-secreting tumour are all required for diagnosis. Volume, electrolyte, and metabolic imbalances are corrected, followed by medication to reduce gastrointestinal

secretion and enhance absorption, and finally surgical excision or debulking of the vipoma. [2]

VIP is a 28-amino-acid straight-chain polypeptide with a wide range of biological activities, and its overproduction by pancreatic endocrine tumours or ganglioneuroblastomas is known to cause profuse watery diarrhoea, the so-called watery-diarrhea-hypokalemia-achlorhydria (WDHA) syndrome.[3] VIP also suppresses stomach acid production, stimulates hepatic glycogenolysis and hyperglycemia, and dilates systemic blood vessels in the periphery. When endocrine tumours release enormous amounts of it, the patient usually suffers from severe secretory diarrhoea, dehydration, flushing, and weight loss. Hypokalemia, achlorhydria, hypercalcemia, hyperglycemia, and metabolic acidosis are all common laboratory findings. [4]

Vasoactive intestinal peptide tumors (VIPoma) are neuroendocrine tumors secreting vasoactive intestinal peptide (VIP) in an unregulated manner. Werner and Morrison first described them in 1958 as a pancreatic tumor resulting in watery diarrhea and hypokalemia. In 1973, the team of Bloom, Polak, and Pearse confirmed that the mediator was VIP. The VIPoma syndrome is also known as Verner-Morrison syndrome, watery diarrhea, hypokalemia, and hypochlorhydria or achlorhydria (WDHA) syndrome, and pancreatic cholera syndrome. [5]

Etiology and pathophysiology:

The best way to understand the pathophysiology of WDHA syndrome is to look at the characteristics of VIP. VIP is a 28-amino-acid regulatory peptide with a half-life of 1-2 minutes that is broadly dispersed throughout the gastrointestinal system and brain. The peptide is released by non–beta islet pancreatic cells in response to fat, protein, and alcohol-containing foods. It travels through the portal circulation to the liver, where it is digested. [1] VIP is a neurohormone generated by neurons in the gastrointestinal (GI), respiratory, and urogenital tracts, as well as the central nervous system. It acts as a vasodilator and smooth muscle regulator, as well as a stimulator of water and electrolyte secretion from the intestinal tract, an inhibitor of gastric acid secretion, and a promotor of blood flow in the gastrointestinal system. [5]

Patients with WDHA syndrome may have high amounts of the 27–amino acid peptide histidine methionine (PHM), which was initially isolated from swine

intestine (ie, peptide histidine isoleucine [PHI]). The inclusion of histidine and isoleucine at the N and C terminals distinguishes PHI from other gastrointestinal peptides, which have amidated C terminal amino acids. Although PHI/PHM operates on target cells through a separate receptor, it shares many characteristics with VIP. Both are generated from the same precursor polypeptide and are encoded by the same messenger ribonucleic acid, for example (mRNA). Furthermore, these peptides are found in the same tissue distribution and have similar pharmacologic effects in enteric neurons and VIPomas. [1]

Some variables in glioma-conditioned media enhanced the cholinergic neuronal development of rat pheochromocytes in experimental research. In two of four pheochromocytomas without concomitant diarrhoea, Mendelsohn et colleagues immunohistochemically found isolated VIP-containing cells that demonstrated unique ganglion cell development. However, because pheochromocytes without ganglionic differentiation markers may stain for VIP, it's been suggested that neoplastic transformation could cause tumour cells to produce VIP. This might be explained by the fact that APUD cells can create numerous polypeptides or amines during neoplastic development, which are unique to not only their differentiated cell types but also to linked APUD cells coming from the common neuroectoderm. [4]

Genetics: In 6% of people with MEN-1 syndrome, WDHA syndrome develops. In the study of the molecular pathogenesis of WDHA syndrome and other pancreatic endocrine cancers, significant progress has been achieved. Several genes have been linked to their relevance in studies, including the following: [1]

- MEN1 gene
- p16/MTS1 tumor suppressor gene
- DPC4/Smad 4 gene - A tumor suppressor gene located on chromosome arm 18q24
- Amplification of the HER2/neu proto-oncogene
- Deletions in chromosome 1
- A possible tumor suppressor gene on chromosome arm 3p

Epidemiology:

Pancreatic endocrine tumours are extremely rare, with less than 10 incidences per million people. According to statistics from a referral facility in Ireland, the

relative frequency of these malignancies is 3.6 instances per million people per year on average. Insulinomas were the most prevalent pancreatic endocrine tumour, with an incidence of 8 times that of VIPomas. There appears to be a minor female preponderance in WDHA syndrome. Individuals with the condition are diagnosed at a bimodal age, ranging from 10 months to 9 years in children and 32-81 years in adults. [1]

VIPomas are uncommon tumours that affect between 0.05 and 2.0 percent of people. They can affect both children and adults. They are most frequent in individuals between the ages of 30 and 50, and they are usually intrapancreatic (95 percent). Colorectal cancer, lung cancer, pheochromocytoma, neurofibroma, and ganglioneuroblastoma are just a few of the tumours that secrete VIP. [2] Every year, 1 in a million persons are diagnosed with VIPomas. The majority of VIPomas are classed as functional pancreatic neuroendocrine (islet cell) tumours because they begin in the pancreas. VIPomas are intrapancreatic in about 95% of occurrences in adulthood. Other VIP-secreting cancers, including as lung cancer, colorectal cancer, ganglioneuroblastoma, pheochromocytoma, hepatoma, and adrenal tumours, have been described. VIPomas in the pancreas are uncommon in youngsters. VIP-secreting tumours are most commonly seen in the sympathetic ganglia and adrenal glands. [6]

VIPomas are most commonly seen as single tumours, however they are also found in around 5% of individuals with multiple endocrine neoplasia type 1 (MEN1) syndromes. By the time they are diagnosed, more than half of VIPomas are spread. They are usually identified in youngsters between the ages of 2 and 4. The majority of VIPomas in children are ganglioneuromas or ganglioneuroblastomas, which arise from sympathetic ganglia neural crest tissue in the mediastinum or retroperitoneum. They can also come from the medulla of the adrenal gland. [5]

VIPomas are most commonly diagnosed in adults between the ages of 30 and 50, and in children between the ages of two and four. Symptomatic pancreatic VIPomas are generally solitary, have a diameter of more than 3 cm, and are found in the tail of the pancreas in 75% of cases. By the time they are diagnosed, 60 to 80 percent of VIPomas have spread to other organs. VIPomas are usually found as single tumours, but in 5% of patients, they are associated with parathyroid and

pituitary tumours, gastrinoma, and other tumours as part of the multiple endocrine neoplasia syndrome type 1 (MEN1), which includes parathyroid and pituitary tumours, gastrinoma, and other tumours. [6]

Clinical Features and Assessment:

The most prevalent symptom is diarrhoea, which affects at least 89 percent of patients. Although diarrhoea is usually mild, it might be episodic at first and be linked with stomach pains. Diarrhea increases profuse with time (stool production >3L daily in 80% of patients). It has a secretory nature and survives fasting. It's commonly said to have the look of weak tea. In 72 percent of patients, weight loss has been documented. Abdominal discomfort is a prevalent symptom that affects 50% of individuals. Flushing is seen in 20% of patients and is thought to be caused by VIP's vasodilatory effects. However, in human trials, prolonged VIP infusion causes tachyphylaxis, which might explain why only a small percentage of patients experience flushing. [1]

VIPoma syndrome, also known as pancreatic cholera syndrome, Verner-Morrison syndrome, and the watery diarrhoea, hypokalemia, hypochlorhydria or achlorhydria (WDHA) syndrome, affects the majority of VIPoma patients. Watery diarrhoea that continues after fasting is a symptom of VIPoma syndrome. Stools are tea-colored and odourless, and they have a volume of more than 700 mL every day. Stool volume might reach 3000 mL per day in 70% of individuals. Abdominal discomfort is either minimal or non-existent. Flushing episodes occur in 20% of patients, as well as signs of hypokalemia and dehydration, such as fatigue, nausea, vomiting, muscular weakness, and muscle cramps. [6-8]

A physical examination may reveal symptoms of dehydration, malnutrition, muscular weakness, or a long medical history. Muscle weakness can be linked to high levels of creatine phosphokinase (CPK) and rhabdomyolysis due to hypokalemia. There are no distinct physical signs or symptoms for WDHA syndrome, and even the flushing that occurs in 20% of patients can occur in a variety of different illnesses. The flushing is thought to be caused by VIP's vasodilatory characteristics. The liver may be visible and nodular on occasion, indicating hepatic metastatic illness. [1]

Treatment:

Prolongation of life, symptom management, and correction of electrolyte imbalances are all aims of treatment. The main treatment is surgical excision, however most of the time the tumor by time of diagnosis has already migrated to regional lymph nodes and/or the liver. Surgical removal of the main tumour, regional lymph node dissection, and, if possible, resection of hepatic metastases are all part of palliative care. Liver transplantation is a procedure that has been used for a long time. [1]

VIPoma is treated with a combination of medicine and surgery The goal of first medical treatment is to reduce symptoms and restore fluids and electrolytes as quickly as possible:

- Somatostatin analogues such as octreotide and lanreotide block VIP secretion and are used to treat symptoms.
- Octreotide is typically begun at 50 to 100 mcg subcutaneously every 8 hours and titrated for symptom relief. A monthly dosage of 20 mg intramuscularly (IM) of a long-acting version of octreotide is started and titrated as needed for best symptom management.
- Patients who have failed to respond to somatostatin analogues are given glucocorticoids.
- Interferon-alpha has also been utilised in patients who haven't responded to the drugs listed above.
- Primary tumours are treated with complete surgical resection, which is commonly a distal pancreatectomy. Surgical debulking may give palliative benefit if the tumour cannot be entirely removed. [5,9,10]

Literature Review & Discussion:

Since Loehy et al. originally characterised the WDHA condition in 1975, fifteen instances of pheochromocytoma have been recorded. Pheochromocytoma was found in ten instances, whereas mixed pheochromocytoma-ganglioneuroma was discovered in five cases. Immunoreactive VIP was restricted to the ganglion cells of the ganglioneuroma component in mixed pheochromocytoma-ganglioneuroma instances, but the pheochromocytes were not stained for VIP. Eeckhout et colleagues described a pheochromocytoma in which VIP was only observed in scattered cells among pheochromocytes. Other researchers, on the other hand, have discovered VIP positive in the pheochromocytes themselves. [4,11-20]

In case report patient had characteristic WDHA syndrome symptoms, which were confirmed by the results of hyperperistalsis on a double contrast small bowel examination. The diagnosis of lung cancer was established after extensive imaging and pathology tests. The WDHA symptoms were entirely reversed following palliative radiotherapy to the lung mass, and his plasma VIP and serotonin levels returned to baseline. His illness progression proved conclusively that the lung mass was the source of WDHA syndrome by generating neurotransmitters such as VIP. a More intriguingly, no indication of neuroendocrine tumour was found in immunohistochemical tests of lung samples and excised lymph nodes via mediastinoscopy. It's fascinating how his lung adenocarcinoma led to an increase in VIP. it's believed that VIP was released from tumour cells so quickly that no VIP was identifiable in the tumour cells owing to low concentration, as has been reported before in pancreatic VIPoma. Alternatively, the neuroendocrine component of the tumour might have been overlooked owing to random sampling, however this is less likely. [21]

A case of WDHA syndrome reported by Matta MK et al: caused by a pheochromocytoma secreting vasoactive intestinal peptide is was described. The patient, a 43-year-old lady, was referred to the doctor because she was experiencing chronic watery diarrhoea, hypokalemia, and weight loss. A mass was discovered in the right adrenal region. Vasoactive intestinal peptide levels were high prior to surgery, raising the possibility of WDHA syndrome. An exploratory laparotomy found a 15 x 15 cm tumour of the right adrenal gland, which was removed. It was discovered to be a pheochromocytoma after a histological investigation. Vasoactive intestinal peptide levels returned to normal after surgery. The patient's problems were completely gone, and she has been OK ever since. [22]

A study done by Ken Yamaguch et al In Japan, 28 people with WDHA were diagnosed between 1967 and 1983. Clinically, these individuals were not dissimilar to those described in western nations, yet we were able to make the following observations. First, patients with pancreatic endocrine tumours and those with neuroblastic tumours were virtually equally represented in the WDHA. Second, variable hypercalcemia was frequently detected in individuals with this condition, but not in any other etiologies of watery diarrhoea. Third, WDHA patients with type 1 multiple endocrine neoplasia (MEN) have several tumours in

the pancreas, indicating that patients with MEN should be treated differently in terms of detecting tumour site and surgical therapy. Many tumours have the capacity to create VIP, and when VIP is produced in significant numbers, plasma VIP levels rise, resulting in the WDHA syndrome. [3]

Conclusion:

The syndrome of watery diarrhoea, hypokalemia, and achlorhydria (WDHA syndrome) is an uncommon disorder, the most prevalent symptom of the disease is severe watery diarrhea which caused by over secretion of the VIP, the main problem with WDHA is that it's often cause by tumoer which may be time of diagnosis has migrated to the regional lymph nodes and/or the liver, main treatment consist of surgery for tumor combined with other treatment to manage the symptoms

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