Vasoactive Intestinal Peptide-secreting Tumor

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ABSTRACT

Vasoactive intestinal peptide-secreting tumor (VIPoma) is one of the tumors which cause "watery diarrhea, hypokalemia, hypochlorhydria and acidosis syndrome" (WDHHA syndrome). These tumor caused by to non-insulin-secreting pancreatic islet tumor that associated with elevated vasoactive intestinal polypeptide (VIP) plasma level. VIP is a potent stimulator of gut cyclic adenosine monophosphate (cAMP) production, which leads to massive secretion of water and electrolytes mainly potassium. Over expression of VIP causes diarrhea and cancerous growth. The other clinical features of VIPomas such as hypercalcemia, abdominal discomfort, tetany, facial flushing are associated with the actions of VIP, which stimulate intestinal secretion, inhibit gastric acid secretion. VIP also regulates the synthesis, secretion, and action of neuroendocrine hormones such as secretin, glucagon, prostaglandin E, somatostatin and pentagastrin as well as cytokines and chemokines. Diagnosis is based on clinical, laboratory test show elevation VIP level, electrolyte and acid base imbalance also imaging such as CT scan or magnetic resonance imaging (MRI) which shows primary tumor in the pancreas and metastasis especially in the liver. Somatostatin receptor scintigraphy may be useful in identifying extrapancreatic VIPomas, i.e. the sympathetic chain, colon, bronchus and occult or distant metastases. Initial treatment is to correct volume, electrolyte, and acid-base abnormalities with intravenous normal saline, potassium chloride, and, sodium bicarbonate. Somatostatin or long acting ocreotide is effective in reducing serum VIP levels and promptly controlling diarrhea. Interferon alpha and glucocorticoid may be useful for reducing symptoms. Surgical resection depends on staging of pancreatic tumor.

***Keywords**: VIPoma, WDHHA syndrome, VIP, non insulin secreting pancreatic islet tumor*

INTRODUCTION

Vasoactive intestinal peptide-secreting tumor (VIPoma) is an extremely rare tumors that cause the watery diarrhea, hypokalemia, and acidosis syndrome (WDHHA syndrome). In 1958, Verner and Morrison first described refractory watery diarrhea and hypokalemia associated with non-insulin-secreting pancreatic islets tumor. The absence of gastric hypersecretion and even achlorhydria were documented in patients with this tumor syndrome later termed pancreatic cholera.[1,2] The appropriate acronym should be WDHHA; watery diarrhea, hypokalemia, hypochlorhydria, and acidosis caused by bicarbonate wasting.[1] Other symptoms include abdominal pain, flushing, muscle weakness, weight loss that often can be mistaken for carcinoid syndrome.[1] Several reported series confirmed the association between certain pancreatic tumors and watery diarrhea syndrome.[2,3,4] In 1970, Said and Mutt extracted the putative hormone causing WDHA from pig gut tissue.[2,5] Finally, in 1973, Bloom reported six watery diarrhea patients due to pancreatic tumors were associated with elevated plasma level these putative hormone. These extirpated tumors were found containing large amounts of Vasoactive intestinal polypeptide (VIP).[2]

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EPIDEMIOLOGY

VIPomas occur with a frequency of 1 per 10,000,000 per year. The incidence of new cases of VIPomas is

0.05-0.5 per million people per year. VIPomas arise from the pancreas in 90% of cases, but they may also be found in periganglionic tissue or other sites including the colon, bronchus, adrenal glands, and liver.[2,3] These tumors are almost always solitary, with only less than 5% of cases being multi-centric. These tumors are usually greater than three cm at the time of diagnosis and are mostly found in the body and tail of the pancreas.[1,2] Approximately 60-80% of VIPomas are malignant and have metastasized at the time of diagnosis. Metastasis occurs most frequently in the liver but may also occur in the lymph nodes, lung, or kidneys. Approximately 5% of VIPomas are associated with multiple endocrine neoplasia type 1 (MEN 1) syndrome. Conversely, 17% of patients with MEN 1 develop VIPomas at some stage of their disease. Approximately 10% of neuroendocrine tumors in the gastrointestinal tract (except carcinoids) are VIPomas. There have been 18 other case reports of elevated plasma levels of VIP that have been associated with neurogenic tumors, including ganglioneuroblastoma, ganglioneuromas, neurofibroma, and pheochromo-cytoma.[1,3,6] In adults these tumor present between ages 30 and 50 years. Peak incidence occurs in the fifth decade of life, but VIPomas may occur in all ages including young children and elderly persons. The male-to-female ratio is approximately 1 : 1. Morbidity and mortality on WDHA syndrome is related to long-standing dehydration with electrolyte and severe acid-base disturbances that may cause chronic renal failure[2].

PATHOPHYSIOLOGY

VIP has 3,381 molecular weight that consists of 28 amino acids, and belongs to the secretin-glucagon family. The VIP gene is located on chromosome 6. VIP is normally expressed in the central nervous system and in the neurons of the gastrointestinal, respiratory, and urogenital tracts, where it functions as a neurotransmitter. VIP regulates the synthesis, secretion, and action of neuroendocrine hormones as well as cytokines and chemokines.

Over expression of VIP causes diarrhea and promotes cancerous growth. In the gastrointestinal tract VIP is largely responsible for the relaxation of vascular, smooth muscleVIP is a potent stimulator of gut cyclic adenosine monophosphate (cAMP) production, which leads to massive secretion of water and electrolytes (mainly potassium).[2] VIP resembles secretin, which stimulates secretion of alkaline pancreatic juices. In the stomach, VIP inhibits histamine and pentagastrin-stimulated acid secretion. VIP stimulates lipolysis and glycogenolysis and has an inotropic effect on the myocardium. It also has anti-inflammatory properties and modulates the immune system.

DIAGNOSIS

Clinical

The dominant symptom of VIPoma is profused cholera-like diarrhea that may persist 3-4 years before the diagnosis established. Diarrhea may be episodic initially but becomes continuous as the tumor progresses. Stool volumes were greater than 3 liters per 24 hour in 70% of cases, and may exceed 6-8 liters per 24 hours. The stool is typically odorless, tea-colored, without blood or mucus. Stools have large amount potassium, and bicarbonate (average potassium 300 mmol/24 hours). These condition cause hypokalemia and metabolic acidosis. Hypokalemia may present as muscle cramps and weakness.[1,2,3]

The diarrhea is always secretory and will not disappear with fasting for 48 hours. This symptom may be confused with the diarrhea found in the Zollinger-Ellison syndrome. Loss of water, sodium, and chloride may lead to volume depletion, dehydration, and exhaustion in patients unable to replace fluid and electrolyte losses.[2,3] Weight loss and even renal failure have been reported in some patients.

The clinical features of VIPomas are associated with the actions of VIP, which stimulate intestinal secretion and glycogenolisis, inhibit of gastric acid secretion, cause hypercalcemia and also cause relaxation of the gallbladder.[8-12] The structural homology between VIP and secretin-glucagon family like secretin, glucagon, gastric inhibitory polypeptide (GIP), peptide histidine and isoleucin may enhance secretion of pancreatic juice and inhibit of gastric acid secretion that cause hypochlorhydria/achlorhydria.[7,11] Hypercalcemia has been noted in nearly 50% of patients and it may relate to dehydration, electrolyte disturbances secondary to diarrhea, coincidental multiple endocrine neoplasia (MEN) accompanied by hyperparathyroidism, and secretion by the tumor of a calcitrophic peptide. Tetany has been reported in several patients and may result from hypomagnesemia secondary to the diarrhea. Nearly 8% of patients demonstrate facial flushing (patchy erythematous) and sometimes urticaria, that attributed to vasodilatory effect. Abdominal discomfort or bloating has also been reported.[1,3]

Physical Examination

Volume depletion may lead to tachycardia, decreased skin turgor, and weight loss. Patients may present with a mildly distended abdomen. Hepatomegaly may be detected if liver metastasis has occurred.

Biochemical

VIP levels in VIPoma patients are markedly elevated, to levels 160-250 pmol/L or higher during severe diarrhea. Normal VIP plasma level is only 20-30 pmol/L or less (determined by radio-immuno assay). VIP levels should be drawn after fasting. Because VIP is degraded rapidly, a protease inhibitor such as aprotinin is added to the blood sample that should be kept frozen at -70°C until processed.[1]

VIP is synthesized as the 170 amino acid precursor pre-pro VIP, which post translationally modified to yield the 28 amino acid VIP as well as peptide histidine and methionine (PHM) and other fragments.[13] False-positive elevations of VIP can be observed in patients with small bowel ischemia or severe low-flow states caused by diarrhea and secondary dehydration not associated with VIP-producing tumors.[14-16]

VIP is not the only agent implicated in the diarrhea syndrome. Gastrin, secretin, glucagon, enteroglucagon, GIP, PP, VIP, thyrocalcitonin (TCT), prostaglandins E, somatostatin, neurokinin, and peptide fragments of pre-pro VIP or any one of a number of combinations have been implicated as possible etiologic agents of the diarrhea syndrome.[16] Between periods of watery diarrhea, the VIPoma, unlike many endocrine tumors of the gut (e.g. insulinoma, gastrinoma), may not be actively secreting VIP. If VIP level is elevated when diarrhea still persists after fasting, a VIPoma should be strongly suspected.

Imaging

Imaging studies are primarily focused on the pancreas because 90% of VIPoma tumors are located in the pancreas. CT scan will successfully identify the primary tumor and metastasis especially in the liver. Peng et al reported that all VIPomas of the pancreatic body and tail were identified on CT, but only 71% of VIPomas in the pancreatic head were successfully identified. Magnetic resonance imaging (MRI) may be used if a CT scan is contra-indicated. VIPomas are observed best on T1-weighted, fat-suppressed images as low-signal intensity masses. Liver metastases may demonstrate intensive peripheral ring enhancement on immediate post-gadolinium spoiled gradient-echo images.

Somatostatin receptor scintigraphy may be useful in identifying extrapancreatic VIPomas, particularly those in the sympathetic chain, or metastases.[2,3] Somatostatin receptor scintigraphy may be useful to characterize an abnormality found on CT scan or to identify occult or distant metastatic disease. It may also be used if postsurgical changes diminish the clarity of a CT scan images. Sensitivity for localization of all pancreatic endocrine tumors has been reported at 80-90%, with 92% sensitivity for tumors larger than one cm. Octreotide scanning may be useful, especially if metastases are being sought, but may not be quite as helpful in small primary lesions.[2] Single-photon emission CT, as suggested by recent investigations. Some reports demonstrate successful VIPoma localization with technetium 99 m sestamibi. Transabdominal ultrasonography (USG) may be used for early screening to exclude liver metastases, which may be present as hepatic calcifications.

Other Test

Hypochlorhydria or achlorhydria is seen in at least 75% patients. This can be determined by measuring gastric pH or basal gastric acid out. Typical stool volumes are more than 3 liters per day if less than 700 ml diagnosis might exclude.

Procedure

Endoscopic retrograde cholangiopancreatography (ERCP) may demonstrate occlusion of the major pancreatic duct. It also may demonstrate calcifications in the body of the pancreas. Colonoscopy may useful to evaluate for a possible villous adenoma as an alternative cause of potassium-losing diarrhea.

Histologic

These tumors, like other pancreatic endocrine tumors, are felt to arise from the pluripotent cells in ductal epithelium. Histologic examination usually reveals sheets of nested, uniform-appearing cells with round nuclei and low mitotic rate, typical for neuro-endocrine tumors. Immunohistochemistry staining is positive for VIP and chromogranin A. Under electron microscopy, neurosecretory granules may be seen clustering around Golgi complexes and the endoplastic reticulum. Classifying a tumor as malignant or benign based on microscopic appearance alone is difficult.

TREATMENT

Medical Treatment

Initial treatment is aimed to correct volume, electrolyte, and acid-base abnormalities with intravenous normal saline, potassium chloride, and, sodium bicarbonate. A trial of prostaglandin synthesis inhibitors (e.g. indomethacin), phenothiazines, and lithium may be warranted.[18] Somatostatin is highly effective in reducing serum VIP levels and promptly controlling diarrhea in more than 90% of patients. Octreotide is delivered subcutaneously at an initial dose of 50-100 mcg 3 times a day, which may be titrated up for symptom control to a maximum of 500 mcg 3 times a day. A long-acting formulation of octreotide called Sandostatin LAR allows for once monthly intragluteal administration which starting dose is 10-20 mg per month. The dose can subsequently be titrated up to a maximum of 40 mg monthly. Diarrhea recurs when treatment is discontinued. It is currently debated

whether somatostatin analogues also diminish tumor size. Long-term octreotide treatment frequently results in gradual resistance to this treatment. When maximum tolerable doses of octreotide are unable to control symptoms, interferon alpha may be added to control diarrhea, with possible modest reduction in tumor size. Glucocorticoids are less effective but less expensive, reducing symptoms in approximately 50% of patients.

Preoperative treatment with a proton pump inhibitor is advisable to prevent rebound gastric acid hypersecretion after surgical removal of tumor. Systemic chemotherapy may be needed in cases of unresectable or progressive disease. Streptozocin, doxorubicin, fluorouracil, or their combination appears to be beneficial, although the number of treated cases has been limited. The use of radiolabeled octreotide to target radiation treatment to VIPoma is based on the affinity of octreotide to the somatostatin receptors on the VIPoma cells. In one trial, half of the patients achieved stabilization of previously progressive tumors, with minimal bone marrow toxicity. This therapeutic approach is still considered experimental.

Surgical Care

All operable patients with apparently resectable disease should receive abdominal exploration with careful staging. Intraoperative USG of the pancreas may aid in locating an unidentified tumor. For patients without nodal or distant metastasis, complete surgical resection offers the only chance for a cure.[1,2,3,19] Pancreatoduodenectomy is indicated when the tumor is in the pancreatic head or processus uncinatus. If tumor is not found at surgery, a distal pancreatectomy may be performed. In most cases, metastatic disease is found at the time of diagnosis. For these patients, tumor debulking may reduce clinical symptoms, but surgical plans ought to include resection of more than 90% of tumor volume for substantial clinical benefit. Postoperative octreotide therapy will usually be needed indefinitely to control symptoms of VIP hypersecretion from residual tumor.

Unresectable liver metastases may be treated with hepatic artery embolization or transcatheter chemoembolization with doxorubicin or cisplatin if embolization is not success or not feasible for liver metastases, percutaneous or intraoperative radiofrequency ablation (RFA) may be attempted to small tumor. All patients having surgery should undergo a cholecystectomy to alleviate concerns of gallstones with somatostatin analogue therapy in case such therapy may be needed in the future. Orthotopic liver transplantation has been performed in a small number of select patients with pancreatic endocrine tumors with approximately a 50% survival rate at five years.

CONCLUSION

VIPomas are extremely rare tumors that cause the "WDHHA syndrome": watery (secretory) diarrhea, hypokalemia, and hypohlorhydria and acidosis (because bicarbonate wasting). These tumor were caused by to non-insulin-secreting pancreatic islet tumor and associated with elevated plasma level vasoactive intestinal polypeptide (VIP). Morbidity and mortality on WDHA syndrome is related to long-standing dehydration with electrolyte and severe acid-base disturbances, that may cause chronic renal failure. The other clinical features of VIPoma such hypercalcemia, abdominal discomfort, tetany, facial flushing are related to secretion and action of VIP and other neuroendocrine hormone such as secretin, glucagon, prostaglandin E, somatostatin, etc. CT scan or MRI will identify the primary tumor in the pancreas and metastasis especially in the liver. Somatostatin receptor scintigraphy may be useful in identifying extrapancreatic VIPomas, i.e the sympathetic chain, occult or distant metastases.

Initial treatment is to correct volume, electrolyte, and acid-base abnormalities with intravenous normal saline, potassium chloride, and, sodium

Table 1. Differentiation of gastrinoma and WDHHA syndrome.[3]

Feature	Gastrinoma	WDHHA
Diarrhea	Acid	Alkaline (HCO_3 loss)
Gastric acid	Increased	Decreased
Gastric volume	Increased	Normal or decreased
Nasogastric suction	Diarrhea improves	Diarrhea unchanged
Motility	Increased*	Increased slightly[†]
Abdominal pain	Marked	Rare (initially)
Stool K+ loss	Slight	Marked
Metabolic acidosis	No (alkalosis with	Yes HCO_3 loss, gastric suction)
Lesion location	Primary pancreas	Primary pancreas, ganglioneuroblastoma also liver, wall of stomach, and duodenum
Mediator	Gastrin	VIP/other

*Motility enhanced secondary to gastric acid stimulation

bicarbonate. Somatostatin or long acting ocreotide is highly effective in reducing serum VIP levels and promptly controlling diarrhea. Interferon alpha and glucocorticoid may be useful for reducing symptoms. Surgical resection of pancreas tumor is based on staging.

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