

## VASOACTIVE INTESTINAL PEPTIDE TUMOR (VIPoma)

**Wouter T. Zandee, MD, PhD**, endocrinologist, Department of Internal Medicine, Division of Endocrinology, University of Groningen, University Medical Center Groningen (UMCG), Groningen, the Netherlands.

**Johannes Hofland, MD, PhD**, endocrinologist, Department of Internal Medicine, Division of Endocrinology, Erasmus Medical Center and Erasmus MC Cancer Institute Rotterdam, the Netherlands.

**Wouter W. de Herder, MD, PhD**, professor of endocrine oncology, Department of Internal Medicine, Division of Endocrinology, Erasmus Medical Center and Erasmus MC Cancer Institute, Rotterdam, the Netherlands.

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### ABSTRACT

Vasoactive intestinal peptide (VIP) is a neurotransmitter which is present in the neurons in the central nervous system, the lung, intestine, adrenals, pancreas, and liver and in neuroendocrine cells in the pancreas. In the gastrointestinal tract, VIP stimulates contraction of enteric smooth muscle cells, secretion from the exocrine pancreas, gastrointestinal blood flow, and inhibition of gastric acid secretion. A VIPoma is a neuroendocrine neoplasm secreting VIP, causing severe watery diarrhea, which can result in hypokalemia and metabolic acidosis. Larger tumors (with highly elevated plasma VIP levels) can cause up to 6-8L of watery stools per day. Other symptoms include hypochlorhydria, stimulation of glycogenolysis, facial flushing, and hypercalcemia. By definition, plasma VIP levels are elevated in all patients with the VIPoma syndrome. VIPomas are usually located in the pancreas (75%) or along the sympathetic chain as seen in ganglioneuromas,

ganglioneuroblastomas, or neuroblastomas. The first step in the treatment of a patient with a VIPoma is to correct the fluid and electrolyte deficits. Administration of a somatostatin analog (SSA) can decrease diarrhea, further aiding in the restoration of fluid and electrolyte imbalances. In patients with a metastatic or unresectable VIPoma, SSAs likely prolong progression-free survival. Other treatment options include peptide receptor radionuclide therapy (PRRT) with radiolabeled SSAs (<sup>177</sup>Lu-DOTATATE), everolimus, sunitinib, cytotoxic chemotherapy, or liver-directed therapies.

### INTRODUCTION

Vasoactive intestinal polypeptide (VIP) is a neurotransmitter found in the central nervous system, in neurons in the intestine, lungs, adrenals, pancreas and liver and in neuroendocrine cells in the pancreas (1). VIP has been localized in axons, dendrites, neuronal cell bodies and presynaptic nerve terminals

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from where VIP is released (1). In the gastrointestinal tract, VIP stimulates contraction of enteric smooth muscle cells, secretion from the exocrine pancreas, gastrointestinal blood flow, and inhibition of gastric acid secretion (2-4). A VIPoma is a neuroendocrine neoplasm (NEN) secreting VIP, causing severe watery secretory diarrhea, which can result in hypokalemia and metabolic acidosis.

In 1958 the US physician John V. Vermer Jr. and the Irish-US pathologist Ashton B. Morrison were the first to report a patient with a VIPoma (5). They presented two similar cases of patients with watery diarrhea and severe refractory hypokalemia. Both patients died of arrhythmias secondary to refractory hypokalemia and autopsy revealed pancreatic tumors. At that time, the syndrome was named watery diarrhea, hypokalemia, achlorhydria (WDHA)-syndrome or Verner-Morrison syndrome.

In 1970, VIP was first isolated from the small intestine of pigs and was reported to act as a potent vasodilator of the splanchnic circulation (6). Consequently, a radioimmunoassay for VIP was developed and in 1973 elevated VIP levels could be measured in a patient with the VIPoma syndrome by the UK physician Stephen R. Bloom and colleagues (7). In 1983, the US gastroenterologist Mary G. Kane and colleagues injected five healthy subjects with porcine VIP, which resulted in high plasma VIP levels and secretory diarrhea in all patients within 4 hours (8).

## CLINICAL PRESENTATION

The clinical features of VIPomas are consistent with the known actions of VIP, which include stimulation of intestinal and pancreatic secretion, contraction of enteric smooth muscle cells, and increase of intestinal blood flow. This causes secretory diarrhea which is the most characteristic symptom of a VIPoma. In severe cases patients can produce over 6-8L of stools per day. The stool is rich in electrolytes like potassium and bicarbonate, resulting in hypokalemia and metabolic acidosis. Other symptoms include hypochlorhydria,

stimulation of glycogenolysis, facial flushing, and hypercalcemia. VIP has a structural homology with secretin, glucagon, and GIP which may account for enhanced secretion of pancreatic enzymes, inhibition of gastric acid secretion, and glycogenolysis (9). Nearly 15-30% of patients present with facial flushing (10). The cause of this patchy erythematous flushing is not clear, but it has been attributed to VIP, or prostaglandins, which may be co-secreted by the tumor. Around 50% of patients have hypercalcemia, but again the mechanism is unknown. The incidence of VIPomas is estimated to be 1–2 per 10 million per year (11). VIPomas can be associated with multiple endocrine neoplasia 1 (MEN1), but they remain rare presenting in less than 1% of patients with MEN1 (12).

## BIOCHEMICAL DIAGNOSIS AND STAGING

In the circulation, VIP has a half-life of less than 1 minute and normally plasma levels of VIP are low (<20pmol/L) (13,14). In the absence of a VIPoma, VIP in plasma originates from VIP-containing nerve fibers and reflects the overflow of VIP from vascular nerves. By definition, plasma VIP levels are elevated in all patients with the VIPoma syndrome. Bloom and colleagues measured plasma VIP levels in nearly 1000 patients with diarrhea and all patients with plasma VIP levels greater than 60pmol/L indeed had a VIPoma (13). Moderately elevated plasma VIP levels can incidentally also be caused by gastrointestinal ischemia, renal insufficiency, or congestive heart failure (15-17).

VIPomas are usually located in the pancreas (75%), or along the sympathetic chain as seen in ganglioneuromas, ganglioneuroblastomas, or neuroblastomas. Pheochromocytomas secreting VIP have also been described (18). Extrapaneatic neurogenic VIPomas are most often diagnosed in children. As the primary pancreatic tumor is larger than 2cm in 80% of VIPomas (19), they can be easily detected with MRI, CT, or endoscopic ultrasound (EUS). Additionally, a positron emission tomography

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(PET)-CT with gallium-labelled somatostatin analogs (DOTATATE, DOTANOC, DOTATOC) should be performed. In a small series with 11 patients, somatostatin receptor scintigraphy was superior to conventional radiology in detecting a VIPoma (20). Similar to work-up for all NENs, a biopsy is advised to confirm the diagnosis and for grading (Ki67 index), as the grade can influence treatment decisions (21). An overview of the current pancreatic NEN (panNEN) staging and grading systems is provided in the chapter “Insulinoma”.

## TREATMENT

The first step in the treatment of a patient with a VIPoma is to correct the fluid and electrolyte deficits. In severe cases, intravenous resuscitation with potassium and bicarbonate can be required. Administration of a somatostatin analog (SSA) can decrease the secretory diarrhea, further aiding in the restoration of fluid and electrolyte imbalances (22). In the acute setting, octreotide can be administered subcutaneously, or via continuous intravenous infusion.

After initial stabilization, a surgical resection should be performed in patients with a locoregionally confined VIPoma. A 5-year survival of 94% has been described in patients with a localized VIPoma (19). In selected patients with limited liver metastases an extended surgical resection also involving the liver can be considered (23).

In case of an unresectable VIPoma, treatment is focused on tumor stabilization and control of VIP secretion. In general, anti-tumor therapy is similar to non-functioning panNENs as described in the guidelines by ENETS, NANETS and ESMO (24-26).

## Somatostatin Analogs

Somatostatin analogs represent the first-line palliative treatment for metastatic or unresectable VIPomas. SSAs are regarded to have an antiproliferative effect, based on randomized trials with mainly non-functioning low grade panNEN. In the CLARINET trial, including grade 1-2 panNENs, treatment with lanreotide autogel 120 mg every 4 weeks deep sc was associated with significantly prolonged median progression-free survival (PFS) of 38 months versus 18 months for placebo (27). Moreover, treatment with SSAs is associated with a high symptomatic response rate. Diarrhea was reduced in approximately 64-85% of patients with a VIPoma who were treated with an SSA (28,29). Despite radiological progression, SSAs can be continued for symptom control when further lines of treatment are started.

## Peptide Receptor Radionuclide Therapy

Treatment with Peptide receptor radionuclide therapy (PRRT) with [Lutetium- 177-DOTA<sup>0</sup>-Tyr<sup>3</sup>]octreotate (<sup>177</sup>Lu-DOTATATE) results in a response rate of 55% for panNETs, with a median PFS of 30 months and median overall survival (OS) of 71 months (30). Only limited numbers of patients with a VIPoma have been described following treatment with <sup>177</sup>Lu-DOTATATE. The symptomatic response rate of VIPomas was approximately 80% in two case series (28,31). Withdrawal from unlabeled SSAs can lead to swift recurrence of severe watery diarrhea, providing rationale to limit the time without SSA before the administration of <sup>177</sup>Lu-DOTATATE. Sub-acute toxicity of PRRT mainly includes nausea, vomiting and CTCAE grade 3/4 toxicity of hematologic parameters. In 70% of patients with toxicity, the hematologic parameters normalize but 1% of patients treated with PRRT developed acute leukemia, and 2% myelodysplastic syndrome (30).

## Everolimus

The mTOR-inhibitor everolimus is registered for the treatment of panNEN based on the result of the the RADIANT-3 trial (32). In this study, 24% of patients had a functioning panNEN and treatment with everolimus resulted in a hazard ratio for disease progression of 0.35 (95% confidence interval 0.25-0.45) when compared to placebo. In the limited number of patients with a VIPoma reported in case series to have been treated with everolimus, a symptomatic response was reported in less than 10% of patients and therefore the role of everolimus in the treatment of metastatic VIPoma is limited (28).

### Sunitinib

Sunitinib is a multitargeted tyrosine kinase inhibitor (TKI) which can be considered for panNENs which progress during treatment with a somatostatin analog. It resulted in an increased progression-free survival in

comparison to placebo (11.4 vs 5.5 months) in a randomized controlled trial including patients with panNEN. Two patients with a VIPoma were included in this trial, but they were both treated with placebo (33). In case series, a symptomatic response rate of 33-100% has been described for patients with a VIPoma treated with sunitinib (28,29).

### Liver Directed Therapy

In patient with liver-dominant disease, liver metastases can be resected or treated by bland embolization, radioembolization (SIRT), radiofrequency ablation (RFA), microwave and cryoablation, high-intensity focused ultrasound (HIFU), laser, brachytherapy and irreversible electroporation (IRE) depending on local availability (23). Reduction of liver tumor burden is associated with a symptomatic response in small series (28,29).

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