European Reference Network
for rare or low prevalence complex diseases
Network Paediatric Cancer (ERN PaedCan)

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A rare case of VIP secreting tumour

Moderation: Raheel Altaf Raja

Funded by the European Union's EU4Health Programme

SIOPE YOUNG

St. Anna Kinderkrebs Forschung

COI declaration

- No declarations

Case presentation

15 months-old who presented with:

1. 7-week history of waking up in pain

2. 6-week history of abdominal distension and loose stools

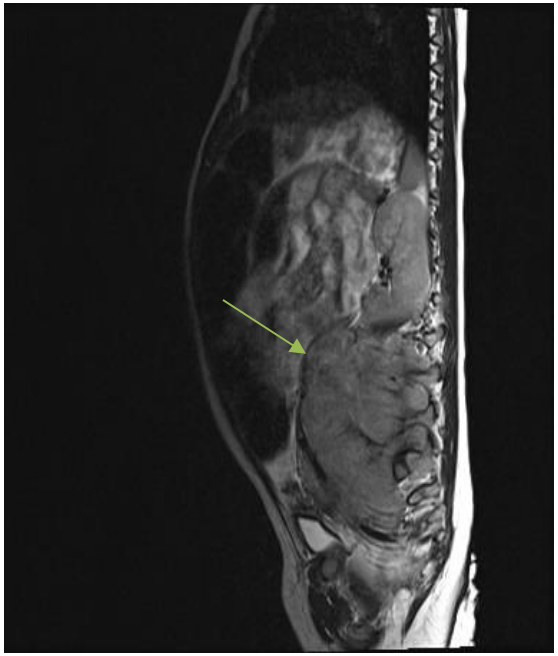
3. Stopped weight-bearing

Case presentation

Presented at their local hospital with worsening abdominal swelling and watery diarrhoea

Initial imaging revealed a large retroperitoneal lesion with marked restricted diffusion.

The abdo-pelvic tumour was wrapped around major vessels and extended between lumbar intervertebral foraminae to occupy the lower lumbar and sacral spinal canal.



Question 1

What is the most likely diagnosis at this stage?

1. Ewing‘s sarcoma
2. Neuroblastoma
3. Germ cell tumour
4. Wilm‘s tumour

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Partial neurological recovery noted.

Pathology

Non-MYCN amplified well differentiated neuroblastoma with numerical chromosomal abnormalities

No bone marrow involvement

Localised (L2) low risk neuroblastoma as per the SIOPEN LINES study.

Ongoing issues

Profuse watery diarrhoea at 2lt per day

Severe electrolyte disturbances with hypokalaemia, hypocloraemia and severe metabolic acidosis.

Question 2

What further investigations should we do at this stage?

1. Stool microscopy and culture
2. Bowel biopsy
3. Gut hormone profile
4. All of the above

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Further investigations

Stool culture -normal

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Bowel biopsy – normal

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Further investigations

Stool culture -normal

Bowel biopsy – normal

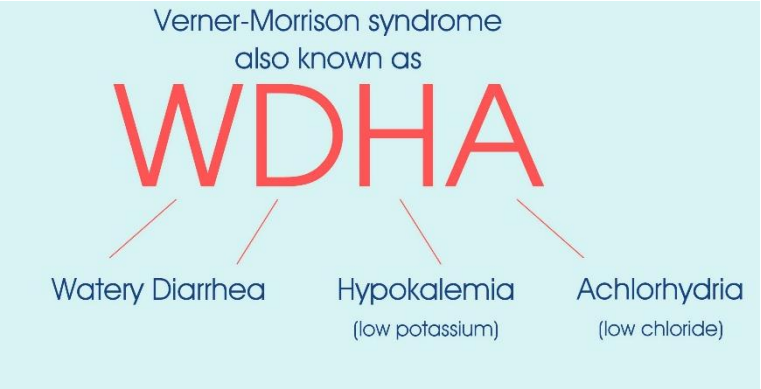
Gut hormone profile demonstrated a high VIP (1086pmol/L),

Treatment initiated with somatostatin analogs and loperamide - no clinical benefit.

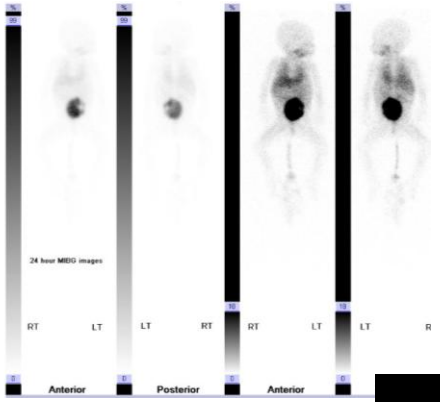
Verner Morrison syndrome

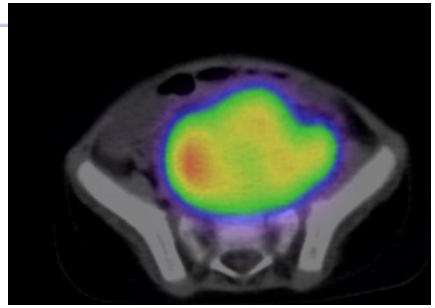
A syndrome of

- profound and chronic watery diarrhea,
- hypokalemia,
- achlorhydria,
- acidosis



Ongoing management





Received a further cycle of carboplatin and etoposide and a 3rd cycle of CADO (Cyclophosphamide, doxorubicin and Vincristine) chemotherapy as per the CCLG LIRNB guidelines - no resolution of clinical signs.

Patient clinically deteriorated, required PICU admission for management of their electrolyte and acidosis

Question 3

How should we further manage this patient?

1. MIBG therapy
2. Surgery
3. Steroids
4. Further chemotherapy

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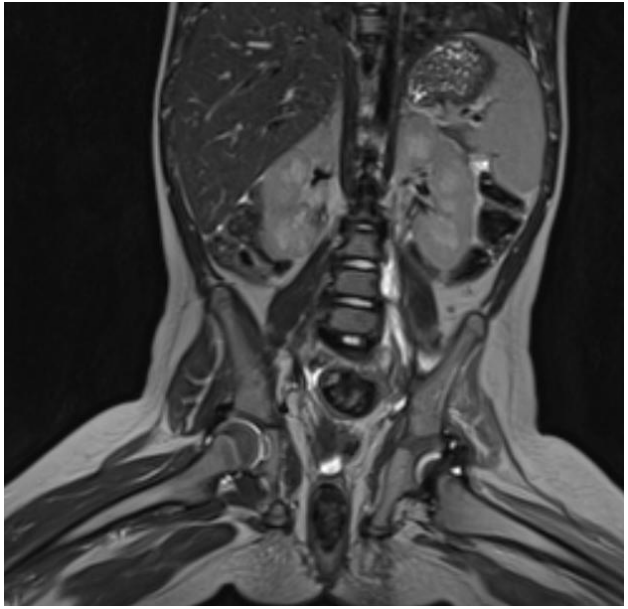
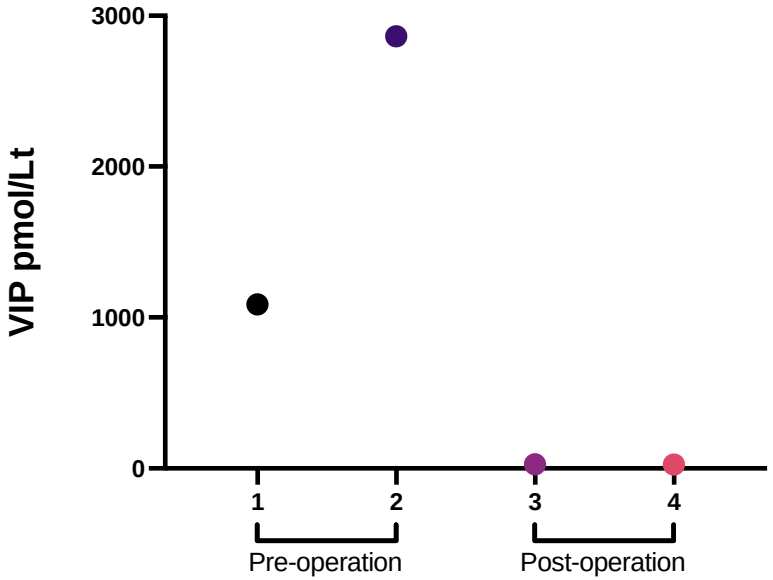
Definitive treatment



Family were very carefully counselled re risks of death, paraplegia, incontinence and damage to the nerves and blood supply to legs.

Patient underwent tumour debulking surgery – Not R0 rescection.

Definitive treatment



Final CADO chemotherapy delivered post surgery

Patient has been in remission on follow up scans with normal stools at clinical follow up appointments.

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DISCUSSION

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VIPomas

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However, in a similar case to ours published by Kabalan et al, patient's symptoms persisted despite tumour debulking surgery demonstrating the complexity of managing these cases.

SSAs have been successfully used in adults with VIPomas however, the paediatric data are limited to just a few case reports.

Take home messages

Consider VIP secreting tumours for patients with persisting secretory diarrhoea

In this case somatostatin analogs were not effective in managing diarrhoea secondary to a VIPoma

For our case debulking surgery was the only option available

Careful surgical planning is needed for unresectable cases to minimise surgical complications

Special thanks

- Dr Dave Hobin, Consultant paediatric oncologist and all the oncology consultants at Birmingham Children's hospital for their help with this case
- I would also like to thank prof Tytgat for her expertise and guidance with this case
- Martin Schalling and Raheel Raja for organizing and co-ordinating this session

References

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2. Kabalan, P., Gifford, A.J. and Ziegler, D.S. (2018), Unresectable VIP-secreting neuroblastoma: Efficacy of debulking and steroids for symptom control. Pediatr Blood Cancer, 65: e27358. https://doi.org/10.1002/pbc.27358
3. Yeh et al. Rare cases of paediatric vasoactive Intestinal Peptide secreting tumor with literature review: a challenging etiology of chronic diarrhea, Front. Pediatr., 05 August 2020, Volume 8 - 2020 | https://doi.org/10.3389/fped.2020.00430

The challenge of non-HR patients

Lieve Tytgat

COI declaration

- No declarations

Risk classification

TABLE 1. INRG Risk Classification System

INRG Stage	Age (months)	Histologic Category	Tumor Differentiation	*MYCN*	11q Aberration	Ploidy	Pretreat Risk Group
L1/L2		GN maturing; GNB intermixed					Very low
L1		Any, except GN maturing or GNB intermixed		Nonamplified			Very low
				Amplified			Intermediate
L2	< 18	Any, except GN maturing or GNB intermixed		Nonamplified			
	≥ 18	GNB nodular; neuroblastoma	Differentiating	Nonamplified	No		Low
				Nonamplified	Yes		Intermediate
			Poorly differentiated or undifferentiated	Nonamplified			Intermediate
				Amplified			High
M	< 18			Nonamplified		Hyper	Low
	< 12			Nonamplified		Diploid	Intermediate
	12 to < 18			Nonamplified		Diploid	Intermediate
	< 18			Amplified			High
	≥ 18						High
MS	< 18			Nonamplified	No		Very low
				Nonamplified	Yes		High
				Amplified			High

Abbreviations: GN, ganglioneuroma; GNB, ganglioneuroblastoma; INRG, International Neuroblastoma Risk Group.

 Pinto NR, et al J Clin Oncol 33:3008-3017, 2015

VIP

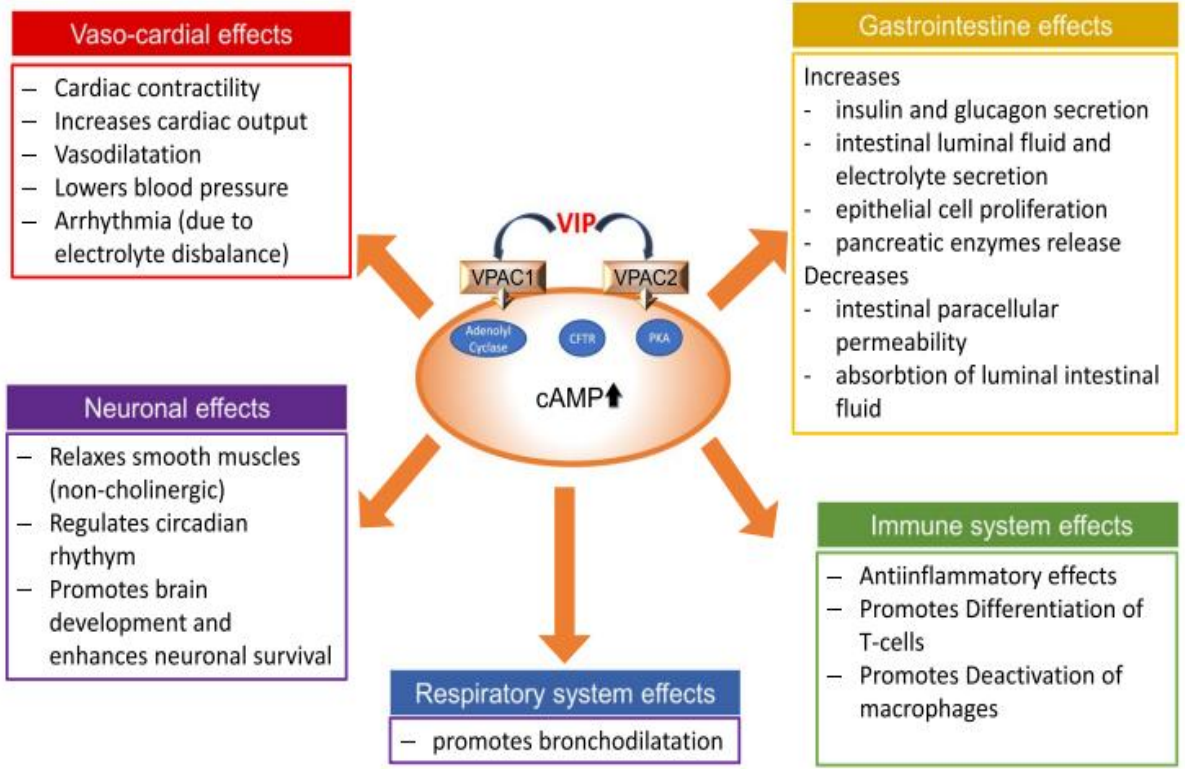
- Display a very large spectrum of biological activities →modulate virtually all the vital functions in the body.
- Main neurotransmitters in the gut
- Play a neuromodulatory role in the central and peripheral nervous systems, at the neuronal and glial levels.

VIP

Differentiation: VIP secreting tumor and postoperative diarrhea

- -> Postoperative diarrhea after the surgical resection of advanced neuroblastoma tumours.
- subadventitial neuroblastoma tumour resection: the surgical field including coeliac trunk regions and the superior mesenteric artery.
- Damage of the enteric autonomic nervous system thus dramatically altering gut transit function
- Postoperative diarrhea is refractory to any treatment

Fig. 1 Overview of the effects of VIP in the human body



- Increased intestinal luminal fluid and electrolyte secretion
- insulin and glucagon secretion
- inhibiting gastric acid secretion

Therapy: rehydration: Electrolyte suppletion; somatostatin analogues (? Decrease VIP levels blood)

steroids; loperamide; Surgery!

Paraneoplastic syndromes

- Opsoclonusmyoclonus syndrome (OMS) – also known as Opsoclonus-Myoclonus-Ataxia Syndrome, OMA, or OMAS –OMS
  - characterized by involuntary eye movements, muscle jerks, and ataxia.
  - OMS is thought to be caused by the production of autoantibodies to tumor antigens that demonstrate cross-reactivity with normal neural tissue. 2% and 3% of all NBs patients
- VIP: vasoactive intestinal peptide secreted by the tumor.
  - <1% all NBB tumors (Bourdeaut et al.,)
- Elevated parathyroid hormone-related peptide (PTHrP), although the clinical presentations of these patients are not well-documented in the literature.
- “ROHHAD” Rapid-Obesity with Hypothalamic Dysfunction and Autonomic Dysregulation,
- anti-ANNA1 (anti -Hu)

ROHHAD

- 1 study: 52 cases: 19 ROHHAD: 61% ganglioneuroma; 22 ganglioneuroblastoma; 17% neuroblastoma

Mitchell Semin Pediatr Neurol 2017

Table 1 Pediatric-Onset Neurological Paraneoplastic Syndromes Associated With Neuroblastic Tumors

PNS	Onset Age (y)	Features
ROHHAD	2-4	Rapid-onset obesity Multiple central endocrinopathie Autonomic dysfunction Hypothalamic dysfunction Hypoventilation/respiratory failure
Anti-ANNA1 (anti-Hu)	Any age	Encephalopathy Seizures Cranial neuropathies Ataxia Intestinal pseudo-obstruction
OMS	0.5-5	Ataxia Polymyoclonias/tremor Opsoclonus Extreme irritability and sleep disturbances Speech and language regression

ROHHAD

- Obesity (3 years)
- Precocious puberty
- Hypothalamic dysfunction
- Autonomous dysregulation (6.2 years)
- Autonomic dysfunction: poor control body temperature; sweating; pupillary abnormalities; sensory problems
- Hypoventilation

ROHHAD

- Endocrinopathies
  - hyperprolactinemia, deficiency of adrenocorticotropic hormone, growth hormone, or thyroid hormone;
  - hyponatremia or hypernatremia.
- Personality changes and developmental regression
- Psychiatric signs/symptoms→ anxiety, insomnia
- High risk cardiopulmonary arrest (anesthesia risk!)

Take home message

- Excessive diarrhea preoperative (diagnosis): consider VIP
- Excessive diarrhea postoperative: consider damage to nerve system
- Paraneoplastic syndromes: Mostly favorable tumors: but neurologic outcome can be dismal
- In case of obesity, pubertas preacox -> consider ROHHAD!