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# Paraneoplastic syndromes in childhood neuroblastoma

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ABSTRACT:
INTRODUCTION: Neuroblastoma is a malignant tumor primarily affecting infants. Originating from embryonic cells of the sympathetic nervous system, NB commonly arises in the adrenal glands, followed by the abdomen, mediastinum, head, and neck. Clinical presentation varies depending on the tumor's location. General symptoms, if present, include fatigue, weight loss, and fever. The paraneoplastic syndrome refers to symptoms and disorders associated with malignant tumors but not directly caused by the tumor itself or its metastases. Opsoclonus-myoclonus syndrome and diarrhea are the most common paraneoplastic syndromes linked to neuroblastoma.
REVIEW METHODS: The article was conducted using PubMed and Google Scholar data concerning paraneoplastic syndromes associated with neuroblastoma.
THE STATE OF KNOWLEDGE: Opsoclonus-myoclonus syndrome is a neurological paraneoplastic syndrome that presents itself with characteristic eye movement disorder, short, involuntary, irregular twitches or spasms occurring in a muscle, sleep disturbance, and changes in behavior. Diarrhea resulting in hypokalemia may be also present as a paraneoplastic syndrome associated with neuroblastoma. Cushing's syndrome is a rare condition in childhood, but it also may be linked to neuroblastoma.
CONCLUSIONS: Neuroblastoma is one of the most common childhood cancers, Paraneoplastic syndromes associated with neuroblastoma are rare conditions. Diagnosing chronic diarrhea, OMS, and Cushing's syndrome should always lead to the exclusion of neuroblastoma. Heightened awareness among pediatricians regarding PNS could result in faster diagnosis, timely treatment commencement, and ultimately enhance patient prognosis.

Keywords: neuroblastoma; paraneoplastic syndrome; opsoclonus-myoclonus syndrome, paraneoplastic diarrhea; paraneoplastic Cushing's syndrome

## 1. INTRODUCTION:

Neuroblastoma (NB) is a malignant tumor that typically affects babies. About 90% of cases are identified by age 5, and the average age of diagnosis ranges from 1 to 2 years old.

Neuroblastoma is a solid tumor originating from the embryonic cells of the sympathetic nervous system. The most frequent location is one of the adrenal glands. Furthermore, the tumor develops in the abdomen, followed by the mediastinum, the head, and the neck. [1, 2, 3] Clinical presentation mostly depends on its location. Neuroblastoma located in the retroperitoneum usually does not give any specific symptoms but typically manifests as a solid indolent mass in the abdomen identified by parents or during routine medical examination. Thoracic tumors can be asymptomatic and may be detected on chest radiographs. Cervical neuroblastoma may lead to Horner syndrome. General symptoms, if they occur, include fatigue, weight loss, and unexplained fever. [4]

The term paraneoplastic syndrome refers to a set of symptoms and disorders occurring in patients with malignant tumors, but they are not directly caused by the tumor itself or its metastases. [5]

The most common paraneoplastic syndromes (PS) associated with neuroblastoma are the opsoclonus-myoclonus syndrome (OMS) and the diarrhea. These two conditions have different pathogeneses. OMS arises from an immune response to the tumor, resulting in damage to brain structures. Diarrhea is caused by the tumor secreting enormous amounts of VIP (vasoactive intestinal peptide). [5, 6] On rare occasion, neuroblastoma can cause paraneoplastic Cushing's syndrome. [7]

## 2. REVIEW METHODS

This article compiles data from publications available on PubMed and Google Scholar and focuses on paraneoplastic syndromes associated with childhood neuroblastoma.

## 3. THE STATE OF KNOWLEDGE

### 3.1 Opsoclonus-myoclonus syndrome (OMS)

Opsoclonus-myoclonus syndrome (OMS) or the dancing eye syndrome is a paraneoplastic neurological syndrome (PNS). Although it is a rare condition, it is the most common PS associated with neuroblastoma. PNS is believed to develop due to an immune reaction targeting antigens or epitopes found in both tumor cells and healthy cells in the central nervous system. [8] The exact mechanism of pathogenesis of OMS remains unclear, but it appears that the immune mechanism is the most likely cause. [5]. In addition, the cause of the OMS may also be infectious including *Streptococcus, Mycoplasma*, adenovirus, EBV, HIV, and dengue virus, among others. [9] Approximately 70% of patients may experience paraneoplastic neurological syndrome 1 to 5 years before the diagnosis of cancer. [10, 11].

OMS classically presents with characteristic eye movement disorder (opsoclonus), where eyes move rapidly and in multidirectional directions, involuntary and irregular twitches or spasms occurring in a muscle, or muscle group (myoclonus). Often these symptoms are followed by sleep disturbance and changes in behavior such as irritability. [9, 12] OMS is more commonly seen in children, and it is worth noticing that although about 50% of kids with this condition are diagnosed with neuroblastoma, only about 2% of children with neuroblastoma develop OMS. [13, 14] However, neuroblastoma associated with OMS typically has a better prognosis than OMS-unrelated cases due to its low malignancy. [11]

Various treatment approaches are used for OMS, yet none have consistently demonstrated complete resolution of all symptoms. [15] While the most effective treatment for OMS remains uncertain, immunotherapy, such as adrenocorticotropic hormone (ACTH) or corticosteroids, plasmapheresis, intravenous immunoglobulin (IVIg), and rituximab or cyclophosphamide, is frequently employed. [13, 16] If this condition is associated with neuroblastoma, the surgical resection of the tumor may lead to symptom resolution. However, studies [17,18] showed that simply removing the tumor in patients with NB is not enough to alleviate OMS. In general, a combination of different therapies is commonly used in treating opsoclonus-myoclonus syndrome. [19] An early diagnosis and treatment correlate with an

improved prognosis and a decreased likelihood of neurological or neuropsychiatric complications. [20]

Long-term outcomes following OMS in children have shown that patients typically achieve relatively good recovery, albeit incompletely in terms of motor function. [21, 22] However, cognitive, and behavioral deficits are often observed, which can significantly impact functioning. Ataxia, apraxia, coordination deficits, and tremors are frequently observed, but they typically do not significantly affect daily functioning. Cognitive deficits may include intellectual impairment, learning difficulties, attention deficits, language expression impairments, spatial function impairments, and behavioral disturbances, even in children with normal intelligence quotients. [23] The risk of poorer cognitive outcomes in OMS is associated with delayed treatment, younger age at symptom onset, and severe clinical presentations.

Differential diagnosis for OMS is challenging, but it should provide for acute cerebellar ataxia, acute infections like meningoencephalitis, and toxins or drug intoxication (e.g. lithium, cocaine, amitriptyline). [24] The diagnostic process is based on the clinical picture, which includes detailed objective and subjective examinations and tests that exclude other diseases like blood, urine, and CSF examinations and brain CT or MRI. For OMS, no abnormalities are characteristic in the above tests.

If a patient is diagnosed with OMS, neuroblastoma should always be eliminated. If the tumors reach a sufficient size, they can be diagnosed using chest or abdominal CT, MRI, or ultrasound. However, if these tests yield negative results, the next most effective approach for detecting hidden NB is whole-body metaiodobenzylguanidine (MIBG) scintigraphy. [25] Three clinical cases described as OMS associated with neuroblastoma will be presented.

S. Galgano et al. described the case [26] of a 21-month-old girl, born at full term, who was admitted to a pediatric neurology clinic due to persistent ataxia, which had begun nine months earlier. Initially, she was diagnosed with acute cerebellar ataxia. According to the parents, her symptoms persisted, and she failed to fully recover. Although she regained the ability to walk at the age of 15 months, her gait remained unsteady, accompanied by intermittent jerks, and she experienced erratic eye movements multiple times a day. Physical examination revealed the absence of deep tendon reflexes, an unsteady wide-based gait, mild hypotonia, and difficulties with grasping objects. Initial brain imaging, EEG, and laboratory tests showed no abnormalities, except for elevated levels of urine vanillylmandelic acid. The suspicion of neuroblastoma and opsoclonus-myoclonus syndrome was raised. A CT scan of the chest, abdomen, and pelvis revealed a tumor surrounding the superior mesenteric artery in the pancreas. The diagnosis was confirmed using MIBG imaging.

The case presented by B. H Chang et al. [27] involves a previously healthy 2.5-year-old girl who was diagnosed with acute ataxia and nystagmus following a flu-like infection. Over the next month, she experienced alternating symptoms of dizziness, clumsiness, and nystagmus. During the physical examination, she appeared irritable, with notable opsoclonus and myoclonus, ataxia, and slightly increased muscle tone. Opsoclonus-myoclonus syndrome was diagnosed, and she underwent an extensive evaluation for neuroblastoma. Imaging studies did not reveal the presence of a tumor, and laboratory tests showed no abnormalities. Idiopathic OMS was diagnosed, and treatment with steroids and benzodiazepines was initiated. However, improvement was minimal after several weeks of prednisone therapy. Treatment was changed to adrenocorticotrophic hormone (ACTH), resulting in significant improvement, but her condition worsened after discontinuation of the medication. Once again started treatment with ACTH which led to a psychotic episode. The medication was discontinued. Treatment with several courses of intravenous immunoglobulin (IVIg) provided only slight improvement. Ten months after symptom onset, the patient was re-evaluated for neuroblastoma, but imaging studies again showed no tumor presence. Rituximab (RTX), IVIg, and ACTH were initiated,

resulting in an excellent response. Twenty months after the initial presentation and 4 months after starting rituximab, a CT scan of the abdomen revealed the presence of a tumor in the left adrenal gland. MIBG and biopsy confirmed the presence of neuroblastoma. The girl had no new symptoms, and her OMS was well controlled.

J. B Abreu et al. detailed the case [28] of a 9-year-old girl with OMS and learning disabilities. At the age of 2, the patient exhibited symptoms of opsoclonus and myoclonus after metoclopramide therapy. She was treated with IVIG and steroids, but ataxia and tremors persisted. At the age of 5, the patient presented with dystonia of the upper limbs and mild ataxia. Propranolol was initiated, resulting in an improvement of the girl's overall condition. At 7 years of age, she experienced nocturnal enuresis. Abdominal ultrasound revealed a mass in the right upper quadrant of the abdomen. MRI and MIBG were performed, leading to the diagnosis of neuroblastoma, which was surgically removed.

### 3.2 DIARRHEA

Neuroblastomas that secrete vasoactive intestinal peptide (VIP) classically develop intractable secretory diarrhea with resultant dehydration and hypokalemia. [6] Studies suggest that less than 1% of all neuroblastoma tumors exhibit signs of VIP secretion. [29] Consequently, diarrhea as the sole initial symptom of NB is seldom encountered. In contrast, postoperative diarrhea may occur following the surgical removal of a neuroblastoma.

The vasoactive intestinal peptide is part of a group of polypeptides that function similarly to other hormones like pituitary adenylate cyclase-activating polypeptide (PACAP), secretin, and glucagon. [30] Its main role is being a neurotransmitter and neuromodulator, released from nerve terminals with a paracrine effect. [31] VIP is also found in cells derived from the neural crest, such as pancreatic islet cells. Like numerous hormones, VIP is first synthesized as a precursor before being enzymatically cleaved into its active form. VIP receptors belong to the G protein-coupled receptor family, with two main types: VPAC1 and VPAC2. [32] When VIP binds to these receptors, it increases intracellular cyclic adenosine monophosphate concentration, activating mechanisms responsible for its effects. VIP is mainly found in both the peripheral and central nervous systems, but it is also present in other organs such as the gastrointestinal tract, respiratory tract, and pancreas. [33, 34] VIP receptors are abundant in the gastrointestinal tract and central nervous system. Its effects on various gastrointestinal tissues include epithelial secretion and absorption in the mucosa of the gastrointestinal tract and bile ducts, smooth muscle relaxation including the lower esophageal sphincter and colon, promotion of growth in certain tumors like gastric cancer, and anti-inflammatory activity. [35] While VIP itself does not disturb intestinal motility, it contributes to diarrhea primarily through its secretory activity. Chronic diarrhea in childhood is a common issue and can result from various gastrointestinal disorders. It stems from four primary pathophysiological mechanisms: osmotic, secretory, dysmotility-related, and inflammatory diarrhea, often overlapping. True secretory diarrhea, which persists during extended fasting, is relatively rare. A low stool osmotic gap indicates secretory diarrhea, while high stool osmolarity and cessation of diarrhea after eliminating meal triggers are characteristic of osmotic diarrhea. Inflammatory diarrhea presents with feces containing blood, mucus, and bacteria. Diarrhea linked with dysmotility, like toddler diarrhea, poses diagnostic challenges and often requires the exclusion of other causes. [36, 37] Usually, a long time passes between the onset of diarrhea and the diagnosis of the tumor. This is confirmed by the results of Bourdeaut's retrospective study [38] on children with neuroblastoma. In Han's retrospective analysis, the duration between the onset of diarrhea and the diagnosis varied from 4 to 12 months. [39]

Treating diarrhea associated with NB is challenging. First and foremost, hydration must be maintained. The potassium deficiency should be corrected. Prolonged diarrhea leads to severe metabolic disturbances. Surgical treatment should be considered as the first line of treatment.

[38] Typically, after tumor removal, diarrhea resolves immediately. Patients, especially 1-3 old, with chronic diarrhea should undergo thorough precise examinations to rule out neuroblastoma. Elevated VIP level and hypokalemia are characteristic abnormalities. [39]
M El Shafie et al. described the case of a 2-year-old girl [6] who was admitted to the hospital due to diarrhea lasting for 5 months. The stools were watery and explosive. Dietary management had no effect. Physical examination revealed no abnormalities. Laboratory tests were normal except for significant hypokalemia at 1.5 mEq/l, the presence of metabolites of catecholamines in urine, and markedly elevated VIP levels in serum. Imaging studies revealed a tumor in the right adrenal gland. Surgical treatment was initiated. Histopathological examination of the tissue showed a typical neuroblastoma. The tumor contained a very high level of VIP. The postoperative period was uneventful, with normal stools. Laboratory tests normalized.
The case described by P. K Gera et al. involve an 18-month-old girl [40] who was admitted with explosive diarrhea lasting for 6 weeks, unresponsive to treatment. On examination, her abdomen was distended with no palpable masses. Upper endoscopy and colonoscopy were performed to rule out celiac disease and Hirschsprung's disease. Abdominal ultrasound revealed a large mass in the right adrenal gland. Laboratory tests showed hypokalemia (2.5 mEq/l), significantly elevated serum VIP levels, and increased catecholamine metabolites in urine. A laparotomy was performed, and the tumor was excised. Immediately after surgery, the diarrhea resolved, and laboratory parameters normalized. Histopathological examination confirmed the presence of neuroblastoma.
The case described by B. Gesundheit et al.[41] concerns a 19-month-old girl, previously healthy, who developed persistent diarrhea, ataxia, and clumsiness. Infantile diarrhea, lactose intolerance, food allergy, and infectious causes were ruled out. At 27 months of age, she was admitted to the hospital after a flu-like infection, as her neurological condition worsened. Physical examination revealed ataxia, and decreased muscle tone, but no nystagmus was observed. Parents reported changes in behavior, irritability, and regression in psychomotor development. Urine testing for catecholamine metabolites showed elevated levels. Imaging studies revealed a lesion in the right adrenal gland. The tumor was surgically removed, and histopathological examination confirmed neuroblastoma. After the surgery, the diarrhea resolved immediately, and there was no detectable elevation in catecholamine metabolites in the urine, but the ataxia persisted. Partial improvement occurred after four courses of IVIg therapy.

### 3.3 CUSHING'S SYNDROME

Cushing's syndrome (CS) is a rare disorder in childhood. [42] CS is a clinical condition characterized by elevated levels of glucocorticoids in the bloodstream, stemming from either internal production or external intake. In most children, the onset of Cushing's syndrome is gradual. [43, 44] The primary symptom observed is weight gain, often accompanied by a lack of height growth. Additional common issues reported in children include facial redness, headaches, high blood pressure, excessive hair growth, glucose intolerance, kidney stones, bone fractures, menstrual irregularities, and delayed sexual maturation. During puberty, affected adolescents may exhibit signs of masculinization. [45] Skin-related symptoms such as acne, purple stretch marks, bruising, fungal infections, darkened skin patches, and accumulation of fat in certain areas like the temples and collarbones are also frequently observed. However, compared to adult patients with Cushing's syndrome, children are less likely to experience sleep disturbances, muscle weakness, memory problems, and the presence of skin stretch marks before the age of 5–7 years old. [42]
CS can be categorized into two groups based on the underlying causes: those independent of adrenocorticotrophic hormone (ACTH) and those dependent on ACTH. [46] The most

common cause of ACTH-independent CS in the children population is exogenous steroid administration due to other conditions. ACTH-dependent CS most commonly is caused by tumors like hyperfunctioning adrenal adenoma or carcinoma. Rarer causes are bilateral macronodular adrenal hyperplasia (BAMH), primary pigmented nodular adrenocortical disease (PPNAD), and McCune Albright syndrome. [47] The diagnosis of Cushing's syndrome should begin with confirmation of hypercortisolism by conducting a 24-hour urine cortisol test and late-night salivary cortisol test. If cortisol levels in these tests are elevated, investigations to determine the cause of hypercortisolism should be initiated. A dexamethasone suppression test (DST) should be performed. Subsequently, imaging studies such as pituitary MRI or adrenal CT should be conducted. [48] The treatment of Cushing's syndrome depends on the underlying cause and is not the subject of this article.

In the literature, several described clinical cases depict Cushing's syndrome or ectopic ACTH syndrome as a PS associated with neuroblastoma.

M Espinasse-Holder et al. [7] described a case report of a four-month-old infant who was diagnosed with NB. The patient was the firstborn to healthy parents. Initially, the child showed symptoms including hyperthermia, diarrhea, vomiting, acne, tachycardia, and high blood pressure, accompanied by a mass under the left ribcage. Until the age of three months, the infant’s development was typical in both somatic and psychomotor aspects. Diagnostic imaging, including abdominal sonography and tomography, revealed a significant tumor in the left adrenal gland. Biochemical analyses indicated a slight increase in urinary dopamine levels but normal levels of vanillylmandelic and homovanillic acids. Tests also showed disrupted adrenal function, evidenced by high cortisol levels, a disrupted daily rhythm of cortisol secretion, and elevated levels of free cortisol in the urine, though levels of adrenal androgens like DHEA and D4-androstenedione remained within normal ranges. The low but normal plasma ACTH values, combined with the presence of an adrenal mass and symptoms of excessive cortisol, initially suggested an adrenal cortical tumor, leading to the surgical removal of the tumor and the adjacent kidney. However, subsequent pathological examination confirmed the presence of a typical neuroblastoma.

The case described by T Normann et al. [49] involved a 12-month-old boy who was the third child of healthy parents. From a young age, he was overweight but had a normal fat distribution. He developed normally both mentally and physically and was in good health until he reached 11 months old. However, over the following month, his condition altered significantly. He experienced rapid weight gain, and excessive thirst, and became easily irritated. On admission at 12 months old, he weighed 11.9 kg, placing him in the 97th percentile for his age, and his height was 75 cm, which was the average for his age group. He exhibited characteristic features including a round face, severe plethora, and significant fat accumulation around his torso. He also had pronounced hirsutism, though there were no skin striations or acne present. His external genitals appeared normal except for the presence of pubic hair. A mass could be felt in the right upper quadrant of his abdomen. Initially, his systolic blood pressure was increased. Radiological analysis showed widespread osteoporosis and delayed bone age assessed at about 8 months. Clinical signs were indicative of Cushing’s syndrome, and the presence of a mass in the right adrenal area suggested an adrenocortical tumor. His health worsened rapidly, necessitating surgical intervention with concurrent steroid treatment. During surgery, two tumors were discovered. The histopathological analysis indicated that both tumors were encased and displayed surfaces with mottled yellow, grey, and hemorrhagic features. Microscopically, both tumors exhibited poorly differentiated tissue organized into irregular lobules and pseudorosettes, with fine fibrous strands separating them. The cells appeared small, with round or oval nuclei that were hyperchromatic and contained several mitotic figures. The predominant histological pattern strongly resembled neuroblastomas.

These case reports suggest that an adrenal mass linked to Cushing syndrome in a child may not always indicate an adrenocortical tumor. It is advisable to conduct preoperative assessments of plasma ACTH and POMC at the time of diagnosis to distinguish potential paraneoplastic Cushing syndrome from an adrenocortical tumor. Consequently, the optimal approach to management may vary.

## 4. CONCLUSIONS

In summary, neuroblastoma is one of the most common childhood cancers, especially in patients under 5 years of age. It is a malignant tumor that usually does not present with characteristic symptoms. Paraneoplastic syndromes associated with neuroblastoma have been described in the literature. Although these are not common conditions, they should be considered in the differential diagnosis. Opsoclonus-myoclonus syndrome (OMS) and chronic diarrhea with hypokalemia are the two most common paraneoplastic syndromes associated with neuroblastoma. Their diagnosis is based on clinical presentation. When any of these syndromes are recognized in a patient, the coexistence of a tumor, especially neuroblastoma, should always be excluded. The diagnostic process should begin with a thorough physical examination, followed by imaging studies, with abdominal ultrasound being the first-line investigation. The confirming test for the presence of neuroblastoma is MIBG scintigraphy. Additionally, levels of catecholamine metabolites in urine should be measured. If a patient suffers from chronic diarrhea with hypokalemia, serum VIP levels should be determined. Delayed diagnosis leads to unfavorable prognosis. The treatment of OMS relies on combined multi-agent therapy. Diarrhea typically resolves immediately after tumor removal. Another very rare paraneoplastic syndrome described in the literature that may accompany neuroblastoma is Cushing's syndrome. When CS symptoms occur in a child, various conditions should be considered - exogenous steroids, a secreting tumor, BAMH, PPNAD, or McCune-Albright syndrome. It is important to remember that an adrenal tumor leading to CS may also be neuroblastoma, and diagnostic workup should be pursued in this direction.

Diagnosing paraneoplastic syndromes is a clinical challenge and typically relies on excluding other potential causes of presenting symptoms. Increased awareness among pediatricians about PNS may lead to quicker diagnosis, prompt initiation of treatment, and ultimately improved patient prognosis.

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REFERENCES:

1. American Cancer Society. Cancer Facts & Figures 2020. Atlanta, Ga: American Cancer Society; 2020. Pages 12-13

2. Maris JM. Recent advances in neuroblastoma. N Engl J Med 2010; 362: 2202-2211 DOI: 10.1056/NEJMra0804577
3. F Alexander. Neuroblastoma. Urol Clin North Am. 2000 Aug;27(3):383-92, vii. doi: 10.1016/s0094-0143(05)70087-2. DOI: 10.1016/s0094-0143(05)70087-2
4. Titilope A. Isholab, Dai H. Chunga. Neuroblastoma. Surg Oncol. 2007 Nov;16(3):149-56. doi: 10.1016/j.suronc.2007.09.005. Epub 2007 Oct 31.
5. Jerome B Posner. Paraneoplastic syndromes in neuroblastoma Pediatr Hematol Oncol 2004 DOI: 10.1097/01.mph.0000139454.22338.17
6. M El Shafie, D Samuel, C H Klippel, M G Robinson, B J Cullen. Intractable diarrhea in children with VIP-secreting ganglioneuroblastomas. Journal of Pediatric Surgery 1983;18:34–6 PMID: 6834224 DOI: 10.1016/s0022-3468(83)80269-3
7. M Espinasse-Holder, A S Defachelles, J Weill, Y De Keyzer, E M de Lasalle, B Nelken. Paraneoplastic Cushing syndrome due to adrenal neuroblastoma. Med Pediatr Oncol. 2000 Mar;34(3):231-3. DOI: 10.1002/(sici)1096-911x(200003)34:3<231::aid-mpo17>3.0.co;2-w
8. Luca Marsili, Samuel Marcucci, Joseph LaPorta, Martina Chirra, Alberto J Espay, Carlo Colosimo. Paraneoplastic Neurological Syndromes of the Central Nervous System: Pathophysiology, Diagnosis, and Treatment. Biomedicines. 2023 May 9;11(5):1406. DOI: 10.3390/biomedicines11051406
9. Maziar Emamikhah, Mansoureh Babadi, Mehrnoush Mehrabani, Mehdi Jalili, Maryam Pouranian, Peyman Daraie, Fahimeh Mohaghegh, Sharmin Aghavali, Maryam Zaribafian, Mohammad Rohani. Opsoclonus-myoclonus syndrome, a post-infectious neurologic complication of COVID-19: case series and review of literature. J Neurovirol. 2021 Feb;27(1):26-34. DOI: 10.1007/s13365-020-00941-1
10. Bruno Giometto, Wolfgang Grisold, Roberta Vitaliani, Francesc Graus, Jérôme Honnorat, Guido Bertolini, Paraneoplastic neurologic syndrome in the PNS Euronetwork database: a European study from 20 centers. Arch Neurol. 2010 Mar;67(3):330-5. DOI: 10.1001/archneurol.2009.341
11. F Graus, J Y Delattre, J C Antoine, J Dalmau, B Giometto, W Grisold, J Honnorat, P Sillevis Smitt, Ch Vedeler, J J G M Verschuuren, A Vincent, R Voltz. Recommended diagnostic criteria for paraneoplastic neurological syndromes. J Neurol Neurosurg Psychiatry. 2004 Aug;75(8):1135-40. DOI: 10.1136/jnnp.2003.034447
12. Andreas Brunklaus, Keith Pohl, Sameer M Zuberi, Carlos de Sousa. Investigating neuroblastoma in childhood opsoclonus-myoclonus syndrome. Arch Dis Child. 2012 May;97(5):461-3. DOI: 10.1136/adc.2010.204792
13. Michael R Pranzatelli, Elizabeth D Tate, Nathan R McGee. Demographic, Clinical, and Immunologic Features of 389 Children with Opsoclonus-Myoclonus Syndrome: A Cross-sectional Study. Front Neurol. 2017 Sep 11:8:468. DOI: 10.3389/fneur.2017.00468
14. E Rudnick, Y Khakoo, N L Antunes, R C Seeger, G M Brodeur, H Shimada, R B Gerbing, D O Stram, K K Matthay. Opsoclonus-myoclonus-ataxia syndrome in neuroblastoma: clinical outcome and antineuronal antibodies-a report from the Children's Cancer Group Study. Med Pediatr Oncol. 2001 Jun;36(6):612-22. DOI: 10.1002/mpo.1138
15. Mandy Hsu, Isbaah Tejani, Nidhi Shah, Rasaq Olaosebikan, Ashutosh Kumar, Sunil Naik. Review of Opsoclonus-Myoclonus Ataxia Syndrome in Pediatric Patients. Children (Basel). 2024 Mar 19;11(3):367. DOI: 10.3390/children11030367
16. Junki Takenaka, Kenji Hirata, Shiro Watanabe, Hideaki Shiraishi, Kohsuke Kudo. Neuroblastoma-related severe hypoperfusion in the cerebellum of an infant: A case of opsoclonus-myoclonus syndrome. Asia Ocean J Nucl Med Biol. 2023;11(1):93-96.

DOI: 10.22038/AOJNMB.2022.65833.1459
17. Agnieszka Mizia-Malarz, Weronika Stolpa, Grażyna Sobol-Milejska. The Treatment of Opsoclonus-Myoclonus Syndrome Secondary to Neuroblastic Tumours-Single-Centre Experience and Literature Review. Medicina (Kaunas). 2020 Aug 14;56(8):412. DOI: 10.3390/medicina56080412
18. Michael R Pranzatelli, Elizabeth D Tate. Dexamethasone, Intravenous Immunoglobulin, and Rituximab Combination Immunotherapy for Pediatric Opsoclonus-Myoclonus Syndrome. Pediatr Neurol. 2017 Aug:73:48-56. DOI: 10.1016/j.pediatrneurol.2017.04.027
19. Armine Galstyan, Colin Wilbur, Kathryn Selby, Juliette Hukin. Opsoclonus-Myoclonus Syndrome: A New Era of Improved Prognosis? Pediatr Neurol. 2017 Jul:72:65-69. DOI: 10.1016/j.pediatrneurol.2017.03.011
20. Marina Auconi, Laura Papetti, Claudia Ruscitto, Michela Ada Noris Ferilli, Fabiana Ursitti, Giorgia Sforza, Federico Vigevano, Massimiliano Valeriani. Opsoclonus-Myoclonus Syndrome in Children and Adolescents: A Therapeutic Challenge. Children (Basel). 2021 Oct 26;8(11):965. DOI: 10.3390/children8110965
21. E De Grandis, S Parodi, M Conte, P Angelini, F Battaglia, C Gandolfo, A Pessagno, V Pistoia, W G Mitchell, M Pike, R Haupt, E Veneselli. Long-term follow-up of neuroblastoma-associated opsoclonus-myoclonus-ataxia syndrome. Neuropediatrics. 2009 Jun;40(3):103-11. DOI: 10.1055/s-0029-1237723
22. Andreas Brunklaus, Keith Pohl, Sameer M Zuberi, Carlos de Sousa. Outcome and prognostic features in opsoclonus-myoclonus syndrome from infancy to adult life. Pediatrics. 2011 Aug;128(2):e388-94 DOI: 10.1542/peds.2010-3114
23. Thomas Rossor, E Ann Yeh, Yasmin Khakoo, Paola Angelini, Cheryl Hemingway, Sarosh R Irani, Gudrun Schleiermacher, Paramala Santosh, Tim Lotze, Russell C Dale, Kumaran Deiva, Barbara Hero, Andrea Klein, Pedro de Alarcon, Mark P Gorman, Wendy G Mitchell, Ming Lim. Diagnosis and Management of Opsoclonus-Myoclonus-Ataxia Syndrome in Children: An International Perspective Neurol Neuroimmunol Neuroinflamm. 2022 Mar 8;9(3):e1153. DOI: 10.1212/NXI.0000000000001153
24. Poonam Bhatia, Jennifer Heim, Patricia Cornejo, Lauren Kane, Jason Santiago, Michael C Kruer. Opsoclonus-myoclonus-ataxia syndrome in children. J Neurol. 2022 Feb;269(2):750-757. DOI: 10.1007/s00415-021-10536-3
25. Alexis B Rothenberg, Walter E Berdon, Giulio J D'Angio, Darrell J Yamashiro, Robert A Cowles. The association between neuroblastoma and opsoclonus-myoclonus syndrome: a historical review Pediatr Radiol. 2009 Jul;39(7):723-6. DOI: 10.1007/s00247-009-1282-x
26. Samuel Galgano, Stuart Royal. Primary pancreatic neuroblastoma presenting with opsoclonus-myoclonus syndrome. Radiol Case Rep. 2015 Nov 28;11(1):36-40. DOI: 10.1016/j.radcr.2015.09.003
27. Bill H Chang, Thomas Koch, Katharine Hopkins, Suman Malempati. Neuroblastoma found in a 4-year-old after rituximab therapy for opsoclonus-myoclonus. Pediatr Neurol. 2006 Sep;35(3):213-5. DOI: 10.1016/j.pediatrneurol.2006.02.008
28. João B Abreu, Catarina R Cordeiro, Ana I Amorim, Tiago G Catanho, Karina D Gama. Combined neuraxial-general anesthesia in opsoclonus-myoclonus syndrome: A case report. Saudi J Anaesth. 2023 Jan-Mar;17(1):94-96. DOI: 10.4103/sja.sja_558_22
29. Suvi Alikärri, Arimatias Raitio, Paul D Losty. Pre and postoperative diarrhoea associated with neuroblastoma resection - A systematic review of published studies. Eur J Surg Oncol. 2023 Oct;49(10):106921. DOI: 10.1016/j.ejso.2023.04.020

30. Mario Delgado, Doina Ganea. Vasoactive intestinal peptide: a neuropeptide with pleiotropic immune functions. Amino Acids. 2013 Jul;45(1):25-39. DOI: 10.1007/s00726-011-1184-8
31. J Fahrenkrug. Transmitter role of vasoactive intestinal peptide. Pharmacol Toxicol. 1993 Jun;72(6):354-63. DOI: 10.1111/j.1600-0773.1993.tb01344.x
32. Anthony J Harmar, Jan Fahrenkrug, Illana Gozes, Marc Laburthe, Victor May, Joseph R Pisegna, David Vaudry, Hubert Vaudry, James A Waschek, Sami I Said. Pharmacology and functions of receptors for vasoactive intestinal peptide and pituitary adenylate cyclase-activating polypeptide: IUPHAR review 1. Br J Pharmacol. 2012 May;166(1):4-17. DOI: 10.1111/j.1476-5381.2012.01871.x
33. C A Maggi, A Giachetti, R D Dey, S I Said. Neuropeptides as regulators of airway function: vasoactive intestinal peptide and the tachykinins. Physiol Rev. 1995 Apr;75(2):277-322. DOI: 10.1152/physrev.1995.75.2.277
34. S Linder, T Barkhem, A Norberg, H Persson, M Schalling, T Hökfelt, G Magnusson. Structure and expression of the gene encoding the vasoactive intestinal peptide precursor. Proc Natl Acad Sci U S A. 1987 Jan;84(2):605-9. DOI: 10.1073/pnas.84.2.605
35. Pradeep Kumar Siddappa, Santhi Swaroop Vege. Vasoactive Intestinal Peptide-Secreting Tumors: A Review. Pancreas. 2019 Oct;48(9):1119-1125. DOI: 10.1097/MPA.0000000000001402
36. Oana Belei, Diana-Georgiana Basaca, Elena Rodica Heredea, Emil Radu Iacob, Laura Olariu, Roxana Folescu, Andrei Gheorghe Marius Motoc, Anda-Maria Nanu, Otilia Mărginean. Chronic Diarrhea Caused by Vasoactive Intestinal Peptide-Secreting Tumor.Life (Basel). 2023 Sep 27;13(10):1974. DOI: 10.3390/life13101974
37. Huysentruyt K., Arts W., van der Werff ten Bosch J., van de Casseye W., Lemmens F., de Koster J., Vandenplas Y., Van Damme A. VIP-Secreting Ganglioneuroblastoma as an Unusual Cause of Watery Diarrhoea in Childhood. J. Med. Cases. 2013;4:234–236. DOI: 10.4021/jmc1009w
38. Franck Bourdeaut 1, Emilie de Carli, Sandra Timsit, Carole Coze, Pascal Chastagner, Sabine Sarnacki, Olivier Delattre, Michel Peuchmaur, Hervé Rubie, Jean Michon. VIP hypersecretion as primary or secondary syndrome in neuroblastoma: A retrospective study by the Société Française des Cancers de l'Enfant (SFCE).; Neuroblastoma Committee of the Société Française des Cancers et Leucémies de l'Enfant et de l'Adolescent. Pediatr Blood Cancer. 2009 May;52(5):585-90. DOI: 10.1002/pbc.21912
39. Wei Han, Huan-Min Wang. Refractory diarrhea: A paraneoplastic syndrome of neuroblastoma. World J Gastroenterol. 2015 Jul 7;21(25):7929-32. DOI: 10.3748/wjg.v21.i25.7929
40. Parshotam K Gera, Colin S Kikiros, Adrian Charles. Chronic diarrhoea: a presentation of immature neuroblastoma. ANZ J Surg. DOI: 10.1111/j.1445-2197.2007.04416.x
41. Benjamin Gesundheit, Charles R Smith, J Ted Gerstle, Sheila S Weitzman, Helen S L Chan. Ataxia and secretory diarrhea: two unusual paraneoplastic syndromes occurring concurrently in the same patient with ganglioneuroblastoma. J Pediatr Hematol Oncol. 2004 Sep;26(9):549-52. DOI: 10.1097/01.mph.0000139414.66455.a4
42. Constantine A Stratakis. An update on Cushing syndrome in pediatrics. Ann Endocrinol (Paris). 2018 Jun;79(3):125-131. Epub 2018 Apr 9. DOI:10.1016/j.ando.2018.03.010
43. M A Magiakou, G Mastorakos, E H Oldfield, M T Gomez, J L Doppman, G B Cutler Jr, L K Nieman, G P Chrousos. Cushing's syndrome in children and adolescents. Presentation, diagnosis, and therapy. N Engl J Med. 1994 Sep 8;331(10):629-36. DOI: 10.1056/NEJM199409083311002

44. Dalia L Batista 1, Jehan Riar, Meg Keil, Constantine A Stratakis. Diagnostic tests for children who are referred for the investigation of Cushing syndrome. Pediatrics. 2007 Sep;120(3):e575-86. DOI: 10.1542/peds.2006-2402
45. Susmeeta T Sharma, Lynnette K Nieman 1, Richard A Feelders. Cushing's syndrome: epidemiology and developments in disease management. Clin Epidemiol . 2015 Apr 17:7:281-93. DOI: 10.2147/CLEP.S44336
46. Helen L Storr 1, Li F Chan, Ashley B Grossman, Martin O Savage. Paediatric Cushing's syndrome: epidemiology, investigation and therapeutic advances. Trends Endocrinol Metab . 2007 May-Jun;18(4):167-74. DOI: 10.1016/j.tem.2007.03.005
47. Valentina Guarnotta, Fabrizio Emanuele, Riccardo Salzillo, Carla Giordano. Adrenal Cushing's syndrome in children. Front Endocrinol (Lausanne). 2023 Dec 12:14:1329082. DOI: 10.3389/fendo.2023.1329082
48. Maya B Lodish, Margaret F Keil, Constantine A Stratakis. Cushing's Syndrome in Pediatrics: An Update. Endocrinol Metab Clin North Am. 2018 Jun;47(2):451-462 DOI: 10.1016/j.ecl.2018.02.008
49. T Normann, J Havnen, O Mjolnerod. Cushing's syndrome in an infant associated with neuroblastoma in two ectopic adrenal glands. J Pediatr Surg. 1971 Apr;6(2):169-75. DOI: 10.1016/0022-3468(71)90313-7