REVIEW

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Verner–Morrison syndrome. Literature review

OANA ANDREEA BELEI[1)], ELENA RODICA HEREDEA[2)], ESTERA BOERIU[3)], TAMARA MARCELA MARCOVICI[1)], SIMONA CERBU[4)], OTILIA MĂRGINEAN[1)], EMIL RADU IACOB[5)], DANIELA IACOB[6)], ANDREI GHEORGHE MARIUS MOTOC[7)], EUGEN SORIN BOIA[5)]

[1)]*First Pediatric Clinic, "Victor Babeş" University of Medicine and Pharmacy, Timişoara, Romania*

[2)]*Department of Pathology, "Louis Ţurcanu" Emergency Children Hospital, Timişoara, Romania*

[3)]*Third Pediatric Clinic, "Victor Babeş" University of Medicine and Pharmacy, Timişoara, Romania*

[4)]*Department of Radiology, "Victor Babeş" University of Medicine and Pharmacy, Timişoara, Romania*

[5)]*Department of Pediatric Surgery, "Victor Babeş" University of Medicine and Pharmacy, Timişoara, Romania*

[6)]*Department of Neonatology, "Victor Babeş" University of Medicine and Pharmacy, Timişoara, Romania*

[7)]*Department of Anatomy and Embryology, "Victor Babeş" University of Medicine and Pharmacy, Timişoara, Romania*

Abstract

Chronic diarrhea in infants is a common condition for addressability to pediatric gastroenterologists. The causes are multiple and the delay in reaching the final diagnosis can lead to complications in the general condition of the child. The purpose of this review is to present the bio-clinical and histogenetic particularities of a rare clinical entity, characterized by tumoral causes of chronic diarrhea. VIPomas are neuroendocrine tumors that autonomously secrete vasoactive intestinal peptide (VIP). Watery diarrhea, hypokalemia and achlorhydria (WDHA) syndrome caused by VIP-producing tumors only rarely occurs in adult patients with non-pancreatic disease. In pediatric patients, it is extremely rare for a VIPoma to originate in the pancreas; instead, WDHA syndrome is usually associated with VIP-secreting neurogenic tumors involving the retroperitoneum or mediastinum. The majority of VIP secreting tumors in pediatric patients are represented by ganglioneuroblastomas or ganglioneuromas originating in the adrenal medulla or sympathetic neural crest. This syndrome of watery diarrhea associated with hypokalemia and achlorhydria was first described by Verner and Morrison, in 1958, and has been assumed to be due to hypersecretion of VIP. In children, as well as in adult patients, the most likely explanation for persistent secretory diarrhea may be an occult VIPoma. In conclusion, the physicians should be aware that there are some rare tumoral causes of chronic diarrhea, often under-diagnosed. If the diagnosis is not considered, extensive gastrointestinal investigations will be undertaken, delaying the diagnosis and avoidable morbidity will occur.

Keywords: diarrhea, vasoactive intestinal polypeptide, ganglioneuroblastoma.

Introduction

Verner and Morrison described, in 1958, chronic secretory diarrhea with electrolytes disturbances such as hypokalemia in patients with non-insulin secreting pancreatic masses [1].

The absence of gastric hypersecretion and even achlorhydria were documented in patients with this tumor syndrome that was later termed pancreatic cholera due to severe diarrhea resembling *Vibrio cholerae* disease [2]. The acronym WDHA (watery diarrhea, hypokalemia, achlorhydria) was proposed, although a more appropriate acronym might be WDHHA, standing for watery diarrhea, hypokalemia, hypochlorhydria and acidosis, considering the bicarbonate waste [3]. Several reported series have confirmed the association between certain pancreatic tumors and watery diarrhea syndrome [4–6]. In adults, this syndrome is most commonly associated with pancreatic islet cell tumors, but is rarely caused by non-pancreatic tumors, such as bronchogenic carcinoma, medullary thyroid carcinoma, retroperitoneal histiocytoma and adrenal pheochromocytoma [7]. In infants, it is extremely rare for a vasoactive intestinal polypeptide (VIP) producing tumor to originate in the pancreas; instead, WDHA syndrome is usually associated with VIP-secreting neurogenic tumors involving the retroperitoneum and mediastinum [5]. Although being reported in children, pancreatic non-beta-cell hyperplasia is considered a rare state. Clinical experience is based mainly on case reports [8, 9].

A wide range of gastrointestinal conditions may cause chronic diarrhea in pediatric patients. In a small percent of cases, diarrhea is due to active intraluminal fluid secretion known as secretory diarrhea. Due to important diagnostic implications, the identification of such pathological cases comes as a necessity. The most likely explanation for persistent secretory diarrhea may be an occult VIPoma – a tumor that secretes VIP.

Sites and nature of tumors secreting VIP

Although rare, Verner–Morrison syndrome is a well-defined clinical and pathological entity that occurs most

often in association with VIP-producing tumor [1]. Tumors secreting VIP usually originate in the pancreas or along the sympathetic chain. In an old mixed series of 62 patients (children and adults), 52 (84%) had pancreatic tumors and 10 (16%) had ganglioneuroblastomas. Of the 10 patients with ganglioneuroblastomas, seven were children [10].

The majority of VIPomas diagnosed in children are either ganglioneuromas or ganglioneuroblastomas, arising from the neural crest tissue of the sympathetic ganglia or from the adrenal medulla. Ganglioneuromas are well-differentiated and benign lesions, whereas ganglioneuroblastomas exhibit a variable differentiation and the prognosis is rather uncertain [11]. These tumors may arise wherever the sympathetic nerve tissue is present. The most common locations include the adrenal glands (35%), paraspinal retroperitoneal ganglia (30–35%), posterior mediastinum (20%), head and neck (1–5%) and pelvis (2–3%); rare locations include the thymus, lung, kidney or anterior mediastinum [12].

In the literature, there have been reported several adult and pediatric case reports/case series of elevated plasma levels of VIP that have been associated with neurogenic tumors, including ganglioneuroblastoma, ganglioneuromas, neurofibroma and pheochromocytoma [13–22]. Primary VIPomas have been reported in other sites as well, including colon, lung, esophagus, jejunum and liver and there are reported the eventual emergence of tumors masquerading as hypernephroma and cutaneous mastocytomas [23]. Most neurogenic tumors associated with the VIPoma syndrome have been found in children. Increasing the circulation in *corpora cavernosa* due to VIP secretion may initiate the occurrence of priapism. This has led to attempts to develop VIP administration as a therapy for impotence [24].

Classification and prognosis of neuroblastic tumors

Neuroblastic tumors arise from undifferentiated embryonic cells of the neural crest as a result of their arrested differentiation. Ganglioneuromas, ganglioneuroblastomas and neuroblastomas differ from one another in terms of the neuroblast maturation stage. Ganglioneuromas have a benign potential being formed by mature ganglion cells. Ganglioneuroblastomas are less mature forms and are regarded as more aggressive tumors that generally develop in small children, the mean age at onset being around two years. Patients diagnosed with ganglioneuroblastomas present a relatively good prognosis considering that these tumors may spontaneously regress or maturate into ganglioneuromas. Regression occurs in 1–2% of all cases and the causes remain unknown [11]. Neuroblastomas can produce metastatic spread by blood or lymphatic dissemination. The most common targets are liver, lungs, bones and the bone marrow.

Neuroblastomas are heterogeneous tumors. Their clinical and morphological characteristics are correlated to their biological features. The *International Neuroblastoma Pathology Classification* is a revised version of the Shimada Classification based on patient age at diagnosis, the abundance of stroma and the stage of differentiation [11] as depicted in Table 1.

Table 1 – *International Neuroblastoma Pathology Classification (Shimada System)*

Stroma-poor neuroblastomas with neuroblasts that are undifferentiated, differentiating, or differentiated.
Stroma-rich ganglioneuroblastomas with differentiated and undifferentiated neuroblasts.
Stroma-dominant ganglioneuromas with maturing neuroblasts and mature ganglion cells.
Composite nodular ganglioneuroblastomas with stroma-rich/ stroma-dominant and stroma-poor cells and neuroblasts with various degrees of differentiation.

The *International Classification* introduced a prognostic index based on the numbers of cells undergoing mitosis and karyorrhexis (MK index or MKI). Table 2 depicts the features of different types of neuroblastic tumors correlated to the prognosis [25].

Table 2 – *Prognosis of neuroblastic tumors classified according to Shimada System*

International Neuroblastoma Classification	Patient age [years]	Histology	Prognosis
Neuroblastoma (stroma-poor)	<1.5	Poorly differentiated or differentiated and low or intermediate MKI tumor	Favorable
	1.5–5	Differentiated and low-MKI tumor	Favorable
	<1.5	Undifferentiated low-MKI tumor	Unfavorable
	1.5–5	Undifferentiated or poorly differentiated tumor (regardless of MKI)	Unfavorable
	>5	All tumors	Unfavorable
Intermixed ganglioneuroblastoma (stroma-rich)	All ages	All tumors	Favorable
Ganglioneuroma (maturing or mature; stroma-dominant)	All ages	All tumors	Favorable
Ganglioneuroblastoma, nodular (stroma-rich, stroma-poor and stroma-dominant)	All ages	All tumors	Unfavorable

MKI: Mitosis–karyorrhexis index.

Diverse systems have been proposed for the staging of neuroblastomas. The stage of the tumor classified according to the *International Neuroblastoma Staging System* (INSS) depicted in Table 3 is a major determinant of prognosis [11].

The tumors can also be divided into risk categories on the basis of prognostic factors as shown in Table 4 [11]. Several clinical and pathological factors including age and stage at diagnosis, histology of tumor, and amplification of MYC-N, an oncogene, have been used to develop a risk stratification for treatment and prognosis.

The MYC transcription factor is a key regulator of normal progression through the cell cycle. It is critical to control MYC levels within the cell to prevent abnormal cell growth. Since MYC mRNA and protein levels must be tightly regulated, it is not surprising that both mRNA and proteins exhibit rapid turnover. Particularly, MYC protein is highly unstable, with a typical half-life of <30 minutes [26]. Considerable effort has been made toward

investigating if reduced MYC protein turnover causes an increased net MYC protein level, which is commonly observed in cancers. An extended half-life for MYC protein has been reported in neuroblastomas and lymphomas. The high levels of MYC protein found in the majority of cancer cells could be due to the impairment of MYC turnover pathways in addition to aberrant transcriptional activation of the MYC genes. MYC-N amplification is the most common genetic alteration in neuroblastoma and plays a critical role in neuroblastoma tumorigenesis. MYC-N regulates neuroblastoma cell differentiation, which is one of the mechanisms underlying its oncogenic function [27].

Table 3 – ***The International Neuroblastoma Staging System***

Stage 1
Localized tumor with complete gross excision, no gross or microscopic residual disease, and negative representative lymph nodes
Stage 2
2A. Tumor with incomplete gross excision and negative representative ipsilateral lymph nodes. 2B. Tumor with incomplete gross excision, positive ipsilateral lymph nodes, and negative contralateral lymph nodes.
Stage 1 + Stage 2A + Stage 2B = 25%
Stage 3
Unresectable tumor infiltrating across the midline, with or without regional lymph node involvement; or midline tumor with bilateral extension consisting of infiltration or lymph node involvement.
Stage 4
Any primary tumor with dissemination to distant lymph nodes, bone, bone marrow, liver, or skin.
Stage 3 + Stage 4 = 65%
Stage 4S ("special" – 10%) Localized primary tumor (as in stages 1, 2A, or 2B) with dissemination limited to skin, liver, and/or bone marrow (no bone involvement) in infants younger than one year. These infants have good adrenal function and more favorable prognoses.

Table 4 – ***Risk stratification based on prognostic factors***

High-risk tumors
Includes disseminated disease with multiple gene alterations including amplification of MYC-N (corresponds to stages 3 and 4). These tumors have the worst prognosis with cure rates less than 20%.
Intermediate-risk tumors
Extensive disease with multiple gene alterations including amplification of MYC-N. These tumors progress slowly and are associated with cure rates of 25–50%.
Low-risk tumors
Small tumors that can be treated with surgery alone (stages 1 or 2). These tumors are associated with cure rates exceeding 90%.

Histopathological and immunohistochemical characteristics of neuroblastic tumors

Neuroblastic tumors are assigned to one of four basic morphological categories: neuroblastomas (Schwannian stroma-poor); intermixed ganglioneuroblastomas (Schwannian stroma-rich); ganglioneuromas (Schwannian stroma-dominant); and nodular ganglioneuroblastomas (composite Schwannian stroma-rich/stroma-dominant and stroma-poor). This nomenclature is widely known and used in clinical practice. Microscopic neuroblastomas are undifferentiated, poorly differentiated and differentiated depending on the neuroblastic features, maturing/mature ganglion cells and on the Schwannian stroma. Undifferentiated neuroblastomas are composed entirely of neuroblasts and lack ganglion cell maturation while poorly differentiated neuroblastomas are predominantly composed of neuroblastic cells forming nests that are separated by incomplete stromal septa with or without limited Schwannian proliferation (<50% of background), <5% maturing/mature ganglion cells and at least one neuropil focus. Differentiating neuroblastomas are >5% composed of maturing/mature ganglion cells. Schwannian stroma-rich and stroma-dominant tumors are characterized by a ganglioneuromatous appearance with mature or maturing ganglion cells individually scattered in a background of highly developed Schwannian stroma. In ganglioneuroblastomas, the number and degree of differentiation of the neuroblastic cells tend to vary from one tumor to another as well as between different microscopic fields in the same tumor. Some pathologists describe ganglioneuroblastomas as all neuroblastic tumors containing a high amount of eosinophilic cytoplasm (interpreted as a sign of ganglion cell differentiation). Others consider ganglioneuroblastoma diagnosis only when dealing with tumors characterized by an abundant Schwannian stroma containing a mixture of immature and mature ganglion cells and differentiating neuroblasts. The *International Neuroblastoma Pathology Classification* (INPC) has restricted the definition of ganglioneuroblastomas to tumors with two distinctive components: a mature Schwannian stromal component with individually scattered mature and/or maturing ganglion cells (*i.e.*, ganglioneuromatous tissue) and a neuroblastic component [2, 3, 12, 25]. Neuroblastomas are defined as neuroblastic, Schwannian stroma-poor tumors, although Schwannian cells (or their precursors) can be detected as slender S-100 protein-positive cells in the delicate fibrovascular septa demarcating more or less well-defined lobules of the neuroblastic cells. Undifferentiated neuroblastoma subtype is a tumor that usually requires supplementary techniques (immunohistochemistry, electron microscopy, and/or cytogenetics) in order to establish the diagnosis. The tumor cells in this subtype are undifferentiated and usually small-to-medium in size, with indiscernible-to-thin rims of cytoplasm and vaguely defined cytoplasmic borders. The nuclei may vary in shape from rounded to elongated and characteristically possess the salt-and-pepper appearance of their chromatin. Also, they may contain distinct nucleoli. Identifiable background neuropil (thin neuritic processes) is absent. Coagulation necrosis, fibrin or collagen fibrils may be mistaken for neuropil, especially in case of poor quality sections. A panel of immunohistochemical markers often used by pathologists to confirm the diagnosis of neuroblastic tumors includes: (*1*) neuron specific enolase, chromogranin A, synaptophysin, tyrosine hydroxylase, protein gene product 9.5, GD2 (disialoganglioside, a ganglioside on human neuroblastoma cell membrane) and NB84 that are positive in a variable proportion of cases; and (*2*) actin, desmin, low-molecular-weight cytokeratin, leukocyte common antigen and vimentin, that are usually negative. Membranous staining for cell surface glycoprotein, p30/32 (a product of the MIC2 gene detected by CD99 antibodies), commonly seen in Ewing sarcoma, is

usually negative in neuroblastic tumors when tested by using paraffin-embedded material [25–27].

Clinical manifestation in Verner–Morrison syndrome

VIPomas often present with diarrhea as the only manifestation. When investigating children with persistent watery stools it is essential to identify those with secretory diarrhea. Secretory diarrhea is characterized by watery stools and in contrast to osmotic diarrhea, it persists while fasting. Biochemical analysis shows a raised stool sodium concentration (typically >50 mmol/L) [28]. In such cases, a VIPoma should be suspected. Diarrhea that is not secretory always results from causes other than endocrine tumors. Secretory diarrhea may be common disorder in developing countries and the differential diagnosis with VIPomas is required. In countries where pathogens that produce enterotoxin such as enterotoxigenic *Escherichia coli* are endemic, secretory diarrhea is frequent. Nowadays, however, persistent secretory diarrhea is uncommon in the developed world [28]. Although bacterial and viral gastroenteritis may cause secretion, persistent secretory diarrhea is rare. Certain rare inherited electrolyte transport defects, such as congenital chloride diarrhea and congenital sodium diarrhea may be responsible, but these present in early infancy, from birth. In older children, secretory diarrhea may occasionally occur in association with various major gastrointestinal disorders – for example, Crohn's disease and the short bowel syndrome, but in such cases the gut disorder is usually obvious. One important consideration is that secretory diarrhea may be caused by repeated laxative administration in Münchausen by proxy syndrome [29]. Laxative abuse may be very difficult to exclude and the measurement of stool electrolytes and osmolarity may be required. Stool electrolytes should account for the osmolarity if the condition results from an endocrine tumor. An osmolarity exceeding that expected from the concentration of electrolytes invariably reflects laxative abuse, which must be carefully excluded.

Biochemical diagnosis

Initially, a hypothesis that has been released in the 1960s regarding Verner–Morrison syndrome, supported the fact that watery diarrhea was caused by catecholamine hypersecretion, a well recognized phenomenon that was associated with neural crest tumors [30]. Later, in the 1970s, researchers have proved that these tumors also secreted VIP [31]. VIP is characterized by a 3381 molecular weight, consisting of 28 amino acids and belongs to the secretin-glucagon family [32]. VIP is normally expressed in the central nervous system and in the neurons of the gastrointestinal, respiratory, and urogenital tracts, where it exerts its role as a neurotransmitter. VIP overexpression causes diarrhea and VIP receptors overexpression promotes cancerous growth. In the gastrointestinal tract, VIP is responsible for vascular and nonvascular smooth muscle cell relaxation and secretion of water and electrolytes. It is released in response to intestinal distention due to food consumption. VIP is a potent stimulator of intestinal cyclic adenosine monophosphate (cAMP) production, which leads to massive secretion of water and electrolytes, mainly potassium. When it is secreted in large amounts from endocrine tumors, patients typically experience massive secretory diarrhea, dehydration, flushing and weight loss [33]. VIP also inhibits gastric acid secretion, promotes hepatic glycogenolysis and hyperglycemia and dilates peripheral systemic blood vessels. Characteristic laboratory abnormalities include hypokalemia, achlorhydria, hypercalcemia, hyperglycemia and metabolic acidosis [32]. Hypercalcemia has been noted in nearly 50% of patients with the syndrome [33]. The cause is not clear, but it may relate to dehydration, electrolyte disturbances secondary to diarrhea, coincidental multiple endocrine neoplasia (MEN) accompanied by hyperparathyroidism, or secretion by the tumor of a calcitrophic peptide. Tetany has been reported in several patients and may result from hypomagnesemia secondary to diarrhea. Nearly 8% of patients demonstrate facial flushing. The cause of this patchy erythematous and sometimes urticarial flushing is not clear, but it has been attributed to VIP or prostaglandins, which may be present in the tumor. The hyperglycemia often noted in patients with the watery diarrhea syndrome probably is secondary to the profound glycogenolytic effect of high portal vein VIP on the liver [33].

By definition, VIP levels are elevated in all patients with the VIPoma syndrome. 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 [34–36].

Biochemical detection of VIP-secreting tumors necessitates a highly sensitive and specific VIP radioimmunoassay. The range of normal VIP concentration is 0–190 pg/mL found by several laboratories [36, 37]. Information gained from a single plasma VIP level may be misleading. The diagnosis of VIPoma in a patient with strong clinical suspicion should not be excluded based on a single normal VIP level. Between periods of watery diarrhea, the VIPoma, unlike many endocrine tumors of the gut (insulinoma, gastrinoma), may not be actively secreting VIP; thus, a normal level creates a false sense of security and may delay a more vigorous search for the cause.

VIP is not the only agent implicated in the diarrhea syndrome. Gastrin, secretin, glucagon, enteroglucagon, gastric inhibitory polypeptide (GIP), pancreatic polypeptide (PP), VIP, thyrocalcitonin (TCT), prostaglandins, and peptide fragments of VIP have been implicated as possible etiologic agents of the diarrhea syndrome [38, 39].

Bloom & Polak reported 1000 adult patients with various forms of diarrhea [40]. Thirty-nine (3.9%) patients had greatly elevated levels of VIP and in each case, a tumor was found. In more than 50% of these patients, the tumor was successfully removed, the symptoms remitted, and the plasma levels of VIP returned to normal. Twelve patients had diarrhea secondary to TCT-producing tumors of the thyroid, 13 had carcinoma of the lung, four had a villous adenoma of the rectum and 24 had carcinoid tumors. All 53 of these patients had normal plasma VIP levels. Eleven additional patients had classic clinical features of the VIPoma syndrome in whom VIP levels

were normal and no tumor was found; they probably were secreting an unidentified humoral substance with the biological properties of VIP [40].

In children suspected of Verner–Morrison syndrome, catecholamine levels also is important and should be obtained. About 90% of children with a neuroblastoma will present an excessive vanillylmandelic and homovanillic acid production. If vanillylmandelic acid and other catecholamine levels are normal, it is less likely for the child to be diagnosed with a neuroblastoma; however, this diagnosis cannot be ruled out [41]. These tumors do not necessarily produce catecholamines at a constant rate; therefore, increases in the hormones and metabolites levels will fluctuate in the urine and may not be increased in the tested samples [42]. Neuron specific enolase (NSE) is a 78 kD gamma-homodimer and represents the dominant enolase-isoenzyme found in neuronal and neuroendocrine tissues. Its levels in other tissues, with the exception of erythrocytes, are non-detectable [43]. Due to its organ-specificity, concentrations of NSE in serum or, more commonly, in the cerebrospinal fluid are often elevated in diseases which result in relative neuronal destruction. NSE is also frequently overexpressed by neural crest-derived tumors. Up to 70% of patients with small cell lung carcinoma present elevated serum NSE concentrations at diagnosis. Other neuroendocrine tumors with frequent expression of NSE include carcinoids (up to 66% of cases), islet cell tumors (typically <40% of cases) and neuroblastoma where the exact frequency of NSE expression remains unknown [44].

Imaging investigations

Imaging studies play fundamental roles in the diagnosis and follow-up of neuroblastic tumors. Ultrasonography, which is easy to perform and does not involve radiation exposure, is the first-line method for both phases. Computed tomography (CT) and magnetic resonance imaging (MRI) are the methods of choice when more accurate information is needed on the location of the disease, its relation to organs and vascular structures, and the presence of spinal involvement. CT is particularly important for evaluating the size of the mass and for identifying the organ of origin, infiltration of tissues and vascular structures and the presence of adenopathy and calcifications, whereas MRI is the method of choice for assessing the extension of spinal tumors. These second-level studies are fundamental for planning surgery [11].

Treatment

Treatment options include surgery, chemotherapy, and radiotherapy. The first step in the treatment of these patients is prompt replacement of fluid and electrolyte losses. Symptoms of severe electrolyte imbalance include cardiac arrhythmias, neuromuscular deficits, profound shock, and cardiovascular collapse. The fluid of choice is an isotonic electrolyte solution containing adequate sodium, potassium and base. If a tumor has been identified, complete surgical excision is the primary form of treatment. If the tumor cannot be removed completely, surgical debulking may have palliative benefit. With malignant tumors, treatment with sandostatin or chemotherapy must be considered. Steroids have provided some symptomatic relief. A trial of prostaglandin synthesis inhibitors (indomethacin), phenothiazines, and lithium may be warranted [45]. Octreotide has been used successfully in managing the diarrhea of VIPoma syndrome. New perspectives are emerging with the use of biological therapy based on the use of immunomodulators and retinoids [46].

Conclusions

When confronted with severe chronic diarrhea, it must be established that the diarrhea is secretory in nature by fasting the patient for 48 hours and measuring stool volume. If diarrhea persists with fasting, VIP-producing tumors should be considered, and plasma samples should be analyzed for VIP in these patients. If the VIP level is elevated, a VIP-secreting tumor (VIPoma) should be strongly suspected. VIPomas often present with diarrhea as the only manifestation, and in such cases, appropriate gastrointestinal investigations and treatment strategies may be undertaken. Ganglioneuroblastomas are controversial clinical and pathological entities, the morphological and immunohistochemical distinction between ganglioneuromas, neuroblastomas and Schwannomas with neuroblastoma-like features being regarded as a difficult diagnostic approach. The final diagnosis of such rare pathological cases is complex and mostly based on the integration of the clinical presentation of the patient, with imaging examination, histopathological routine analysis and additional immunohistochemical evaluation of the specimens.

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Corresponding authors

Emil Radu Iacob, Lecturer, MD, PhD, Department of Pediatric Surgery, "Victor Babeş" University of Medicine and Pharmacy, 2 Eftimie Murgu Square, 300041 Timişoara, Timiş County, Romania; Phone +40745–614 590, e-mails: radueiacob@umft.ro, radueiacob@yahoo.com

Daniela Iacob, Associate Professor, MD, PhD, Department of Neonatology, "Victor Babeş" University of Medicine and Pharmacy, 2 Eftimie Murgu Square, 300041 Timişoara, Timiş County, Romania; Phone +40742–558 574, e-mail: danielariacob@yahoo.com

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