Neurological manifestations of Proteus syndrome – review of the literature.

Objawy neurologiczne w zespole Proteusza – przegląd literatury

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ABSTRACT

Introduction. Proteus syndrome is a rare disorder associated with a mutation in the AKT1 gene. Its various clinical features have been broadly reviewed. However, no review on neurological complications has been provided since the MRI imaging became a routine and the cause of the disease has been discovered. Considering that roughly 40% of patients with Proteus syndrome develop neurological symptoms, it is essential to increase the awareness among pediatric neurologists. **Aim, material and methods.** The aim of this review is to present the most common neurological complications in patients with Proteus syndrome, emphasize the role of neuroimaging as well as assess the literature regarding available treatment. Articles available through PubMed and Medscape have been reviewed and those containing neurological complications have been collected for further analysis. **Results.** The most common clinical manifestation is cognitive impairment, followed by epilepsy. Other symptoms such as gait disturbance, hand tremor, headache, and abnormal muscle tone seem to occur sporadically. As regards seizures, the early-childhood onset was present in all cases and they were poorly controlled on antiepileptic drugs. The large number of brain lesions in CT and MRI scans have been documented, out of which the most common was hemimegalencephaly. Other CNS abnormalities were: meningiomas, lipomas, vascular malformations, lissencephaly, cortical dysplasias, cysts, hydrocephalus and cerebellar malformations. It was noted that Proteus syndrome patients can suffer from spinal cord compromise due to tumors' infiltrations, scoliosis or bone abnormalities causing spinal stenosis. **Conclusions.** The neurological manifestations of Proteus syndrome are frequent and important hallmark of the disease. The awareness of them among neurologists may increase efficacy of the syndrome management.

Key words: Proteus syndrome, epilepsy, hemimegalencephaly, intellectual disability

STRESZCZENIE

Wstęp. Zespół Proteusza to rzadka choroba, której podłoże upatruje się w mutacji genu *AKT1*. W literaturze medycznej ukazało się wiele prac przeglądowych dotyczących rozmaitych objawów klinicznych towarzyszących zespołowi. Zważywszy, że około 40% pacjentów z zespołem Proteusza rozwija objawy neurologiczne, przybliżenie tej problematyki neurologom dziecięcym wydaje się uzasadnione. **Cel, materiał i metody.** Celem tej pracy jest przedstawienie najczęściej występujących powikłań neurologicznych u pacjentów z zespołem Proteusza, podkreślenie roli neuroobrazowania oraz podsumowanie dostępnych metod leczenia. Prace dotyczące tego zagadnienia dostępne w wyszukiwarkach PubMed oraz Medscape zostały przeanalizowane pod kątem informacji istotnych dla neurologa klinicysty. **Wyniki.** Najczęściej opisywanym objawami są opóźnienie rozwoju psychoruchowego i padaczka. Inne objawy, takie jak zaburzenia chodu, drżenie rąk, ból głowy, zaburzenia napięcia mięśniowego opisywano sporadycznie. We wszystkich udokumentowanych przypadkach padaczka rozpoczęła się we wczesnym dzieciństwie i zachodziły znaczne trudności w jej leczeniu. Badania neuroobrazowe uwidoczniły wiele zmian: oponiaki, tłuszczaki, malformacje naczyniowe, lizencefalię, dysplazje korowe, torbiele, wodogłowie, zmiany w budowie móżdżku. Najczęściej jednak opisywano hemimegalencefalię. U pacjentów z zespołem Proteusza występowały kilkakrotnie objawy wynikające z ucisku rdzenia kręgowego, co spowodowane było rozrostem nowotworu, znacznym skrzywieniem kręgosłupa lub zmianami w obrębie kręgów rdzeniowych. **Wnioski.** Objawy neurologiczne są ważnymi i często występującymi cechami zespołu Proteusza. Wiedza o nich wśród neurologów może przyczynić się do efektywnego leczenia pacjentów z tym zespołem.

Słowa kluczowe: zespół Proteusza, padaczka, hemimegalencefalia, niepełnosprawność intelektualna

INTRODUCTION

Even though Proteus syndrome (PS) is considered a very rare disorder, typing "Proteus syndrome" into Google search gives more than a half million results and well over 600 articles in PubMed. The aim of this work was to search cases of Proteus syndrome with neurological manifestations.

Considering there has been no published neurological review since 1998 [1], a year before diagnostic criteria were announced and when a broadly available, sensitive MRI era was about to start, this review may be a useful material for both pediatric and adult neurologists.

Proteus syndrome is a rare condition that affects less than one in a million people worldwide. It has been named for the first time by Wiedemann et al. in 1983 [2]. The name derived from the Greek god Proteus who had the ability to constantly change his shape. The best example of how rapid the change of body may occur in this syndrome is that of Joseph Merrick's biography [3, 4], probably the most well-known case believed to be Proteus syndrome. He was born as a normal child and was a 5-year-old when first symptoms started to appear. At the age of 11 he was able to attend school and one year later began to work. However, at the age of 17 he was deformed so severely that he started being called an "elephant man". Joseph Merrick died at the age of about 28, most probably as a result of spinal cord compression due to the head overgrowth.

It has been recently proven that his disorder was caused by an activation of AKT1, a kinase that plays the central role in the PI3K/AKT/mTOR pathway. The PI3K/AKT/mTOR pathway is a network important in tumor cell growth and proliferation. It is activated by many types of cellular stimuli. The PTEN protein, in contrast, opposes PI3K and as a result, negatively regulates AKT signaling [5–7].

A vast number of disorders is associated with the dysregulation of the PI3K/AKT/mTOR pathway. Among those proven to be caused by *PTEN* mutations are: Bannayan-Riley-Ruvalcaba syndrome, Cowden syndrome or SOLAMEN syndrome [8, 9]. Mutations in *TSC1* and *TSC2* genes result in tuberous sclerosis phenotype [10]. The activating somatic mutation in AKT1 gene causes PS, a mosaic, postnatal overgrowth syndrome [11].Considering the network of signaling pathway, it is understandable that all aforementioned syndromes present with overlapping clinical characteristics.

Correct differential diagnosis requires the knowledge of diagnostic criteria listed in the Table I.

Although there are no delineated criteria concerning central nervous system, the involvement of this system is observed in nearly two fifths of PS patients [12].

Table I. Proteus syndrome diagnostic criteria. Adapted from Biesecker et al.[13,14]. *Kryteria diagnostyczne zespołu Proteusa. Adaptacja tabeli z Biesecker et al. [13,14].*

General criteria:	
Mosaic distribution Progressive course Sporadic occurence	Mandatory criteria and:
Specific criteria:	**Either :**
Category A 1. Cerebriform connective tissue nevus	Category A, or:
Category B 1. Linear epidermal nevus 2. Assymetric, disproportionate overgrowth of one or more: a. Limbs b. Hyperostoses of the skull c. Hyperostoses of the external auditory meatus d. Megaspondylodysplasia e. Viscera 3. Specific tumors before the 2nd decade, either one: a. Ovarian cystadenomas b. Parotid monomorphic adenoma	Two from category B , or:
Category C 1. Dysregulated adipose tissue, either one: a. Lipomas b. Lipohypoplasia 2. Vascular malformations: a. capillary malformations b. venous malformations c. lymphatic malformations 3. Lung cysts 4. Facial phenotype a. Dolichocephaly b. Long face c. Downslating palpebral fissures and/or minor ptosis d. Low nasal bridge e. Wide or anteverted nostrils f. Open mouth at rest	Three from Category C

METHODS

Published cases of Proteus syndrome were identified using PubMed and Medscape search engines. Search terms included "Proteus syndrome", "Proteus syndrome seizures", "Proteus syndrome neurological", "Proteus syndrome CNS", "overgrowth syndromes neurological". Just under a hundred articles, including those which titles were non-suggestive of neurological manifestations, have been read but only those reporting such sequelae were reviewed. Cases not fulfilling the diagnostic criteria were not included. A total number of 33 articles containing case reports have been assessed.

NEUROLOGICAL MANIFESTATIONS

A total of 38 cases have been reviewed. The youngest case described is a newborn whereas the oldest patient was a 65-year-old. There were significantly more pediatric (32) than adult (6) cases.

Among the most common neurological manifestations are epilepsy and mental retardation followed by spinal cord compromise. Other signs due to various malformations have been reported and are mentioned in the review. Interestingly, the occurrence of neurological deficits preceded overgrowth manifestations in three cases [1, 15, 16].

Seizures

According to Dietrich et al. [1] only 13% of Proteus syndrome patients have seizures. However, the overall percentage of epilepsy among Proteus syndrome patients is not relevant, since many cases do not mention neurological examination or the information concerning epilepsy is not given. As a result, this percentage may be much higher.

Epilepsy was noted in eleven cases in the reviewed literature. In all patients it started in an early childhood, and in eight out of eleven it appeared in the first 12 months. In all reported cases epilepsy appeared below 5 years of age.

In two cases infantile spasms were diagnosed, one child was treated with valproate with good seizure control [17]. In the second case, the child died in early childhood during an epileptic seizure [18].

There are two reported cases of triple association of Ohtahara syndrome, hemimegalencephaly (HME) and Proteus syndrome [15]. In the majority of patients with Proteus syndrome seizures were treated by multiple anticonvulsants with poor control.

More than a half of seizures were related to HME. Although it is evident that those patients could benefit from the surgery, only two such cases are reported. In the first case [19] initial partial hemispherectomy at the age of 8 months had not resulted in a good seizure control and further resection of an epileptic focus in the frontal lobe was performed 10 months later resulting in an improvement. In the second case [20] it was a 3-year-old boy who underwent frontal lobectomy and remained seizure-free for 12 months afterwards. The ictal SPECT with MRI, performed when the child redeveloped seizures, demonstrated small seizure focus. Seeing that Proteus syndrome is a progressive disorder, it is possible that new foci may arise on follow-up.

Mental retardation

According to Cohen et al. [21], nearly 30% of Proteus patients suffer from mental retardation, ten times more than in general population. In contrast to those in the latter group which are mostly mildly affected, patients with PS seem to be more often profoundly disabled.

In the collected literature we found mental retardation in 16 out of 21 cases in which patients' development was described. The degree of retardation was mild to severe. There was no specific general pattern of the development of the disability. Hassani et al. [16] reported a case of a child whose intellectual development was noted to deteriorate by the age of 4 years. That was long after the first symptoms- progressive skeletal overgrowth.

In well-documented cases an association between mental retardation and seizures was noted. In the case of the most severe cognitive deficit, consisting of lack of interaction with surroundings, generalized seizures were observed as early as on the second day of life and could not be controlled even on multiple drugs [22]. However, in one case, even though a seizure-free state was reached, further mental regression was observed in one year follow-up [17].

Facial dysmorphia

In all studied cases of delayed mental development, an abnormal facial phenotype, if assessed, has been described. Its most common manifestations are: dolichocephaly, long face, minor downslanting palpebral fissures and/or minor ptosis, low nasal bridge, wide or anteverted nares and an open mouth at rest. The association of facial dysmorphia with mental retardation was noticed for the first time in 1993 by Cohen et al. [23]. All mentally deficient patients had brain malformations, but noteworthy, not all brain malformations have been accompanied by mental deficiency.

Spinal cord compromise

Clinical signs varied among patients from back pain and gait disturbance, signs of corticospinal tract damage to paraplegia. Causative factors were angiolipomatous hamartomas, significant scoliosis, spinal stenosis due to bony abnormalities, tethered cord and multiple meningiomas [24–28]. It was observed in a few cases that even substantial spinal cord lymphangiolipoma infiltration and adipose tissue invasion of the vertebral column had not resulted in any neurological deficit [29, 30].

Scoliosis is a common complication in Proteus syndrome, however only 5-10% of patients with scoliosis would suffer from neurological deficit. Interestingly, tumor's presence was associated with progressive scoliosis twice (White et al. [27] and Whitley et al. [29]). Therefore it was recommended by White et al. that all scoliosis cases should be examined for the presence of any serious findings.

Hemimegalencephaly

We have reviewed sixteen cases of HME in PS in the published literature. In the cases with described neurological status, HME was associated with epilepsy in 8 out of 10 cases. Other cases of hemimegalencephaly did not include information on neurological status.

In 62% of cases HME was associated with mental retardation, a fact noted previously by Cohen et al. [23]. This association has been observed in non-PS cases as well [30].

Other neurological complications

The number of CNS lesions described in MRI and CT examinations are included in the table II. Even though diagnostic criteria consist of vascular malformations, they were not as common as could be expected in neurological clinical settings. However, another complication related to blood supply was observed which is dural sinus thrombosis. No relation to possible causative factors has been found in the case reported by Dietrich et al. [1]. In the patient reported by Dandine et al. [31] hypercoagulopathy was present. This fact is important to remember because the most common complication and a cause of premature deaths of PS patients is deep venous thrombosis, a condition which often coexists with dural sinus thrombosis.

Neoplasms are another pathological features of PS. Lipomas are the most common type and they can occur in brain [20] or spinal cord [33] as well. The most common central nervous system tumors in Proteus syndrome are meningiomas. They have been described in four cases, often coexisting with tumors in various locations [33].

Noteworthy, in the reviewed literature we found five cases of cerebellar anomalies [20, 24, 33, 34, 35]. Abnormal cerebellum co-existed with headache and hand tremor in two cases [33, 34]. In one case, an overgrowth of frontal sinus is believed to cause increased intracranial pressure in an adult man [31]. Symptoms were relieved completely by the craniotomy. Finally, abnormal muscle tone, both hypotonia and hypertonia, were observed [15, 18].

Table II. Neurological findings (excluding spinal cord compromise cases) and their prevalence in neurological patients with Proteus syndrome. [1,15-20,22-23,25,31-49]. *Lista objawów neurologicznych oraz częstość ich występowania wśród pacjentów z zespołem Proteus i objawami neurologicznymi (z wyłączeniem przypadków z objawami ucisku rdzenia kręgowego). [1,15-20,22-23,25,31-49].*

Neurological finding	Number of cases identified	Number of cases assessed	Percentage
Developmental delay:	16	21	76%
Epilepsy:	11	17	65%
Hemimegalencephaly:	16	30	53%
Abnormal cerebral cortex:	15	30	50%
Dilated ventricles:	9	30	30%
Macrocrania	7	32	22%
Abnormal vasculature:	6	30	20%
Abnormal white matter	6	30	20%
Headache:	3	17	18%
Cerebellar malformations:	5	30	17%
Cysts, various:	5	30	17%
Meningiomas:	4	30	14%
Hydrocephalus:	4	30	13%
Pachygyria:	4	30	13%
Visual problems:	2	17	12%
Limb tremor:	2	17	12%
Increased arachnoid space:	3	30	10%
Brain lipoma:	3	30	10%
Polimycrogyria:	3	30	10%
Cortical atrophy:	2	30	7%
Megalencephaly:	2	30	7%
Thin corpus callosum:	2	30	7%
Cerebellar tonsillar herniation:	2	30	7%
Lissencephaly:	2	30	7%
Thicker cortex:	2	30	7%
Macrogyria:	2	30	7%
Decreased sulcation:	2	30	7%
Sinus thrombosis:	2	32	6%
Hearing loss:	1	17	6%
Facial palsy:	1	17	6%
Hipotonia:	1	17	6%
Hipertonia:	1	17	6%
Hyperreflexia:	1	17	6%
Schizencephaly:	1	30	3%
Calcifications:	1	30	3%

Neurological finding	Number of cases identified	Number of cases assessed	Percentage
Subependymal nodules:	1	30	3%
Subdural hematoma:	1	30	3%
Cortical dysplasia:	1	30	3%
Abnormal grey-white matter differentiation:	1	30	3%
Hypodense area:	1	30	3%
Periventricular leukomalacia:	1	30	3%
Periventricular astrogliosis:	1	30	3%

Cysts in various locations, calcifications, hypoplastic white matter, lissencephaly, pachygyria, polimycrogyria seem to occur rather sporadically.

AVAILABLE TREATMENT

Antiepileptic treatment

In most of the reviewed cases antileptic drugs were unsuccessful in limitation of seizures. The onset of epilepsy in infancy was associated with drug-resistance and further deterioration of neurological status.

Neurosurgical treatment

Obviously, there are two abnormalities in which neurosurgery might be the curing option- epilepsy associated with hemimegalencephaly and spinal cord compression.

Hemispherectomy has not only proven to be effective in controlling medically intractable epilepsy but may result in better mental development [50]. It has been shown that children who underwent this surgery had significantly higher postoperative developmental quotient even in a long term follow-up [51].

Spinal cord decompression may result in a complete recovery as in the case described by White et al. [27] when the symptoms were noticed early and the procedure was performed promptly.

Rapamycin (Sirolimus)

Rapamycin is a chemical drug that inhibits the mTOR pathway. Marsh et al. [52] has reported a case of a child with clinical diagnosis of Proteus syndrome who underwent rapamycin treatment with great success. The boy was fed by a nasogastric tube, was unable to sit and had respiratory difficulty partially due to the progressive enlargement of soft--tissue masses. The treatment resulted in their reduction and an improvement in patient's functioning- he started to eat and was able to walk independently.

Use of prophylaxis heparin

In order to prevent thrombosis, warfarin or heparin may be considered. However, there is currently no clear indication for life-long treatment [53]. Each patient should be evaluated independently.

CHALLENGES IN THE MANAGEMENT OF PROTEUS SYNDROME

Proteus syndrome is a complex disorder with many distinct manifestations. A patient with this rare disorder may be referred to nearly any specialist. However since 40% of patients with PS have CNS complications, sometimes before the development of other manifestations probability that the neurologist will become a leading doctor is high.

The knowledge about the existing diagnostic criteria is essential for proper diagnosis and management. According to the study of Turner et al. roughly two fifths of 200 cases published by 2004 did not meet diagnostic criteria and just under a half were ‚real' PS cases. This is the proof that clinical diagnosis of PS might be challenging. In some cases the use of genetic testing of biopsied affected tissues for the c.49G > A (p.Glu17Lys) mutation in AKT1 may be useful [54]. However, positive genetic test is not always positive and should not replace thorough clinical examination.

The other challenge represents a lack of any recommendations concerning neurological examinations and neuroimaging studies. It may be partially caused by superficial descriptions of neurological status in the publications, even in the patients with evident mental retardation. In order to provide PS patients with the best care further research on epilepsy management is also required.

CONCLUSION

We hope that this review will promote further discussion on the management of patients with neurological complications of Proteus syndrome.

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