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Phelan-McDermid syndrome and seizures provoked by fever — clinical and electroencephalographic comparisons of two patients

Napady prowokowane gorączką w zespole Phelan-McDermid — porównanie elektroencefalograficzne i kliniczne dwóch pacjentów z tym zespołem

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ABSTRACT

Phelan-McDermid Syndrome (PMS) is a rare genetic disorder mainly characterized by neuropsychiatric problems such as global developmental delay, intellectual disability, delayed or absent speech, and autistic features resulting from chromosome 22q13.3 deletion. Neurologic problems include seizures, which occur in 17–70% of cases. The lack of data on the characteristic seizure type, specific electroencephalography patterns, and changes thereof over time in PMS make the diagnosis of epilepsy challenging. Here we describe two patients with a confirmed genetic diagnosis of PMS who presented similar types of seizure semiology provoked only by fever. In both cases the seizures occurred infrequently; in patient 1 (a 7.5-year-old boy) there was a single episode and in patient 2 (an 11-year-old girl), there were a few recurrent episodes during fever. Seizures were easily controlled pharmacologically in the girl while the boy did not require any anticonvulsant drugs. In summary, although there is a variety of seizure types in PMS, in some patients seizures are provoked by fever, rarely occur, and respond well to or do not require antiepileptic treatment.

Keywords: 22q13.3 deletion, seizure, fever, benign course, Phelan-McDermid syndrome

STRESZCZENIE

Zespół Phelan-McDermid to rzadka genetycznie uwarunkowana choroba wynikająca z delecji fragmentu 13.3 ramienia q chromosomu 22, którą charakteryzuje występowanie globalnego opóźnienia w rozwoju psychoruchowym, niepełnosprawność intelektualna, opóźnienie lub brak rozwoju mowy oraz cechy autystyczne. Do manifestacji neurologicznych tego zespołu należą napady padaczkowe, które występują u 17–70% pacjentów. Jednak rozpoznanie padaczki u dzieci z delecją 22q13.3 stanowi wyzwanie diagnostyczne co wynika z niewielkiej ilości danych dotyczących charakterystycznego typu napadów padaczkowych oraz wzorców EEG w tym zespole. Dlatego też poniżej przedstawiamy dwoje pacjentów (7,5-letniego chłopca oraz 11-letnią dziewczynkę) z zespołem Phelan-McDermid oraz zbliżoną semiologią napadów padaczkowych. U obojga pacjentów napady występowały rzadko, były prowokowane gorączką, dobrze odpowiadały na leki przeciwnapadowe.

Słowa kluczowe: delecja 22q13.3, napady, gorączka, łagodny przebieg, zespół Phelan-McDermid

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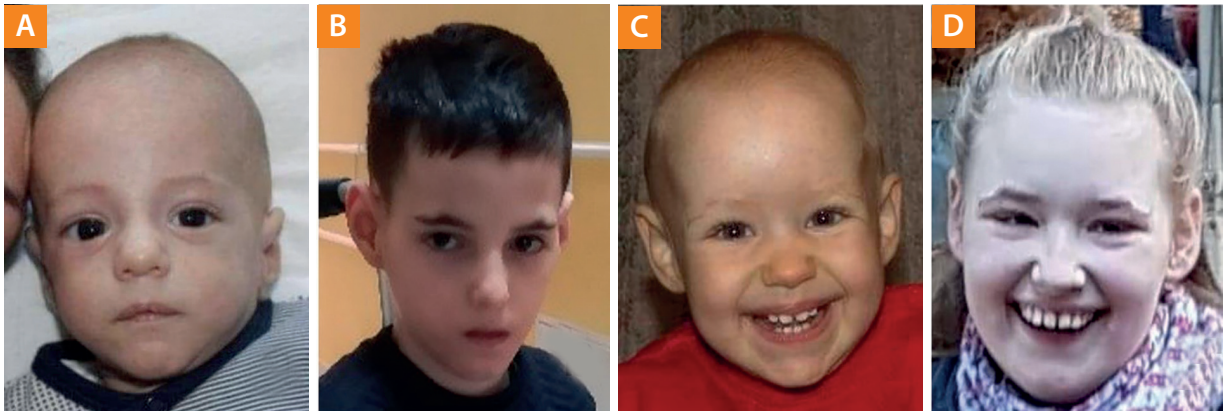

Figure 1. Facial dysmorphic features of patient number 1 and patient number 2. **A, B.** Patient number 1 in infancy and now; **C, D.** Patient number 2 in infancy and now

Rycina 1. *Cechy dysmorfii twarzy u pacjenta numer 1 i 2.* ***A, B.*** *Pacjent 1 w okresie niemowlęctwa i obecnie;* ***C, D.*** *Pacjent 2 w okresie niemowlęctwa i obecnie*

INTRODUCTION

Phelan-McDermid syndrome (PMS) is a rare genetic disorder resulting from the deletion of chromosome 22q13.3 and loss of the *SHANK3* gene. The SHANK 3 gene encodes a postsynaptic structural protein that plays an important role in signal transduction at glutamatergic synapses [1]. *SHANK3* gene defects are responsible for a variety of neuropsychiatric and neurologic problems in PMS patients including neonatal hypotonia, global developmental delay, and moderate-to-profound intellectual disability as well as seizures [1], which are observed in 17–70% of cases [2]. The spectrum of seizure semiology is broad, encompassing generalized tonic–clonic, focal, and absence types. Seizures can be provoked by fever but may occur without an increase in body temperature. There is little information about specific seizure types in patients with PMS, although it was reported that atypical absence seizures are most common [3].

Abnormalities in electroencephalography (EEG) recordings are observed in up to 70% of patients with PMS [4]. Most studies have not reported any typical EEG findings except for one that found multifocal paroxysmal abnormalities in the frontal-central or -temporal regions with clear sleep activation [5]. Behavioral symptoms of the syndrome include autism-like behavior with impaired communication, reduced social interaction, poor eye contact, unusual sensory interests, and sleep disturbances. Dysmorphic features are subtle and change with age; the most common are deep-set eyes, full cheeks, puffy eyelids, long eyelashes, bulbous nose, large and fleshy hands, and dysplastic toenails [2].

As neither the neurologic nor dysmorphic features are specific to PMS, the prevalence of this syndrome is likely underestimated. To date, there is a lack of data on the typical semiology of seizures, EEG patterns, and effectiveness of antiepileptic treatments in PMS. Here we present two cases, including a 7.5-year-old boy with a single seizure during febrile infection and an 11-year-old girl with recurrent seizures provoked by fever.

MATERIAL AND METHODS

Patient 1

The first patient was a 7.5-year-old boy born preterm at 35 weeks by cesarean section because of acute fetal distress, with a birth weight of 1020 g and 1-, 3-, and 5-min Apgar scores of 1, 6, and 7, respectively. After birth, he presented mildly dysmorphic features (prominent nose; dysplastic and asymmetric ears; and micrognathia) and required intensive care for respiratory failure and sepsis. The parents had no history of mental disorders or heritable diseases.

Genetic test

Given the presence of dysmorphic features we performed a karyotype analysis, which revealed 46,XY and *de novo* terminal deletion (del [22] [pter->q13.31]) of 22q13.31.

Physical examination and additional tests

Psychomotor development was severely delayed, and the patient is unable to sit unaided, walk, speak, and does not make eye contact. A physical examination at the age of 7 years showed microcephaly (with a cranial circumference of 47.5 cm, which is significantly below the 3rd percentile), plagiocephaly, low-seated ears, and cachexia (Fig. 1a, b). A neurologic examination revealed increased muscle tone in the lower limbs, hypotonia in the central axis, involuntary movements of upper and lower limbs and trunk, generalized brisk tendon reflexes, and an absence of pathologic symptoms. The evaluation of cranial nerves was normal, but the assessment of cerebellar functions was impossible due to a lack of cooperation. Neuropsychological testing at 6 years old indicated severe intellectual disability: the total Developmental Quotient was 16 (psychomotor de-

velopment was evaluated using the Brunet–Lezine Scale of Psychomotor Development).

Types of seizure

The patient had an episode at the age of 3.5 years that consisted of a lack of reaction (no response to his parents' voices), apnea, cyanosis, and left-sided nystagmus during a febrile infection (body temperature of 38.7°C). The episode lasted 15 min and afterwards, the patient was sleepy for a few hours. To our knowledge, this was the first and only episode of a complex febrile seizure in that patient. At the age of 6 years, his parents observed upper limbs movements resembling myoclonus starting from about 20 min after the patient fell asleep and occurring several times during the night.

Magnetic resonance imaging examination

Brain MRI performed at the age of 3.5 years showed a dilated ventricular system, cisterna magna cerebri, and cisterna pontis as well as corpus callosum thinning (Fig. 2a–c).

EEG examination

Because of diagnostic uncertainty regarding the nature of myoclonus (epileptic vs nonepileptic) presented by the patient, EEG recordings (also long-term video recording) were repeated several times, but myoclonus was not recorded.

All EEGs were abnormal. The background activity was poorly organized and too slow relative to the age standard. The epileptiform discharges (complexes of sharp and slow waves, spikes with slow waves, and spikes with sharp and slow waves) were localized bilaterally, predominantly in temporal and occipital regions of the left hemisphere. Changes in EEG morphology during sleep were similar to those registered during activity. Photostimulation did not stimulate EEG activity.

Treatment

At 3.5 years of age, the patient started treatment with valproic acid (VPA). The patient came to our attention at the age of 6 years and levetiracetam (LEV) was additionally administered based on suspicion of the epileptic character of the myoclonus. Myoclonus temporarily reduced the frequency of episodes although they occurred regardless of VPA and LEV treatment. Increasing the antiseizure medication (ASM) dosage had no effect. VPA was discontinued when the patient was 7 years old while LEV was continued and oxcarbazepine (OXC) was initiated based on suspicion of the focal character of the myoclonus. The parents reported dominance of one side of the body during myoclonus. As there was no improvement in the number of myoclonus episodes after 4 months of LEV + OXC treatment, LEV was

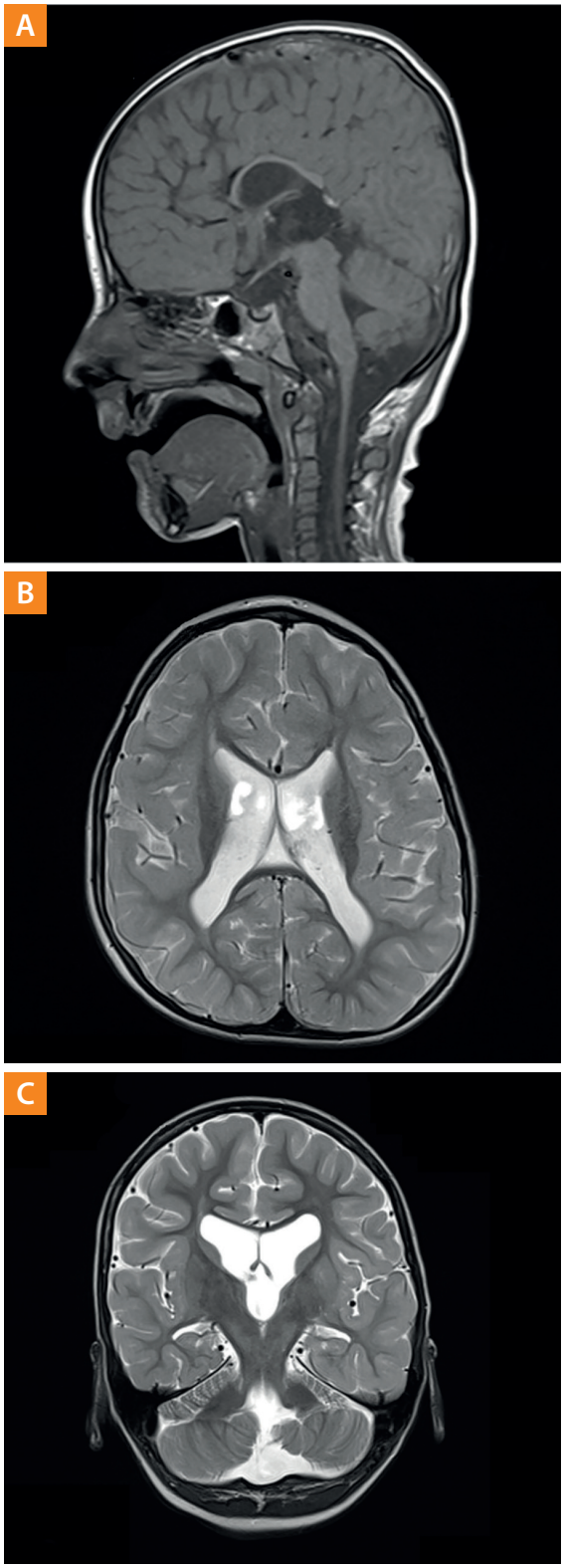

Figure 2. Brain MRI (patient number 1) showed dilatated ventricular system, dilatated cisterna magna cerebri and cisterna pontis, corpus callosum thinning **A.** Sequences T1 saggital plane, **B.** Sequences T2 transverse plane; **C.** T2 coronal plane

Rycina 2. *Rezonans magnetyczny mózgowia (pacjent numer 1) — poszerzony układ komorowy, poszerzony zbiornik wielki mózgu i zbiornik mostu, ścieńczenie ciała modzelowatego.* ***A.*** *T1 płaszczyzna strzałkowa,* ***B.*** *T2 płaszczyzna poprzeczna,* ***C.*** *T2 płaszczyzna wieńcowa*

stopped and the dosage of OXC was gradually reduced. Discontinuation of the drugs had no effect on the development and functioning of the patient, and there was no recurrence of focal seizures or change in the number of myoclonus episodes. It is likely that the myoclonus reported by the parents was nonepileptic (i.e., sleep myoclonus).

Patient 2

The second patient was an 11-year-old girl born by cesarean section because of breech presentation. She was born at term and her birth weight was 2140 g (below the 3rd percentile), with an Apgar score of 9 points. Jaundice (requiring phototherapy) and transient neonatal breathing disorder were present at birth. At the age of 1 year she underwent surgery because of patent ductus arteriosus (with placement of an Amplatzer plug), and at present she does not require any cardiologic treatment. There was no family history of intellectual disability, epilepsy, or genetic disorders.

Genetic test

Because of delayed psychomotor development and subtle dysmorphic features such as pointed chin and bulbous nose, karyotyping and molecular testing [multiplex ligation-dependent probe amplification (MLPA) with P297 probe mix (MRC Holland, Amsterdam, The Netherlands)] were carried out. The karyotype was normal (46,XX) and MLPA revealed de novo microdeletion in 22q13.3. The patient was diagnosed with PMS at 6 years of age.

Physical examination and additional tests

The patient showed delayed psychomotor development, sitting unaided at 12 months and starting to walk at 23 months. Severe language impairment was also present: her first words were produced at the age of 2 years, and her expressive language skills regressed thereafter until they were completely lost. Neuropsychological testing at 6 years showed severe intellectual disability: the total Developmental Quotient was 30 (psychomotor development was evaluated with the Brunet–Lezine Scale of Psychomotor Development). The hearing test was normal. The patient presented with aggression, oppositional behavior, and autistic-like features (eg, reduced social interaction, playing alone, resistance to changes, and repetitive activities such as switching the light on/off). A physical examination at the age of 11 years revealed a cranial circumference of 52.5 cm (between the 10th and 25th percentiles), normal weight and height, convergent strabismus of the right eye, long eyelashes, bulbous nose, full cheeks, pointed chin, and malocclusion (Fig. 1c, d). The patient is able to walk with little assistance and she uses a few words but does not understand instructions. Otherwise, we did not find other abnormalities in a neurologic examination.

Types of seizure

The patient presented with an episode of lack of reaction (no response to her parents' voices) and an initial decrease in muscle tone with apnea and cyanosis followed by a tonic increase in muscle tone. The first seizure was observed at the age of 2 years during febrile illness. Seizures lasting up to 2 min recurred once with almost every infection with fever until the patient was in her 8th year of life, when AED treatment was initiated.

MRI examination

At the age of 5 years, the patient's brain MRI revealed a dilated cisterna magna and 10-mm arachnoid cyst in the posterior fossa of the cranium.

EEG examination

First and second EEG examinations (before treatment) performed at 2 and 4 years of age, respectively, while the patient was awake or sleeping were normal. The third EEG (during LEV therapy) performed at 11 years was abnormal. Activity was localized in the parieto-occipital and temporal regions of the left hemisphere as single and groups of slow theta waves, sharp waves, and complexes of sharp and slow waves with an amplitude higher than background that moved to the opposite side. The background activity showed normal organization and consisted of a theta rhythm in the parietal and occipital regions. Hyperventilation and photostimulation did not stimulate EEG activity.

Treatment

VPA treatment was initiated at the age of 8 years (6 years after the first seizure) because of an increase in seizure frequency, but was stopped after a few months because of weight gain. At the age of 9 years, LEV treatment was started and there have been no seizure episodes since. The patient came to our attention at the age of 11 years.

DISCUSSION

PMS results from the de novo deletion of chromosome 22 in 80–85% of patients. Neurologic and psychiatric symptoms are mainly attributable to the loss of one copy of the *SHANK3* gene, but 90 other deleted genes may contribute to the heterogeneity of neurologic symptoms.

The first manifestation of PMS is severe neonatal hypotonia, which can contribute to feeding problems and delayed psychomotor development to varying degrees. The average age for rolling and sitting in these patients is 18 months and for walking, 27 months. While some patients remain nonambulatory, others present gait abnormalities including

steppage gait, toe walking, and broad-based ataxic gait [2, 3, 6]. Although neither of our patients presented hypotonia, motor milestones were severely delayed or absent in both: patient 1 is unable to walk, and patient 2 requires support when walking.

Deletion of 22q13 is one of the most common chromosomal defects associated with autism; it is estimated that up to 84% of children with PMS meet the criteria for autism spectrum disorders [7] both patients in our study presented autistic behaviors such as poor eye contact and reduced socialization, but these were more pronounced in the girl. The impairment of expressive and receptive language in PMS has been confirmed in many reports [2–5] but the degree of language ability varies from a complete absence of language to minor articulation difficulties. In PMS patients who acquire verbal language skills, regression can occur as observed as in our patient 2.

Patients with PMS exhibit many types of behavioral problems including hyperactivity, chewing of nonfood items, teeth grinding, tongue thrusting, and aggression. Behaviors specific to autistic patients include repetitive, stereotyped behaviors and hand mannerisms [7, 8]. Therefore, in these patients, distinguishing epileptic from nonepileptic episodes can be difficult even for an experienced pediatric neurologist.

The prevalence of seizures in PMS ranges from 17% to 70% [2, 3]. The spectrum of seizure semiology is broad. Patients may present febrile or afebrile and generalized tonic–clonic, focal, or absence seizures. Many attempts have been made to identify a characteristic type of seizure in PMS but with the exception of one study that reported atypical absence seizures as the most frequent type [3], the findings have been inconclusive. In another study, three out of six patients had epilepsy with myoclonic or generalized tonic–clonic seizures [5] Additionally, clinical seizures were reported in 13/32 (41%) patients with 22q13.3 deletion; of these, 7 (22%) had febrile seizures, 4 (13%) had nonfebrile seizures, and 2 (6%) had both types [7]. Among patients with nonfebrile seizures, 83% had generalized and 17% had focal seizures.

Although the age of seizure onset is highly variable, in some individuals they begin in infancy while in others, the onset is later (in childhood or even in adulthood), but the seizure frequency is typically highest around puberty [5]. The frequency of seizures increases with age [10]. Both of our patients had only febrile seizures (a single episode in patient 1 and recurrent episodes in patient 2), which started in early childhood (at the age of 3.5 and 2 years, respectively). During these episodes, the parents of both children reported a lack of reaction with apnea and cyanosis. Based on the parents' descriptions, the seizures were determined to be focal. The girl's seizures stopped after initiation of LEV treatment while discontinuation of ASM in the boy did not result in seizure recurrence. Because of a previous report of two patients with PMS presenting myoclonic seizures [5], we had problems in interpreting the character of myoclonus in patient 1, and therefore repeated the EEG and administered three different ASM. We did not record any myoclonus during video EEG and observed no effects of the ASM on myoclonus reduction, and concluded that the myoclonus was nonepileptic and discontinued all ASM**.**

EEG abnormalities are present in nearly all patients with PMS. In one observational study, 75% of patients (12/16) had epileptiform abnormalities during overnight EEG as compared to 18.75% in routine EEG (4). EEG abnormalities have also been observed in individuals with PMS without epilepsy [4, 5]. In the above mentioned observational study, 75% of patients had epileptiform discharges but only about half were diagnosed with epilepsy [4]. The reported EEG changes included generalized slowing, multifocal slowing, absence or slowing of occipital dominant rhythm, focal spike and slow wave discharges, and generalized spike and slow wave discharges. To date, no specific patterns of EEG morphology or localization have been linked to 22q13.3 deletion syndrome [3, 4, 9], apart from one study in which all 6 patients with PMS showed multifocal paroxysmal abnormalities on EEG recordings predominantly over the fronto-temporal regions that were activated in sleep [5]. EEGs in our patients did not exhibit any characteristic changes. In patient 1 the background activity was poorly organized whereas in patient 2, the background activity was normal. In patient 1, epileptiform discharges were mainly bilateral with predominance in the left hemisphere and localization in temporal and occipital regions; in patient 2, they were localized in the left hemisphere and in the parietal and occipital regions.

Neuroimaging is used in the diagnosis of epilepsy. In one study, the most common MRI abnormalities reported in PMS were a thin or morphologically atypical corpus callosum (in 29% of participants) and deep white matter hyperintensities in T2-weighted imaging (in 24%) [3]. However, these abnormalities were not helpful for the diagnosis of epilepsy in PMS because they were observed in patients with as well as those without a history of seizures. Other frequent MRI findings in PMS were ventricular dilation [32% (19/59 patients)] and interventricular, cerebellar, or temporal sylvian arachnoid cysts [14% (8/59 patients)] [9]. Both of our patients showed posterior fossa malformation in the form of dilated cisterna magna, in line with a previous report of mega cisterna magna or cerebellar vermis hypoplasia in 8/10 patients with PMS [11].

Abnormalities of cortical development such as focal cortical dysplasia are a frequent cause of epilepsy. It was therefore suggested that cortical malformations cause epi-

leptic seizure in PMS although this seems unlikely as such malformations were not observed in that cohort, possibly because of the small number of participants (3 patients with epilepsy out of 15 with PMS) [12]. The diagnosis of epilepsy in PMS is made difficult by the lack of typical seizure semiology and EEG patterns and because episodes can mimic epileptic seizures. The antiseizure treatment is also problematic [5]. It was suggested that epilepsy associated with the 22q13.3 deletion is mild and easily controlled pharmacologically, but individuals with Lennox–Gastaut syndrome with intractable seizures have been described [3] and there was another report of a patient with difficult-to-treat late-onset epileptic spasms [13]. To date there is no information on whether certain anticonvulsant medications are more effective than others in these patients.

In summary, although PMS patients present with a variety of seizures types, in some the seizures are provoked by fever, occur rarely, and respond well to or do not require antiepileptic treatment. The strength of our study is that we presented two cases of PMS with similar seizure morphology and age of onset. However, a major limitation is that we examined only two patients with the 22q13.3 deletion and it is unclear whether they are representative of the whole population with this genetic abnormality. Further clinical and EEG studies on a larger sample are needed to determine whether PMS has a specific EEG pattern and seizure profile.

ARTICLE INFORMATION AND DECLARATIONS

Conflict of interest

The authors declare that there is no conflict of interest.

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