*diseases*

*Case Report*

# Phelan-McDermid Syndrome in a 4-Year-Old Girl: A Case Report

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## Abstract

Phelan-McDermid syndrome (PMS; OMIM #606232) is a rare genetic disorder caused by terminal or interstitial deletions involving chromosome 22q13 or by pathogenic variants in the *SHANK3* gene, which plays a critical role in synaptic function and neurodevelopment. PMS is characterized by marked clinical heterogeneity, with core manifestations including neonatal hypotonia, intellectual disability, severe speech impairment, epilepsy, and autism spectrum disorder. We report the case of a 4-year-old girl presenting with intellectual disability, severe speech delay, and craniofacial dysmorphism. Cytogenetic and molecular cytogenetic analyses identified a ring chromosome 22, with variation in *SHANK3* signal loss across tissues and retention of the 22q subtelomeric probe. This case highlights the importance of early genetic diagnosis for the timely identification of associated comorbidities and the initiation of multidisciplinary rehabilitation and developmental interventions, ultimately improving long-term functional outcomes and quality of life.

**Keywords:** Phelan-McDermid syndrome; 22q13 deletion syndrome; *SHANK3*; ring chromosome 22; case report

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## 1. Introduction

The widespread implementation of conventional cytogenetic testing and advanced molecular cytogenetic techniques into clinical practice has substantially improved the detection of chromosomal abnormalities and has played a pivotal role in the identification and characterization of novel genetic disorders. Phelan-McDermid syndrome (PMS) was named after the American medical geneticist Katy Phelan and the Canadian molecular geneticist Heather McDermid. In 1985, during cytogenetic evaluation of a 14-year-old adolescent presenting with profound intellectual disability, absent speech, and distinctive dysmorphic features, they identified a pericentric inversion of chromosome 22, thereby providing the first description of the disorder [1–3].

In the following years, additional reports described patients with autism spectrum disorder who predominantly harbored terminal deletions of the long arm of chromosome 22. Based on published evidence and their own investigations, Anderlid et al. in 2002 [4] defined the critical region associated with Phelan-McDermid syndrome as an approximately 100-kb interval within chromosome band 22q13.3 containing the *ACR*, *RABL2B*, and *SHANK3* genes [5,6]. Subsequent studies failed to demonstrate a direct contribution of *ACR* and *RABL2B* to the PMS phenotype [3], whereas *SHANK3* was identified as the principal disease-causing candidate gene underlying the syndrome [7].

The *SHANK3* gene encodes the scaffold protein Shank3, which is expressed in the brain, heart, kidneys, and several other tissues. Its most critical function, however, is in the central nervous system, where Shank3 serves as a key structural component of the postsynaptic density at excitatory glutamatergic synapses, particularly those containing N-methyl-D-aspartate (NMDA) receptors. Glutamate is the principal excitatory neurotransmitter in the central nervous system, and glutamatergic neurotransmission is essential for synaptic plasticity, neuronal network formation, learning, and memory. *SHANK3* expression begins during fetal development, underscoring its pivotal role in early neurodevelopment and synaptogenesis. Alterations in the structure, function or levels of the Shank3 protein disrupt synapse formation and maturation. In particular, *SHANK3* deficiency has been shown to reduce dendritic spine density in hippocampal and cerebellar neurons, resulting in impaired synaptic connectivity and contributing to the neurodevelopmental abnormalities characteristic of Phelan-McDermid syndrome [8]. Similar synaptic abnormalities have also been reported in other neurodevelopmental disorders, including Rett syndrome and tuberous sclerosis complex, although they arise through distinct molecular mechanisms [9].

Phelan-McDermid syndrome results from the loss of genetic material from the terminal region of the long arm of chromosome 22. In some patients, this alteration represents a “pure” deletion, defined as an isolated deletion of chromosome 22q13 with an otherwise normal chromosomal complement. In other cases, the deletion is associated with more complex chromosomal rearrangements involving additional losses or gains of genetic material on other chromosomes. Loss of the 22q13 region may also occur as a consequence of ring chromosome 22 formation. Ring chromosomes arise following breaks in both chromosomal arms and subsequent end-to-end fusion, typically resulting in the loss of terminal sequences from both the short and long arms. Approximately 75% of PMS cases are attributable to pure terminal deletions involving the distal portion of chromosome 22q13. The remaining cases include interstitial deletions, in which an internal segment of 22q13 is deleted while the terminal region of the chromosome remains intact [5,10,11].

Haploinsufficiency of *SHANK3* is widely recognized as the principal molecular mechanism underlying the neurological manifestations of PMS [7,12]. Nevertheless, the broad spectrum of genomic alterations affecting the 22q13 locus—including terminal and interstitial deletions, ring chromosome 22, unbalanced chromosomal rearrangements, and

pathogenic *SHANK3* sequence variants—accounts for the marked genetic heterogeneity of the syndrome and likely contributes to its substantial clinical variability.

The precise prevalence of Phelan-McDermid syndrome remains unknown. Current estimates suggest an incidence of approximately 2–10 cases per 1,000,000 live births. Deletions involving chromosome 22q13 occur with similar frequency in males and females. The underlying chromosomal abnormalities may arise de novo or be inherited from a parent carrying a balanced structural rearrangement [6]. To date, only a limited number of patients with Phelan-McDermid syndrome have been reported in Russia [13–15].

*Clinical Manifestations*

The clinical phenotype of Phelan-McDermid syndrome (PMS) is characterized by a constellation of distinctive dysmorphic features and neurodevelopmental abnormalities. Typical craniofacial characteristics include macrocephaly with a dolichocephalic skull configuration, midface hypoplasia, a pointed chin, prominent ears, and periorbital fullness. Other frequently observed physical findings include large, fleshy hands and hypoplastic or dysplastic toenails, which are considered among the most characteristic somatic features of the syndrome [16,17].

One of the cardinal manifestations of PMS is moderate-to-profound intellectual disability, reported in more than 95% of affected individuals [10,18,19].

Behavioral abnormalities represent another major component of the clinical phenotype. Patients commonly exhibit stereotypic movements, reduced or absent eye contact, severe speech impairment, and deficits in social interaction and communication [20,21]. Given the overlap of these manifestations with the core diagnostic features of autism spectrum disorder (ASD), careful differential diagnosis is required, particularly during early childhood when the clinical presentation may closely resemble nonsyndromic ASD.

In 2015, Richards et al. published a systematic review and meta-analysis examining the phenotypic characteristics of autism spectrum disorder (ASD) across a range of genetic and metabolic syndromes [22]. The authors reported that ASD is observed in approximately 18–33% of individuals with fragile X syndrome, 25–60% of those with tuberous sclerosis complex, 19–36% of patients with Prader–Willi syndrome, 50–81% of those with Angelman syndrome, 93% of individuals with Smith–Magenis syndrome, and 20–31% of patients with 22q11.2 deletion (DiGeorge) syndrome. In contrast, Phelan-McDermid syndrome is now recognized as being consistently associated with autism spectrum disorder, with ASD-related features representing a core component of its neurobehavioral phenotype [23].

The clinical manifestations of Phelan-McDermid syndrome evolve with age and may be broadly categorized according to developmental stage. During infancy, the predominant clinical feature is generalized hypotonia, frequently accompanied by a weak cry, feeding difficulties, and delayed motor development. Affected infants typically demonstrate delayed acquisition of major developmental milestones, including head control, rolling over, crawling, independent sitting, and walking, reflecting a global delay in psychomotor development [7].

The clinical course of neonatal hypotonia in Phelan-McDermid syndrome is variable and age-dependent. In some individuals, hypotonia persists throughout life, whereas in others it gradually improves. Less commonly, generalized hypotonia may evolve into dystonia or hypertonia during later childhood or adolescence. Hypotonia presenting in the neonatal period and persisting throughout the first months of life may represent the earliest—and occasionally the only—clinical indication for genetic testing aimed at identifying 22q13 deletion syndrome (Phelan-McDermid syndrome) [24].

During early childhood, severe speech and language impairment becomes increasingly evident, ranging from a markedly limited expressive vocabulary to complete absence of functional speech [25]. Epileptic seizures may occur in PMS [26]; however, nonepileptic paroxysmal events have also been reported [27], necessitating differential diagnosis.

As children grow older, the behavioral phenotype becomes more pronounced, with progressive manifestations of autism spectrum disorder, including hyperactivity, attention deficits, aggressive behavior, and self-injurious behaviors [18]. Neurological dysfunction affects both gross and fine motor skills, resulting in impaired coordination and reduced motor performance [7].

Core manifestations of autism spectrum disorder (ASD) in children with Phelan-McDermid syndrome include a diminished or absent response to their name, poor or absent eye contact, impaired comprehension and execution of simple instructions, and marked difficulties engaging in age-appropriate social interactions, reflecting profound deficits in social communication and reciprocal social behavior [12].

In many children with PMS, receptive language skills are relatively better preserved than expressive language abilities. Consequently, early intervention should focus on the development of both verbal and augmentative forms of communication. Depending on the child's developmental profile, sign language, augmentative and alternative communication (AAC) devices, speech-generating devices, touchscreen-based communication systems, and the Picture Exchange Communication System (PECS) may facilitate the acquisition of functional communication skills. Complementary interventions—including adapted physical activity, music therapy, and sensory integration therapy—may further enhance environmental engagement, improve self-awareness, and increase motivation for social communication.

Recurrent otitis media, particularly when accompanied by absent or severely limited expressive speech, may raise concern for concomitant hearing impairment. Such patients should undergo comprehensive evaluation by an otolaryngologist and pediatric audiologist, as persistent middle ear disease may ultimately require tympanostomy tube placement [28].

Ophthalmic abnormalities in Phelan-McDermid syndrome remain insufficiently characterized and are frequently underrecognized in routine clinical practice. According to clinical case series and international consensus recommendations, abnormalities of ocular alignment and eyelid position constitute part of the characteristic phenotypic spectrum of the disorder and may be evident from early childhood [29].

Furthermore, in patients with ring chromosome 22 or large deletions involving the long arm of chromosome 22, multiple genomic loci may be affected simultaneously, resulting in an overlapping phenotype that combines features of Phelan-McDermid syndrome and neurofibromatosis type 2 (NF2), whose causative gene is located more proximally at 22q12.2 [24,30].

The true prevalence of ophthalmic involvement in Phelan-McDermid syndrome is likely underestimated because of the profound cognitive impairment, limited communication abilities, and behavioral challenges commonly observed in affected individuals, limiting ophthalmologic exams—as well as the absence of standardized ophthalmologic screening protocols for this patient population [29].

## 2. Detailed Case Description

We report the clinical and genetic findings of a 4-year-old girl diagnosed with Phelan-McDermid syndrome caused by ring chromosome 22 associated with a deletion encompassing the SHANK3 gene. The patient's phenotype was characterized by distinctive dys-

morphic features, autism spectrum disorder with intellectual disability, and muscle dystonia. This case highlights the importance of early genetic evaluation and counseling in neonates presenting with dysmorphic features and generalized hypotonia, as these manifestations may represent the initial signs of an underlying genetic disorder. All clinical assessments and diagnostic procedures were conducted in accordance with current ethical standards.

A 4-year-old girl was referred to our clinic because of the absence of expressive speech and poor heat tolerance.

According to the medical history, she was born from her mother's second pregnancy, which was complicated by early gestational toxicosis, and was delivered at term by spontaneous vaginal delivery. Her birth weight was 3760 g and birth length was 51 cm. The perinatal course was uneventful, with Apgar scores of 8 and 9 at 1 and 5 min, respectively. She cried immediately after birth with a strong, vigorous cry and was breastfed within the first 24 h of life.

Physical examination during the neonatal period revealed mild generalized hypotonia, feeding difficulties, and craniofacial dysmorphism. Her head circumference at birth was 33 cm. Before discharge from the maternity hospital, she received routine neonatal immunizations against tuberculosis (BCG) and hepatitis B, and underwent the national newborn screening program for congenital hypothyroidism, cystic fibrosis, congenital adrenal hyperplasia, galactosemia, and phenylketonuria, all of which yielded normal results.

Vaccinations were administered only during the neonatal period in the maternity hospital, after which the parents declined further routine immunizations. The family history was notable for multiple cutaneous hemangiomas in the patient's mother. In addition, two children of the patient's paternal uncle had a history of psychomotor developmental delay, although no definitive diagnosis had been established at the time of evaluation. The father's relatives were advised to consult a clinical geneticist to determine whether further testing is warranted.

During the first month of life, the patient demonstrated poor postnatal weight gain, characterized by a flat growth trajectory. Consequently, breastfeeding was discontinued, and formula feeding was initiated at 2 months of age. Thereafter, weight gain was appropriate for age and sex.

Gross motor development was delayed. She achieved stable head control at 3.5 months and rolling over at 6 months. At 12 months of age, a routine developmental assessment revealed significant global developmental delay: she was unable to pull to stand independently, could stand and walk only with support and poor stability, and had no expressive speech. She was therefore referred for neurological evaluation and diagnosed with global developmental delay. Although neurorehabilitation was initiated, only modest clinical improvement was observed.

Subsequent developmental milestones remained substantially delayed: independent sitting was achieved at 14 months, crawling at 15 months, pulling to stand at 18 months, and independent walking at 2 years and 7 months.

Three episodes of transient loss of consciousness accompanied by generalized muscle hypotonia ("becoming limp") during febrile illness were documented at 15 months, 3 years and 2 months, and 3 years and 3 months of age. No further episodes have been documented since that time.

Owing to severe social communication deficits and aggressive behavior toward peers, the patient was not attending a preschool educational institution.

On physical examination at 4-year-old, the patient measured 110 cm in height (Z − score + 1.52 SD), weighed 20 kg, corresponding to a body mass index (BMI) of 16.7 kg/m$^2$, head circumference 52 cm (Z − score + 1.88 SD). Her general condition was satisfactory,

with appropriate nutritional status. Appetite was markedly selective. She was awake but exhibited poor social engagement and was minimally responsive during the examination. Eye contact was absent. Pupils were equal, round, and reactive to light.

Dysmorphic examination revealed deep-set eyes with long eyelashes, esotropia, epicanthal folds, bilateral ptosis, and periorbital edema. The skull was dolichocephalic, with a broad forehead and nasal bridge, a prominent nose, and a pointed chin. The neck was short. The auricles were low-set and dysplastic. The hands were large and fleshy, while the toenails demonstrated hypoplasia. Additional skeletal anomalies included bilateral syndactyly of the second and third toes and clinodactyly of the fifth finger of the left hand.

The skin was pale and dry, without rashes, café-au-lait macules, or areas of hypopigmentation. Prominent periorbital darkening and an accentuated superficial venous pattern over the anterior chest wall were noted. Subcutaneous fat distribution was normal. The oral mucosa was pink and moist. The mouth remained partially open at rest, with intermittent tongue protrusion. The tonsils were not enlarged. Widely spaced teeth and bruxism were observed. Nasal breathing was unobstructed, with no nasal discharge.

Musculoskeletal examination demonstrated a cone-shaped thorax with reduced anteroposterior diameter and thoracic kyphosis. The shoulders were elevated and protracted, with asymmetry of the shoulder girdle and waist triangles. Range of motion was restricted in both the elbow and knee joints, and genu valgum was present. The patient's gait was broad-based and unsteady, while muscle tone was reduced, with a tendency toward generalized hypotonia.

Pulmonary auscultation revealed normal vesicular breath sounds without adventitious sounds. The respiratory rate was 20 breaths/min. Cardiac examination demonstrated regular heart sounds with a systolic murmur best heard at the cardiac apex; the heart rate was 108 beats/min. The abdomen was mildly distended and hypotonic. An umbilical hernia was palpable, and the liver edge was palpable 1.5 cm below the right costal margin. Urination was normal. The patient had formed stools with a tendency toward chronic constipation.

At 4-year-old the patient demonstrated no apparent comprehension of spoken language and lacked purposeful, goal-directed behavior. Her behavioral profile was characterized by pronounced stereotypic and restrictive behaviors, including an intense fixation on a single animated film, insistence on following identical routes, ritualistic behaviors, and pica.

The patient was evaluated by a psychiatrist and diagnosed with autism spectrum disorder (ASD). The diagnosis was established in accordance with applicable clinical guidelines, with the support of the validated Autism Diagnostic Observation Schedule, Second Edition (ADOS-2).

Laboratory investigations revealed iron deficiency without anemia (latent iron deficiency) and vitamin D insufficiency. Serum biochemical parameters, including markers of hepatic, pancreatic, and thyroid function, were within normal limits. Electrocardiography showed no abnormalities. Transthoracic echocardiography demonstrated an aneurysm of the perimembranous interventricular septum without evidence of hemodynamic compromise. Renal ultrasonography revealed right-sided calyceal ectasia (caliectasis) and incomplete duplication of the right kidney. Abdominal ultrasonography showed no structural abnormalities of the gastrointestinal organs.

Electroencephalography (EEG) could not be performed because of the patient's severe behavioral disturbances and inability to cooperate with the examination. The examination was recommended to be performed under sedation; however, the parents declined.

Electroencephalography (EEG) and brain magnetic resonance imaging (MRI) are planned as part of the patient's future evaluation.

The child was referred for consultation with a clinical geneticist and underwent testing as recommended. Cytogenetic and molecular cytogenetic analyses were performed to detect chromosomal abnormalities.

Conventional karyotyping of peripheral blood lymphocytes using G-banding revealed an abnormal karyotype: 46,XX,r(22), indicating the presence of a ring chromosome 22.

To characterize the structure of the ring chromosome 22 and assess involvement of the *SHANK3* locus (22q13.3), molecular cytogenetic analysis by fluorescence in situ hybridization (FISH) was performed using probes targeting the *SHANK3* locus (22q13), the control locus *TBX1* (22q11.2), the centromeric region of chromosome 22 (D22Z1), the subtelomeric marker of the long arm at 22q13.33 (STDJ402G11A), the short arms of acrocentric chromosomes (Acro-P), and telomeric repeats (pan-tel). The analysis was performed on metaphase spreads and interphase nuclei from cultured skin fibroblasts, as well as on interphase nuclei from blood lymphocytes, urinary sediment, and buccal epithelium.

A locus-specific DNA probe, Kreatech KBI–40104 [DiGeorge *TBX1* (22q11)/*SHANK3* (22q13); Kreatech, the Netherlands], was used to assess the copy number of the *TBX1* (22q11.2) and *SHANK3* (22q13) loci. The subtelomeric DNA probe 22qter (Kreatech SubTelomere 22qter) was used to characterize the subtelomeric region of the long arm of chromosome 22. The Acro-P probe (MetaSystems, Germany) was used to detect the short arms of acrocentric chromosomes. The probes were selected based on their availability and were appropriate for the aims of the study.

Metaphase FISH analysis revealed the structure of the ring chromosome. In one series of metaphase spreads, ring chromosome 22 contained the centromeric region, the *TBX1* and *SHANK3* loci, and the subtelomeric region of the long arm (ish r(22) (Acro-P−, D22Z1+, TBX1+, SHANK3+, STDJ402G11A+)). Material from the short arms of acrocentric chromosomes was absent from the ring. In another series of metaphase spreads, ring chromosome 22 contained the *TBX1* locus and the subtelomeric region of the long arm but lacked the *SHANK3* locus (ish r(22) (TBX1+, SHANK3−, STDJ402G11A+)). Additional analysis using a pan-telomeric probe did not detect telomeric regions on ring chromosome 22 (r(22) (pan-tel−, Acro-P−, D22Z1+, STDJ402G11A+, pan-tel−)).

Interphase FISH analysis demonstrated the copy number of the loci. Among the 100 interphase nuclei examined from cultured skin fibroblasts, mosaicism in the copy number of *SHANK3* was identified: 79% of nuclei had one copy of *SHANK3* (SHANK3 × 1), and 21% had two copies (SHANK3 × 2). The copy numbers of *TBX1* and STDJ402G11A were two in all nuclei (TBX1 × 2, STDJ402G11A × 2). A single copy of *SHANK3* (SHANK3 × 1) was detected in all nuclei analyzed from blood lymphocytes (600 nuclei), urinary sediment (100 nuclei), and buccal epithelium (100 nuclei).

Cytogenetic and molecular cytogenetic (FISH) analyses identified a ring chromosome 22, with variation in *SHANK3* signal loss across tissues and retention of the 22q subtelomeric probe. The precise extent of the deletion cannot be determined without chromosomal microarray analysis, which was not performed because it was not technically available.

Interphase FISH (nuc ish) detected one copy of the *SHANK3* locus (SHANK3 × 1) in 79% of cultured skin fibroblast nuclei and two copies (SHANK3 × 2) in 21%. Importantly, interphase analysis allows the number of locus copies to be counted but does not determine which chromosome 22—normal or ring—carries a given signal. Therefore, the presence of two *SHANK3* signals in 21% of nuclei does not provide evidence of a normal karyotype. Both signals could be located on two normal chromosome 22 homologs or on a normal chromosome 22 and a ring chromosome retaining the *SHANK3* locus. The observed proportions of cell lines reflect mosaicism in the copy number of the *SHANK3* locus.

In addition, metaphase FISH (ish) showed that ring chromosome 22 contained the *SHANK3* locus (SHANK3+) in one series of metaphase spreads but lacked it (SHANK3−) in another. These findings are not contradictory because metaphase analysis characterizes the structure of an individual ring chromosome in a particular cell, rather than the proportion of such cells in the population. The detection of both *SHANK3*-positive and *SHANK3*-negative ring chromosomes reflects mitotic instability of ring chromosome 22. Ring chromosomes are prone to secondary rearrangements and segmental loss during cell division, resulting in cell lines with different ring structures.

Because metaphase FISH was performed only on cultured fibroblasts, a culture-related artifact cannot be ruled out. Nevertheless, detection of the *SHANK3* deletion by interphase FISH in all tissues examined—blood lymphocytes, urinary sediment cells, and buccal epithelial cells—supports a systemic loss rather than a culture-specific finding.

The most likely mechanism is postzygotic loss of *SHANK3* in progenitor cells, leading to the formation of mosaic cell lines. An alternative mechanism is instability of ring chromosome 22, with secondary loss of the distal segment, including *SHANK3*, in a subset of cells during mitotic divisions. These mechanisms are not mutually exclusive and may occur concurrently. Chromosomal microarray analysis or another high-resolution method is required to distinguish between them and determine the precise size of the deletion.

However, the combination of the karyotype, FISH analysis across different tissues, and the clinical presentation was considered sufficient to establish the diagnosis.

Karyotyping was performed in the proband's parents to assess their genetic status. The results were within the normal reference range.

These findings are consistent with previous reports indicating that most cases of Phelan-McDermid syndrome result from *de novo* genomic alterations [11].

The patient underwent an ophthalmologic examination. As with other assessments, evaluation was limited by her cognitive impairment. Convergent strabismus was observed, and cycloplegic retinoscopy revealed mild hyperopia. Fundoscopic examination of the macula revealed abnormalities that could not be further characterized without optical coherence tomography (OCT). Further evaluation is warranted given the risk of NF2-related disease. OCT has not yet been performed, and efforts are underway to arrange the examination. OCT has not yet been performed; efforts are underway to identify an opportunity to do so.

The patient was also evaluated by an audiologist. Tympanometry showed a type A curve, and otoacoustic emissions were present. Auditory brainstem response (ABR) testing could not be performed because of the patient's behavioral difficulties; it is planned for a future visit under sedation. The audiologist's impression was a developmental disorder with suspected hearing loss.

Following completion of the diagnostic work-up, the patient underwent reevaluation by a clinical geneticist and a multidisciplinary team. Based on the clinical history, physical examination, and the results of cytogenetic and molecular cytogenetic analyses, the following diagnosis was established:

Primary diagnosis: Phelan-McDermid syndrome: 46,XX,r(22) (p10q13.33), associated with autism spectrum disorder and intellectual disability.

Associated conditions: Iron deficiency without anemia (latent iron deficiency); vitamin D insufficiency; aneurysm of the perimembranous interventricular septum without hemodynamic significance; right renal caliectasis; incomplete duplication of the right kidney; mild hyperopia; esotropia; umbilical hernia; dental malocclusion; and unspecified connective tissue abnormalities.

Latent iron deficiency and vitamin D insufficiency were treated. The patient received a ferrous iron preparation at half the therapeutic dose for 3 months and a water-soluble vitamin D preparation at 2000 IU daily for 1 month, followed by laboratory monitoring.

Both deficiencies resolved during treatment. Long-term use of the water-soluble vitamin D preparation at 1000 IU daily was recommended.

An individualized multidisciplinary management plan was recommended with the primary goals of optimizing quality of life, preserving functional abilities, and minimizing the risk of long-term complications. The rehabilitation program included structured physical therapy, occupational therapy focused on fine motor skills, and intensive speech and communication interventions. In addition, the family was advised to avoid excessive heat exposure, prolonged sunlight exposure, and environmental factors that could increase the risk of skin injury, given the patient's impaired heat tolerance and reduced awareness of environmental hazards. Clinicians should also remain alert to complications associated with Phelan–McDermid syndrome (PMS).

During the reported follow-up period, the therapeutic management remained unchanged. No adverse or unanticipated events were reported.

The three reported episodes of loss of consciousness in the girl, accompanied by hypotonia during febrile illness, were analyzed in detail. In the absence of EEG confirmation, it is currently not possible to determine definitively whether these episodes are epileptic or nonepileptic. However, the clinical presentation—transient impairment of consciousness accompanied by muscle hypotonia and occurring only during febrile episodes—may be consistent with nonepileptic hypotonic collapse rather than epileptic seizures. This interpretation is based on the hypothesis that children with PMS may have baseline muscle hypotonia and autonomic nervous system dysfunction, including impaired sweating and a tendency to overheat, as described in the literature [ [24,31]]. Febrile seizures are a recognized cause of fever-associated loss of consciousness in young children and have also been reported in PMS [32]. They typically present with convulsive motor manifestations rather than isolated hypotonia. Therefore, the predominantly hypotonic, nonconvulsive nature of the episodes in this patient is more consistent with nonepileptic events than with febrile seizures.

However, epileptic seizures cannot be definitively ruled out without the results of EEG monitoring. The episodes warrant EEG monitoring during sleep or under sedation, which was planned for a future evaluation.

Given the high risk of neurofibromatosis type 2/schwannomatosis in individuals with ring chromosome 22 [11], annual detailed examinations by a dermatologist, ophthalmologist, audiologist, and neurologist were recommended. Brain MRI was recommended from the age of 10 years [33].

Some ring chromosome 22 structures may be substantially more complex than can be detected by conventional karyotyping or fluorescence in situ hybridization. Therefore, chromosomal microarray analysis is recommended in these patients [11]. This analysis is planned for the patient at a later stage.

For clarity, the main events in the patient's clinical course—from the neonatal period to the diagnosis and development of the management plan at 4 years of age—are summarized chronologically in Table 1.

**Table 1.** Timeline of the patient's clinical course, diagnostic evaluation, and management.

| Age/Time | Clinical Events and Findings | Diagnostic and Therapeutic Interventions or Outcomes |
|---|---|---|
| Pregnancy | Second pregnancy, complicated by early gestational toxicosis | — |
| Birth | Term spontaneous vaginal delivery; birth weight 3760 g; birth length 51 cm; Apgar scores 8 and 9 at 1 and 5 min | Breastfeeding initiated within the first 24 h |

| | | |
|---|---|---|
| Neonatal period | Mild generalized hypotonia, feeding difficulties, and craniofacial dysmorphism; head circumference 33 cm | Newborn screening for congenital hypothyroidism, cystic fibrosis, congenital adrenal hyperplasia, galactosemia, and phenylketonuria was normal. BCG and hepatitis B vaccinations were administered |
| Day 3 of life | Neonatal jaundice | Phototherapy |
| Day 4 of life | Discharged from the maternity hospital | Follow-up by the primary care pediatrician; exclusive breastfeeding recommended |
| First month | Poor postnatal weight gain with a flat growth trajectory | Breastfeeding was subsequently discontinued |
| 2 months | — | Formula feeding initiated; subsequent weight gain was appropriate for age and sex |
| 3.5 months | Achieved stable head control at 3.5 months and rolling over at 6 months | — |
| 12 months | Marked global developmental delay; unable to pull to stand independently, stood and walked only with support and poor stability, and had no expressive speech | Neurological evaluation; global developmental delay diagnosed. Neurorehabilitation initiated, with modest clinical improvement reported |
| 14–18 months | Achieved independent sitting at 14 months, crawling at 15 months, and pulling to stand at 18 months | — |
| 15 months | Transient loss of consciousness with generalized hypotonia (“floppiness”) during a febrile illness | — |
| 2 years 7 months | Achieved independent walking | — |
| 3 years | Further episodes of transient loss of consciousness with generalized hypotonia during febrile illnesses | No further episodes were documented. At subsequent follow-up, a nonepileptic nature of the episodes was considered; EEG monitoring during sleep or under sedation was planned |
| 4 years | Referred because of absent expressive speech and poor heat tolerance. Examination showed dysmorphic features, generalized hypotonia, developmental delay, and behavioral abnormalities | Psychiatric assessment supported a diagnosis of autism spectrum disorder, with the Autism Diagnostic Observation Schedule, Second Edition (ADOS-2). Owing to behavioral difficulties, EEG and brain MRI under sedation were recommended. |
| | Laboratory and systemic evaluation | Iron deficiency without anemia and vitamin D insufficiency identified. ECG was normal; echocardiography showed an aneurysm of the perimembranous interventricular septum without hemodynamic compromise. Renal ultrasonography showed right-sided caliectasis and incomplete duplication of the right kidney; abdominal ultrasonography showed no structural gastrointestinal abnormalities |
| | Clinical genetic evaluation | Peripheral blood karyotyping showed 46,XX,r(22). FISH was performed in cultured skin fibroblasts, peripheral blood lymphocytes, urinary sediment cells, and buccal epithelial cells. The reported results showed a ring chromosome 22 with mosaic loss of *SHANK3*: one *SHANK3* signal was observed in all examined blood, urinary, and buccal cells and in 79% of skin fibroblast nuclei; 21% of fibroblast nuclei had two *SHANK3* signals. Chromosomal microarray analysis was unavailable and was planned for a later stage |

| | | |
|---|---|---|
| | Family genetic evaluation | Parental karyotypes were within the normal reference range. |
| | Ophthalmologic and audiological evaluation | Ophthalmologic examination showed convergent strabismus, mild hyperopia, optical coherence tomography was planned but had not yet been performed. Tympanometry showed a type A curve and otoacoustic emissions were present; auditory brainstem response testing under sedation was planned |
| | Diagnosis established after completion of the diagnostic work-up | Phelan–McDermid syndrome associated with 46,XX,r(22)(p10q13.33), autism spectrum disorder, and intellectual disability |
| After diagnosis | Iron deficiency without anemia and vitamin D insufficiency treated | Ferrous iron was given at half the therapeutic dose for 3 months; water-soluble vitamin D was given at 2000 IU/day for 1 month, followed by laboratory monitoring. Both deficiencies resolved; long-term vitamin D at 1000 IU/day was recommended |
| | Individualized multidisciplinary management plan recommended | Physical therapy, occupational therapy, and speech and communication interventions; advice to avoid excessive heat, prolonged sunlight exposure, and environmental hazards |
| Reported follow-up | — | Therapeutic management remained unchanged, and no adverse or unanticipated events were reported. Annual dermatological, ophthalmological, audiological, and neurological examinations were recommended; brain MRI was recommended from age 10 years |

## 3. Discussion

As discussed above, the clinical phenotype of Phelan-McDermid syndrome (PMS) is highly heterogeneous, with considerable interindividual variability in both the severity and spectrum of clinical manifestations. Table 2 summarizes the principal clinical features observed in our patient and compares them with their reported prevalence in individuals with PMS based on published data [29].

**Table 2.** Clinical features observed in the present patient compared with the reported frequency in individuals with Phelan-McDermid syndrome.

| Clinical Feature | Reported Prevalence in PMS | Present in the Patient |
|---|---|---|
| Neurodevelopmental features | | |
| Global developmental delay | Overwhelming majority | present |
| Autism spectrum disorder | Overwhelming majority | present |
| Epilepsy | 17–41% | indeterminate |
| Sleep disturbances | 25–75% | absent |
| Gastrointestinal disorders | | |
| Constipation/diarrhea | 19–84% | present |
| Gastroesophageal reflux | 42–59% | absent |
| Pica | >50% | present |
| Kidney and urinary tract disorders | | |
| Kidney and urinary tract abnormalities | 24–40% | present |
| Lymphedema | 1–23% | absent |
| Cardiovascular disorders | | |
| Congenital heart defects/anomalies | >25% | present |
| Endocrine disorders | | |

| | | |
|---|---|---|
| Short stature (<5th percentile) | up to 13% | absent |
| Tall stature (>96th percentile) | up to 31% | absent |
| Low birth weight (<2.5 kg) | up to 18% | absent |
| Hypothyroidism | 3–6% | absent |
| Precocious puberty | 12% | absent |
| Visual disorders | | |
| Ptosis | 3–57% | present |
| Strabismus | 6–29% | present |
| Hearing disorders | | |
| Hearing loss | ~3% | indeterminate |
| Respiratory disorders | | |
| Recurrent infections | up to 60% | absent |
| Cellulitis | 7% | absent |
| Musculoskeletal disorders | | |
| Joint hypermobility | Characteristic | absent |
| Pes planovalgus | Characteristic | absent |
| Skin and appendage disorders | | |
| Toenail dysplasia | Characteristic | present |
| «Café-au-lait spots» | Risk of neurofibromatosis type 2 | absent |

As shown in Table 2, the clinical manifestations observed in our patient are consistent with the phenotypic spectrum and frequencies reported in the published literature [16,17,26,34–36].

Phelan-McDermid syndrome is a multisystem disorder that may affect a wide range of organs and physiological systems. The remarkable phenotypic diversity and variability in disease severity are thought to reflect multiple genetic determinants, many of which remain the subject of ongoing investigation. Although several hundred patients with PMS have been reported in national cohorts from a number of countries, epidemiological data for the Russian population are currently unavailable [37].

Genetic testing for Phelan-McDermid syndrome is available in the Russian Federation; however, greater clinical awareness and broader implementation of genetic testing in children presenting with neonatal hypotonia, autism spectrum disorder, intellectual disability, or global developmental delay would likely lead to a substantial increase in the number of diagnosed cases. Early clinical recognition followed by molecular confirmation is essential for timely referral to multidisciplinary specialists, implementation of individualized rehabilitation programs, and appropriate long-term medical surveillance. Furthermore, improved case ascertainment and the establishment of larger patient cohorts would facilitate both natural history studies and the development of more effective targeted therapeutic strategies.

Given the molecular pathogenesis of the disorder, current therapeutic research is focused on interventions aimed at modulating neurotrophic signaling, enhancing synaptogenesis, and improving synaptic plasticity [38–40]. These approaches represent promising avenues for the development of disease-modifying therapies for Phelan-McDermid syndrome. In summary, expanding opportunities for the early diagnosis of Phelan-McDermid syndrome (PMS) creates a foundation for the development of personalized management strategies, including the future application of targeted molecular therapies, with the ultimate goal of improving long-term functional outcomes and quality of life. Once the diagnosis of PMS has been molecularly confirmed, patients should undergo a comprehensive multidisciplinary evaluation to identify syndrome-associated comorbidities and to establish an individualized long-term management plan. Ongoing follow-up should involve a multidisciplinary team that includes a pediatrician, clinical geneticist, neurologist,

child psychiatrist, ophthalmologist, otolaryngologist, and other specialists as indicated by the patient's clinical manifestations [24].

The absence of national clinical guidelines for Phelan-McDermid syndrome in the Russian Federation continues to hinder the organization of standardized patient care, coordinated long-term follow-up, and the timely implementation of therapeutic and rehabilitation interventions. Furthermore, although several standardized and well-validated instruments are available internationally for the assessment of intellectual functioning, cognitive performance, language development, and adaptive behavior, most have not yet undergone comprehensive cultural adaptation and psychometric validation for Russian-speaking populations. This limitation complicates both routine clinical assessment and the objective evaluation of treatment outcomes in affected children.

In conclusion, the diagnosis of Phelan-McDermid syndrome (PMS) may be challenging because of the limited clinical indications that currently prompt referral for genetic testing. Nevertheless, the presence of congenital hypotonia in combination with craniofacial dysmorphism should raise suspicion of an underlying chromosomal disorder, including Phelan-McDermid syndrome.

Owing to the absence of pathognomonic involvement of major organ systems, the marked phenotypic variability and nonspecific clinical presentation, and the lack of specific clinical or laboratory biomarkers, PMS frequently remains unrecognized in routine clinical practice. Consequently, its true prevalence is likely underestimated [12]. Conversely, early diagnosis followed by timely, individualized multidisciplinary intervention plays a pivotal role in improving functional outcomes, mitigating behavioral difficulties, and enhancing quality of life. Comprehensive management should therefore incorporate evidence-based recommendations addressing mental health, sensory processing dysfunction, and the development of communication, language, and speech skills, which constitute key components of long-term care for individuals with Phelan-McDermid syndrome [21,25,41].

Clinically significant findings frequently encountered by child psychiatrists, including impaired visual fixation, eye contact, and visual perception, should prompt a comprehensive ophthalmologic evaluation. These abnormalities may reflect not only ocular pathology but also dysfunction of the visual pathways and cortical visual processing networks. Such impairments may further compromise neurodevelopment, social interaction, and adaptive functioning. These observations underscore the importance of a comprehensive assessment of visual function in patients with Phelan-McDermid syndrome, incorporating both conventional ophthalmologic examination and evaluation of the neurodevelopmental mechanisms underlying visual perception [29,42].

Genetic counseling is an essential component of family management. In families with a child diagnosed with Phelan-McDermid syndrome, prenatal genetic testing should be considered in subsequent pregnancies. Such testing is recommended even when neither parent carries a detectable SHANK3 pathogenic variant, 22q13.3 deletion, or balanced chromosomal rearrangement, because of the residual recurrence risk associated with parental germline mosaicism [11].

## 4. Conclusions

In conclusion, although Phelan-McDermid syndrome is not typically associated with life-threatening organ dysfunction, it imposes a substantial long-term medical, psychological, educational, and socioeconomic burden on affected individuals and their families. Increasing awareness of PMS among healthcare professionals and caregivers is essential for facilitating earlier diagnosis, timely initiation of multidisciplinary medical, psychological, and educational interventions, and ultimately improving long-term functional outcomes, social participation, and quality of life for affected patients.

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## Abbreviations

| | |
|---|---|
| PMS | Phelan-McDermid syndrome |
| OMIM | Online Mendelian Inheritance in Man |
| del(22)(q13.3) | deletion of the long arm of chromosome 22 |
| SHANK3 | SH3 and multiple ankyrin repeat domains 3 |
| ACR | acrosin |
| RABL2B | member of RAS oncogene family like 2B |
| ASD | autism spectrum disorder |
| NF2 | neurofibromatosis type 2 |
| BMI | Body Mass Index |
| EEG | Electroencephalography |
| 46,XX,r(22) | female karyotype harboring a ring chromosome 22 |

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