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CASE REPORT

Phelan-McDermid syndrome: a case report and review of the literature

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ABSTRACT

Background: Phelan-McDermid syndrome (PMS) is a rare genetic condition caused by a heterozygous deletion in chromosome 22 in the 22q13 region or by a heterozygous pathogenic variant in SHANK3 gene. PMS is one of the important etiologies in children presenting mainly with intellectual delay, epilepsy, or autism spectrum disorder.

Case Presentation: We describe a case of a 9-year-old male with a nonspecific neurodevelopmental disorder characterized by early signs of autism noticed from the age of 2 years. During his infancy, the patient exhibited slow gains of his milestones. He was later diagnosed with PMS and speech and intellectual disability.

Conclusion: This study presented a novel case of a patient diagnosed with PMS in Saudi Arabia. Therefore, highlighting the clinical findings is essential to establish a common understanding of the disease. Patient education and awareness is a major part of the management plan since many families might require further explanation as they might need to deliver special education to their children affected by the syndrome. PMS is gaining great interest in research and patient awareness.

Keywords: SHANK3, autism, pediatrics, seizures, chromosomal abnormality, congenital anomaly.

Introduction

Phelan-McDermid syndrome (PMS) is a rare genetic condition which was initially described in the medical literature in 1985 (1). The group of clinical characteristics associated with the syndrome can be typically seen in a patient detected to have a heterozygous deletion in chromosome 22 in the 22q13 region or by a heterozygous pathogenic variant in a gene called *SHANK3* on molecular genetic testing (see Figure 1).

This gene mutation can occur in males and females equally. *SHANK* mutations are found in approximately 1% of the patients with autism spectrum disorder (ASD), with varying degrees of cognitive impairment. Mutations in *SHANK3* were found in 0.69% of the patients with ASD and up to 2.12% of the cases with moderate intellectual disability (2). The group of clinical findings can include neonatal hypotonia, absent to severely delayed speech, developmental delay, and minor dysmorphic facial features. Most affected individuals have moderate to profound intellectual disability. Other features include large fleshy hands, dysplastic toenails, and decreased perspiration that results in a tendency to overheat. Patients with PMS can be distinguished from others with autosomal chromosome disorder in normal head size and build of the body. Behavioral characteristics include mouthing or chewing nonfood items, decreased perception of pain, and autism spectrum disorder or autistic-like affect and behavior (3). These signs and symptoms can be mostly developed anywhere between the first 6 months of the gene carrier's life and until their early childhood. No clinical diagnostic criteria have been established for PMS. The diagnosis is based on genetic molecular testing (3). No specific treatment is currently available for PMS patients. Treatment currently addresses specific symptoms of each case individually and it is centered on screening and treating any associated abnormalities. Because the enamel can be destroyed by constant chewing, professional dental hygiene, routine brushing, and fluoride therapy are essential (3). Clinical trials are currently ongoing to reach a therapeutic option for the syndrome. The literature addressing the syndrome in Saudi Arabia is extremely limited and the present study aimed to bridge the current gap. Nevertheless, in this study, we presented a new novel case from Saudi Arabia.

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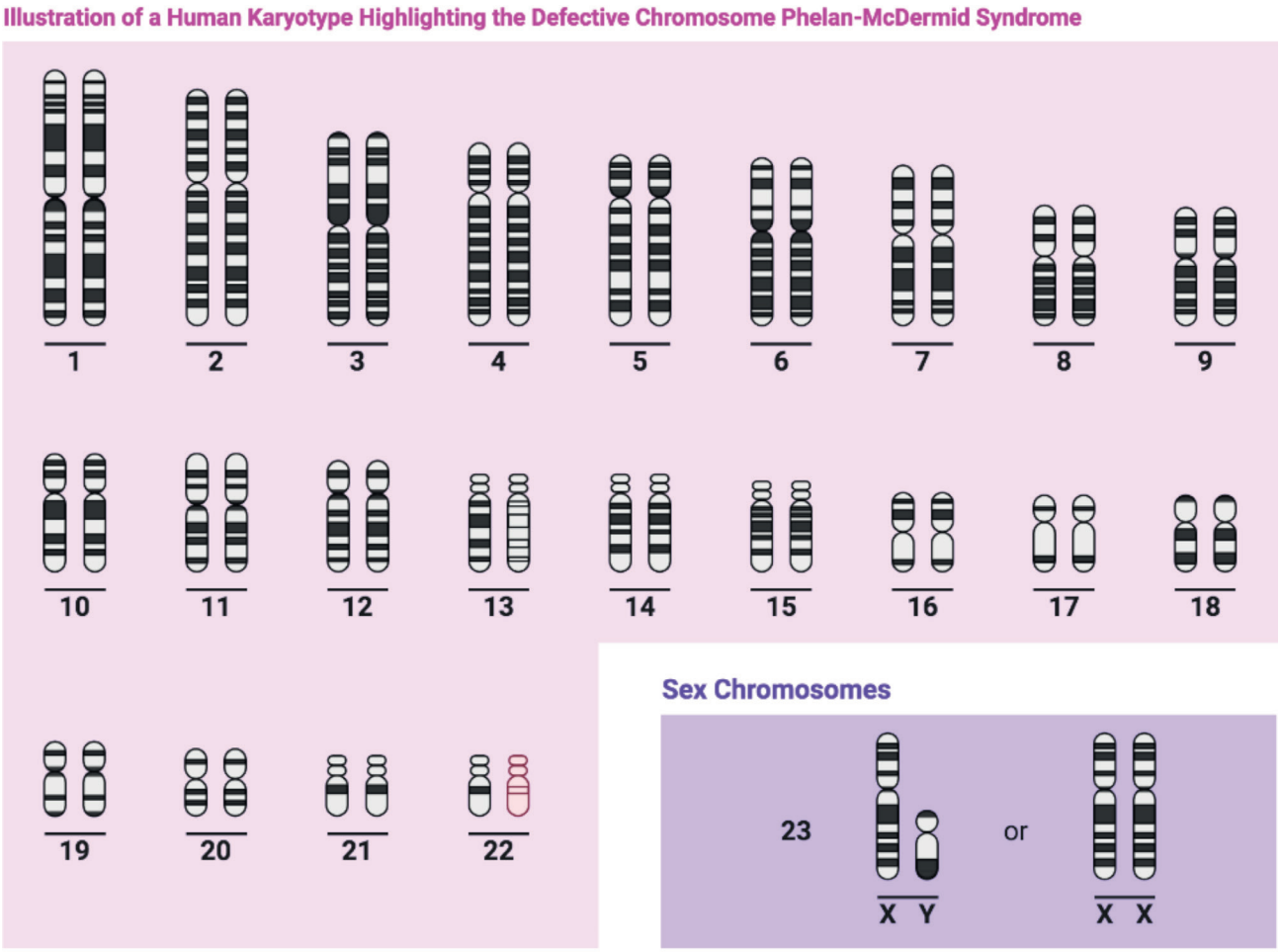

Figure 1. *Illustration of a human karyotype highlighting the defective chromosome of Phelan-McDermid syndrome.*

Case Presentation

In this study, we present a case of a 9-year-old Pakistani male with a nonspecific neurodevelopmental disorder characterized by early signs of autism noticed from the age of 2 years, cognitive delay, and generalized myoclonic and tonic seizures. Initially, the mother reported a normal pregnancy, uncomplicated delivery, and normal postnatal course. The infant was noticed to be floppy in the first 6 months of life, with slow gains of milestones. From his second to third year of life, it was noticed that he had minimum interaction with the surrounding and was diagnosed with ASD and speech and intellectual delay. At the age of 5 years, he started to have generalized tonic and myoclonic seizures and occasional head drops. His antiseizure medications included levetiracetam, valproic acid, and topiramate. His previous medications were clobazam and cannabinoids. There was no consanguinity in the patient's parents, and he had three healthy siblings. There was no history of abortions and no similar reported cases in the family. Upon physical examination, the child's growth parameters were within normal percentiles. He was poorly attentive and was not interactive. He had mild dysmorphic features like full brows and large or prominent ears (see Figure 2).

The upper and lower limbs were hypotonic. His power was 4 out of 5 and symmetric. Deep tendon reflexes were normal. Cranial nerve examination was normal, but the gait was unsteady. Electroencephalogram showed multiple independent spike waves. Ultrasound of the kidneys was normal. Echocardiogram was also normal. Magnetic resonance imaging brain was normal. Whole exome sequencing test outcomes included the carrying of a heterozygous pathogenic variant in the *SHANK3* gene, which was primarily associated with acquiring the syndrome's clinical manifestations as described in the literature. Hence, the diagnosis of PMS was made.

Discussion

Phelan-McDermid syndrome is a rare genetic condition characterized by intellectual and speech delay, autistic features, dysmorphic features, and seizures. Most cases are caused by 22q13 deletions encompassing many genes, including *SHANK3*. In this study, a thorough comparison of different reported cases carrying the same genetic mutation is presented in Table 1.

Upon searching the literature, 11 different cases were identified and their clinical profiles were obtained, organized, and analyzed; the mean age was 15 years (see Figure 3).

Clinical data2 acquisition focused primarily on the following aspects: the presence of any developmental

Figure 2. *The patient's clinical presentation showing dysmorphic features.*

delay, the appearance of dysmorphic features, whether the patient had or was still experiencing any muscle weakness, speech or expressive abnormalities, the presence of autism signs, or a diagnosis of autism spectrum disease, which is one of the earliest clinical symptoms in *SHANK3* alongside hypotonia (4). The analysis of each case yielded the following results: 81% of the cases experienced developmental delay. Görker et al. (5) reported mild developmental delay associated with neuromotor delay, while Karaman et al. (6) reported developmental and psychomotor delay. Dysmorphic features were present in 72% of the cases, which varied between different cases. Deibert et al. (7) reported general dysmorphic features, while others were more specified. For example, Johannessen et al.'s (8) case study included mild dysmorphic features that included full lips and protruding ears. Ujfalusi et al. (9) reported a case of two siblings of an 18-year-old female with sparse and fine hair, hypertelorism, down slanting palpebral fissures, strabismus, wide/high nasal bridge, low set ears, long philtrum, short neck, and small hands. Meanwhile, her 22-year-old male sibling had also manifested hypertelorism, down slanting palpebral fissures, strabismus, wide/high nasal bridge, long philtrum, and short neck. The similarity of the two cases can possibly be interoperated by their familial genetic inheritance. Ha et al. (10), on the other hand, reported very minimal features, which included esotropia and genu valgum, commonly known as "knock-knee". In children, genu valgum is a common orthopedic condition. The physiologic variants account for the vast majority of cases, which resolve normally. However, there are pathologic conditions linked with skeletal dysplasia that are caused by both focal and systemic mechanisms, and in which the deformity frequently worsens and requires therapy (11). In the same study, the authors also reported a second case of a 6-year-old female patient with jaundice, but it was attributed to physiological conditions, macrocephaly, lower limb abnormalities characterized by femoral anteversion and pronated feet, hyperopia and astigmatism. Muscular hypertonia was present in 36% of the cases (5-7,12). Speech abnormalities that ranged from absent speech, expressive and receptive speech delay, motor delay, severe articulation impairment, and hypernasality were reported in 27% of the cases (10,12,13). Autism, the diagnosis of ASD or autistic features, was present in 27% of the cases. Atypical ASD was reported in a single case (8) and symptoms of the autism spectrum like repetitive stimulating behavior were reported in another single case (12). Mental or psychiatric problems were observed in 45% of the cases which included object permanence, which is an important milestone in the brain development, psychotic alteration, bipolar disorder, and sleep disordered breathing (8-10,12,14). Cardiac and metabolic abnormalities were both equally present in 27% of the cases. Cardiac abnormalities included a single episode of supraventricular tachycardia at 280 beats/minute in one patient accompanied with very small residual patent ductus arteriosus (PDA) and patent foramen ovale (7). However, PDA was reported in another case included in the review. Furthermore, a case of moderate aortic root dilation was also reported (10). Impaired eye contact was reported in 18% of the cases (6,12). Multisystem abnormalities were also reported to approximately half of the cases (45%) and included lymphedema which was associated with the same patient who was reported with metabolic disorder (13). A nonfunctioning, multicystic, dysplastic left kidney, moderate to severe pelvocaliectasis, and hydronephrosis of the right kidney were all reported in a single patient (7). Other symptoms involved mild fever episodes (14). Secondary amenorrhea was reported in an 18-year-old female patient (9). Vesicoureteric reflux, Eustachian tube dysfunction, Chiari malformation type 1 and ventriculomegaly was reported in a 6-year-old female patient (10). Fever associated seizure was present in a 22-year-old male patient and with a percentage of 9% in this review (9). Ha et al. (10) reported in-toeing gait in their 4-year-old male patient. Finally, the inability to sit probably was found in 9% of the patients (6). Additionally, the present 9-year-old male patient was also represented in the same table and compared to the other findings. In regards to the present case, developmental delay presented alongside 81% of the cases, which exhibited the same condition. Dysmorphic features were present and manifested in the form of full brows and prominent ears, which was consistent with the findings of Johannessen et al. (8) and in 72% of the reported cases. Hypotonia was also present in the present case as well as for the 36% of cases. Speech and intellectual delay, which was reported in 27% of the cases, was present in the present patient. Our patient was diagnosed with ASD, which was characterized early in his life (2 years old) and was also present in 27% of the cases. Around the same age (2 years old), the present patient started to manifest

Table 1. *Clinical phenotype of patients with 22q13 mutation (including SHANK3 gene). The present case is also included for comparison. +/− shows the presence/absence of the symptom.*

Authors	Age	Sex	Genetic mutation	Developmental delay	Dysmorphic features	Hypotonia	Speech problems	Autism	Mental/ psychiatric problems	Cardiac abnormality	Metabolic disorder	Impaired eye-contact	Multisystem abnormality	Seizures	Abnormal gait	Sitting problem
Our case	9y	Male	N/A	+	+	+	+	+	+	−	−	−	−	+	+	−
Xia et al. (5)	20y	Female	*TRABD:c.39C>A, HDAC10:c.880G>A,* and *CELSR1:c.7061G>A*	+	−	−	+	−	−	−	+	−	+ (lymphedema)	−	−	−
Jesse et al. (6)	mid-twenties	Female	N/A	+	−	+	+	+	+	−	−	+	−	−	−	−
Deibert et al. (7)	33m	Female	N/A	−	+	+	−	−	−	+	−	−	+	−	−	−
Jungová et al. (8)	30y	Female	*chr22:51,122,321–51,176,567; HG19*	−	−	−	−	−	+	−	−	−	+ (fever episodes)	−	−	−
Johannessen et al. (9)	NA	Male	N/A	+	+	−	−	+	+	−	−	−	−	−	−	−
Ujfalusi et al. (10)	18y	Female	N/A	+	+	−	−	−	−	−	+	−	+ (amonorrhea)	−	−	−
Ujfalusi et al. (10)	22y	Male	N/A	+	+	−	−	−	+	−	+	−	−	+ (fever associated)	−	−
Ha et al. (11)	4y	Male	N/A	+	+	−	−	−	−	+	−	−	−	−	+	−
Ha et al. (11)	6y	Female	N/A	+ (mild)	+	−	+	−	+	+	−	−	+ (vesicoureteric reflux)	−	−	−
Görker et al. (12)	9y	Female	N/A	+ (mild with neuromotor delay)	+	+	−	−	−	−	−	−	−	−	−	−
Karaman et al. (13)	8m	Male	N/A	+ (with psychomotor delay)	+	+	−	+	−	−	−	+	−	−	−	+

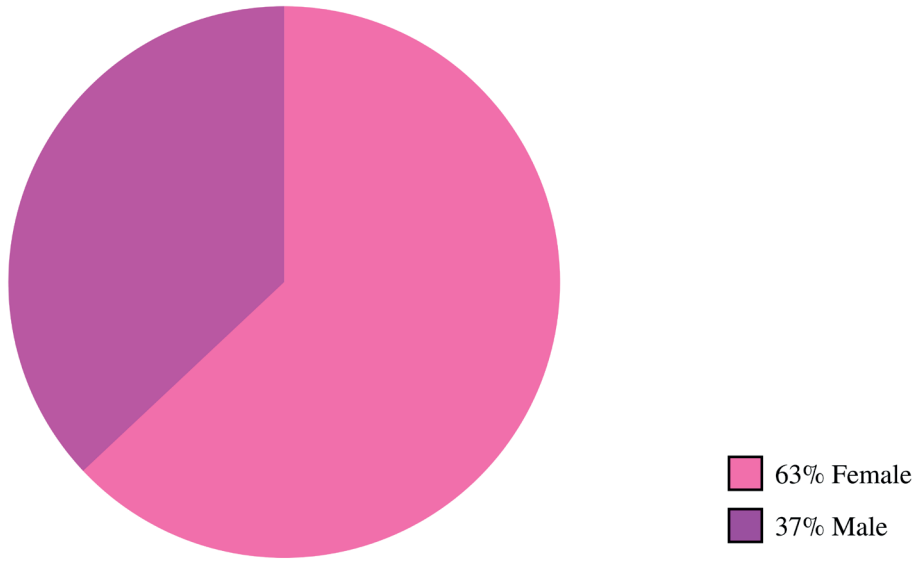

Figure 3. *Demographic characterization graph of the included patients from the literature review.*

generalized myoclonic and tonic seizures, which was consistence with 9% of the cases but had no fever association, as reported by Ujfalusi et al. (9). Unsteady gait was present in the present patient, similarly Ha et al. (10) reported an abnormal gait. Moreover, other findings like cardiac and renal involvement were not present in our case which can be explained by genetic heterogenicity. Furthermore, in regards to treating PMS syndrome, insulin-like growth factor 1 for its effect on social and aberrant behaviors, intranasal insulin for benefits in cognitive and social skills, and lithium for reversing regression and stabilizing behavior have all been explored in clinical trials investigating PMS treatments.

Conclusion

The current study presented a novel case of a patient diagnosed with Phelan-McDermid syndrome in Saudi Arabia. To the best of our knowledge, this is the first reported case of the syndrome in Saudi Arabia. Therefore, highlighting the clinical findings is essential to establish a common understanding of the disease. Patient awareness remains a major part of the management plan since many families might require further explanation to deliver a special education to their children affected by the syndrome.

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List of Abbreviations

ASD	Autism spectrum disorder
PDA	Patent ductus arteriosus
PMS	Phelan-McDermid syndrome

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The authors of this report have no affiliations with or involvement in any organization or entity with any financial interest or nonfinancial interest in the subject matter or materials discussed in this manuscript.

Consent for publication
Informed consent was obtained from the parents.

Ethical approval
Ethical approval is not required at our institution to publish an anonymous case report.

Authors' contributions
OM conceived and designed the study and wrote the manuscript. AA wrote the manuscript, conducted the statistical analysis and collected data.

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References

1. Watt JL, Olson IA, Johnston AW, Ross HS, Couzin DA, Stephen GS. A familial pericentric inversion of chromosome 22 with. J Med Genet. 1985;283-7. https://doi.org/10.1136/jmg.22.4.283

2. Leblond CS, Nava C, Polge A, Gauthier J, Huguet G, Lumbroso S, et al. Meta-analysis of SHANK Mutations in Autism Spectrum Disorders: A Gradient of Severity in Cognitive Impairments. PLoS Genet. 2014;10(9). https://doi.org/10.1371/journal.pgen.1004580

3. Phelan K, Rogers RC, Boccuto L. Phelan-McDermid Syndrome [Internet]. GeneReviews®. 1993. Available from: https://pubmed.ncbi.nlm.nih.gov/20301377/

4. Lutz AK, Pfaender S, Incearap B, Ioannidis V, Ottonelli I, Föhr KJ, et al. Autism-associated SHANK3 mutations impair maturation of neuromuscular junctions and striated muscles. Sci Transl Med. 2020;12(547). https://doi.org/10.1126/scitranslmed.aaz3267

5. Görker I, Gürkan H, Demir Ulusal S, Atli E, Ikbal Atli E. A 9-year-old-girl with Phelan McDermid Syndrome, who had been diagnosed with an autism spectrum disorder. Balk J Med Genet. 2016;19(2):85-90. https://doi.org/10.1515/bjmg-2016-0041

6. Karaman A, Aydin H, Geçkinli B GK. The deletion 22q13 syndrome: a new case. Genet Couns [Internet]. 2015;26(1):53-60. Available from: https://pubmed.ncbi.nlm.nih.gov/26043508/

7. Deibert E, Crenshaw M, Miller MS. A patient with Phelan-McDermid syndrome and dilation of the great vessels. Clin Case Reports. 2019;7(4):607-11. https://doi.org/10.1002/ccr3.2003

8. Johannessen M, Haugen IB, Bakken TL, Braaten Ø. A 22q13.33 duplication harbouring the SHANK3 gene: Does it cause neuropsychiatric disorders? BMJ Case Rep. 2019;12(11):1-5. https://doi.org/10.1136/bcr-2018-228258

9. Ujfalusi A, Nagy O, Bessenyei B, Lente G, Kantor I, Borbely AJ, et al. 22q13 Microduplication Syndrome in Siblings with Mild Clinical Phenotype: Broadening the Clinical and Behavioral Spectrum. Mol Syndromol. 2020;11(3):146-52. https://doi.org/10.1159/000507103

10. Ha JF, Ahmad A, Lesperance MM. Clinical characterization of novel chromosome 22q13 microdeletions. Int J Pediatr Otorhinolaryngol [Internet]. 2017;95:121-6. Available from: http://dx.doi.org/10.1016/j.ijporl.2016.12.008 https://doi.org/10.1016/j.ijporl.2016.12.008

11. White, Mencio. Genu Valgum in Children: Diagnostic and Therapeutic Alternatives. J Am Acad Orthop Surg [Internet]. 1995 Oct;3(5):275-83. Available from: http://journals.lww.com/00124635-199509000-00003 https://doi.org/10.5435/00124635-199509000-00003

12. Jesse S, Delling JP, Schön M, Boeckers TM, Ludolph A, Senel M. Phelan mcdermid syndrome: Multiple sclerosis as a rare but treatable cause for regression-a case report. Int J Mol Sci. 2021;22(5):1-5. https://doi.org/10.3390/ijms22052311

13. Xia S, Liu Z, Yan H, Chang K, Sun Y, Wang J, et al. Lymphedema complicated by protein-losing enteropathy with a 22q13.3 deletion and the potential role of CELSR1: A case report. Medicine (Baltimore). 2021;100(24):e26307. https://doi.org/10.1097/MD.0000000000026307

14. Jungová P, Čumová A, Kramarová V, Lisyová J, Ďurina P, Chandoga J, et al. Phelan-McDermid syndrome in adult patient with atypical bipolar psychosis repeatedly triggered by febrility. Neurocase [Internet]. 2018;24(4):227-30. Available from: https://doi.org/10.1080/13554794.2018.1542007 https://doi.org/10.1080/13554794.2018.1542007