Phelan-Mcdermid syndrome: three case reports and a literature review

Berrada Sarah[1]*, Tazzite Amal[2,3], Fatima Maarouf[1], Gazzaz Bouchaib[2,4], Dehbi Hind[1,2]

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ABSTRACT

Background: Phelan-McDermid syndrome (PMS) [OMIM: 606232] is a neurodevelopmental disorder commonly due to a deletion of chromosome 22q13.3. It is characterized by neonatal hypotonia, severely delayed absenting speech, developmental delay, and minor dysmorphic facial features.

Case Presentation: The Comparative genomic hybridization array was performed on three patients referred to our genetics department for an autism spectrum disorder and facial dysmorphia. The results showed a deletion of chromosome 22.

Conclusion: In summary, the genotype-phenotype of PMS is still not clear. Moreover, the penetrance of this deletion seems to be incomplete for some genes, leading to variable phenotypes in patients with the same deletion.

Keywords: Phelan-McDermid syndrome, 22q13 deletion syndrome, neurodevelopmental disorder.

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Correspondence to: Berrada Sarah
*Medical Genetics Laboratory, Ibn Rochd University Hospital, Casablanca, Morocco.
Email: sarah.berrada.gen@gmail.com
Full list of author information is available at the end of the article.

Background

Phelan-McDermid syndrome (PMS) [OMIM: 606232] is a rare genetic disorder compromising the 22q13 terminal region and affecting the *SHANK3* gene. It is a neurodevelopmental disorder characterized by a large variety of clinical features with considerable heterogeneity in disease severity [1]. Clinically, affected patients present neonatal hypotonia, global developmental delay, absent speech, and moderate to profound intellectual disability (ID). The *SHANK3* gene is a gene candidate for PMS, localized in the PMD region, as a result of an intragenic deletion or point mutation.

Described for the first time in 1958, PMS is now considered a relatively common cause of autism spectrum disorder (ASD) and ID. It is one of the most common sub telomeric deletions after 1p36.3 deletion syndrome. Indeed, it accounts for 1% of all ASD cases [2].

More than 1,200 cases have been reported worldwide and the prevalence is between 1/10,000 and 1/20,000 newborns. The deletion occurs with similar frequency in males and females [3]. However, PMS seems to be underdiagnosed, and its exact prevalence is still unknown [4]. To the best of our knowledge, no studies have been conducted on the Moroccan population [5].

Herein, we will present the clinical and genetic features of three patients with suspected PMS syndrome.

Cases Presentation

Cases 1 and 2: Five and 6-year-old Moroccan boys born from nonconsanguineous parents by normal delivery with a generalized neonatal hypotonia. The patients presented with delayed psychomotor development, absence of speech, autistic features, and common dysmorphic features. The first case presents lumbar depression, occult spina bifida, and bilateral flat feet. The second case presents a single palmar crease, a valgus foot, pylo-urethral junction, and right renal atrophy with dilatation of the excretory cavities and significant cortical atrophy with unremarkable medical history. There was no family history of a similar case.

Both cases have a normal constitutional karyotype (46, XY). However, the CGHarray testing showed a 3.2 Mb deletion in chromosome 22 (arr[GRCh37]22q 13.31q13.33(47962298_51197766)x1). This deletion includes 50 genes including, the *SHANK3* gene.

Case 3: A 19-year-old Moroccan female born to nonconsanguineous parents by normal delivery with a generalized neonatal hypotonia. The patient presented with ID, absence of language, and facial dysmorphia. The investigation of the family did not demonstrate any similar case. The standard constitutional karyotype was normal (46, XX). The chromosomal microarray analysis detected a microdeletion of 1.543 Mb in the region 22q13.33:

arr[GRCh37] 22q13.33(49654561_51197838)x1. This deletion includes 42 genes, including the *SHANK3* gene.

Discussion

PMD syndrome is a rare genetic disorder. Only a few mechanisms of this disease have been reported. Most of them consist of terminal chromosome 22q13 deletions that usually occur de novo, but in about 20% of cases, one parent carries a balanced translocation, intragenic *SHANK3* deletions, or unbalanced translocations. Other chromosomal rearrangements lead to the formation of a ring chromosome 22, or disruptive point mutations in the *SHANK3* gene [6].

The microdeletion identified in the 22q13.3 regions is the main cause of this syndrome. It is a recurrent and pathogenic copy number variant (CNV) susceptible to inducing neurodevelopmental disorders and absent or severely delayed expressive speech. The chromosomal deletion can reach several genes, including the *SHANK3* gene, which contributes to the large interindividual phenotypic variability. Moreover, deletion sizes vary considerably among PMS patients, ranging from intragenic deletions of 100 Kb to around 9 Mb [4,5].

The karyotype should be the first genetic test to detect a rearrangement or a ring chromosome followed by a CGH array or FISH, because of the presence of large CNVs that cannot be identified by sequencing. Finally, a multigene panel including *SHANK3* and other genes of interest has been developed to detect a heterozygous pathogenic variant [7].

The prevalence of PMD syndrome is still unknown. More than 1,500 individuals have been registered in the Foundation of PMS (Venice, Florida, 2017) [7]. Most of the patients included in the previous genotype-phenotype analyses carried microdeletions [8]. Indeed, the proportion of patients with *SHANK3* variants is about 3%-25% (ClinVar, Varsome, LOVD databases), or 8.6% according to the PMS International Registry.

The Genotype-phenotype correlation in PMS is complex. Many studies have shown a relationship between deletion size and severity of features. Undeniably, the penetrance of the nonmosaic 22q13.3 deletion, including *SHANK3* gene deletion is complete. However, small deletions non including *SHANK3* are associated with nonpenetrance and variable expressivity. Pathogenic variants in *SHANK3* have been associated with PMS, nonsyndromic autism, and schizophrenia [7].

The haploinsufficiency of *SHANK3*, relates to many features, but most neurological and behavioral symptoms are also present in patients carrying interstitial 22q13 deletions without *SHANK3* deletion [9]. This suggests that this gene may not be responsible for the entire clinical spectrum of PMS [4]. A new classification of this disorder has been defined, comprising two categories: PMS-*SHANK3* related for cases with deletions or pathogenic variants affecting *SHANK3*, and PMS-*SHANK3* unrelated for the remaining cases where *SHANK3* is preserved [6].

Individuals with the same size deletion may be vastly different in their degree of disability. Different factors are related, in the first the deletion sizes, and second, the environmental factors [5]. In the third, presence of variants in the remaining copy.

The prevalence of different features of Phelan-McDermid syndrome reported in the literature in comparison with that report in our case is represented in Table 1.

The PMS is caused by a deletion or a mutation of the *SHANK3* gene with an autosomal dominant inheritance. Pathogenic variants in *SHANK3* are usually de novo [7]. However, the terminal deletion could be inherited from an affected parent, which is very rare, and only one case has been described in the literature [10].

For all patients, a genetic investigation is needed to conduct full genetic counseling. In the present case, genetic screening of the parents could not be done because of lack of resources.

Table 1. *Frequency of different features of PMS.*

FEATURES	PREVALENCE[A]	OUR STUDY
Neonatal hypotonia	75%	3/3
Developmental delay	75%	3/3
Absent or severely delayed speech	75%	3/3
Normal growth	75%	3/3
Decreased perception of pain	75%	3/3
Mouthing /chewing/tooth grinding	75%	3/3
Autism/autistic-like behavior	75%	3/3
Dolichocephaly	25%	1/3
Full or puffy eyelids	50%	3/3
Strabismus	25%	1/3
Full brow	50%	3/3
Epicanthal folds	25%	3/3
Long eyelashes	50%	2/3
Prominent or large ears	50%	3/3
Flat midface	50%	2/3
Wide nasal bridge	50%	3/3
Bulbous nose	50%	3/3
Feeding difficulties	50%	3/3
wide-spaced teeth	25%	3/3
Large, fleshy hands	50%	3/3
Hyperextensibility	50%	2/3
Gastroesophageal reflux	25%	2/3
Renal abnormalities	38%	1/3
Cardiac defect	3% to 25%	0/3
Seizures	25%	3/3

[A]Phelan et al. [7] genetic counseling.

Germline mosaicism may be a significant mechanism for the generation of de novo pathogenic CNVs. If the 22q13.3 variant found in the proband cannot be detected in the leukocyte DNA of either parent, the recurrence risk in siblings is estimated to be 1% because of the theoretical possibility of parental germline mosaicism [1]. Indeed, prenatal testing and preimplantation genetic testing for PMS are possible for future pregnancies at increased risk [7].

Conclusion

In summary, the genotype-phenotype of PMS is still not clear. Moreover, the penetrance of this deletion seems to be incomplete for some genes, leading to variable phenotypes in patients with the same deletion. Sequencing of the genes localized in this region can identify variants in the remaining copy.

What is new

The penetrance of this deletion seems to be incomplete for some genes, leading to variable phenotypes in patients with the same deletion.

List of Abbreviations

PMS	Phelan-McDermid syndrome
PMD	Phelan-McDermid
CGH	Comparative genomic hybridization
ID	Intellectual disability
ASD	Autism spectrum disorder
CNV	Copy number variant
FISH	Fluorescence In Situ Hybridization

Declarations

The authors would like to thank the patients and the parents for their participation and for agreeing to the publication of this report.

Conflict of interests

The authors declare that there is no conflict of interest regarding the publication of this article.

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Consent for publication

Written informed consent was obtained from the parents.

Ethical approval

Our institution does not require ethical approval for reporting individual cases or case series.

Author details

Berrada Sarah[1], Tazzite Amal[2,3], Fatima Maarouf[1], Gazzaz Bouchaib[2,4], Dehbi Hind[1,2]

1. Medical Genetics Laboratory, Ibn Rochd University Hospital, Casablanca, Morocco
2. Laboratory of Cellular and Molecular Pathology, Faculty of Medicine and Pharmacy, Hassan II University of Casablanca, Casablanca, Morocco
3. Institut Supérieur des Professions Infirmières et Techniques de Santé de Casablanca, Casablanca, Morocco
4. Genetics Anlysis Institute, Royal Gendarmerie, Rabat, Morocco

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Summary of the case

		Case 1	Case 2	Case 3
1	**Patient (gender, age)**	5 year-old, male	6 year-old, male	19-year-old, female
2	**Final diagnosis**	PMS	PMS	PMS
3	**Symptoms**	Neonatal hypotonia Developmental delay Absent delayed speech Autism Facial dysmorphia Lumbar depression, occult spina bifida, and bilateral flat feet.	Neonatal hypotonia Developmental delay Absent delayed speech Autism Facial dysmorphia Single palmar crease Valgus foot Pylo-urethral junction right renal atrophy with dilatation of the excretory cavities cortical atrophy	Neonatal hypotonia Developmental delay Absent delayed speech Autism Facial dysmorphia
4	**Medications**	Symptomatic treatment given	Symptomatic treatment given	Symptomatic treatment given
5	**Clinical procedure**	Symptomatic treatment given	Symptomatic treatment given	Symptomatic treatment given
6	**Specialty**	Requires multidisciplinary management	Requires multidisciplinary management	Requires multidisciplinary management