Clinical synopsis of the European consensus guideline for Phelan-McDermid syndrome

Introduction

This is a shortened version of the European consensus guideline for Phelan-McDermid syndrome (PMS). More information including extended background information, methods and literature references can be found in the Special Issue of the European Journal of Medical Genetics published in 2023.

This guideline covers recommendations for individuals with ***SHANK3*-related PMS**, but may also partly be applicable for non-*SHANK3*-related PMS. It is written for professionals. A clinical surveillance scheme, emergency card and lay versions in multiple languages are available at https://ern-ithaca.eu/documentation/phelan-mcdermid-guideline/.

Phelan-McDermid syndrome

For detailed background information see: Schön et al., EJMG 2023.

Phelan-McDermid syndrome (PMS) presents with a disturbed development, neurological and psychiatric characteristics, and sometimes other comorbidities. The incidence of PMS in European countries is at least 1 in 30,000, underdiagnosis being very likely. PMS-*SHANK3* related is defined by the presence of *SHANK3* haploinsufficiency, either by a deletion involving region 22q13. 3 or a pathogenic variant in *SHANK3*.

The phenotype of individuals with PMS is highly variable, depending in part on the deletion size or, whether only a variant of *SHANK3* is present (table 1).

Sign / Symptom	22q13.3 deletions *(%)*	*SHANK3* variants *(%)*	Sign / Symptom	22q13.3 deletions *(%)*	*SHANK3* variants *(%)*
Development			**External phenotype**		
Developmental delay	493/504 (98%)	48/50 (96%)	Dolichocephaly	84/319 (26%)	2/28 (7%)
Speech impairment	507/572 (88%)	31/44 (70%)	Long eyelashes	149/312 (48%)	19/39 (49%)
Neurology			Down-slanting fissures	16/74 (22%)	3/10 (30%)
Seizures (one or more)	148/542 (27%)	14/53 (26%)	Periorbital fullness	69/239 (29%)	7/39 (18%)
Hypotonia	333/451 (74%)	42/51 (82%)	Ptosis	62/286 (22%)	2/28 (7%)
Structural brain anomalies	118/223 (53%)	12/42 (29%)	Epicanthal folds	122/378 (32%)	8/39 (21%)
Senses			Ear anomalies	232/492 (47%)	16/41 (39%)
Vision disturbances	70/316 (22%)	9/34 (26%)	Wide nasal bridge	156/349 (45%)	15/42 (36%)
Strabismus	59/243 (24%)	4/28 (14%)	Broad nose	169/349 (48%)	15/40 (38%)
Hearing loss	32/372 (8%)	3/29 (10%)	Short philtrum	22/138 (16%)	0/21 (0%)
Increased pain tolerance	204/314 (65%)	38/48 (79%)	Thin upper vermillion	15/56 (27%)	3/11 (27%)
Behaviour			Thick lower vermillion	4/44 (9%)	5/21 (24%)
ASD	162/282 (57%)	26/33 (79%)	Malocclusion	109/297 (37%)	10/29 (34%)
Hyperactivity	33/112 (29%)	21/29 (72%)	Retrognathia	29/115 (25%)	0/31 (0%)
Aggression	50/267 (19%)	18/49 (37%)	Pointed chin	154/309 (50%)	18/29 (62%)
Self-injury	10/80 (13%)	8/27 (30%)	Large fleshy hands	180/392 (46%)	11/28 (39%)
Sleep disorder	62/237 (26%)	24/46 (52%)	Clinodactyly 5th finger	79/405 (20%)	10/28 (35%)
Internal organs			2-3 Syndactyly of toes	65/232 (28%)	5/11 (45%)
Gastro-oesophageal reflux	31/122 (25%)	5/29 (17%)	Sandal gap	30/56 (54%)	6/9 (7%)
Cardiac anomalies	49/387 (13%)	3/46 (7%)	Small / malformed nails	138/438 (32%)	13/29 (45%)
Freq. airway infections	75/280 (27%)	15/47 (32%)	Lymphedema	29/270 (11%)	0/34 (0%)
Urogenital problems	9/62 (15%)	0/24 (0%)	Eczema	48/225 (21%)	14/46 (30%)
Renal abnormalities	20/137 (15%)	0/17 (0%)	Hypohidrosis	31/84 (37%)	2/24 (8%)
Growth			Hyper-extensible joints	4/18 (22%)	6/10 (60%)
Short stature (≤ P3)	37/392 (9%)	4/41 (10%)			
Tall stature (≥ P98)	84/392 (21%)	3/41 (7%)			
Macrocephaly (≥ P98)	55/329 (17%)	6/39 (15%)			
Microcephaly (≤ P3)	53/329 (16%)	5/52 (10%)			

Table 1. Main phenotypic findings with frequencies in patients with PMS caused by a deletion of segment 22q13 (irrespective of the mechanism) and those caused by a *SHANK3* variant. For references see Schön et al. 2023.

Results of clinical trials using insulin-like growth factor I (IGF-1), intranasal insulin, and oxytocin are available, other trials are in progress.

European consensus recommendation on clinical trials

- Enrolment in a clinical treatment trial may be considered and discussed with individuals with PMS (if possible) or their representatives.

Counselling in PMS

For detailed background information see: Koza et al., EJMG 2023.

A diagnosis of Phelan-McDermid syndrome requires genetic testing and most families will be referred to a clinical geneticist for counselling. Counselling will address the clinical picture and genotype-phenotype associations. If indicated, family members will be tested and- the risk of recurrence discussed. Most individuals have a de novo deletion or pathogenic variant. However, the 22q13.3 deletion could result from a derivate chromosome 22 of a parental balanced chromosomal anomaly. In rare cases, the deletion could be inherited from a parent carrying a deletion of 22q13.3, which can also be mosaic.

European consensus recommendations on counselling

- All individuals with PMS and their parents (or direct relatives[1]) should be referred for genetic counselling. In genetic counselling, the clinical geneticist or other experienced clinician should explain the relationship between the genotype and phenotype (e.g. effect of deletion size or *SHANK3* variant) and determine if there is an increased recurrence risk for another child with PMS for parents and other relatives.
- After a diagnosis of PMS has been made, further genetic studies should be performed for proper genetic counselling (see Figure 1).
- Follow-up of individuals with PMS should include a check whether genetic work-up has been complete and up-to-date.
- In subsequent pregnancies, the parents of the child with PMS should be offered prenatal diagnostic testing.

[1] In case of adult individuals with PMS and questions from siblings discuss also referral for genetic counselling.

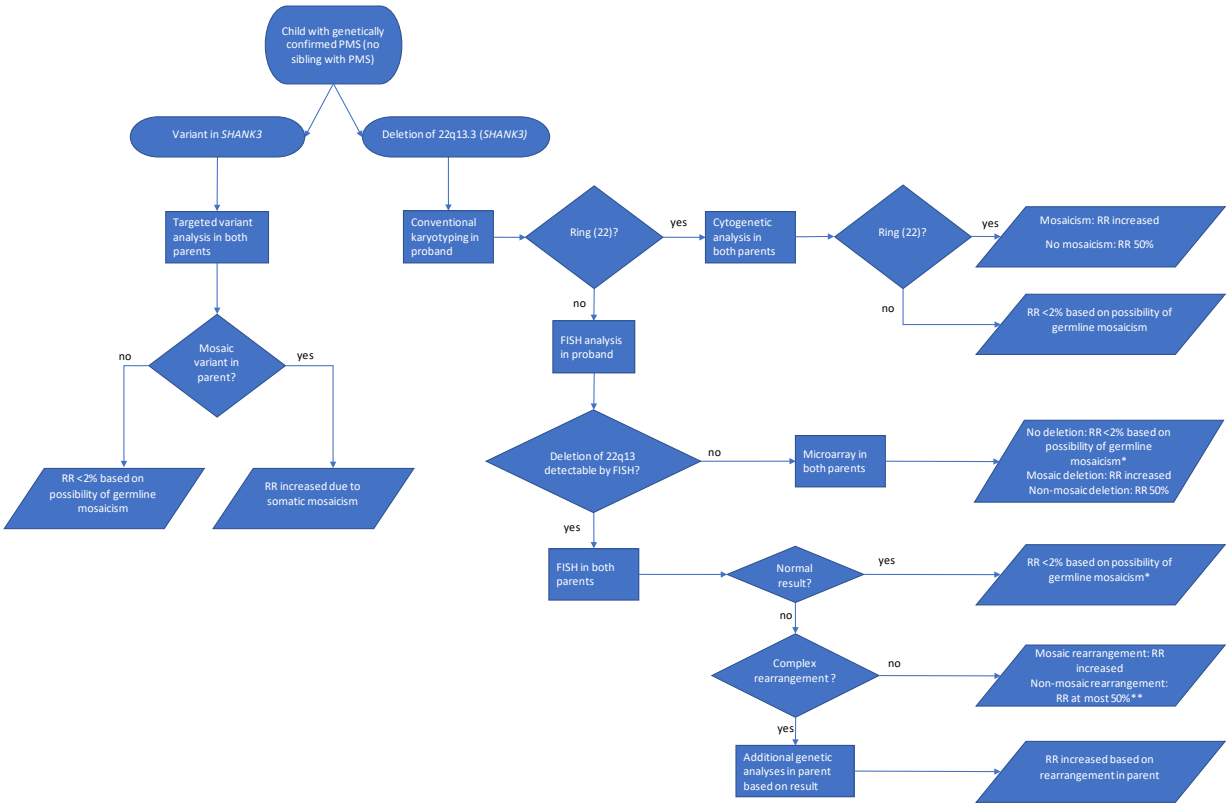

Figure 1. Genetic follow-up testing in Phelan-McDermid syndrome

PMS due to a ring chromosome 22

For detailed background information see: Koza et al., EJMG 2023.

Few genotype-phenotype relationships have been reported. However, certain clinical characteristics distinguish Phelan-McDermid syndrome due to a ring chromosome 22 from a simple deletion 22q13.3. A ring chromosome 22 confers increased risk of NF2-related schwannomatosis (formerly neurofibromatosis type 2) and atypical teratoid rhabdoid tumours associated with the tumour suppressor genes NF2 and SMARCB1, respectively, both located on chromosome 22. The prevalence of PMS due to ring chromosome 22 is estimated at 10-20%, while the risk of developing a tumour although not fully known is estimated at 2-4%. However, those who do develop them, often have multiple tumours.

European consensus recommendations concerning ring chromosome 22

- In an individual with a ring chromosome 22, personalized monitoring for potential NF2-tumors should be discussed with the patient or their representatives[1].
- In an individual with a ring chromosome 22, cerebral imaging (MRI) is recommended at the age of 14 to 16 years, if not already available. In case of obvious hearing loss discuss with the patient or their representatives repeating of the MRI[2].

[1] There is currently no screening guideline, however, this may include annual hearing screening as well as eye and neurological examinations every 1-2 years starting between the ages of 15 and 20 years.

[2] If the MRI is made under general anaesthesia, combine with spinal MRI. Discuss repeating the MRI every 5 years (in the absence of symptoms).

Communication, language and speech

For detailed background information see: Burdeus-Olavarrieta et al. EJMG 2023.

Marked speech impairment is present in up to 95% of individuals with a 22q13.3 deletion and in 69% with a pathogenic *SHANK3* variant. Absence of speech affects 50%-80% of the individuals with PMS. Loss of language and other developmental skills is reported in around 40% of the individuals, with variable course. Deletion size and possibly other clinical variables (e.g., conductive hearing problems, neurological issues, intellectual disability…) are related to communicative and linguistic abilities.

European consensus recommendations on communication, language and speech

- Hearing should be checked in every individual with PMS at the time of diagnosis and subsequently put into surveillance according to national guidelines.
- Every individual with PMS should be assessed by a specialized multidisciplinary team to evaluate all factors that may influence communication, speech and language.
- Preverbal and verbal communicative skills and cognitive development should be thoroughly evaluated in individuals with PMS prior to intervention and treatment.
- Parents of individuals with PMS should be counselled by a specialist on supporting, facilitating, and stimulating communication, language and speech from an early age on.
- Use of augmentative and alternative communication (AAC) tools is recommended to facilitate communication for individuals with PMS when communication is limited; these approaches do not delay the active language development.

Chewing, swallowing and gastrointestinal problems

For detailed background information see: Matulevicienne et al., EJMG 2023.

Gastrointestinal (GI) problems are common in PMS. Chewing and swallowing difficulties, dental problems, reflux disease, cyclic vomiting, constipation, incontinence, diarrhoea, and nutritional deficiencies have been most frequently reported. To detect GI-problems in a timely fashion signs such as e.g. behavioural changes, sleep disorders, self-injurious mouthing behaviours should lead to investigation of possible underlying gastrointestinal causes. Gastrointestinal problems have a detrimental effect on the health of people with PMS and are a significant burden for their families.

European consensus recommendations on Chewing, swallowing and GI problems

- Both gastroesophageal reflux and constipation should be considered if behavioural changes are observed in individuals with PMS.
- In individuals with PMS, evaluation of faecal incontinence is advised. Somatic causes should be excluded, and behavioural modifications should be considered (if needed, a behavioural specialist should be consulted).
- For treatment of gastroesophageal reflux, diarrhoea and constipation in individuals with PMS, refer to general national or international guidelines.
- If zinc deficiency is present in an individual with PMS, dietary zinc supplementation should be considered.
- A referral to a pre-verbal speech therapist for chewing and swallowing disorders should be considered.

Altered sensory functioning

For detailed background information see: Walinga et al. EJMG 2023.

Altered sensory functioning is often observed in individuals with PMS. Compared to typically developing individuals and individuals with an autism spectrum disorder, distinctive features of sensory functioning in PMS exist, of which reduced responsiveness

to sensory input may lead to safety risks and as such is highly relevant for clinical practice. More hyporeactivity symptoms and less hyperreactivity and sensory seeking behaviour are seen, particularly in the auditory domain. Hypersensitivity to touch, possible overheating or turning red easily and reduced pain response are often seen.

European consensus recommendations on altered sensory function

- Caregivers and health care providers should be aware that individuals with PMS often have a reduced responsiveness to sensory stimuli such as pain, sudden sounds and heat. After every (suspected) trauma or physical incident the individual should be carefully examined.
- Every individual with PMS needs to be screened for hearing and visual disturbances at the time of diagnosis and subsequently put under surveillance according to national guidelines.
- Sensory integration functioning should be checked in every person with PMS using a validated screening instrument. If altered sensory function is present a sensory integration therapist should be consulted.
- In case of behavioural changes in individuals with PMS, evaluation of possible causes should include a search for pain and altered sensory function. The use of a validated non-verbal pain scale is recommended.

Epilepsy

For detailed background information see: de Coo et al., EJMG 2023.

Comorbid epilepsy is common in PMS and manifests itself in a variety of seizure semiologies. Further diagnostics using electroencephalogram (EEG) and brain magnetic resonance imaging (MRI) are important in conjunction with the clinical picture of the seizures to decide whether anticonvulsant therapy is necessary.

European consensus recommendations on epilepsy

- In every individual with PMS, irrespective of age, caregivers should be alert for seizures and epilepsy.
- In every individual with PMS in whom seizures are suspected but EEG studies are nonconclusive, overnight prolonged EEG studies should be considered.
- Brain imaging, preferably by MRI, is advised in every individual with PMS who has epileptic seizures, and indicated when new neurological signs and symptoms, including seizures, occur.
- A paediatric neurologist or neurologist should be involved in the therapy for epilepsy.
- Anticonvulsant treatment of epilepsy in individuals with PMS should be provided according to national guidelines.

Sleeping problems

For detailed background information see: San José Cáceres et al. EJMG 2023.

Early onset sleep problems and disorders are reported in up to 90% of individuals with PMS. Not to be taken lightly, sleep problems and disorders may have a major impact on the health, behaviour, functioning and learning opportunities of affected individuals, as well as on the well-being and resilience of their parents and caregivers, ultimately affecting the whole household's (mental) health and well-being. Country-specific prevalence rates reported ranged between 24% -46% of sleep difficulties. However, a world-wide survey amongst parents reported an alarming 59%. The main problems include difficulty falling asleep and numerous night awakenings. Also common are restless sleep, night-time incontinence and teeth grinding.

European consensus recommendations on sleeping problems

- Every individual with PMS and sleep problems should be evaluated for somatic, and/or environmental and/or neuropsychiatric causes.
- Mental health conditions co-occurring with sleep problems in individuals with PMS need to be investigated and treated.
- In individuals with PMS with sleep problems, sleep hygiene should be evaluated, and caregivers should be supported in establishing a structured approach (behavioural interventions).
- If sleep problems persist despite appropriate interventions, the individual with PMS should be referred to a specialist experienced in sleep problems or a specialist sleep centre.

Lymphedema

For detailed background information see: Damstra et al. EJMG 2023

Lymphedema can be a clinical feature in up to 25% of the patients with PMS due to a 22q13 deletion and has thus far not been reported in individuals with a pathogenic *SHANK3* variant. The mechanism causing lymphedema in PMS is unknown and it can be treated using existing general management guidelines, taking the functioning of the PMS patients into account.

European consensus recommendations on lymphedema

- The health care provider should pay attention to the possible development of lymphedema in individuals with a 22q13 deletion, including ring chromosome 22, and start treatment (e.g., compression bandages and garments, skincare and advice) when needed.
- Refer individuals with PMS with lymphedema impacting daily functioning to a lymphedema centre of expertise for further investigations and treatment.

Mental health issues

For detailed background information see: van Balkom et al. EJMG 2023.

Behavioural problems and psychiatric comorbidities are common in PMS. It is important to consider developmental level of the individual with PMS when assessing mental health and behavioural issues. Understanding how the discrepancy between developmental level and chronological age may impact behaviours offers insight into the meaning of those behaviours and informs care for individuals with PMS. Taking factors of cognitive, developmental and adaptive functioning into account may enable clinicians to understand the meaning of behaviour, address unmet (mental health) care needs and inform treatment, thereby improving quality of life.

European consensus recommendations on mental health

- At diagnosis for individuals with PMS a comprehensive evaluation should be made of factors influencing mental health, which include physical, psychiatric, psychological, developmental, communicative, social, educational, environmental, and economic domains, and general wellbeing as informed by caregivers.
- In individuals with PMS cognitive and socio-emotional level, communication, adaptive and sensory functioning should be assessed at diagnosis using appropriate tools, which may include a Functional Behavioural Assessment.
- In individuals with PMS a baseline measurement of individual functioning and skill level is useful, preferably in early childhood.
- Monitor behavioural status regularly including mood, affect, communication, interests and day/night routines in every individual with PMS, especially at important changes in daily environment, allowing early recognition of behavioural changes.
- Individuals with PMS who demonstrate noteworthy behavioural changes should be physically examined and evaluated for the presence of medical issues, including physical signs of abuse.
- If concerns are raised regarding mental health, functioning and behaviour of an individual with PMS, a psychiatric assessment is indicated to determine (comorbid) diagnoses, considering the developmental level of the individual.

Organization of care

For detailed background information see: van Eeghen et al. EJMG 2023.

The manifestations of Phelan-McDermid syndrome (PMS) are complex, warranting expert and multidisciplinary care in all life stages. Assessment and care should consider all life domains, which can be done within the framework of the International Classification of Functioning, Disability and Health (ICF). This framework assesses disability and functioning as the outcome of the individual's interactions with other factors. The different roles within care, such as performed by a centre of expertise, by regional health care providers and by a coordinating physician are addressed.

A surveillance scheme and emergency card are provided.

European consensus recommendations on organization of care

- Every person with PMS should receive PMS-specific care by a dedicated expert team, preferably in a centre of expertise.
- A coordinating professional should initiate and monitor the multidisciplinary care for a person with PMS. The multidisciplinary team should be established based on the surveillance scheme (Table 2).
- For every person with PMS, specific care needs and the responsible professionals should be recorded in the medical records and the individual care plan, if available.
- For every teenager with PMS, the transition from paediatric to adult care is timely initiated and monitored by the coordinating paediatric professional. Coordinating should be transferred to a professional in adult care. This should be recorded in the medical records and individual care plan.
- Caregivers of individuals with PMS should be informed about the patient registry of the PMS when established.