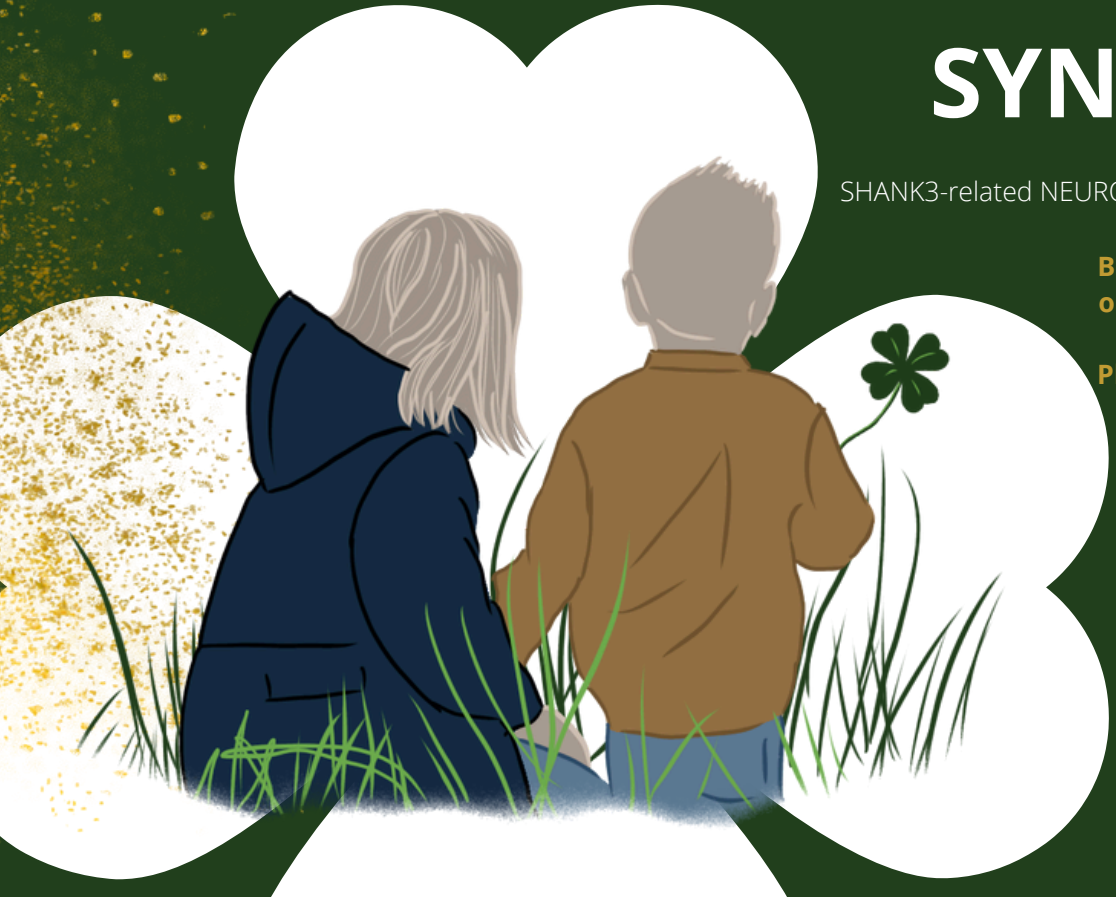
PHELAN-McDERMID SYNDROME

22Q13 DELETION SYNDROME
SHANK3-related NEURODEVELOPMENTAL DISORDER



Booklet written for relatives or caregivers involved in the care of individuals with Phelan-McDermid syndrome in line with the European guidelines on PMS

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SHORT DESCRIPTION

This booklet provides an adapted summary of the European consensus guidelines on Phelan-McDermid syndrome and includes information on clinical features, diagnosis, treatment and recommendations. The entire guideline is published as special issue of the European Journal of Medical Genetics (https://www.sciencedirect.com/journal/european-journal-of-medical-genetics/special-issue/103SFTL92SC) and all information including the most recent updates are available at the website of ERN-ITHACA (https://ern-ithaca.eu/documentation/guidelines/, see QR-code).

For detailed medical information, please consult your doctor. There are also some helpful tools, organizations, websites and social media listed at the end of this booklet.

Link to all PMS guidelines materials

Nothing in life is to be feared, it is only to be understood. Now is the time to understand more, so that we may fear less.

Marie Curie

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WHAT DOES THIS DOCUMENT COVER?

This is an informative document for relatives or caregivers involved in the care of individuals with Phelan-McDermid syndrome (PMS). The document is an adapted version of the European consensus guideline for Phelan-McDermid syndrome. The guideline was developed by a consortium consisting of professional and parents as lived-experience experts representing 14 European countries, and based on the results of a worldwide survey completed by almost 600 families. The most updated version of the guideline can be found at https://ern-ithaca.eu/documentation/phelan-mcdermid-guideline/.

In this booklet, you can find information about clinical features, diagnosis, treatment, recurrence risk and the consensus recommendations as published in the European guideline (see Do's).

Receiving a diagnosis of Phelan-McDermid syndrome can be very intense for the individual, the family and other caregivers, and some of the information in this booklet may be overwhelming. Do not hesitate to ask your doctor for support. Other sources of information, including family or PMS-specific healthcare organizations that can offer support can be found at the end of this booklet.

With the guideline and this booklet, we aim for an optimal care for your family member with PMS. We hope that this booklet supports you in the journey that you face with your son/daughter or relative with PMS.

WHAT IS PHELAN-McDERMID SYNDROME?

Phelan-McDermid syndrome (PMS), also known as 22q13 deletion syndrome (as the most common cause), can be either a chromosomal or a mono-genic disorder. Chromosomes, which consist of genetic material or DNA, are found in the nucleus of cells. Each cell has 23 pairs (46) of chromosomes. For each pair, one chromosome comes from the mother and the other from the father. When a piece of hereditary material in a chromosome is missing, it is called a deletion. In PMS, a part of chromosome 22 can be missing: deletion 22q13. The gene SHANK3 is located in this part of the chromosome and thus it is lost in one of the chromosomes of pair 22 (Figures 1 and 2). Another cause of PMS is a change (mutation) within one of the two copies of the SHANK3 gene itself (mono-genic form of PMS). Here, no genetic material is lost but the SHANK3 gene is dysfunctional.

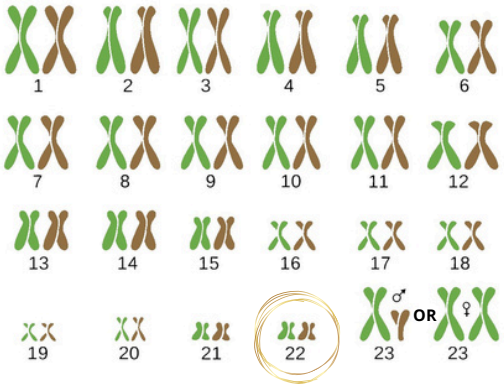


Figure 1. 23 pairs of chromosomes as present in each human cell (chromosome 22 is circled).

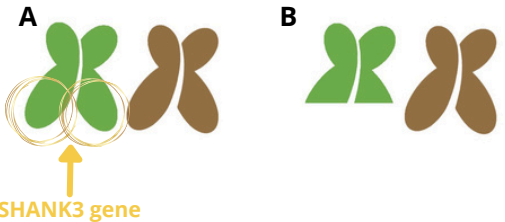


Figure 2. A shows two complete copies of chromosome 22. B shows one incomplete chromosome 22 due to a deletion. The missing part results in the loss of one copy of the SHANK3 gene, which is responsible for most of the clinical manifestations in individuals with PMS.

22q13 deletion/s can be a simple deletion as depicted in Figure 2B. However, sometimes it is caused by the formation of a ring chromosome 22. Such a ring arises when both ends of the chromosome fuse, as explained in Figure 3.

Figure 3. Ring chromosome 22.

DIAGNOSIS

The symptoms of PMS are not very specific and can vary widely between individuals. Therefore, the diagnosis of PMS is based on genetic testing. It can be made by detailed chromosome studies (microarray) by identifying a 22q13 deletion or by DNA studies (usually whole exome sequencing (WES)) identifying a mutation in the SHANK3 gene.

If a 22q13 deletion is detected, further studies are needed to determine whether it is caused by a ring chromosome 22 (Figure 3). This is important because individuals with a deletion due to a ring chromosome 22 can have additional health problems.

Further genetic studies, including studies in parents, may be needed to establish recurrence risk for future pregnancies.

WHO IS AT RISK?

PMS is a condition that is already present at birth, but usually becomes apparent after a few months or years. It affects both men and women and it has been estimated to be present in approximately one in 30,000 newborns.

WHY DOES MY CHILD HAVE PHELAN-McDERMID SYNDROME?

PMS usually is caused by a change in or deletion of the SHANK3 gene in the child, that is not present in the parents (called *de novo*). Why this mutation or deletion sometimes happens is not known and the chance that it happens again in a future pregnancy is low in most families (approximately 1-2%).

Sometimes one of the parents has the genetic defect in part of the cells (mosaic) causing no or fewer symptoms but resulting in an increased recurrence risk.

Also, a parent can be a carrier of a so-called translocation, where part of chromosome 22 has exchanged with another chromosome. This means that the parent is healthy, but children are at increased risk of a 22q13 deletion.

WHAT ARE THE CLINICAL FEATURES OF PHELAN-McDERMID SYNDROME?

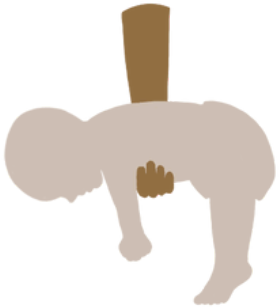
GENERAL SYMPTOMS

The main features of this syndrome are moderate to severe intellectual disability; communication, speech and language problems and low muscle tone (hypotonia). Individuals diagnosed with PMS will need additional support to their daily lives.

Newborns usually look like other babies with average growth parameters and no specific facial features. In childhood, balance and fine motor skills may be less well-developed. Progress in cognitive, language, social and emotional development is slower than in other children, but parents describe their children as happy, sociable, friendly, and affectionate. There is commonly a severe delay in speech development and most individuals have an increased tolerance to pain.

In addition, there can be mild external features (long eyelashes, bushy eyebrows, bulbous nose, long shaped ears, pointed chin, large hands, and dysplastic toenails). However, these external features are non-specific and the diagnosis cannot be made by looking at the individual's appearance.

Loss of previously acquired skills (regression) can occur during different developmental phases (childhood, adolescence, adulthood). Puberty development is mostly normal, but can also be precocious or delayed. Adults with PMS typically attain an average height and experience limited physical problems but generally have an Intellectual disability (ID). Epilepsy is a common feature and can develop at all ages with onset more common in puberty. Also, lymphedema can start at a young age, but becomes more prominent at older ages. Specific mental health issues like mood disorders tend to develop during adolescence or in adulthood.



Life expectancy is usually normal and an increasing number of adults with PMS is known.

Each individual is unique and exhibits a different combination of the clinical features listed in Table 1. So, only part of the features listed in the table will be present in your family member with PMS. Some features are more common in individuals with a 22q13 deletion than in those with a SHANK3 variant and vice-versa. Also some features may be more pronounced in individuals with a large deletion than in those with a small deletion of chromosome 22q13.

For some features listed in the table, information was available from over 500 individuals. while for other features the figures are based on 50 or less individuals. A wider range is given in the latter group because the figures are less precise (Table 1).

Table 1. List of the clinical features observed in individuals with PMS.

Clinical feature	PMS individuals with 22q13 deletions (%)[1]	PMS individuals with *SHANK3* variants (%)[1]
Global developmental delay	95-100	85-100
Marked speech impairment	85-90	60-80
Seizures / epilepsy[2]	25-30	20-35
Low muscle tone (hypotonia)	70-75	75-90
Structural brain anomalies (MRI)	50-60	20-40
Vision disturbances	20-25	15-35
Strabismus	20-30	5-25
Hearing loss	5-10	0-15
Malocclusion of the teeth	30-40	25-45
Gastro-oesophageal reflux	20-30	5-35
Cardiac anomalies	10-15	0-15
Frequent airway infections	20-30	25-45
Urogenital problems	10-25	-[3]
Renal abnormalities	10-20	-
Eczema	15-25	20-40
Less sweating (hypohidrosis)	30-45	0-20
Lymphedema[2]	5-15	-
Small / malformed nails	30-35	35-55
Increased pain tolerance	65-70	70-90
Autism	50-60	70-90
Hyperactivity	25-35	60-80
Sleep disorder	20-30	40-60

1 The percentages represent the number of individuals with that feature per 100 individuals with PMS.
2 Some features may become more prevalent at older ages, like epilepsy and lymphedema.
3 - = not been described in these individuals thus far.
The information in the table is based on the review by Schön et al. Eur J Med Genet 2023

COMMUNICATION, LANGUAGE AND SPEECH PROBLEMS

Speech and language skills are particularly affected in PMS. Different presentations can occur: problems with acquiring language, articulation or pronunciation, or absent speech and impaired ability to communicate, either verbally or non-verbally. Receptive abilities are usually more preserved than expressive communication abilities. It is important to be aware that PMS individuals might feel problems differently (reduced pain sensitivity) and might not have the cognitive or verbal abilities to express them properly. Care-givers should therefore be alert for warning signs of medical problems.

CHEWING, SWALLOWING, AND GASTROINTESTINAL PROBLEMS

Gastrointestinal problems are very common in PMS. Chewing and swallowing difficulties, constipation, incontinence, diarrhoea, and gastroesophageal reflux disease (GERD) have been reported.

Making a diagnosis of GERD can be complicated due to limited communication with the individual. Alarm signals may be lack of appetite, food refusal, dental complaints, teeth grinding, nutritional deficiencies, regurgitation, and vomiting. However, atypical complaints, such as sleep disorders due to night-time reflux, restlessness, behavioural problems, and self-injuring behaviour, can also occur.

ALTERED SENSORY FUNCTIONING

People with PMS can have atypical responses to sensory stimuli. All types of senses can be affected, including posture and movement, balance, seeing, hearing, smell, taste, touch, pain, or heat regulation. In PMS, hypersensitivity to touch, decreased response to sounds, reduced pain response and heat regulation problems are seen more often. Altered sensory functioning can mask underlying problems, such as pain and influence for instance sleep and concentration.

EPILEPSY

Many individuals with PMS suffer epilepsy during their lives. Epilepsy is an uncontrolled electrical discharge in the brain cells that can result in a rhythmic motor or sensory expression of the body. These epileptic seizures can sometimes be elicited by febrile periods. It is important to recognize the seizures and their frequency. The most common type of seizure is an atypical absence (see glossary) which can be difficult to detect. This type of seizure starts with staring into space, usually with a blank look, while the child does not respond when, for example, their name is called. Symptoms can be a sudden stop in motion, gazing and lip smacking. The age at first seizure onset is different in every individual, and may be at later ages, with a preponderance during adolescence.

SLEEP ISSUES

Most people with PMS experience sleep issues that influence daytime functioning, and cause fatigue, sleepiness, irritability, and/or reduced concentration and performance. These problems affect the individual and the well-being and resilience of their parents and caregivers.

The most commonly reported sleep problems in PMS involve difficulties falling asleep and multiple night awakenings. There is some evidence that parasomnias (see glossary) increase drastically with age. Overall, sleep problems in PMS persist and increase during adolescence, and multiple sleep problems can occur simultaneously.

Given the high co-occurrence of physical and mental health issues in PMS, sleep issues can be caused or enhanced by any of these factors (e.g. reflux, diabetes, asthma, anxiety, depression), but incorrect sleep hygiene (e.g. lack of routines, exposure to external noises, sensory difficulties, etc.) also needs to be considered.

LYMPHEDEMA

Lymphedema is a clinical feature that occurs only in individuals with PMS due to a 22q13 deletion and is only incidentally reported in those with a SHANK3 mutation. It is caused by an alteration of the lymphatic flow, resulting in the accumulation of fluid in the limbs. It can occur already at a young age and symptoms become more pronounced with ageing, impacting daily functioning if left untreated.

MENTAL HEALTH ISSUES

Cognitive development is generally delayed, and adaptive skills are at a low level of functioning. People with PMS may exhibit mental health issues, such as autism spectrum disorder, loss of skills, hyperactive or agitated behaviour, bipolar disorder/mood cycling, anxiety, catatonia, or psychosis. You can find explanations of these terms in the glossary.

Newly emerging behaviour that is not typical for the individual should be treated as a warning sign. Examples are increases in anxiety-related behaviours, social withdrawal or decrease in previously enjoyed activities, changes in sleep patterns, and other behavioural changes such as crying more often or loss of adaptive skills (e.g. toileting, eating independently). Monitoring the typical routine and emotions observed in individuals with PMS is useful as a baseline.

OTHER ISSUES

As can be seen in Table 1, congenital abnormalities of, for instance, the heart and kidneys can also be present, especially in individuals with a 22q13 deletion. They are most often not of major concern, but should be checked by your doctor because some might require treatment or surveillance. Therefore, they are also listed in the Surveillance Scheme.

Individuals with a ring chromosome 22 have a slightly increased risk for tumours. These tumours are not cancerous (they do not cause metastases), but due to their location in the brain they may cause problems due to compression of, for example, the hearing nerve. The prevalence of these tumours in individuals with a ring chromosome 22 is not exactly known, but has been estimated to be 2 to 4%.

TREATMENT

There is no standard policy for a specific treatment, either with medication or behavioural interventions, although some recommendations can be given regarding the treatment of mental health and sleep disorders in PMS. However, difficulties such as mental health issues, behavioural problems, sleep, and other problems need to be assessed individually. Interventions (environmental, behavioural, or pharmacological) should be considered based on the individual's presentation and care needs, and be continuously evaluated. To date, there is no curative therapy for PMS and no recommended pharmaceutical treatment for intellectual disabilities.

WHO WILL BE INVOLVED IN THE TREATMENT?

It is important in your role as a relative/caregiver to report the individual's clinical symptoms. It is essential that the doctors have all the information about the symptoms and signs to diagnose and treat the health problems in the best way possible. The treatment for PMS should be continuously adapted to best fit the individual with PMS. This typically requires the coordinated efforts of a team of specialists that may include the primary care physician, paediatricians, neurologists, nephrologists, gastroenterologists, orthopaedics, psychiatrists, psychologists, speech/language therapists, physical or occupational therapists and rehabilitation specialists. In some countries a physician for the intellectually disabled will also be involved.

Since treatment should always be individualised, it is not possible to provide one treatment that suits every individual with PMS. Optional treatment options are listed below. See also the European guideline recommendations that have been listed in the chapter on Do's (starting on page 21).

WHAT ARE THE POSSIBLE TREATMENTS FOR COMMUNICATION, LANGUAGE AND SPEECH PROBLEMS?

- Preverbal therapy that focuses on oral motor skills or supported communication in the form of gestures, photos, pictograms, or a communication device with speech output. At a later stage, if the communicative development of the child permits, attention can shift to receptive and/or expressive language.
- There is a free online tool for mapping the communicative skills of people with severe or multiple disabilities called “Communication Matrix”. It helps families and professionals to understand the communication status, progress and needs of individuals that use other forms of communication besides speaking or writing. https://www.communicationmatrix.org/

WHAT ARE THE POSSIBLE TREATMENTS FOR CHEWING, SWALLOWING, AND GASTROINTESTINAL PROBLEMS?

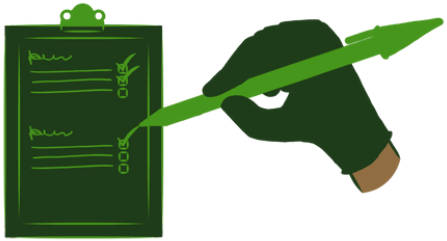
- Speech therapy at an early age for chewing and swallowing problems and saliva loss.
- Nutritional therapy.
- Easy-to-mash food.
- High fluid intake. In case of dehydration, infusions by medical staff.
- Toilet training for loss of coordination for defecation and urgency sensations (recognition of non-retentive stool incontinency).
- Active physical mobility to improve the digestive process and prevent obstipation.
- Medication such as oral laxatives for constipation prescribed by a gastroenterologist or family doctor/paediatrician.
- Vitamin or mineral supplements in the diet if necessary (consult nutritional therapist).

WHAT ARE THE POSSIBLE TREATMENTS FOR ALTERED SENSORY FUNCTIONING?

- Caregivers should be aware that individuals with PMS often have a reduced reaction to sensory stimuli such as pain, sudden sounds and heat.
- Screening for hearing and vision problems.
- Sensory integration functioning should be checked using a validated screening instrument, such as the "Short Sensory Profile 2" (see Glossary). This can be done by a sensory integration therapist.
- In case of behavioural changes, evaluation of possible causes should include a search for pain and altered sensory functioning. The use of a validated non-verbal pain scale is recommended.
- Environmental adjustments for patients such as a good acoustic space, avoidance of sudden noises, abrupt changes in heat or cold, or sudden touch are also recommended.

WHAT ARE THE POSSIBLE TREATMENTS FOR EPILEPSY?

There are many different epilepsy medicines that can manage and keep seizures under control, but not cure them. Antiepileptic medication to reduce or prevent epileptics seizures or absences are usually prescribed according to national guidelines on the treatment of epilepsy. It is common in epilepsy therapy that several medications need to be tried until a positive effect is observed. The doctor will advise on this aspect. The main potential side-effects of taking antiepileptic medicines are feeling tired, dizzy, or sick at the beginning of the treatment or after an increase in dose.



WHAT ARE THE POSSIBLE TREATMENTS FOR SLEEP DISORDERS?

There are currently no specific pharmacological treatments for sleep problems in PMS. However, the most essential elements for treatment are:

- Exploring possible health problems.
- Promoting good sleep hygiene.
- Treating behavioural problems.
- If necessary, pharmacological intervention under the guidance of an expert.

Medication is only indicated temporarily to allow the therapeutic interventions to take effect. If sleeping problems persist, it is advisable to consult a specialised sleep centre.

WHAT ARE THE POSSIBLE TREATMENTS FOR LYMPHEDEMA?

- Physical activity to increase mobility and stimulate fluid circulation.
- A healthy diet to avoid overweight.
- Compression therapy (such as bandaging, garments and Velcro wraps).
- Skin care to prevent skin infections.
- Surgical treatment is generally not indicated. If regular treatment is not successful, visit a multidisciplinary expert centre.

WHAT ARE THE POSSIBLE TREATMENTS FOR MENTAL HEALTH ISSUES?

Depending on the type and frequency of the mental health issues (hyperactive or agitated behaviour, bipolar disorder/mood cycling, and catatonia), behavioural or environmental interventions should be considered first. A Functional Behaviour Assessment may be conducted to understand the function of behaviours. If needed, pharmacotherapy can be considered.

HOW LONG WILL THE TREATMENT LAST?

People with PMS are treated based on their symptoms. There are no medications or therapies specifically for this syndrome. A management team consisting of several medical and developmental/educational specialists may be needed to address the areas of concern.

See also the chapter "How can I get additional support?, including centres of expertise on Phelan-McDermid syndrome (page 28).

CAN IT HAPPEN AGAIN?

The pregnancy of a child with PMS is usually uneventful, the first sign being low muscle tone at birth. But often the diagnosis is made later on, when the child appears to develop slower than its peers.

As explained on page 9 under "Why does my child have Phelan-McDermid syndrome?", in most individuals with PMS the genetic alteration is not inherited: the chromosomal deletion or the SHANK3 mutation happens spontaneously during egg or sperm formation.

So, in most instances, if you have a child with PMS, and you get pregnant again, the chance of that new child having the syndrome is low (1-2%). However, after the diagnosis in the child with PMS has been made, a genetic test will be carried out to determine if the parents have an increased recurrence risk. See also the chapter on Do's.

Prenatal diagnosis is always an option that can be discussed in new pregnancies. The doctor will inform the couple about the possible results of prenatal testing, and the risk for the mother and for the child.

DO'S

Listed below you will find the European consensus recommendations for Phelan-McDermid syndrome as agreed upon by the European PMS guideline consortium. They have been translated into lay language and *examples* have been added. Some more general do's have been added as well whenever relevant.

WHAT ARE THE RECOMMENDATIONS FOR MANAGING COMMUNICATION, LANGUAGE AND SPEECH PROBLEMS?

- Hearing should be checked at the time of diagnosis and regularly thereafter to detect possible hearing loss.
- A specialized multidisciplinary team should evaluate all factors that may influence communication, speech and language. *This includes, for example, hearing, cognition, oral motor coordination and palate function.*
- Preverbal and verbal communicative skills and cognitive development should be evaluated prior to speech therapy and other interventions *because the individual should be addressed at the appropriate cognitive level. One should also be aware that the individual may need more time to process information.*
- Parents should be instructed and supported by a specialist on supporting, facilitating, and stimulating communication, language and speech from an early age. *This may include talking slowly, in an articulated manner and face-to-face.*
- The use of communication aids is recommended to facilitate communication for individuals with PMS. These aids do not delay active language development. *Examples are speaking with gesture support, speech computers and other tools.*

WHAT IS RECOMMENDED TO MANAGE CHEWING, SWALLOWING AND GASTROINTESTINAL PROBLEMS?

- Ask your doctor to refer your child to a pre-verbal speech therapist if chewing and swallowing problems are present.
- Both gastroesophageal reflux and constipation should be considered if behavioural changes are observed.
- If faecal incontinence is present, other internal organ diseases should be excluded and behavioural interventions should be considered (if needed, a behavioural specialist should be consulted). *As a parent, keeping a stool diary can be very helpful.*
- For treatment of gastroesophageal reflux, diarrhoea and constipation, general national or international guidelines can be followed. *As a parent, you may give attention to: portion sizes and how fast they are eaten, potential intolerance to specific food, sufficient fluid and high-fibre intake, toilet routine and sufficient body exercise.*
- If zinc deficiency is present, dietary zinc supplementation should be considered.

WHAT IS RECOMMENDED TO MANAGE ALTERED SENSORY FUNCTIONING?

- Caregivers and healthcare providers should be aware that individuals with PMS often have a reduced responsiveness to sensory stimuli such as pain, sudden sounds and heat. *As a parent, you can carefully check your child after every (suspected) trauma, and be aware of easily overheating (adjust dress and cool when needed).*
- Every individual with PMS needs to be screened for hearing and visual disturbances at the time of diagnosis and subsequently monitored in accordance with national guidelines.
- Sensory integration functioning should be checked in every person with PMS. If altered sensory function is present, a sensory integration therapist should be consulted. *In case of impaired functioning of the sensory integration, suggestions for exercises or tools can be given by the therapist.*
- In case of behavioural changes, evaluation of possible causes should include a search for pain and altered sensory function. The use of a non-verbal pain scale is recommended.

WHAT IS RECOMMENDED TO MANAGE EPILEPSY?

- In every individual with PMS, irrespective of age, caregivers should be alert for seizures and epilepsy. *As a parent, you are advised to seek help whenever you suspect seizures or absences. Making a video of the situation can be very helpful.*
- When seizures are suspected but EEG studies are non-conclusive, overnight prolonged EEG studies should be considered.
- Brain imaging, preferably by MRI, is advised in every individual with PMS who has epileptic seizures.
- A paediatric neurologist or neurologist should be involved in the therapy for epilepsy.
- Anticonvulsant treatment of epilepsy in individuals with PMS should be provided in accordance with national guidelines.

In case of epilepsy, general rules for caregivers apply:

- *During seizures, try to keep calm and lay the patient on their side or cushion their head with a pillow. Make sure there is nothing in the mouth.*
- *Be careful with water, heights, sharp objects, and electrical equipment.*
- *Do not leave the child with epilepsy unattended while outside or in a swimming pool. Let the child wear a protective helmet if needed.*
- *Try to avoid flashing or flickering lights directed towards the patient.*
- *Do not run out of any dose of medicine. Missing a dose could make the individual more likely to have a seizure.*

WHAT IS RECOMMENDED TO MANAGE SLEEPING PROBLEMS?

- In case of sleeping problems, try to exclude physical, mental or environmental problems. *Examples of these are pain, epilepsy, anxiety, depression, side effects of medication, uncomfortable noise, light or mattress.*
- If mental health problems like anxiety and depression are present, ask your doctor to investigate and treat them.
- Sleep hygiene and behavioural intervention are very important. *This includes: no stimulating activities or drinks before bedtime, a constant bedtime routine with fixed bed times, a comfortable sleeping environment, weighted blankets and behavioural techniques such as gradual distancing or bedtime fading (glossary).*
- If sleeping problems do not resolve with the abovementioned interventions, discuss with your doctor referral to a specialist experienced in sleep problems or a specialist sleep centre.

WHAT IS RECOMMENDED TO MANAGE LYMPHEDEMA?

- Your doctor should pay attention to the possible development of lymphedema if your child has a 22q13 deletion. Treatment may include compression bandages and garments, but also skincare and advice.
- If the lymphedema is impacting daily functioning, your doctor may refer your child to a lymphedema centre of expertise for further investigation and treatment.

In case of lymphedema, general rules for caregivers apply:

- *Follow a healthy diet and do regular physical exercise to prevent obesity.*
- *Use a soap-free cleanser and carefully dry the skin to avoid infections or tissue maceration.*
- *In case of fluid retention in the legs, elevate the foot-end of the bed.*
- *Check the skin daily for any changes such as breaks in the skin (scratches, cuts, burns, abrasions), leakage of lymph fluid, pressure points from compression garments or changes in colour.*
- *Pay attention to nail care, obtain a medical pedicure, or see a podiatrist for toenail problems.*
- *Seek medical attention when there is a suspicion of a skin infection (redness, rash, warmth, or tenderness/pain) or leakage of lymph fluid.*

WHAT IS RECOMMENDED TO MANAGE MENTAL HEALTH ISSUES?

- In each individual 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 and adaptive (self-care daily life activities) 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.

As a parent, it is important to be alert on the following:

- *Note if there are warning signs and discuss with your doctor referral for psychiatric assessment when indicated (see page 14 under "Mental health issues", for warning signs).*
- *Monitor regularly for further changes in symptoms, cognitive development and adaptative functioning, changes in behaviour, including challenging behaviour, and for psychomotor agitation, loss of skills, bipolar disorder/mood cycling and psychosis.*
- *Sleep disturbances may be related to cause mental health issues. Improving sleep and sleep hygiene are important (see recommendation for sleeping problems).*
- *Consider environmental factors or stressors as a cause of agitated or anxious behaviour.*

WHAT IS RECOMMENDED REGARDING GENETIC COUNSELING AND RECURRENCE RISK?

- All individuals with PMS and their parents should be referred for genetic counselling. In genetic counselling, the clinical geneticist or other experienced clinician explains the clinical effect of the 22q13 deletion size or of the SHANK3 mutation. He/she also determines if there is an increased recurrence risk for another child with PMS for the parents and other family members.
- Further genetic studies should be performed for proper genetic counselling of recurrence risk and to exclude a ring chromosome 22 (when a 22q13 deletion was detected by microarray). *A scheme for this can be found at https://ern-ithaca.eu/documentation/phelan-mcdermid-guideline/.*
- During follow-up of individuals with PMS the doctor should check whether genetic work-up is complete and up-to-date.
- In subsequent pregnancies, the parents of the child with PMS should be offered prenatal diagnostic testing.

WHAT IS RECOMMENDED IN CASE OF A RING CHROMOSOME 22?

- In an individual with a ring chromosome 22, personalized monitoring for potential NF2-tumours should be discussed with the patient or their representatives.
- 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, the doctor should discuss repeating the MRI.

WHAT IS RECOMMENDED IN CASE OF OTHER ISSUES?

The guideline does not cover consensus recommendations regarding issues that were not identified by parents as major. However, in the Surveillance Scheme advice is given regarding screening for congenital abnormalities of, amongst others, the kidneys and heart. See *https://ern-ithaca.eu/documentation/phelan-mcdermid-guideline/*.

HOW CAN I GET ADDITIONAL SUPPORT?

WHAT IS RECOMMENDED REGARDING MANAGEMENT OF CARE?

- The individual with PMS and the family should receive integrated care provided by clinical experts and caregivers/relatives (treatment team), usually divided over different levels of care: centres of expertise or academic hospitals, general regional or local hospitals and local therapy centres (for rehabilitation, physical therapy, logopaedics, psychological support, etc).

- The professionals should coordinate their activities as much as possible so that the individual with PMS receives all the care and guidance needed in the most optimal way. A coordinating professional should be appointed. A multidisciplinary team should be established based on the PMS surveillance scheme (https://ern-ithaca.eu/documentation/phelan-mcdermid-guideline/).

- Specific care needs should be noted in the medical records and the individual care plan, if available.

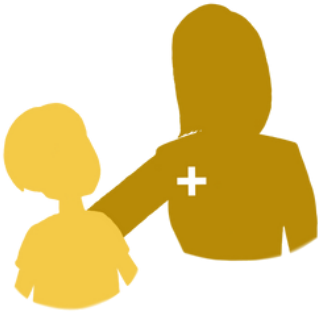
- For every teenager with PMS, the transition from paediatric to adult care is initiated on a timely basis and monitored by the coordinating paediatric professional. Coordination should be transferred to a professional in adult care. This should be recorded in the medical records and individual care plan.

Additionally:

- Enrolment in a clinical treatment trial may be considered and discussed with caregivers of individuals with PMS.

Caregivers and their families often experience elevated stress and tension related to issues in PMS such as sleeping problems or trying to organise adequate care. The team involved in the treatment of the family member with PMS can initiate additional support to help reduce stress in caregivers and their families.

The centre of expertise or the (academic) hospital should provide highly specialized care and is responsible for the management and general coordination of the integrated care chain (Figure 4).



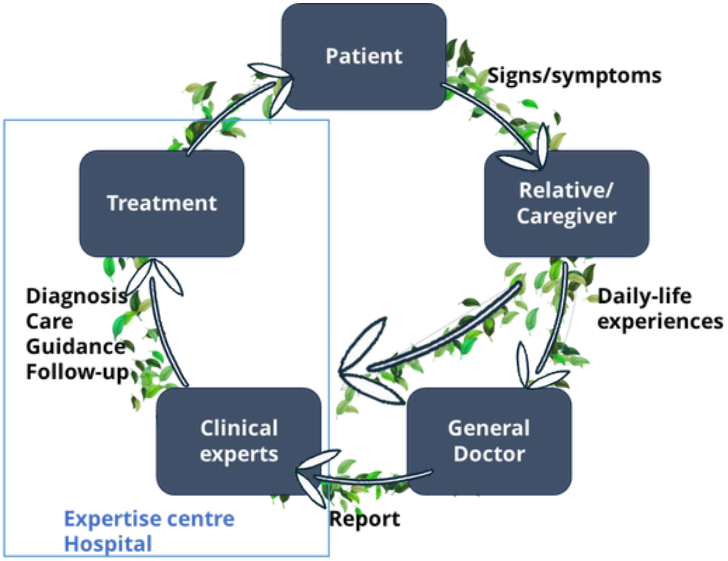


Figure 4. Loop of people involved in the treatment and care of patients with PMS. A multidisciplinary team is formed by several specialists. These care providers can be present in one care setting or spread over several care institutions.

SURVEILLANCE SCHEME AND EMERGENCY CARD

The guideline consortium has developed a Surveillance Scheme that advises on investigations to be performed at different ages: upon diagnosis, 0-2 years, 2-12 years, 12-16 years, >16 years. The most recent version of the Surveillance Scheme can be downloaded from: https://ern-ithaca.eu/documentation/phelan-mcdermid-guideline/ (see also QR code).

For parents an Emergency Card has been prepared. This is a one-page information leaflet with on one side the core information about PMS, including emergency situations, and on the other side a form that can be completed with information about the individual with PMS. This form can be handed over in emergency situations or when visiting a doctor who is not familiar with the syndrome or the patient. The Emergency Card will be made available in different languages and can be downloaded from: https://ern-ithaca.eu/documentation/phelan-mcdermid-guideline/ (see also QR code).

CENTRES OF EXPERTISE

This is the link to the website where 72 centres of expertise for rare syndromes with intellectual disabilities from all over Europe can be found: https://ern-ithaca.eu/about-us/expert-centers/

Dedicated centres of expertise on Phelan-McDermid syndrome are present in amongst others Groningen (NL), Leuven (BE), London (UK), Madrid (ES), Paris (FR) and Ulm (GE). See Orphanet: https://www.orpha.net

ECHO: PMS NEUROPSYCHIATRIC CONSULTATION GROUP

The Phelan-McDermid Syndrome Foundation (PMSF) and the Seaver Autism Center at Mount Sinai have initiated a service that helps doctors care for people with Phelan-McDermid syndrome (PMS) with challenging neuropsychiatric or behaviour problems. Information can be found at: https://pmsf.org/neuropsychiatric-consultation-group/

GROUPS AND ORGANISATIONS OUTSIDE THE HOSPITAL

Families of people affected by PMS have created patient organisations and a Facebook community in some EU countries like Denmark, Finland, France, Germany, Ireland, Italy, Lithuania, Netherlands, Norway, Poland, Portugal, Spain and Sweden to share information and provide support.

There is an international PMS support organisation in the US with satellite organisations in the EU: https://pmsf.org.

There are also other social networks as Twitter, Instagram and YouTube. By scanning the following QR code you can find the information attached on a pdf.

GLOSSARY

Adaptive functioning: This refers to the way in which an individual responds to the demands of daily life such as communicating, socializing, personal care and tasks around home and community.

Anxiety: This accompanies mood dysregulation, agitation, irritability, disruptive behaviour, withdrawal or avoidance, increased echolalia (repetition of what is said by other people as if echoing them), shouting, sleep disturbance and self-injury.

Apnoea: A temporary stopping of breathing during sleep, accompanied by loud snoring and feeling tired next day.

Atypical absence: An atypical absence is a type of seizure that may be longer, have a slower onset and offset, and involve different symptoms. The seizure still starts with staring into space, usually with a blank look. There is usually a change in muscle tone and movement. You may see blinking over and over that may look like fluttering of the eyelids, smacking the lips or chewing movements and rubbing fingers together or making other hand motions. An atypical absence seizure lasts longer, up to 20 seconds or more.

Autism spectrum disorder (ASD): A neurodevelopmental disorder affecting social interaction, communication, behaviour, and sensory processing. Symptoms usually become evident at a young age, but autism can be diagnosed at any age.

Bedtime fading: Technique to gradually close the gap between current bedtime and target bedtime in steps of 15–30 minutes a day.

Bipolar disorder/mood cycling: A psychological disorder characterized by alternating episodes of depression and mania. Symptoms include behavioural instability, irritability, distractibility, aggression, screaming disinhibition, hyper-sexuality, alternating with periods of apathy and depression. Sleep problems are usually present as well.

Catatonia: A psychomotor disturbance characterized by behavioural, affective, and motor disturbances (muscle rigidity, stupor, mutism, purposeless movements, negativism, echolalia, and inappropriate or unusual posturing).

Chromosomal microarray analysis (CMA): This is a genetic test that is often recommended for children with global developmental delays, birth defects, or several unexplained serious medical problems. It gives information on whether (part of) chromosomes are missing or duplicated. Changes in the genes themselves cannot be detected by microarray (see whole exome sequencing).

Chromosome: A threadlike structure, found in the nucleus of each cell, that carries almost all of the genes in the cell of an organism. Each cell contains 23 pairs of (46) chromosomes.

Constipation: A disorder of problems with the evacuation of faeces (greater than 48-72 hours) that occurs with hardening of the stool, decrease in volume or retention in the rectum for a prolonged period.

Deletion: The absence of a section of genetic material from a chromosome.

DNA: An abbreviation for deoxyribonucleic acid, a complex molecule that is inside the nucleus of the cells and is the main constituent of chromosomes.

Dysplasia: Abnormal growth or development of organs or cells.

Gastroesophageal reflux (GER): This occurs when the stomach contents come back up into the oesophagus. GER may cause heartburn.

Gene: The basic unit of material that passes traits from parent to child.

Genetic testing: A type of medical test that identifies changes in chromosomes, genes or proteins. The results can diagnose, confirm, or discard a genetic condition or help determine the likelihood that a person will develop or pass down a genetic disorder.

Gradual distancing (or gradual withdrawal): Technique in which the parent sits near the child and increases the distance every couple of nights.

Hypotonia: The state of having a low muscle tone.

Incontinence: Involuntary passing of urine or faeces.

Karyotype: A photographic image or other representation of all the chromosomes in a cell usually arranged in pairs from largest to smallest.

Lymphedema: This refers to tissue swelling caused by an accumulation of protein-rich fluid that's usually drained through the body's lymphatic system. It most commonly affects the arms or legs, but can also occur in the chest wall, abdomen, neck, and genitals.

Obstipation: Severe and obstinate constipation.

Parasomnias: Physical events during sleep, or on the transition to/from sleep such as for example sleepwalking, sleep talking, night terrors and nightmares, grinding teeth, bed wetting, apnoea, or night convulsions.

Psychomotor agitation: Behaviours suggestive of hyperactivity and attention deficit including motor restlessness, impulsivity, and distraction.

Psychosis spectrum disorders: These include two main symptoms, hallucinations, and delusions, that may cause severe distress and change behaviour. Behavioural changes include unusual mood manifestations, aggressive outbursts, apathy, loss of initiative, loss of appetite, loss of previously acquired skills.

Regression/loss of skills: A prolonged (minimum of 3 months) loss of previously acquired skills that can occur during or following psychiatric episodes or stressors like infections, mood episodes, and environmental stress, but can also occur without correlation to a known event.

Regurgitation: Spitting up from the oesophagus or stomach incompletely digested food.

Seizure: A sudden, uncontrolled burst of electrical activity in the brain. It can cause changes in behaviour, movements, feelings, and levels of consciousness. Also called a convulsion.

SHANK3: This gene (a sequence of chromosome 22) encodes the protein SHANK3. The latter is an important molecule at the contact sites of nerve cells, the synapses.

Short Sensory Profile 2: A method to screen for sensory functioning, see also "User's manual. Dunn, W. (2014). San Antonio: Psychological Corporation".

Psychological trauma: An emotional response that is caused by experiencing a single or a series of emotionally/ psychologically distressing events. Some signs of trauma can include longstanding periods of hyper- or hypo-arousal, increased or reduced verbalising, forgetfulness, being lost in thought, an increase in anxiety-related behaviours, an increase in repetitive behaviours, recurring nightmares, flashbacks, panic attacks and heightened avoidance of specific situations or people.

Whole Exome Sequencing (WES): Previously called Next generation sequencing (NGS). A genetic technique that supports the diagnosis of patients with common and rare diseases by determining the DNA sequence of all genes. For example, over 2500 genes are known to be involved in development. By testing all these genes in one single WES test, it is easier to find the cause for the developmental delay in a child (but a diagnosis can still not be made in every child).

The beauty of the universe consists not only of unity in variety, but also of variety in unity.

Umberto Eco