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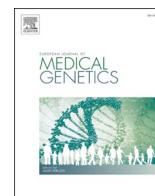
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Consensus recommendations on mental health issues in Phelan-McDermid syndrome

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ABSTRACT

Phelan-McDermid syndrome is a rare genetic condition caused by a deletion encompassing the 22q13.3 region or a pathogenic variant of the gene *SHANK3*. The clinical presentation is variable, but main characteristics include global developmental delay/intellectual disability (ID), marked speech impairment or delay, along with other features like hypotonia and somatic or psychiatric comorbidities. This publication delineates mental health, developmental and behavioural themes across the lifetime of individuals with PMS as informed by parents/caregivers, experts, and other key professionals involved in PMS care. We put forward several recommendations based on the available literature concerning mental health and behaviour in PMS. Additionally, this article aims to improve our awareness of the importance of considering 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 concerning behaviours offers insight into the meaning of those behaviours and informs care for individuals with PMS, enabling clinicians to address unmet (mental health) care needs and improve quality of life.

1. Introduction

Phelan-McDermid Syndrome (PMS) (OMIM#606232) is a rare (est. 1/30,000 live births) genetic syndrome, caused by a deletion of 22q13.3 (including *SHANK3*) or by a pathogenic variant of *SHANK3*. Deletions in the 22q13.3 region not involving *SHANK3* typically lead to a similar phenotype and are considered as a *SHANK3*-unrelated diagnosis of PMS (Phelan et al., 2022). The syndrome is characterized by global developmental delay, moderate to profound intellectual disability (ID) and marked speech impairment, among other clinical manifestations

(Phelan and McDermid, 2011; Schön et al., 2023, this issue). In fact, the phenotypic presentation is variable, including expression, severity, and impact of psychiatric symptoms. Phenotypical differences between 22q13 deletions and *SHANK3* variants are discussed in Schön et al. (2023, this issue). The aetiology of different developmental and psychiatric outcomes within the syndrome is yet to be established, and there is competing evidence about the influence of deletion size thus far (Droogmans et al., 2020; Levy et al., 2022; Nevado et al., 2022; Sarasua et al., 2014). It is important to keep in mind that the psychiatric phenotype is variable, and symptoms do not apply to all individuals with

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PMS. Some may be spared of psychiatric and behavioural challenges, while others may have several co-occurring symptoms. However, a recent meta-analysis reported a higher risk of physical or mental health concerns in individuals with ID (Mazza et al., 2020). Additionally, there is evidence that the clinical presentation of mental health issues in people with intellectual disability may be different, making them difficult to recognize and ascertain (Fletcher et al., 2016).

Neurodevelopmental and psychiatric disorders have interrelated dimensions that may explain some of the behavioural difficulties. Behaviours are influenced by reciprocal interactions with the individual's internal and external environments. Any behavioural problem should always be considered within the context of environment as well as within the context of the individual's level of cognitive, social and emotional development. Monitoring development and individual functioning for the emergence of new associated issues should be considered at stages of transition, key developmental milestones, and when important changes occur in educational/daytime environments.

Where possible, standardized tools, validated for use in intellectual disability (ID), should be used, although assessing individuals with PMS and severe/profound ID, even with these instruments, may be difficult due to the individual's limitations, e.g., lack of understanding or motivation, difficulties expressing thoughts and feelings, and limited stress regulation abilities (DiStefano et al., 2020; Sappok et al., 2022). The sensitivity of instruments, such as ADOS and ADI-R, is reduced in severe/profound ID but there is some published guidance regarding the clinical evaluation of different domains in individuals with PMS and other conditions associated with severe/profound ID (Oliver et al., 2022; Soorya et al., 2018).

In this paper we discuss a wide range of mental health issues, with overlapping diagnostic categories. Understanding the issues associated with PMS, as well as the emotional reference age of the individual associated with ID, will help to contextualize certain behaviours and provide a basis for more personalized interventions that may improve quality of care. Especially in severe/profound ID, it may be hard to disentangle mental health concerns from behavioural manifestations related to intellectual or developmental level and confer a meaning to certain behaviours. Some considerations for assessing mental health in conditions like PMS will be presented later in the manuscript, in Table 1.

The present paper is part of a series of papers together comprising the European best clinical practice Guideline on Phelan-McDermid Syndrome (van Ravenswaaij-Arts et al., 2023, this issue). It aims to recommend practical approaches to identify and address mental health issues in individuals with PMS, while emphasizing the importance of understanding the meaning of behaviours and/or symptoms within the context of developmental and cognitive level, and level of adaptive functioning.

Table 1
Warning signs for mental health concerns in PMS, based on ID generally.

Increase in anxiety-related behaviours, e.g., avoidance, more or less vocalizations than usual, unusual loss of appetite or food refusal, increased motor restlessness/agitation, increased repetitive behaviours.
Increase in challenging and/or self-injurious behaviours, e.g., verbal and/or physical aggression towards self or others such as hitting, throwing objects, biting, head banging, slapping, pinching.
Withdrawal and no longer seeking to participate in social interactions the individual would previously have enjoyed.
Other behavioural changes such as increased demands for attention, crying more often than usual or crying for no discernible reason.
Changes in sleep pattern, e.g., trouble getting to sleep, trouble staying asleep, sleeping more than usual. As sleep disorders are common in PMS it is important to establish what should be considered atypical for a specific individual.
Loss of previously established adaptive skills or daily living skills, such as getting dressed, toileting, eating independently, general self-care.

2. Methods

The European PMS consortium includes patient representatives, European health professionals and researchers; more information can be found in the editorial of this special issue. The working group designated to cover the topic of mental health issues in PMS was composed of three psychiatrists (IvB, AM, AV), two psychologists (MBO, JC) and a patient representative (AT). A data analyst (GdC) designed the figures and made content suggestions. As PMS is a rare condition, we performed a general scientific literature search for Phelan-McDermid syndrome. We reproduced the search terms used for the original Dutch guidelines in early 2021 in PubMed (“telomeric 22q13 monosomy syndrome”[Supplementary Concept] OR “shank3 protein, human”[Supplementary Concept] OR “chromosome 22 ring”[Supplementary Concept] OR (“ring 22[tiab] OR “Phelan-McDermid[tiab] OR (((22q[tiab] AND terminal [tiab]) OR 22q13[tiab] OR SHANK3[tiab]) AND (deletion[tiab] OR monosomy[tiab] OR syndrome[tiab]))) and EMBASE (“phelan-mcdermid syndrome”/exp OR ‘ring chromosome 22’:ab,ti OR ‘phelan mcdermid’:ab,ti OR (“22q terminal”; ab,ti OR 22q13:ab,ti OR shank3:ab,ti) AND (deletion:ab,ti OR monosomy:ab,ti OR syndrome:ab,ti))) AND [embase]/lim. The database search yielded 1381 publications, of which we excluded 1305 after title and minor abstract read. We manually extended the search in PubMed to cover published papers until June 2022, which provided 12 potentially relevant papers. We revised a total of 87 abstracts with the following exclusion criteria: 1) Sample: SHANK3-unrelated PMS or familial studies; 2) Scope: Topic covered by other European PMS guideline chapter or redundant characterisations/reviews or focus other than neuropsychiatric phenotype (genetic, brain imaging ...) or general descriptions of SHANK3 alterations in psychiatric disorders; 3) Methodology: n < 15 unless clear neuropsychiatric focus. After this process, additional 58 studies were excluded, which resulted in 29 included papers after critical whole manuscript read. A flowchart describing the search process is presented in Fig. 1. Literature beyond PMS was also considered when relevant, for instance, studies addressing mental health in populations with intellectual disability.

Important concerns to be addressed within the guideline were defined by a consortium of experts and patient representatives, as well as informed by the answers of parents/caregivers to an online global survey on lived experiences (Landlust et al., 2023, this issue). The literature was selected and sorted following the fundamental questions based on the original Dutch guidelines (Federatie Medisch Specialisten, 2018) and raised by the consortium and caregiver survey. Concretely, the following questions regarding mental health issues were formulated for this paper:

- 1) Which mental health issues (or symptoms of mental disorders) are found in individuals with PMS?
- 2) Are there distinguishable warning signs for mental health issues?

Literature was reviewed to answer formulated questions and to articulate recommendations as part of the development of the above-mentioned guideline for Phelan-McDermid Syndrome following methodology based on the AGREE II instrument (Appraisal of Guidelines for Research and Evaluation II) (Brouwers et al., 2010). Broader literature from research on ID was also consulted, and relevant studies stemming from the work on the same PMS European guideline are referenced as “this issue”.

In various on-line meetings members of the working group discussed the literature to reach agreement on the recommendations (see Table 2) to be proposed to all consortium members. Wording of text and recommendations was critically reviewed by consortium members. At a consensus meeting in June 2022 proposed recommendations were discussed at length and rephrased until consensus was met. Our recommendations focus on early detection and documentation of mental health issues and status. Treatment of mental health disorders should be individualized and according to (inter)national standards as long as no

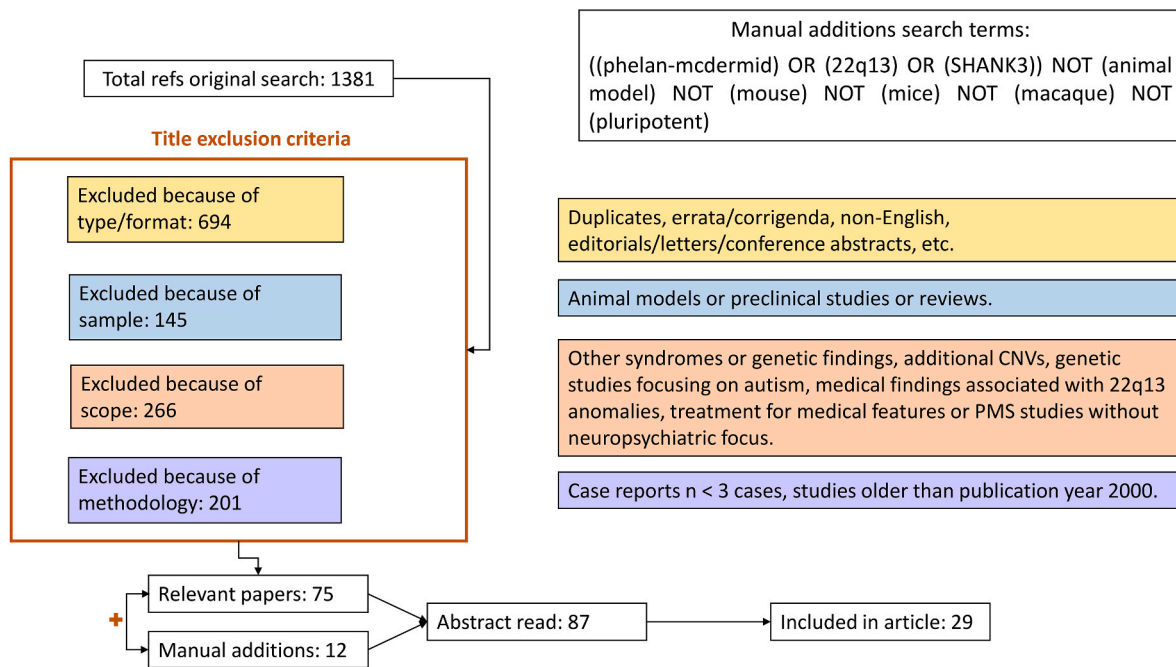


Fig. 1. Flowchart describing the selection process, title exclusion criteria and manual search terms.

Table 2

Recommendations as agreed upon by the European Phelan-McDermid syndrome consortium.

Recommendations
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.

evidence for PMS specific treatment exists. Consortium members subsequently voted on the reliability of each recommendation (van Ravenswaaij-Arts et al., 2023, this issue).

3. Conclusions from literature

The following paragraphs describe relevant domains and concerns to consider in mental health issues, taking into account the context of developmental, cognitive and adaptive level of the individual with PMS.

Our search had a focus on clinically relevant publications, or papers including characterizations that directly addressed the neuropsychiatric phenotype in PMS samples. We sorted the literature based on what the working group considered to be the clinical topics addressed in each publication.

With these fundamental clinical themes in mind, we explored how these connect to one another in the selected scientific literature. As mentioned earlier, we want to emphasize the importance of

understanding behaviours and/or symptoms within the individual context. The clinical picture of PMS is complex and characteristics such as the presence of intellectual disability or co-occurring medical events are key factors for mental health status. In the abstracts of the selected publications, we searched for the identified clinical themes or other related terms (e.g., “aggression” would be categorized within “Behaviour” or repetitive behaviour within “Autism”, etc.) and made a co-occurrence table to see how often these topics appeared together. Afterwards, we produced a network analysis to graphically show these connections (Fig. 2). While some topics are presented together, often these clinical themes are addressed as standalone or single themes, with few links to the individual context or other clinically relevant variables of the subjects.

The order in which we discuss these clinical themes responds to how commonly these seem to occur and how worrying these are to families (Landlust et al., 2023, this issue), moving from pervasive features such as cognitive or communicative impairments to concerning psychiatric

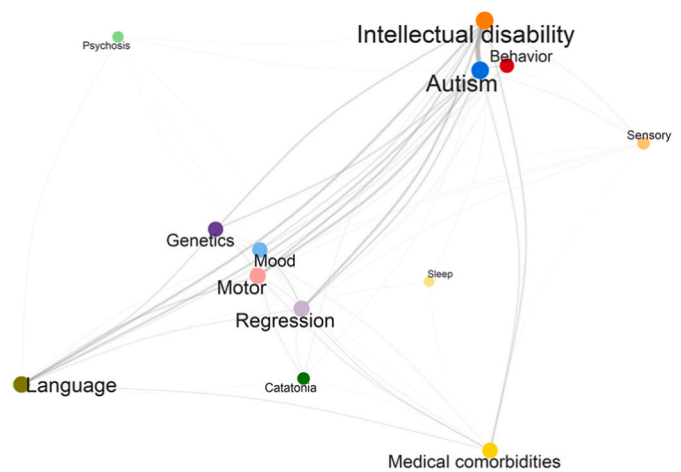


Fig. 2. Network analysis for clinical themes based on abstracts of published literature. Bolder connecting lines and larger dots indicate higher frequency of co-occurrence of certain topics in the same publication.

conditions like catatonia.

3.1. Cognitive development and adaptive functioning

Earlier publications on PMS have described global delays in intellectual development, generalized hypotonia, and severely delayed or absent speech (De Rubeis et al., 2018; Phelan and McDermid, 2011; Xu et al., 2020). Developmental delay ranges from moderate to profound within the existing literature on PMS (estimates from several studies show very low mental age equivalents on developmental scales, often below 24 months (Denayer et al., 2012; Droogmans et al., 2020; Glaser and Shaw, 2011; Zwanenburg et al., 2016)), and is a common feature in individuals with 22q13 deletions or *SHANK3* variants (present in over 95% of the cases). The influence of deletion size on the severity of the impairment has been disputed. A recent study found no significant differences in relation to deletion size regarding cognitive development, adaptive behaviour, verbal and non-verbal communication, emotional and behavioural problems, symptoms of ASD and sensory dysfunction (Droogmans et al., 2020). Commonly reported behavioural characteristics include sensory stimulating behaviours, such as mouthing or chewing of objects (other than food), and decreased pain perception (Vogels et al., 2020). In a study exploring toileting skills, individuals with PMS showed high rates of urinary incontinence in all age groups (Hussong et al., 2020). They suggest an association with difficulties attaining adaptive and daily living skills due to slow maturation in intellectual disability, note that improvement in toileting skills is possible and emphasize the importance of assessing medical comorbidities.

Adaptive functioning refers to how an individual responds to the demands of daily life, such as communicating, socializing, personal care, and tasks around the home or in the community. It is linked to cognitive/developmental level, individuals with ID often show reduced adaptive and self-help skills, and may be further impacted in individuals with co-occurring autism because they are likely to find navigating daily social situations challenging. Examination of adaptive abilities must systematically accompany assessment of intellectual functioning. Assessment must be carried out with current and validated tools to avoid misinterpretation or incomplete diagnoses (Landlust et al., 2022). Evaluations should be completed by an experienced psychologist or allied professional and appropriate to the individual's age and (estimated) developmental and language level.

3.2. Communication and language issues

Language delay and/or absent speech are among the most common characteristics in PMS, with both expressive and receptive communicative abilities affected. Recent studies show marked speech impairment in up to 95% of cases with 22q13 deletions and 69% of cases with *SHANK3* variants (De Rubeis et al., 2018; Xu et al., 2020). However, other communicative behaviours may be preserved, such as sounds, single words, or gestures. Studies have shown that impairments in expressive language are highly likely to contribute to challenging behaviours, particularly self-injury, in those people with severe to profound ID (see Meta-analysis by McClintock et al. (2003)). There is some evidence that challenging behaviour is linked to anxiety and depression in ID, but this is limited in severe to profound ID (Moss et al., 2000). For more guidance on communication and language in PMS, see Burdeus-Olavarrieta et al. (2023, this issue).

3.3. Autism spectrum disorder (ASD)

ASD symptoms include limitations in social-communication and social interaction with repetitive behaviours and restricted interests, as well as sensory issues. Recent estimates of ASD rates point to a European median prevalence of 1/100 individuals, of which around 21% have co-occurring ID (Zeidan et al., 2022). It has been suggested that PMS accounts for up to 0.5% of ASD cases (Soorya et al., 2013). In PMS, as is the

case for other conditions with severe ID, diagnosing ASD is challenging and care should be exerted to establish whether the frequency and intensity of autism symptoms go beyond what would be expected given the individual's developmental level (Thurm et al., 2019).

Several studies report a prevalence of around 65% in patients with 22q13 deletions (Denayer et al., 2012; Richards et al., 2017; Samogy-Costa et al., 2019; Tabet et al., 2017; Xu et al., 2020) and around 76% in cases of *SHANK3* variants (De Rubeis et al., 2018; Xu et al., 2020), with a variable profile of deficits in the two defining domains (Oberman et al., 2015). Comparative studies suggest that the presentation of autism symptoms in PMS may be different to that of autistic individuals (i. e., less withdrawn behaviours, higher mood and less repetitive behaviours (Glaser and Shaw, 2011; Richards et al., 2017)), although it is unclear whether these findings entail PMS individuals with or without a comorbid diagnosis of ASD, so generalizability is limited.

3.4. Regression/loss of skills

Regression is defined as a prolonged (minimum 3 months) loss of skills previously acquired, and it can occur during or following psychiatric episodes or other stressors (Kohlenberg et al., 2020). Stressors preceding regression may include e.g., infections, mood episodes, environmental stress. Studies describing regression in PMS have reported on small study samples and findings need to be replicated. Denayer et al. (2012) described that a progressive loss of skills was often seen early in adulthood in individuals with PMS. Verhoeven et al. (2020) found episodic catatonic symptoms, as well as a progressive loss of skills during the third or fourth decade in individuals in their study sample.

Loss of speech is most frequently reported, but loss of motor, communicative, and social interaction skills have been described at variable ages beyond the first 3 years of life. In a study of 42 individuals aged 4–48 years (Reierston et al., 2017), parent-reported regression was found in 43% of the participants, with onset at about six years of age. This is in contrast with early regression previously reported in ASD or Rett syndrome. Interestingly, around 40% of these individuals re-gained skills after a period ranging from 1 month to 10 years. Burdeus-Olavarrieta et al. (2021) also reported on regained skills after regression in their study of 60 young individuals (mean age 8.5 years, SD = 7.1). Regressive episodes have sometimes been reported in co-occurrence with bipolar or mood cycling symptoms (Kolevzon et al., 2019); see section 10 in this paper).

3.5. Hyperactive and agitated behaviour

Behaviours suggestive of hyperactivity and attention deficit, including motor restlessness, impulsivity and distraction, are commonly reported in the literature on PMS (Shaw et al., 2011). However, these behaviours are not specific to PMS, may not meet criteria for a DSM-classification of ADHD (American Psychiatric Association, 2022), and should always be considered in the context of the developmental level of the individual. Changes in behaviour should be monitored over time with a mind to what is typical and within a routine for a given individual.

Hyperactivity was reported in the literature in about 29% of participants with PMS carrying a 22q13 deletion (Denayer et al., 2012; Tabet et al., 2017; Xu et al., 2020) and in 72% of participants with *SHANK3* variants (De Rubeis et al., 2018; Xu et al., 2020).

A study by Kohlenberg et al. (2020) investigated mental health difficulties in PMS. These difficulties may be associated with agitated behaviour and may include affective symptoms: these are discussed in section 10.

3.6. Sensory issues

Sensory dysfunction occurs in several domains for patients with PMS, reduced pain perception, heat regulation disorder, changed sensitivity,

hearing and vision impairment are often reported. Certain behavioural problems such as agitation or aggression may be linked to the sensory dysfunction present in PMS, as is sometimes the case in ASD/ID (Summers et al., 2017). For further details, see Walinga et al. (2023, this issue).

3.7. Sleep difficulties

Sleep disturbances are frequently reported in individuals with PMS. These problems include difficulties with sleep onset, frequent waking, restless sleep and night-time incontinence, which may negatively affect health, behaviour and functioning of the individual, as well as impact well-being of caregivers. For further details, see San José Cáceres et al. (2023, this issue).

3.8. Trauma

There is currently no literature specific to trauma and PMS. However, trauma reactions have been studied more broadly in ID. The risk of abuse is significantly increased for individuals with psychological and/or emotional disabilities, who are 4–10 times more likely to experience violence, abuse, or neglect (Govindshenoy and Spencer, 2007). There is consistent evidence that intelligence plays a protective role against the manifestation of Post-Traumatic Stress Disorder (PTSD), therefore those with ID may be compromised in their ability to process and cope with traumatic events. Individuals with ID are at increased risk of experiencing a traumatic event, such as abuse, threat, serious injury, neglect, or sexual violence, and rates of PTSD among those with ID are known to range from 2.5% to 60% (Mevisen and De Jongh, 2010). Trauma needs to be assessed using appropriate and validated tools for ID, and observable signs may include, but are not limited to, longstanding periods of hyper- or hypo-arousal, increased or reduced verbalising, forgetfulness, being lost in thought, an increase in anxiety-related or repetitive behaviours, recurring nightmares, flashbacks, panic attacks or heightened avoidance of specific situations or people.

3.9. Anxiety

Anxiety often accompanies mood dysregulation and co-occurs with a range of mental health issues and neurodevelopmental conditions. As a result, anxiety can be difficult to discern in individuals with severe to profound ID and/or expressive language difficulties (Kerns et al., 2021). Some behaviours associated with anxiety are agitation, irritability, disruptive behaviour, withdrawal or avoidance, increased repetitive behaviours, increased echolalia, shouting, sleep disturbance, and self-injury (Huisman et al., 2018; Kolevzon et al., 2019).

3.10. Bipolar and affective disorder/Mood cycling

Several studies have reported diagnoses of bipolar disorder in PMS (Denayer et al., 2012; Egger et al., 2016; Vogels et al., 2020). Notable symptoms include behavioural instability, mood cycling, irritability, distractibility, aggression, screaming, disinhibition, hypersexuality, and sleep disturbance (e.g., insomnia) (Egger et al., 2016; Vogels et al., 2020) and for some this coincides with a progressive loss of acquired skills early in adulthood (Denayer et al., 2012). In the recent study by Kohlenberg et al. (2020), onset of mental health difficulties was mostly between ages 10 and 18 years (28/38; 74%); with symptoms emerging between the ages of 7 and 10 years in 5/38 individuals (13%), while 5/38 (13%) developed symptoms between ages 21 and 32 years. In the study first episodes met criteria for a manic episode in 17/38 participants (45%) and for a depressive episode in 14/38 (37%). First episodes in the remaining individuals included six (16%) with a mixture of mood and anxiety symptoms, and one case of disorganized, bizarre behaviour that suggested a brief psychotic episode. Most participants (27/38; 71%) had experienced a mood episode in the year before the study. The

aftermath of acute episodes was associated with higher baseline levels of anxiety and irritability, and with regression.

Although a connection between PMS and bipolar disorder is possible, further research is necessary to establish the unique profile of symptoms. Current evidence suggests that treatment with a mood stabilizer appears to be effective (Denayer et al., 2012; Egger et al., 2016).

In diagnostic assessment, a thorough workup is warranted, including comprehensive physical examinations of medical or other causes (e.g., epilepsy, immunologic, metabolic issues, or neuropsychiatric causes). Catatonia should also be considered and ruled out (see section 11 in this paper). Antipsychotics in monotherapy should be closely monitored in PMS patients as they have the potential of inducing catatonia (Kohlenberg et al., 2020).

3.11. Catatonia

Catatonia often goes unrecognized and poorly treated in children and in individuals with developmental disabilities (Benarous et al., 2018). It is characterized by behavioural, affective and motor disturbances, and has a high morbidity and mortality, treatment is important to avoid life-threatening complications (Kohlenberg et al., 2020; Rasmussen et al., 2016). It often co-occurs with other psychiatric issues and is a specifier in the DSM category of ASD, bipolar disorder, schizophrenia, depression, delirium and postpartum psychosis (American Psychiatric Association, 2022). When suspected, clinician-informed standardized rating scales can be useful, such as the Bush-Francis Catatonia Rating Scale (BFCRS) (Bush et al., 1996) as well as administering 1–2 mg of lorazepam as diagnostic challenge, with reduced catatonic symptoms confirming the diagnosis.

Failing to identify catatonia and the resulting lack of appropriate treatment can lead to dangerous medical complications. Without timely treatment a patient may develop autonomic instability with hyperthermia, intense excitement, rigidity and delirium (malignant catatonia with a mortality as high as 20%). As far as we know, malignant catatonia has not been described in individuals with PMS.

Catatonia may be preceded by acute triggers like moving residence, infection or surgery. The first symptoms may emerge during adolescence or adulthood with an age at onset as early as 16 years. Symptoms fitting a diagnosis of catatonia have been reported previously, most often in the context of a comorbid psychiatric diagnosis, such as a bipolar disorder (Denayer et al., 2012; Kohlenberg et al., 2020; Kolevzon et al., 2019). Earlier descriptions of possible catatonia symptoms have been highly variable, but motor symptoms seem prominent with stereotyped postures (bending limbs, stooped posture, instability, spasticity), lack of movement (apathy, bradykinesia) and stereotyped movements (upper limb tremor at rest, restlessness, other stereotyped movements). In addition to motor issues, other common features include stupor, mutism, and oppositional behaviour. In the study by Kohlenberg et al. (2020), carriers of *SHANK3* pathogenic variants met criteria for catatonia more often than participants with 22q13 deletions.

Besides benzodiazepines, antipsychotics have been used in the treatment of catatonia, however, in PMS antipsychotic agents in monotherapy are generally poorly tolerated and may induce catatonia (Kohlenberg et al., 2020). Electroconvulsive therapy (ECT) for catatonia has yielded variable results (Breckpot et al., 2016; Kohlenberg et al., 2020). As recent studies suggest that *SHANK3* expression is modulated by inflammatory stimuli, immunomodulatory therapy (intravenous immunoglobulin, IVIG) has been started in a few patients with some improvement (Bey et al., 2020; Kohlenberg et al., 2020). There is not yet sufficient data to generalize a course of action.

3.12. Psychosis spectrum disorders

Psychosis has two main symptoms, hallucinations and delusional thinking, which can cause severe distress and change behaviour. Psychotic symptoms are likely to overlap heavily with other psychiatric

symptoms and may arise as part of a complex presentation (Kolevzon et al., 2019; Vogels et al., 2020). Therefore, behaviour should be monitored over time to establish the accuracy and necessity of diagnosis (Vogels et al., 2020). The evidence-base for psychosis in PMS is currently very limited, though emerging evidence suggests that psychotic symptoms can frequently co-occur with symptoms of depression, catatonia, and bipolar disorder (Kolevzon et al., 2019). There is some indication that those with ASD have higher risk of developing psychotic symptoms, so co-occurring neurodevelopmental conditions should be considered (Shaw et al., 2011). Reported behavioural changes include (but are not limited to) aggressive outbursts, apathy, loss of initiative, loss of appetite, loss of previously acquired skills, flattened mood, and/or mood disturbance, and it has been purported that psychotic presentation can emerge after acute events, such as infection, seizure, or changes to the individual's environment (Kolevzon et al., 2019).

Sleep disturbances have also been found to precede severe regression and/or psychotic symptoms in PMS (Kolevzon et al., 2019). Sleep problems are common in PMS (for more information on sleep in PMS see San José Cáceres et al. (2023, this issue)), therefore, monitoring of sleep hygiene and day/night routines should be relative to what is typical for a given individual. At present, there is no consensus on the use of drug treatment for psychosis in PMS.

3.13. General considerations and implications for practice

The clinical presentation of PMS is variable and encompasses a wide range of comorbidities or behaviours that may be indicative of mental health challenges, like the themes discussed above exemplify.

In this paper, we refrain from extensively discussing interventions/treatment options for the clinical themes described, as not only is this outside the scope of the paper but also because there is currently little evidence-base for effective treatment in PMS. Therefore, it is recommended to provide treatment on the basis of individual presentation and considerations. Additionally, our understanding of clinical trajectories in this condition is still limited, especially when individuals reach adulthood. Available literature suggests that behavioural changes or the onset of psychiatric symptoms may occur as individuals age past adolescence. Schön et al. (2023, this issue) discuss lifespan in PMS from pregnancy to adulthood, including descriptions of developmental, behavioural and psychiatric issues.

Although some individuals with PMS may be spared of psychiatric symptoms or present a relatively typical development with little cognitive or communicative difficulties, most individuals exhibit global delays and intellectual disability in the moderate to profound ranges. Based on clinical experience, parents/caregivers' input and literature from research on ID, we include several important principles and considerations for assessing mental health, behavioural and adaptive functioning, as well as planning interventions for individuals with PMS:

1. A comprehensive diagnostic formulation is needed to establish a holistic understanding of the individual within their context. Such a formulation should consider factors that influence mental health. These include physical, psychiatric, psychological, developmental, educational, social, environmental, and economic domains as well as caregiver reported general wellbeing. The coordinating physician should develop a health care plan jointly with the individual, caregivers/family members, educators, and health care professionals (see van Eeghen et al. (2023, this issue), as well as ensure appropriate assessments and ongoing monitoring to maintain the best possible outcome.
2. It is important to rule out any underlying medical issues for psychiatric or behavioural presentations, especially when the individual with PMS has limited communicative abilities. Periodic physical assessments in individuals with PMS are helpful for establishing the typical health status of the individual.

3. For individuals with limited communicative language a Functional Behavioural Assessment (FBA) by a psychologist or allied health professional is useful to establish the context of presenting behaviours.
4. It is crucial to understand the typical behaviour/affect/routine of an individual so that atypicalities can be identified and monitored over time. For example, sustained changes in behaviour could signify the onset of psychiatric issues but this will not always be the case. Monitoring of irregularities over time is therefore important and should always include a holistic formulation of the individual to consider the context and function of presenting behaviours.
5. Be aware that phenotype may change with aging, e.g., PMS individuals may appear more lethargic in adolescence than their peers. Data reported by parents and caregivers showed that the prevalence for problems with sleep, loss of skills, mood and severe psychiatric problems increased significantly with age (Landlust et al., 2023, this issue).
6. Be mindful of the impact that long-term and newly presenting behaviours can have on the wellbeing of those close to the individual, such as family and close caregivers. Promoting the wellbeing of support systems around the individual is crucial to their ongoing mental health.

Several warning signs, informed also by the current evidence base for mental health concerns in intellectual disabilities, are presented in Table 1 (Eaton et al., 2021; Herrera and Sulkes, 2021; Huisman et al., 2018; Kolevzon et al., 2019).

All warning signs should be considered in the context of what is typical behaviour for a given individual with PMS. Psychiatric assessments should always be considered when other possible medical/somatic/environmental causes have been explored and addressed.

3.14. Consensus recommendations

The following recommendations have been proposed based on expert opinion, parents'/caregivers' considerations and after critical read of the available literature covering a wide array of themes connected to mental health in Phelan-McDermid syndrome and intellectual disability. These recommendations, presented in Table 2, have been agreed upon by all PMS European consortium members during the consensus meeting in June 2022.

4. Discussion and considerations

PMS is a complex disorder and research interest has focused rather more on genetic advances than on neuropsychiatric presentations with associated symptoms. Many questions on genotype/phenotype associations and their significance for clinical practice still remain.

An extensive literature search was conducted with a focus on recent publications covering prominent clinical themes relevant to mental health and functioning in PMS, as well as broader literature on intellectual disability. Most members of the multidisciplinary working group have clinical or lived experience tackling the clinical themes and neurodevelopmental and mental health issues discussed in this paper. Although the working group is multidisciplinary, not all disciplines are represented and it is likely that our understanding might have benefited from input from other relevant disciplines, such as early intervention-professionals, treatment staff and social sciences. Our main focus was on behavioural issues emphasized by parents and caregivers (Landlust et al., 2023, this issue). Mental health, development and behaviour not only impact the individual and their daily functioning or wellbeing, but also affect their immediate context of family, living arrangement, and caregivers. Parental stress, especially stress concerning the future including the transition of care from paediatric to adult services for the affected individual, is potentially sustained over the years (Droogmans et al., 2021; Landlust et al., 2023, this issue; van Eeghen et al., 2023, this

issue). The strength of this paper is a broader perspective on the possible interplay of psychiatric, psychological, and social issues with developmental functioning that may arise in Phelan-McDermid syndrome. Currently, most of the literature covering PMS is focused on isolated psychiatric issues and, in some cases, potential treatments. To improve understanding life with PMS, there is a need for specific research on PMS, that provides a more complete view of the affected individual's behaviour within the context of that individual's level of cognitive and adaptive functioning and the impact on daily life. For example, when the gap between developmental and chronological age is large, severe discrepancies on the occurring vs. expected behaviours may arise. Distress or other externalizing symptoms observed might be interpreted as psychopathology, although a better explanation might be the low level of socio-emotional functioning and the disparity that this causes between the level of functioning expected for chronological age and the level of actual functioning of the individual (Sappok et al., 2022). An individual may be exhibiting certain conduct judged as "inappropriate" and may face expectations of behaviours difficult to comply with. This may, in turn, result in complications in daily life for the individual, caregivers or professionals across social contexts. There is also a need for more research focused on treatment beyond pharmacological interventions, such as behavioural and environmental interventions.

Available literature on mental health in PMS is limited, and publications considering individual, as well as environmental factors are even more scarce. This has constrained our selection of papers covering topics relevant to mental health and factors influencing mental health. For this paper we have delineated prominent themes across the lifetime of individuals with PMS as informed by experts, parents/caregivers and other key professionals involved in care. With factors of cognitive, developmental and adaptive functioning taken into account, clinicians could offer a more suited, or improved individualized care-plan.

In conclusion, publications on the genetics of PMS are increasing, while the number of studies addressing daily-life, behavioural and developmental problems are not increasing at the same pace, impacting the use of translational approaches. This publication delineates mental health, developmental and behavioural themes across the lifetime of individuals with PMS as informed by parents/caregivers, experts and other key professionals involved in PMS care. Another aim is to improve awareness of the importance of considering the developmental level of the individual with PMS when assessing mental health and behavioural problems. Understanding how the discrepancy between developmental level and chronological age may impact worrying behaviours, offers insight into the meaning of those behaviours, supports decision making in clinical practice and improves quality of life. 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.

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Data availability

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