



Consensus recommendations on chewing, swallowing and gastrointestinal problems in Phelan-McDermid syndrome

Ausra Matuleviciene^{a,**}, Kamile Siauryte^a, Els Kuiper^c, Andreas M. Grabrucker^{b,c,d,*}, European Phelan-McDermid syndrome guideline consortium

^a Dept. of Human and Medical Genetics, Institute of Biomedical Sciences, Faculty of Medicine, Vilnius University, Vilnius, Lithuania

^b Bernal Institute, University of Limerick, Limerick, Ireland

^c Dept. of Biological Sciences, University of Limerick, Limerick, Ireland

^d Health Research Institute (HRI), University of Limerick, Limerick, Ireland

^e Patient Representative from the European Consensus PMS Group, the Netherlands

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ABSTRACT

Gastrointestinal (GI) problems are common in Phelan-McDermid syndrome (PMS). Chewing and swallowing difficulties, dental problems, reflux disease, cyclic vomiting, constipation, incontinence, diarrhoea, and nutritional deficiencies have been most frequently reported. Therefore, this review summarises current findings on GI problems and addresses the fundamental questions, which were based on parental surveys, of how frequent GI problems occur in PMS, what GI problems occur, what consequences (e.g., nutritional deficiencies) GI problems cause for individuals with PMS, and how GI problems can be treated in individuals with PMS. Our findings show that gastrointestinal problems have a detrimental effect on the health of people with PMS and are a significant burden for their families. Therefore, we advise evaluation for these problems and formulate care recommendations.

1. Introduction

Phelan McDermid Syndrome (PMS) (22q13 deletion syndrome) is characterised by the deletion or mutation of the genetic material of the distal long arm of chromosome 22. Given that pathogenetic variants and deletions of the *SHANK3* gene located in this region were reported to result in a phenotype consistent with PMS, the functional impairment of *SHANK3* has been considered a key feature and, in part, defining criterium of a PMS diagnosis. However, PMS may also result from deletions and mutations not directly involving the *SHANK3* gene (Vitrac et al., 2023, this issue). Thus, PMS can be further classified as PMS-*SHANK3* related or PMS-*SHANK3* unrelated (Phelan and McDermid, 2012). In this review, the term PMS is used as the reported findings may apply to PMS in general. However, most of the presented and underlying research data is based on *SHANK3-related* PMS; thus, the review and its conclusions and recommendations are geared towards *SHANK3-related* PMS.

The clinical phenotype of individuals with PMS is very

heterogeneous and results from multiple organ systems being affected, leading to, among others, communication, speech and language problems, sensory dysfunction, epilepsy, sleeping problems, lymphedema, and mental health issues (Schön et al., 2023, this issue). In addition, features most likely from alterations and impairments in the gastrointestinal (GI) system have been reported. For example, individuals with PMS show high prevalence of zinc deficiency and altered metabolic profiles that may be linked to a reduced ability to metabolize major energy sources and a higher metabolism of alternative energy sources (Moffitt et al., 2023).

Research on the underlying causes of GI problems in PMS is still in its infancy. However, studies using *Shank3* knockout mice have reported a significantly altered microbiota composition and abnormal gastrointestinal morphology hinting at an increased gastrointestinal barrier permeability (“leaky gut”) (Wei et al., 2017; Tabouy et al., 2018; Sauer et al., 2019). Probiotics treatment (Tabouy et al., 2018; Sgritta et al., 2019) and zinc supplementation (Fourie et al., 2018; Hagemeyer et al., 2018) induced attenuation of some autism-like behaviours in these

* Corresponding author. Bernal Institute, University of Limerick, Limerick, Ireland.

** Corresponding author.

E-mail addresses: ausra.matuleviciene@mf.vu.lt (A. Matuleviciene), andreas.grabrucker@ul.ie (A.M. Grabrucker).

mice.

Further, enterocytes, cells in the gastrointestinal system responsible for absorbing dietary components created from induced pluripotent stem cells (iPSCs) from individuals with PMS, revealed impaired zinc uptake mechanisms (Pfaender et al., 2017). In addition, gastrointestinal transit and motility abnormalities were found in a zebrafish model of PMS (James et al., 2019).

In line with these findings from cell and animal models for PMS, GI problems are relatively common in humans with PMS. For example, gastroesophageal reflux is seen in 25% of PMS individuals with 22q13.3 deletions (Tabet et al., 2017; Denayer et al., 2012; Samogy-Costa et al., 2019; Lindquist et al., 2005), and 17% of PMS individuals with SHANK3 variants (De Rubeis et al., 2018; Schön et al., 2023, this issue). The prevalence of these symptoms may be linked to the genetic background of the patients and, in some studies, showed a correlation with deletion size (Tabet et al., 2017). However, gastroesophageal reflux has a non-genetic component, and the association might be secondary.

Constipation, urinary and stool incontinence are frequent issues in individuals with PMS, with prevalence comparable to individuals with intellectual disability in general, similar across all age groups. For example, constipation appears in 26–57% of children and adults with intellectual disabilities (Morad et al., 2007; Veugelers et al., 2010). In addition, complaints of constipation and/or diarrhoea are seen in about 40% of individuals, with no relationship to age (Kolevzon et al., 2014; Sarasua et al., 2014). Furthermore, about 10% of adults with PMS are overweight (Phelan et al., 2005).

Therefore, here, we summarise current findings on GI problems and address the questions of how frequent GI problems occur in PMS, what GI problems occur, what consequences (e.g. nutritional deficiencies) GI problems cause for individuals with PMS, and how GI problems can be diagnosed and treated in individuals with PMS. This review is derived from work conducted as participants in the European consortium on PMS that led to the publication of best practice clinical guidelines (van Ravenswaaij-Arts et al., 2023, this issue). These guidelines include information on chewing, swallowing and gastrointestinal problems in PMS mirrored in this review.

2. Methods

For this review, we performed a literature search on PMS to summarise the current state of the art for GI problems in PMS and draw the conclusions presented below. We selected keyword combinations for each of the gastrointestinal problems in PMS, such as “Phelan- McDermid syndrome AND incontinence (OR chewing, constipation, gastroesophageal reflux, etc.)”, as search terms on PubMed (<https://pubmed.ncbi.nlm.nih.gov/>), Web of Science (<https://www.webofscience.com/wos/woscc/basic-search>) databases, and reviewed the results up to the year 2021. AGREE II instrument (Appraisal of Guidelines for Research & Evaluation II; Brouwers et al., 2010) was used to evaluate use in clinical practice.

The search found no specialised research into gastrointestinal disorders in individuals with PMS. Most data is part of a broader clinical assessment of individuals with PMS (Tabet et al., 2017; Denayer et al., 2012; Samogy-Costa et al., 2019; Lindquist et al., 2005; De Rubeis et al., 2018). However, eight pre-clinical research studies using cells from individuals with PMS and *Shank3* animal models yielded some mechanistic insights. General guidelines (listed in Other sources) also essentially apply to individuals with PMS. Therefore, this review’s literature summary, conclusions, and recommendations are partially based on a parental survey (Landlust et al., 2023, this issue), pre-clinical studies, PMS reviews, general guidelines for non-PMS individuals and reached through consensus by voting of the European PMS consortium in a meeting on June 2022, including patient representatives.

3. Results

3.1. Gastroesophageal reflux disease (GERD)

Reflux disease develops when stomach acid flows to the oesophagus, damaging the mucous membrane and causing an inflammatory reaction. Reflux disease is more common in people with intellectual disabilities when there is obesity, drug use (anti-epileptics, benzodiazepines), spasticity, scoliosis, and an IQ under 35. Using feeding tubes in children with nutritional problems and neurological limitations increases the risk of reflux disease. Long-term reflux complaints can cause complications in the form of anaemia, strictures, or a Barret oesophagus (Böhmer et al., 1999).

3.2. Cyclic vomiting

Cyclic vomiting syndrome (CVS) is characterised by recurring, acute episodes of severe nausea and vomiting for weeks (Li and Balint, 2000; Li, 2018). While the underlying aetiology is unknown, the pathophysiology involves aberrant brain-gut and cellular pathways, including migraine, autonomic and hypothalamic-pituitary-adrenal axis hyperactivity, and mitochondrial dysfunction (Romano et al., 2018). The literature advises treating cyclic vomiting in children, such as infusions for (imminent) dehydration.

3.3. Constipation/diarrhoea

Constipation is influenced by the following factors: pain, fever, dehydration, dietary and fluid intake, psychological issues, toilet training, medicines and impaired gastrointestinal motility. Furthermore, zinc deficiency may contribute to diarrhoea (Hassan et al., 2020). Reduced thyroid function can also cause constipation, as hypothyroidism is slightly more common than average in PMS (approximately 6%) (Sarasua et al., 2014).

The following factors are thought to contribute to the occurrence of constipation in PMS:

Impaired gastrointestinal motility: The gut’s neuronal network has many connections to the central nervous system. Therefore, depending on the nature and extent of the individuals’s neurological problems, the intestine’s motility may be impaired. This manifests as delayed gastric emptying, delayed colonic passage time, and constipation or diarrhoea.

Insufficient control over defecation: Children with intellectual disabilities, including children with PMS, may have difficulty achieving normal toilet training. This is related to insufficient conscious coordination of the (pelvic floor) musculature and the inability to integrate sensations of urgency into an adequate response that leads to defecation.

Nutrition and moisture: Individuals with PMS may receive easy-to-mash food, which can be low in fibre. This may contribute to the development of constipation. In addition, the fluid balance may be disturbed (including swallowing problems, vomiting, diarrhoea, and excessive loss of saliva), which increases the risk of constipation.

Side effects of medication: Medications such as anti-epileptics (including valproic acid) (de Coo et al., 2023, this issue), anticholinergics, phenothiazines (including promethazine), and opiates negatively influence colonic transit time. Constipation is, therefore, a significant side effect of these drugs.

Reduced mobility: Reduced mobility can arise from frequent hypotonia, fatigue, and sleep problems in persons with PMS. This increases the risk of constipation.

Recognizing non-retentive stool incontinence and functional constipation will help providers recommend more appropriate personalised therapies.

3.4. Zinc deficiency

Zinc deficiency has been investigated in two studies using blood

(Grabrucker et al., 2014) and hair samples (Pfaender et al., 2017) from individuals with PMS. 22% of individuals with PMS were zinc deficient, and 42% displayed abnormally low zinc/copper ratios. Low zinc status was associated with seizures, ADHD or other attention and hyperactivity issues, and signs of immunodeficiency in these individuals (Grabrucker et al., 2014).

3.5. Chewing and swallowing problems

Chewing and swallowing problems occur in more than half of the people with PMS. There are several reasons for this. They often have hypotonia (57–85%), making chewing and swallowing more difficult. In addition, more than 25% have dental problems, including malocclusion, widely spaced teeth, and a high palate. Teeth grinding and pica (craving or eating inedible objects) have been described in 25% and 60–88% of people with PMS, respectively (Ivanoff and Ivanoff, 2014). The anatomical abnormalities, combined with the hypotonia and the typical chewing and mouthing behaviour, can lead to chewing and swallowing problems and saliva loss. Therefore, it is reasonable to involve a pre-verbal speech therapist at an early stage (van den Engel-Hoek et al., 2017).

Taken together, chewing and swallowing disorders and gastrointestinal problems such as reflux, cyclic vomiting, and constipation are frequent in PMS across all age groups, in part due to limited cognitive development, hypotonia, abnormal chewing patterns, pica, dental problems, and a functional role of SHANK3 in the gastrointestinal system. In addition, some of the observed gastrointestinal problems or their treatments such as proton pump inhibitors may affect nutrient uptake, as reported for the trace mineral zinc, and thereby potentially contribute to other clinical features, such as chronic pro-inflammatory signalling in the body. However, further studies should investigate which gastrointestinal problems are drivers of impaired nutrient uptake and how, which may inform PMS-specific micronutrient supplementation strategies.

4. Discussion of clinical considerations

4.1. Gastroesophageal reflux (GERD)

Diagnosis and treatment of GERD in PMS following the “Pediatric Gastroesophageal Reflux Clinical Practice Guidelines: Joint Recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN), 2019”, and guidelines for “Gastro-oesophageal reflux disease in children and young people: diagnosis and management, National Institute for Health and Care Excellence (NICE) guidelines, 2019”, can be complicated by different factors. For example, making a diagnosis of GERD can be difficult due to limited communication with the individual with PMS. However, alarm signals may be lack of appetite, food refusal, dental complaints, teeth grinding, regurgitation and vomiting. In addition, atypical complaints, such as sleep disorders due to night-time reflux, restlessness, behavioural problems, and self-injuring behaviour, can occur.

Additional investigations may be necessary for diagnosing and treating GERD in PMS, including a radiological gastrointestinal tract examination with contrast (barium X-rays), gastroscopy including biopsies, screening for drug toxicity, and pH/impedance testing.

During treatment, it is essential to provide individualised lifestyle advice. Given the high prevalence of GERD in people with intellectual disabilities, consideration can be given to starting trial treatment with a proton pump inhibitor in older children and adults without diagnostic testing. However, this is only possible if there are apparent symptoms, and the symptoms can be evaluated before and after a 4-week trial period.

Long-term use of proton pump inhibitors is necessary to control

symptoms. However, if the proton pump inhibitor's effect proves insufficient or reflux complaints recur, this may indicate under-dosage (Hassall, 2012; Romano et al., 2017).

4.2. Cyclic vomiting

Infections, increased intracranial pressure, migraine, epilepsy, intestinal obstruction, and a reaction to medication or food should be excluded before the diagnosis of cyclic vomiting is made (Romano et al., 2018).

Romano et al. (2018) give an overview of the possibilities for drug treatment in children. For example, Cyproheptadine (<5 years) and amitriptyline (>5 years) are cited as the first choice for prophylaxis (interemetic 5 phase). During the emetic phase, one must be alert for dehydration.

4.3. Constipation

Following the guidelines for “Constipation in children and young people: diagnosis and management, National Institute for Health and Care Excellence (NICE) guidelines, 2017”, a constipation diagnosis can be made based on the frequency, quantity, consistency of defecation, and a careful physical examination (e.g. using ROME III criteria: diagnosis of functional constipation is made when at least two of the following criteria are met for the last 3 months with symptom onset at least 6 months prior to diagnosis: a) straining on >25% of defecations; b) lumpy or hard stools on >25% of defecations; c) sensation of incomplete evacuation on >25% of defecations; d) sensation of anorectal obstruction/blockage on >25% of defecations; e) manual manoeuvres on >25% of defecations; and f) less than 3 defecations per week (Miller et al., 2017)). A constipation list can also be helpful, such as the Bristol Stool Scale (Lewis and Heaton, 1997). It is crucial for treatment to determine the defecation problem phase: constipation with or without distension of the rectum (‘megarectum’) and with or without faecal incontinence. When in doubt, barium X-rays can be made to get more clarity.

Informing parents and carers is an essential part of the treatment. Information should aim to identify and adequately treat constipation at an early stage. It is also important to pay attention to sufficient fluid intake, increase the fibre content of the diet, and, where possible, discontinue or reduce medication that can promote constipation.

Treatment with oral laxatives (osmotic, volume-increasing, or contact laxatives) is often necessary. Medication dose should only be gradually reduced over a period of months in response to stool consistency and frequency. Keeping a stool diary is also valuable, as it can track whether there is sufficient stool production. Some patients may require ongoing laxative therapy.

4.4. Incontinence

ROME IV and ICSS criteria may be used to evaluate incontinence. It is necessary to conduct medical examinations, including ultrasound, a 48-h bladder diary, and uroflowmetry and exclude organic reasons for incontinence, such as urinary tract infections, renal anomalies, and vesicourethral reflux, as individuals with PMS are at higher risk of these conditions (Von Gontard, 2013).

Incontinence in individuals with PMS is mainly classified as non-retentive (bowel movements in places and at times that are inappropriate, without signs of faecal retention) (Hyams et al., 2016). Studies have shown positive behavioural therapy effects for such individuals, mainly if applied early in life (Kroeger and Sorensen, 2010; Levato et al., 2016). A recent study reports that in all age groups, PMS has significant rates of incontinence. The data shows that 86% of investigated participants had nocturnal enuresis (NE), 73% daytime urine incontinence, and 79% faecal incontinence. Rates were comparable across all age groups (children, teens, adults). Significantly greater “anxiety/depression” subscale ratings were seen in people with NE (Hussong et al., 2020).

4.5. Zinc deficiency

Currently, no reliable indicators or biomarkers are available to assess humans' zinc status (Wieringa et al., 2015). However, the most commonly employed methods to determine zinc status include measuring plasma zinc concentrations, urinary zinc concentrations, hair/nail zinc concentrations, and dietary assessments. Unfortunately, none of these assessments is suited to determine mild (subclinical) zinc deficiency, which may already affect an individual with PMS and modify or cause clinical phenotypes.

Measuring plasma zinc is most frequently used in clinical practice and should be performed under fasting conditions. Plasma and urinary assessments must be repeated several times to detect chronic zinc deficiency. Alternatively, a hair sample may be sent to a certified lab for analysis using inductively-coupled plasma mass spectrometry (ICP-MS).

Prevention or treatment of zinc deficiency can be achieved using zinc supplementation. The recommended dosages vary between countries and recommending institutions (e.g., national agencies, World Health Organization (WHO)), and the recommended dosage is based on the requirements of an average healthy individual on an average diet. The recommendations below are based on Daily Values (DVs) set by the U.S. Food and Drug Administration (FDA). DVs are reference amounts of trace metals to consume each day.

For example, if the recommended dietary intake (DV) of zinc (3 mg/day 0–3 years; 11 mg/day 4+ years) is not met through nutritional sources or impaired through factors such as reduced gastrointestinal absorption, diarrhoea, or the presence of drugs affecting zinc uptake such as proton pump inhibitors (Farrell et al., 2011), dietary supplementation should be considered. However, the recommended daily values have been set for healthy individuals, and no values have been established yet for individuals with PMS that may have impaired zinc absorption.

The WHO recommends short-term zinc supplementation for treating acute childhood diarrhoea (20 mg of zinc per day, or 10 mg for infants under 6 months, for 10–14 days) (WHO/UNICEF).

A limitation is that research on the underlying factors of GI symptoms and the treatment options outlined above are currently not well investigated for PMS specifically. Therefore, many clinical interventions rely on data generated from more general guidelines, such as NICE guidelines.

5. Conclusions

In this review, we summarised current knowledge on gastrointestinal problems in PMS. We conclude that when behavioural problems, sleep disorders, self-injurious, mouthing behaviours or other behavioural changes are observed, underlying causes such as gastroesophageal reflux and constipation should be considered. A crucial component of PMS treatment should be informing parents and caregivers of potentially present gastrointestinal pathologies and their impact on many features relevant to PMS. Evaluation for faecal incontinence and exclusion of its somatic causes is advised as early introduction of behavioural modifications may improve quality of life. Specialists should refer to national or international guidelines to treat these gastrointestinal problems. Moreover, for zinc deficiency, dietary zinc supplementation should be considered. Lastly, if a chewing and swallowing disorder is present, a referral to a pre-verbal speech therapist is advised. Recommendations for specific treatment and improvement of care of the patient with PMS are summarised below (Table 1).

CRedit authorship contribution statement

Ausra Matuleviciene: Conceptualization, Writing – original draft, Writing – review & editing. **Kamile Siaurys:** Conceptualization, Writing – original draft, Writing – review & editing. **Els Kuiper:** Conceptualization, Writing – review & editing. **Andreas M.**

Table 1

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

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. ^a
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.

^a see other sources.

Grabrucker: Writing – original draft, Writing – review & editing.

Data availability

No data was used for the research described in the article.

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