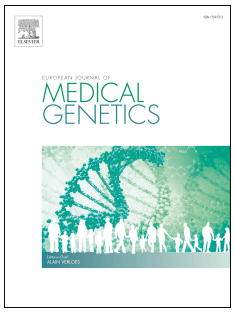

Consensus recommendations on lymphedema in Phelan-McDermid syndrome

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Abstract

Phelan-McDermid syndrome (PMS) is a neurodevelopmental disorder caused by deletions 22q13.3 or pathogenic variants in the *SHANK3* gene. Lymphedema can be a clinical feature in 10-25% of individuals with PMS due to a deletion 22q13.3, but is not observed in those with a *SHANK3* variant. This paper forms a part of the European consensus guideline for PMS and focuses on what is known regarding lymphedema in PMS in order to present clinical recommendations.

The mechanism causing lymphedema in PMS is unknown. Lymphedema can be suggested by pitting oedema of the extremities or, in later stages, non-pitting swelling. It can occur already at a young age and be progressive if untreated, impacting daily functioning. Lymphedema can be treated using existing general multidisciplinary management guidelines, taking the functioning of the individual with PMS into account. Furthermore, well-known risk factors for the development of lymphedema as lack of physical activities and weight gain / obesity should be addressed. Diagnosis and treatment are best performed in a multidisciplinary centre of expertise.

Introduction

Phelan-McDermid syndrome is a neurodevelopmental disorder mainly characterized by intellectual and physical disabilities, epilepsy, sleeping disorder, dysmorphic features, and cardiac and kidney malformations (reviewed in Schön at al, 2023, this issue). PMS is caused by a deletion of chromosome 22q13.3 or mutations in the gene *SHANK3* in that region. Lymphedema is a well-known clinical feature and has been reported in up to 25% of the patients with PMS due to a deletion 22q13.3 (Sarasua et al., 2014), although this might be an overestimation.

Lymphedema is not a diagnosis but a symptom of impaired lymphatic flow presenting as chronic peripheral swelling. It has various pathophysiological mechanisms. There may be a defective lymphatic system (anatomical; functional, increased afterload) that leads to swelling, but there may also be an overload of the lymphatic system (dynamic lymphatic insufficiency or increased preload) leading to swelling. Chronic impaired lymphatic flow and lymph stasis lead to tissue modifications (adipose deposition with fibrosis and cutaneous thickening) leading to partial irreversibility of the lymphedema (Wolf S et al, 2022). Clinically the major sign to confirm lymphedema in the lower limb, is the Stemmer's sign which is the inability to pinch the skin at the base of the second toe confirming skin thickening. If untreated the lymphedema can get worse and may be complicated by infections (cellulitis/erysipelas).

In PMS, the lymphedema may present at birth or childhood. It may be progressive and therefore can have important consequences for the patient if left untreated. Treatment of lymphedema is multidisciplinary and personalized to the patient dependent of the co-morbidities. In general, compression therapy (low-stretch bandage, elastic garments) is the cornerstone of lymphedema management, in combination with physical activities and weight control, because obesity may have a poor impact on lymphedema volume. Lymphedema control and skin care are also important to prevent infection (cellulitis/erysipelas) in the affected limb(s).

This paper forms part of the European consensus guidelines for Phelan-McDermid syndrome (van Ravenswaaij et al, 2022, this issue) and reviews the current knowledge of lymphedema in PMS in order to present recommendations for surveillance and treatment.

Methods

This paper is part of the guidelines on PMS and based on the AGREE II instrument (Appraisal of Guidelines for Research & Evaluation II; Brouwers 2010). For the present paper about lymphedema the following fundamental questions were formulated:

- How often does lymphedema occur in PMS and what is known about the origin and pathogenesis?
- What is the best management for lymphedema in individuals with PMS?
- Are there options for early diagnosis and early management?

A literature search was performed using the terms, Phelan McDermid syndrome, 22q13 deletion, *SHANK3,* lymphedema and swelling. For this paper we included the following papers: Dhar et al., 2010; Kolevzon et al., 2014; McGaughran et al., 2010; Nesslinger et al., 1994; Phelan et al., 2005; Sarasua et al., 2014; Soorya et al., 2013.Gordon et al 2020. Further, we made use of the Dutch guideline on Lymphedema (NVDV, 2014). Text and recommendations were critically reviewed by the consortium members, including the patient representatives. The final text was discussed in detail with all consortium members during a consensus meeting in June 2022 and recommendations were rephrased until consensus was met. A voting process allowed each member to vote regarding the reliability of each recommendation (van Ravenswaaij, 2023, this issue).

Prevalence of lymphedema in PMS

The association between lymphedema and PMS was first described in 1994 (Nesslinger et al., 1994). Sometimes there is an early presentation with late childhood progression. Ascites and pleural effusion are occasionally described (McGaughran et al., 2010). A few patients are described with ring chromosome 22 with deletion of *SHANK3* who also have primary lymphedema (personnel observations S. Mansour; Mahajan et al, 2012) presumable as they are also deleted for *SHANK3,* or for another gene responsible for lymphedema in close proximity.

A large clinical study of 201 subjects with PMS listed the following prevalence figures based on physical examination: total group 24% (26/108), <5 years of age: 17% (8/47), 5-10 years of age: 18% (6/34), 10-18 years of age: 35% (7/20) and >18 years of age: 71% (5/7). Although the numbers are small, there seems to be an increase in prevalence with age (Sarasua et al., 2014) but an ascertainment bias may also be present.

A large review (Kolevzon et al., 2014) cited three smaller studies in addition to Sarasua's study that report the following prevalence rates for lymphedema: 29% (2/7) (Nesslinger et al., 1994), 23% (3/13) (Dhar et al., 2010) and 22% (7/32) (Soorya et al., 2013). The four studies together yield a prevalence of 25%. However, the cohorts used in these studies overlap, while lymphedema has not been mentioned in other studies, so the figures may be an overestimation. A more reliable estimation of 11% was made by Schön et al (2023, this issue) based on originally reported patients only. This review includes the recently published large cohort paper of 210 individuals with PMS by Nevado et al. (2022) presenting a prevalence of lymphedema of 10%.

Mechanism of lymphedema in PMS

The lymphedema in PMS is considered primary lymphedema, but usually is not evident at birth. It is most likely caused by an inadequate lymphatic system. Nothing is known about the underlying mechanism resulting in this lymphatic system insufficiency in PMS.

Samogy-Costa et al. (2019) attempted a genotype-phenotype correlation, looking at the effect of the deletion size on the presence of lymphedema. Four out of 30 of their patients, had lymphedema (13%), and all four had large deletion sizes of over 4.3Mb. It is likely that there is an, as yet unidentified, gene in this region for primary lymphedema, or that *SHANK3* itself has a role in lymphangiogenesis. However, thus far lymphedema has not been described in individuals with PMS due to a *SHANK3* pathogenic variant: In their review of originally published individuals, including the Nevado cohort, Schön et al found no cases of lymphedema in 34 patients with a pathogenic variant in *SHANK3* but lymphoedema was present in 29 of 270 (11%) individuals with PMS due to a deletion 22q13.3 (Schön et al, 2023).

CELSR1 located at 22q13.31 also has been suggested as candidate gene for lymphedema (Gonzalez-Garay et al., 2016), but *CELSR1* was not included in the deleted region in four patients with PMS and lymphedema due to a deletion 22q13 (S.M., personal observations 2021), which makes it less likely to be the cause, except if other molecular mechanisms like a position effect on the *CELSR1* expression, are involved. One recent report describes a patient with a relatively large 22q13 deletion which included *SHANK3* and *CELSR1.* This patient presented with lymphedema of the left leg and a protein losing enteropathy with hypoalbuminaemia (Xia et al 2021).

One has to keep in mind that, although the deletion 22q13.3 is an obvious risk factor for lymphedema, it may develop in any individual with restricted mobility, particularly if they are overweight/obese or if there is raised lymphatic preload by physical impairment and thus may also occur in individuals with other neurodevelopmental disorders, including those with PMS due to a *SHANK3* pathogenic variant.

Managing lymphedema in PMS

Lymphedema can be suggested by pitting oedema on the feet and legs and sometimes the hands and arms. When more persistent, the toes get swollen and Stemmer's sign is present. If the oedema fails to resolve overnight, the term lymphedema stage 2 of the International Society of Lymphology (ISL) classification (Executive Committee of the International Society of Lymphology 2020) is used. When the chronic oedema lasts longer, irreversible changes can occur such as fibrosis, papillomatosis of the skin and adipose tissue deposition in the affected limb(s) (stage 3).

Awareness of the possible onset of lymphedema in patients with PMS (particularly due to a deletion of 22q13.3) is important for early detection and management. This can be done by examining the lower limbs and performing a 'pitting test' during routine follow-up. Cellulitis (erysipelas) of the limb may be the first sign of lymphatic impairment.

No systematic studies on the management of lymphedema in PMS have been performed. Therefore, only general advices can be offered according to existing general guidelines on lymphedema (NVDV, 2014), of which there also is a patient version (NVDV, 2014), summarized in the European Reference Network for Primary and Paediatric Lymphoedema patient pathway (https://vascern.eu/wp-content/uploads/2019/12/General-Patient-Pathway-for-PPL_08112019).

General advices include the use of compression therapy such as low-stretch bandaging, elastic garments, Velcro wraps and intermittent pneumatic compression therapy in more severe forms and for immobile patients. Also encouraging physical activities and weight control preventing obesity are

important. Thus, management of lymphedema in patients with PMS include reduction of the main risk factors (obesity and immobility), the use of compression stockings in the maintenance phase (NVDV, 2013), skin care and oedema control to prevent erysipelas/cellulitis (Phelan and Rogers 2005; Kolevzon et al., 2014, Vignes et al., 2021).

A few patients with PMS have presented with systemic involvement including ascites and pleural effusion (McGaughran et al., 2010) and with intestinal lymphangiectasia (protein losing enteropathy) (personal communication S. Mansour, Xia et al 2021). Investigations for this complication include blood levels of albumin, immunoglobulins, fat soluble vitamins, lymphocytes subsets, and stools to measure alpha1 antitrypsin clearance. The treatment is based on a strict low-fat and high-protein diet, replacing the long chain triglycerides with medium chain triglycerides (MCT) with liposoluble vitamins.

More invasive procedures that are sometimes used in end-stage 3 lymphedema, like reduction surgery to remove either adipose tissue formation, lumb formation by the knee or papillomatosis of the toes, or reconstructive surgery, as lympho-venous anastomosis should all be considered very carefully in the perspective of the intellectual and physical disability of the patient with PMS. Because of the typically severe intellectual disability it is particularly important to take the expectations and possibilities for help from the caregivers / parents into account and set realistic goals. This can markedly influence the final treatment program.

Conclusions and recommendations

Compared to many other syndromes, lymphedema is relatively common in PMS due to a deletion 22q13.3 (between 10-25%). Little is known about the natural course, but early onset and progression from late childhood have been reported. Prevalence seems to increase with age although this may also be a biased observation. It is important that the healthcare provider pays attention to this co-morbidity so that management can be started on time.

Compression therapy, weight reduction and stimulating mobility are the cornerstone in the (early) treatment. Compression therapy can be highly effective in reducing not only the swelling, but also reducing the frequency of cellulitis. Systemic involvement (intestinal lymphangiectasia, pleural effusions and ascites) occurs rarely but should be considered and investigated. Primary lymphedema management can be complicated and should be performed in an expert centre with a multidisciplinary approach (see Guideline lymphedema). The European Reference Network has a special working group for paediatric and primary lymphedema (PPL) within the VASCERN (vascular diseases; https://vascern.eu/expertise/rare-diseases-wgs/primary-lymphedema-wg/#1598883110128-027619aa-dfda), with expert centres throughout Europe.

Further research into the pathogenesis of lymphedema in PMS is required. Additional investigations such as lymphoscintigraphy is often impossible due to the intellectual disability of the patients. Also, the molecular genetic background remains uncertain, as *SHANK3* may be involved but also other genes in the 22q13.3 region.

Recommendations

The health care provider should pay attention to the possible development of lymphedema in individuals with a 22q13 deletion (including ring chromosome 22). Treatment (e.g., compression bandages and garments, skincare and advice) should be instigated as required.

Refer individuals with PMS with lymphedema impacting daily functioning to a lymphedema centre of expertise for further investigations and treatment*.

*see VASCERN PPL-WG: https://vascern.eu/expertise/rare-diseases-wgs/primary-lymphedema-wg/

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- Centre of Expertise for Lympho-vascular medicine (ERN-PPL) are listed here: https://vascern.eu/expertise/rare-diseases-wgs/primary-lymphedema-wg/#1598883110128-027619aa-dfda