Consensus recommendations on altered sensory functioning in Phelan-McDermid syndrome

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ABSTRACT

Altered sensory functioning is often observed in individuals with SHANK3 related Phelan-McDermid syndrome (PMS). Compared to typically developing individuals and individuals with an autism spectrum disorder, it has been suggested that there are distinctive features of sensory functioning in PMS. More hyporeactivity symptoms and less hyperreactivity and sensory seeking behaviour are seen, particularly in the auditory domain. Hypersensitivity to touch, possible overheating or turning red easily and reduced pain response are often seen.

In this paper the current literature on sensory functioning in PMS is reviewed and recommendations for caregivers, based on consensus within the European PMS consortium, are given.

1. Introduction

Phelan McDermid Syndrome (PMS) is a neurodevelopmental disorder with neurological and psychiatric symptoms and variable other characteristics, most commonly due to a 22q13.3 deletion or pathogenic variant involving SHANK3 (Schön et al., 2023, this issue). The phenotype is very variable, common characteristics are a global developmental delay with a marked speech impairment. Autism spectrum disorder and to a lesser extent hyperactivity are relatively common (Schön et al., 2023, this issue). In PMS atypical responses to sensory stimuli are often reported (Kolevzon et al., 2014; Mieses et al., 2016; Phelan et al., 2022; De Rubeis et al., 2018; Soorya et al., 2018; Tavassoli et al., 2021; Tomchek and Dunn, 2007).

This paper describes the specific characteristics of sensory functioning in individuals with SHANK3 related Phelan-McDermid syndrome. It aims to offer recommendations to parents/caregivers and clinicians about how to recognize, assess, support and address altered sensory functioning in PMS.

Sensory processing differences have been described in syndromic and non-syndromic autism spectrum disorders (ASD) and can be seen in people with an intellectual disability (Battaglia, 2011; Boyd et al., 2010; Tavassoli et al., 2017).

Atypical sensory responses are a DSM-5 (American Psychiatric Association, 2013) criterium of ASD and described as hyper- or hyporeactivity to sensory input or unusual interests in sensory aspects of the environment. Hyperreactivity describes a strong reaction to a sensory stimulus (e.g. covering ears in response to normal sounds, avoiding wearing clothes of a certain texture). Hyporeactivity is characterized by delayed or absent responses to sensory stimuli (e.g. not reacting to alarming sounds). Sensory seeking behaviour can be seen as fascination with certain sensory stimuli (e.g. repeatedly touching certain textures or intentionally squinting).

The seven sensory systems include the proprioceptive system (posture and movement), vestibular system (balance), visual system (vision), auditory system (hearing), olfactory system (smell), gustative system (taste) and tactile system (touch, pain, physical sensations).

Processing the sensory stimuli, also called sensory integration, is described as a neurological process that organizes sensory sensations, resulting in an effective use of the body in its environment (Ayres, 1972). A sensory processing disorder, formerly referred to as a "sensory

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integration dysfunction”, influences all domains of sensory modalities. In a general European PMS consensus meeting in June 2022, the more positive sounding term “altered sensory functioning” was preferred above the terms ‘dysfunction’ and ‘disorder’.

2. Methods

Starting in 2020, a Dutch guideline on 22q13-deletion syndrome (Nederlandse Richtlijn 22q13 deletiesyndroom (PMS), 2018) was adapted to the European situation, initiated by the European Reference Network ITHACA (Intellectual disability, TeleHealth, Autism and Congenital Anomalies). The established international consortium of experts and patient representatives discussed and determined the subjects of this special issue on PMS. One of the discussed subjects was the altered sensory functioning in PMS. The most important questions that needed to be addressed were defined by a working group on sensory functioning and a literature search was performed. Search terms were added during the process (also using AND/OR) and included: sensory dysfunction, sensory processing disorder, sensory profile, senses, Phelan McDermid, 22q13, SHANK3, autism, heat, temperature, pain, balance, hearing, auditory, vision. The presented text on Altered Sensory Functioning was critically reviewed and discussed by the members of the consortium and the recommendations were approved during the final consensus meeting.

The following fundamental questions were formulated, substantiated by the parental survey (Landlust et al., 2023, this issue).

- Does altered sensory functioning occur in patients with PMS? How often and of what kind?
- What is the mechanism behind the altered sensory functioning seen in PMS?
- What should healthcare professionals and parents/carers pay attention to regarding altered sensory functioning in patients with PMS?

For the basic question about the occurrence of altered sensory functioning, the following articles were included: Battaglia (2011); Kolevzon et al. (2014); Mieses et al. (2016); Phelan et al. (2001); Phelan et al. (2005); Philippe et al. (2008); De Rubeis et al. (2018); Sarasua et al. (2014); Soorya et al. (2013); Tavassoli et al. (2017, 2021); Xu et al. (2020).

For the basic question about the mechanism of altered sensory functioning the following articles were included: Han et al. (2016); Li et al. (2017); Noda et al. (2020); Oreifice et al. (2016); Philippe et al. (2008).

For the basic question about points of attention regarding altered sensory functioning the following articles were included: Denayer et al. (2009); Mieses et al. (2016); Philippe et al. (2008); Siper et al. (2017, 2021); Soorya et al. (2018) and Denayer et al. (2009) Dunn (2007). The conclusions from literature are summarized in Table 1.

3. Review of the literature; results

In general, in people with PMS alterations in sensory functioning, such as vision and hearing impairments, reduced pain perception, heat regulation disorder and changed sensitivity are commonly reported (Kolevzon et al., 2014). Altered sensory functioning affects behaviour and can lead to increased anxiety and uncertainty. Sensory stimuli can produce unexpected and aberrant behaviour. While sensory reactivity symptoms are widely reported in people with ASD, few studies have examined sensory symptoms in PMS. Altered sensory processing in PMS may be associated with ASD, but the haploinsufficiency of SHANK3 may also have a direct effect on sensory processing.

Using the Short Sensory Profile test (Kientz and Dunn, 1997; Dunn 2014), Mieses et al. (2016) and Tavassoli et al. (2017) found that children with PMS have less pronounced altered sensory functioning than children with ASD and low intellectual functioning, but they have an equally reduced response to pain. Tavassoli et al. (2021) also found a specific sensory reactive phenotype in children with PMS, who demonstrated greater hypo-reactivity symptoms and fewer hyperreactivity and sensory seeking symptoms across visual, tactile, and auditory sensory domains, compared to children with ASD and typically developing children. Differences were particularly prominent in the auditory domain. No differences were found between the different sizes of 22q13.3 deletions or the SHANK3 variants.

Below the characteristics of the seven sensory systems are described.

3.1. Proprioceptive system (posture and movement)

Stimulus seeking proprioceptive behaviour is reported in PMS, like repetitive use of objects, specific body postures or complex motor mannerisms, repetitive hand and finger movements (Soorya et al., 2013). Xu et al. (2020) mentioned repetitive behaviour in 65% if people with a 22q13.3 deletion and in 86% of people with a SHANK3 variant. Gait abnormalities (ataxic, wide based) were mentioned in 82–93% (De Rubeis et al., 2018). Differentiating stimulus seeking behaviour from underlying discomfort or pain can be difficult, this is further addressed below in Discussion and considerations.

3.2. Vestibular system (balance)

In PMS individuals with a ring chromosome 22, attention should be given to vestibular schwannoma, related to neurofibromatosis type 2, which can also cause dizziness and balance problems (Denayer et al., 2009; Koza et al., 2023, this issue).

3.3. Visual system (vision)

In order to assess the visual sensory processing, it is important to rule out vision problems due to other medical causes. Vision may be impaired due to strabismus and myopia (Sarasua et al., 2014; Soorya et al., 2013). Phelan and McDermid H (2011), registered that in a few cases (6%) cortical visual impairment was detected. Vision disturbances occur in 22% of individuals with a 22q13.3 deletion (Brignell et al., 2021; Richards et al., 2017; Tabet et al., 2017) and in 29% of people with a SHANK3 variant (De Rubeis et al., 2018). Tavassoli et al. (2021) demonstrated that children with PMS show more hyporeactivity symptoms (e.g. delayed or absent responses to the sight) than children with ASD or typically developing children. Noda et al. (2020) found impaired somatosensory evoked potentials (SEP) in individuals with ASD (not PMS), suggesting that visual attention affects the later stages of somatosensory processing.

3.4. Auditory system (hearing)

It is important to be aware of hearing problems before assessing the sensory processing. Hearing is normal in most individuals with PMS, but hearing loss could arise due to conduction problems as a result of frequent middle ear infections (Soorya et al., 2013). When PMS is caused by a ring chromosome 22, hearing loss can occur as one of the first
symptoms of an acoustic neuroma (Koza et al., 2023, this issue; Phelan et al., 2005).

An important finding regarding the sensory processing is that there is often a delayed response to verbal and auditory cues. Ten individuals with PMS underwent auditory evoked potentials, most of them showed longer N250 latency (related to language) compared to the norm for age (Ponson et al., 2018), but given the small sample size, statistical analyses could not be made. Tavassoli et al. (2021) found that children with PMS showed more hyporeactivity symptoms and less hyperreactivity than children with ASD and typically developing children, particularly seen in the auditory domain. Additionally, people with PMS may have difficulties to distinguish words from background noises (Phelan and McDermid H., 2011). The delayed or absent response to auditory cues is relevant for care-givers, because there can also be an under-responsiveness to warning sounds. In a small study (n = 8), Philippe et al. (2008) found that children with PMS had an overreaction to sudden sounds.

3.5. Olfactory system (smell) and gustative (taste) system

Research from Mieses et al. (2016) showed that children with PMS had fewer sensory reactivity symptoms on taste/smell sensitivity, as compared to children with ASS. Behaviour characterized by inappropriate chewing of clothing, toys, or other non-food items, licking objects or smelling things or people was observed in 70% of children with PMS. These behavioural characteristics decrease as children grow older (Phelan et al., 2001).

4. Temperature sense, tactile and pain perception

Abnormal reactions to changes in temperature, touch and pain have been reported in individuals with PMS (Phelan et al., 2001; Tavassoli et al., 2021). In people with PMS, heat regulation disorder was reported in 68% by Sarasua et al. (2014), described as overheating or turning red easily and having decreased perspiration (60%). The underlying cause is unclear but individuals with PMS may not always be able to react adequately to temperature changes by changing clothes for example.

In a study with 201 participants of all ages with PMS, Sarasua et al. (2014) mentioned in 46% a hypersensitivity to touch. Philippe et al. (2008) also mentioned an overreaction to touch in children. Oreﬁce et al. (2016) investigated the effect of peripheral mechanosensory nerve dysfunction on tactile response and behaviour in multiple mouse models for ASD, including a SHANK3 model. The mice showed altered tactile discrimination and were hypersensitive to soft tactile stimuli. In this way, they showed that a disturbance in the peripheral sense of touch contributes to behavioural problems such as increased anxiety and decreased social interaction in mice (Oreﬁce et al., 2016).

In a review of Kolevzon et al. (2014) based on 13 publications describing approximately 584 cases with PMS, reduced pain response is mentioned in parental reports with an average of 42%. Other papers mention a much higher prevalence; reduced pain response was found in 62% (70/114) of individuals with a 22q13.3 deletion (Jeffries et al., 2005; Phelan et al., 2001; Samogy-Costa et al., 2019; Xu et al., 2020) and in 79% (23/29) of individuals with a SHANK3 variant (De Rubeis et al., 2018; Xu et al., 2020). Sarasua et al. (2014) reported a small increase with age: 69% at the age of 5 years, 79% at 5–10 years, 84% at 10–18 years and 89% at 18–65 years. Pain experience can be expressed verbally or vocally, by facial expression, or by other behaviours (Rattaz et al., 2013). In PMS, heterozygous deletion of SHANK3, which is involved in the formation and stabilization of postsynaptic glutamate receptors, is suggested to contribute to the altered pain response (Roussignol et al., 2005). Han et al. (2016) showed that SHANK3 is expressed in sensory nerves and the spinal cord and that SHANK3 haploinsufﬁcient mice showed reduced pain sensitivity. In addition, the authors showed that SHANK3 influences peripheral pain regulation via presynaptic pain transmission. Based on the current literature, however, we cannot verify that SHANK3 is responsible for the altered sensory information processing in PMS, so other factors may also play a role.

5. Discussion and considerations

5.1. Assessing and supporting altered sensory functioning

In PMS, altered sensory functioning can be seen. Individuals have a reduced pain-response and show a distinct sensory pro ﬁle with more hypo-reactivity symptoms particularly in the auditory domain, a general hypersensitivity to touch and a tendency to overheat easily. These are relevant ﬁndings for parents and caregivers as well as clinical physicians and other healthcare workers.

Awareness of safety concerns resulting from sensory hypo-reactivity is there for very important. Individuals with PMS can have somatic complications due to a high pain threshold or overheating, but also have an under-responsiveness to warning sounds such as sirens or for example a car passing by. Environmental adjustments such as a good acoustic space, avoidance of sudden noises, abrupt changes in heat or cold, or sudden touch, could be considered.

It is conceivable that altered sensory functioning can inﬂuence language development (Burdde M. et al., 2023, this issue) and cause or worsen behavioural problems (van Balkom et al., 2023, this issue). Because of the possible altered pain response and reduced expressive communication, injuries or inﬂammation may be diagnosed late or may remain unnoticed. This hinders effective recognition and treatment by clinicians and parents or caregivers. Extra attention should therefore be paid to the possibility of ear infections, gastroesophageal reﬂux, dental problems, constipation and other medical conditions.

It is also useful to know the persons individual behaviour and recognize changes in behavioural and emotional patterns.

To track down possible sensory impairments, ﬁrst thorough medical and (psycho-)neurological examination should be done (Kolevzon et al., 2014). The frequency of screening vision and hearing was discussed in our consortium and there was consensus to screen at least once and furthermore according to the national guidelines (Matuleviciene et al., 2023, this issue).

Self-report of pain is preferable, but in case of suspicion of pain, reliable and valid tools for signalling pain in people with intellectual disabilities who have less verbal expression are available (Herr et al., 2019). Suggested pain scales for children are Non-communicating Children’s Pain Checklist – Revised (NCCPC-R, Breau et al., 2002), r-FLACC (Malviya et al., 2006) or the Paediatric Pain Proﬁle (Hunt et al., 2004). For adults the Chronic Pain Scale for Nonverbal Adults with Intellectual Disabilities (Lotan et al., 2009) can be used.

For the assessment of the sensory proﬁle of a person with PMS, several tools are available. The Short Sensory Proﬁle (SSP) is one of the most commonly used measures of sensory features in children with autism spectrum disorder. The SSP is a shortened form of Dunn’s Sensory Proﬁle 2 caregiver questionnaire (Dunn, 2014) developed as a screening tool to identify children aged 0 to 14; 11 years with sensory processing difﬁculties. The SSP has demonstrated discriminate validity of over 95% in identifying children with and without sensory modulation differences (Tomchek and Dunn, 2007).

The recently developed SAND (Sensory Assessment for Neuro-developmental Disorders), a clinician-administered observation and corresponding caregiver interview that captures sensory symptoms based on the DSM-5 criteria for autism spectrum disorder, can also be used (sensitivity 95.5% and speciﬁcity 91.7% Siper et al., 2017 and2021). After assessing the sensory proﬁle, appropriate support can be given.

Based on these considerations, recommendations were formulated and unanimously adopted during a European consensus meeting (Table 2). As agreed in this ﬁnal consensus meeting; the most important recommendation is, that in the event of a change in behaviour, always take into account that the change can be caused by pain or other
underlying sensory problems.

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Margreet Walinga: Conceptualization, Writing – original draft, Writing – review & editing. Sarah Jesse: Writing – review & editing. Norma Alhambra: Writing – review & editing. Griet Van Buggenhout: Review & Editing, Funding acquisition.

Data availability

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