Translated from 20181029 Richtlijn 22q13DS (geautoriseerd)

Guideline 22q13 deletion syndrome (Phelan-McDermid syndrome)

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Introduction

What does this guideline cover?

This guideline is for 22q13 deletion syndrome (Phelan-McDermid syndrome, PMS), which we have shortened to 22q13DS in this guideline. For this guideline 22q13DS is defined as a deletion of 22q13.3 including the *SHANK3* gene, regardless of the cause of the deletion (see General, Definition Module).

The following subjects are covered in this guideline:

1. General: definition, incidence, prevalence, clinical features and the relationship between genetic anomalies and clinical features.
2. (Genetic) counselling: reference to clinical geneticist and chance of recurrence.
3. Prevalence, mechanism and the treatment/guidance for specific symptoms in individuals with 22q13DS: language and speech problems; chewing, swallowing and gastrointestinal problems; sensory dysfunction; epilepsy; sleep disorders; lymphedema and mental disorders.
4. Drug treatment for development and behaviour.
5. Organization of care.

For whom is this guideline intended?

This guideline is primarily for all healthcare professionals involved in the care of children and adults with 22q13DS. A brief explanation has been added at the end of this module for parents and relatives that includes links to relevant sources of information.

How did this guideline come about?

This guideline was created with a grant from ZonMw in collaboration with the Rare Chromosome Diseases expertise centre of the University Medical Centre Groningen. The guideline has been drawn up by a multidisciplinary committee with representatives from clinical genetics, paediatrics, child psychiatry, neurology, speech therapy and a doctor for the mentally handicapped. Two patient representatives sat on the working group. In addition, a digital survey was distributed to patient representatives, and the survey results have been used in the selection of the fundamental questions for the guideline.

For parents and family members

22q13 deletion syndrome (22q13DS), also known as Phelan-McDermid syndrome (PMS), is a chromosomal disorder. Normally, two complete copies of chromosome 22 are present. In 22q13DS, one end of one of the two chromosome 22s is missing a piece of hereditary material (see Figure 1). This is called a 22q13 deletion. A ring chromosome 22 can also lead to a 22q13 deletion.

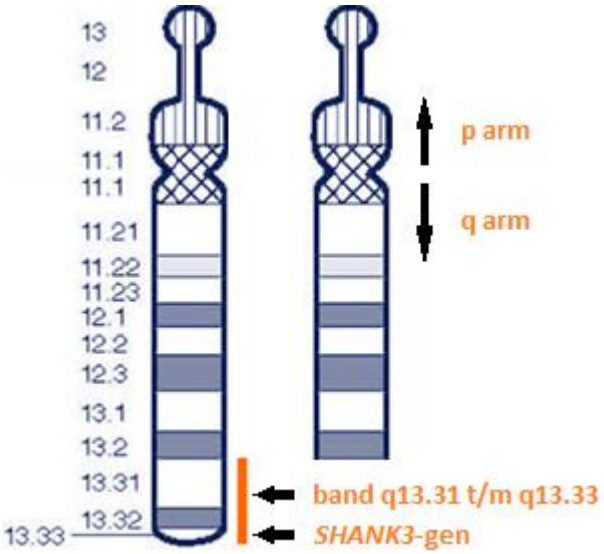

Figure 1. Chromosome 22

The missing piece of chromosome 22q13 contains a hereditary factor (gene) that is involved in the development of the nervous system, the *SHANK3* gene. This *SHANK3* gene encodes the SHANK3 protein, which plays a role in the nerve cells where signals between nerve cells are transferred (synapses). In 22q13DS there is a shortage of SHANK3 protein in the nerve cells, and as a result the signal transfer works less well.

It is estimated that 22q13DS occurs in 1 in 30,000 births. This is based on a national inventory: the number of 22q13DS diagnoses for live births from 2010 to 2014 compared to the total number of live births in those years (source Statistics Netherlands).

The main features of this syndrome are low muscle tone after birth (hypotonia), an overall developmental delay at young age and moderate to severe intellectual disability at older ages. Other features that often occur are a high pain threshold, hypersensitivity to heat, joint mobility (hyperlaxis), behavioural traits appropriate for an autism spectrum disorder and health problems (feeding problems, gastroesophageal reflux, constipation, epilepsy, vesicoureteral reflux and frequent upper respiratory tract infections). Mood disorders and lymphedema can develop at older ages. In addition, some people with 22q13DS have a number of inconspicuous external features (for an extensive description, see the Module Clinical Features).

You can find more information about 22q13DS at the following links:
http://www.uniek-erfelijk.nl/22q13-deleties. The 'Uniek folder voor ouders' was developed based on this guideline.
http://www.kinderneurologie.eu/ziektebeelden/syndromen/phelan%20mcdermid.php
http://www.rug.nl/research/genetics/research/phelan-mcdermid-syndrome/

1. General

1.1 Definition

General

22q13 deletion syndrome (22q13DS) is a chromosomal disorder that manifests as a syndromal and neurodevelopmental disorder. This condition is caused by loss of the end of chromosome 22, specifically band q13.3. In approximately 79% (30/38) of subjects this loss of material is due to an isolated, usually terminal, deletion; in 16% (6/38) it is due to a ring chromosome 22; and in 5% (2/38) it is due to an unbalanced translocation (data from (Bonaglia et al. 2011)). In rarer cases, the 22q13 deletion is due to a more complex chromosomal anomaly (Slavotinek et al. 1997; Tagaya et al. 2008; Jafri et al. 2011; Watt et al. 1985). See also module 2 (Genetic) counselling.

In 2001, Katy Phelan and Heather McDermid described the clinical and cytogenetic characteristics of 37 people with a 22q13.3 deletion (Phelan et al. 2001). Since then, 22q13DS has also been referred to in the literature as Phelan-McDermid syndrome or PMS.

The most important gene in the deletion is the *SHANK3* gene (Luciani et al. 2003; Wilson et al. 2003). Although many more variants of the *SHANK3* gene have now being described as a result of the advent of new technologies (Betancur and Buxbaum 2013), the effects of these variants (point mutations, indels and intragenic deletions) and the clinical picture associated with them has not yet crystallized. Therefore, 22q13DS is defined in this guideline as a deletion of 22q13.3 including the *SHANK3* gene, regardless of the cause of this deletion. Data on individuals with an isolated variant in *SHANK3* are not considered.

1.2 Incidence and prevalence

General

It is not known exactly how many children are born annually with a 22q13 deletion because the diagnosis is usually only made in childhood. The birth prevalence in the Netherlands is estimated at 1 in 30,000 births (calculation based on the number of diagnoses made in the 8 Dutch cytogenetics laboratories in the period 2010–September 2017 for children born from 2010–2014, and the birth figures from Statistics Netherlands in the same period). This is probably an underestimate, because some of the diagnoses, despite the early presentation of developmental delay, are only made at an older age.

In addition, research has been conducted into how often 22q13DS occurs in different populations. It is estimated that a 22q13 deletion occurs in approximately 0.25% (maximum 3.33%) of people with developmental delays and/or intellectual disabilities (Ravnan 2006; Utine et al. 2009; Gong et al. 2012; Xu et al 2016) and in 0.19% (maximum 0.88%) of people with autism spectrum disorder (ASD) (Nair-Miranda et al. 2004; Betancur and Buxbaum 2013; Leblond et al. 2014; Chen et al. 2017). This percentage increases to 0.39% (maximum 4.48%) if there is an intellectual disability in combination with ASD (Cooper et al. 2011; Waga et al. 2011; Leblond et al. 2014) and to 2.1 % if there is moderate to severe intellectual disability (Leblond et al. 2014). However, these percentages depend strongly on the selection criteria of the study population and the diagnostic techniques used.

In the Netherlands, at least 65 children and 40 adults with a 22q13 deletion have been reported to the Expertise Centre for Chromosome Diseases in Groningen, which has 22q13DS as one of its

specific areas of attention. This number is probably an underestimate because not everyone is registered at this centre and because a large number of adults with a mental disability and/or behavioural problems have never been extensively genetically tested.

1.3 Clinical Features

General

Important features

The features of 22q13DS that are most common and often the first to stand out are (neonatal) hypotonia and an overall developmental delay at an early age, accompanied by inconspicuous appearance, height, head circumference and weight (Rollins et al. 2011; Sarasua et al. 2014). The developmental problems manifest themselves mainly in the areas of speech/language and cognition and result in a moderate to severe intellectual disability at older ages.

Other frequently occurring features are a high pain threshold, heat intolerance, hyperlaxis and psychological problems (Luciani et al. 2003; Jeffries et al. 2005; Soorya et al. 2013; Sarasua et al. 2014). The psychological problems manifest themselves with characteristics of the autism spectrum, such as social communication, social interaction and sensor dysfunction. Approximately 53% of subjects with 22q13DS meet the clinical criteria for autism spectrum disorder (ASD) (Oberman et al. 2015; Mieses et al. 2016).

Health problems

Associated health problems do not occur in everyone with the 22q13DS. These problems include swallowing problems, gastrointestinal problems (such as gastroesophageal reflux, vomiting, constipation and diarrhoea), febrile seizures and/or epilepsy, urinary tract abnormalities (including congenital renal abnormalities and vesicoureteral reflux), sleep problems, frequent upper respiratory infections and lymphedema (Luciani et al. 2003; Jeffries et al. 2005; Soorya et al. 2013; Sarasua et al. 2014).

What is striking about the 22q13DS is (temporary) loss of skills and mood problems, especially starting from puberty. Brain abnormalities can also occur, including a thin corpus callosum, white matter abnormalities, arachnoid cysts and dilated ventricles, but the clinical significance of this is unclear (Kolevzon et al. 2014).

Finally, there are a number of symptoms that have been described, but where it is insufficiently clear whether these are part of the condition. These include congenital heart disease, early or late puberty, a sacral dimple, hypothyroidism and an excessive immune response (autoimmune hepatitis) (Luciani et al. 2003; Jeffries et al. 2005; Soorya et al. 2013; Sarasua et al. . 2014).

External features

Most people with 22q13DS do not have a noticeably altered appearance. Sometimes nonspecific features (dysmorphias) are present, such as broad and straight eyebrows, full eyelids with long eyelashes, full cheeks, a bulbous nose, a pointed chin, large ears, large fleshy hands and feet, malformed toenails and widely spaced adult teeth (Luciani et al. 2003; Jeffries et al. 2005; Soorya et al. 2013; Sarasua et al. 2014; Egger et al. 2016). Because the external features are nonspecific and not conspicuous, 22q13DS is usually not recognized based on appearance.

1.4 Relationship between the genetic anomaly and clinical features

General

Improvements in our ability to determine the underlying genetic abnormality (genotyping) and the description and reporting of clinical characteristics (phenotyping) have led to better knowledge of the relationship between the cause and characteristics of 22q13DS. In addition to the important common characteristics, there are characteristics and health problems that do not occur in all people with a 22q13 deletion. The challenge now is to gain more insight into who is at risk for certain health problems and to learn about the course of the characteristics in the course of life, so that a better explanation about expectations can be given following diagnosis.

The discovery of ring chromosome 22

The first publications on individuals who most likely had a 22q13 deletion described G deletion syndrome II, consisting of intellectual disability, hypotonia, epicanthal folds and a 2-3 syndactyly of the toes. It was hypothesized that G deletion syndrome II was caused by a ring chromosome 22 in which part of chromosome 22 was lost, which was then called partial monosomy (Reisman et al. 1967; Weleber et al. 1968; Warren and Rimoin 1970; Chauvel et al. 1972). Proof of this was provided in 1973 with the introduction of the chromosome banding that made it easier to recognize chromosomes (Warren et al. 1973).

Terminal 22q13 deletion

Only in 1985 was a terminal 22q13 deletion described without ring chromosome 22 (Watt et al. 1985). Almost all publications on 22q13 deletions at that time consisted of case reports and the exact size of the deletions could not yet be determined molecularly (Herman et al. 1988; Kirshenbaum et al. 1988; Romain et al. 1990; Narahara et al. 1992; Phelan et al. 1992).

The first description of '22q13 deletion syndrome' as such was published in 1994: seven individuals with a terminal 22q13.3 deletion who shared the common features of an overall developmental delay, a severe delay in speech development, hypotonia, normal or increased growth and mild dysmorphias consisting of dolichocephaly, ptosis, epicanthal folds and dysplastic ears. However, the minimal critical deletion region was still large and was estimated at 5 million base pairs (Nesslinger et al. 1994).

Microdeletions and the critical region

In the years that followed, more and also smaller deletions of 22q13.3 were detected using the FISH and MLPA techniques. The first description of a terminal microdeletion with a size of approximately 130,000 base pairs (130 kb) was made in 1995 (Flint et al. 1995; Wong et al. 1997). The candidate gene for the traits characteristic of 22q13DS was found in 2001 in a girl with a balanced translocation with the breakpoint running straight through the *ProSAP2* gene (*SHANK3*) (Bonaglia et al. 2001). The following year, a microdeletion of approximately 100kb was described with interruption of the *SHANK3* gene and, in addition, a deletion of the *ACR* and *RABL2B* genes (Anderlid et al. 2002). Subsequent larger studies confirmed this minimal critical region, with *SHANK3* being identified as the main candidate gene for the overall developmental delay, speech/language problems and behavioural problems (Luciani et al. 2003; Wilson et al. 2003).

Function of SHANK3

The *SHANK3* gene encodes the SHANK3 protein. Specifically, this protein is located in nerve cells of the cerebral cortex, hippocampus and cerebellum (Sheng and Kim 2000), areas of the brain involved in integrating and coordinating information, including learning, planning, emotion and memory (Hampson and Blatt 2015).

The SHANK3 protein is important for the development of the connections (synapses) between nerve cells. It functions as a "scaffold" protein, determining the structure of excitatory synapses through interactions with other proteins (Sheng and Kim 2000). SHANK3 controls the number of receptors and connections with other structural proteins and the cytoskeleton, and the coordination in signalling between the pre- and post-synapses. These functions are important for the number and size of the synapses, which in turn affect signalling between nerve cells and the maintenance of these networks (Bockmann et al. 2002; Roussignol et al. 2005; Halbedl et al. 2016).

When the *SHANK3* gene is turned off in neuronal cell cultures, lower expression of *SHANK3* mRNA and the SHANK3 protein is observed, resulting in lower expression of excitatory receptors and synapses, an altered morphology of synapses and reduced synaptic plasticity (Verpelli et al. 2011; Arons et al. 2012; Shcheglovitov et al. 2013). Research in Shank3-deficient animal models also shows deviations in social behaviour, vocalizations, repetitive behaviour and problems with learning and memory (Bozdagi et al. 2010; Peça et al. 2011; Wang et al. 2011).

The SHANK3 protein is also found in other tissues, such as the heart, liver and thymus (Lim et al. 1999; Redecker et al. 2006). Anomalies in these organs have not been reported in 22q13DS. It is possible that these organs are less sensitive to reduced expression of the SHANK3 protein.

Other genes and clinical features

The differences in clinical presentation in people with the 22q13DS may be explained by a difference in the length of the deletion, additional deletions and duplications of other chromosomes, epigenetic factors and other variations in the hereditary material (Tabet et al. 2017). This means that other factors can influence the amount of SHANK3 protein that is produced, but also that other genes besides *SHANK3* can influence the clinical features and health problems in 22q13DS. In addition, it is not yet well known whether a number of features are particularly noticeable at an older age. A number of relationships between the genotype and phenotype are now known.

Small versus large deletions

Thanks to improved genetic techniques, more and more people are now being diagnosed with a microdeletion of 22q13. In practice it is becoming increasingly clear that individuals with the previously described terminal microdeletion of approximately 130kb that contains three genes have a more favourable course of general development than individuals with a larger 22q13 deletion (Zwanenburg et al. 2016). People with a microdeletion are regularly diagnosed in later childhood because the developmental delay and behavioural problems is not apparent until later.

Why deletions larger than 130kb have a more serious prognosis is less well understood. A correlation has been reported between the length of the deletion and the degree of developmental delay (Sarasua et al. 2013), but it is still unknown which other genes influence this.

Isolated deletions versus ring chromosome 22

People with an isolated 22q13 deletion have the same clinical features as people with a ring chromosome 22 because both lack the part of chromosome 22q13 that includes the *SHANK3* gene (Jeffries et al. 2005). In theory it may be that, with an array-determined deletion of identical size, the functional deletion in a ring chromosome is greater due to a "silencing" effect of the p-arm on the genes of the q-arm. This has been demonstrated for ring chromosome 14 versus isolated terminal deletion 14q (van Karnebeek et al. 2002). However, the absence of *SHANK3* is the major determinant of the phenotype at 22q13DS, so any added effect will be small.

However, there is another important clinical difference. People with a ring chromosome 22 have an increased risk of developing neurofibromatosis type 2 (NF2) (Denayer et al. 2009; Zirn et al. 2012). This is because ring chromosomes can cause cell division problems due to their irregular shape. The ring chromosome 22 can be lost, leaving only the normal chromosome 22 in the cell. As a result, only one copy of the *NF2* gene remains in the cells where this occurs. In the nervous system (spinal cord or brain), such a cell can develop into a benign tumour (schwannoma or meningioma) if a somatic mutation develops in the remaining *NF2* gene. This may not have any physical effects, but can sometimes lead to epilepsy, deficits or other neurological problems due to the suppression of normal tissue. People with a ring chromosome 22 should therefore be aware of the possibility of a benign tumour as the cause for these symptoms or for general deterioration. They can then benefit from a treatment, for example with laser therapy (gamma knife).

Due to the risk of NF2, it is important that if a 22q13 deletion is determined by array testing, chromosome research follows to exclude a ring chromosome 22 (see Module (Genetic) counselling).

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5

2. (Genetic) counselling

Introduction

The term 22q13 deletion syndrome (22q13DS) is used in this guideline; this is also referred to as Phelan-McDermid syndrome (PMS).

The diagnosis 22q13DS can be made by various medical specialists. Usually the paediatrician, intellectual disability physician and clinical geneticist are involved in making the diagnosis, assisted on occasion by other medical specialists.

The diagnosis has consequences not only for the patient (see Module Clinical Characteristics and Module Specific complaints in 22q13 deletion syndrome), but possibly also for family members. Determining if there is an indication for an investigation of family members, and determining the manner of this investigation, is the expertise of the clinical geneticist. In addition, the clinical geneticist will explain the variability of the clinical picture and the relationship between genotype and phenotype, and discuss reproductive options.

Fundamental questions

Based on an analysis of bottlenecks carried out by the guideline working group, and with advice from the patient representatives, the following starting questions were formulated:

- When should individuals with 22q13DS be referred to the clinical geneticist?
- When is there an increased chance of recurrence for parents of a child with 22q13DS and what follow-up testing is needed to estimate this?

Search and selection of sources (method)

Since 22q13DS is a rare condition (birth prevalence 1: 30,000), in developing this guideline we chose to perform a generic search for Phelan-McDermid syndrome. The literature was then selected and sorted based on the predetermined fundamental questions (see Search Justification).

No specific literature emerged about counselling and the chance of recurrence from this generic search for 22q13DS. We then examined which causes of recurrence in 22q13DS have been described in the literature. The extent to which scientific evidence was available was taken into account in formulating the recommendations.

Literature summary

Referral to a clinical geneticist

The scope of the clinical geneticist covers providing explanations, often for rare and complex genetic and congenital disorders. This explanation includes: the phenotype and the expected variation within it; the underlying cause (genotype) and its effect on the phenotype; the probability of recurrence, as well as what research is needed to determine this; and the possibilities for prenatal diagnosis and other reproductive options (Galjaard 1997).

Discussing the effect of the genotype on the phenotype and the likelihood of recurrence is particularly important for a diagnosis of 22q13DS. 22q13DS is caused by a deletion of chromosome 22q13. This deletion can result from a pure (isolated) deletion, both terminal and interstitial (Luciani

et al. 2003), but it can also result from a ring chromosome 22 or an unbalanced translocation (Bonaglia et al. 2011).

If the deletion is terminal and this has been determined by array-testing, the effect on the phenotype can be estimated based on the size of the deletion, although the phenotype has also been found to vary in individuals with the same deletion size (Zwanenburg et al. 2016). Next, it is important to follow this up with chromosome testing to rule out a ring chromosome because of the risk of NF2 in ring chromosome 22 (even if the *NF2* gene itself is not deleted in the ring chromosome) (Zirn et al. 2012).

Chance of recurrence and the method of follow-up research with parents

There is no empirical data on the probability of recurrence in 22q13DS. Most people have a *de novo* deletion, which means that the chance of recurrence for parents is effectively zero (Sarasua et al. 2014). The risk of germline mosaicism is much lower (<1%) for structural chromosomal abnormalities than, for example, for *de novo* point mutations in genetic material. However, the probability is not zero, and parents of a child with a *de novo* deletion can use prenatal diagnostics if desired.

However, the chance of recurrence is clearly increased when one of the parents is a carrier of a balanced chromosomal anomaly in which chromosome 22q13 is involved. The exact chance of recurrence depends on the chromosomal aberration in the parent concerned and cannot always be given as a clear percentage. Typically, the chromosomal anomaly involves a balanced reciprocal translocation (Phelan et al. 2001; Rodríguez et al. 2003; Wilson et al. 2003; Manning et al. 2004), but interstitial translocation (insertion) and pericentric inversion have also been described (Slavotinek et al. 1997; Jafri et al. 2011). The chance of recurrence is also increased when one of the parents has a deletion of chromosome 22q13 in mosaic form (Tabolacci et al. 2005; Verhoeven et al. 2012). An increased chance of recurrence because one of the parents themselves has 22q13DS has only been described once (Denayer et al. 2012).

With regard to recurrence investigations, it is important that the person requesting the test realizes that balanced chromosome anomalies cannot be determined by array-testing and that Fluorescent in situ Hybridization (FISH) is preferably used for this purpose because it can also reveal submicroscopic changes (Zwijnenburg et al. 2014).

Conclusions

Following a 22q13DS diagnosis, referral to a clinical geneticist is always indicated for counselling on (the relationship between) the genotype and phenotype and estimation of the probability of recurrence for parents (Galjaard 1997).
Following diagnosis of 22q13DS using array, it is important to initiate follow-up research (karyotyping) into a ring chromosome 22 because of its effect on the phenotype (Zirn et al. 2012).
The 22q13 deletion in a patient with 22q13DS may be the result of a balanced chromosome aberration or mosaic deletion 22q13 in one of the parents, giving an increased chance of recurrence (Manning et al. 1990; Phelan et al. 2001; Rodríguez et al. 2003; Wilson et al. 2003).

Considerations

Referral to the clinical geneticist

There is always an indication for referral to a clinical genetics centre when a diagnosis of 22q13DS is made. Special points of consideration are the effect of the genotype on the phenotype, the chance of recurrence and the exclusion of a ring chromosome (NF2). The latter requires microscopic chromosome testing that can be combined with FISH to determine a suitable probe for the 22q13 region for the purpose of parental testing for a possible increased recurrence risk (see below).

Recurrence risk and follow-up with parents

Because array analysis cannot demonstrate a balanced translocation in parents, the preferred method of investigation to determine the recurrence probability of 22q13DS is FISH with a probe for 22q13 in both parents. It is recommended that you take a sample from the child as a positive control. To investigate if there is carrier status of the deletion or a balanced translocation, both parents are advised to undergo metaphase analysis. Mosaic deletion studies in parents, preferably done in tissues other than blood (e.g. cheek mucosa or urine), are only advised if a second child with 22q13DS is born into the family without a genetic explanation.

When carrier status of a chromosomal anomaly has been determined in one of the parents, the chance of recurrence is increased, but the chance of recurrence cannot always be given by an exact number because it depends on the properties of the chromosomal anomaly (fracture points of the translocation or percentage of mosaicism in the germ cells). In any case, parents are always eligible to discuss reproductive options when they wish to have children, because a mosaic deletion 22q13 in parents can be missed even by FISH (for example with germ cell mosaicism).

In conventional (microscopic) karyotyping, a deletion 22q13 can be missed. Thus FISH or array-testing must also be performed prenatally if there is a possibility of 22q13DS.

Even if parents do not wish to have more children themselves, further investigation in both parents is important to determine the chance of a child with 22q13DS for other family members.

Recommendations

Refer all individuals with 22q13DS to a clinical geneticist to explain (the relationship between) the genotype and phenotype and to determine if there is an increased recurrence risk for another child with 22q13DS for parents (and other family members).
With a terminal deletion 22q13 found by array, perform karyotyping to exclude a ring chromosome 22 (due to the risk of NF2).
To determine the recurrence rate for parents, fluorescent in situ hybridization (FISH) with a probe for locus 22q13 in both parents is the first choice to demonstrate a possible balanced translocation.
Because low-grade mosaicism of the 22q13 deletion in parents of a child with 22q13DS can never be ruled out with certainty, parents should be offered prenatal diagnostics for subsequent pregnancies if they wish to have more children.

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3. Specific symptoms in 22q13 deletion syndrome

This module describes some common health problems in 22q13DS, based, in part, on a survey of Dutch parents conducted by the guideline working group. These are: language and speech problems, swallowing and gastrointestinal problems, problems related to sensory dysfunction, epilepsy, sleep disorders, lymphedema, mental disorders and behavioural problems. Various treatment options are mentioned in the different submodules, with reference made to existing guidelines as much as possible. For practical reasons, the most important recommendations from these guidelines are mentioned (each revision of this guideline will check whether these recommendations are still current).

3.1 Language and speech problems

Introduction

The term 22q13 deletion syndrome (22q13DS) is used in this guideline; this is also referred to as Phelan-McDermid syndrome (PMS).

Language and speech problems occur in all children with 22q13DS (Sarasua et al. 2014). This creates limitations in communication and is one of the most common problems that parents experience. The survey of parents carried out in preparation for this guideline showed that all parents experience speech/communication problems. Individuals with language and speech problems also have an increased risk of social, emotional and behavioural problems (Lindsay et al. 2007).

Normal language and speech development is a complex process because different sensory, cognitive and motor skills are involved. Language can be divided into language comprehension (language perception, receptive language), language production (language expression, structure and meaning) and speech production (motor control and implementation of speech sounds). Language perception requires the ability to perceive, recognize and process information. Language expression requires the ability to recall information from memory and to process it into words and sentences, after which sounds and words are ultimately realized through speech production processes.

A language development disorder can only be said to exist if the level of language ability is substantially and quantifiably below the level that can be expected by age (Auris).

In 22q13DS there can be problems at different levels. However, few studies have looked specifically at the different aspects of language and speech problems in 22q13DS.

Fundamental questions

Based on the bottleneck analysis by the guideline working group and the results of the survey of patient representatives, the following fundamental questions have been formulated:

- What is the prevalence of language and speech problems in 22q13DS, and are these specific types of problems?
- What is the mechanism behind the language and speech problems in 22q13DS?
- What is the treatment and/or guidance for language and speech problems with 22q13DS?

Search and selection of sources (method)

Since 22q13DS is a rare condition (1 in 30,000 live births), in developing this guideline we chose to perform one generic scientific literature search for Phelan-McDermid syndrome. The literature was then selected and sorted based the predetermined Fundamental Questions (see Search Justification).

Specifically for this module, one article was selected from this generic search for 22q13DS (Rankine et al. 2017). Use was also made of other publications on 22q13DS in which language and speech were described and of general information about language and speech problems. The extent to which scientific evidence was available was taken into account in formulating recommendations.

Literature summary

Prevalence of language and speech problems in 22q13DS

Language and speech problems occur in all individuals with 22q13DS, but the extent varies from no spoken language (50%), to a maximum of 40 words (27%), to more than 50 words and use of sentences (10%), to good communication with full sentence usage (13%) (Sarasua et al. 2014).

In children with 22q13DS the delay in language development is more pronounced than in other developmental areas such as cognition, motor skills and social skills. Both their receptive language level and expressive language level are limited but, on average, children with 22q13DS score slightly better on receptive language than on expressive language. In a study of 34 children, Zwanenburg et al. found a maximum level of receptive and expressive language of 34 months. Approximately 25% of the children scored better on receptive language, while 20% scored better on expressive language. The difference in receptive language level compared to expressive language level in 22q13DS is therefore limited in practice. More specific to 22q13DS is that children initially speak a few words, but they can later lose them. It is striking that the developmental quotient (development age/calendar age) for both perceptive and expressive language development decreases with age. This means that the language deficiency increases with age compared to the standard (Zwanenburg et al. 2016).

Mechanisms of language and speech problems in 22q13DS

No studies have looked specifically at the mechanism(s) underlying the language and speech problems in 22q13DS. Some possible causes are:

- Conduction problems and hearing impairment as a result of frequent middle ear infections (Wilson et al. 2003; Soorya et al. 2013).
- Delays in cognitive skills such as processing information, using memory and applying stored information (Zwanenburg et al. 2016).
- Problems with adaptive behaviour and social-emotional development that make language difficult to understand as a means of communication (Oberman et al. 2015; Zwanenburg et al. 2016).
- A high palate that can lead to problems with tongue positioning and abnormal mouth habits (Sarasua et al. 2014).
- Neurological problems such as hypotonia that cause problems with oral motor skills and motor programming and control problems (verbal dyspraxia/speech apraxia) (Sarasua et al. 2014).

Treatment and/or guidance of language and speech problems in 22q13DS

One study has been published in the literature on the approach to language and speech problems in 22q13DS. This included research in the US on the use of a voice recorder in 18 children with 22q13DS

with ASD and a serious language development disorder between the ages of 30 months and 14 years (Rankine et al. 2017). LENA (Language Environment Analysis) can be used by parents of children between 0 and 5 years of age to analyse and stimulate spontaneous language. This study showed that LENA is sufficiently valid to analyse expressive language in children with 22q13DS, with its reliability decreasing above the age of 4 years. Further research into the added value for individuals is to follow.

Conclusions

Language and speech problems occur in all individuals with 22q13DS, but the extent differs per individual (Sarasua et al. 2014).
The majority of individuals with 22q13DS appear to have problems with speech production (Sarasua et al. 2014).
It is possible that individuals with 22q13DS have a higher level of the receptive language than of the expressive language (Zwanenburg et al. 2016).
A number of factors can influence language/speech problems in 22q13DS, such as frequent ear infections, cognitive skills, behavioural and neurological problems (Wilson et al. 2003; Soorya et al. 2013; Sarasua et al. 2014; Oberman et al. 2015; Zwanenburg et al. 2016).
Tools for analysing expressive language, such as LENA, may contribute to communication between individuals with 22q13DS and the people around them (Rankine et al. 2017).

Considerations

From the moment of diagnosis, practitioners should keep in mind that there is a serious threat to language and speech development in children with 22q13DS. Various factors can influence this, including frequent ear infections, developmental delay, behavioural problems and neurological problems. The relative contributions of these factors in individuals with 22q13DS is difficult to determine and can also differ per individual. This may explain the varying severity of language and speech problems in this group.

In consequence, proper treatment and counselling for language and speech difficulties in individuals with 22q13DS should take into account the various factors that affect these abilities. It is recommended that practitioners start treatment/counselling as early as possible, preferably around the 1st year. It is essential to refer patients to an audiology centre or other multidisciplinary team where all these factors can be analysed. Conditions for communication are essential. Care must be taken to avoid premature speech therapy in the strict sense if the cognitive skills are not yet well developed, as this can lead to frustration in the child, parents and practitioner. An expert speech therapist is of great importance.

Diagnostics

It is important that the conditions for communication, receptive and expressive language, and oral motor skills/articulation are identified by a skilled speech therapist using appropriate tests while taking into account the child's level of development. Attention should also be paid to any supportive communication when speaking does not seem to start.

For the early detection of language disorders, the Guide to Uniform Identification of Language Deficiencies in Young Children is used (NCJ, 2013). The JGZ Guideline Speech Language Development

is expected in 2018. Available screening instruments are, for example, VTO Language 2-year-olds and the SNEL (Speech and Language Standards First Line).

The communication matrix (www.communicationmatrix.org) is a digital questionnaire that maps communicative functions. This tool can provide information about the conditions for communication and control of the communicative functions. In addition, the communication matrix can provide information to determine the direction of supported communication.

Treatment

It is preferable to work on the communication skills as a whole (verbal and non-verbal), while taking into account the child's cognitive skills.

One of the central treatments for language and speech problems is speech therapy. Speech therapy can focus on receptive and/or expressive language and oral motor skills, or on offering supported communication in the form of gestures, photos, pictograms, or a dynamic tool such as specific communication equipment with speech output. Supportive communication can be deployed at a very early stage without hindering the development of spoken language (Romski and Sevcik 2005).

For children where spoken language does not initiate, we recommend turning to the International Society for Augmentative and Alternative Communication (ISAAC-NF) for help with stimulation of non-verbal communication.

Parents can try to stimulate communication at a very young age in collaboration with a specialized speech therapist. For examples, see the NCJ brochure 'Tips for Language' or the 'Checklist Communication and Education' by BOSK. However, the child's cognitive development level must be taken into account.

In addition, research is being conducted into the possible applications of LENA in the Netherlands by the Dutch Foundation for the Deaf and Hard of Hearing Child (NSDSK) in collaboration with the Kentalis Audiological Centre.

Recommendations

In children with 22q13DS be aware of a serious threat to language and speech development from the moment of diagnosis.
To enable early detection and treatment, refer patients to an audiology centre or other multidisciplinary team where the various factors influencing language/speech problems in 22q13DS can be analysed.
Speech therapy aimed at the development of receptive and expressive language, speech motor skills and/or supported communication to improve communication ability is a central part of the treatment.
A specialist speech therapist can counsel parents on how to stimulate speech/language development from an early age.

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3.2 Chewing, swallowing and gastrointestinal problems

Introduction

The term 22q13 deletion syndrome (22q13DS) is used in this guideline; this is also referred to as Phelan-McDermid syndrome (PMS).

Gastrointestinal problems are common in 22q13 deletion syndrome (see Prevalence), and chewing and swallowing problems, dental problems, reflux disease, cyclic vomiting, constipation and diarrhoea in particular have been reported. This guideline focuses in particular on reflux disease and constipation.

Fundamental questions

Based on the bottleneck analysis by the guideline working group and the results of the survey of patient representatives, the following fundamental questions have been formulated:

- How frequently do gastrointestinal problems occur?
- How should reflex and constipation be treated in individuals with 22q13DS?

Search and selection of sources (method)

Since 22q13DS is a rare condition (1 in 30,000 live births), in developing this guideline we chose to perform one generic scientific literature search for Phelan-McDermid syndrome. The literature was then selected and sorted based the predetermined fundamental questions (see Search Justification). The literature search found no specific research into gastrointestinal disorders in individuals with 22q13DS.

The literature summary, conclusions and recommendations in this module are based on reviews of 22q13DS and the general guidelines below. These guidelines also seem to apply to 22q13 deletion syndrome.

- The NVK guideline *Gastroesophageal Reflux (Disease) in Children Aged 0-18 years* (NVK, 2012)
- The Guideline *Reflux Disease in People with Serious Mental Disability*, Part 1: Clinical Protocol (NIVEL, 2008)
- The NVK guideline *Constipation in Children from 0-18 years* (NVK/NHG, 2016)
- The NVK workbook *Care for Children with Multiple Severe Disabilities*, chapter on "Constipation" (NVK, version June 2016).
- The NHG-Standards Constipation (NHG, 2010).

The extent to which scientific evidence was available was taken into account in formulating the recommendations.

Literature summary

Prevalence of chewing and swallowing problems

Chewing and swallowing problems occur in more than 50% of people with 22q13DS. There are several reasons for this. They often have hypotonia (57-85%), which can make 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 and chewing inedible objects have been described in 25% and 60-88% of people with 22q13DS, respectively. The anatomical abnormalities, in combination with the hypotonia and the typical chewing and mouthing behaviour,

can lead to chewing and swallowing problems and loss of saliva. It therefore makes sense to involve a preverbal speech therapist at an early stage (van den Engel-Hoek 2015)

Prevalence of gastrointestinal problems

Gastroesophageal reflux is seen in 30-50% of people with 22q13DS, and cyclic vomiting is seen in about 25% (Phelan and McDermid 2012; Sarasua et al. 2014).

Constipation generally occurs frequently (26-57%) in children and adults with intellectual disabilities (Morad et al. 2007; Veugelers et al. 2010). In individuals with 22q13DS, 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).

About 10% of adults with 22q13DS are overweight, possibly due to reduced exercise and excessive eating due to typical mouth behaviours (Phelan and Rogers 2005).

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. Placing a feeding tube 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 (Bohmer et al. 1999).

Cyclic vomiting

The literature does provide advice with regard to treating cyclic vomiting in children, such as excluding increased intracranial pressure and giving infusions for (imminent) dehydration, but the underlying aetiology is not known (Romano C et al. 2018).

Constipation

As mentioned, constipation occurs in 40% of individuals with 22q13DS (Kolevzon et al. 2014) and is the influenced by the following factors:

- Impaired gastrointestinal motility. The gut's neuronal network has many connections to the central nervous system. Depending on the nature and extent of the neurological problems in the child, the motility of the intestine may be impaired (NVK workbook, chapter constipation). This manifests as delayed gastric emptying, delayed colonic passage time and constipation or diarrhoea.
- Insufficient control over defecation. Mentally disabled children, including children with 22q13DS, may have difficulty achieving normal toilet training (NVK workbook, chapter constipation). 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. Their food can be low in fibre, as is often the case with easy-to-mash food. This contributes to the development of constipation. In addition, fluid balance may be disturbed (including by swallowing problems, vomiting, diarrhoea and excessive loss of saliva), which increases the risk of constipation (NVK workbook, chapter constipation).
- Side effects of medication. Medications such as anti-epileptics (including valproic acid), anti-cholinergics, phenothiazines (including promethazine) and opiates have a negative influence on

the colonic transit time (NVK workbook, chapter constipation). Constipation is therefore an important side effect of these drugs.

- Reduced thyroid function can cause symptoms of constipation. Hypothyroidism is slightly more common than average in 22q13DS (approximately 6%) (Sarasua et al. 2014).
- Immobility (NVK workbook, chapter constipation). Immobility can arise from the frequently occurring hypotonia, but also from fatigue and sleep problems in persons with 22q13DS. This increases the risk of constipation.

Conclusions

Chewing and swallowing disorders and gastrointestinal problems such as reflux, cyclic vomiting and constipation are frequent in 22q13DS, in part due to limited cognitive development, hypotonia, abnormal chewing patterns, pica, dental problems and hypothyroidism (Phelan and McDermid 2012; Kolevzon et al. 2014; Sarasua et al. 2014).

Considerations

Gastroesophageal reflux (GERD)

The considerations below are based on:

- NVK guideline *Gastroesophageal Reflux (Disease) in Children Aged 0-18 years* (NVK, 2012)
- Guideline *Reflux Disease in People with Serious Mental Disability, Part 1: Clinical Protocol* (NIVEL, 2008)

Diagnosis of gastroesophageal reflux disease (GERD)

Making a diagnosis of GERD is complicated by the sometimes limited communication with the patient. Alarm signals may be lack of appetite, food refusal, dental complaints and regurgitation and vomiting, but can also be atypical complaints such as sleep disorders due to night-time reflux, restlessness, behavioural problems and self-injuring behaviour. Additional investigations, especially in young children, may include radiological examination of the gastrointestinal tract with contrast, gastroscopy including biopsies, screening for drug toxicity and pH/impedance testing.

Treatment of gastroesophageal reflux disease (GERD)

During treatment it is important to provide individualized lifestyle advice.

Given the high prevalence of GERD in the mentally disabled, consideration can be given to starting trial treatment with a proton pump inhibitor in older children and adults without diagnostic testing. This is only possible if there are clear symptoms and the symptoms can be evaluated before and after a 4-8 week trial period.

Long-term use of proton pump inhibitors has been shown to be necessary to control symptoms. If the effect of the proton pump inhibitor proves to be insufficient, or if reflux complaints recur, this may indicate under-dosage (Hassall 2012; Romano et al., 2017).

Cyclic vomiting

Diagnosis of cyclic vomiting

Infections, increased intracranial pressure, migraine, epilepsy, intestinal obstruction and a reaction to medication or food should be excluded (Romano et al. 2018).

Treatment of cyclic vomiting

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

Constipation

The recommendations below are based on:

- NVK guideline *Constipation in Children from 0-18 years* (NVK/NHG, 2016)
- NVK workbook *Care for Children with Multiple Severe Disabilities,* Chapter on "Constipation" (NVK, version June 2016).
- NHG-Standards Constipation (NHG, 2010).

Diagnosis of constipation

Various definitions have been formulated for the diagnosis of constipation. A generally accepted definition was established in the ROME III criteria and is described in the NVK Guideline Constipation (NVK/NHG, 2016). A constipation list can also be helpful, such as the Bristol Stool Scale (Lewis and Heaton 1997). A diagnosis of constipation can be made on the basis of the frequency, quantity and consistency of defecation and a careful physical examination. It is important for treatment to determine the phase of the defecation problem: constipation with or without distension of the rectum ('megarectum'), and with or without faecal incontinence. When in doubt, an X-BOZ can be made to get more clarity.

Treatment of constipation

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, increasing the fibre content of the diet and, where possible, discontinuing or reducing medication that can promote constipation.

Treatment with oral laxatives (osmotic, volume increasing or contact laxatives) is often necessary. Keeping a stool diary is also valuable, as it can be used to track whether there is sufficient stool production. For specific treatment, see the guidelines mentioned above.

Recommendations

Treatment of gastroesophageal reflux includes providing information, nutritional advice and possible treatment with proton pump inhibitors.
Treatment of constipation includes providing information to parents/carers, dietary advice and, if necessary, treatment with oral laxatives.
When increases in behavioural problems, sleep disorders, mouthing behaviour or self-mutilation are seen, underlying causes such as gastroesophageal reflux and constipation should be considered.
Consider referral to a pre-verbal speech therapist for chewing and swallowing disorders.

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- Guideline *Reflux Disease in People with Serious Mental Disability, Part 1: Clinical Protocol* (NIVEL, 2008).
- NVK guideline *Constipation in Children from 0-18 years* (NVK/NHG, 2016).
- NVK workbook *Care for Children with Multiple Severe Disabilities,* Chapter on "Constipation" (NVK, version June 2016).
- NHG-Standards Constipation (NHG, 2010).

3.3 Sensory dysfunction

Introduction

The term 22q13 deletion syndrome (22q13DS) is used in this guideline; this is also referred to as Phelan-McDermid syndrome (PMS).

Parents often report reduced or altered pain tolerance in children with 22q13DS. This is called a sensory dysfunction, the inability to process stimuli such as visual, auditory, touch, smell, or pain sensations. Sensory dysfunction is the loss of sense of stimuli and its central coordination. Causes can include ageing, physical trauma or genetic causes. For example, sensory dysfunction can occur with certain forms of intellectual disability (Battaglia 2011), sometimes in combination with a disorder within the autism spectrum (ASD). An abnormal sensitivity to stimuli occurs in 40-70% of children with ASD, for whom a stimulus of average intensity can be observed as extremely intense or strongly deadened (Biersdorff 1994; Tavassoli et al. 2017). The same stimuli can therefore cause different reactions in the same individual at different times. Pain experience can be expressed verbally/vocally, by facial expression, or by other behaviours (Rattaz et al. 2013).

People with 22q13DS always have an intellectual disability and often exhibit behaviour characteristic of ASD. This can partly explain why they experience the decreased pain perception described in literature and by parents. However, there may also be a direct influence of SHANK3 haploinsufficiency.

Fundamental questions

Based on the bottleneck analysis carried out by the guideline working group and the results of the survey of patient representatives, the following fundamental questions have been formulated:

- How often do we see sensory dysfunction in patients with 22q13DS? And of what kind?
- What is the mechanism behind the sensory dysfunction seen in 22q13DS?
- What should doctors and parents/carers pay attention to regarding sensory dysfunction in patients with 22q13DS?

Search and selection of sources (method)

Since 22q13DS is a rare condition (1 in 30,000 live births), in developing this guideline we chose to perform a generic scientific literature search for Phelan-McDermid syndrome. The literature was then selected and sorted based the predetermined fundamental questions (see Search Justification).

- For the basic question about the *occurrence of sensory dysfunction*, the following articles were included: Phelan et al. 2001; Philippe et al. 2008; Battaglia 2011; Kolevzon et al. 2014; Sarasua et al. 2014; Mieses et al. 2016.
- For the basic question about the *prevalence of sensory dysfunction*, the following articles were included: Phelan et al. 2001; Philippe et al. 2008; Battaglia 2011; Kolevzon et al. 2014; Sarasua et al. 2014; Mieses et al. 2016.
- For the basic question about the *mechanism of sensory dysfunction,* the following articles were included that describe the relationship between sensory dysfunction and a *SHANK3* defect in mice: Han et al. 2016; Orefice et al. 2016; Li et al. 2017.

- For the basic question *what should doctors and parents/carers pay attention to regarding sensory dysfunction* two articles are included that specifically examined sensory reactivity in people with 22q13DS: Philippe et al. 2008; Mieses et al. 2016.

In addition, reference is made to the multidisciplinary guideline *Signalling Pain in People with Intellectual Disabilities* (Trimbos Institute, 2015)

The extent to which scientific evidence was available was taken into account in formulating the recommendations.

Literature summary

Prevalence of decreased response to pain and sensory dysfunction

Reduced pain perception is seen in 42-75% of individuals with 22q13DS (Phelan and Rogers 2005; Kolevzon et al. 2014). A large cohort study reported a small but significant increase with age: 69% to 5 years, 79% 5-10 years, 84% 10-18 years and 89% 18-65 years. Other sensory dysfunctions were also mentioned in this study: heat regulation disorder in 68%, decreased sweating in 60% and hypersensitivity to tactile stimuli in 46% (Sarasua et al. 2014). There can also be overstimulation in response to the environment, such as panic from unexpected sounds, the phone ringing, or a rapid change in the field of view. What is striking is that there is also stimulus-seeking behaviour, especially oral (chewing paper, licking of glass or iron objects), smell (smelling things or people) or proprioceptive (lying on the floor or moving on the knees), and these behaviours decrease as children grow older (Phelan et al. 2001).

Sensory dysfunction and decreased pain response in 22q13DS

A diminished response to pain may be due to a sensory dysfunction associated with ASD. Two publications have compared sensory dysfunction in children with ASD and 22q13DS. They show that the sensory dysfunction in 22q13DS differs from that in children with idiopathic ASD, although there is a similarly altered response to pain.

In their small study (n=8), Philippe et al. found that children with 22q13DS showed a greatly reduced response to verbal and pain stimuli, but an overreaction to other stimuli (touch, sudden sounds). However, in these eight 22q13DS children, the authors found no other behaviours such as lateral eye angle oriented or movement-related fascinations and auditory hypersensitivity (Philippe et al. 2008).

Mieses et al showed that children with 22q13DS have less pronounced sensory dysfunction than children with idiopathic ASD. Nevertheless, the authors also found a reduced response to pain in 22q13DS children that was not different from the control group with ASD. They compared sensory reactivity between 24 children with 22q13DS and 61 age-matched children with idiopathic ASD and low IQ, using the Short Sensory Profile test (Kientz and Dunn 1997; Dunn 1999). The most striking finding in this study was that children with 22q13DS were overly sensitive, but showed less pronounced sensory sensitivity than children with ASD. A side note about this study is that there were relatively more girls in the 22q13DS group and their (verbal) IQ was lower (Mieses et al. 2016).

Thus, children with 22q13DS have less pronounced sensory dysfunction than children with ASD, but both groups show an equally reduced response to pain compared to normally developing children (Mieses et al. 2016; Tavassoli et al. 2017).

The cause for decreased pain response in 22q13DS

In the 22q13DS, heterozygous deletion of the *SHANK3* gene, which is involved in the formation and stabilization of postsynaptic glutamate receptors, is believed to contribute to the altered pain perception (Roussignol et al. 2005). Based on the current literature, however, we cannot verify that *SHANK3* is the only gene responsible for the altered sensory information processing in 22q13DS, so other factors may also play a role. However, Han et al. 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 (Han et al. 2016).

Orefice et al. 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).

Li et al. examined in a mouse model whether, in addition to an altered response to pain, there was also an altered sensitivity to anaesthesia. They found an increased sensitivity to the aesthetic isoflurane in Shank3-haploinsufficient mice (Li et al. 2017). The significance of this for humans has yet to be investigated.

Diagnosis, treatment and guidance for sensory dysfunction and reduced pain perception in 22q13DS

Little literature is available on this topic. However, general advice can be given (see Considerations below) based on, among other things, the guideline *Signalling Pain in People with Intellectual Disabilities* (Trimbos Institute 2015).

Conclusions

A significant number of sensory dysfunctions have been reported in people with 22q13DS, including reduced pain perception, heat regulation disorder, decreased sweating and a hypersensitivity to tactile and environmental stimuli (Phelan and Rogers 2005; Kolevzon at al. 2014; Sarasua et al. 2014).
Children with 22q13DS have atypical sensory reactivity compared to children with idiopathic ASD, namely a reduced pain response but also less pronounced sensory sensitivity (Philippe et al. 2008; Mieses et al. 2016).
Individuals with 22q13DS and idiopathic ASD appear to have a different profile on the Short Sensory Profile test (Mieses et al. 2016; Tavassoli et al. 2017).

Considerations

Diagnosis of sensory dysfunction in 22q13DS

The combination of intellectual disability with sensory dysfunction makes testing difficult. The Short Sensory Profile (SSP) test to be taken by caregivers can provide insight into the sensory profile of 22q13DS (Kientz and Dunn 1997; Dunn 1999). Atypical SSP results are part of ASD and can be distinguished from the profile in 22q13DS.

For 22q13DS, it is recommended that a referral is made to a therapist (physiotherapist, occupational therapist or speech therapist) who specializes in sensory information processing. After taking a Sensory Profile (SP-NL), appropriate support or therapy can be provided.

Treatment and support for sensory dysfunction and reduced pain perception in 22q13DS

Despite the lack of scientific underpinning for treatment and guidance, we can identify some points for attention, such as the altered pain perception in 22q13DS. Sensory dysfunction affects behaviour and can lead to increased anxiety and uncertainty. Sensory stimuli can produce unexpected behaviours, and pain is experienced and communicated differently. Environmental adjustments such as a good acoustic space should therefore be considered, as should avoidance of sudden noises, abrupt changes in heat/cold, or sudden touch.

Higher pain tolerance and reduced expressive communication can lead to injuries or inflammation being discovered late or going unnoticed (e.g. bone fractures or dental problems). One should therefore pay extra attention to the possibility of, e.g., ear infections, gastroesophageal reflux, dental problems, constipation and other medical conditions, leading to changed behaviour. For this we refer to the guideline *Signalling Pain in People with Intellectual Disabilities* (Trimbos Institute, 2015), which discusses the different pain behaviours and measuring instruments for objectifying pain. The most important recommendation from this guideline is that, in the event of a change in behaviour, a care provider or counsellor must always take into account that the change can be caused by pain. In addition, longstanding notable behaviour can also be caused by pain.

Recommendations

If there are concerns about sensory stimulation processing or misunderstood behaviour, refer the person with 22q13DS to a sensory information therapist for examination, treatment, and advice regarding sensory information processing.
Be alert for possible reduced/changed pain perception whereby somatic complaints may go unnoticed.
For general diagnosis and treatment of pain signalling, see the guideline *Signalling of pain in people with intellectual disabilities* (Trimbos Institute, 2015). The main recommendation from this are: In the event of a change in behaviour, a health care professional or counsellor should always consider that this change may be caused by pain. Longstanding notable behaviour can also be caused by pain.

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3.4 Epilepsy

Introduction

The term 22q13 deletion syndrome (22q13DS) is used in this guideline; this is also referred to as Phelan-McDermid syndrome (PMS).

Epilepsy occurs relatively frequently in 22q13DS. In their review, Kolevzon and colleagues arrived at a prevalence of fever-related and non-fever-related seizures of 24% (Kolevzon et al. 2014).

Epilepsy is a common neurological disorder with a prevalence of approximately 1%, but it is more common in people with ASD both with and without intellectual disability (21.5% and 8%, respectively) (Amiet et al. 2008; Suren et al. 2012). In 22q13DS, the intellectual disability, ASD and epilepsy have an underlying pathogenesis that is, at minimum, shared.

Fundamental questions

Based on the bottleneck analysis carried out by the guideline working group and the results of the survey of patient representatives, the following fundamental questions have been formulated:

- What is the prevalence of epilepsy in 22q13DS, and is this a particular kind of epilepsy?
- What is the mechanism underlying epilepsy in 22q13DS?
- What is the treatment for epilepsy in 22q13DS?

Search and selection of literature sources

Since 22q13DS is a rare condition (1 in 30,000 live births), in preparing this guideline we chose to perform a general scientific literature search for Phelan-McDermid syndrome. The literature was then selected and sorted based the predetermined Fundamental questions (see Search Justification).

- For the fundamental question about *the prevalence, type and mechanism of epilepsy* in 22q13DS, the following articles were included: Lund et al. 2013; Shcheglovitov et al. 2013; Soorya et al. 2013; Figura et al. 2014; Sarasua et al. 2014; Holder and Quach 2016; Yi et al. 2016; Reierson et al. 2017.
- For the fundamental question about *treatment of epilepsy in 22q13DS*, the following articles were included: Lund et al. 2013; Soorya et al. 2013; Figura et al. 2014; Holder and Quach 2016.
- In addition, reference is made to the guideline *Diagnosis and Treatment of Epilepsy*, chapter on "intellectual disability" (NVN, version June 2017).

The extent to which scientific evidence was available was taken into account in formulating the recommendations.

Literature summary

Prevalence of epilepsy in 22q13DS

The average prevalence of fever- or non-fever-related seizures in 22q13DS is 24% based on a large review (Kolevzon et al. 2014). In the largest cohort (n=201), the prevalence of "any type of seizures" was 27%, with a significant increase with age: 11% under 5 years of age, 26% between 5 and 10 years old, 43% between 10 and 18 years old and 60% over the age of 18 (Sarasua et al. 2014). Thus, the prevalence of epilepsy reported in studies in 22q13DS may be influenced by the age of the population studied.

In a study of 32 people with 22q13DS, parents reported seizures in 41%, of whom 22% had febrile seizures, 13% had non-febrile seizures and 6% had both. The non-febrile seizures included generalized and complex partial seizures and had proven EEG abnormalities. Notably, 13% of the subjects in this study had no clinical seizures, but did have an abnormal EEG (Soorya et al. 2013). Thus, in 22q13DS, epileptiform EEG abnormalities are seen in both individuals with (history of) epilepsy and those without clear manifestations of epilepsy.

In another study of 20 individuals with 22q13DS, 45% had ever had an attack. The type of clinical convulsion based on the then-current epilepsy classification varied from atypical absences (most) to tonic, atonic, tonic-clonic and myoclonic (Holder and Quach 2016). About 50% had a combination of seizure types, and 25% had a status epilepticus. No specific EEG abnormalities were seen in this study, and brain imaging by MRI in this group found no structural abnormalities to explain the epilepsy. Nor did they find an explanation for why one individual with 22q13DS developed a simple type of seizure while another had complex seizures with a tendency toward pharmacoresistance. A possible predictive factor for the development of difficult-to-treat epilepsy is a slow or missing occipital dominant rhythm on the EEG (Holder and Quach 2016).

In a group of 50 people with 22q13DS, it was investigated whether there was a relationship between epilepsy and the regression around the age of 6 years that was observed in 43% of the participants. Both abnormal EEG and epilepsy did not appear to be associated with an increased risk of regression (Reierson et al. 2017).

Mechanism underlying epilepsy in 22q13DS

A large cohort study showed no relationship between the size of the deletion and the risk of having epilepsy (Sarasua et al. 2014). This means that the *SHANK3* deletion alone is sufficient for the increased risk of epilepsy. In addition, the size of the deletion was not correlated with the severity of the epilepsy, but was correlated with the chance of having an abnormal EEG (Reierson et al. 2017). However, the EEG deviations themselves are often not specific for 22q13DS, but a slow background pattern is frequently seen (Holder and Quach 2016).

Studies using excitatory neurons formed from pluripotent cells from subjects with 22q13DS indicate increased excitability of these cells. This may be associated with the increased susceptibility to developing epilepsy (Shcheglovitov et al. 2013). Studies in mice with a loss-of-function mutation in *SHANK3* have not yet clarified the mechanism of epilepsy. This study hypothesized a role for a subunit of the hyperpolarization-activated cyclic nucleotide gated channel (HCN), and therefore provides a possible explanation as to why haploinsufficiency of *SHANK3* yields an increased susceptibility to epilepsy and why there are multiple seizure types, with atypical absences, seen on EEG (Yi et al. 2016).

Treatment of epilepsy in 22q13DS

A study of 6 people with 22q13DS diagnosed easily treated epilepsy (Figura et al. 2014). However, the literature also occasionally describes the development of difficult to untreatable epilepsy, with, for example, Lennox-Gastaut syndrome (Lund et al. 2013). One person with 22q13DS required temporal lobectomy due to treatment-resistant epilepsy (not further specified) (Soorya et al. 2013).

Only one study has specifically looked at the treatment of epilepsy in 22q13DS. A spectrum of anti-epileptic drugs, most frequently lamotrigine, levetiracetam and topiramate, was given to 20 subjects with 22q13DS. There was no mention of a preferred antiepileptic. Epilepsy that manifested as only

one type of seizure seemed to respond better to a single antiepileptic than when multiple epileptic manifestations were present. A vagus nerve stimulator was implanted in two people with pharmacoresistant epilepsy, and a modest improvement in seizure frequency was seen (<50% reduction in attacks) (Holder and Quach 2016).

Conclusions

Seizures occur in about 24% of individuals with 22q13DS (Kolevzon et al. 2014).
Febrile seizures are the most frequent events seen in 22q13DS (Sarasua et al. 2014). The most frequent type of seizure is an atypical absence, but there is no specific type of seizure associated with 22q13DS (Holder and Quach 2016)
In 22q13DS, EEG abnormalities are found in both individuals with and individuals without clinical signs of epilepsy. There are no EEG findings specific to 22q13DS, but a slow background pattern is most common (Holder and Quach 2016).
A deletion of the *SHANK3* gene, regardless of the size of the deletion, increases the risk of epilepsy (Sarasua et al. 2014). The size of the deletion is not associated with the severity of the epilepsy (Reierson et al. 2017).
There is no specific treatment for epilepsy in 22q13DS. However, individuals with only one kind of seizure seem to respond better to an anti-epileptic than those with multiple types of seizures (Holder and Quach 2016).

Considerations

Given that epilepsy occurs with and without clinical manifestations in a relatively high frequency (24%) of people with 22q13DS, it is a concern. There are both fever-related attacks and non-febrile attacks, generalized and complex partial attacks. The frequency of epilepsy also appears to increase with age.

With clinical manifestation, the epilepsy should be evaluated. If just one type of seizure is present, the seizures are easy to treat. In a minority of individuals with 22q13DS, epilepsy develops into a difficult-to-treat form. There is no evidence that individuals with 22q13DS benefit from any specific pharmacotherapeutic treatment for epilepsy.

An EEG is important for diagnosis but has a less clear role in predicting the development of the epilepsy. The contribution of imaging (MRI) is likely to be limited, but little research has yet been conducted on cerebral imaging in 22q13DS. An MRI can therefore be considered, especially in the case of epilepsy that is less responsive to therapy, preferably in the context of expert care, including evaluation of this care.

Recommendations

People should be alert for epilepsy in individuals with 22q13DS because of the high prevalence of epilepsy in this group.
In the absence of clinical symptoms, an EEG is not recommended.
By suspected seizures or indications of seizures, by which one should be alert for atypical seizures, further investigation by a (paediatric) neurologist or paediatrician is recommended.
Epilepsy in 22q13DS is treated according to common principles, whereby monotherapy is usually

sufficient (see guideline *Diagnosis and Treatment of Epilepsy*, chapter on "intellectual disability" (NVN, version June 2017)).

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3.5 Sleep Disorders

Introduction

The term 22q13 deletion syndrome (22q13DS) is used in this guideline; this is also referred to as Phelan-McDermid syndrome (PMS).

Sleep problems are common in people with intellectual disabilities. Prevalence rates range from 15% to 88%, depending on the study design and definitions used. Severe sleep disorders occur in 9.2%. Sleeping problems are also more common in children and adults with epilepsy, vision disorder, an autism spectrum disorder (ASD) or ADHD. The sleep pattern may be disrupted or the sleep efficiency inadequate. Biological clock disorders, in which melatonin production is disturbed, can cause problems falling or staying sleep. This can result in an early sleep phase disorder (tired early, awake early), a delayed sleep phase disorder (falling asleep late and sleeping in for a long time), or a disturbed sleep pattern (short naps both at night and during the day). Other sleep disorders are problems around bedtime, parasomnias (involuntary movements during sleep), sleep apnoea syndrome (respiratory disorder) and narcolepsy (excessive sleep) (van de Wouw et al. 2012).

Sleep disorders not only have a major impact on the health, behaviour, functioning and learning opportunities of affected individuals, but also on the well-being and resilience of their parents or caregivers.

Fundamental questions

Based on the bottleneck analysis carried out by the guideline working group and the results of the survey of patient representatives, the following fundamental questions have been formulated:

- How often do sleep disorders occur in 22q13DS, and are they of a specific type?
- How can sleep problems be managed and treated in 22q13DS?

Search and selection of literature sources

Since 22q13DS is a rare condition (1 in 30,000 live births), in developing this guideline we chose to perform a general scientific literature search for Phelan-McDermid syndrome. The literature was then selected and sorted based the predetermined Fundamental questions (see Search Justification).

- Out of this general search two articles were selected for this module: Figura et al. 2014; Bro et al. 2017.
- We also considered two case series, Soorya et al. 2013; Sarasua et al. 2014, and a review, Kolevzon et al. 2014.

In addition, use was made of the chapter on “Sleep Disorders” in the online workbook *Care for Children with Multiple Severe Disabilities* in the section on “Hereditary and congenital disorders (EAA)” of the Dutch Association of Paediatrics (NVK).

The formulation of the recommendations took into account the extent to which scientific evidence was available.

Literature summary

Prevalence of sleep disorders in 22q13DS and types of sleep disorders

Studies focusing on sleep problems in 22q13DS are limited. In a large cohort study of 201 subjects with 22q13DS (median age 6.2 years, age range 0.4-64.2 years), data are only available for 26 subjects. Sleep problems occurred in 12 out of the 26 (46%). No sleep apnoea was identified, but the authors did not say whether the disorders had to do with falling or staying asleep (Sarasua et al. 2014). Another cohort study states that 13 of 32 (41%) individuals had sleep disorders (Soorya et al. 2013), but also did not elaborate on the type of sleep disorders. The prevalences reported in these studies together yield a prevalence of 25/58 (43%). This percentage does not agree with a more recent questionnaire study among 193 caregivers of persons with 22q13DS. Using the Children's Sleep Habits Questionnaire (CSHQ), this study found that 90% of subjects with 22q13DS had sleep disorders (median age 8 years, range <1 to >40 years). However, only 22% had undergone a sleep study, and 17% had been formally diagnosed with a sleep disorder (Bro et al. 2017). It should be noted that the questionnaire was sent out to 1035 members of a 22q13DS parent association and the response was only 19%, so there may be reporting bias.

It is notable that this study looked at the type of sleep disorders, which were found to cover the entire spectrum. About half (40%) of the individuals were described as having difficulty falling asleep, often requiring a parent to be present while falling asleep. Most individuals with 22q13DS do not fall asleep within 20 minutes. Sleeping problems occurred in just over half (59%), with individuals often being awake for more than 15 minutes. It was striking that children are often (70%) restless in their sleep, incontinent at night (67%) and grind their teeth (54%). The sleep study in the 17% (n=32) with a formal diagnosis of sleep disorder provided the following information: 20/32 (63%) had sleep apnoea and 6/32 (19%) had insomnia. Furthermore, this study found that an increase in sleep disorders in the child correlated with an increase in sleep disorders and daytime sleepiness in the parent (Parents Sleep Habits Questionnaire) (Bro et al. 2017).

In a small study in 6 people with 22q13DS (median age 19.5, range 11-20 years), research was conducted into EEG patterns during waking and falling asleep. Three subjects had relatively mild myoclonic or tonic-clonic seizures and paroxysmal EEG abnormalities, especially fronto-temporal anomalies, that increased during sleep. The authors indicate that epilepsy can also be subclinical. A relationship between epilepsy and sleep disorders is not identified, but is theoretically possible (Figura et al. 2014).

Treatment and guidance for sleep disorders in individuals with 22q13DS

The questionnaire study of 193 caregivers of individuals with 22q13DS concluded that screening for and evaluating sleep problems in people with 22q13DS is important and can have a long-term impact on their well-being and that of their caregivers. In addition, approximately 1/3 of individuals receive sleep medication, with melatonin (76%) and clonidine (18%) being given most often (Bro et al. 2017)

Melatonin is often used for sleeping problems in children with an ASD, and 85% of parents in this group reported an improvement in sleep patterns with the use of melatonin (Andersen et al. 2008). Although this has not yet been systematically investigated in 22q13DS, melatonin is also the most frequently prescribed sleep medication in this group.

Based on a meta-analysis of studies in people with intellectual disabilities, it has been concluded that melatonin is effective and safe in the treatment of sleep problems (Braam et al. 2009). Because there is still little information about its safety with long-term use, Braam suggests that melatonin should preferably only be given if research has revealed an impaired biological melatonin rhythm, for example in saliva (Pandi-Perumal et al. 2007).

A Dutch guideline for the treatment of sleep disorders for intellectual disability does not exist yet. There is a chapter on sleep disorders in the book *Medical Care for Patients with an Intellectual Disability* (Braam, 2014). See also the NVK workbook *Care for Children with Multiple Severe Disabilities*, chapter "Sleep Disorders" (NVK, version June 2016)

Important points of attention from the online workbook and the chapter on sleep disorders are:

- To rule out somatic causes (reflux, aspiration, coughing, (subclinical) epilepsy (Figura et al. 2014), sleep apnoea, spasticity, pain, spasms, hip dislocation, constipation, enuresis, allergies, postural restrictions).
- To give attention to the sleep environment (noise, ambient light, room temperature, mattress, bed linens, etc.).
- To optimize sleep hygiene and thus the biological clock (fixed and appropriate bed times, soothing routine before bed, reduce caffeine or caffeinated drinks).
- If necessary, to treat mental disorders (ADHD, ASD).
- To treat problematic sleep behaviour with the help of an experienced behavioural expert. Bedtime fading, extinction and gradual distancing are evidence-based treatments for people with intellectual disabilities (Richdale and Wiggs 2005) that can be provided in a sleep centre.
- To investigate whether there is a disruption of the circadian melatonin rhythm, endogenous melatonin production can be measured at different times by means of saliva tests (www.slaapstoornissen.nl; www.melatoninecheck.nl).
- Other research into the sleep pattern may include keeping a sleep diary, video recordings, actigraphy (measuring movement during sleep) or polysomnography. You can make a referral to a specialized sleep centre for this.
- Light therapy (minimum 3000 lux, minimum 15 minutes) can be used to influence the body's own melatonin production. The melatonin production can thus be shifted forward or backward.
- Medicinal treatment of sleep problems depends on the underlying problem.
- If there is a proven or suspected shift of the circadian rhythm, a trial of melatonin can be started (start with 0.5-1 mg in children and adults and gradually increase this to a maximum of 3 mg in children and a maximum of 5 mg in adults). Evaluate the effect per week in children and per 2 weeks in adults.

Other drug therapy mainly consists of clonidine, sedating antidepressants, atypical neuroleptics and antihistamines.

Conclusions

Sleeping problems occur in a substantial percentage of individuals with 22q13DS (Soorya et al. 2013; Sarasua et al. 2014; Bro et al. 2017).
There may be a link between epilepsy and sleep problems in individuals with 22q13DS, but it is not clear whether this is a causal link, and further research is needed into this relationship (Figura et al. 2014).
Problems with falling asleep and staying asleep both occur in individuals with 22q13DS. However, little information from formal sleep studies is available (Bro et al. 2017).
The most important elements of counselling/treatment are: excluding somatic problems, good sleep hygiene, treating behavioural problems (possibly with the help of a sleep centre) and, if necessary, drug treatment (melatonin, clonidine) (Braam, 2014; NVK workbook chapter on "Sleep Disorders").

Considerations

Sleep problems have a major influence on the health, behaviour and functioning of the person with 22q13DS and the people in their immediate environment. Instructions regarding sleep hygiene are important, and therefore diagnosis and treatment of sleep disorders are of great importance. Somatic causes (including epilepsy) should be excluded. Behaviour, mood, epilepsy and motor skills can also improve by treating the sleeping problem.

Melatonin is widely used in the treatment of sleep problems and has proven to be a safe medication. A trial treatment with a low starting dose and a good effect evaluation often gives the desired effect. If an insufficient or negative effect is observed, an examination of the biological melatonin rhythm in saliva or blood can be done.

It is preferable to have melatonin prescribed by doctors with experience in treating sleeping problems (paediatricians specializing in heritable and congenital disorders, intellectual disability physicians, psychiatrists).

Recommendations

The recommendations given below are largely based on the NVK workbook: *Care for Children with Multiple Severe Disabilities*, chapter on "Sleep Disorders" (NVK, version June 2016). See Literature Summary.

Somatic causes for sleep problems should be ruled out.
Ensure good sleep hygiene and a structured approach (behavioural problems) to sleep problems.
Consider a sleep EEG to monitor night-time restlessness.
Monitor the sleep pattern using a sleep diary or additional research (actigraphy, polysomnography).
Consider referral to a specialist experienced in sleep problems (paediatricians specializing in heritable and congenital disorders, intellectual disability physicians, psychiatrists) for drug treatment (melatonin, clonidine).
Consider a saliva test for endogenous melatonin production, especially if a trial with melatonin does not have the desired effect.
Consider referral to a specialized sleep centre: www.slaapstoornissen.nl

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- NVK workbook *Care for Children with Multiple Severe Disabilities*, chapter on “Sleep Disorders” (NVK, Version June 2016).
- Cooperating Dutch Sleep Centres: www.slaapstoornissen.nl
- Melatonin check: www.melatoninecheck.nl

3.6 Lymphedema

Introduction

The term 22q13 deletion syndrome (22q13DS) is used in this guideline; this is also referred to as Phelan-McDermid syndrome (PMS).

Lymphedema is considered to be a clinical feature that can occur in 22q13 deletion syndrome. Lymphedema can be progressive in later life and therefore have important treatment consequences. Although lymphedema can also occur in other syndromes, it is a rare phenomenon in other chromosomal conditions.

Lymphedema is a symptom of an impaired lymphatic flow and has various pathophysiological mechanisms. On the one hand, there may be a defective system (anatomical or functional) that leads to swelling, but there may also be an overload of an initially good or weak lymphatic system, a situation known as dynamic lymphatic insufficiency or increased preload.

Fundamental questions

Based on the bottleneck analysis carried out by the guideline working group and the results of the survey of patient representatives, the following fundamental questions have been formulated:

- How often does lymphedema occur in 22q13DS and what is known about the underlying mechanism?
- What is the best treatment for lymphedema in people with 22q13DS?
- Are there options for early diagnosis and early treatment?

Search and selection of literature sources

Since 22q13DS is a rare condition (1 in 30,000 live births), in developing this guideline we chose to perform a general scientific literature search for Phelan-McDermid syndrome. The literature was then selected and sorted based the predetermined fundamental questions (see Search Justification).

For this module we included the following articles: 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. Further, we made use of the Dutch guideline on Lymphedema (NVDV, 2014) and consulted a webinar.

The formulation of the recommendations took into account the extent to which scientific evidence was available.

Literature summary

Prevalence of lymphedema in 22q13DS

The association between lymphedema and 22q13 deletions was first described in 1994 (Nesslinger et al., 1994). Sometimes there may be an early presentation with late childhood progression. Ascites and pleural effusion are occasionally described (McGaughran et al., 2010).

A large clinical study of 201 subjects with 22q13DS listed the following prevalence figures based on physical examination: total group 24% (26/108), under 5 years of age 17% (8/47), 5-10 years of age 18% (6/34), 10-18 years of age 35% (7/20) and over 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).

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%. Lymphedema has not been reported in other studies, so this may be an overestimation.

Underlying mechanism of lymphedema in 22q13DS

The lymphedema in 22q13DS is considered congenital lymphedema, most likely caused by an inadequately constructed lymphatic vessel system. Nothing is known about the underlying mechanism of the lymphedema in 22q13DS. According to OMIM, there are no genes in the region associated with lymphedema.

If lymphedema develops at an older age in people with mobility disorders and/or overweight, pre-load problems often also play a role.

Treating lymphedema in 22q13DS

In the literature on 22q13DS and lymphedema, no specific treatment is discussed other than those used with other forms of lymphedema: the use of compression stockings, elevating the foot of the bed and, in more severe forms, pneumatic compression therapy and surgery (Phelan and Rogers 2005; Kolevzon et al., 2014). Because no systematic studies on the effect of treatment of lymphedema in 22q13DS have been performed, reference is made here to the existing general guideline on lymphedema (NVDV, 2013), of which there is also a patient version (NVDV, 2014).

According to this guideline, primary treatment options include: reduction of risk factors (obesity and lack of movement), skin care to prevent erysipelas, compression technology and the use of compression stockings in the maintenance phase (NVDV, 2013).

Conclusions

Primary lymphedema occurs in approximately 25% of subjects with 22q13 deletion syndrome (Kolevzon et al., 2014; Sarasua et al., 2014).
The exact mechanism underlying the lymphedema in 22q13DS is unknown.
There is no syndrome-specific treatment for the lymphedema in 22q13DS.

Considerations

Compared to other syndromes, lymphedema is relatively common in 22q13DS. Little is known about the natural course, but early onset and progression from late childhood have been described. In any case, prevalence seems to increase with age. It is important that the healthcare provider pays attention to this possible co-morbidity so that treatment can be started on time.

Treatment of primary lymphedema can be complex and, if insufficient effect is achieved, we advise referral to a specialized centre (see Guideline lymphedema). Since this is a complication in a rare condition where there is still relatively little expertise, referral to a centre of expertise for lymphedema is indicated.

Recommendations

The health care provider should pay attention to the possible development of lymphedema in individuals with 22q13DS.
Refer individuals with 22q13DS with progressive lymphedema to a lymphedema centre of expertise.

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Other sources

- Guideline *Lymphedema* (NVDV, 2013)
- Guideline *Lymphedema*, patient version (NVDV, 2014)
- Phelan-McDermid Syndrome Foundation. Webinar lymphedema.
- Online Mendelian Inheritance in Man (OMIM)

Expertise Centre Lymphedema

Ziekenhuis Nij Smellinghe, Compagnonsplein 1, 9202 NN Drachten
Postbus 20200, 9200 DA Drachten. Telefoon 0512-588 888
https://www.nijsmellinghe.nl/195/expertisecentrum-voor-lymfo-vasculaire-geneeskunde

3.7 Mental Disorders

Introduction

The term 22q13 deletion syndrome (22q13DS) is used in this guideline; this is also referred to as Phelan-McDermid syndrome (PMS).

Individual with 22q13DS have mental disorders, or characteristics/symptoms thereof, including features of autism spectrum disorder (ASD) and mood disorders. The symptoms of mental disorders can be considered as part of the behavioural phenotype of 22q13DS, but can and should also be profiled and documented from a behavioural therapeutic point of view so that (treatment) advice to help reduce these symptoms can be derived from this profile.

By (characteristics of) mental disorders we mean all kinds of disturbances in behaviour, regardless of the cause. The psychiatric classification manual DSM-5 (American Psychiatric Association, 2013) only describes clusters of behaviours, and their classification does not refer to a specific cause or combination of causes. The term mental disorders includes various types of behavioural clusters (behavioural phenotypes), such as developmental disorders (including mental development disorder, ASD, ADHD and tic disorders), mood disorders (including depression and bipolar disorder), psychotic disorders, anxiety disorders and personality disorders. According to the DSM-5, a mental disorder is present when there are a sufficient number of symptoms. With every type of symptom there is usually a continuum, which means that the associated advice can often be important even in the presence of only some of the symptoms of a mental disorder.

Fundamental questions

Based on the bottleneck analysis carried out by the guideline working group and the results of the survey of patient representatives, the following fundamental questions have been formulated:

- What kinds mental disorders (or symptoms of mental disorders) are found in individuals with 22q13DS, and how often?
- What is the treatment for mental disorders in 22q13DS?

Search and selection of literature sources

Since 22q13DS is a rare condition (1 in 30,000 live births), in developing this guideline we chose to perform a general scientific literature search for Phelan-McDermid syndrome. The literature was then selected and sorted based the predetermined fundamental questions (see Search Justification).

The following articles were included for this module: Denayer et al., 2012; Egger et al., 2016; Egger et al., 2017; Glaser et al., 2011; Oberman et al., 2015; Serret et al., 2015; Soorya et al., 2017; Verhoeven et al., 2012; Verhoeven et al., 2013.

We also made use of the following guidelines:

- Multidisciplinary guideline *Diagnosis and Treatment if Autism Spectrum Disorders in Adults* (NVvP/NIP, 2013).
- Guideline *Diagnosis and Treatment of Autism Spectrum Disorders in Children and Adolescents* (NVvP, 2009).

The formulation of the recommendations took into account the extent to which scientific evidence was available.

Literature summary

Mental disorders and specific behaviours in 22q13DS

Psychiatric disorders, or features thereof, that can occur in 22q13DS are (symptoms of) ASD (such as repetitive movements and withdrawn behaviour), mood disorders (in particular bipolar disorder), ADHD, psychosis and catatonia.

In a study of seven people with 22q13DS, including three children, all seven had ASD characteristics and one of the children was diagnosed with ADHD (Denayer et al., 2012). ASD symptoms were also described in another study of 40 children and adolescents with 22q13DS (Oberman et al., 2015). These ASD symptoms included socio-communicative symptoms (limitations in social reciprocity and communication) and restrictive and repetitive behaviours (e.g. limited and repeated patterns of movements and/or interests). The social-communicative symptoms were present in 90% (36/40) of individuals and the restrictive and repetitive behaviours were present in 55% (22/40) (Oberman et al., 2015). In another study, 18 children with 22q13DS were compared with 19 children with ASD without a 22q13 deletion. Here, the researchers found less withdrawn behaviour in the children with 22q13DS than in the children with ASD without a 22q13 deletion (Glaser and Shaw, 2011).

The four adults with 22q13DS from the first study also had bipolar disorder, and one of them also had psychotic symptoms and catatonia (Denayer et al., 2012). In another study of seven adults, both ASD and bipolar disorder symptoms were seen (Egger et al., 2016). An atypical bipolar mood disorder was also described in two case reports (Egger et al, 2017; Verhoeven et al., 2013). It is striking that a progressive loss of skills is often seen early in adulthood (Denayer et al., 2012). A connection with bipolar disorder is possible, but further research is needed into this, as well as into the effect of treatment of the psychological problems on the preservation of skills.

Diagnosis and treatment

There is no literature specifically on the treatment of ASD in 22q13DS. Diagnosis and treatment of ASD in children, adolescents and adults are described in the NVvP guidelines:

- Guideline *Diagnosis and Treatment of Autism Spectrum Disorders in Children and Adolescents* (NVvP, 2009).
- Multidisciplinary guideline *Diagnosis and Treatment if Autism Spectrum Disorders in Adults* (NVvP/NIP, 2013).

We also refer to the NVAVG standard Prescribing Psychiatric Drugs (NVAVG, 2016). The three scientific papers describe the positive effect of lithium in adults with 22q13DS. In the Egger et al. study, the symptoms of bipolar disorder could be effectively treated with mood stabilizers (Egger et al., 2016). Verhoeven et al. also report successful treatment of two adult brothers with 22q13DS and an atypical bipolar disorder with a mood stabilizer (Verhoeven et al., 2012). Serret at al. describe improvement in two (young) adults with 22q13DS, ASD, symptoms of catatonia and disruptive behavioural problems on lithium treatment (Serret et al., 2015). See also Module Drug Treatment.

Conclusions

The socio-communicative symptoms of ASD occur in almost all children and adolescents with

22q13DS and restrictive and repetitive symptoms occur in half (Oberman et al., 2015).
Mood problems are relatively common in adults with 22q13DS, in particular symptoms of bipolar disorder, and treatment with a mood stabilizer appears to be effective (Denayer et al., 2012; Egger et al., 2016; Verhoeven et al., 2012).
In adults with 22q13DS, progressive skill loss may occur (Denayer et al., 2012).

Considerations

Mental disorders are diagnosed by a psychologist, psychiatrist and/or intellectual disability physician who maps the problem behaviours and behavioural symptoms with the help of multiple informants, such as parents/carers, counsellors, pedagogical staff and teachers. A mental disorder is diagnosed when sufficient criteria are met for the condition in question as described in the DSM-5 classification system. Even if a complete picture from DSM-5 is not met, it is good to document the relevant symptom domain and to focus treatment and guidance on this profile if the behaviour concerned disrupts functioning. Diagnostics often use questionnaires and standardized diagnostic tools. For more information, see the Knowledge Centre for Child and Adolescent Psychiatry: Diagnostics/Instruments. A framework for neuropsychological research in 22q13DS is described by Soorya et al. (2017).

There is no curative treatment for the core symptoms of ASD (problems in social contact and restrictive/repetitive behaviours). However, additional problems in ASD, such as anxiety, aggression, frenetic behaviour and sleeping problems can often be treated with behavioural interventions and/or pharmacotherapy. Advice can also be given for any other additional problems, such as when children are bullied by other children.

In addition to the periodic tracking of behavioural symptoms as a basis for any (new) treatment and counselling advice, it is also good to follow the individual's development. Even after childhood and adolescence, it is useful to periodically chart the level of development with intelligence/development metrics, so that the cognitive decline or loss of skills that occurs often in 22q13DS can also be followed and the guidance adjusted.

Recommendations

Consider periodically analysing problem behaviour in children/adolescents with 22q13DS (e.g. at the (transition) ages of 3, 7, 11, 15 and 18 years) and in adults with 22q13DS (e.g. every five years), and if necessary in between, to see if there is a treatable mental disorder or symptom component, especially ASD, mood disorders (in particular bipolar disorder), ADHD, psychosis and catatonia. Transition ages are the ages at which a (possible) transition between day-care, school type or work situation is imminent.
At the times mentioned above, consider the level of development in children, adolescents and adults with 22q13DS using intelligence/development tests in order to identify a possible cognitive decline or a loss of skills and to tailor the supervision to this.
Consider having this periodic evaluation/behavioural diagnosis carried out in an expertise centre by a team that includes a (child and youth) psychiatrist. These results can yield periodic advice, which can preferably be carried out by your own practitioner(s) in your own region. These periodic behavioural diagnostics will also contribute to an increase in knowledge about 22q13DS.

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- NVAVG standard Prescribing Psychiatric Drugs (NVAVG, 2016)

4. Drug treatment of development and behaviour

Introduction

The term 22q13 deletion syndrome (22q13DS) is used in this guideline; this is also referred to as Phelan-McDermid syndrome (PMS).

There is currently no standard policy for drug treatment in 22q13DS regarding the most important characteristics: developmental delay, intellectual disability and behavioural problems (see Module Clinical Features). Delayed development is observed in the first two to three years of life, after which the rate of development decreases or even stagnates (Zwanenburg et al. 2016b). Children often experience a (temporary) loss of acquired skills, and this loss can be progressive in adults with 22q13DS (Denayer et al. 2012; Reierson et al. 2017). In addition, a subset of people with the 22q13DS experience atypical mood problems starting from puberty, possibly aggravated by other psychological problems or somatic disorders (Egger et al. 2016).

Two randomized controlled clinical trials (RCTs) in humans with 22q13DS have been reported in the literature that investigated the effect of intranasally administered insulin and subcutaneously administered IGF-1 on development and/or behaviour (Kolevzon et al. 2014; Zwanenburg et al. 2016a). Insulin and IGF-1, in addition to their function as hormones in the systemic circulation, function as a neurotransmitter and a neurotrophic factor in the brain. Both bind to the same receptors, but with a different affinity. Amongst a number of functions, the insulin IGF-1 pathway is involved in the formation of nerve shoots and the synaptic connections between them (Lee et al. 2011). The formation of these synaptic connections is impaired in 22q13DS due to reduced expression of SHANK3 (see Module General).

In addition, on the basis of preclinical research, there are a number of drugs that can be an interesting treatment strategy for developmental and behavioural problems, but that have not yet been systematically investigated in 22q13DS. These are valproic acid, lithium and oxytocin. **Valproic acid** is prescribed for certain types of epilepsy or bipolar disorder. **Lithium** is used to treat mood disorders, namely bipolar disorder, and sometimes, in combination with an antidepressant, unipolar depression (depression without manic episodes). **Oxytocin** is a hormone that influences social behaviour. Clinical studies with intranasal oxytocin in people with ASD, fragile-X syndrome and Prader-Willi syndrome suggest it has a positive effect on social behaviour, but the results are ambiguous. The exact mechanism of action of intranasal oxytocin is unknown, but it is possible that the dopaminergic pathway is involved (DeMayo et al. 2017).

The literature on the above-mentioned medications is described in more detail below. The rest of the literature consists of case reports, evidence from which is very limited and the treatment not specific for 22q13DS. The quality of the scientific evidence in this module is assessed for the RCTs with intranasal insulin and subcutaneous IGF-1 in 22q13DS.

Fundamental question

- Is there added value of medication in development and behaviour in children with 22q13DS?

Search and selection of literature sources

Following a generic search strategy, we searched for articles about 22q13DS (see Search Justification), and all studies that investigated drug therapies at both the fundamental and clinical levels specific for SHANK3 haploinsufficiency were subsequently selected from the resulting list. In addition, 9 studies were selected to evaluate the full text: Schmidt et al. 2009; Bozdagi et al. 2013; Shcheglovitov et al. 2013; Kolevzon et al. 2014; Darville et al. 2016; Egger et al. 2016; Liu et al. 2016; Zwanenburg et al. 2016a; Harony-Nicolas et al. 2017. Two RCTs were then included to answer the basic question: Kolevzon et al. 2014; Zwanenburg et al. 2016a. These RCTs have been assessed according to the GRADE system.

For the introduction and supplemental background information, additional references were found via reference tracking or by a targeted search in Pubmed (Lee et al. 2005; 2011; Denayer et al. 2012; DeMayo et al. 2017; Reierson et al. 2017)

Crucial outcome measures

The following crucial outcome measures were determined for this basic question:

- Significant and clinically relevant improvement of development.
- Significant and clinically relevant improvement of behavioural problems.

Literature summary

Valproic acid and lithium

Research in the brains of zebrafish has shown that valproic acid increases certain isoforms of shank3 mRNA (Liu et al. 2016). Research in neurons developed from pluripotent stem cells from two individuals with a pathogenic *SHANK3* mutation showed that both valproic acid and lithium increase the number of synapses with SHANK3 protein, as well as their activity. One of the individuals whose stem cells were examined developed a mood disorder with regression. Lithium treatment had a positive effect on manic symptoms, cognitive function and the severity of the autism traits in this individual (Darville et al. 2016). A case series of previously published and unpublished subjects with 22q13DS (n=18) also showed that a mood stabilizer, such as lithium or valproic acid, supplemented with an antipsychotic (e.g. quetiapine) had a positive effect on functioning and mood when there was bipolar disorder (Egger et al. 2016).

Oxytocin

Research in rats with a *Shank3* deficiency showed that intracranial injections of oxytocin had a positive effect on social memory, attention and the plasticity of the synapses (Harony-Nicolas et al. 2017). At the same time, a clinical pilot study has been started in the US into the effect of intranasal oxytocin on attention, social memory, socialization, language and repetitive behaviour in children with 22q13DS (www.clinicaltrials.gov, NCT02710084).

Insulin and Insulin-like Growth Factor-1 (IGF-1)

The underlying hypothesis for research into the effect of treatment with insulin and IGF-1 is that activation of the insulin IGF-1 pathway, via the insulin receptor, increases PSD-95 (Lee et al. 2005). PSD-95, like SHANK3, is a post-synaptic compound protein. Increase in PSD-95 may reduce the limitation in cell signalling due to haploinsufficiency of SHANK3. Indeed, treatment with IGF-1 in Shank3-deficient animal models and in neuronal cell lines of humans with 22q13DS shows an increase in PSD-95 expression and in the number of synapses with PSD-95 (Bozdagi et al. 2013; Shcheglovitov et al. 2013).

The first clinical pilot study of subcutaneous IGF-1 injections in people with 22q13DS showed a positive effect on social and restrictive behaviour in practice (Kolevzon et al. 2014).

The first clinical pilot study with intranasally administered insulin in 6 children with 22q13DS showed positive effects on motor activity, cognitive function, non-verbal communication and autonomy (Schmidt et al. 2009). Administering the insulin via a nasal spray allows it to be directly transported to the brain fluid and cross the blood-brain barrier while avoiding effects on blood glucose and insulin levels (Born et al. 2002; Benedict et al. 2004). However, the intranasal insulin pilot study was not blinded or placebo-controlled.

Both the IGF-1 study and the intranasal insulin pilot study resulted in a randomized double-blind placebo-controlled trial to validate these positive effects (Kolevzon et al. 2014; Zwanenburg et al. 2016a), and both studies will be described in more detail below.

Description of the available RCTs

Two randomized double-blind placebo-controlled trials in humans with 22q13DS have been published, one on the effect of intranasal insulin and one on the effect of subcutaneous IGF-1 on development and behaviour (Zwanenburg et al. 2016a, Kolevzon et al. 2014;).

Method

Intranasally administered insulin: This was an RCT in 25 children (1-16 years) with a proven 22q13.3 deletion including the *SHANK3* gene. A stepped wedge design was used where participants were randomized over three groups for the study interval in which the insulin nasal spray was started. The intervention consists of a daily dose of intranasal insulin or intranasal albumin (as placebo) for intervals of 6 months. Once started on the insulin nasal spray, participants received intranasal insulin until the end of the study. The outcome measure was the increase in developmental age in terms of development and development of behaviour, measured using various instruments (Bayley-III-NL or WPPSI-III-NL, Vineland screener 0-6 and the Experimental Scale for the assessment of the Social - Emotional Development Level (ESSEON))(Zwanenburg et al. 2016a).

Subcutaneously administered IGF-1: An RCT was completed in 2016 (www.clinicaltrials.gov, NCT01525901). Unfortunately, the results have not yet been published. Therefore, we will discuss the previously conducted pilot study in nine children (5-15 years) with a proven 22q13.3 deletion including the *SHANK3* gene or a mutation in *SHANK3*. A cross-over design was used, in which participants were randomized across two groups for the order of treatment versus placebo. After a drug build-up phase, the intervention consisted of twice-daily subcutaneous IGF-1 injections or saline (as placebo) for a period of 12 weeks, followed by 4 weeks without treatment (wash out), and then another 12 weeks of treatment. The outcome measure was the difference in the score for socially withdrawn behaviour and restrictive behaviour, two subscales of validated tests (ABC and Repetitive Behaviour Scale (RBS)) (Kolevzon et al. 2014).

For further details, please refer to the Evidence Table appended to this guideline.

Quality of evidence

Intranasally administered insulin: Strengths of the study are randomisation, use of placebo, double blinding, limited loss to follow-up and use of an intention-to-treat analysis. However, the quality of evidence is low due to the risk of results bias due to inaccuracy (impresicion -2). The study covers a

relatively small and variable study group (age, height deletion, level of development). Furthermore, the increase in development and development of behaviour at 22q13DS is limited, so that the magnitude of the effect of insulin on this and the significance of the result are limited. Moreover, outcome measures such as development and behaviour strongly depend on the circumstances around and during the test collection. Finally, it is still unknown how much of the administered dose arrives at its destination and which dose is sufficient for the desired effect (Zwanenburg et al. 2016a).

Subcutaneously administered IGF-1: Strengths of the study are use of placebo, double-blinding and the use of an intention-to-treat analysis. However, the quality of evidence is very low due to a high risk of biased results due to inaccuracy (impresicion -2). It concerns a very small and variable study group (age, level of development), for which the genetic details (genotype) are missing. Furthermore, there is a risk of bias (risk of bias -1), as the method of randomisation and the blinding of the intervention allocation are not described. In addition, only the most notable results have been reported and the significance of the effect has only been described for medication versus placebo and not whether the treatment itself produces a significant change. In this study, the outcome measure also strongly depends on the circumstances around and during the test collection, and it is unknown how much of the administered dose arrives at the destination and which dose is sufficient for the desired effect (Kolevzon et al. 2014).

For further details regarding the design of the studies, please refer to the Risk of Bias Table appended to this guideline.

Desired effects

Intranasally administered insulin: Under baseline conditions (without treatment), significant progress was seen, on average, in 3 out of 11 development domains, with a maximum increase in developmental age of 1.8 months per 6-months of calendar age. During intranasal insulin use, an additional increase in the developmental age is seen in 8 of the 11 developmental domains. This increase varies per domain and is a maximum of 1.4 months (=average additional increase in development age per 6-month increase in calendar age). This additional effect of insulin, on top of baseline development, is not statistically significant in itself, and the range of the increase is large. The increase in developmental age with intranasal insulin was significant in 10 of the 11 domains, while the increase without insulin (baseline) was only significant in 3 developmental domains. It is striking that the additional increase in developmental age with insulin treatment was greater in the subgroup of children older than 3 years. In this group, an additional effect of insulin was seen on 9 developmental domains, with the maximum increase in the developmental age for a given domain of 1.5 months (per 6-months calendar age), on average, and a significant effect of insulin on 2 developmental domains. Thus, in the total group, there was significant development with insulin in 10/11 domains, while this was significant in only 3/11 domains without insulin. This effect is stronger in children >36 months of age, probably because they show less spontaneous development than younger children.

An increase in developmental age in any domain, even if this increase is limited, makes a difference in developmental level in 22q13DS with respect to whether or not certain skills are acquired. Thus, while the additional effect of intranasal insulin across the group was not statistically significant, the effect on development is clinically relevant and even greater in the subgroup of children older than 3 years (Zwanenburg et al. 2016a).

Subcutaneously administered IGF-1: Treatment with IGF-1 showed an average decrease of 8 points on the subscale of socially withdrawn behaviour (from 15.8 to 7.6) and of 2 points on the subscale of restrictive behaviour (from 5 to 3), while those under placebo saw a decrease of only 1.5 points (from 11.2 to 9.7) and an increase of 0.7 points (from 3.6 to 4.3), respectively. This difference between IGF-1 and placebo is statistically significant for both subdomains (Kolevzon et al. 2014).

Undesired effects

Intranasally administered insulin: The administration is non-invasive, and no invasive controls are required to measure blood glucose or insulin levels because systemic effects are avoided. However, local side-effects were reported such as irritation of the nose and nosebleeds due to the preservative metacresol, both during intranasal insulin and intranasal placebo use. In addition, recurrent upper respiratory tract infections and gastroenteritis were reported in both the insulin and placebo groups. No "serious adverse advents" or "serious adverse reactions" occurred. Long-term adverse effects are not known (Zwanenburg et al. 2016a).

Subcutaneously administered IGF-1: The administration is invasive. Most adverse events were reported in both groups and do not appear to have been related to IGF-1. The side effects that were more common with IGF-1 than placebo are hypoglycaemia (7 versus 3), sleep disturbances (7 versus 2), an increase in cravings (4 versus 0) and a rash (3 versus 0). No "serious adverse advents" or "serious adverse reactions" occurred. Long-term adverse effects are not known (Kolevzon et al. 2014).

Cost-effectiveness

Intranasally administered insulin: This preparation is based on a standard product used for diabetes mellitus, which is supplemented with physiological salt for intranasal use. Its cost is low compared to other rare disease medications, while the potential effect for the person with 22q13DS and his or her family and environment is clinically relevant. The costs for the treatment are approximately 500 euros per half year. These costs are not yet reimbursed by the health insurer (application is submitted).

Subcutaneously administered IGF-1: This preparation is based on a standard product used in the USA to treat growth disorders, and its cost corresponds to the costs of its current use in clinical practice. The potential effect for the person with 22q13DS and his or her family and environment seems favourable, but results are only known for two behavioural domains. The costs are not known to the Netherlands where IGF-1 is not included in the Pharmacotherapeutic Compass.

Conclusions

Low	The quality of evidence for the effect of intranasal insulin on development and behaviour is low (Zwanenburg et al. 2016a).
Very low	The quality of the evidence for the effect of subcutaneous IGF-1 on development and behaviour is very low (Kolevzon et al. 2014).

Considerations

Intranasally administered insulin

Insulin nasal spray treatment showed an improvement in development. The statistical significance of this could not be demonstrated for all domains in the small research group. Since any increase in skills at 22q13DS is of interest to the person with 22q13DS, their family and people in their environment, a trial treatment can be justified within a centre of expertise (see attachment). The administration of insulin through the nose is safe, non-invasive and has no unwanted systemic effects. The potential local side-effects are limited, and no serious incidents or reactions have occurred. The product is easy to prepare, and the social costs for this preparation and relatively small patient group are limited.

At the end of the Dutch intranasal insulin study, a number of parents indicated that they saw so much positive effect that they wanted to continue with treatment. Other parents also requested treatment. In accordance with Articles 34 and 37 of the Declaration of Helsinki, the working group is of the opinion that although there is a need for validation of the insulin trial in a larger study group, a (trial) treatment cannot be withheld if parents ask for it (Article 34), provided that monitoring and registration takes place (Article 37), in part to prevent the uncontrolled use of the nasal spray. If a trial treatment is considered, the guideline advises doing this according to the procedure laid out in the appendix.

Subcutaneously administered IGF-1

The working group is of the opinion that there is currently insufficient evidence for a positive effect of IGF-1 on development and behaviour in individuals with 22q13DS to recommend it in practice. It is also questionable whether the possible clinical effect of subcutaneous IGF-1 outweighs the burden of administration and any undesirable side effects. IGF-1 has invasive administration and possibly systemic effects such as hypoglycaemia, although the latter seems limited. There is no experience with this product in the Netherlands, which means that practical implementation is not yet possible.

Recommendations

Consider a trial of insulin nasal spray in any patient with 22q13DS (see appendix).
There should be centralized registration and follow-up of all 22q13DS patients treated with insulin nasal spray.

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5. Organization of care

Introduction

The term 22q13 deletion syndrome (22q13DS) is used in this guideline; this is also referred to as Phelan-McDermid syndrome (PMS).

This chapter describes the organization of care for individuals with 22q13DS. A guide is also included with an overview of advice with respect to specific controls.

Fundamental questions

Based on the bottleneck analysis performed by the guideline working group and the results of the survey of patient representatives, the following fundamental questions have been formulated:

- What is the role of the expertise centre and treatment team in 22q13DS?
- Which disciplines are involved in 22q13DS, both at the expertise centre and within the treatment team?
- What is the role of a coordinating physician, and who is this in 22q13DS?
- What guidelines exist for medical supervision of individuals with 22q13DS?
- How is transition care arranged for individuals with 22q13DS?

Search and selection of literature sources

To answer each fundamental question, we searched for as much relevant literature as possible. In addition, expertise and consensus within the guideline working group were applied. The formulation of the recommendations took into account the extent to which scientific evidence was available.

Literature summary

Expertise centres and the treatment team

The definition of an expertise centre is defined by the (assessment) criteria that the expertise centre must meet (see Table 1). An expertise centre provides highly specialized (top referent) care and is responsible for the management and general coordination of the integrated care chain.

Integrated care is care in which different care providers coordinate their activities as much as possible so that the individual receives all the care they need. Shared care means that, in addition to highly specialized care from the expertise centre, specialist care and basic care are also provided by a treatment team at local or regional level (Vajda, 2015).

The treatment team is the local or regional team around the person with 22q13DS that is responsible for direct care and guidance in coordination with the expertise centre. In addition to reporting and periodically sharing medical data/findings, the treatment team regularly consults with the expertise centre on the breadth of the care offered (when a patient is referred to the expertise centre) and for special cases. Whether a patient is primarily treated and/or monitored in a centre of expertise or by a local/regional treatment team depends on several factors. The goal here is to provide as much care as possible nearby and only travel further when absolutely necessary (Vajda et al., 2015).

In practice, 22q13DS involves shared care by one central centre of expertise for rare chromosome disorders (see next paragraph) and the local/regional treatment team.

Themes	Quality criteria for the national assessment of centres of expertise for rare disorders
I. Quality of care	The EC is able to provide highly specialized complex patient care for the specific rare condition, including: □ diagnostics, □ treatment and aftercare, □ follow-up.
	The EC provides care within an established multidisciplinary team.
	The EC contributes to the development of care standards and guidelines and contributes to their dissemination, together with representatives from involved patient organizations.
	The EC coordinates the care offered for the specific condition throughout the care chain.
	The EC is aware of and contributes to the most recent (basic) scientific developments with regard to diagnostics, causal and/or symptomatic treatment, secondary and tertiary preventive measures, and/or specific psychosocial support for the patient group.
	The EC has a system in place to guarantee the quality of care.
II. Transition	The EC ensures, where necessary, the continuity of the care provided from childhood through adolescence, and into adulthood (transition care).
III. Continuity of EC	The EC is responsible for training and/or transferring knowledge to (new) experts of the MD team.
	The EC is recognized by the Board of Directors.
	The EC is willing to be audited.
IV. Cooperation with other parties	The EC works, on the basis of a cooperation agreement, with patients and patient organizations to improve the quality of care.
	The EC collaborates with other centres of expertise nationally and abroad in the fields of research and patient care.
V. Information & communication	The EC acts as an information portal and source of information for healthcare providers, patients and their families.
	The EC provides information about the (cluster of) rare condition(s) to healthcare professionals outside the EC and to other healthcare professionals.
VI. Research	The EC carries out (basic) scientific research and publishes in the field of the rare condition.
	The EC is responsible for data registration of patients with the relevant disorder.
VII. Healthcare across borders	The EC coordinates and advises, if necessary, cross-border healthcare with designated ECs in other EU countries, to which patients or biological samples can be referred.

Table 1: Quality criteria for the national assessment of centres of expertise for rare disorders

Expertise centres for rare chromosomal disorders

For an up-to-date overview of the national expertise centres for rare diseases in the Netherlands that are recognized by the Dutch Ministry for Health, Welfare and Sport (VWS), see the website www.zichtopzeldzaam.nl.

The publication of this module recognizes the following centres of expertise for rare syndromes with intellectual disabilities, all of which are members of the European Reference Network ITHACA:

- University Medical Centre Groningen: Centre of Expertise for rare chromosome disorders
- Radboudumc Nijmegen: Centre of Expertise for genetic neurodevelopmental disorders
- Maastricht UMC+: Centre of Expertise for rare syndromes and cognitive disorders
- Erasmus MC Rotterdam: Centre of Expertise for neuro-developmental disorders (ENCORE)
- Amsterdam UMC: Amsterdam Expertise Centrum voor Ontwikkelingsstoornissen (AECO)

Expertise for rare chromosome disorders is mainly present in the UMCG and Radboudumc, with specific expertise in the field of 22q13DS at the UMCG.

Multidisciplinary team for 22q13DS at the expertise centre and the treatment team

The multidisciplinary treatment team for individuals with 22q13DS can consist of specialist(s), a general practitioner, paramedics and other relevant care providers. These care providers can be present in one care setting (centre of expertise) or spread over several care institutions (treatment team).

Care providers who may be involved in some or all phases of the care process are listed in the Guide and Conclusions. All the disciplines mentioned are present in the expertise centre, except for the general practitioner, and are available for consultation depending on the care needed. The composition of the treatment team depends on the care needs and age of the person with 22q13DS.

Good mutual communication and information transfer between care providers in the multidisciplinary teams is essential for good care for individuals with 22q13DS. The coordinating physician (see next paragraph) plays a central role in this, including in communication with (the coordinator of) the expertise centre.

Coordinating physician

Each person with 22q13DS has one coordinating physician, sometimes in the expertise centre but usually within the treatment team where the person with 22q13DS is being treated/monitored (Roos et al., 2013, Zorgstandaard ADCA).

The supervising physician:

- Maintains a medical overview, provides and maintains direction, monitors and coordinates the total (lifelong) multidisciplinary care of a person with 22q13DS, including follow-up, monitoring and the transition from child to adult care (when the role of coordinating physician can be transferred to another medical specialist).
- Is the point of contact for (carers of) the person with 22q13DS for questions about care.
- Draws up the individual care plan together with (the caregivers of) the person with 22q13DS (with possible consultation of the multidisciplinary treatment team and the expertise centre) and supervises its implementation and appropriateness.
- Supports the self-management of (the carers of) the person with 22q13DS
- Has access to recent scientific developments and new treatment methods in 22q13DS (possibly via the expertise centre).

All those involved (representatives and care providers of a person with 22q13DS) know who the coordinating physician is. This information is recorded in the individual care plan.

The coordinating physician is primarily the medical specialist who has made the diagnosis of 22q13DS (clinical geneticist/paediatrician). Depending on the care needs, the role of coordinating physician may subsequently be transferred to another medical specialty (intellectual disability physician).

The duties of a supervising physician can be performed by one medical specialist, but can also be partially delegated to another healthcare provider, e.g. a medical resident or physician assistant. However, the supervising physician remains ultimately responsible (Roos et al., 2013).

Primary care practitioner

A primary care practitioner bears ultimate responsibility for a specific part of the treatment process (e.g. the neurologist is responsible for the treatment of epilepsy, the orthopaedist for the treatment of scoliosis). A primary care practitioner is always a medical specialist and usually a member of the multidisciplinary team (Zorgstandaard ADCA). This is preferably a medical specialist "close to home".

Depending on the stage of life and personal circumstances of the individual with 22q13DS, this may be in an academic, top clinical or peripheral hospital. The distinction of primary care practitioner - as legally determined - can therefore lie with various specialists with clearly defined legal status in the various care phases.

Depending on the individual with 22q13DS, the form of collaboration and the phase of the care process, there may be one or more primary practitioners. However, there is only one main practitioner per specialty and always only one coordinating physician. The person with 22q13DS and the main practitioner(s), together with the coordinating physician, record this in the individual care plan, possibly after consultation with the other care providers and the expertise centre.

Individual care plan

An individual care plan (ICP) is a dynamic set of agreements between the patient and the care provider (s) about care and self-management. These agreements are based on the individual goals, needs and situation of the patient. They come about through joint decision-making (CPZ, 2012). The ICP is a flexible document that grows with the problems of a patient: it is simple and short, if possible, but complex and extensive if necessary (Heijmans, 2015).

The coordinating physician ensures that the ICP is drawn up and that it is updated. The interpretation is done in collaboration with the (caretakers of the) person with 22q13DS. At diagnosis, the ICP contains, at minimum, the contact information of the coordinating physician and the initial treatment plan. The development of an ICP aimed at 22q13DS is beyond the scope of this module.

Medical counselling guide for persons with 22q13DS

See the sub-module Counselling guide

Transition of care

Transition is the deliberate systematic transition of adolescents and young adults with a chronic condition from a child-oriented care system to a care system aimed at adults (Blum et al., 1993). In the guide to transition of care for adolescents with a mental disability, the following is recommended:

- Timely reporting of the moment of transition, at least from the age of 14.
- Good transfer of written documentation including patient history.
- At least one joint consultation with a multidisciplinary team (for transfer between paediatric and adult specialists).

The coordinating physician organizes the transition, if necessary in consultation with the expertise centre. The coordinating physician during childhood (paediatrician/AVG) and the future coordinating physician during adult care (AVG) both agree to the transfer and inform the expertise centre and the treatment team.

Registration 22q13 deletion syndrome

A European register for 22q13DS does not exist yet. However, there is an international register for people with 22q13DS in the United States. The UMCG Expertise Centre for Rare Chromosome Disorders also manages a local register for people with 22q13DS in the Netherlands. Individuals with

22q13DS must be well informed at all times and can choose whether or not to give permission for inclusion in the register.

Conclusions

In the Netherlands, there are centres of expertise for rare syndromes with intellectual disabilities. Specific expertise in the field of 22q13DS is available at the UMCG (for an up-to-date overview of expertise centres in the Netherlands recognized by the VWS see http://www.zichtopzeldzaam.nl).
The multidisciplinary team for individuals with 22q13DS consists of a paediatrician/intellectual disability physician, clinical geneticist, (child and youth) psychiatrist, (child) neurologist, general practitioner, rehabilitation doctor, youth healthcare doctor and paramedics. Depending on the symptoms/limitations that the person with 22q13DS experiences, this can be supplemented with other specialists (ENT doctor, ophthalmologist, vascular surgeon/dermatologist, or other specialist).
The care providers of multidisciplinary treatment team for 22q13DS can be located in one or more care settings. In the expertise centre, all healthcare providers are represented, with the exception of the primary care physician (GP).
The coordinating physician for an individual with 22q13DS is a paediatrician or intellectual disability physician in the expertise centre or treatment team. Tasks can also be partly delegated to another care provider (e.g. a medical resident or physician assistant), but the supervising physician remains ultimately responsible.
If the coordinating physician does not work in the expertise centre, the expertise centre arranges (low frequency) follow-up with advice and periodic tests (see Guideline), as well as the transfer of new knowledge from research and literature. The coordinating physician and expertise centre work together to keep each other informed.
The coordinating physician ensures that the individual care plan is drawn up and updated.
The coordinating physician coordinates the transition to adult care, if necessary in consultation with the expertise centre and treatment team.
The UMCG Expertise Centre for Rare Chromosome Disorders manages a local register with data from individuals with 22q13DS.

5

Considerations

Not applicable.

Recommendations

The working group is of the opinion that every person with 22q13DS should be referred to a centre of expertise for rare chromosome disorders recognized by the VWS (for an up-to-date overview of the expertise centres in the Netherlands recognized by the VWS see www.zichtopzeldzaam.nl/expertisecentra).

After diagnosis, the person with 22q13DS will be informed which medical specialist is responsible, as coordinating physician, for their medical management and coordination of care. This will usually be a paediatrician or intellectual disability physician.
In each care phase, the coordinating physician determines via consultation who the main practitioner is for the relevant care phase and records this in the individual care plan.
At diagnosis, at minimum, the contact information of the supervising physician and the initial treatment plan should be recorded individual care plan.
It is recommended that the guidance presented here be used for follow-up. The centre of expertise is responsible for timely adjustment of the guidelines to include new insights.
The coordinating physician during childhood (paediatrician/intellectual disability physician) coordinates the transfer of care with the future coordinating physician during adulthood (intellectual disability physician) and communicates this with the expertise centre and the treatment team.
Individuals with 22q13DS should be informed about the patient registry.

References

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Vajda I, van Breukelen S, Segers M. VSOP Visiedocument Concentratie en organisatie van zorg bij zeldzame aandoeningen. Soest: VSOP; 2015.

Other sources

- Coordination platform for care standards for chronic diseases. Framework Individual Care Plan; 2012.
- Guide *Transition of Care for Adolescents with an Intellectual Disability* (NVAVG/NVK/NVKN/VRA kinderrevalidatie, 2013)
- *Care Standard for Rare Disorders*. Zorgstandaard ADCA. Soest: ADCA Vereniging Nederland; 2015.

5.1 Medical counselling guide for persons with 22q13DS

The guideline below provides an overview of points for attention in the follow-up of individuals with 22q13DS. The coordinating physician is usually a paediatrician, paediatric specialist in heritable or congenital disorders, or intellectual disability physician, who regularly sees the person with 22q13DS (frequency depends on age, problems and the level of care needed). The treatment team consists of the specialists in the organ systems named. The guideline also indicates when referral to an expertise centre (EC) is recommended.

The coloured boxes in the chart below indicate when a check with regard to this health item is recommended. If necessary, additional information is provided in the coloured box (no text does not mean no attention should be paid). The columns contain items that are advised at least once when making the diagnosis.

5 Colour = pay attention to this. If necessary, further details are given in the coloured boxes

For substantiation see the relevant chapters in this guideline. If not discussed in the guideline, a brief explanation will follow below the scheme or the prevalence data will be shown in the table.

		AT DIAGNOSIS	0-2 YEARS	2-12 YEARS	12-16 YEARS	>16 YEARS
GENETICS	Clinical diagnosis and genetic testing - Array or exome sequencing					
	Genetic counselling: - Explain phenotype 22q13DS - Recurrence risk: poss. FISH and karyotyping - Discuss reproductive options					
	Refer to 22q13DS expertise centre (EC) for counselling about updates on 22q13DS, participation in scientific research and questions (combined with general follow-up).		Yearly EC	Every 2 years EC	Every 2 to 3 years at EC	Every 3 to 5 years at EC
COGNITIVE BEHAVIOUR	General developmental delay, especially in the field of spoken language and cognition (moderate to severe intellectual disability). Characteristics of autism spectrum disorder.			Investigate development and behaviour at 3, 7 and 11 years of age	Investigate development and behaviour at 15 years of age	Investigate development and behaviour at 18 years of age
	Sleep disorders: - Exclude somatic causes - EEG for nigh-time restlessness - If needed, refer to sleep clinic					
	Refer questions regarding trial treatment with intranasal insulin to the 22q13DS expertise centre					
SPEECH/ LANGUAGE	Problems with language and speech	Refer to an audiology centre	Audiology centre or speech therapist	Speech therapy at home/school	Speech therapy at home/school	As needed
ENT, HEARING, DENTISTRY	Recurrent middle ear infections (60%), hearing problems (20%), delayed responses to speech	Refer to an ENT specialist: audiometry and tympanometry				
	Malocclusion, crowding and skewing of the teeth; reduced quality of enamel; teeth grinding/mouthing behaviour.		Dentist	Dentist, consider referral to Special Dentistry	Dentist, consider referral to Special Dentistry	Dentist, consider referral to Special Dentistry
	Swallowing problems due to hypotonia		Consider swallowing study	Consider swallowing study		
VISION	Strabismus (35%), central vision disorder (6%), ptosis (65%)	Consult eye specialist				
GASTROINTESTINAL	Feeding problems (reduced sucking reflex, chewing)		Speech therapy	Speech therapy		
	Gastroesophageal reflux (30%): Consider further testing and: - Dietary advice - Proton pump inhibitors					
	Cyclic vomiting (25%)		Refer to paediatrician	Refer to paediatrician		
	Overweight (10%): nutritional and exercise advice (dietician, physiotherapist)					

	Constipation (40%): - Dietary advice - Laxatives					Consider testing for megacolon
HEART AND LUNGS	Congenital abnormalities max. 8% (including TI, ASD, PDB) - (paediatric) cardiologist on indication	Consult cardiology: ECG, echocardiogram (<2 years) if indicated				
	Recurrent upper airway infections 40%					
NEUROLOGY	Cerebral construction disorders (15%)	Low-threshold MRI of the brain at indication (paediatric)neurologist				
	Hypotonia: poor head control, feeding problems, fatigue, insufficient movement.		Paediatric physiotherapist, occupational therapy, speech therapy	Paediatric physiotherapist, occupational therapy, speech therapy	Advise sports, possibly under the supervision of a physiotherapist	Advise sports, possibly under the supervision of a physiotherapist
	Delayed motor development, motor dyspraxia		Paediatric rehabilitation doctor, child physiotherapist, occupational therapy	Paediatric rehabilitation doctor, child physiotherapist, occupational therapy		
	Epilepsy (25-50%), frequent febrile seizures		EEG and paediatric neurologist at indication	EEG and paediatric neurologist at indication	EEG and paediatric neurologist at indication	EEG and neurologist at indication
Sensory Dysfunction	Decreased response to pain: being alert for somatic problems					
	Decreased or abnormal responses to sensory stimuli (temperature, touch, sound, balance, images)			Referral to therapist for sensory information processing		
ENDOCRINE	Height					
	Hypothyroidism (5%)	TSH	TSH 1x per year	TSH 1x per year	TSH 1x per year	TSH 1x per 2 years
RENAL UROGENITAL	Congenital abnormalities: vesicoureteral reflux, cystic or dysplastic kidneys, or hydronephrosis	At least once, perform ultrasound of kidneys/urinary tract				
	Recurrent urinary tract infections					Exclude underlying problems and consider prophylaxis
	Birth control and family planning					
SKIN AND LYMPH	Dysplastic, thin toenails that frequently become ingrown (80%)					
	Primary lymphedema (19-25%), prevalence increasing with age				Consider referral to an expert centre for lymphedema	Consider referral to an expert centre for lymphedema
	Heat intolerance due to reduced perspiration (60%)					

Dentistry

The most frequent dental problems seen in 22q13DS are malocclusion and crowding of teeth (>25%). Low muscle tone, tooth grinding and excessive chewing (on objects) and tongue movements can contribute to this. Malocclusion can play a role in swallowing problems and drooling. Medication (antibiotics), reflux and long-term bottle feeding can contribute to poor tooth enamel.

Congenital heart defects

In many cohort studies, no congenital heart defects are mentioned. Only two studies report congenital heart defects in 4/30 and 1/32 subjects with 22q13DS (TI = tricuspid insufficiency, ASD = atrial septal defect, PDB = Persistent Duct Botalli).

Urogenital defects

Urinary tract infections (8%) are seen in 22q13DS, and hydronephrosis (5%) and vesicoureteral reflux (14%) have also been reported. Polycystic kidneys (5%) and congenital renal anomalies are incidental. In general, kidney problems are reported in about 25% of individuals with 22q13DS.

Appendix 1 Conditions for trial treatment with intranasally administered insulin

Rationale

Based on the implications for developmental and behavioural problems in patients with 22q13DS and for their environment, the working group believes that every child with 22q13DS should have access to trial treatment with intranasal insulin at the request of parents and under specific conditions to prevent uncontrolled and unevaluated use. That is why the working group believes that central registration and follow-up should take place in the Expertise Centre for Rare Chromosome Disorders in Groningen (see also Module Organization of Care). This is due this centre's experience with the product in and its ability to collect data and evaluate the (long-term) effects of the test treatments. Central registration and (centrally coordinated) follow-up are therefore a precondition for (trial) treatment with insulin nasal spray.

Important conditions for the trial treatment:

- Coordination with all parties involved to determine whether test treatment is desirable and possible: parents, paediatrician/intellectual disability physician or other main practitioner, day-care staff, etc.
- Determination of when it is most optimal to start the trial treatment, i.e. preferably in a quiet period without changes in personal situation such as moving house, change of care, etc.
- A baseline measurement of the level of development and behaviour, for example with a developmental test such as the Bailey-III-NL, Vineland Screener or Stages and Ages Questionnaire (this can also be done in your own environment if results are shared with the expertise centre).
- Prescription and informational sheets about the medication are supplied by the UMCG Expertise Centre for Rare Chromosome Disorders.
- After 6 months of treatment with insulin nasal spray, a follow-up development test is performed to evaluate the effects (this can also be done in the home environment if results are shared with the expertise centre).
- If a clear improvement is seen on the developmental or behavioural test, or if a relapse in development or behaviour occurs after stopping medication, a new prescription can be requested.
- The maximum period for subsequent treatments is 2 years. After this point, treatment will be stopped for half a year to evaluate the effect.

There is currently no experience with this treatment in adults, but if a trial treatment is desired, this can be discussed with the expertise centre. The positive effect on development and behaviour may not only apply to persons with 22q13DS, but also to persons with severe developmental delay and behavioural problems of other causes. However, further research will have to be done on this.

Appendix 2 Knowledge gaps

During the development of this guideline for 22q13 deletion syndrome, we systematically searched for research findings that could be useful for answering the fundamental questions. Some (or parts) of the fundamental questions could be answered with the results of these searches, but other aspects could not.

By using the evidence-based methodology, it has become clear that gaps in the available knowledge still exist in the field of 22q13 deletion syndrome. The working group is of the opinion that (further) research is desirable to provide clearer answers to questions from practice in the future. For this reason, the guideline working group has prioritized the following five top gaps in knowledge, for which further investigation is most urgent:

1. Knowledge on the relationship between the genetic defect and clinical characteristics for the purpose of risk assessment of health problems (Module General).
2. Knowledge about whether the pathogenesis of 22q13DS lies in the central nervous system or the peripheral nervous system (Module General).
3. Knowledge on the cause and treatment of cyclic vomiting in children with 22q13DS (Module Chewing, Swallowing and gastrointestinal problems).
4. Data on the course of cognitive development and mental disorders in persons with 22q13DS (Module Mental Disorders).
5. Data on the effect of intranasally administered insulin on mood disorders in adults with 22q13DS (Module Drug treatment of development and behaviour).

Appendix 3 Indicators

In the guideline working group, four indicators have been developed to evaluate the implementation of the guideline:

1	FISH testing in parents of newly diagnosed individuals with 22q13DS (Module Counselling)	Process indicator
2	Karyotyping in individuals with terminal deletions in 22q13DS determined by Array (Module Counselling)	Process indicator
3	Referrals of newly diagnosed individuals with 22q13DS to expertise centre (Module Organisation of Care)	Process indicator
4	Having a coordinating physician for persons with 22q13DS (Module Organisation of Care)	Process indicator

1. FISH testing	
Relationship with quality	Recommendation from Module Counselling: In order to determine the recurrence rate for parents (or other family members), Fluorescent In-Situ Hybridization (FISH) with a probe for locus 22q13 is the first choice diagnostic to rule out a balanced translocation.
Definition	The percentage of parents of newly diagnosed persons with 22q13DS who undergo FISH testing.
Numerator	Number of parents of newly diagnosed persons with 22q13DS who undergo FISH testing.
Denominator	Number of parents of newly diagnosed persons with 22q13DS.
Type indicator	Process indicator
Inclusion and exclusion criteria	Inclusion: parents of newly diagnosed persons with 22q13DS (available from the genome diagnostics laboratories) Exclusion: deceased or otherwise unavailable parent
Quality domain	Effectiveness
Frequency of measurement	1x per reporting year
Study interval	01-07-2018 to 01-07-2022
Frequency of reporting	1x per reporting year

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2. Karyotyping	
Relationship with quality	Recommendation from module Counselling: Perform karyotyping on an array-determined terminal deletion in 22q13 to exclude a ring chromosome 22 (NF2 risk).
Definition	The percentage of subjects with 22q13DS with array-determined terminal deletion in whom karyotyping has been performed.

Numerator	The number of people with 22q13DS with array-determined terminal deletion in whom karyotyping has been performed.
Denominator	The number of people with 22q13DS with array-determined terminal deletion.
Type indicator	Process indicator
Inclusion and exclusion criteria	Inclusion: all individuals with a newly diagnosed array-determined 22q13 terminal deletion (available from the genome diagnostics laboratories) Exclusion: persons who have had karyotyping in the past, persons over the age of 40*, persons who have already been diagnosed with NF2.
Quality domain	Effectiveness
Frequency of measurement	1x per study year
Study years	01-07-2018 to 01-07-2022
Frequency of reporting	1x per study year

* The chances of developing schwannomas after this age are slim.

3. Expertise centre	
Relationship with quality	Recommendation from the Care Organization Module: The working group is of the opinion that every person with 22q13DS should be referred to a centre of expertise recognized by VWS for rare chromosome disorders.
Definition	Percentage of newly diagnosed individuals with 22q13DS who have been referred to a centre of expertise
Numerator	The number of newly diagnosed individuals with 22q13DS who have been referred to a centre of expertise
Denominator	The number of newly diagnosed individuals with 22q13DS
Type indicator	Process indicator
Inclusion and exclusion criteria	Inclusion: all newly diagnosed individuals with 22q13DS (available from the genome diagnostics laboratories) Exclusion: persons living abroad
Quality domain	Effectiveness, Patient focus
Frequency of measurement	1x per study year
Study years	01-07-2018 to 01-07-2022
Frequency of reporting	1x per study year

4. Coordinating physician	
Relationship with quality	Recommendation from module Organization of care: Following diagnosis, the person with 22q13DS will be informed which medical specialist, as coordinating physician, is responsible for the medical management and coordination of care. This will usually be a paediatrician or AVG.

Definition	Percentage of people with 22q13DS who have a coordinating physician
Numerator	Number of people with 22q13DS who have a coordinating physician
Denominator	Number of people with 22q13DS
Type indicator	Process indicator
Inclusion and exclusion criteria	Inclusion: all newly diagnosed individuals with 22q13DS (send survey to applicants through genome diagnostics labs to ensure anonymity) Exclusion: persons living abroad
Quality domain	Effectiveness, Patient focus
Frequency of measurement	1x per study year
Study year	2022
Frequency of reporting	1x per study year

Appendix 4 Accountability

After the comment and authorization phase has been completed, Accountability is included in the Guidelines Database (www.richtlijnendatabase.nl). References to "related products" can be found in the current version of the guideline text as appendices (see table of contents for the guideline).

Authorization Date and Validity

Last reviewed: 29-10-2018
Last authorized: 29-10-2018

The workgroup is not in a position to assess how up-to-date the guideline is.

In 2022, at the latest, the board of the Association of Clinical Genetics of the Netherlands (VKGN) will determine, in consultation with the UMCG Expertise Centre for Rare Chromosome Diseases, whether this guideline or module is still up to date. If necessary, a new working group will be set up to revise the guideline. The validity of the guideline will expire sooner if new developments give cause to start a review process.

As the registrar of this guideline (module), the Association of Clinical Genetics in the Netherlands is primarily responsible for the current of this guideline. The other scientific associations associated with the guideline or users of the guideline share the responsibility to inform the primary responsible party about relevant developments within their field.

General information

Initiative

Prof C.M.A. van Ravenswaaij, Clinical Geneticist, University Medical Centrum Groningen, Association of Clinical Genetics of the Netherlands - Vereniging Klinische Genetica Nederland (VKGN)

In cooperation with:

The Dutch Society for Paediatrics - Nederlandse Vereniging voor Kindergeneeskunde (NVK)
The Dutch Society for Speech Therapy and Phoniatrics - Nederlandse Vereniging voor Logopedie en Foniatrie (NVLF)
The Dutch Society for Psychiatry - Nederlandse Vereniging voor Psychiatrie (NVvP)
The Society for Intellectual Disability Physicians - Vereniging van Artsen voor Verstandelijk Gehandicapten (NVAVG)

And supported by:

Association of Cooperating Parent and Patient Organizations - Vereniging Samenwerkende Ouder- en Patiëntenorganisaties (VSOP)

Financial support

Guideline development was financed from the VIMP subsidy from ZonMw (VIMP-80-83600-98-50003 under the Good Use of Medicines program). Patient participation for this guideline was partly financed by the Quality Funds for Patients Consumers (SKPC) within the KIDZ program.

Goal and target group

Goal

The aim of the guideline is to provide recommendations for resolving the bottlenecks experienced in practice and to achieve more uniform and better-coordinated care. The recommendations are based on a careful weighing of the latest scientific insights, expert opinion and patient preferences. The guideline supports healthcare professionals in their clinical decision-making and provides transparency to patients and third parties.

Target group

This guideline is written for all members of the professional groups involved in the care of persons with 22q13 deletion syndrome (Phelan-McDermid syndrome).

Composition of the working group

A multidisciplinary working group was set up in 2017 to develop the guideline. The working group members have been mandated by their professional association to participate. The working group is responsible for the full text of this guideline.

- Ms J.M. Carbin, Patient representative
- Dr I.F.M. de Coo, Neurologist, Coordinator NeMo expertise centre
- Ms M.E. Doornbos, MA, Paediatrician for Heritable and Congenital Disorders, Albert Schweitzer Hospital Dordrecht, NVK
- Dr S.G. Kant, Clinical geneticist, Leiden University Medical Centre, VKGN
- Ms E. Kuiper, Patient representative
- Ms C. Navis, Clinical preverbal speech therapist, Erasmus Medical Centre, Rotterdam, NVLF
- Dr P.F.A. de Nijs, child and adolescent psychiatrist, Erasmus Medical Centre, Rotterdam, NVvP
- Prof C.M.A. van Ravenswaaij, Clinical geneticist, University Medical Centre Groningen, VKGN (chair)
- Ms D. Stemkens, MA, policy officer VSOP;
- Ms M.J. Walinga, MA, intellectual disability physician, Paterswolde, NVAVG
- Ms R.J. Zwanenburg, MA, Clinical geneticist in training, University Medical Centre Groningen, VKGN

For the development of the Language and Speech Sub-module:

- Ms Anne Marie van de Zande, speech therapist/clinical linguist, Rijndam paediatric rehabilitation

Declarations of interest

The code to prevent improper influence through a conflict of interest has been followed.

All working group members have stated in writing whether they have had direct financial interests (related to a commercial company, personal financial interests, research funding) or indirect interests (personal relationships, reputation management, knowledge valorisation). Declarations of interest can be obtained from the VSOP, an overview can be found below:

Name workgroup member	Conflicts, Yes / No	Interest

Ms J.M. Carbin	No	Mother of a daughter with 22q13DS
Dr I.F.M. de Coo	No	NA
Ms M.E. Doornbos, MA	No	NA
Dr S.G. Kant	No	NA
Ms E. Kuiper	No	Mother of a daughter with 22q13DS; Board member of VG Networks; Administrator Facebook group Phelan-McDermid syndrome
Ms C. Navis		NA
Dr P.F.A. de Nijs	No	Employer (Erasmus MC, Department of Child and Adolescent Psychiatry/Psychology); Sells the ASEBA questionnaires (CBCL, TRF, YSR, etc.) in the Netherlands and Belgium.
Prof. C.M.A. van Ravenswaaij	No	This guideline is partly based on research that we have conducted on a large group of patients with Phelan-McDermid syndrome. However, the literature was systematically searched and assessed for the drug treatment module. As a result, an objective consideration was made to arrive at well-founded advice, stating the degree of evidence. It is possible that advice may directly relate to certain centres of expertise, including the UMCG Expertise Centre for Rare Chromosome Disorders (for example, central monitoring and evaluation of the advice given in the guideline).
Ms D. Stemkens, MA	No	NA
Ms M.J. Walinga, MA	No	NA
Ms R.J. Zwanenburg, MA	No	The guideline is partly financed with the aid of a ZonMw VIMP subsidy. The purpose of this grant is to promote the implementation of findings from previous research. ZonMw has no primary interest in this.

Input on patient perspective

A digital survey was conducted among patient representatives for the bottleneck analysis, and a report on this is included under related products (see Appendix). In the development of the guideline attention was also paid to the patient perspective through the participation of two patient representatives in the working group. Finally, the draft guideline was submitted to the Patient Federation of the Netherlands for comment.

Implementation

The implementation of the guideline and the practical feasibility of the recommendations were taken into account in the various phases of the guideline development. In doing so, special attention was paid to factors that may promote or hinder the implementation of the guideline in practice. The working group has also developed quality indicators to monitor and strengthen the application of the guideline in practice (see Appendix).

The guideline is distributed digitally among all relevant scientific associations. The guideline is also presented to the Guidelines Database and the Register of the Netherlands Healthcare Institute.

Process

AGREE

This guideline has been drawn up in accordance with the requirements stated in the report on Medical Specialist Guidelines 2.0 of the Guidelines Advisory Committee of the Quality Council. This report is based on the AGREE II instrument (Appraisal of Guidelines for Research & Evaluation II; Brouwers, 2010), which is an internationally accepted instrument.

AQUA

This guideline has been developed on the basis of the Quality Standards Guideline of the Quality Standards Advisory and Expert Group (AQUA; 2015)

Bottleneck analysis

During the preparatory phase, members of the guideline working group identified the bottlenecks. A bottleneck analysis was also carried out among patient representatives via a digital survey. A report of this is included under related products (see Appendix results bottleneck analysis)

Fundamental questions and outcomes

The bottlenecks identified by the guideline working group and the survey of patient representatives have been discussed and prioritized. Prioritized bottlenecks were converted into fundamental questions. The working group did not define the aforementioned outcome measures a priori, but used the definitions used in the studies.

Strategy for searching and selecting literature

Since 22q13 deletion syndrome is a rare condition (1 in 30,000 live births), in researching this guideline we chose to perform one generic search for 22q13 deletion syndrome in different electronic databases using specific search terms. An additional search was made for studies based on the bibliographies of the selected articles. Selected articles were used to answer the fundamental questions. If no evidence specific to 22q13 deletion syndrome could be found in the literature, reference is made to general guidelines.

The databases that have been searched, the search strategy and the selection criteria used can be found in Search Accountability.

Quality assessment of individual studies

For the Module "Drug treatment of development and behaviour", individual studies were systematically assessed using GRADE to estimate the risk of biased study results (risk of bias). These assessments can be found in the Risk of Bias (ROB) tables (Appendix Tables).

Assessing the strength of the scientific evidence

A) The Module "Drug treatment of development and behaviour"

The strength of the scientific evidence was assessed using the GRADE method. GRADE stands for Grading Recommendations Assessment, Development and Evaluation (see http://www.gradeworkinggroup.org/).

GRADE distinguishes four grades for the quality of the scientific evidence: high, moderate, low and very low. These grades refer to the degree of certainty that exists about the conclusions of the literature (Schünemann, 2013).

GRADE	Definition
High	There is a high degree of certainty that the true effect of treatment is close to the estimated effect of treatment as stated in the literature claim. It is very unlikely that the literature conclusion will change when results of new large-scale research are added to the literature analysis.
Moderate	There is moderate assurance that the true effect of treatment is close to the estimated effect of treatment as stated in the literature claim. The conclusion may change when results of new large-scale research are added to the literature analysis.
Low	There is little assurance that the true effect of treatment is close to the estimated effect of treatment as stated in the literature claim. There is a real chance that the conclusion will change when results of new large-scale research are added to the literature analysis.
Very low	There is very little assurance that the true effect of treatment is close to the estimated effect of treatment as stated in the literature claim. The literature conclusion is very uncertain.

Summarizing the literature

For the Module "Drug treatment of development and behaviour" the relevant research data of the selected articles are presented clearly in an evidence table (Appendix Tables). The main findings from the literature are described in the Literature Summary for each module.

Formulating the conclusions

A) In the module "Drug treatment of development and behaviour", the scientific evidence was summarized as conclusions from literature where the level of evidence was determined according to the GRADE method.

B) The other modules took into account the extent to which scientific evidence was available when formulating the conclusions.

Considerations (from evidence to recommendation)

In addition to (the quality of) the scientific evidence, we have taken into account other aspects that are also important to arrive at a recommendation. These include the expertise of the workgroup members, the values and preferences of the patient, costs, the availability of facilities and organizational issues. If they are not part of the literature summary, these aspects are listed and assessed (weighted) under the heading Considerations.

Formulating recommendations

The recommendations answer the fundamental question and are based on the available scientific evidence, main considerations and a weighting of the beneficial and adverse effects of the relevant

interventions. The strength of the scientific evidence and the weight assigned to the considerations by the working group together determine the strength of the recommendation. In accordance with GRADE methodology, a low evidential value of conclusions in the systematic literature analysis does not exclude a strong recommendation a priori, and weak recommendations are also possible with high evidential value. The strength of the recommendation is always determined by weighing all relevant arguments together.

Because 22q13 deletion syndrome is a rare condition and the scientific evidence is limited, the opinion of (experienced) experts in the field of 22q13 deletion syndrome (described under Considerations) has been weighed heavily.

Preconditions (Organisation of Care)

The organization of care has been taken into account in the development of the guideline. Preconditions that are relevant for answering a specific basic question are part of the considerations for the specific basic question. More general, overarching, or additional aspects of the organization of care are discussed in the Module Organisation of Care.

Indicator development

In parallel with the development of the draft guideline, internal quality indicators were developed to monitor and strengthen the application of the guideline in practice (Appendix Indicators).

Knowledge Gaps

During the development of this guideline, we systematically sought research where the results contribute to answering the fundamental questions. For each fundamental question, the working group checked whether (additional) scientific research is desired to be able to answer this fundamental question. These subjects were subsequently prioritized, and four subjects were selected for which (additional) scientific research is considered important. These are described in the Appendix Knowledge Gaps.

Comment and authorization phase

The draft guideline was submitted for comment to the relevant (scientific) associations, the Dutch Neurology Association, the Dutch Patient Federation, the Dutch Health Insurers and the centres of expertise for rare syndromes with intellectual disabilities:

- UMC Groningen: Centre of Expertise for rare chromosome disorders
- Radboudumc Nijmegen: Centre of Expertise for genetic neurodevelopmental disorders
- Maastricht UMC+: Centre of Expertise for rare syndromes and cognitive disorders
- Erasmus MC Rotterdam: Centre of Expertise for neuro-developmental disorders (ENCORE)
- Amsterdam UMC: Amsterdam Expertise Centrum voor Ontwikkelingsstoornissen (AECO).

The guideline was also sent to the chromosome polyclinic of the Department of Clinical Genetics of the LUMC. Comments were collected and discussed with the workgroup. Following the comments, the draft guideline was amended and finalized by the working group. The final guideline was sent to the participating (scientific) associations and submitted to the Dutch Patient Federation for authorization.

Authorised by:

- Dutch Association of Physicians for the Mentally Handicapped
- Dutch Association of Paediatrics
- Dutch Association for Speech Therapy and Phoniatrics
- Dutch Association for Psychiatry
- Dutch Patient Federation (Patiëntenfederatie Nederland)
- Association of Clinical Genetics Netherlands

Health Insurers Netherlands has no objection to the inclusion of the guideline in the Register of the Healthcare Institute Netherlands. A quality standard describes what good care is, regardless of the Financing source (Health Insurance Act (Zvw), Long-term care Act (Wlz), Social Act Support (Wmo), additional insurance or personal payment by the client/patient). Registration of a quality standard in the Register of the Netherlands Healthcare Institute therefore does not necessarily mean that the care described in the quality standard is insured.

Search justification

Background

Since 22q13 deletion syndrome is a rare condition (1 in 30,000 live births), in preparing this guideline we chose to initially perform one generic and broad search for 22q13 and/or *SHANK3* deletion. Subsequently, two working group members (D. Stemkens, R.J. Zwanenburg) independently made the initial selection (based on title/abstract) and the second selection (based full text) of the articles found via PubMed (PM). The search in Embase (EB) was carried out by one workgroup member (R.J. Zwanenburg), and 82 hits were found that were not found in PM. These hits were submitted to a second workgroup member (D. Stemkens) for verification for the two inclusion selection steps.

The following exclusion criteria were used in the selection:

- No 22q13 and/or *SHANK3* deletion
- Ring chromosome 22 (n = 24 PM + 23 EB). Although this was initially searched for, these were excluded from the final selection in connection with complex patterns and mosaics due to the ring shape, and often due to a lack of specific genetic data, which meant that the phenotype cannot be compared with a pure terminal 22q13 deletion.
- (Un)balanced translocations
- Interstitial 22q13 deletions not involving the *SHANK3* gene
- *SHANK3* mutation
- Cell and animal studies that did not match one of the fundamental questions in terms of subject.
- Case reports
- Languages other than Dutch/English.

The articles were then selected on the basis of subject and divided over the predetermined fundamental questions (see "Search and Selection" paragraph of the relevant modules). In addition, we examined, per module, whether reference could be made to existing Dutch guidelines on that subject and additional (not 22q13DS-specific) literature was searched for on that specific subject.

Database	Date	Search terms	Total	Total articles

			articles found	**selected**
Pubmed	10 May 2017	**P=** (("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])))	457 hits	61
Embase	28 July 2017	**P=** ('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	525 hits, of which 82 were new hits compared to PubMed	1 new hit not found in PubMed
Guidelines				
Guidelines International Network	28 July 2017	Phelan-McDermid* 22q13*	0	0

[1] P stands for ‘’Patient’’ or ‘’Problem’’ in the PICO method for scientific research.

Appendix 5 Results Bottleneck Analysis

Bottleneck analysis guideline working group

Following the VIMP subsidy from ZonMw, drug treatment of development and behaviour in persons with 22q13DS is described in the guideline. On 28 March 2017, an inventory was made in the guideline working group of the additional subjects that are important to describe in the guideline.

The guideline working group focused on the following subjects:

- General: definition, prevalence, clinical features, genotype-phenotype relationship.
- (Genetic) Counselling: referral to a clinical geneticist, (diagnostic testing for determination of) recurrence risk.
- Treatment and support of specific complaints of patients with 22q13DS: language and speech problems, sensory dysfunction, epilepsy, gastrointestinal problems, lymphedema and mental disorders.

Bottleneck analysis patient representatives

Subsequently, a digital survey was conducted in May 2017 to determine which subjects the family members of individuals with 22q13DS found important to describe in the guideline. This digital survey was distributed via the private Facebook group and the UMCG Expertise Centre for Chromosome Disorders in Groningen. The survey was fully completed by 47 patient representatives, which is a good response as in the Netherlands at least 65 children and 40 adults with a 22q13 deletion have been reported to the UMCG Expertise Centre for Chromosome Disorders.

Most of the topics that patient representatives considered important had also been prioritized by the guideline working group. Following the survey, the following subjects were added to the guideline:

- Heat intolerance, hypotonia and the relationship between ring chromosome and Neurofibromatosis type 2, which are now described in the General Module.
- Module on Sleep Disorders
- Module on Organisation of Care

As a result of the survey, the guideline working group was expanded to include a speech therapist, and a clinical linguist contributed to the language and speech problems module.

Appendix 6 Tables

Evidence table

Study reference	Study characteristics	Patient characteristics[2]	Intervention (I)	Comparison / control (C)[3]	Follow-up	Outcome measures and effect size[4]	Comments
Zwanenburg, 2016	Type of study: Prospective randomized, controlled study Setting: University Medical Centre Groningen Country: The Netherlands Source of funding: Grants from the Netherlands Organization for Health Research and Development (ZonMw)	Inclusion criteria: Patients recruited from a group of 38 Dutch children with PMS who had been diagnosed in the Clinical Genetics department of the University Medical Centre Groningen or referred to this centre from other hospitals in the Netherlands A molecularly confirmed 22q13.3 deletion including SHANK3, a calendar age between 12 months and 18 years, and having parents who understand and speech Dutch. Exclusion criteria: Children with severe (perinatal) brain damage or with a metabolic or neuromuscular disease N total at baseline: 25	Recombinant human insulin solution consisted of the licensed parenteral drug Humuline Regular 100 IU/ml. One spray was 0,1 ml; containing 10 IU of insulin. The insulin dose was calculated on both estimated body eight and head circumference. The medication was administered twice a day.	The composition and packaging of the placebo solution was identical to the insulin buffer solution. In the placebo solution, insulin was replaced by human albumin (Albuman 200g/l) to a concentration of 3,47mg/ml.	Length of follow-up: 18 months Loss to follow-up: N=2 (8%) Incomplete outcome data: N=2 (8%) 2 children did not finish the whole-treatment period of the study due to non-SAEs	Primary: 1.General developmental (Bayley-III-NL) or WPPSI-III-NL). 2. Behaviour (Vineland screener 0-6 and ESSEON). Raw scores were converted to a developmental age equivalent (DAE) Secondary: Behavioural problems (BRIEF-p and CBCL/1.5-5) Adverse affects	Stepped wedge design: In the clinical trial phase, each subsequent treatment period consisted of 6 months at the end of which time development and behaviour were assessed (6-6, t=12 and t=18 months). Immediately after each assessment, participants switched to a new set of nose sprays. Once started on intranasal insulin, participants remained on insulin until the end of the trial.
Schmidt, 2009	Type of study: Observational study Setting: Not stated Country: Germany Source of funding Not stated	Inclusion criteria: Children with 22q13 deletion syndrome Exclusion criteria: - N total at baseline: 6	Insulin (40 IU/ml) was diluted with 0,9% saline solution to a concentration of 10 IU/ml. So that each 0,1 ml puff contained a dose of 2 IU insulin. Subjects received 1 dose of 2 IU insulin per day during the	-	Length of follow-up: 13 months Loss to follow-up: - Incomplete outcome data: -	After 6 weeks and 1 year of treatment, parent were asked to fill in a behavioural questionnaire for the assessment of developmental progress. Ratings were compared with clinical observations	Intranasal insulin treatment for 12 months

			first 3 days. Dosage was increased gradually at 3 day intervals, until the final dosage of about 0,5-1,5 IU/kg/day was reached.			made by the examiner and with observations of psychologists, physiotherapists and occupational therapists made during routine examinations.	
Study reference	**Study characteristics**	**Patient characteristics[2]**	**Intervention (I)**	**Comparison / control (C)[3]**	**Follow-up**	**Outcome measures and effect size[4]**	**Comments**
Kolevzon, 2014	Type of study: Randomized, placebo-controlled pilot study Setting: Recruited as part of ongoing studies in PMS at the Seaver Autism Center for Research and Treatment at the Icahn School of Medicine at Mount Sinai, New York Country: USA Source of funding Not stated	Inclusion criteria: Children between 5 and 15 years old with PMS and confirmed to have SHANK3 deletions of mutations based on chromosomal microarray of high-throughput or targeted sequencing. All subjects were on stable medication regimes for at least 3 months prior to enrollment. Exclusion criteria: 1) Closed epiphyses 2) Active or suspected neoplasia 3) Intracranial hypertension 4) Hepatic insufficiency 5) Renal insufficiency 6) Cardiomegaly/valvulopathy 7) Allergy to IGF-1 8) Patients with comorbid conditions deemed too medically compromised to participate N total at baseline: 9	IGF-1 is an aqueous solution for injection containing human insulin-like growth factor-1 produced by recombinant DNA technology. Dose titration was initiated at 0,04 mg/kg twice daily by subcutaneous injection, and increased, as tolerated, every week by 0,04 mg/kg per dose to a maximum of 0,12 mg/kg twice daily. Doses could be decreased according to tolerability by 0,04 mg/kg per dose. Medication was administered twice daily with meals.	Placebo consisted of saline prepared in identical bottles by the research pharmacy at Mount Sinai.	Length of follow-up: 12 weeks Loss to follow-up: N=1 Incomplete outcome data: -	Primary: Behavioural features (ABC-SW subscale) Repetitive behaviour (RBS-R) Cognitive abilities (Mullen Scales for Early Learning of the Leiter International Performance Scale-Revised) Adaptive functioning (Vineland Adaptive Behavior Scales) Secondary Safety, tolerability and adverse events (SMURF)	

Notes

1.Prognostic balance between treatment groups is usually guaranteed in randomized studies, but non-randomized (observational) studies require matching of patients between treatment groups (case-control studies) or multivariate adjustment for prognostic factors (confounders) (cohort studies); the evidence table should contain sufficient details on these procedures

5 2.Provide data per treatment group on the most important prognostic factors [(potential) confounders]

3.For case-control studies, provide sufficient detail on the procedure used to match cases and controls

4.For cohort studies, provide sufficient detail on the (multivariate

Risk of bias table

Study reference (first author, publication year)	**Describe method of randomisation**[1]	**Bias due to inadequate concealment of allocation?**[2] (unlikely/likely/unclear)	**Bias due to inadequate blinding of participants to treatment allocation?**[3] (unlikely/likely/unclear)	**Bias due to inadequate blinding of care providers to treatment allocation?**[3] (unlikely/likely/unclear)	**Bias due to inadequate blinding of outcome assessors to treatment allocation?**[3] (unlikely/likely/unclear)	**Bias due to selective outcome reporting on basis of the results?**[4] (unlikely/likely/unclear)	**Bias due to loss to follow-up?**[5] (unlikely/likely/unclear)	**Bias due to violation of intention to treat analysis?**[6] (unlikely/likely/unclear)
Zwanenburg, 2016	Randomisation was done by the Department of Clinical Pharmacy and Pharmacology of the University Medical Centre Groningen using a restricted randomization method with permuted blocks of three groups	Unlikely	Unlikely, parents and participants were blinded for treatment allocation. Placebo was used.	Unlikely, care providers not involved	Unlikely, study investigators were blinded for treatment allocation	Unlikely, all primary outcome measures reported in methods section were described.	Unlikely, 2 patients loss to follow-up (8%). Reasons are described and intention-to-treat analysis is performed	Unlikely, groups were analyzed according to randomization.
Kolevzon, 2014	Method of randomization is not described	Unclear	Unlikely, double-blind design study	Unlikely, care providers not involved	Unlikely, study investigators were blinded for treatment allocation	Unclear, outcome measures are not reported in the method section. It is a pilot as part of an on-going study.	Unlikely, 1 patient loss to follow-up (11%). Reasons are described and intention-to-treat analysis is performed	Unlikely, groups were analysed according to randomization.

Notes

1. Randomisation: generation of allocation sequences have to be unpredictable, for example computer generated random-numbers or drawing lots or envelopes. Examples of inadequate procedures are generation of allocation sequences by alternation, according to case record number, date of birth or date of admission.
2. Allocation concealment: refers to the protection (blinding) of the randomisation process. Concealment of allocation sequences is adequate if patients and enrolling investigators cannot foresee assignment, for example central randomisation (performed at a site remote from trial location) or sequentially numbered, sealed, opaque envelopes. Inadequate procedures are all procedures based on inadequate randomisation procedures or open allocation schedules.
3. Blinding: neither the patient nor the care provider (attending physician) knows which patient is getting the special treatment. Blinding is sometimes impossible, for example when comparing surgical with non-surgical treatments. The outcome assessor records the study results. Blinding of those assessing outcomes prevents that the knowledge of patient assignment influences the process of outcome assessment (detection or information bias). If a study has hard (objective) outcome measures, like death, blinding of outcome assessment is not necessary. If a study has “soft” (subjective) outcome measures, like the assessment of an X-ray, blinding of outcome assessment is necessary.
4. Results of all predefined outcome measures should be reported; if the protocol is available, then outcomes in the protocol and published report can be compared; if not, then outcomes listed in the methods section of an article can be compared with those whose results are reported.
5. If the percentage of patients lost to follow-up is large, or differs between treatment groups, or the reasons for loss to follow-up differ between treatment groups, bias is likely. If the number of patients lost to follow-up, or the reasons why, are not reported, the risk of bias is unclear
6. Participants included in the analysis are exactly those who were randomized into the trial. If the numbers randomized into each intervention group are not clearly reported, the risk of bias is unclear; an ITT analysis implies that (a) participants are kept in the intervention groups to which they were randomized, regardless of the intervention they actually received, (b) outcome data are measured on all participants, and (c) all randomized participants are included in the analysis.