How to diagnose and care for children and adults with Pitt-Hopkins syndrome: clinical guidelines.

SECTION 1: INTRO

About these guidelines

Pitt-Hopkins syndrome (or PTHS) is a rare genetic condition that affects a child's development and causes learning disabilities. It's so rare that up to now there have been no clear guidelines for doctors on how to diagnose and manage the condition.

Doctors, psychologists, support groups and families from all over the world got together to put this right. They collected all the knowledge from research and their own experience and discussed the results at the first PTHS world conference in May 2018.

The result was the first internationally-agreed guidelines on how to diagnose Pitt-Hopkins and how to care for and manage a child or adult when problems arise.

I'm a parent; how can these guidelines help me?

* Read about the signs and symptoms that are used to diagnose Pitt-Hopkins.

* Find out , about problems that might arise, and how best to manage them with the help of doctors and specialists

* See the 40 recommendations that together make up best practice medical guidance on looking after someone with Pitt-Hopkins.

Because Pitt-Hopkins is a very rare condition, your doctor has probably never come across it before. You can share the guidelines with doctors to make sure the child or adult you're caring for gets all the tests and treatments he or she needs.

Diagnosing Pitt-Hopkins: the signs and symptoms

Genetic tests

Prenatal tests for further pregnancies

Digestive problems

Changes in breathing

Senses: vision, hearing, smell and pain

Seizures and other neurological problems

Muscles and bones

Checks and care for babies and children

SECTION 2: DIAGNOSIS

Signs and symptoms - how Pitt-Hopkins is diagnosed

Pitt-Hopkins is caused when a specific gene is not working properly either because it is missing or has what's known as a spelling mistake in it (meaning a mutation or variant).. This gene is called TCF4 and is on chromosome 18.

However, it is possible that someone who has a change in the TCF4 gene may not have Pitt-Hopkins but some other condition. That's why it is important to be able to make a diagnosis not just from genetic testing but from obvious signs and symptoms. This is called a clinical diagnosis.

Someone with Pitt-Hopkins typically has:

* learning disabilities

* delays in their development, such as being slow learning to walk

* lack of speech

* distinctive facial features

* possible changes in their breathing, including periods of breathing very fast (hyperventilation), or times when they stop breathing before restarting (apnoea)

* possible seizures (epilepsy)

* digestive problems, particularly constipation.

Doctors and parents have agreed which of these signs are most important and have created a points system that will allow a doctor to make a diagnosis.

This is based on the number of signs or symptoms someone has and the resulting overall score. This system helps distinguish a child or adult with Pitt-Hopkins from an individual with two other syndromes that can both resemble Pitt-Hopkins, Rett Syndrome and Angelman Syndrome.

The most important signs a doctor will look for (known as cardinal signs) are:

Unusual facial features:

- a narrow forehead

- the outer part of the eyebrows are thin compared to the inner part

- a wide and prominent nose

- the wings of the nostrils (alae) flare outwards a bit

- full cheeks

- large mouth, with a 'cupid's bow' in the upper lip, and a full lower lip

- rims of the ears that are thick and slightly folded.

These facial features together are given 4 points.

Moderate to severe learning difficulties (with no or only limited speech). **This is given 2 points**.

Unusual breathing patterns: rapid breathing (hyperventilation or hyperbreathing) and pauses in breathing (apnoea). **This is given 2 points**.

Less important signs (known as supportive signs) are:

- short sight (myopia)

- constipation

- unusual hands: slender fingers, and abnormal creases in the palm

- unstable gait when walking.

1 point for each of the above.

How points lead to a diagnosis

With a score of **9 or more**, a doctor will diagnose a child or adult with PTHS. You should then be offered genetic testing to look for a fault in the TCF4 gene, which causes Pitt-Hopkins.

If the score is between **6 and 8** and the unusual facial features are present, it is possible for a doctor to diagnose PTHS and you should be offered genetic testing.

If the score is **below 6** it is unlikely the child or adult has PTHS, and you won't need further testing for the syndrome.

Some doctors who have a lot of experience of PTHS will be able to make a confident clinical diagnosis without going through the checklist. Nonetheless this scoring system provides a clear way to diagnose PTHS.

We also need a scoring system to show how severely a person with the syndrome is affected. No such system exists and needs to be developed.

Recommendations

1/ The clinical diagnosis of PTHS is based on a combination of signs and symptoms. The diagnosis is made by a score of 9 or higher. With a score between 6 and 8 including the facial features there is a possibility of PTHS and genetic (DNA) studies should be carried out to confirm.

2/There is currently no set of criteria that indicates how severely someone is affected by PTHS. Health care professionals together with families need to develop a scoring system to measure this.

SECTION 3: GENETIC TESTING

Genetic tests to confirm a diagnosis of Pitt-Hopkins

Pitt-Hopkins is caused by a change in a specific gene, and that is why someone who has received a clinical diagnosis should be offered genetic testing.

We know of one gene, TCF4, that causes Pitt-Hopkins syndrome. This gene is responsible for many important developments, for example the formation of the brain before birth, the formation of the tissues of the face, the way nerves function, and how the body fights infections.

Sometimes the gene is missing or partially missing (this is known as microdeletion). This can either affect the TCF4 gene alone, or other genes nearby on chromosome 18 as well. A child or adult found to have the TCF4 gene missing is said to have ‘18q microdeletion syndrome’. If this is the case someone may show the features of Pitt-Hopkins, and other unusual signs and symptoms as well.

Some children with a change in the TCF4 gene may be delayed in their development but they do not have PTHS. For example, they do not have the characteristic facial features or breathing problems. Such children or adults should not be diagnosed with Pitt-Hopkins. A doctor should use the points system in these guidelines to diagnose or rule out PTHS.

Pitt-Hopkins is a genetic condition. Most cases are caused by a change in the TCF4 gene that has happened for the first time in that individual. This is known as a 'de novo' case, which means 'new'.

In rare cases a parent may carry the gene change that causes Pitt Hopkins Syndrome in a proportion of the cells in their body but not show signs themselves. The parent is referred to as having ‘mosaic’ PTHS.

What are the chances of someone being born with Pitt-Hopkins syndrome?

* If two parents have a child with Pitt-Hopkins syndrome, the chances of them having another child with the same syndrome is only 2% (The group who created these guidelines had details of 273 people with PTHS. In five of these families there were two children with PTHS, and on this basis the group calculated the 2% figure.) This small risk is present because of the chance that one of the parents may be have the mosaic form.

* A healthy brother or sister of someone with Pitt-Hopkins has no greater risk of having a child with the syndrome than anyone in the general population

* If someone with PTHS had a child, there would be a 50% (one in two) chance of the baby being born with the syndrome as well. This is because they already have the altered gene that causes the syndrome and there is a 50% (one in two) chance of any child of theirs inheriting it.

How are genetic tests carried out?

Nowadays there are many ways of performing genetic (DNA) tests. A technique that is often used is called 'next generation sequencing'. This means either all of an individual's genes, or a selected group of genes can be checked for changes.

Sometimes a change in the TCF4 gene is found in a child who does not show the signs and symptoms of Pitt-Hopkins syndrome.

In such a case it could be either that the particular TCF4 gene change involved is not causing any problems or that the child has a variant in another part of the TCF4 gene, which is causing problems in his or her development, but not PTHS.

In this case it can be very difficult to determine whether the change in the gene will cause any harm or not. Doctors need to evaluate the child very carefully, and make all the following checks:

* Is there is anyone in the family with PTHS or a similar syndrome?

* Has this particular change in TCF4 been seen and reported before?

* If it has been reported before, was it in a healthy person or someone with PTHS or another disorder?

* Where exactly in the gene is the change is located, and what type of change is it? The answers to these can make a significant difference. There are international criteria available for this.

All together this means the doctor needs time and experience to check all the above, before deciding whether or not a change in the TCF4 gene is harmful or not.

Recommendations

3/ Changes in the gene TCF4 can cause PTHS but can also cause other syndromes that are linked to cognitive problems. The latter group of children and adults should not be labelled as having PTHS.

4/ If a family has a child with PTHS and the diagnosis is confirmed by DNA studies, the statistical chance that the same couple will have another child with PTHS is around 2%.

5/ If a change in the TCF4 gene is found through DNA testing, it is not always easy to determine whether it is doing

any harm or not. Especially if the characteristics do not resemble PTHS very much. Several checks need to be carried out: carefully checking the child; checking whether the same or similar syndrome occurs in the family; whether this particular genetic change has been seen in anyone before; what the type of change is and precisely where within the gene it has occurred.

SECTION 4: PRENATAL STUDIES

Prenatal tests for families who have a child with Pitt-Hopkins

The chance of parents who have a child with PTHS having a second child with PTHS is low - estimated to be about 2%. But because the chance is not zero, parents who have further pregnancies will want to know about whether their unborn baby can be tested for Pitt-Hopkins.

It is recommended that all families who have a child with PTHS speak to s genetic counsellor as the situation is different in different cases.

Although an expectant mum will be offered ultrasound scans, it won't be possible to diagnose PTHS this way as there are usually no signs or symptoms in a developing baby that can be seen on a scan.

The prenatal tests for Pitt-Hopkins are genetic tests and they look for a change in TCF4, the gene that causes Pitt-Hopkins. Any parents whose child has been found to have a genetic change that causes Pitt-Hopkins can be offered

prenatal tests in any further pregnancies to see if the same genetic change is present in the unborn baby. Prenatal testing for Pitt-Hopkins in these cases is very reliable.

Health care professionals should discuss prenatal testing with parents during any subsequent pregnancies and offer it if parents want to go ahead.

The tests can be carried out in different ways:

* a sample of cells is taken from the placenta (chorionic villi biopsy)
* a sample of cells is taken from the fluid that surrounds the unborn baby in the womb (amniocentesis)
* testing is done during in vitro fertilisation (IVF), when an egg from a woman is fertilised by sperm in a laboratory.

Recommendations

6/ If a family has a child with PTHS, confirmed by DNA testing, health care professionals should discuss with parents the small chance of having another child with the syndrome, and discuss and offer prenatal testing. Families

should also be offered referral to a genetic service for more detailed discussion.

7/ Prenatal testing for PTHS should not be offered to parents unless they already have a child with the syndrome, as there are problems in interpreting the findings in a reliable way.

SECTION 5: GASTROENTEROLOGY

Digestive problems: feeding, reflux and constipation

Digestion problems are common in children and adults with PTHS.

Feeding

When a baby with PTHS has muscle weakness (known as hypotonia) it can lead to feeding problems. Typically, paediatricians will closely monitor the newborn's feeding and if needed will offer advice how to deal with any problems. This is the same as for any newborn baby with feeding problems.

Generally the problems sort themselves out as children with PTHS get older. Feeding difficulties at a later age, such as gagging, refusing to eat, and only eating at a certain time or place, or a certain type of food, can happen. But in general those with PTHS are described as excellent eaters.

Constipation

Most children with PTHS have constipation. In adults it occurs a bit less, but still frequently. Many with PTHS have severe constipation all their lives. Hirschsprung Disease (when nerves are missing in parts of the intestine), causes very severe constipation and has been associated with PTHS. However this is very rare - it has only been seen in one child with PTHS - and so it could be a coincidence.

A study with mice that had a deletion of the TCF4 gene similar to that in a human showed slower movement from the mouth down to the beginning of the large intestine and from the end of the large intestine. There is not much data on the speed of food going through the bowel in humans.

The treatment for constipation is similar as for the general population. Regularly sitting on the toilet for a set period after every meal and using positive reinforcement through a reward system is also helpful. Effective control of constipation includes keeping constipation diaries, the Bristol stool form scale, and filling in a dedicated questionnaire for children (section C of the Questionnaire on Paediatric Gastrointestinal Symptoms). Children or adults should see a doctor when necessary.

Reflux

About 40% of PTHS children and adults experience acid flowing back from the stomach into the oesophagus, the tube leading from the stomach to the mouth (gastroesophageal reflux disease.) A third of them experience excessive burping.

The treatment for reflux is similar to that of the general population. The first thing to try is a medicine that reduces acid in the stomach (proton pump inhibitor). People with PTHS respond well to these if the medication is given in high enough doses (omeprazole 0.7-3.5 mg/kg/day).

Episodes of breathing fast can lead to swallowing air. This causes the stomach to swell, leading to discomfort and burping. This was the case for just under half of those present at the World Congress in 2018.

One child had this so badly that she had had a tube inserted into her stomach via a small opening (gastrostomy) to let air escape a few times a day. This fixed her problems, and we have a similar positive experience in some others as well. Health care professionals should consider a gastrostomy if the swelling of the stomach is causing problems in a child or adult.

The 47 individuals with PTHS who attended the World Congress did not seem to show more food intolerance than would be expected in the general population.

Other gut problems include a narrowing of the opening of the stomach to the first part of the intestine (pyloric stenosis) and a twisted gut (malrotation), but these are not common. They can be treated in the same way as in children and adults without PTHS.

Recommendations

8/ Children and adults with PTHS often experience occasional or chronic constipation and should be monitored and assessed. This can be done by keeping a diary or by using a dedicated questionnaire.

9/ Treatment for constipation will follow the same treatment that would be given to anyone else. This might include some strategies to change behaviour.

10/ If someone with PTHS has problems with reflux, the treatment will not differ from any other person. Anti-reflux medications can sometimes help but usually need prescribing in their maximum dosage.

SECTON 6: RESPIRATION

Changes in breathing

Irregular breathing patterns - either hyperbreathing or pausing the breath - are common in children and adults with PTHS. It is one of the main criteria for a clinical diagnosis of the syndrome.

Many processes, including breathing, are automatically managed by your nervous system. This is called your autonomic nervous system. In someone with PTHS, this unconscious control system does not always work as it should (dysautonomia).

This can show up as dilated pupils with sluggish response to light, unstable body temperature, decreased circulation in hands and feet, constipation, or not emptying the bladder completely. Changes in breathing could be a part of this.

Breathing changes can start at different ages. We gathered information on 256 children and adults with PTHS and found that 123 (48%) had episodes of hyperbreathing. The true figure may be higher.

The average age this started was 6, but it could be as early as 3 months or as late as 37 years. When we looked at how common this was by age group we found that breathing changes developed in:

* 20% of children before 2 years of age
* 23% between 3 and 5 years
* 22% between 6 and 10 years
* 69% between 11 and 15 years and
* more than 90% of older individuals.

Rarely, hyperbreathing has started to occur in a young child and then, after months or even years, disappeared again for several years. We did not see a relation between the particular change in the gene and the occurrence of hyperbreathing.

The typical breathing pattern consists of hyperbreathing, sometimes regular sometimes irregular, followed by a pause in breathing. It usually takes 2 to 5 minutes. It may occur several times per hour to a few times per year. Parents have not reported these spells during sleep.

Pauses in breathing and hyperbreathing may also happen independent of each other. Periods of hyperbreathing may

be triggered by excitement, stress, or anxiety, but it sometimes happens without any obvious cause.

The amount of oxygen in the blood (known as oxygen saturation) may decrease during a spell of abnormal breathing. When someone with PTHS pauses breathing their lips and skin can take on a blue tinge as their oxygen levels decrease and - rarely - they may lose consciousness.

We are not aware of any instance that the heart stopped beating provoked by a pause in breathing~~.~~ Sometimes a person will develop epilepsy first, and have seizures,, followed by breathing changes after months or years.

Things can develop the other way round as well, but only rarely is a spell of changes in breathing followed immediately by a seizure ~~fit.~~

Many of those who have this irregular breathing also develop clubbing of fingers (broadening of the tips of the fingers) within a few years after the start of the breathing irregularities.

Clubbing was present in 9 of 49 individuals with PTHS whose hands were evaluated during the 2018 PTHS World

Conference. In some the clubbing had been noted before the hyperbreathing had started but it is more likely the hyperbreathing ~~fast breathing~~ had gone unnoticed before.

Other effects

This abnormal breathing can also leads to swelling of the abdomen and excessive burping. Breathing spells may make the person anxious, as well as the parent or carer. But many do not seem to be disturbed by it and remain comfortable. Others stop what they are doing, some sit down to prevent a fall, and a minority pass out.

There have been a few instances where someone with PTHS has irregular breathing at night. Parents have reported a pause in breath after inhaling and groaning when exhaling, both during sleep.

Unusual behaviour during sleep like nightmares and sleepwalking (parasomnias) were reported in 10 of the attendees of the PTHS World Conference. Although sleep studies (known as polysomnographies) are not available to enable us to study these sleep problems, it has been suggested that the breathing problems at night may also have a different cause and be obstructive in nature (this is known as obstructive sleep apnoea).

There is a report from Belgium on two children with PTHS who had marked spells of hyperbreathing which decreased in number and duration when they were given a medicine called acetazolamide. It worked in another adult too.

Acetazolamide is used in acute mountain sickness which in some ways is similar to the breathing problems in PTHS. However, it's still uncertain how this medicine may work in someone with PTHS. A major side effect may be low potassium levels which in several children and adults has been a reason to stop the medication.

In people who don't have PTHS, other medicines such as triazolam and zolpidem have been used for pauses in breathing~~breath holding~~ in sleep, but because the cause of breathing problems in people with PTHS is different, we must assume the positive effect on them will not be so good.

In a mouse model of another syndrome which also leads to breathing problems, Rett syndrome, a medicine called sarizotan has been shown to reduce the incidence of hyperbreathing and pauses in breathing ~~fast breathing and~~. A clinical trial is now underway. If successful it may help us to know how to manage the breathing problems in PTHS.

Recommendations

11/Doctors should explain to caregivers that spells of hyperbreathing~~rapid breathing~~, despite being disturbing to those who see it, are unlikely to be harmful.

12/ For children and adults with Pitt-Hopkins whose breathing is disturbed at night, doctors should consider sleep studies (polysomnography) to exclude obstructive sleep apnoea as a cause.

SECTION 7: SENSES

Sight, hearing, smell and pain

Vision

The structure of the eyes (lens, iris) of children with PTHS is usually normal. About 10% of children may have blocked tear ducts. If it causes prolonged problems it can be treated in the usual way.

Sight issues are common, with about two thirds of children with PTHS needing glasses, often before the age of 2.

The most common sight problems are:

* short-sightedness (myopia) 50%
* cross-eyes (strabismus) 45%
* eyes moving rapidly from side to side (nystagmus) 14%.

In rare cases a child will have wide pupils that react slowly to light. As sight problems are so common in PTHS, every child should be seen by an opthamologist at a young age and regularly followed up.

Hearing

Only about 10% of people with Pitt-Hopkins have hearing loss. However, as it is so important for speech development, it is wise to check the hearing in all children with PTHS.

There are tests that can be carried out that do not need any type of feedback from the child (in medical terms, optoacoustic emission and auditory evoked potential), so testing can be done reliably in every child, including the ones who are not willing or able to cooperate.

Smell

There have been no studies of the sense of smell in children with PTHS. Possibly some have a decreased sense of smell and others are sensitive to some smells, but this is not yet certain.

Pain

Recognising and dealing with pain is challenging in children and adults with PTHS as the majority can't tell us this. From what we know it seems they can react in a different way to pain. Some parents have said that their child is more bothered by and sensitive to minor pain, such as a small

scrape or cut, while they seem less bothered by something others would find far more painful such as pain after surgery.

Others are showing less pain generally. This is important to realise if the behaviour of a child has changed as for instance a broken bone can go unnoticed.

It may be that people with Pitt-Hopkins experience pain in a different way, with a different sensation: the gene that is affected, TCF4, makes a protein that works in pain signalling in the Pitt-Hopkins mouse.

There are questionnaires that have been developed to recognise and assess pain in children with special needs (such as the FLACC pain scale). Health care professionals caring for children with PTHS should use them if there is any doubt whether or not the child is in pain.

Recommendations

13/ Every child with PTHS should have their eye sight checked on diagnosis and then regularly monitored.

14/ Everyone with PTHS should have their hearing tested regularly.

15/ Parents and carers should be aware of the various types of pain felt by those with PTHS; if in doubt, there are special questionnaires that can help assess pain.

SECTION 8: NEUROLOGY

Epilepsy

Up to half of people with PTHS have epilepsy with different types of seizures, which can vary in how severe they are. Someone with PTHS may have their first seizure before they are one year old, or not until early adulthood.

Seizures can easily be misdiagnosed when someone tends to ~~hold~~ experience pauses in their breathing (apnoea) since in both the lips and skin can go blue. Children with PTHS may have episodes of ~~breath holding~~ apnoea or hyperbreathing just before a seizure, but the abnormal breathing is not itself part of the seizure.

The drugs most commonly prescribed to control seizures are valproic acid, levetiracetam, lamotrigine, and carbamazepine. We don't yet have enough data to say whether one drug is better than another.

Recordings of brain activity (electroencephalographic or EEG for short) in people with Pitt-Hopkins are usually abnormal, and the patterns will change over time.

If the EEG is normal doctors should be careful not to miss the possibility that there is no seizure, but a pause in breathing (apnoea). The EEG patterns are not usually so specific that they can show up a certain type of seizure.

As it is difficult to tell the difference between seizures and pauses in breath, doctors who are not sure should carry out an EEG and look at it while bearing this in mind. There is no need to make an EEG in everyone with PTHS.

Other neurological problems

Neurological problems relate to the brain, the nerves and the nervous system. They are not very common in people with PTHS. Seven of the 47 people with PTHS who attended the PTHS World Conference were shown to have a tremor (shake) that did not get worse over time.

The wide standing position and movement that is common to children and adults with PTHS may be linked to problems with the nervous system, but there has not been enough study into it.

There is a noticeable difference in muscle tone in people with PTHS: three-quarters have weakness of the muscles in their torso (truncal hypotonia); less than 10% have a high muscle tone (hypertonia). One-third have this high muscle tone in arms and legs. It has been suggested the difference in muscle tone is due to the autonomic nervous system being disrupted.

Sleep problems

Many parents say that their child sleeps extremely well, and sleep problems are seen in only a small number. Some parents mention that their child does not sleep through the night or has night terrors.

Melatonin, a natural hormone that controls sleep, had been used by 10 of the 51attendees who answered this question at the 2018 World Conference. In two it had worked well, in six it had no effect and in the remaining two the result was uncertain. Sleep has not been looked at in full detail yet and we need further studies.

Different brain scans (MRIs) have been done and smaller changes in the formation of the brain have been seen in some but in most the scans show normal results.

Almost invariably the results are not important in how a child with PTHS should be looked after. So it is suggested that an MRI is only needed when there are neurological signs and symptoms, such as repeated seizures. Nor is an MRI needed just because a child has a small head (microcephaly).

Recommendations

16/ EEG studies should only be carried out when there are clear seizures or when a doctor is unsure if someone with PTHS is showing seizures or pauses in breathing ~~breath holding~~.

17/ Seizures can be treated just the same as in the general population; there is no evidence that one specific drug works better than others.

18/ MRI brain scans need only be carried out if there are neurological signs and symptoms and a scan would provide useful information to guide further management.. A small head (microcephaly) alone does not mean a child should have an MRI.

SECTION 9: ORTHOPAEDICS

Muscles and bones

Children and adults with PTHS often have problems with their muscles and bones (musculoskeletal).

Their hands are quite small and slender and the fingers are often tapering. But this does not appear to cause major problems. The thumbs can be bowed less than usual in half of the children and rarely even not at all. Usually no therapy is needed.

Rarely someone with PTHS cannot move all his or her fingers in the normal way; then physical therapy in the first year of life might improve this.

There are often major problems with the feet: these are almost always slender and flat, can be turned outwards, and with a high arch (pes cavus). Overlapping toes are common.

Minor limb anomalies do not require therapy but the shape and function of the feet and ankles often require special

footwear, inserts, or devices known as orthotics. In selected cases, surgery may help, for example, flat foot reconstruction.

Curving of the spine to one side (scoliosis) has been reported in 18% of children with PTHS. It can develop during puberty but also in younger children. There is no study available on the results in larger groups on the management of scoliosis.

Our joint experience indicates that the way a doctor deals with the scoliosis should be the same as for the general population. Someone with a scoliosis should be followed regularly, as that is the best way to show if treatment is needed or not.

Very infrequently other orthopaedic problems occur such as forward bending of the upper part of the spine (kyphosis), chest bone running inward (pectus excavatum), and decreased mobility in a knee. Each can be treated as in anyone with this problem without PTHS.

Recommendations

19/ Flat feet and feet that are turned outwards often require special footwear, inserts, or orthotics. Surgical correction may be necessary if problems with walking remain.

20/ Individuals with PTHS should have their spine checked regularly from an early age.

21/ The way doctors need to deal with a curved spins (scoliosis) in individuals with PTHS can be the same as in the general population.

SECTION 10: PAEDIATRIC MEDICAL FOLLOW-UP

Checks and care in the early years

Walking

In the first year of life most children with PTHS have a low muscle tone and their development is delayed. Motor skills develop late: about one-third walk unaided between 3 to 5 years of age, and three-quarters between 6 to 10 years of age.

They walk typically with a wide-based, unsteady gait (ataxic gait). Some may walk only with help, and still others never learn to walk on their own. Some achieve independent mobility by using a wheelchair.

Speech

Speech is often very delayed, with many never speaking. Up to 55% of individuals speak single words before 10 years of age, and only a minority (less than 10%) use whole sentences.

Of 47 individuals who answered this question at the 2018 PTHS World Conference:

* 39 used 0 to 5 words

* two used 10 to 20 words and

* six were able to use short sentences.

Few children can dress themselves or use the toilet alone. One in five children will be toilet trained for urine between 11 and 15 years of age.

Size and growth

Growth in length and weight is usually normal at birth; under 10% of babies with PTHS are small at birth. After birth, height drops well below average in one-third of the children, and head circumference will be well below average in half of the children.

No major teeth anomalies have been reported and teething and the loss of milk teeth occur at a normal age. Increased spacing of teeth is common. It is prudent to have children with PTHS evaluated regularly (usually every 6 months) by a dentist as children with developmental problems are more likely to have unmet dental needs.

Digestive problems

Burping (28%), reflux (38%), and constipation (80%) are common in children. During feeding they may gag, choke, and not chew properly. Some refuse food or have very strict rituals during feeding. In general, however, many are described as excellent eaters.

Drooling is seen in 80%, usually more prominent in young children, and teeth grinding occurs in one third.

Infections and the immune system

Repeated infections of the airways (otitis media, tonsillitis, bronchitis) and kidney and bladder have been reported in one third, mainly in childhood.

An abnormality in the way the children and adults deal with infections (in medical terms: immunological disturbances) are reported only a few times and include low levels of several proteins needed to fight infections (in medical terms: low IgA, IgM, and IgG levels).

Of 49 affected individuals at the 2018 PTHS World Conference immunological testing was performed in seven, and abnormalities in levels of antibodies which help fight infections (immune-globulin levels) were found in three.

Children should have the usual vaccinations that are offered nationally. There are still many unanswered questions regarding infections in PTHS, and it seems wise for doctors to perform detailed immunological studies in everyone who experiences repeated infections.

It's unusual for a child to have abnormalities with their heart, lungs, kidneys, liver and intestines. Only children with symptoms should have ultrasounds of the heart and kidneys. In one third of boys the testicles have not descended. Infrequently girls have small or fused (glued together) labia majora, and a small womb. As far as we know now puberty develops at a normal age and pace.

The paediatrician, preferably one with experience in PTHS, should play a central role in the clinical care for children with PTHS. He or she should regularly check for health problems (surveillance), coordinate care from other health care professionals, and oversee the child's whole social support system.

Recommendations

22/ Children with PTHS should have regular check-ups for their teeth.

23/ Vaccinations should be given to every child with PTHS according to national guidelines.

24/ Ultrasounds of heart and kidneys should be done only in children showing signs or symptoms that would suggest there is an abnormality of the heart or kidneys.

25/ Every child with PTHS needs regular follow-up, preferably by a paediatrician familiar with PTHS.

SECTION 11: ADULT MEDICAL FOLLOW-UP

Checks and care for adults

Height and weight

About one-fifth of adults is just below the expected height. There are no reports of related hormonal (endocrine) issues such as shortage of growth hormone or abnormal functioning of the thyroid gland.

Some become somewhat overweight as time goes on, but excessive weight gain is not often a problem in most with PTHS. A quarter of adults have a slightly smaller than normal head (microcephaly). Adult facial characteristics do not change much from those in in infancy.

Digestive problems

Feeding problems are not common in adults with PTHS. Problems with drinking and swallowing solids is seen in about 10%. Constipation is very common and occurs in three-quarter of adults (LINK). Gastroesophageal reflux is present in one-third and usually responds well to anti-reflux medicine.

Flat feet (pes planus) and turned out feet (pes valgus) are seen in half of the adults. These should be checked, as orthopaedic shoes or other orthotic devices, physiotherapy, or other specific treatments may be needed. When an adult with PTHS has limited mobility, physiotherapy is required to prevent the mobility to become permanently affected (contractures).

Other, usually less important, problems include overriding toes, a curved spine (scoliosis), and limited thumb mobility.

Although frequent infections are not common, urinary tract infections can be missed or show up as unusual behaviour changes.

Adults with PTHS have widely spaced teeth. Many grind their teeth and drooling is seen often. A protruding jaw (prognathism) may develop and can cause problems with chewing. Advice from a speech therapist may be helpful. If there are unexplained behavioural changes, the teeth should be checked as they could be a cause of pain.

In about a third of those with PTHS genital differences are seen such as undescended testes (cryptorchidism), a small penis, and unusual labia. Adult males should be checked for undescended testes, as this may have been missed when

they were younger. This can be managed as in the general population.

It is hard to give an accurate idea of the life span of someone with PTHS as only few older people have been diagnosed, and most are still young adults. It is thought that they will have a typical life span. Three adults are known who have developed a form of cancer: two with Hodgkin lymphoma, and one with medulloblastoma; there is also a child with a rhabdomyosarcoma.

It is uncertain whether there is a relation between these types of cancer and Pitt-Hopkins, as this can well be explained by coincidence. We don't have information on diseases associated with older age, such as cardiovascular functioning, osteoporosis, and dementia in adults with PTHS.

Recommendations

26/ Special shoes or ankle foot devices (known as ankle foot orthoses or AFOs) should be looked at to improve the stability and mobility of those with PTHS.

27/ When there is a change of behaviour in someone with PTHS it could be caused by pain and there should be careful

physical exams for constipation, infections and dental problems.

28/ A speech therapist can advise on dealing with issues such as drooling and chewing.

29/ Every male with PTHS should be checked to see that both testes have come down into the scrotum. If they haven’t, the treatment should be the same as in the general population.

SECTION 12: CARE PLANNING

Planning lifelong care

Medical care

It is important that everyone with PTHS has lifelong care from a team of medical professionals, each with a different specialty. This holistic approach to healthcare helps avoid problems and improves their quality of life.

Regular follow-up by a paediatrician, neurologist, psychologist/psychiatrist, and speech therapist will have great benefit.

Children and adults need to have their development assessed to make sure they get all the medical services they need. They should be re-checked from time to time by a physician who is coordinating their care, or by a clinical geneticist who knows most up to date medical information about PTHS.

Information booklets designed to give guidance on syndrome-specific issues (intellectual and physical disabilities) and family support groups are helpful.

There are several factors that could influence the outcome (prognosis) for someone with PTHS. These include: their age when they were diagnosed, their degree of intellectual disability, whether they have epileptic seizures, how well they can communicate, verbally or non-verbally, and their access to multidisciplinary medical and social care.

Transition from child to adult care

Transition of care is an important aspect of the care of adolescents and young adults, due to the rapid changes involved in their physical growth, sexuality, environment, and development of independence depending on their skills.

Transition should be a purposeful and planned change, and the involvement of parents is an essential part of this process. The person with PTHS should be involved as much as possible, depending on their ability to participate.

There is no research information specifically about transition. However, general principles apply, using as starting point the needs of the individual with PTHS, and based on standard health care for adults with intellectual disability.

Identifying the health care needs of the person with PTHS and careful communication and coordination between paediatric and adult care providers are essential.

Sexuality and reproduction

The external and internal reproductive organs of people are often underdeveloped in people with PTHS. For example, in males, a small penis and undescended testes and, in females, labial fusions, and, rarely, no vagina, uterus or ovaries. No data are available on fertility in either males or females.

Someone with PTHS should receive sex education that is tailored to suit their level of emotional and cognitive functioning. National recommendations for the general population regarding contraceptive options should be followed, if possible adapted for persons with intellectual disability. In several countries there are special standards for this information for people with an intellectual disability.

If a female with PTHS is finding it difficult to deal with her periods, doctors should consider prescribing contraceptives to suppress menstruation. Females and males should have

the usual screening for cervical and breast cancer as well as prostate cancer.

Recommendations

30/ People with PTHS and their families require lifelong care, preferably provided by a multidisciplinary healthcare team. Adults should have as a minimum an annual health check carried out by their family doctor

31/ Preparations for transition of care from child to adult services should start early, even in puberty. Transition should include early and careful handing over of all information that is available on the child with PTHS, including medical information and information on behaviour.

32/ Information on sex and contraception should be offered to every adult with PTHS. If it is available, the special standards for this for individuals with intellectual disability should be used. If unavailable, the information for the general population can be used.

SECTION 13: COGNITION AND BEHAVIOUR

Learning and behaviour

Learning

The gene that causes Pitt-Hopkins is necessary for the development of the nervous system and it plays an important role in learning (cognition) and behaviour. Children and adults with PTHS often have problems with filtering the stimuli coming from outside their body and within.

If parents and caregivers manage to make the environment quieter (‘filtering’) the children and adults are no longer overloaded with information, will find it easier to get the relevant information and often have fewer behavioural problems as well.

It is difficult to identify suitable assessment tools for people with PTHS. However, everyone with PTHS in publications shows moderate to severe intellectual disability. In most reported people with PTHS their developmental ages range from 9 months to 3 years (and an average of 14-16 months).

It's been reported that some people have only a mild cognitive delay, but they had unusual changes in the gene and when assessed more carefully it is clear they do not have PTHS.

People with PTHS have mild to severe problems learning to roll, sit and walk, and often make repeated movements such as hand clapping and flapping, repeated hand to mouth movements, head shaking, head banging, body rocking, washing, finger crossing, and rubbing toes together.

They are delayed in learning to roll, sit and walk and also in self-care skills like feeding themselves. Very few learn to dress themselves or use the toilet on their own. It has been seen that many can help with dressing, like unzipping their coats.

Skills can continue to develop as they get older. But a very small number of older people lose this ability. Once someone is diagnosed with PTHS, they should have developmental assessments to work out the services and educational solutions they need to help with their development.

Language and communication

Children and adults with PTHS usually have problems with remembering words and developing language. Most never learn to speak. Just over a half will say single words before the age of 10, but many will have no speech at all their whole life. Everyone with PTHS should be assessed for the best communication options to them.

Speech therapy including access to augmentative and alternative communication (AAC) should be considered. Other areas to consider are special education services focusing on the development of life skills and help aimed at changing behaviour such as self-harming and anxiety.

Physiotherapy and occupational therapy are recommended for the development of motor coordination, with the goal that a child can carry out an intended movement like picking up a toy. When a child is being assessed for communication and language abilities all aspects including motor abilities should be taken into account.

Behaviour

Most children with PTHS are described as friendly and show loveable behaviours. Half are described as having a smiley appearance. But many will also pull hair, have temper tantrums, throwing their arms and legs out, and banging on

or throwing or kicking objects. Some also self-harm, such as pinching, pressing, or hitting themselves, and also have problems connecting with others.

Other behaviours are anxiety, distress, repetitive actions, and autism spectrum disorder (ASD). Problems in filtering and processing sensory input like bright lights puts a person with PTHS at risk of either being under- or over-stimulated and can lead to inappropriate behaviours, for example head shaking.

However, there is evidence that for some children their mood is improved by music. Children and adults with PTHS need a sensory processing assessment to help work out what to avoid or to introduce to prevent under- and/or overstimulation.

Anxiety and agitation

More than one-third of people with PTHS have anxious, agitated and/or aggressive behaviours. There could be several things contributing to this:

* the frustration of not being able to communicate

* pain that's gone unrecognised or other sensory or body issues

* changes in routine - this can lead to aggression and shouting

* the onset of puberty can increase these behaviours.

Repetitive behaviours

Most with PTHS studied show repeated movements such as flapping, twisting body movements or flicking hands or fingers. This can be seen in the way they hold objects like toys, which some will turn over in their hand, or being fascinated by certain objects.

These repeated behaviours may become stronger when they are anxious or when they are not able to get away from difficult situations like a room with loud music.

Autism spectrum disorder

It is common for children with PTHS to lack the skills they need to interact socially and communicate with others. This goes along with repeated behaviour patterns, such as hand clapping and flapping, head banging, body rocking, or finger movements. They are also likely to have fewer adaptive skills that allow them to adapt to different environments, to other people and to solve problems.

Often a person's lack of skills can't be explained by their degree of intellectual disability, and therefore it's important to carefully observe their behaviour and assess them for autism. If someone with PTHS gets a diagnosis of autism spectrum disorder, this can help parents or carers, for instance they can avoid over-stimulation and/or under-stimulation.

Medication for behaviour

When behaviour like self-harming persists, it can be very distressing and it needs to be treated. Health care professionals should first consider if physical, mental, and environmental issues are leading to the problematic behaviour. This should be done through careful assessments and looking for solutions that include changing the person's environment, such as softer lighting, and behavioural therapy.

If these solutions are not enough, the person with PTHS may benefit from medication. There is not much scientific proof that drugs that affect a person's mental state (psychotropic medication) is effective in children with PTHS, and there have been no controlled studies. Still, in a survey on medication during the PTHS World Conference, 28 families gave their experience on different types of medication and their effects and side effects.

Melatonin and/or gabapentin was used for sleep problems, methylphenidate and clonidine were used for irritability, agitation and hyperactivity, and lorazepam for agitation. Antipsychotic agents, pipamperon and promethazine, were used to help with challenging behaviour.

Doctors should carefully monitor the prescribing and use of these antipsychotic drugs because we don't have enough evidence of how effective they are and using them long-term may lead to significant harmful effects such as weight gain, high blood pressure and diabetes.

Overall, parents reported they were satisfied with medications their children had been prescribed and noted few significant side effects, but no single medication was found to be extraordinarily effective. In general, prescriptions should start at low doses and gradually give more or less medication, in a slow way, to find out what works best.

Doctors should monitor the person's health before starting and while giving medications and consider from time to time if stopping of continuing medication is useful. Doctors should make sure they ask the parents or carers how well the medicine is working.

Recommendations

33/ Everyone with PTHS should be assessed for their levels of cognition, social-emotional development, and communication.

34/ Most people with PTHS cannot speak. Every effort should be made to explore other methods of communication in both children and adults including augmented communication techniques.

35/ Someone with PTHS should get additional developmental and educational support to maximise their learning and educational potential, taking into account how well the children and adults can communicate.

36/ Special education strategies should focus on learning skills to enhance daily life skills and to modify anxious and/or self-harming behaviours.

37/ Assessing the sensory processing profile in children and adults with PTHS helps care, especially in preventing under- and/or over-stimulation.

38/ The first signs of anxiety, agitation or aggression may be difficult to recognise in someone with PTHS as they may have problems communicating. Health care professionals should carry out face-to-face assessments and observations in the person's own environment.

39/ Doctors should consider a separate diagnosis of autistic spectrum disorder in everyone with PTHS. If such diagnosis is made, specific interventions will be helpful.

40/ No specific medication is known to be generally effective in helping problematic behaviour of children or adults with PTHS, and doctors should follow prescribing practices as in the general population.

SUMMARY OF RECOMMENDATIONS

1/ The clinical diagnosis of PTHS is based on a combination of signs and symptoms described in these guidelines. The diagnosis is made by a score of 9 or higher. With a score between 6 and 8 including the facial features there is a possibility of PTHS and DNA (genetic) studies should be carried out to confirm.

2/ There is currently no set of criteria that indicates how severely someone is affected by PTHS. Health care professionals together with families need to develop a scoring system to measure this.

3/ Changes in the gene TCF4 can cause Pitt-Hopkins but can also cause other syndromes that are linked to cognitive problems. The latter group of children and adults should not be labelled as having PTHS.

4/ If a family has a child with PTHS and the diagnosis is confirmed by DNA studies, the chance that the same couple will have another child with PTHS is 2%.

5/ If a change in the TCF4 gene is found through DNA testing, it is not always easy to determine whether it is doing any harm or not. Especially in an individual who seems healthy, with no signs or symptoms of PTHS. Several checks need to be carried out: carefully checking the child; checking whether the same or similar syndrome occurs in the family; whether this particular change in the gene has been seen in anyone before; what the type of change is and precisely where within the gene the change has occurred.

6/ If a family has a child with PTHS, confirmed by DNA testing, health care professionals should discuss with parents the small chance of having another child with the syndrome, and discuss and offer prenatal testing.

7/ Prenatal testing for PTHS should not be offered to parents who don't already have a child with the syndrome, as in this case there are problems in interpreting the findings in a reliable way.

8/ Children and adults with PTHS often experience occasional or chronic constipation and should be monitored and assessed. This can be done by keeping a diary or by using a dedicated questionnaire.

9/ Treatment for constipation will follow the same treatment that would be given to anyone else. This might include some strategies to change behaviour.

10/ If someone with PTHS has problems with reflux, the treatment will not differ from any other person. Anti-reflux medications can sometimes help and should be prescribed in their maximum dosage.

11/ Doctors should explain to caregivers that spells of hyperbreathing, despite being disturbing to those who see it, are unlikely to be harmful.

12/ If breathing disturbances occur at night, sleep studies (polysomnography) should be considered in individuals with PTHS to exclude obstructive sleep apnoea.

13/ Every child with PTHS should have their eyesight checked on diagnosis and then regularly monitored.

14/ Hearing should be tested regularly in everyone with PTHS.

15/ Parents and carers should be aware of the various types of pain felt by those with PTHS; if in doubt specific questionnaires can be used to assess pain.

16/ EEG studies should only be carried out when there are clear seizures or when a doctor is unsure if someone with PTHS is showing seizures or pauses in breathing.

17/ Clinical seizures can be treated just the same as in the general population; there is no evidence that one specific drug works better than others.

18/ MRIs need only be carried out if there are neurological signs and symptoms that this would be useful. A small head(microcephaly) alone does not mean a child should have an MRI.

19/ Flat feet and feet that are turned outwards often require special footwear, inserts, or orthotics. Surgical correction may be necessary if problems with walking remain.

20/ Individuals with PTHS should have their spine checked regularly from an early age.

21/ The way doctors need to deal with a curved spins (scoliosis) in individuals with PTHS can be the same as in the general population.

22/ Children with PTHS should have regular check-ups for their teeth.

23/ Vaccinations should be given to every child with PTHS according to national guidelines.

24/ Ultrasounds of heart and kidneys should be done only in children showing signs or symptoms that would suggest there is an abnormality of the heart or kidneys.

25/ Every child with PTHS needs regular follow-up, preferably by a paediatrician familiar with PTHS.

26/ Special shoes or ankle foot devices (known as ankle foot orthoses or AFOs) should be looked at to improve the stability and mobility of those with PTHS.

27/ When there is a change of behaviour in someone with PTHS it could be caused by pain and there should be careful physical exams for constipation, infections and dental problems.

28/ A speech therapist can advise on dealing with issues such as drooling and chewing.

29/ Every male with PTHS should be checked to see that both testes have come down into the scrotum. If they haven't, the treatment should be the same as in the general population.

30/ People with PTHS and their families require lifelong care, preferably provided by a multidisciplinary healthcare team.

31/ Preparations for transition of care from child to adult services should start early, even in puberty. Transition should include early and careful handing over of all information that is available on the child with PTHS, including medical information and information on behaviour.

32/ Information on sex and contraception should be offered to every adult with PTHS. If it is available the special standards for this for individuals with intellectual disability should be used. If unavailable, the information for the general population can be used.

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38/ The first signs of anxiety, agitation or aggression may be difficult to recognise in someone with PTHS as they may have problems communicating. Health care professionals should carry out face-to-face assessments and observations in the person's own environment.

39/ Doctors should consider a separate diagnosis of autistic spectrum disorder in everyone with PTHS. If such diagnosis is made, specific interventions will be helpful.

40/ No specific medication is known to be generally effective in helping problematic behaviour of children or adults with

PTHS, and doctors should follow prescribing practices as in the general population.

SECTION 14: AREAS FOR FUTURE RESEARCH

We now have the first-ever clinical guidelines for children and adults with Pitt-Hopkins syndrome. The recommendations in these guidelines aim to improve a doctor's judgement of signs and symptoms in someone with PTHS and to better support carers and families to look after a child or adult with PTHS.

The recommendations on how to clinically diagnose PTHS allow this to be done by doctors anywhere, by looking at specific signs and symptoms, whether or not they have access to modern technology.

We realise that local circumstances such as differences in national health systems and medicine-related legal systems (medicolegal environments) may cause changes to the recommendations. Together with the various national PTHS support groups we aim to review the guidelines from time to time, to improve the recommendations.

As a result of the first PTHS World Conference, where these guidelines were created, we identified some major issues for further research:

- What is the natural history of Pitt-Hopkins syndrome in adults and older individuals?

- Breathing anomalies: what are the long-term consequences of breathing anomalies, both physically and cognitively? How prevalent is obstructive sleep apnoea? Can breathing anomalies be decreased if needed?

- Seizures: are seizures primary or consequences of breathing anomalies?

- Other symptoms caused by problems with the autonomic nervous system: what is the exact pathogenesis? If needed, can consequences (especially drooling and constipation) be influenced?

- Immune system: what are the consequences of PTHS variants causing Pitt-Hopkins syndrome for immunological functioning, including reactions to vaccination?

- Motor functioning: what is the pathogenesis of the foot position anomalies? Can physical therapy, drugs or surgical procedures effectively influence these anomalies?

- Communication: what are the communication abilities? Are there biomarkers that predict these abilities? Which approach best increases communicative abilities?

- Behaviour: what are the specific characteristics of autism or autism spectrum disorder in individuals with Pitt-Hopkins syndrome? In which way do factors such as autonomic dysregulations, food or other environmental factors influence behaviour?

Is it possible to address behavioural difficulties effectively through psychotherapy, contextual adjustments and/or drugs if needed?

- Genotype – phenotype correlations

- Molecular characteristics: can a functional study be developed that indicates with sufficient certainty causality of a Pitt-Hopkins phenotype? Can the mRNA derived from the wild type allele be stabilised in vitro? Does this lead to increase protein formation and if so, does this influence the consequences of haplotype insufficiency for TCF4 in animal models?

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