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Pitt-Hopkins Syndrome: Diagnosis, Clinical Presentation, and Management

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Abstract

Pitt–Hopkins syndrome (PTHS) is a rare neurodevelopmental disorder caused by pathogenic variants in the TCF4 gene. It is characterized by severe intellectual disability, absent or minimal speech, distinctive facial features, behavioral abnormalities, and episodic hyperventilation with apnea. The estimated prevalence ranges from 1 in 100,000 to 1 in 300,000 individuals. Clinical manifestations typically emerge in early childhood and include hypotonia, global developmental delay, epilepsy, gastrointestinal disturbances, and musculoskeletal abnormalities. Diagnosis is based on clinical features and confirmed by molecular genetic testing. Differential diagnoses include several neurodevelopmental syndromes with overlapping phenotypes. Management is supportive and multidisciplinary, focusing on rehabilitation therapies, communication strategies, and treatment of associated complications. Although no curative therapy exists, early intervention significantly improves outcomes and quality of life. Advances in genetic research are expected to further enhance understanding and management of this condition.

Keywords: Pitt–Hopkins syndrome, PTHS, TCF4 gene, neurodevelopmental disorder, intellectual disability, speech impairment, genetic diagnosis, hyperventilation, apnea.

Introduction

Pitt–Hopkins syndrome (PTHS) is a rare neurodevelopmental disorder characterized by distinctive morphological, cognitive, and behavioral features [1]. It is caused by abnormalities in the TCF4 gene, located on chromosome 18q21.2, and most cases de novo [2]. The syndrome was first described in 1978 by David Pitt and Ian Hopkins, who reported two unrelated patients presenting with intellectual disability, episodic hyperventilation, and shared facial characteristics [3]. In 2007, three independent research groups identified TCF4 as the causative gene by describing patients with deletions involving 18q21.2 [4]. Subsequent studies have refined the phenotypic spectrum of PTHS, which includes global developmental delay, usually severe intellectual disability with absent or limited speech, characteristic facial features, stereotypic behaviors, episodic hyperventilation and apnea, and frequent comorbidities involving gastrointestinal, orthopedic, ophthalmological, and ENT systems.

Prevalence

The prevalence of PTHS has not been definitively established. A prevalence of 1 in 225,000 to 1 in 300,000 was estimated considering the number of patients in the United Kingdom and the Netherlands [5]. It was estimated that the frequency of 18q21 deletions associated with PTHS is between 1/34,000 and 1/41,000 [6]. Based on cohorts of patients with intellectual disability (ID) whose genetic study was performed using non-targeted approaches (ID gene panels, exome, or genome) . It was found that PTHS was a relatively frequent cause of ID, estimating it at approximately 0.7% of moderate to severe ID, which suggests an overall prevalence of PTHS between 1/100,000 and 150,000. PTHS affects men and women equally and regardless of origin [7].

Circumstances of Discovery

In the Perinatal Period: During pregnancy, there are no signs that specifically suggest a diagnosis of PTHS. Conversely, the diagnosis may be made incidentally during chromosomal analysis on a DNA chip or high-throughput sequencing (exome or genome sequencing) prompted by one or more ultrasound findings, an abnormality in serum markers, etc. At birth, newborns may present with nonspecific signs such as hypotonia and/or feeding difficulties. More rarely, suggestive morphology may be noted, but most often the morphological signs become more evident with age [8].

In childhood and adolescence: During the first year of life, various signs may prompt a consultation, such as persistent hypotonia, psychomotor delay, feeding difficulties, and constipation. Epilepsy may begin early in some. Subsequently, the delay in psychomotor development is evident, and the children develop with intellectual disability (ID), most often severe. Walking is delayed, and language is absent or limited. Behavioral disturbances are common, including motor restlessness, stereotypies, and hyperventilation. Facial features are often suggestive. Epilepsy may be present, as well as other variable signs [1].

In adulthood: The diagnosis is sometimes made in adulthood in the absence of prior specialist consultation. Adults have severe intellectual disability with reduced autonomy. Behavioral signs are also present and sometimes exacerbated (restlessness, anxiety, stereotypies, hyperventilation). Morphological characteristics are more pronounced than in children. Adults exhibit the other signs described in this syndrome to varying degrees [1].

Diagnostic Confirmation

When PTHS is clinically suspected, it is essential to confirm the diagnosis by identifying the molecular abnormality of the TCF4 gene in the patient (using a blood sample). This will also allow for more precise genetic counseling [9].

Available genetic tests include:
targeted sequencing of the TCF4 gene, or high-throughput sequencing of a gene panel including TCF4, to detect intragenic variants or very small deletions.

exome or genome sequencing (to detect intragenic variants, and rearrangements using genome sequencing).

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Chromosomal microarray analysis can be used to identify large deletions that include TCF4 or several exons of the gene, while karyotyping helps detect translocations affecting 18q21.2.

Differential diagnoses

If genetic tests do not reveal abnormalities in the TCF4 gene, doctors should also consider other syndromes that may show symptoms like PTHS. Examples include Angelman syndrome , ATRX syndrome , Rett syndrome , Kleefstra syndrome , Mowat-Wilson syndrome and syndromes linked to the genes CDKL5 This list is not exhaustive, and other neurodevelopmental disorders may present similarly to PTHS [5,10].

Clinical Signs

Perinatal Period: Pregnancy is usually uneventful. During pregnancy, mild intrauterine growth restriction (IUGR) was seen in 23% of patients; however, only 8% of infants were born with low birth weight (T ≤ -2 SD). In the neonatal period, axial hypotonia was present in 75% of infants, persisting into the first year of life, sometimes associated with digestive problems (feeding difficulties, gastroesophageal reflux, constipation, vomiting) [11].

Neurodevelopmental Disorders: Delayed motor development is always present. Most patients acquire hand grasping, head control, and sitting, but with delay and at varying ages. Independent walking is achieved in approximately 75% of patients, always delayed, with an average onset between 5 and 7 years of age (ranging from 2 to 14 years), and is often unsteady and ataxic. Fine motor abilities are restricted. Reports of loss of hand function are uncommon [12].

Language and Communication: Patients with PTHS typically have no verbal language or language limited to a few words. 55% of individuals express only one word before the age of 10, and most have little or no expressive language throughout their lives. Even among those who were able, their communicative intent was often unclear. Qualitative difficulties, including both immediate and delayed echolalia, were also noted [5].

Cognitive Impairment, Autonomy: Severe intellectual disability (more rarely moderate) is present in most individuals with PTHS, and there is little detailed information regarding cognitive abilities. Patients are difficult to assess with standard tests due to their motor difficulties and near absence of language. To assess individuals with PTHS, it is necessary to adapt communication methods to understand their true potential [13]. Therefore, preliminary work is necessary to determine the most suitable communication method for a given individual. By using an augmentative and alternative communication (AAC) tool with a patient, you can evaluate their ability to understand spoken language, assess their vocabulary skills, and gain insight into their cognitive reasoning. A range of typical non-verbal tasks are achievable, alongside modified verbal exercises and established phrases.

Morphological Signs: A distinctive facial morphology remains the primary diagnostic criterion. This condition is marked by sunken eyeballs, a noticeable nasal root, a wide nasal bridge, a broad and hooked tip of the nose, a large mouth, an outward-turned lower lip, an upper lip shaped like a gendarme hat with a pronounced Cupid's bow, and prominent ears featuring a thick, overly conspicuous, horizontally oriented helix. Most patients present with a typical facial morphology, either from early childhood or which becomes typical with age. Hand characteristics include a single transverse palmar crease (63%), persistence of the fetal pads of the fingertips (61%), long/thin fingers (65%), camptodactyly, and reduced thumb mobility that can progress to thumb ankylosis (13%). Foot abnormalities are frequently observed, with flat feet occurring, and overlapping toes present . This report details five patients who exhibit brachydactyly affecting one or more of their three smallest toes [15].

Height and weight growth and head circumference: At birth, growth parameters are normal for most patients. However, moderate postnatal short stature (slightly less than -2 SD) is present in 18% of adults. So far, no hormonal causes like growth hormone deficiency or hypothyroidism have been identified. Moderate microcephaly, defined as between -2 and -3 standard deviations, occurs in about 50% of cases, while postnatal fractures are seen in 25% of patients. Overweight or obesity are rare. It is advisable to track high and weight growth, following the usual practices for the general population [5].

Neurological Signs

During the first year of a child's life, hypotonia is observed in about 75% of cases; it may appear as early as the newborn stage and frequently remains throughout this period. Peripheral hypertonia has been noted in one-third of patients, and axial hypertonia is rare [16]. Patients with PTHS often exhibit a gait that is unstable and may occasionally display signs of ataxia [17].

Imaging: Brain MRI scans in patients with PTHS often show a range of non-specific abnormalities. Approximately 40% show alterations in the corpus callosum, which may include shortening, thinning, or complete absence. Approximately 30% of cases show enlarged ventricles, while posterior fossa abnormalities are also seen in about 30%. Posterior fossa abnormalities are variable [18]:

cerebellar atrophy, vermian hypoplasia, thin brainstem, enlarged cisterna magna,
retrocerebellar cysts, verticalized tentorium cerebelli, and hyperintensity of the dentate nuclei.
Additional, less common findings include underdeveloped hippocampi, increased signal intensity in the temporal lobe, underdevelopment of the frontal lobe, or enlargement of the caudate nuclei. Brain imaging is recommended only if there are neurological symptoms or signs, as it has no impact on treatment decisions once the diagnosis is confirmed.

Epilepsy: Epilepsy occurs in 37% to 50% of individuals with PTHS, and its features such as seizure type and severity can vary widely. Reported seizures are varied, including absence seizures, generalized tonic-clonic seizures, and infantile spasms [19]. The age of onset is variable and can range from the first year of life to young adulthood. For most patients, antiepileptic medications effectively manage seizures. Individuals with respiratory stereotypies might frequently stop breathing and develop cyanosis, which could be mistaken for epilepsy and create difficulties in accurate diagnosis and treatment. Conversely, epileptic seizures can sometimes present as respiratory stereotypies and delay diagnosis. More rarely, episodes of respiratory distress can trigger a seizure [20].

If there is uncertainty, a video-assisted EEG may be provided to support the determination of suitable treatment. Interictal EEG tracings in individuals with PTHS can be normal or abnormal and may change over time, but most often the results are nonspecific. It is recommended performing an EEG combined with video at the slightest suspicion in individuals with PTHS, particularly due to the difficulty in distinguishing epileptic seizures from apneas [21].

Valproic acid, levetiracetam, lamotrigine, and carbamazepine are the most used antiepileptic drugs, but there is insufficient data to indicate whether one drug is more effective than another. The selection

of antiepileptic therapy will depend on the seizure type and underlying abnormalities and will involve guidance from a specialist neurologist or pediatric neurologist. When an episode continues for more than five minutes or occurs frequently, doctors may prescribe oral midazolam or rectal diazepam to parents.

Respiratory abnormalities

Disruption of respiratory regulation is one of the cardinal criteria of PTHS and is linked to general dysautonomia, which can also manifest as dilated pupils with slow reactivity to light, unstable body temperature, vasomotor disturbances of the extremities, constipation, or urinary retention [5]. Hyperventilation is present in more than half of patients, occurring spontaneously or triggered by emotional situations (stress, joy). The age of onset varies among patients. In the literature, the youngest patient is 9 months old and the oldest is 16 years old. In certain cases, patients may experience hyperventilation for several years before symptoms diminish or become less frequent. Around half of patients experience apnea episodes, which can happen on their own, separate from hyperventilation, and may also occur during sleep. The typical respiratory pattern consists of rapid breathing, both regular and irregular, followed by a cessation of breathing.

The duration is usually 2 to 5 minutes. The occurrence of episodes demonstrates considerable variability, with frequencies ranging from multiple times per hour to just a few instances annually. Following a period of apnea, cyanosis may occur and, in rare cases, it can lead to loss of consciousness. Oxygen saturation may decrease during a period of abnormal breathing. No deaths related to an episode of hyperventilation or apnea have ever been reported (22). Respiratory abnormalities may precede or follow the onset of a seizure, but it is rare for an episode of hyperventilation to cause a seizure [22,23]. Clubbing of the fingers often appears in people with PTHS a few years after respiratory issues begin [24]. Respiratory problems can be alarming, but most patients do not appear bothered and remain comfortable. In some cases, these problems cause anxiety in patients; others stop their activities, some sit down to prevent a fall, and in a minority of cases, loss of consciousness may occur. In a small number of patients, irregular breathing at night and catathrenia have been reported. Most often, no treatment is necessary for hyperventilation and apnea, as they do not cause major consequences. Some studies have analyzed the effect of certain drug classes on respiratory disorders. Studies have shown that daily acetazolamide treatment leads to a decrease in the frequency and duration of hyperventilation and apnea episodes and an improvement in oxygen saturation in individuals with post-hyperventilation syndrome (PHTS) [25,26]. Nonetheless, this treatment can cause significant hypokalemia, so caution is advised and it is not considered a first-line option.

Behavioral Disorders

Stereotypies: Stereotyped movements are present in almost all PTHS patients, including arm flapping , hand biting , finger movements , wrist movements , hand-washing gestures , and head movements , particularly rotation. Repetitive motions of the lower limbs have occasionally been observed, often taking the form of continuous flexing and extending movements. Typical movements like these frequently become more noticeable when a person experiences strong emotions, whether those feelings are positive such as joy or excitement or negative, like anxiety or stress. Engaging repeatedly with toys or objects, exhibiting intense interest in particular items, and consistently performing certain actions have also been observed [27].

Anxiety and Agitation: Beyond stereotypical behaviors, individuals with PTHS often display a typically cheerful expression and may also exhibit spontaneous laughter without apparent cause. Anxiety is common among these patients . Initially described as having a cheerful demeanor, patients with PTHS more often appear anxious but with a smiling demeanor [28]. Agitation is frequently mentioned , often characterized by calm but incessant movements, possibly related to anxiety.

Autistic Disorders: Difficulties with social interaction and communication are frequently observed in patients with PTHS. Limited data exists regarding precise assessments of autism spectrum disorder, although various studies have reported on language development and emphasized the similarity to patients with ASD and the behavioral patterns of repetitive behaviors and stereotypies [29]. It was described as more severe communication and interaction difficulties in individuals with PTSD compared to those with Angelman syndrome, where the cognitive phenotype is similar, with a usual absence of expressive language [30]. Therefore, careful behavioral observations and autism-specific social functioning assessments are warranted to determine whether deficits in social communication skills and behavioral patterns are greater than expected for the individual's level of cognitive development.

Sleep Disorders: Sleep disturbances are reported in a minority of individuals, with many parents stating that their child sleeps well. More rarely, some have been described as experiencing sleep difficulties or night terrors. Nighttime problems may also have other causes, such as obstructive sleep apnea syndrome or seizures. In a small number of patients, irregular breathing at night and catathrenia (inspiratory apnea and expiratory moaning during sleep) were reported [31]. Some individuals were treated with melatonin or gabapentin

Digestive Signs

Gastrointestinal problems are common in children and adults with PTHS and include constipation, gastroesophageal reflux , and belching [32].

Feeding difficulties: Feeding difficulties are sometimes encountered in early childhood (poor food intake, gastroesophageal reflux), but overall, individuals with PTHS have a normal appetite. Food refusal and/or very strict mealtime rituals are rare. If feeding difficulties are accompanied by oral motor disorders, speech therapy should be considered to work on orofacial motor skills and oral stimulation. It is rarely necessary to use feeding aids such as nasogastric tubes or gastrostomy tubes [33].

Constipation: Constipation is common and severe, generally present throughout life. Hirschsprung's disease, initially described in PTHS syndrome, is ultimately rare, having been reported in only one individual [34]. The management of constipation is like that of the general population. Medication (mild laxatives) is often prescribed if lifestyle modifications (a diet with sufficient fiber, adequate hydration, physical activity, and/or regular standing) are insufficient to regulate constipation.

Gastroesophageal Reflux Disease (GERD): Management of GERD is like that of the general population. Proton pump inhibitors (PPIs) are the first-line treatment. People with PTHS respond well to medication administered at sufficient doses. It is particularly important to consider this option in cases of unusual behavioral changes and/or the onset of sleep disturbances in a patient who did not previously experience these symptoms [35].

Other Digestive Problems: Hypersalivation and/or salivary incontinence are common , especially young children. Speech therapy

can be helpful, particularly if salivary incontinence is related to oral hypotonia and swallowing difficulties [36]. If salivary incontinence becomes problematic (for example, due to skin irritation), medical treatments may be prescribed. Scopolamine patches, placed behind the ear, reduce saliva production but can have significant side effects: drowsiness, constipation, urinary retention, thickening of bronchial secretions, etc.

Sensory Disorders:

Ophthalmological Signs: Refractive errors are common and consist of myopia in half of those affected and hyperopia less often. Myopia is generally severe (greater than -6 diopters), and children usually require glasses before the age of 2. Strabismus has been reported in approximately 50% of cases. Less frequently, nystagmus, lacrimal duct obstruction, optic nerve hypoplasia, macular degeneration, and dilated pupils with a slow response to light have been noted [37]. Visual impairments are therefore common, and once a clinical diagnosis of PTHS is suspected, the child or adult should be referred for an ophthalmological consultation, with regular follow-up thereafter. The management and treatment of visual problems are the same as for the general population. In cases of strabismus, preventing amblyopia is essential, and patching, glasses, or surgery may be considered to prevent or correct the strabismus.

Hearing and ENT (Ear, Nose, and Throat): Hearing loss (usually conductive) is present in PTHS. It is recommended to have a hearing assessment at the time of diagnosis and then regularly thereafter. Management will be the same as for the general population. Hearing aids should be offered if necessary to avoid further disability [38].

Pain: It is difficult to recognize and manage pain in people with PTHS due to their limited ability to communicate verbally and their sometimes-different ways of reacting to pain. Some parents' anecdotal evidence suggests that children with PTHS are more bothered and more sensitive to minor painful stimuli, such as a small scratch or cut, than to major painful events such as post-surgical pain [39]. Tools have been developed to aid in the recognition and assessment of pain in children with intellectual disabilities (ID), and their use in children with post-traumatic stress disorder (PTSD) is recommended [40].

Other sensory signs: It is reported that most individuals with PTSD enjoy music, and parents have mentioned using music to improve their child's mood [5]. De Winter et al. reported hypersensitivity to odors in 4 out of 101 patients, and anosmia in two. There is no detailed assessment of the sense of smell in individuals with PTSD in the literature. Individuals with PTSD may experience difficulties processing sensory information perceived by the brain (reception, filtering, and interpretation) [41]. Difficult to understand and anticipate, these sensory disturbances vary depending on the time of day, fatigue, or stress levels. An assessment may be recommended to establish a sensory profile, which will help identify appropriate methods and accommodations. Occupational therapists or psychomotor therapists are specifically trained in sensory integration.

Orthopedic Signs

Musculoskeletal problems are common in people with PTHS and particularly affect the feet and spine [42].

Foot Abnormalities: The feet are most often narrow and flat, and a valgus deformity is often present. More rarely, some patients have high arches. Overlapping toes are also described. Most individuals require orthopedic shoes, insoles, and/or orthotics to facilitate walking and prevent further deformity or contractures. An assessment of whether these devices are necessary requires consultation with a physical medicine and rehabilitation specialist and/or an orthopedist. In some cases where symptomatic treatments fail, surgery may be indicated and beneficial, for example, surgical treatment of flat feet [43].

Spinal Anomalies: Scoliosis is reported and can occur during puberty but also at an earlier age. The literature does not describe any specific characteristics of scoliosis and its treatment. Currently, it is recommended to manage scoliosis as well as the general population, with follow-up in Physical Medicine and Rehabilitation and/or orthopedics as needed [44].

Other Orthopedic Signs: Thumb mobility may be reduced. A less pronounced or absent distal thumb flexion crease is present [45]. Thumb ankylosis has been reported but is infrequent. Camptodactyly has been reported in five individuals with a microdeletion. Joint hypermobility has been described.

Urogenital Signs

Genital abnormalities have been reported, with hypoplastic penis in boys and abnormal labia (fusion or hypoplasia) in girls. Cryptorchidism is observed in 33% of boys and should be surgically corrected if it persists. Rarely have absence of the vagina, uterus, and ovaries have been reported (1). Most individuals reach puberty at a typical age and pace. Little data is available on male or female fertility; however, it was described a patient with typical PTHS who gave birth to a boy who was also affected [46]. Sex education should be offered according to the individual's level of emotional and cognitive functioning. Contraceptive options for women can be considered, particularly when the woman is receiving care in a group setting. Menstrual suppression using contraceptives may also be considered for some adolescent girls and women who experience significant difficulties managing their periods. From a urological standpoint, there are no common abnormalities in PTHS. However, episodes of bladder distension in adulthood have sometimes been reported and should be investigated in cases of discomfort or changes in behavior.

Dental Signs

No dental abnormalities are observed other than increased interdental spacing. The age of dentition and the loss of deciduous teeth are normal. Bruxism is described in some patients. Regular follow-up should be implemented with the same methods and treatments as for the general population.

Other clinical signs

Visceral malformations are rarely observed, but as a matter of course, an assessment for cardiac and abdominal-renal malformations should be performed at the time of diagnosis. Overall, general health is relatively well preserved, and life expectancy appears normal. There does not appear to be a higher incidence of cardiovascular disease or cancer than in the general population. There is no specific treatment for Pitt-Hopkins syndrome, and therefore, the variability of the clinical presentation necessitates personalized monitoring and management, depending on the symptoms. Pediatric and adult follow-up is required, as for the general population, for growth monitoring, vaccinations, management of intercurrent illnesses, screenings.

Conclusion

Pitt-Hopkins syndrome is a rare but increasingly recognized genetic disorder with a distinctive combination of developmental, behavioral, and respiratory features. Although there is no curative treatment, early diagnosis and a comprehensive multidisciplinary approach can significantly improve quality of life and functional outcomes. Advances in genetic testing have enhanced diagnostic accuracy, while sup-

portive therapies particularly in communication and motor development play a crucial role in patient care. Ongoing research is essential to better understand the condition and develop targeted therapies in the future.

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