Diagnosis and Management in Pitt-Hopkins Syndrome: First International Consensus Statement


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Abstract

Pitt-Hopkins syndrome (PTHS) is a neurodevelopmental disorder characterized by intellectual disability, specific facial features, and marked autonomic nervous system dysfunction, especially with disturbances of regulating respiration and intestinal mobility. It is caused by variants in the transcription factor TCF4. Heterogeneity in the clinical and molecular diagnostic criteria and care practices have prompted a group of international experts to establish guidelines for diagnostics and care. We collaborated with national support groups and the participants of an international PTHS conference to achieve this first international consensus statement.

Introduction

Pitt-Hopkins syndrome (PTHS) (MIM #610954) is caused by deletions of or variants in the TCF4 gene located at 18q21.2 and encoding Transcription Factor 4 (MIM #602272). Prevalence is estimated as one in 225,000-300,000. A group of experts recognized that there was variability in practices in various countries with respect to diagnostics and management of individuals with PTHS and formed an International PTHS Consensus Group.

Diagnostic criteria

Currently, aberrations in only a single gene (TCF4) is known to cause PTHS: heterozygous loss-of-function variants or hemizygosity leading to haploinsufficiency of TCF4. Clinical diagnostic criteria for PTHS were defined by cardinal (highly specific) features and supportive features. With a score of ≥ 9 the diagnosis of PTHS can be clinically confirmed (although molecular confirmation remains desirable). This score can only be reached if at least two of the three cardinal features are present. A score of 6-8 needs further confirmation by molecular testing (Table 1).

Table 1. Clinical Diagnostic Criteria for Pitt-Hopkins Syndrome.

Cardinal	Supportive
1. Face (at least 3 of 7) a. Narrow forehead b. Thin lateral eyebrows c. Wide nasal bridge/ridge/tip d. Flared nasal alae e. Full cheeks/ prominent midface f. Wide mouth/full lips/cupid bow upper lip g. Thickened/overfolded helices **4 points**	1. Myopia 2. Constipation 3. Hand (slender fingers and/ or abnormal palmar creases) 4. Unstable gait **each 1 point**
2. Severe intellectual disability with absent or limited (<5 words) speech **2 points**	
3. Breathing regulation anomalies (intermittent hyperventilation and/or apnea) **2 points**	

Overlapping phenotypes

Pitt-Hopkins-like syndromes I and II are epileptic encephalopathies caused by autosomal recessive aberrations in CNTNAP2 or NRXN1 with clinical overlap to PTHS in some patients. Other entities with overlapping phenotypes are Angelman syndrome, X-linked recessive variants in ATRX (Alpha-Thalassemia/mental retardation syndrome), or are associated with variants in MECP2 (Rett syndrome), CDKL5 (Epileptic encephalopathy, early infantile), FOXG1 (Rett syndrome, congenital variant), EHMT1 (Kleefstra syndrome), MEF2C, ZEB2 (Mowat-Wilson syndrome) or RHOBTB2 (developmental and epileptic encephalopathy).

Pattern of inheritance

Variants in TCF4 usually occur de novo. Recurrence risk for sibs of affected individuals is therefore generally low. However, germline or low-grade parental mosaicism has been reported.[1,2] To our knowledge, no individual with typical PTHS has reproduced. Several TCF4 variants with milder phenotypes, not fulfilling the diagnostic criteria of PTHS, have been segregating in an autosomal dominant pattern. In these families, recurrence risk is 50%.

Molecular genetic testing

The first tier-test is evaluation of a chromosomal imbalance using chromosomal microarray analysis, as chromosomal imbalances represent a significant proportion of PTHS-causing aberrations. If the clinical phenotype is compatible also with Angelman syndrome, we recommend methylation analysis, either subsequently or in parallel (e.g. MLPA or PCR) of the Angelman syndrome locus.

If Next-Generation-Sequencing (NGS) testing is available, the most effective second tier test is exome sequencing or panel sequencing for genes associated with intellectual disability, as there are several clinical entities that resemble PTHS that can be assessed in this single analysis. If NGS availability is limited or absent, or if the clinical suspicion of PTHS is very strong, targeted analysis by Sanger sequencing of TCF4 and deletion/duplication testing by MLPA is the alternative second tier. Classical karyotyping to check for a balanced translocation should be considered if studies yield negative results and clinical suspicion is high.

Pediatric Medical Follow-Up

Growth

Growth parameters at birth are usually within the normal range, intrauterine growth retardation has been observed in 8% of newborns. Postnatal height drops below -2 SD in about 30% of individuals, as does head circumference in 25%, resulting in an OFC between -3 and -2 SD in approximately half of the individuals.[2,3,4]

Development

Most affected children present in the first year of life with hypotonia and developmental delay. Motor skills are delayed with approximately 30% of children walking unaided at 3-5 years of age, and 75% at 6-10 years of age.[3] Those who walk independently often have a wide-based, unsteady and somewhat ataxic gait. Some individuals may walk only with assistance, while others do not acquire independent walking skills.[3] Of those individuals unable to walk alone, some achieve independent mobility by using a manual wheelchair, including navigating through doors. Speech is typically significantly delayed, with many individuals remaining non-verbal. Up to 55% of individuals speak single words before 10 years of age, with only a minority using whole sentences (<10%). Few individuals develop dressing or toileting skills, with up to 20% of individuals being toilet trained for urine between 11 and 15 years of age.[3]

Cognition and behavior

Individuals with PTHS have moderate to severe intellectual disability and often engage in stereotypic and repetitive 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.[3,5,6] Most children with PTHS are described as amiable and exhibit lovable behaviors, but many also engage in hair pulling, temper tantrums, inappropriate laughing, hyperextending limbs, and throwing, banging on, or kicking objects.[3,5,7] A 'smiling appearance' was reported in 51%.[3]

Self-injurious behaviors such as pinching, pressing, and hitting oneself are also observed along with high levels of self-absorption and difficulties engaging socially.[3,5] The behavioral phenotype is further characterized by anxiety, agitation, repetitive behaviors, and autism spectrum disorder.[5,7] Difficulties in filtering and processing sensory input increase the risk of under- or overstimulation and may lead to maladaptive behaviors.

Epilepsy

The prevalence of epilepsy has been reported as 37-50%, with a variation in seizure types and severity.[3] The onset of seizures may be as early as the first year of life.[1]
Sleep disturbances are reported in a minority of affected individuals, with many parents explicitly mentioning that their child sleeps excellently, and others mentioning difficulties in sleeping through the night and night terrors.[3]

Respiration disturbances

Disturbed regulation of respiration (rapid breathing, both regular and irregular, and by apnea, either following one another or occurring indepently) is one of the cardinal

Male with PTHS
at 1 years of age

Male with PTHS
at 3 years of age

Male with PTHS
at 16 years of age

Male with PTHS
at 25 years of age

Male with PTHS
at 8 years of age

Male with PTHS
at 21 years of age

Female with PTHS
at 32 years of age

features of PTHS. It is most likely part of the general dysautonomia that occurs in PTHS and which might also manifest as dilated pupils with sluggish response to light, instability of temperature, decreased distal circulation, constipation, or urinary retention.[3] The age of onset of hyperbreathing is variable (mean age of 6.1 years, 90% in people > 15 years of age).

Gastroenterology

Feeding issues generally resolve with age. Eructation (burping) (29%), reflux (38%) and constipation (80%) are common in children. Behaviors during feeding include gagging, choking, and not chewing properly. Some individuals refuse food, or have very strict rituals during feeding. However, in general, many individuals are described as excellent eaters.[3] A cleft palate occurs only rarely, a highly arched palate is common. Drooling is seen in 80% of individuals, usually more prominent in young children, and teeth grinding occurs (29%).[3]

Immunology

Recurrent respiratory infections (otitis media, tonsillitis, bronchitis) and urinary tract infections have been reported in one-third of affected individuals, occurring mainly in the pediatric period.[3] Immunological disturbances are sporadically reported and include low IgA, IgM and IgG levels.[3]

Vision

Visual impairments are common. Myopia is typically severe (>6Dpt) and children usually need glasses before two years of age.

Malformations

Visceral malformations are uncommon (2%), and ultra-sounds of the heart and kidneys are only indicated in case of suggestive symptoms.[3] Urogenital problems consist of cryptorchidism (33%), fusion or underdevelopment of labia majora, and underdeveloped internal genitalia.[3] Present (limited) data indicate that puberty develops at a typical age and pace.

Scoliosis

Scoliosis has been reported in 18% of individuals and can arise during puberty but also at younger ages. There is a marked variability in tone, most individuals (76%) had a truncal hypotonia though hypertonia was found in 7%, and 34% had a peripheral hypertonia.[3,4]

Pain

There is anecdotal evidence that children with PTHS are more bothered by and sensitive to minor painful stimuli such as a small scrape or cut, while in contrast they seem less bothered by major painful events such as post-surgical pain.

Adult Medical Follow-Up

Gestalt

Adult height is mildly below the expected target height in 18% of patients.[3] There is no report of related endocrine issues (growth hormone deficits; thyroid dysfunction) to explain this. Some individuals tend to become somewhat overweight with time, but overall, excessive weight gain is not a major problem in PTHS. Mild microcephaly was reported in 23.5% of adults.[4] Facial characteristics in adults are similar to those in children, as the change in facial gestalt is limited after infancy.

Epilepsy

The prevalence of epilepsy has been reported as 37-50%, with a variation in seizure types and severity.[3] Seizures may start at early adulthood.[1]

Gastroenterology

Feeding problems are uncommon in adults with PTHS: problems with drinking and swallowing solid foods were each reported in 8% of individuals.[3] Constipation is common and occurs in 70% of adult individuals.[3] Gastroesophageal reflux is present in one-third of adults and typically responds well to adequate anti-reflux medication.[3]

Neuromotor

Frequent musculoskeletal signs in adults are pes planus or valgus (~50%), overriding toes (28%), scoliosis (25%), and limited thumb mobility (~25%).[3]

Senses

Visual impairments are common. Refractive errors are present in 64% of individuals, consisting of myopia in 52% and hypermetropia in 22%. Myopia is typically severe (>6 Dpt). Strabismus was reported in 44% of individuals. Hearing loss is found in 10% of individuals with PTHS and is typically conductive.[3]

Teeth

Teeth remain widely spaced in adults with PTHS, bruxism occurs, and drooling is frequent. Prognathism may develop and lead to mastication difficulties.

Malformations

Genital anomalies (cryptorchidism, small penis, abnormal clitoris or labia) are described in 30% of individuals.

Lifespan

Thirty-six adults with molecularly confirmed PTHS have been reported.[3,9] Most of them are young adults (<35 years). According to published and unpublished data, expected life span seems typical.[10] In a questionnaire study of 101 individuals, the oldest participant was 32 years, with an excellent physical condition.[3]

Diagnosis and Management recommendations

For recommendations, major research issues for individuals with PTHS and complete list of references, please see the full text of the article: Zollino M, Zweier C, Van Balkom ID, Sweetser DA, Alaimo J, Bijlsma EK, et al. Diagnosis and management in Pitt-Hopkins syndrome: First international consensus statement. Clin Genet. 2019;95:462-78. doi: 10.1111/cge.13506.

PTHS center of expertise

Two of the authors, Leonie Menke and Sylvia Huisman, work at the PTHS pediatric and adult clinic, respectively, housed at the Amsterdam Expertise Center for Orphan Disorders (AECO) at Amsterdam UMC. For questions please contact: PittHopkins@amsterdamumc.nl or referrals to l.a.menke@amsterdamumc.nl or s.a.huisman@amsterdamumc.nl or via ZorgDomein.

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Legends

Table 1. Clinical Diagnostic Criteria for Pitt-Hopkins Syndrome. Clinical diagnosis of Pitt-Hopkins syndrome: **Score ≥ 9.** Molecular confirmation indicated; Possible clinical diagnosis of Pitt-Hopkins syndrome: Presence of facial characteristics + additional criteria, either cardinal or supportive, totaling a **score of 6-8**. This score warrants TCF4 molecular analysis; Insufficient clues for the presence of Pitt-Hopkins syndrome: **Score <6**. No further studies specifically for Pitt-Hopkins syndrome indicated. Further studies for other etiologies indicated.