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CASE REPORT

Pitt-Hopkins Syndrome: Report of the first case in the Dominican Republic

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Abstract

Pitt-Hopkins syndrome (PTHS) is a rare genetic disorder characterized by a molecular variant in the *TCF4* gene involved in neuronal differentiation during embryonic development. Patients with PTHS present with syndromic facies, psychomotor retardation and intellectual disability. In addition, they may present with early-onset myopia, seizures, constipation, and episodes of hyperventilation and apnea. Some cases also meet criteria for autism spectrum disorder. In this article, we review the current literature on Pitt-Hopkins syndrome and present the first molecularly diagnosed case in the Dominican Republic. The patient in question exhibits typical facial features and a pattern of developmental delay consistent with PTHS. To date, no molecularly confirmed case of PTHS has been reported in the Dominican Republic, which makes this case an important contribution to scientific knowledge in the country.

INTRODUCTION

Pitt Hopkins syndrome (PTHS) is a very rare condition and so far approximately 500 patients have been reported worldwide, of which not all are genetically confirmed. Usually, people with variants affecting exons 1 to 5 in the *TCF4* gene associate mild intellectual disability (ID). Exons 5 to 8 of this same gene have been associated with moderate to severe ID and patients may sporadically present with features of PTHS. Variants starting from exon 9 to exon 20 are associated with a typical PTHS1 phenotype.

Pitt-Hopkins syndrome (PTHS) is characterized by significant developmental delays with moderate to severe intellectual disability and behavioral differences, characteristic facial features and episodic hyperventilation and/or difficulty breathing while awake. Speech is significantly delayed and most individuals do not speak with receptive language. Other common findings include autism spectrum disorder symptoms, sleep disturbances, stereotypic hand movements, seizures, constipation, and severe myopia [2].

Patients with PTHS are characterized not only by specific physical and genetic manifestations, but also by specific behavioral and cognitive features. The study of behavior and cognition can improve diagnosis and prognosis, allows the recognition of comorbidities and contributes to the appropriate counseling of families [3]. Early treatment of strabismus and myopia positively influences motor development and should be included in rehabilitation programs for patients with PTHS [4].

Once Pitt-Hopkins syndrome is clinically suspected, the diagnosis is confirmed by molecular genetic testing of the *TCF4* gene [5]. The identification of rare copy number variants together with genome-wide association studies have provided important information on genetic risk factors for schizophrenia.

Recently, a meta-analysis of several genome-wide association studies found, in addition to several other markers, a single nucleotide polymorphism in intron 4 of the *TCF4* gene to be associated with schizophrenia. *TCF4* encodes a basic helix-loop-helix transcription factor that interacts with other

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transcription factors to activate or repress gene expression. Therefore, variants in the *TCF4* gene may be associated with a variety of neuropsychiatric phenotypes, including schizophrenia.

Recessive forms of Pitt-Hopkins syndrome are caused by mutations in *NRXN1 and CNTNAP2*. Interestingly, *NRXN1* deletions have been reported in schizophrenia, whereas *CNTNAP2* variants are associated with several neuropsychiatric phenotypes. The data suggest that *TCF4, NRXN1 and CNTNAP2* may participate in a biological pathway that is altered in patients with schizophrenia and other neuropsychiatric disorders [6].

METHODOLOGY

The present case study describes the clinical and genetic evaluation of a 4-year-old girl, weighing 14.5 kg, of Hispanic origin and Dominican nationality, daughter of a mother with obstetric history of G4, A2, P2. The patient has a confirmed diagnosis of Pitt Hopkins syndrome (PTHS) through a next generation sequencing genetic test, specifically with a panel of genes associated with epilepsy ordered by the Medical Genetics service of the ChromoMED Institute, in the Dominican Republic (Supplementary image 2).

The objective of the research was to document the dysmorphological, therapeutic and diagnostic reevaluation, as well as the neurocognitive, neurophysiological and motor aspect of the patient to help in the planning of the intervention, as well as to evaluate and manage her clinical management and protocolized follow-up through the collaboration of several specialized medical services.

The research protocol consisted of reviewing the clinical record with prior authorization from the center and the patient's mother, obtaining informed consent, reevaluation by the investigator, and performing complementary paraclinical studies.

These included cranial tomography, otoacoustic emissions, evoked potentials, strain echocardiogram and thyroid function tests. In addition, a family tree was performed and documentation of the indicated studies was compiled, as well as an updated literature review of Pitt Hopkins syndrome.

A further reevaluation was performed to address and document the patient's dysmorphologic evaluation. In addition, informed consent was obtained for purposes of publication and release of photographs related to the study.

This case study has provided a comprehensive clinical and genetic evaluation of a patient with Pitt Hopkins syndrome. The results obtained provide important information to better understand this rare genetic condition and may contribute to the appropriate care and management of patients with PTHS.

RESULTS

The investigation revealed significant results in the physical and neurological evaluation of the patient with Pitt Hopkins syndrome. Regarding dysmorphologic alterations, typical features of the disease phenotype were observed, such as epicanthus, telecanthus, narrow forehead, thin eyebrows in their lateral portion, flattened nasal bridge, broad nasal ridge and tip, prominent midface, prominent midface, prominent cheeks, wide mouth and thick or overlapping ear helix (See Figure 1 A,C). These findings support the clinical diagnosis of Pitt Hopkins syndrome and are consistent with those described in the medical literature.

In addition to the dysmorphic alterations, other relevant physical findings were found, such as marked bilateral myopia and convergent strabismus, fundus without alterations (See figure 1 B). These visual problems are common in patients with Pitt Hopkins syndrome and require appropriate management to preserve the ocular health of the patient.

Regarding psychomotor development, a severe and early-onset alteration was observed, characterized by severe hypotonia and genu valgum (See figure 1D).

These problems affect the patient's motor skills and balance, which may influence her quality of life and functional abilities. In addition, the presence of absence seizures at a frequency of once a day, under maintenance pharmacological treatment, is an important clinical manifestation to be taken into account in the patient's management.

The radiographic study revealed a heart of normal size and morphology, with cardiothoracic index of 0.46 mm (See figure 2).

Figure 1. Facies of the patient with Pitt- Hopkins Syndrome.

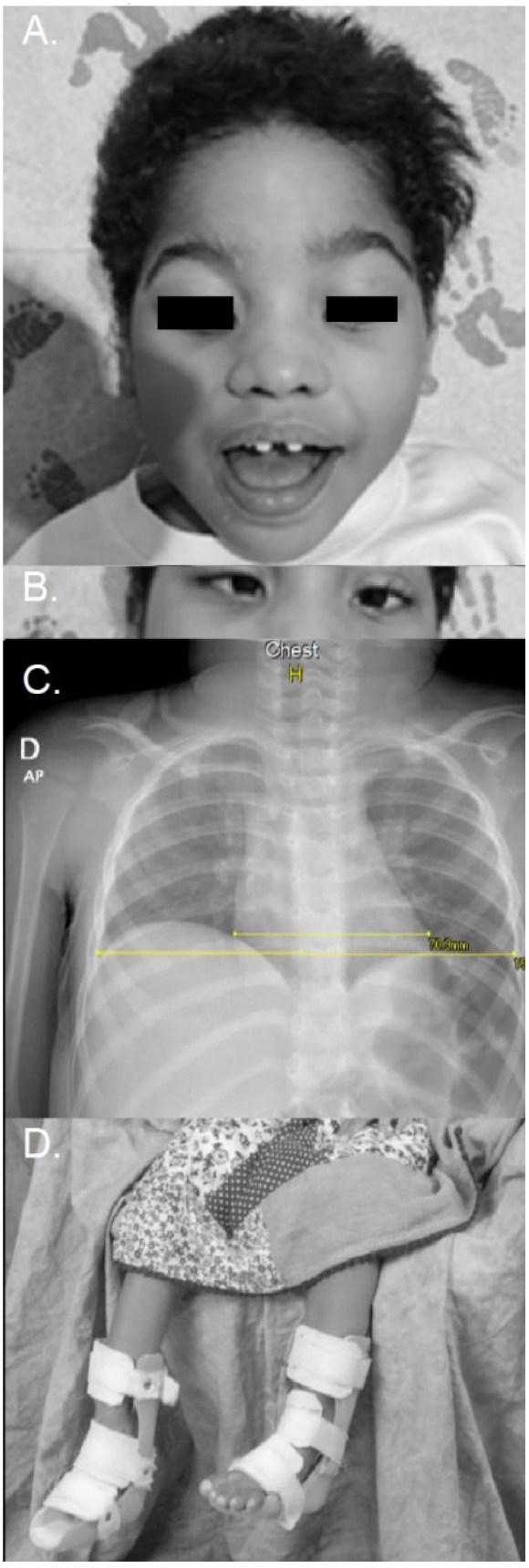
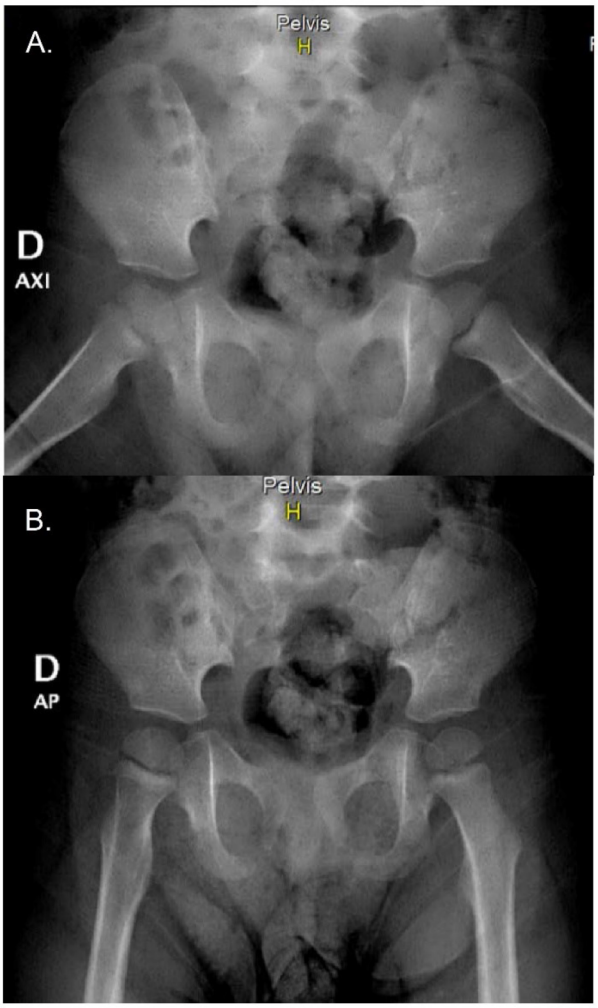
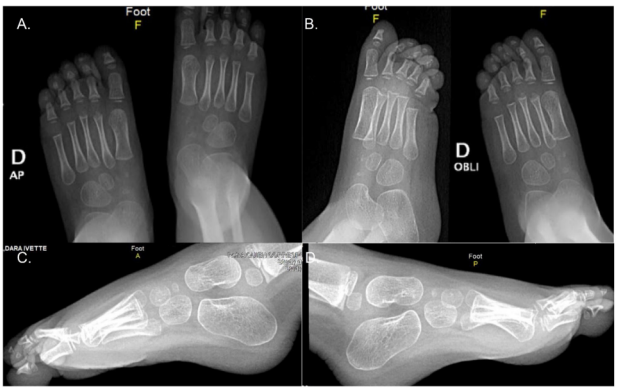


Figure 2. Radiographic study: pelvic images.



The radiographic study revealed a heart of normal size and morphology, with cardiothoracic index of 0.46 mm. Platypeloid pelvis with bone morphology within normal parameters. Source. ChromoMED Institute.

Figure 3. Radiographic study: images of feet.



The radiographic study revealed a heart of normal size and morphology. Growth plates of normal aspects and morphology. Source. ChromoMED Institute.

Platypeloid pelvis with bone morphology within normal parameters, growth plates of normal aspect and morphology.

It is relevant to note that the patient also presents synechiae of labia minora. In addition, it was identified that the patient is a carrier of sickle cell anemia and suffers from hypothyroidism, conditions that are managed in a comprehensive manner in her medical care, with a multidisciplinary approach. Neurologically, global impairment was observed in all areas of functioning of intellectual executive functions, including attention, memory, visual-motor, fine motor, academic, adaptive, emotional and behavioral. These results are consistent with the expected neurological profile in patients with Pitt Hopkins syndrome.

From the pharmacological point of view, our patient is followed with a scheme that keeps her stable to date, among them are levetiracetam and valproic acid, which are administered in doses of 6 ml and 4 ml respectively, twice a day continuously. Also used are clonidine, which is taken in the form of drops before bedtime, and levothyroxine, in doses of 25 mg and frequency of once daily, used for the treatment of hypothyroidism.

In this review, the results of multiple electroencephalogram (EEG) studies performed over several years on a specific patient are analyzed. Different patterns of brain activity were observed at different times of wakefulness and sleep.

In July 2019, short bursts of large amplitude peak-wave activity were found during both wakefulness and sleep (See Suplementary image 1). These findings raised interest in correlating them with the patient's clinical symptomatology.

In March 2020, no epileptic activity was recorded during wakefulness and phases I-II of sleep. However, in August 2020, high-voltage spike-wave activity was observed in the left occipital region during sleep in those same phases.

In March 2021 and October 2021, no epileptic activity was detected during wakefulness and sleep in EEGs performed on those dates.

In addition to EEGs, a brain MRI was performed in August 2020, which showed no pathological abnormalities.

Within our reevaluation we included cranial tomography, otoacoustic emissions, evoked potentials, strain echocardiogram and thyroid function tests, which were normal. However, it can be inferred that the patient demonstrated skills beyond those detailed in the literature, such as the use of complete sentences and the ability to learn and communicate in a promising manner. These unexpected skills may be a positive aspect to consider in the management and follow-up of the patient.

The patient was referred to the orthopedic surgery service and surgery was performed on both lower limbs with corrective surgery, in order to provide the patient with the possibility of a coordinated gait, with the help of physiotherapy and rehabilitation services (Supplementary Image 3).

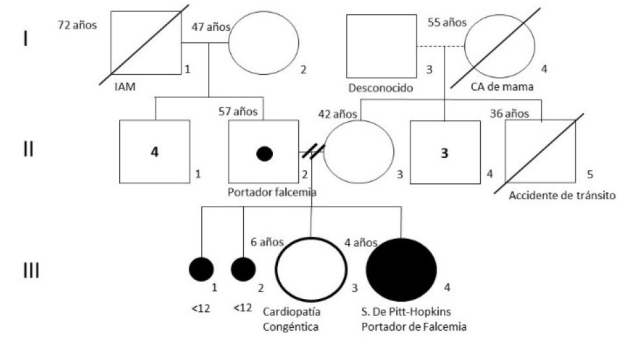
The results of this research highlight the presence of important dysmorphic alterations, visual problems, alterations in psychomotor development and neurological profile in a patient with Pitt Hopkins syndrome. These findings support the clinical diagnosis of the disease and provide relevant information for planning the clinical management of the patient, including therapies focused on her current needs. Familial genetic screening is an important part of research to determine possible genetic risks and germline inheritance patterns.

During the re-evaluation a genealogical examination of the patient was performed, which has allowed us to identify an autosomal recessive transmission pattern of sickle cell disease. This finding was confirmed by hemoglobin electrophoresis, a laboratory technique that distinguishes hemoglobin variants and is therefore instrumental in the diagnosis of hemoglobinopathic disorders such as Sickle Cell Disease. In this analysis, both the patient and her father showed a carrier status for this condition.

In addition, a congenital cardiac anomaly was documented in the patient's sister. The presence of this disease within the family health profile provides further context about the genetic susceptibilities that the patient may have.

Thus, we were able to confirm Pitt-Hopkins syndrome in the index case, a rare genetic condition characterized by cognitive delay, developmental difficulties and unique facial features.

Figure 4. Patient's family tree.



Source. ChromoMED Institute.

DISCUSSION

This case report highlights the importance of recognizing the spectrum of abilities beyond what is documented in the literature in children with Pitt Hopkins syndrome (PTHS). Failure to recognize this spectrum can lead to a delay in accurate diagnosis, and a deterioration in the patient's health by failing to receive an early approach to the most relevant clinical aspects, such as motor, communicative, and intellectual functions.

Documenting each case of PTHS is becoming increasingly relevant, as it drives research into the social and medical determinants that could benefit these patients. This includes the development of parent associations, as well as the study of new targeted and personalized therapies for the treatment of the epileptic disorders present in the syndrome. The possibility of redirecting drug targets and combinations for treatment more effectively is addressed by the "Genomic Precision Medicine" approach.

Treatment recommendations for patients with PTHS include coordination of medical services, speech, occupational and behavioral therapies, education, home behavior management, social skills development, safety planning and guardianship considerations, as well as supportive resources for parents. This highlights the importance of a multidisciplinary approach in the treatment team to improve the quality of life for individuals with PTHS and their families.

PTHS is likely underdiagnosed, emphasizing the need for comprehensive genetic screening methods in patients with developmental delays to investigate the possible presence of an underlying genetic etiology. While routine cytogenetic testing is indicated in the evaluation of children with developmental delay without a clear etiology, the use of more advanced genetic testing, such as whole exome sequencing, may allow obtaining a diagnosis or considering specific commercially available gene panels.

In conclusion, we highlight the importance of recognizing the spectrum of abilities in patients with PTHS beyond what is documented, the need to document each case to encourage research and the development of personalized therapies, as well as the importance of a multidisciplinary approach in the treatment of these patients.

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