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CLINICAL CASE

# Pontocerebellar hypoplasia secondary to CASK gene deletion. Case report

## Hipoplasia pontocerebelosa secundaria a deleción en el gen CASK. Caso clínico

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## Abstract

**Introduction:** Pontocerebellar hypoplasia (PCH) is a reduction of the size of the cerebellum and pons secondary to an alteration in its development, and can be caused by neurodegenerative diseases of genetic origin, of which there are known 10 subtypes (PCH 1-10), cortical malformations, metabolic and genetic diseases. **Objective:** To present the case of a child with microcephaly, PCH and West syndrome, in which the genetic study allowed to make the diagnosis of a deletion on chromosome X. **Case report:** This is a female infant of 7-month at diagnosis, without family or obstetric history of interest, head circumference at birth -1.5 standard deviations (SD). She had little weight and growth in head circumference progression. In addition, physical examination revealed no fixating gaze, hypotonia with preserved deep tendon reflexes. Progressively developed refractary seizures. Brainsteam Auditory Evoked Potential demonstrated involvement of pontomesencefphalic ways and neuroimaging Pontocerebellar hypoplasia. The genetic study (aCGH) showed heterozygous deletion on the X chromosome, affecting the CASK gene. **Conclusions:** Given the wide differential diagnosis proposed at the PCH, new cytogenetic techniques have improved the classification of HPC and in some cases establish their etiology, so in these cases can provide appropriate genetic counseling to families.

**Keywords:**
CASK gene;
Intellectual disability;
Microcephaly;
Pontocerebellar hypoplasia;
Psicomotor retardation;
West Syndrome

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## Introduction

Pontocerebellar hypoplasia (PCH) is a heterogeneous group of neurodegenerative diseases with a genetic origin, from which only 10 subtypes are known (PCH 1-10). The term PCH is used generically to describe a size reduction of the cerebellum and also the protuberance. According to entities, in addition to the aforementioned ones, there are other entities with PCH that may also be included, such as cortical malformations, metabolic diseases and genetic diseases[1-3]. Patients with cerebellar hypoplasia usually present muscular hypotonia and a delayed cognitive development, from moderate to severe. They may also develop ataxia, altered eye movements, dysarthria, intentional tremor, seizures and other neurological symptoms[1,3].

Regarding the genetic etiology, mutations in the CASK gene related to this disorder have been described. CASK gene is located on the X chromosome and it encodes a protein that takes action in transcription (directly and indirectly), as well as in synapse and genetic expression. Patients with mutations in the CASK gene present cerebellar hypoplasia, microcephaly and severe mental retardation. It may be associated other symptoms as well, such as ataxia, nystagmus and sensorineural deafness[4-6].

The main objective of this study is to show the case of a girl with microcephaly, PCH and West Syndrome, in which the genetic study allowed the diagnosis of a delation in the X chromosome.

## Clinical Case

A 5-year-old female, student at primary school, who was monitored from an early age in the outpatient neuropediatrics clinic, due to a severe delay in her psychomotor development, in addition to hypotonia and microcephaly.

Single child of healthy parents, who are not blood relatives, with no relevant family history. The gestation period was under control. The mother did not report any alcohol consumption or any other drugs during pregnancy, which was a period without incidents or intercurrent diseases, so she did not mention she have received any type of medication either. The gestation period was lived in Spain, without reporting trips to areas at risk of zika virus infection.

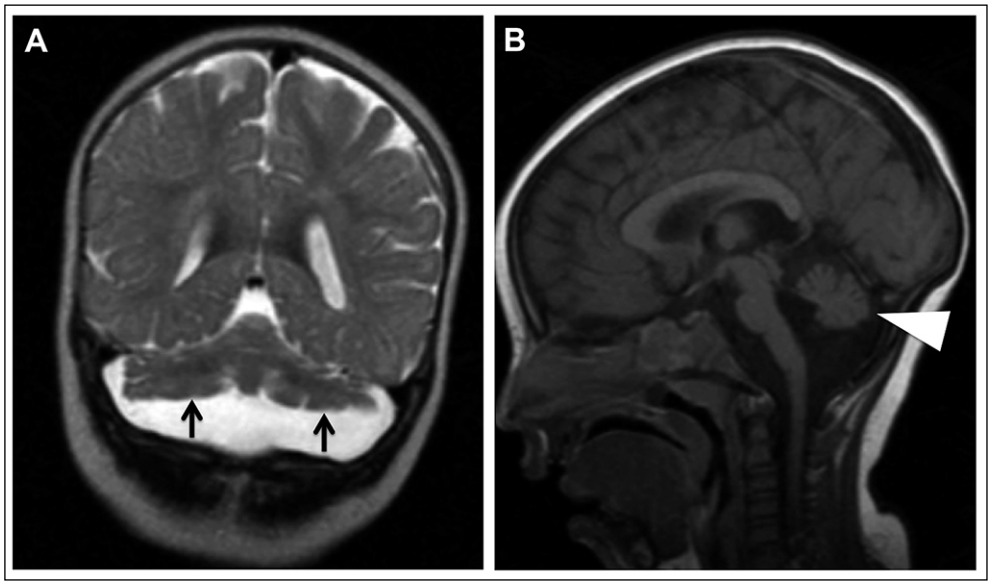
The delivery was at term by cesarean section for breech presentation of the baby, with Apgar 9-10, with birth weight of 3010 g and cephalic perimeter (CP) of 31 cm (-1.5 standard deviations (SD)). During her first months of life, our patient developed a low level of stenosis, the main reason for which she was derived for study at her 6 months of age. At that age, a global developmental delay was evident, with absence of visual fixation and overall hypotonia of central dominance, with preserved osteotendinous reflexes, along with marked microcephaly (CP 37.5 cm, -11 SD), occipital flattening and microretrognatia . Laboratory tests were normal (biochemical profile, liver and renal function, thyroid profile, coagulation tests and muscle enzymes, as well as the basic metabolic study (acid-base balance, ammonia, lactic acid and pyruvic acid, pre-and post-and pyruvic acid in cerebrospinal fluid (CSF), amino acids in plasma, urine and CSF, organic acids in urine and CSF, serum sialotransferrin profile and acylcarnitine profile in tandem masses) and karyotype (46,XX). Normalcy of the cardiological study (electrocardiogram and echocardiography), ophthalmologic examination and abdominal ultrasound was also demonstrated.

At the neurophysiological level, electroencephalogram (EEG), visual evoked potentials, as well as electromyography and nerve conduction velocity were also normal. However, auditory evoked potentials (AEP) showed a severe compromise of the pontomesencephalic pathways. Magnetic resonance of the brain showed hypoplasia at a pontocerebellar level, with no other significant findings (figure 1A and B).

The patient started with episodes of spasms in flexion of upper limbs, at her 15 months of age. She had any background of having abnormal movements previously. In the first EEG performed at her 6 months of age, there was any epileptiform activity observed. According to the appearance of this new symptomatology, a video-EEG was performed, in which hypsarrhythmia was demonstrated in the tracing. Again, a new magnetic resonance was performed without appreciating significant changes regarding the previous study. In front of this debut of a cryptogenic West Syndrome, we iniciated an anticonvulsant treatment with vigabatrin, which starting showing good results.

A Comparative Genomic Hybridization Array study (aCGH) was requested, detecting a partial deletion of the CASK gene involving the first 5 exons (deletion of 254.01Kb in the Xp11.4 cytobanda of one of the X chromosomes [Xp11.4 (41 623 672 - 41 877 684) x1]) (figure 2). A aCGH study was performed on both parents without any alterations, which was a confirmation of the presence of a 'De novo mutation' in our patient. This mutation is located in the CASK gene region, which is associated with intellectual disability, microcephaly, and X-linked pontocerebellar hypoplasia.

At the moment of this report's writing, the patient was 5 years old. Her overall evolution has been unfavorable, with severe psychomotor retardation, extreme microcephaly, staturo-ponderal delay and intellectual disability. Although it initially presented a good res-




**Figures 1 A y B.** Brain magnetic resonance (**A:** coronal plane, T2FSE sequence; **B:** sagittal plane, T1 sequence). Note: Hypoplasia of vermis and cerebellar hemispheres affecting its lower portion. No supratentorial anomalies are shown. The findings described would be compatible with a pontocerebellar hypoplasia.

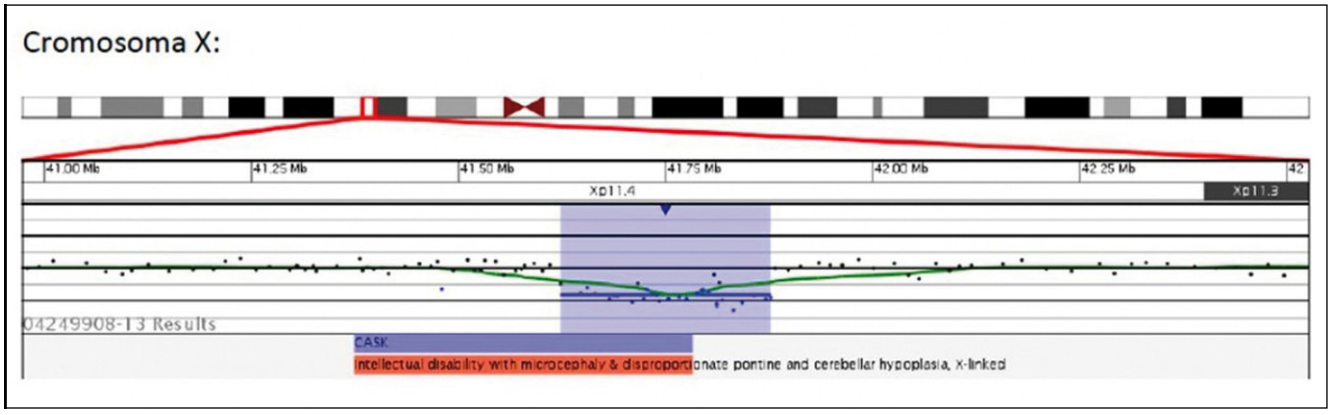



**Figure 2.** Comparative Genomic Hybridization Array (aCGH). Note: Chromosomal formula arr[hg19] Xp11,4(41 623 672- 41 877 684)x1. A partial deletion of the CASK gene involving the first 5 exons is observed (254.01 kb interstitial deletion in the Xp11.4 region).

ponse to vigabatrin treatment, the epileptic episodes, that were refractory to anticonvulsive polytherapy, subsequently reappeared.

## Discussion

Patients with PCH usually present muscular hypotonia and delayed development, from moderate to severe. Regarding our clinical case, it was observed this retardation, which was actually the symptom that alerted the parents and their pediatrician. In addition, they may develop ataxia, altered eye movements, dysarthria, intentional tremor, convulsions, intellectual disability, dyskinesia and choreic movements[1,3]. In our clinical case, we could observe that progressively appeared convulsions and intellectual disability, without observing abnormal eye movements, trembling or choreic movements.

The PCH etiopathogenesis includes cortical malformations and metabolic diseases, such as congenital disorders of glycosylation of proteins, predominantly type 1a, but also type 1q. Also, we could include genetic alterations: mutations in the CASK gene, cerebellar agenesis secondary to mutations in PTF1A, -dystroglicopathies such as Walker-Warburg Syndrome, Musculoskeletal Disease or Fukuyama Disease, posterior fossa malformations such as pontine tegmento dysplasia and structural lesions, as cerebellar agenesis or cerebellar damage secondary to prematurity (eg. Johnsen-Tarby-Lewis syndrome)[1,3].

With regard to genetic alterations, CASK gene mutations related to this disorder have been described. CASK gene is located in the chromosome Xp11.4, and

encodes a multi-domain structural protein that interacts with the TBR1 transcription factor, regulating the expression of genes, which are responsible for brain development and neuronal migration (eg, reelin and NR2b ). Mutations in the CASK gene are usually 'De novo' and they affect more to women than to men, as in our clinical case, who is a girl, in who a mutation of 'De novo' was confirmed when we could not see alterations in her parents, observing the genetic study previously performed[1,4].

The CASK gene encodes a calcium-dependent serine protein kinase-calmodulin, which belongs to the family of membrane-associated guanylate kinases (MAGUK). The CASK protein has 5 domains in its structure, which shares with the rest of the family of MAGUK proteins: PDZ, SH3, two L27 and GK. It is classified in the subfamily p55, for it has an additional domain Calcium/calmodulin-like at its N-terminus. This protein has a high expression in the nervous system of mammals, because it takes care of signaling at the synaptic level and it contributes to the neural development and to the gene expression. besides it is part of the synapse at the level of the exchange in the ion channels and as a protein of transmembrane anchorage. Thus, it contributes also to the neurotransmission process, and it has activity in the nucleus of the neurons, regulating the gene expression[6]. It has been shown that the function of the CASK gene varies in relation to the period of brain development in which the individual is. During embryonic development, some CASK proteins enter to the nucleus of neurons (mainly at the cerebral cortex, hippocampus and olfactory bulb), regulating the gene expression. In the youthful state, the CASK protein is located at the axonal level, contributing to transportation and excretion. Finally, it is distributed at the synaptic level in adulthood, playing its part as an adapter protein and organizing the synapse and its signaling.

We could conclude that there is an implication of the CASK protein in the development of the cerebral cortex due to its collaboration with the Tbr-1 transcription factor and with the nucleosomal assembly protein CINAP, which acts as a chaperone during transcription. The interaction between this protein and CINAP would modulate the chromosomal structure of Tbr-1, thereby regulating its expression. Tbr-1, in turn, regulates expression in the extracellular matrix of the Reelin protein, which is responsible for neuronal migration and lamination[4,6,10].

Patients with CASK gene mutations has pontocerebellar hypoplasia, microcephaly and severe mental retardation. Cases of ataxia, nystagmus and sensorineural deafness have been described[1,4,5,8,10-12]. We could observe pontocerebellar hypoplasia on the magnetic resonance imaging, as well as altered conduction of the pontomesencephalic pathways in brainstem auditory evoked potentials (AEP). CASK gene mutations cause learning and memory disorders, which produces an intellectual disability and neurological defects[9].

According to a Japanese research, 16 patients are described with CASK gene mutations. They presented microcephaly, saturo-ponderal delay, epilepsy, and PCH observed in a cerebral magnetic resonance imaging, being similar to our clinical case[13].

In genetic studies of patients with mental retardation linked with X, mutations have been found in the CASK gene[7]. Several types of genetic abnormalities have been described: variations in copy numbers and mutations (duplications, deletions, inversions and mutations in the exon-intron junction) in patients with PCH and absence of karyotype alterations. In the genetic studies performed in our patient, it was demonstrated a deletion on the X-chromosome in the CGH array, with a normal karyotype (46, XX). Most of these are null mutations, they do not express proteins, thus, although there are different genotypic alterations, patients have a similar phenotype. Furthermore, it has not been possible to relate the magnitude of the genetic alteration to a particular phenotype. Patients with large deletions are phenotypically indistinguishable from patients with limited deletions to the CASK gene. In a series of 8 cases in men with mutations in the CASK gene[8,14], they propose that patients with a more severe phenotype present a type of compromise in the germinal line, finding mosaicisms in patients with attenuated phenotype[15]. Several studies report the association of epilepsy in patients with PCH, but only in one previously published[16], we describe the presence of a West Syndrome, just as our patient, which was detected in the video-EEG, tracing hypsarrhythmia. In this study, Burglen and colleagues performed an aCGH on 14 patients with PCH, and only in one case it was observed an intellectual disability associated with microcephaly. They detected mutations in the CASK gene in 13 patients, all of them 'De novo'. Although the cohort is small, they could observe a more serious phenotype among males, and also they could suggest that those cases in which the mutation causes an inactivation of the protein, it would be recognizable, although the phenotype is variable[16].

## Conclusions

Given the wide differential diagnosis of PCH, the new cytogenetic techniques have allowed to improve the its classification and, in some cases, to establish its etiology, being able to offer in these cases an adequate genetic counseling to parents and relatives. The CASK gene should be analyzed if it is a girl with intellectual disability, microcephaly and PCH. The CASK gene is

widely distributed in the nervous system, with an important role in the processes of signaling, transportation of proteins and regulation of gene expression. To acquire more knowledge regarding its function could clarify the pathogenesis of PCH in patients with CASK gene mutations, which would also help to identify candidate genes for related diseases.

## Ethical Responsibilities

**Human Beings and animals protection:** Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

**Data confidentiality:** The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

**Rights to privacy and informed consent:** The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

## Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

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