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CLINICAL CASE

Congenital Hydrocephalus: Gómez-López-Hernández syndrome. An underdiagnosed Syndrome. A clinical case

Hidrocefalia Congénita: Síndrome de Gómez-López-Hernández, un síndrome subdiagnosticado. Caso clínico

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Abstract

Introduction: Hydrocephalus is defined as complex conditions influenced by genetic and environmental factors. Excluding hydrocephalus acquired from infection or brain tumors, congenital hydrocephalus with a genetic cause may occur isolated (hydrocephalus isolated, pure or non-syndromatic) or as a component of a genetic syndrome (syndromic hydrocephalus). **Objective:** To present a syndromic congenital hydrocephalus with a known diagnosis, in order to be considered in the study of this pathology and to perform a review of hydrocephaly with a genetic cause. **Clinical case:** Preschool with a prenatal diagnosis of hydrocephalus and rhombencephalosynapsis, karyotype and study of TORCH was normal. At the moment of birth, the prenatal diagnoses were confirmed and a malformation of cerebral cortical development was excluded. During the first week of life, peritoneal ventricle shunt was performed. A reevaluation at age 4, the absence of corneal reflexes bilateral parietal and congenital focal alopecia associated with rhombencephalosynapsis, meet definitive criteria for cerebello-trigeminal-dermal displasia or Gómez-López-Hernández syndrome (GLHS). **Conclusions:** GLHS is an uncommon neurocutaneous syndrome, possibly a sporadic condition that is underdiagnosed. Due to the new imaging and genetic technologies pre and post-natal, today it is possible to achieve a better and more accurate diagnosis of hydrocephalus with a genetic origin, in which the high suspicion of teams of clinical specialists is essential. Without accurate diagnosis, we can not access to a long-term prognosis, prevention of aggregate morbidity or an adequate genetic counseling, which are required in today's pediatrics.

Keywords:
Cerebello-trigeminal-dermal dysplasia;
rhombencephalosynapsis,
neurocutaneous disorder;
alopecia;
trigeminal anaesthesia

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Introduction

Hydrocephalus is defined as an active distension of the ventricular system, of the brain resulting from inadequate passage ofcerebrospinal fluid (CSF) from its poin of production with the cerebral ventricles to its pont of absorption into the systemic circulation[1-3]. The prevalence varies from 0.5 to 3.2 per 1,000 newborns, whether or not hydrocephalus following intraperiventricular hemorrhage is included[4,5].

Causes of hydrocephalus can be classified according to the main clinical symptoms[1,6]. There are classifications according to the onset (prenatal or postnatal), localization of lesions (communicating or non-communicating), pressure dynamics of CSF (hypertensive hydrocephalus or normal pressure hydrocephalus), non-genetic causes (infections, hemorrhage, and tumors, among others). Genetic causes of hydrocephalus are classified as isolated hydrocephalus (IH) or syndromic hydrocephalus (SH).

Genetic hydrocephalus must be investigated considering recurrence and family aggregation risks. Among SH, the Gómez-López-Hernández syndrome (GLHS) or cerebello-trigeminal-dermal dysplasia is an uncommon and underdiagnosed cause of SH, its phenotype was described by Gómez in 1979[7] and López-Hernández in 1982[8]. The characteristic clinical triad includes rhombencephalosynapsis (RS), alopecia mainly bilateral parieto-occipital and trigeminal anesthesia[9-11]. RS is an uncommon cerebellar malformation with absence of vermis and fusion of cerebellar hemispheres[12]. Alopecia can be bilateral parietal, occipital and/or symmetrical temporal and can be a neonatal finding or appear in the adolescence, thus the absence of alopecia during childhood does not exclude this syndrome (table 1). Trigeminal anesthesia affects the ophthalmic nerve (less sensibility in the forehead and cornea), which increases the risks of microtraumas, ulcers, corneal opacity and, eventually, blindness[13].

A clinical case of a child with hydrocephalus whose etiology is a cerebellotrigeminal-dermal dysplasia or GLHS is presented and a review of genetic hydrocephalus is performed. The Institutional Ethics Committee approves this study.

Clinical Case

The patient is a child of non-related parents, without family morbidity history. The pregnancy was normal, there was no specific supplementation of vitamins or trace elements. During the 20th week of gestation, hydrocephalus was detected, it was confirmed by a magnetic resonance imaging (MRI), which also showed a malformation of the posterior fossa like rhombencephalosynapsis (RS). The cariotype (46XY) and antenatal TORCH were normal. It was born by cesarean delivery, at the 37th week of gestation, the newborn was large for gestational age, weight 11.1 lbs (5040 grams), height 21.2 in (52 centimeters), macrocephaly of 22 in (56 centimeters), APGAR 6-9 at the 1st and 5th minute. The postnatal cerebral MRI confirmed the antenatal findings, excluding anomalies in the cortical development. A ventriculoperitoneal shunt was installed in the first week of life. During this period, a geneticist did not find specific dysmorphias in the patient and requested ambulatory controls.

During the neonatal period, the patient developed central hypothyroidism, had low levels of 25-hydroxy-vitamin D and presented anomalies in the GH/IGF1 axis. Levothyroxine and vitamin D were supplemented. Despite the height compromise, growth hormone was not indicated. The parents were warned about the possible appearance of hypoglycemia in future visit controls. The patient achieved head control, sedestation and crawling, but did not achieve independent gait. Since the beginning of breastfeeding, the patient showed "no-no" head tremors, which were frequent and persistent. Due to episodes of valve dysfunctions, four valve replacements were performed, with regressions and recovery of motor and cognitive development.

Table 1. Gomez-Lopez-Hernandez Proposed Diagnostic Criteria

Rhombencephalosynapsis + (scalp alopecia and trigeminal anesthesia)	GLHS definitive
Rhombencephalosynapsis+ (scalp alopecia and 1 major craniofacial criteria)	GLHS definitive
Scalp alopecia + trigeminal anesthesia without CNS imaging	GLHS probable
Scalp alopecia without trigeminal anesthesia + one major craNiofacial criteria without CNS imaging	GLHS possible
Scalp alopecia without trigeminal anesthesia or major cranio-facial criteria, but with 2 or more neurologic or minor cranifacial criteria	GLHS possible

From Rush ET, Adam MP, Clark RD et al. Four new patients with Gomez-Lopez-Hernandez syndrome and proposed diagnostic criteria.Am J Med Genet A. 2013 Feb;161A(2):320-6.

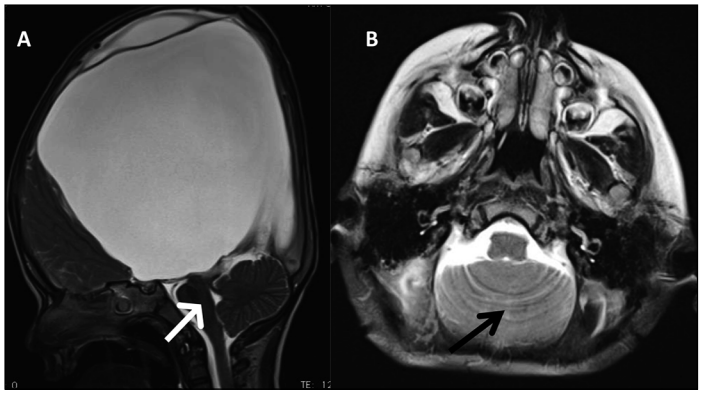

Figure 1. MRI brain, T2 (A y B). **A:** Corte sagital, Severe supratentorial non comunicant hydrocephaly with normal IV ventricle (White arrow) and acueductal stenosis. MRI showed brachycephaly and turricephaly. **B:** Corte axial. Infratentorial showed Rhombencephalosynapsis without vermis anterior, posterior y nódulo (black arrow).

At four years and six months old, the patient was evaluated by the pediatric neurology team due to a new valvular dysfunction and the physical examination showed macrocephalia with turri-brachycephaly, bilateral parietal alopecia, hypertelorism, absence of corneal reflexes, strabismus, low-implanted ears , midface hypoplasia, generalized hypertonia, stretch reflexes slightly increased and motor skill developmental delays both gross and fine. According to the analysis of clinical findings, brain imaging performed during the prenatal period that showed triventricular hydrocephalus, fusion of cerebellar hemispheres (rhombencephalosynapsis), with absence of vermis, (figure 1) were essential criteria for the definitive diagnosis of GLHS (table1).

Discussion

The inclusion of new diagnostic technologies have contributed to an early prenatal of congenital pathology diagnosis and the next-generation sequencing platforms have contributed to more accurate diagnosis, which makes possible the documentation of gene alterations involved in many processes related to hydrocephalus[1,14].

Genetic hydrocephalus, known as isolated hydrocephalus (IH) or syndromic hydrocephalus (SH), vary according to their frequency and number of associated genes. The empirical risk rates for IH due to aqueductal stenosis, X-linked (HSAS; phenotype MIM 307000), is 10% in males (mutations of the cell adhesion molecule L1CAM). The others IH, with gen non-L1CAM known, comprise 1-4% of them[15]. The some identify genes are AP1S2 gene (adaptor-related protein complex 1" sigma-2 subunit), MPDZ gene (multiple PDZ domain proteins), and CCDC88C gene (coiled-coil domain-containing protein 88C).

SH are more common than IH and are associated to more than 100 genes, where the L1CAM mutation is included and can cause IH and SH (MASA syndrome: Mental retardation, Aphasia, Spastic paraplegia and Adducted thumbs). Due to the large number of symptoms, the SH are classified according to the mutated protein (table 2). Among the SH, there are SH associated with glycosylation disorders or dystroglycanopathies (Walker Warburg syndrome, muscle-eye-brain disease, among others)[1,16]; with planar cell polarity and neural tube disorders (spina bifida, anencephaly, Arnold Chiari Malformation). SH associated with RA Sopathies (Noonan syndrome, neurofibromatosis, Costello syndrome and cardio-facio-cutaneous syndrome), among others.

The exact cause of GLHS is poorly understood, however, an autosomal recessive inheritance is hypothesized, which is associated with a non-identified gene. It has also been related to a teratogen or multifactorial causes. Reported patients, as well as our patient, had a normal cariotype. In some cases, the CGH array detected some partial deletions classified as variables without pathological relevance or as of uncertain significance. The participation of the ACP2 gene has also been proposed since a regressive mutation of the ACP2 was associated with alterations in the cerebellum and coat of rodents[17-21]. Due to cases of parental consanguinity, a possible autosomal recessive pattern was proposed.

The extended phenotype of GLHS includes various clinical symptoms, such as dermatologic, neurologic, psychiatric and radiological (table 3). From the mandatory criteria, the patient had a fusion of cerebellar hemispheres (prenatal diagnosis), focal alopecia on the parietal area at the age of four years and probably absent in neonatal stage. Despite being very characteristic, the trigeminal anesthesia is a difficult finding to confirm before the 12th week of life, it requires a clinical suspicion and a research directed by serial examinations over time since the clinical symptoms of many genetic disorders do not appear right after the birth. The control of our patient was mainly pediatric (serial controls inherent to the pediatric period) and neurosurgical because the prevalent morbidities were the ventriculoperitoneal valve dysfunction and intracranial hypertension, which required multiple surgical explorations.

The main craniofacial criteria are turri-brachycephaly or brachycephaly and midface hypoplasia, which were evident in our case (figure 1). Strabismus, hypertelorism, plagiocephaly, and craniosynostosis are minor criteria[17,21,22], which were also present in the

Table 2. Genes encoding major pathway components mutated in isolated or syndromic hydrocephalus

Disorder	Hydrocephalus	Genetic locus	Major clinical features	Mode of inheritance
Neuronal adhesion	X-linked hydrocephalus with aqueductal stenosis	L1CAM	Adducted thumbs, corpus callosal atrophy	X-linked
	MASA/CRASH syndrome		ID, aphasia, shuffling gait, adducted thumbs	X-linked
Vesicle trafficking	Pettigrew syndrome	AP1S2	Intelectual disability	X-linked
Dystroglycano-pathies	Walker-Warburg syndrome (muscular dystrophy-dystro-glycanopathy)	POMT1, POMT2, FKRP, POMGNT1	Brain and eye anomalies, anomalies, ID, limb-girdle	AR
		FKTN	Anomalías ojo-cerebro debilidad cinturas, DI, CC	AR
		POMK, DAG1, LARGE, B3GNT1, B3GALNT2,	Brain and eye anomalies	AR
Ciliopatías	Bardet-Biedl Syndrome	CEP290	Obesity, retinitis pigmentosa, kidney failure, polydactyly, renal cystic,dysplasia, ID, posta-xial polydactyl	AR
	Kartagener syndrome	DNAI1, DNAH5	Ciliary dyskinesia, situs inversus, dextrocardia	AR
	Joubert syndrome 2 and 9	TMEM 67	PMD,hindbrain malformations, breathing Ab.	AR
	X-linked VACTERL	ZIC3	Dextrocardia an CHD	X-linked
	VATER association	PTEN	Vertebral, renal andanal anomalies, CHD	AR
	Marfan syndrome	FBN1	Skeletal, ocular,fibrous connective anomalie, CHD	AD
RASopathies	Neurofibromatosis, type I	NF1	Fibromatous skin tumors	AD
	Costello syndrome	HRAS	Distinctive facial appearance, failure to thrive	AD
	Noonan syndrome	PTPN11, SOS1	Distinctive facial appearance, CHD, failure to thrive	AD
PI3K-AKT-mTOR pathway	Megalencephaly polymi-crogyria polydactyly-hydro-cephalus	PIK3R2, AKT3, CCND2	Polymicrogyria, polydactyly	AD
Planar cell polarity and neural tube defects	Susceptibility to neural tube defects	VANGL1, CCL2	Neural tube defects, craniorachischisis	AD
	Neural tube defects	VANGL2	Neural tube defects, myelomeningocele	AD
	Adams Oliver Syndrome	ARHGAP31	PMD, aplasia cutis, congenital, limb defects	AD
Lysosomal storage disorders	Mucopolysaccharidosis VI	ARSB	Short stature, CHD, hepatosplenomegaly	AR
	Gaucher typo III c	GBA	Cardiac and neurological anomalies	AR
Growth factors	Apert Syndrome	FGFR2	Craniosynostosis	AD
	Achondroplasia	FGFR3	Dwarfism	AD
	Di George syndrome	TBX1	Hypocalcemia, cardiac defects	AD
	Cousin Syndrome	TBX15	Dwarfism, facial dysmorphisms, skeletal ab.	AR

Source: Kousai and Katsanis, Annu. Rev. Neurosci. 2016. 39:409–35. Abbreviations: AD, autosomal dominant; AR, autosomal recessive; MASA syndrome, mental retardation, aphasia, shuffling gait, and adducted thumbs, CHD congenital heart disease, ID intelectual disability, PMD psychomotor delay, Wnt, wingless/integrated.

evaluation. The neuropsychiatric symptoms, in older patients, are suicidal tendencies, depression, bipolar disorder, obsessive-compulsive disorder self- and hetero-aggression. Despite the normal or borderline psychometrics, some common diseases are developmental delay, ataxia, hypotonia and intellectual disability.

Among the neurological findings, persistent, stereotyped figure-8 and side-to-side head shaking (yes-yes or no-no) is remarkably common in patients with

Table 3. Findings in 30 Patients Reported in the Literature as Well as our New Patient with GLHS

Trait	%	Criterios
Craniofacial		
Scalp alopecia	100	Obligate Criteria
Midface retrusion	82	Mayor criteria
Brachycephaly and/or turricephaly	83	Mayor criteria
Low-set ears	89	Minor criteria
Strabismu	83	Minor criteria
Trigeminal anesthesia	61	Minor criteria
Absent corneal reflexes	62	Minor criteria
Plagiocephaly	48	Minor criteria
Craniosinostosis	80	Minor criteria
Neurodevelopmental		
Delayed motor milestones	100	Minor criteria
Ataxia	82	Minor criteria
Hypotonía	82	Minor criteria
Intellectual disability	69	Minor criteria
Head shaking or other stereotypic behavior	80	Minor criteria
Radiological		Minor criteria
Rhombencephalosynapsis	100	Obligate criteria
Ventriculomegaly/hydrocephalus	65	Minor criteria
Cerebellar hypoplasia	38	Minor criteria
Other		
Hypoplastic labia major	86 (only woman)	Minor criteria
Normal growth at birth	78	Minor criteria
Short stature	67	Minor criteria

Modifies from Rush ET, Adam MP, Clark RD et al. Four new patients with Gomez-Lopez-Hernandez syndrome and proposed diagnostic criteria.Am J Med Genet A. 2013 Feb;161A(2):320-6.

RES. Since this hindbrain malformation affects midline and paramidline cerebellar structures, the dysfunction mayoccur at the level of the vestibulocerebellum. This movement was observed in our patient but was underdiagnosed. Some research have demonstrated a deficit in the central vestibular processing, thus, this stereotype is an involuntary movement to obtain additional sensorial information. The pattern of movement, would activate semicircular canals and afferent nerve fibers, which increases the inputs in an abnormal vestibular system[23].

The cerebral magnetic resonance, a study of choice in GLHS besides showing rhombencephalosynapsis (Figure 1) and triventricular hydrocephalus, it can highlight corpus callosum hypoplasia, absence or septum pellucidum lipoma and septo-optic dysplasia with hypothalamic-pituitary dysfunction. Other findings are cerebellar-brainstem fissures, fornix fusion, arachnoid cyst, hippocampal malrotation, thalamic fusion, hippocampal atrophy, temporal lobe hypoplasia, olivary nuclei, anterior commissure and optic chiasm[19]. In our case, the cerebral magnetic resonance showed a fusion of both cerebellar hemispheres (rhombencephalosynapsis), absence of septum and triventricular hydrocephalus with thin corpus callosum (Figure 1). The absence of septum is usually associated with hypothalamic-pituitary dysfunction, which was detected and treated.

The prognosis varies according to the presence and severity of the associated anomalies, both intra and supratentorial. The oldest patient was 39 years old at the moment of the publication[10].

In conclusion, since the hydrocephalies were frequent, with the fortification of folic acid and the optimization of perinatal care of the preterm child, hydrocephalies due to neural tube defects or intraventricular hemorrhage of prematurity have decreased. Currently, genetic hydrocephalus has started to be relevant, therefore, it is essential to know, classify and study them. With the new medical imaging and genetic pre- and postnatal technologies, it is possible to make a precise diagnosis, where the high degree of suspicion among clinical specialists is essential. Thus, considering this case, the reevaluation in all chronic patients with hydrocephalus is recommended. Without the precise diagnosis, it is not possible to determine the long-term prognosis, the prevention of aggregate morbidity and an adequate genetic advice, which are required in the current pediatrics.

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.

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Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

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