Gomez–Lopez-Hernandez syndrome: An easily missed diagnosis

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Abstract

Gomez–Lopez-Hernandez syndrome (GLHS) is a rare syndrome comprising the triad rhombencephalosynapsis (RS), parietal alopecia, and trigeminal anesthesia. Other typical findings are skull abnormalities, craniofacial dysmorphic signs, and short stature. Intellectual impairment is typical but cases with normal cognitive functions have also been reported. Only 15 cases of GLHS have been described so far, all sporadic. We report four further patients with GLHS: one neonate, two children and a middle aged man. In all cases the diagnosis was made only in retrospect; one child died as neonate due to esophageal atresia. All patients presented RS and parietal alopecia, three intermittent head stereotypies, two had obvious trigeminal anesthesia, and one normal cognition. Alopecia and also trigeminal anesthesia can be very mild and can be easily missed. However, the dysmorphic signs including bilateral alopecia are already present in the neonatal period and are highly suggestive of GLHS. RS should be looked for in this situation. It is important to mention that neuroimaging does not allow distinguishing between isolated RS and GLHS. If RS is diagnosed the clinical signs of GLHS should be sought. The diagnosis of GLHS can only be made by the combination of the typical dysmorphic signs and neuroimaging in the neonatal period, but not prenatally.

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1. Introduction

Gomez–Lopez-Hernandez syndrome (GLHS, OMIM 601853) or cerebello-trigeminal-dermal dysplasia is a rare syndrome characterized by rhombencephalosynapsis (RS), trigeminal anesthesia, and bilateral parietal alopecia [6,10,12]. Other findings listed as typical are craniofacial anomalies such as a turricephaly and a distinct facial appearance (midface hypoplasia, hypertelorism, and low-set, posteriorly rotated ears), clinodactyly, short stature, strabismus, and corneal opacities secondary to trigeminal anesthesia. Mental ability is usually impaired, although two patients with normal cognitive function have also been reported [12,15].

Here, we report four new patients with GLHS to extend the spectrum of this syndrome and to illustrate possible difficulties in making the correct diagnosis. We would like to stress the point that the key features of GLHS have to be actively looked for when examining the patient and analyzing the brain scans. In our four patients the features defining GLHS were not detected during routine examination thus leading to a substantial delay in the correct diagnosis.

2. Methods

2.1. Patients

Between April 1999 and April 2006, 10 patients with RS were diagnosed at our department. Reviewing this series of patients, the diagnosis of GLHS was made in four patients. The six remaining patients had non-syndromic RS.

2.1.1. Patient 1 (male)

At birth, his weight was 3450 g (10–50th centile) and the length 52 cm (50–90th centile). As a newborn, Patient 1 showed global muscular hypotonia and brachycephaly, hypertelorism, midface hypoplasia, and low-set, posteriorly rotated ears. At the age of 14 months bilateral corneal ulcers were noted, due to bilateral trigeminal anesthesia with absent corneal reflexes. His development was globally delayed and at the age of 2 years truncal ataxia as well as intermittent head nodding (as head movements which describe an infinite sign like a horizontally positioned number 8) was found. Since the age of 6 he suffered from a neurogenic bladder dysfunction. At the age of 8 years he developed aggressive and hyperactive behavior, which improved only partially over the course of several years. He attended a special school and a supported workplace, corresponding to moderate mental retardation. He is working in industry and accomplishes simple repetitive manual work. In daily life activities he requires particular support in functions requiring good coordination and high cognitive capacities. At the age of 34 he was reassessed regarding the typical dysmorphic signs of GLHS. Neurological examination showed global ataxia, reduced eye abduction, and bilateral trigeminal anesthesia with several scars on the forehead, absent corneal reflexes, and corneal opacities. Furthermore, there was bilateral parietal alopecia and the dysmorphic signs described (Fig. 1). The intermittent head nodding was still present. His height was 179.9 cm (50–75th centile) and head circumference 55 cm (10–25th centile). An MRI previously performed elsewhere for headache was reviewed. There was RS (not reported) with mild ventriculomegaly, which led to the diagnosis of GLHS. Chromosomal analysis revealed a normal male karyotype (46,XY).
2.1.2. Patient 2 (female)

An ultrasound scan at 30 weeks gestation showed hydrocephalus without posterior fossa abnormalities. Delivery and neonatal adaptation were uneventful. At birth, her head circumference was 34.5 cm (50th centile). A postnatal ultrasound scan confirmed ventriculomegaly. Subsequently the head grew along the 50–75th centile with no signs of increased intracranial

Fig. 1. Patient 1 at 34 years. (A) Front view showing broad, high forehead, hypertelorism, strabismus, small nose, and short and flat philtrum. Note the premature aging and scars on the forehead. (B) Left sideview revealing pronounced brachyurricephaly, low-set, posteriorly rotated ears, prognathism, midface hypoplasia, and parietal alopecia. (C) Posterior view demonstrating bilateral parietal alopecia.
pressure and the child presented with axial muscular hypotonia with poor head control. At 5 months MRI confirmed the ventriculomegaly due to a narrow but patent aqueduct of Sylvius. At the age of 20 months she began to walk and developed intermittent posterior head nodding. At 4 years neurological examination showed mild truncal ataxia, axial muscular hypotonia, limb muscular hypertonia, and an alternating strabismus. The findings on follow up MRI were unchanged but RS was diagnosed on the basis of the typical MRI findings. However, in retrospect, RS could be seen on all the previous MRIs (Fig. 2). At the age of 8 years and 8 months she was attending a normal school and had no particular difficulties in her daily

Fig. 2. Patient 2 at 9 years. (A) Left sideview showing hidden parietal alopecia and low-set, posteriorly rotated ears. (B) Posterior coronal T2W MRI demonstrating fused cerebellar hemispheres, abnormal horizontal orientation of cerebellar folia, and ventriculomegaly. (C) Lower axial T2W MRI demonstrating fusion of the cerebellar hemispheres with no intervening vermis and characteristic keyhole appearance of the fourth ventricle (white arrow).
life activities. She still had intermittent posterior head nodding. Neurological examination showed minimal truncal ataxia, convergent strabismus, normal trigeminal facial sensation, but bilateral absence of the corneal reflex without corneal opacities. Furthermore, she showed mild midface hypoplasia, low-set and posteriorly rotated ears, and mild bilateral parietal alopecia (more pronounced on the left side and perfectly hidden by other hair), but no hypertelorism or skull deformities (Fig. 2). Head circumference and stature were both on the 50th centile. Wechsler Intelligence Scale for Children-III [18] revealed normal results in all domains tested (intelligence, attention and processing speed, memory span, learning and memory, language, visual perception and visuospatial constructional ability, and executive functions) with a full scale IQ of 112. Diagnosis of GLHS was only made at this age while reviewing our series of patients with a previous diagnosis of RS. Chromosomal analysis revealed a normal female karyotype (46,XX).

2.1.3. Patient 3 (male)

At birth his weight was 3540 g (50th centile), length 53 cm (50–90th centile), and head circumference 34 cm (10–50th centile). As an infant, he showed no neurological abnormalities but had turriccephaly and bilateral parietal alopecia (Fig. 3). An MRI showed RS, mild ventriculomegaly, and malrotated hippocampi. At the age of 3 years, truncal ataxia, convergent strabismus on the left side, intermittent lateral head nodding, and bilateral trigeminal anesthesia with absent corneal reflex and secondary corneal opacities were present. At 5 years he could undress himself, eat, drink, brush his teeth, and wash his hands, but he needed help to dress. He knew different colors and some alphabetic characters and numbers. At the age of 7 years he was integrated in a normal school, but he needs remedial teaching due to moderate mental retardation. Neurological examination demonstrated global ataxia and muscular hypotonia. Head circumference was 49 cm (1.5 cm below 3rd centile) and height 104.4 cm (10th centile). The diagnosis of GLHS was made at this age on review of undiagnosed cerebellar malformations. Chromosomal analysis revealed a normal male karyotype (46,XY).

Fig. 3. Patient 3 at 7 years. (A) Front view showing discrete hypertelorism, deep set ears, smooth philtrum, thin lips, and strabismus. (B) Left sideview demonstrating parietal alopecia.
2.1.4. Patient 4 (female)

An ultrasound scan at 31 weeks gestation showed hydrocephalus with abnormal brain structures and polyhydramnios. A fetal MRI at 32 weeks demonstrated RS and a hypoplastic corpus callosum. The child was born by Caesarean section at 38 weeks. At birth, her weight was 3030 g (50th centile), the length 49 cm (50–75th centile), and the head circumference 36 cm (90–95th centile). Neonatal adaptation was difficult because of cyanosis, excessive salivation, and floppiness. A diagnosis of esophageal atresia Type IIIb was confirmed. Examination demonstrated global muscular hypotonia, hypertelorism, midface hypoplasia, turricephaly, and low-set and posteriorly rotated ears (Fig. 4). MRI on day 2 confirmed the prenatal findings and in

Fig. 4. Patient 4 aged 1 day. (A) Front view showing marked hypertelorism, narrow palpebral fissures, smooth philtrum, thin lips, and excessive salivation. (B) Left sideview revealing parietal alopecia and low-set, posteriorly rotated ears with overfolded helix. (C) Posterior coronal T2W MRI demonstrating fused cerebellar hemispheres and ventriculomegaly. (D) Coronal T2W MRI indicating absent septum pellucidum (black arrow), fused thalami (white arrow), and ventriculomegaly.
addition showed the absence of the septum pellucidum and fused thalami (Fig 4). In view of such complex malformations involving two different systems and the uncertain prognosis, the parents decided to decline surgical treatment and the baby died at the age of 3 days. The diagnosis of GLHS was made only after review of the photos of the child, which clearly showed bilateral parietal alopecia (Fig. 4). Chromosomal analysis of a post mortem skin biopsy revealed a normal female karyotype (46,XX).

2.2. Molecular cytogenetic analysis

Metaphase chromosome preparations were obtained from PHA-stimulated lymphocyte cultures according to standard procedures. Analysis was carried out on CTG banded chromosomes at a 600 band level.

2.3. Literature review

The public Internet database Pubmed was searched using three MeSH terms (Gomez–Lopez-Hernandez syndrome; cerebello-trigeminal-dermal dysplasia; rhombencephalosynapsis). Titles and abstract were reviewed to determine whether the article could be relevant.

3. Results

Eleven reports were found, documenting 15 patients with features of GLHS. The clinical and neuroradiological findings in four patients with GLHS are summarized in Table 1, such as together with the previously published patients.

4. Discussion

Gomez–Lopez-Hernandez syndrome is a rare disorder first described in 1979 by Gomez [6] and in 1982 by Lopez-Hernandez [10]. We add a series of four new patients to the 15 previously published cases (Table 1). The etiology of GLHS remains unknown but a genetic basis seems very likely. All cases reported so far are sporadic and all but one had been born to non-consanguineous parents [7]. The number of girls and boys affected is equal and there is no gender difference in terms of severity. This constellation renders an autosomal recessive or X-linked mode of inheritance very unlikely and favors either spontaneous dominant mutations or de novo chromosomal rearrangements. However, no chromosomal abnormalities (determined by routine karyotyping or subtelomere screening) have been reported in GLHS. The only published case of GLHS studied by high-resolution array-CGH analysis showed five copy number variations without pathogenetic significance [16]. It has been speculated that the nax mouse, in which a novel recessive mutation of the lysosomal monoesterase Acp2 gene induces disturbed cerebellar cortical architecture, ataxia and delayed hair appearance, might constitute an animal model for GLHS [11]. However, the involvement of the human homologue, ACP2, in GLHS still remains to be demonstrated. Other genes may be considered as potential candidate genes for GLHS. The homeobox genes Tlx-1 and Tlx-3 are both early expressed in placode-derived cranial neurons, including the trigeminal placodes, and the hindbrain in chicken [1,9]. However, the involvement of these genes in GLHS remains to be demonstrated.

RS constitutes a key feature of GLHS. RS is characterized by dorsal fusion of the cerebellar hemispheres, agenesis or hypogenesis of the vermis, and fusion of the dentate nuclei and
| Patients | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 |
| Author (patient’s number) | Gomez Lopez (1) | Lopez (2) | Munoz (1) | Munoz (2) | Brocks (3) | Tan | Truwit (1) | Whetsell (2) | Bowdin (1) | Schell-Apacik (2) | Purvis (1) | Gomy (2) | Gomy (1) | Poretti (2) | Poretti (3) | Poretti (4) | |
| Age at study (years) | 4 | 10 | 11 | 15 | 14 | 9 | 19 | 4 Months | 18 Months | 2 | 15 | 10 | 26 | n.d. | 34 | 9 | 7 | 2 Days |
| Sex | f | f | f | f | f | m | m | m | m | f | m | m | m | m | f | m | f |
| Brain MRI | RS | n.d. | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + | + |
| Central nervous system | Truncal ataxia | + | + | + | + | + | + | + | n.a | + | + | + | + | n.d. | n.d. | + | + | + | + | n.a. |
| Trigeminal anesthesia | + | + | + | – | n.d. | – | + | – | – | + | + | – | – | – | – | – | – | – | + | n.a. |
| Corneal opacities | + | + | + | + | + | + | – | + | n.d. | – | + | – | – | – | + | + | – | – | + | n.a. |
| Mental retardation | + | + | + | + | + | + | + | n.a | – | n.a. | n.a. | + | + | + | + | + | + | + | + | n.a. |
| Craniofacial | Parietal alopecia | + | + | + | + | + | + | + | + | n.d. | + | + | + | + | + | + | + | + | + | + | + |
| Brachycephaly | + | + | + | + | + | + | + | n.d. | + | + | + | + | + | + | + | – | – | – | – | + | + |
| Midface hypoplasia | + | + | + | + | + | + | + | n.d. | + | + | + | + | + | + | – | + | + | + | + | + | + |
| Hypertelorism | + | + | + | + | + | + | + | n.d. | n.d. | + | + | – | n.d. | n.d. | + | – | + | + | + | + | + |
|---------------|--------------|------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Genitalia     | Hypoplasia   | n.d. | +   | +   | +   | +   | +   | +   | n.a. | n.a. | n.a. | n.a. | n.a. | n.a. | n.a. | n.a. | n.a. | n.a. | n.a. | n.a. | –   | n.a. | +   |
| Growth        | Short stature| n.d. | +   | +   | +   | +   | +   | +   | n.d. | n.d. | +   | –   | +   | +   | –   | –   | –   | –   | –   | –   | n.a. | n.a. | n.a. | n.a. | n.a. | n.a. | n.a. | –   | –   | –   |

* Only absent corneal reflex; **, asymmetrical; RS, rhombencephalosynapsis; asp, absent septum pellucidum; ca, cortical atrophy; dc, Dupuytren contracture; ea, esophageal atresia; epi, seizures; ft, fused thalami; ha, atrophy of the hippocampal formations; hcc, hypoplastic corpus callosum; mh, malrotated hippocampi; mic, microcephaly; mo, months; n.a., not applicable; nbd, neurogenic bladder dysfunction; n.d., not described; str, strabismus; vm, ventriculomegaly; we, weeks.
superior cerebellar peduncles. RS is often associated with hydrocephalus or ventriculomegaly (all our patients) and, in about half of the cases, with an absent septum pellucidum (three out of four) and/or a hypoplastic corpus callosum (two out of four). A spectrum of additional associated CNS abnormalities has been reported (in our series malrotated hippocampi in three patients and fused thalami in one) [19,20]. RS has been described in all cases of GLHS. In our series of RS, 4 of 10 patients had GLHS. Barth reviewed the reported cases of RS until midst of 2005. He found 58 cases of RS, whereof only 5 had GLHS [2]. Indeed, the majority of patients with RS are non-syndromic and, in those patients, RS occurs as an isolated feature or is associated with other CNS anomalies [19]. Carefully comparing the neuroimaging findings in our series of isolated RS patients (data not shown) with those in the patients with GLHS revealed no differences. Therefore, the typical clinical findings of GLHS must be accurately sought in all patients with RS, otherwise the diagnosis can be easily missed, as in our patients. RS is the only sign of GLHS that can be diagnosed in utero, as in Patient 4 [13,17]. Therefore, it is not possible to distinguish between non-syndromic RS and GLHS prenatally.

The clinical findings of GLHS can vary considerably in severity and are sometimes not easy to detect. Ataxia can be very mild and not restricting, as in Patient 2. Scalp alopecia too may be only moderate and easily hidden. The typical alopecia in GLHS is bilateral, involving the parietal regions in a band-like pattern, and is present from the neonatal period [12,15]. Therefore, GLHS should also be considered in the differential diagnosis of focal congenital alopecia. Trigeminal anesthesia most often affects the ophthalmic branch with abnormal sensation of forehead and cornea. As in Patients 1 and 3, this can cause repetitive microtrauma and subsequent corneal opacities [12]. Absent corneal reflexes due to lack of corneal sensation is an early and sensitive sign of abnormal trigeminal function and can even occur with normal sensation on the forehead, as in Patient 2. However, cases without trigeminal anesthesia have also been reported [3,7,15]. Several dysmorphic signs are also typical of GLHS (Table 1) [12]. These dysmorphic signs including bilateral alopecia are present in the neonatal period and, if discovered, they are highly suggestive of GLHS. In these cases RS must be sought and, if present, the diagnosis of GLHS can be made in the neonatal period.

Three of the patients in our series presented with rhythmical, regular, intermittent head stereotypies from the first years of life. In Patient 1 they correspond to an infinite sign (∞, as head movements which describe an infinite sign like a horizontally positioned number 8), in Patient 2 to back head nodding, and in Patient 3 to a side-to-side head movement. In all cases, they improved over the course of several years in frequency and intensity, but always persisted. Similar stereotypies have been reported in other cases of GLHS, such as head banging [4], head rolling [17], or side-to-side head movements [21]. Head stereotypies were also reported in RS and other cerebellar malformations [8]. Therefore, this sign does not help to differentiate between GLHS and non-syndromic RS.

Most reported cases of GLHS are not associated with other diseases. Only one case was associated with growth hormone deficiency [4]. In our series, Patient 1 also suffered from neurogenic bladder dysfunction and Patient 4 from esophageal atresia. These symptoms have not been reported in GLHS previously. Both can occur isolated or associated with other diseases (neurological or otherwise) [5,14]. Furthermore, Patient 3 showed microcephaly.

Mental retardation has been reported in the majority of patients with GLHS. However, two patients with normal cognition have also been reported [12,15]. In our series, two patients had significant mental retardation. Patient 1 has achieved a certain independence in daily life activities but needs support in functions requiring good coordination and high cognitive capacities and Patient 3 has several cognitive difficulties. However, Patient 2 attends a normal school and
her full scale IQ was 112. This confirms that patients with GLHS may have normal cognitive functions.

In conclusion, GLHS is a well defined entity but the clinical signs (alopecia, trigeminal anesthesia, ataxia, and head stereotypies) can be very mild and easily missed when not actively looked or asked for. There is a broad range of cognitive impairment in GLHS; furthermore, cognition can even be normal. The phenotypic spectrum includes microcephaly, esophageal atresia, and neurogenic bladder dysfunction. More patients with GLHS have to be identified to further characterize the clinical spectrum and facilitate genetic studies to reveal the underlying genetic cause. Identifying the causative gene(s) and understanding the pathogenesis in GLHS might give important clues about the complex processes orchestrating hindbrain development.

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References


