Clinical Report
Two New Brazilian Patients With Gómez–López-Hernández Syndrome: Reviewing the Expanded Phenotype With Molecular Insights

Israel Gomy,1 Benjamin Heck,1 Antônio Carlos Santos,3 Maria Silvia L. Figueiredo,2 Carlos E. Martinelli Jr,4 Maria Priscila C. Nogueira,2 and João M. Pina-Neto1*

1Department of Genetics, Division of Medical Genetics, School of Medicine of Ribeirão Preto, University of São Paulo, Ribeirão Preto, Brazil
2Departments of Neurology, Psychiatry, and Medical Psychology, School of Medicine of Ribeirão Preto, University of São Paulo, Ribeirão Preto, Brazil
3Department of Clinical Medicine, Division of Radiology, School of Medicine of Ribeirão Preto, University of São Paulo, Brazil
4Department of Puericulture and Pediatrics, Division of Endocrinology, School of Medicine of Ribeirão Preto, University of São Paulo, Ribeirão Preto, Brazil

Received 2 September 2007; Accepted 11 October 2007

Gómez–López-Hernández (GLH) syndrome or cerebello-trigeminal dysplasia is a neurocutaneous disorder whose etiology is unknown at the present time. We report two additional Brazilian patients, including the oldest one known to date (age 29). Here, we review the expanded phenotype in four patients with new clinical, psychiatric, radiological, and molecular investigations. One patient may have hypomania within the bipolar spectrum disorder with onset in childhood and adolescence. Primary growth hormone (GH) deficiency was ruled out in all patients, although one of them might have developed secondary GH deficiency due to partial hypopituitarism following severe hydrocephalus. Brain magnetic resonance angiography disclosed no azygous anterior cerebral artery (ACA) but only normal variants. Molecular analysis of the lysosomal acid phosphatase gene (ACP2) was performed, but no pathogenic mutations were identified. We present an overview of the phenotypic features of all patients described to date. There are currently 12 unrelated patients reported in the literature, 5 of whom are Brazilian. We discuss new molecular insights and speculate about the pathogenesis of GLH syndrome.

Key words: neurocutaneous disorder; alopecia; rhombencephalosynapsis; bipolar disorder; growth hormone; acid phosphatase 2; azygous anterior cerebral artery


INTRODUCTION

Gómez–López-Hernández (GLH) syndrome or cerebello-trigeminal-dermal dysplasia (OMIM 601853) is a neurocutaneous disorder whose etiology is unknown at the present time. The main findings include craniosynostosis, craniofacial anomalies, localized scalp alopecia, trigeminal anesthesia, cerebellar ataxia, mental retardation, and rhombencephalosynapsis, a unique anomaly of the cerebellum. GLH syndrome is a recurrent-pattern syndrome, a similar or identical set of anomalies in two or more unrelated patients. The validity of a recurrent-pattern syndrome increases as more abnormalities are found in the condition and more patients are recognized as having the syndrome [Cohen, 1997].

The first patient was described by Gómez in 1979 and nine other cases have been reported since then [López-Hernández, 1982; Pascual-Castroviejo, 1983; Muñoz et al., 1997; Brocks et al., 2000; Tan et al., 2005; Whetsell et al., 2006; Schell-Apacik et al., 2007].

Correspondence to: João M. Pina-Neto, Department of Genetics, School of Medicine of Ribeirão Preto, São Paulo University, Av. Bandeirantes, 3900, Ribeirão Preto, SP 14049-900, Brazil.
DOI 10.1002/ajmg.a.52173
Brocks et al. [2000] proposed an expansion of the phenotype to include psychiatric problems in a 19-year-old patient with bipolar disorder (BD) and growth hormone (GH) deficiency. Tan et al. [2005] described a case with prenatal MRI findings. Whetsell et al. [2006] reported a patient with a single anterior cerebral artery (ACA, azygous) and suggested that this finding expanded the phenotype. Bowdin et al. [2007] described a 2-year-old boy with hydrocephalus, rhombencephalosynapsis, scalp alopecia with seborrhea, but without facial dysmorphism, and suggested a diagnosis of GLH syndrome. Recently, Schell-Apacik et al. [2007] reported an additional patient who was investigated for submicroscopic abnormalities with BAC array, which detected rearrangements of no pathogenic relevance at five different loci (1p, 8q, 10q, 19p, and Xq).

Here, we describe two new patients with GLH syndrome for whom we performed GH, psychiatric, and radiological investigations as in two previous cases reported by Munoz et al. [1997]. Moreover, we review the relevant literature and the expanded phenotype. A novel spontaneous recessive mutation in a gene encoding lysosomal acid phosphatase (Acp2) has been reported to cause hair and cerebellar abnormalities in the naked ataxic (nax) mouse [Mannan et al., 2004]. Because the phenotype of nax mice is reminiscent of a neurocutaneous syndrome and resembles cerebello-trigeminal-dermal dysplasia, it was hypothesized that mutations in the human homolog ACP2 gene might cause GLH syndrome [Mannan et al., 2004; Tan et al., 2005]. To verify this, complete sequencing of the gene was performed. Because the etiology of this syndrome remains unknown at the present time, new molecular insights are proposed for other candidate genes.

**CLINICAL REPORTS**

**Patient 1**

The propositus, a 29-year-old male, was the 11th child of young nonconsanguineous parents. His 10 other siblings were normal and there was no family history of similar cases. He was delivered by uneventful vaginal delivery, weighing 2,600 g. At 7 months, he was admitted to an intensive care unit with marasmic malnutrition, diarrhea, acute otitis media, and a scalp abscess. His neuromotor development was delayed but no precise milestone measurements were available. At 21 months, he was evaluated by an ophthalmologist, who observed apical leukoma in the right eye and corneal ulceration in the left eye. He later developed retinal detachment with a hematoma in the left eye. The social and family history was so compromised that he was institutionalized at 8 years. At 9 years, his height was 122 cm (3rd centile); his weight was 23 kg (10th–25th centile); and his head circumference was 50 cm (−1 SD); inner canthal distance was 36 mm (>97th centile), and outer canthal distance was 95 mm (>97th centile). He had brachycephaly, hypertelorism, small nose, thin lips and low-set, posteriorly angulated ears with hypoplasia of both antihelices. Scalp alopecia was present in the biparietal, temporal, and occipital regions. Trigeminal anesthesia and corneal opacities were absent (Fig. 1). He had abducens paresis and convergent strabismus. Spastic paraplegia was also evident. Skull radiographs disclosed macrocephaly with tower-like brachycephaly. Electroencephalogram (EEG) showed focal epilepsy and CT scan demonstrated supratentorial hydrocephalus. Brain MRI showed absence of the septum pellucidum and severe ventricular enlargement, with a thin cerebral cortex and corpus callosum, and a normal fourth ventricle due to aqueductal stenosis. Fusion of cerebellar hemispheres and absence of the cerebellar vermis (rhombencephalosynapsis) were evident (Fig. 2). It was not feasible to evaluate his height because of severe fibrotendinous retractions, although at 25 years, his bone age was normal for adult osseous maturation. G-banding karyotype was normal (46,XY).

**Patient 2**

The propositus was a 12-year-old boy who was the 4th child of young nonconsanguineous parents. There were no similar cases in the family. He was born by uneventful vaginal delivery, weighing 2,600 g. At 7 months, he was admitted to an intensive care unit with marasmic malnutrition, diarrhea, acute otitis media, and a scalp abscess. His neuromotor development was delayed but no precise milestone measurements were available. At 21 months, he was evaluated by an ophthalmologist, who observed apical leukoma in the right eye and corneal ulceration in the left eye. He later developed retinal detachment with a hematoma in the left eye. The social and family history was so compromised that he was institutionalized at 8 years. At 9 years, his height was 122 cm (3rd centile); his weight was 23 kg (10th–25th centile); and his head circumference was 50 cm (−1 SD); inner canthal distance was 36 mm (>97th centile), and outer canthal distance was 95 mm (>97th centile). He had brachycephaly, hypertelorism, small nose, thin lips and low-set, posteriorly angulated ears. Biparietal-temporal scalp alopecia was also evident (Fig. 3). On neurological examination he was noted to have strabismus, corneal and trigeminal anesthesia with facial scarring, and ataxia. EEG demonstrated an epileptiform pattern in the right temporal region, although he never had seizures. MRI showed normal cerebral structures, a small lipoma in quadrigeminal plate,
FIG. 1. Patient 1. Turicephalic brachycephaly, midface hypoplasia, thin lips, and low-set posteriorly angulated ears (A,B). Bilateral temporal-parietal alopecia is striking (C,D). No facial scarring or corneal opacities were found.
and fusion of cerebellar hemispheres with absence of the cerebellar vermis (rhombencephalosynapsis) (Fig. 4). G-banding karyotype was normal (46,XY).

Psychiatric Investigation

Psychiatric evaluation was carried out in four patients based on the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) and the Structured Clinical Interview for DSM-IV—Clinical Version (SCID-CV) [Del Bem et al., 2001]. The first [Muñoz et al., 1997, patient 1] was referred at the age of 6 years to a psychiatrist because she had irritability, agitation, insomnia, and self-aggressive behavior which included putting fingers into her eyes, resulting in cloudy corneas. She was medicated with good response, although verbal aggressiveness remained when she was frustrated. Specific psychiatric evaluation at 14 years showed moderate mental retardation with social, occupational, and learning disabilities. The second [Muñoz et al., 1997, patient 3] was 14 years of age at a high school where any psychiatric disorder could be detected. He had normal learning and social skills. The third (our patient 1) had psychomotor delay and had never been to school because of socioeconomic problems. At 24 years of age, he had moderate mental retardation and absence of psychiatric problems. The fourth (our patient 2) had been neglected since infancy and was institutionalized at 8 years of age. He was first evaluated at the age of 9 years due to psychomotor agitation and aggressiveness. He had severe attention deficit with hyperactivity disorder (ADHD) and was medicated with a poor response. By 11 years of age, there was some doubt whether he had ADHD and infantile affection disorder or whether he had early onset of hypomania within the bipolar spectrum disorder with onset in childhood and adolescence.

Growth Hormone Investigation

GH secretion was evaluated by the L-DOPA stimulation test in the same four patients, three of them during childhood/adolescence and the other during early adulthood (Table 1). GH peak \( \geq 10 \text{ ng/ml} \) was considered indicative of normal GH status in children and adolescents, and GH peak \( \geq 3 \text{ ng/ml} \) was considered normal for adults. In the first patient [Muñoz et al., 1997, patient 1], the GH peak (16 ng/ml) was normal and IGF-I levels supported normal GH status (370.0 ng/ml) (−1 SDS). The second [Muñoz et al., 1997, patient 3] also showed normal GH peak (28 ng/ml) and although it was above 20 ng/ml, GH insensitivity was unlikely as IGF-I levels were normal for age and sex (390.0 ng/ml) (−0.5 SDS). The third (our patient 1) showed low GH levels in two different GH stimulation tests: L-DOPA (peak: 1.4 ng/ml) and Glucagon test (peak: 2.0 ng/ml). IGF-I determined in three different moments (169, 59, and 78 ng/ml) (−0.9, −2.2, and −2.0 SDS, respectively) were
FIG. 3. Patient 2. Normal height (A). Brachycephaly, hypertelorism, midface hypoplasia, and low-set posteriorly angulated ears (B). Scalp alopecia (C, D). Scarring of the face and corneal opacity due to trigeminal anesthesia. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

FIG. 4. Brain MRI. Top row, arrow 1 points to a small lipoma in the quadrigeminal plate. Bottom row, fusion of the cerebellar hemispheres with absence of the cerebellar vermis (arrow 2).
compatible with partial GH deficiency. Finally, GH secretion (GH peak: 13.2 ng/ml) was normal in the fourth patient (our patient 2).

**Radiological Investigation**

In addition to MRI, we also performed brain MR angiography (MRA) in the same patients. The first [Muñoz et al., 1997, patient 1] disclosed hypoplasia of the A1 segment of both ACA particularly the right one (Fig. 5A). The second [Muñoz et al., 1997, patient 3] showed mild asymmetry of both ACA particularly the right one (Fig. 5B). In the third (our patient 1), MRA demonstrated strikingly right dominant ACA with hypoplastic A1 segment of the left ACA (Fig. 5C). MRA was normal in the fourth (our patient 2) (Fig. 5D). No typical single ACA (azygous) was found in any of the patients.

**Molecular Investigation**

Complete direct sequencing of all 11 exons of the *ACP2* gene was performed on an ABI Prism 3730 genetic analyzer using Big Dye terminator cycle sequencing kit (Applied Biosystems) according to Mannan et al. [2004]. The sequences were analyzed and did not show any pathogenic mutations in the four patients. All variations identified were interpreted as heterozygous single nucleotide polymorphisms.

**DISCUSSION**

Of the 12 cases with GLH syndrome reported to date, five are Brazilian, including the oldest (age 29), which is the only case associated with consanguinity (our patient 1). All cases have been sporadic, making it difficult either to assert or to rule out Mendelian inheritance. Brocks et al. [2000] proposed an expansion of the phenotype to include psychiatric disorders and GH deficiency. Thus, we reviewed two previous Brazilian cases [Muñoz et al., 1997] and both of our patients to verify whether any further phenotypic expansion was warranted. A clinical overview of all reported cases to date is summarized in Table II.

Our patient 1 had subnormal responses to GH stimuli and showed low IGF-I levels, and we considered it likely that he had partial GH deficiency. This could be explained by partial hypopituitarism as a consequence of untreated and severe congenital

---

**TABLE I. Growth Hormone (GH) Status**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>GH peak (ng/ml)</th>
<th>IGF-I (ng/ml) SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muñoz et al. [1997] (case 1)</td>
<td>12/13</td>
<td>16.0</td>
<td>370.0</td>
</tr>
<tr>
<td>Muñoz et al. [1997] (case 3)</td>
<td>16/18</td>
<td>27.8</td>
<td>390.0</td>
</tr>
<tr>
<td>Patient 1</td>
<td>23/27</td>
<td>2.0</td>
<td>169.0</td>
</tr>
<tr>
<td>Patient 2</td>
<td>9</td>
<td>13.2</td>
<td>NP</td>
</tr>
</tbody>
</table>

SD, standard deviation; NP, not performed.

*In children and adolescents, GH status is considered normal when GH peak $\geq 10.0$ ng/ml; in adults, $\geq 3.0$ ng/ml.

---

FIG. 5. Brain MR angiography (MRA) in the four patients (A–D). Note hypoplasia of the A1 segment of both ACA predominantly the right one (A, arrow 1). Mild asymmetry of both ACA predominantly the right one (B, arrow 2) and severe hypoplasia are evident (C, arrow 3). No variant (D, arrow 4). No typical single ACA (azygous) was found in all four patients.
hydrocephalus, which subsequently led to severe motor and cognitive impairment. Unfortunately, it was not possible to measure his height due to fibrotendinous retractions, although his other pituitary hormones and pubertal development were normal. A patient with rhombencephalosynapsis and an abnormality of the pituitary gland was reported by Michaud et al. [1982]. Yachnis [2002] described a patient with rhombencephalosynapsis and massive hydrocephalus, although pituitary dysfunction was not found. Considering that three of four patients had neither GH deficiency nor extensive brain damage, it is still not possible to include GH deficiency as part of the extended phenotype of GLH syndrome.

The psychiatric evaluation of these patients did not disclose any psychotic, depressive, manic, obsessive, compulsive, or anxiety disorders. None had a familial history of psychiatric disorders. The application of SCID has confirmed the absence of Axis I diagnosis in the first three patients. BD, proposed by Brocks et al. [2000] as an expanded phenotype of GLH syndrome, was ruled out in these patients. However, our patient 2 showed symptoms of hyperactivity, inattentiveness, severe speech problems, and sleep disturbance which led us to distinguish ADHD from BDCA. BD symptoms often begin in the late 20s or during the 30s, whereas those with early onset are thought to harbor some genetic susceptibility. Some reviews consider the distinction between ADHD and BDCA. Geller et al. [2002] highlighted only manic symptoms such as euphoria and outgoing humor to be diagnostic of BDCA; irritability and hyperactivity were considered too nonspecific to differentiate the disorders. Children with BDCA have greater mood impairment and their activities tend to be more direct than children with ADHD. Moreover, the presence of psychotic symptoms in some cases of (hypo)mania help to distinguish one from the other. Co-morbidity between both is rather common in prepubertal BD [Geller et al., 2002]. Absent self-magnificence, euphoria, disruptive behavior, extreme irritability,
tantrums, depressive, or psychotic symptoms in our patient 2 are more likely to correspond to ADHD. Nevertheless, it cannot be ignored that this patient will not present some of those BD symptoms later. Thus, patient 2 should be followed-up to establish the diagnosis correctly. Because of these considerations, it is not possible to rule out psychiatric problems as being part of the extended phenotype of GLH syndrome.

Tan et al. [2005] described the first case of GLH syndrome with prenatal MRI findings and proposed that the diagnosis of this syndrome should be considered whenever rhombencephalosynapsis is found prenatally.

Whetsell et al. [2006] reported a patient with a single ACA consistent with an azygous ACA. They suggested that this finding could represent an expansion of the phenotype, as it has not been reported in previous cases, probably because MRA had not been pursued. Nevertheless, this could be an incidental finding, as an azygous ACA is known to be a normal variant. Since none of our four patients had typical azygous ACA but only normal variants, we consider it not to be part of the expanded phenotype of GLH syndrome.

Bowdin et al. [2007] described a 2-year-old boy with hydrocephalus, rhombencephalosynapsis, and scalp alopecia and hypothesized the diagnosis of GLH syndrome. Considering that scalp alopecia was associated with seborrhea and other features were absent, including facial dysmorphism, craniosynostosis, and trigeminal anesthesia, we suggest this child should be followed-up to confirm or exclude this hypothesis.

**Molecular Insights**

Gómez [1979] proposed that the origin of the condition was a developmental arrest in the ectoderm from which the cerebellar swellings, visceral fibers of the trigeminal nerve, and epidermal cells arise. The common embryological derivation from the neural ectoderm may provide an important clue to the pathogenesis of this syndrome [Tan et al., 2005]. The distinctive morphologic feature of rhombencephalosynapsis probably results from failure of induction of midline structures, rather than failure of fusion, and is best classified as focal dysplasia [Patel and Barkovich, 2002]. This anomaly could be caused by a lack of expression of known cerebellar patterning genes, such as WNT1, FGF8, FGF17, and OTX2. The fgf8 and fgf17 mouse homologs were localized to specific sites in midline structures of the forebrain and midbrain-hindbrain junction, particularly in the cerebellar vermis, as well as in the epithelium [Xu et al., 2000]. Another candidate gene for rhombencephalosynapsis has been identified in a neurological mutant mouse Drehed (dr), which harbored a homozygous mutation of the Lmx1a gene that resulted in agenesis of the vermis with apparent fusion of the cerebellar hemispheres [Millonig et al., 2000]. Boulshauser [2004] suggested that Mendelian inheritance of this unique malformation appears to be ruled out because all reported cases have been sporadic. However, one patient with additional facial anomalies was associated with consanguinity [Romanengo et al., 1997]. Our patient 1 is the first bona fide GLH syndrome case to be associated with consanguinity.

Mannan et al. [2004] found that nax mice were reminiscent of a neurocutaneous condition that resembles cerebellotrigeminal-dermal dysplasia, and it was hypothesized that ACP2 mutations could cause GLH syndrome. Because no pathogenic mutations were found in 11 exons of the ACP2 gene in the four unrelated patients that we assessed, it is unlikely to be a candidate gene for GLH syndrome.

Chromosomal abnormalities are not associated with GLH syndrome to date. Subtelomeric analysis was recently performed by using multiplex ligation-dependent probe amplification (MLPA) [Tan et al., 2005] and fluorescence in situ hybridization (FISH) [Schell-Apacik et al., 2007], but no abnormalities were detected. Comparative genomic hybridization (CGH) analysis with 36k BAC clones was first performed by Schell-Apacik et al. [2007] in a patient with GLH syndrome. However, all abnormalities found (partial deletions at 1p, 8q, 10q, Xq, and a partial duplication at 19p) were considered normal variants of no pathogenic relevance.

We speculate that some target genes should be studied as possible candidates for GLH syndrome: FGF8, particularly FGF8, 17, and 20, which are crucial for cerebellar and epithelial development, and FGF22, which plays a role in hair follicle development.

**ACKNOWLEDGMENTS**

The authors would like to thank Dr. André Reis, Cornelia Kraus, and Martin Zenker of the Institute of Human Genetics of the University of Erlangen-Nuremberg, Germany for sequencing the ACP2 gene in our patients. We also thank the patients, families, and caregivers.

**REFERENCES**


