Fetal Diagnosis and Therapy

Prenatal Diagnosis

Fetal Diagn Ther 2023;50:92–97
DOI: 10.1159/000530643

Received: January 20, 2023
Accepted: April 4, 2023
Published online: April 14, 2023

Prenatal Diagnosis of Gómez-López-Hernández Syndrome

Léo Pomar[a, b] Wawrzyniec Rieder[a] Estelle Dubruc[c] Fabienne Giuliano[d]
Isis Atallah[d] Sébastien Lebon[e] Yvan Vial[a]

[a]Ultrasound and Fetal Medicine Unit, Department Woman-Mother-Child, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland; [b]School of Health Sciences (HESAV), HES-SO University of Applied Sciences and Arts Western Switzerland, Lausanne, Switzerland; [c]Department of Pathology, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland; [d]Department of Medical Genetics, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland; [e]Pediatric Neurology Unit, Department Woman-Mother-Child, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland

Established Facts

- Gómez-López-Hernández syndrome is a rare neurocutaneous disease characterized by the association of rhombencephalosynapsis with trigeminal anesthesia, alopecia, and facial dysmorphism.
- A genetic etiology for this syndrome is postulated, although no recurrent chromosomal or genetic variants have been identified to date.
- Postnatal framework to diagnose Gómez-López-Hernández syndrome is inappropriate for prenatal diagnosis.

Novel Insights

- As the exact genetic etiology remains unknown, prenatal diagnosis is mainly based on imaging and adaptation of postnatal criteria to fetuses.
- The association of rhombencephalosynapsis with characteristic facial dysmorphism on ultrasound is evocative of Gómez-López-Hernández syndrome.

Keywords
Rhombencephalosynapsis · Gómez-López-Hernández syndrome · Neurosonography · Cerebellum · Ventriculomegaly

Abstract
Introduction: Gómez-López-Hernández syndrome (GLHS), also known as cerebello-trigeminal-dermal dysplasia, is an extremely rare neurocutaneous disease, classically described

karger@karger.com
www.karger.com/fdt

Correspondence to:
Léo Pomar, Leo.pomar@chuv.ch

by the triad of rhombencephalosynapsis (RES), bilateral focal alopecia, and trigeminal anesthesia. The clinical and radiographic spectrum of GLHS is now known to be broader, including craniofacial and supratentorial anomalies, as well as neurodevelopmental issues. ***Case Presentation:*** Here, we present a case of antenatally diagnosed GLHS with RES, hydrocephaly, and craniofacial anomalies identified on ultrasound (low-set ears with posterior rotation, hypertelorism, midface hypoplasia, micrognathia, and anteverted nares) which were confirmed by autopsy after termination of pregnancy at 23 weeks of gestation. ***Discussion:*** As no known genetic causes have been identified and the classical triad is not applicable to prenatal imaging, prenatal diagnosis of GLHS is based on neuroimaging and the identification of supporting features. In presence of an RES associated with craniofacial abnormalities in prenatal (brachycephaly, turricephaly, low-set ears, midface retrusion, micrognathia), GLHS should be considered as "possible" according to postnatal criteria.

Introduction

Gómez-López-Hernández syndrome (GLHS), also known as cerebello-trigeminal-dermal dysplasia, is an extremely rare neurocutaneous disease, described in less than 40 patients to date. It presents with a classical triad of rhombencephalosynapsis (RES), bilateral focal alopecia, and trigeminal anesthesia [1]. Supporting features such as facial dysmorphism (midface hypoplasia and low-set ears) and growth retardation are frequent [2]. The majority of patients will display some degree of intellectual disability and behavioral disorders. To date, its etiology remains unclear, and no known genetic causes have been identified [3]. Diagnosis is usually late with only few cases detected during the neonatal period. Here, we present a case of antenatally diagnosed GLHS.

Case Report

We present a case of a 26-year-old primigravida woman. She had an uneventful first trimester of pregnancy, and her routine serology screening, performed at 8 weeks of gestation, did not reveal recent infection with rubella, cytomegalovirus, or syphilis. Both she and her partner had an uncomplicated personal and family history and were not consanguineous. There was no exposure to teratogenic factors. The patient was first referred to our ultrasound unit by her physician for a first-trimester ultrasound that was performed at 12 weeks and 4 days. The crown-rump length of 65 mm was consistent with the last menstrual periods, fetal nuchal translucency was measured at 1.2 mm, and no fetal abnormalities were found at this early stage. Results of the combined screening showed a low risk for trisomy 21 (1/2,253) but an increased risk for trisomy 13 and 18 (1/320) indicated by low PAPP-A and B-hCG levels (0.251 MoM and 0.561 MoM, respectively). The patient has been offered a non-invasive prenatal testing which showed a low risk for common aneuploidies. Retrospective assessment of the first-trimester imaging suggested mild dilatation of the third and lateral ventricles with a "dangling choroid" aspect, suggestive of ventriculomegaly (online suppl. Fig. 1; for all online suppl. material, see www.karger.com/doi/10.1159/000530643).

An early anatomy scan performed at 16 weeks and 4 days showed bilateral ventriculomegaly (13 mm) and a dilated third ventricle (4 mm). The transverse cerebellar diameter was measured below the 5th centile (13 mm), and a fused aspect of the cerebellar hemispheres, without identification of the vermis, was characteristic of a complete RES (online suppl. Fig. 2). The rest of fetal biometrics were within the normal range, and full examination did not find other structural abnormalities. Following a genetic counseling, amniocentesis was performed. No chromosomal or subchromosomal anomalies were identified on CGH array (500 kb resolution). Whole-exome sequencing was performed and no pathogenic or likely pathogenic variants were identified.

A dedicated neuro-sonography was performed at 21 weeks and confirmed the presence of obstructive hydrocephaly with lateral ventricles, measuring 21 mm (left) and 19 mm (right). The third ventricle measured 5 mm. Cavum septi pellucidi could not be clearly identified, and a gap suggestive of a destructive process was seen in the anterior interhemispheric fissure. The corpus callosum was complete but laminated. The gyri of the cerebral parenchyma were difficult to identify, with no visible Sylvian or calcarine fissures. Finally, the aspect of the cerebellum was typical of an RES: complete fusion of the cerebellar hemispheres without vermis (Fig. 1). Signs of facial dysmorphism including retrognathism, hypertelorism, midface retrusion, anteverted nares, and low-set ears with posterior rotation of the left one were noticed on extracerebral examination (Fig. 2).

In view of the association between hydrocephaly and RES, a multidisciplinary counseling with a pediatric neurologist informed the patient regarding a high risk of neurodevelopmental delay. The prognosis of RES diagnosed prenatally, being often complete, could be worse than those diagnosed postnatally (including more often partial RES with better prognosis) [4]. In addition, the presence of a dysmorphic face and head was suggestive of a syndromic association such as GLHS. The couple opted for a termination of pregnancy, and a feticide was performed at 23 weeks and 3 days. Following induction of labor, she delivered a male fetus of 705 g.

Fetal autopsy confirmed the presence of RES and dilated lateral ventricles (Fig. 1). Aqueduct of Sylvius was permeable. Fetal face presented with external appearance of turricephaly without signs of craniosynostosis, hypertelorism, low-set ears with posterior rotation of the left one, micro-retrognathia, a large mouth with a smooth philtrum, and a thin upper lip (Fig. 2). Those findings are consistent with the diagnosis of GLHS. Given the early gestational age, the presence nor the absence of alopecia could be assessed because the morphology of pilosebaceous follicles was not yet evaluable.

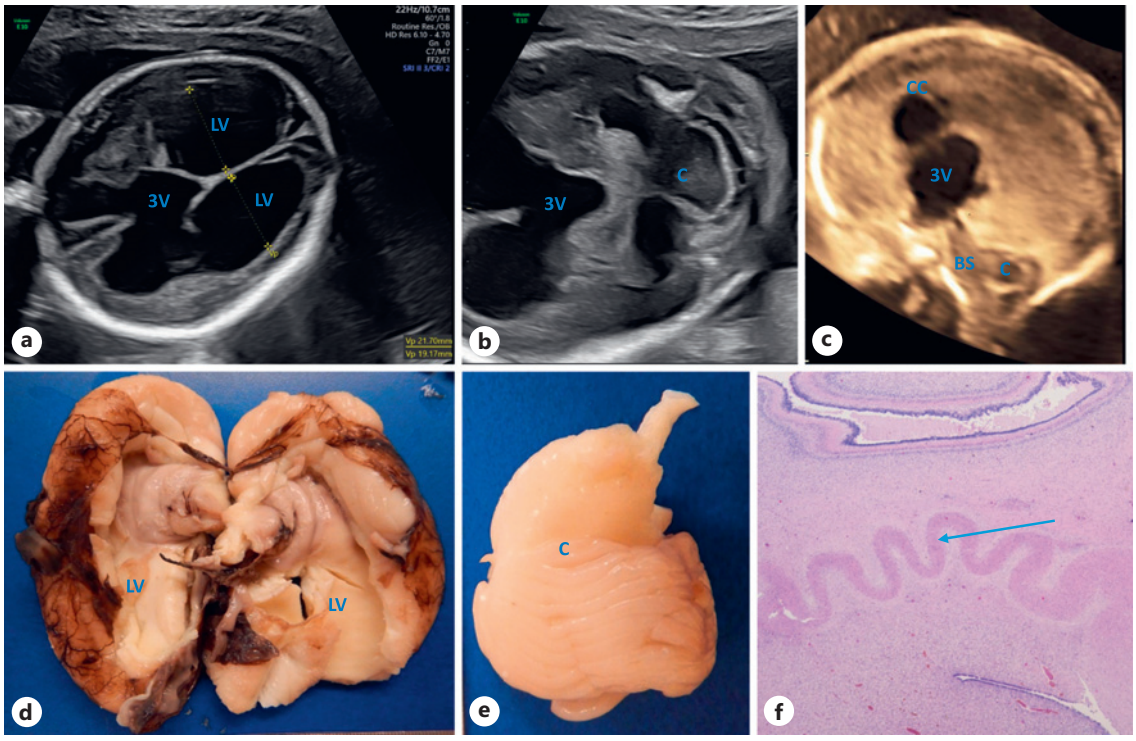

Fig. 1. Correlation between neurosonography at 21 weeks and neuropathology. **a** Trans-ventricular US axial view with severe ventriculomegaly, destruction of the septal leaflets, and simplified gyrus. **b** US axial view of RES: complete fusion of the cerebellar hemispheres without vermis. **c** US mid-sagittal view with dilated 3rd ventricle, obstructive hydrocephaly, and laminated corpus callosum. **d** Sagittal sections of the brain with ventriculomegaly and no gyrus identified. **e** Macroscopic aspect of RES: complete fusion of the cerebellar hemispheres. **f** Microscopic axial section of the cerebellum with fusion of the dentate nucleus (arrow). 3V, third ventricle; BS, brainstem; C, cerebellum; CC, corpus callosum; LV, lateral ventricles; US, ultrasound.

Discussion

The first clinical presentation of cerebello-trigeminal-dermal dysplasia was described in 1979 in a female infant presenting with severe developmental delay associated with brachycephaly, hypertelorism, keratitis, and facial analgesia [5]. In 1982, López-Hernández described two other infants with similar features associated with a pontocerebellar fusion and a fourth ventricle atresia on computed tomography. Both patients had midfacial hypoplasia, bilateral corneal opacities, low-set ears, and a neurodevelopmental delay [6].

Although GLHS syndrome was classically described as a triad of RES, bilateral alopecia, and trigeminal anesthesia [1, 2, 7], the spectrum of the disease appears to be broader. Indeed, craniofacial anomalies such as low-set ears, brachycephaly, plagiocephaly, midface retrusion, strabismus, and hypertelorism are found in 80–90% of cases [8]. Severe ventriculomegaly/hydrocephaly is seen in two-thirds of these cases and cerebellar hypoplasia in one-third [8, 9]. Neurodevelopmental issues are frequent. Almost all patients fail to reach appropriate motor milestones and 70% present some degree of intellectual disability. Behavioral disorders such as hyperactivity, self-injurious behavior, and bipolar disorders have also been reported [10]. In addition, while RES and scalp alopecia are found in all cases, associated trigeminal dysfunction has been reported in less than 60% of cases [11].

To date, no genetic causes have been identified. A recent report identified a 1.05 Mb copy duplication at 15q21.3 in one case which was classified as of unknown clinical significance [3]. A mutation in the *ACP2* gene has caused a similar phenotype in mice and has been proposed as a possible candidate in the past but no such pathogenic or likely pathogenic variant has been found in humans [12, 13]. One child with GLHS was born to consanguineous parents, raising the possibility of a yet undiscovered recessive mutation [14]. Overall, the exact genetic etiology remains unknown, and the diagnosis remains based on neuroimaging and clinical criteria.

When considering prenatal imaging, RES is a hindbrain malformation evocative but not specific to GLHS as it can also be consecutive to global brain division anomalies

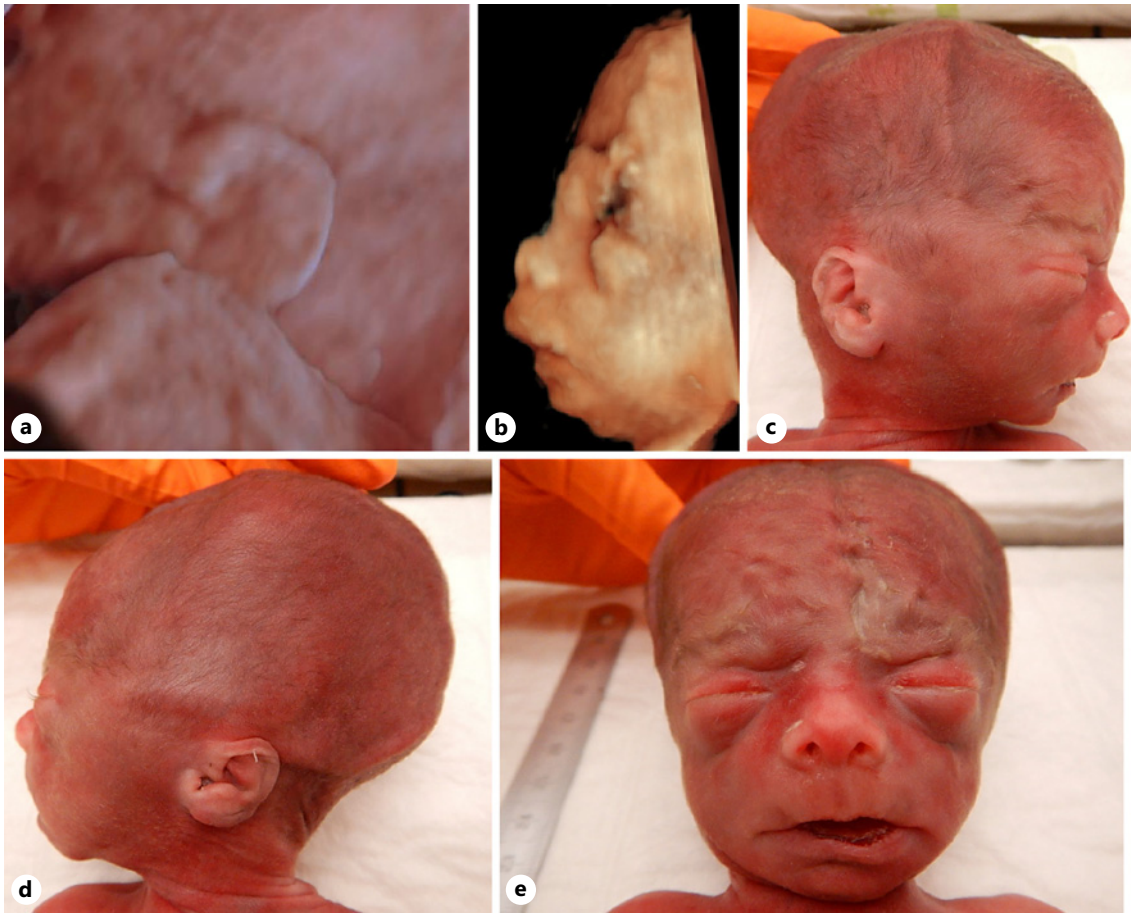

Fig. 2. Correlation between craniofacial anomalies on 3D ultrasound and fetal autopsy. **a** Three-dimensional ultrasound (3D US) view of the left ear: low-set with posterior rotation. **b** 3D US view of the profile: micrognathia, midface retrusion, and overhanging nostrils. **c** Postmortem aspect of the profile, confirming turricephaly, micrognathia, midface retrusion, low-set ears, and overhanging nostrils. **d** Postmortem aspect of the left ear presenting a posterior rotation. **e** Postmortem aspect of the face: hypertelorism, large mouth with long domed philtrum and thin upper lip.

(holoprosencephaly and diencephalo/mesencephalosynapsis), neural tube defects, or VACTERL association [4, 15, 16]. Thus, the absence of pro/mesencephalic division, vertebral, anal, cardiac, tracheal, and limb abnormalities is primordial to evoke GLHS. In addition, the diagnosis of RES can be difficult on prenatal imaging, especially if it is a partial form where the cerebellar diameter is often in the normal range without supratentorial anomalies [15]. Similarly, even if RES is diagnosed, the facial anomalies found in the syndrome may also be difficult to diagnose prenatally, as shown by a case describing RES confirmed by prenatal MRI but where facial dysmorphism was only found after birth [17]. Conversely, the craniofacial features described in GLHS are not specific and might also be encountered in other known syndromes or consecutive to important hydrocephalus or RES without any other etiology being found [16]. Their association with turricephaly and RES is suggestive of GLHS, but we cannot exclude that another etiology, undiagnosable on WES, could be related to these features.

Current diagnostic criteria as proposed by Rush et al. [8] include either the classical triad (RES, scalp alopecia, and trigeminal anesthesia) or the presence of RES, alopecia, and a major craniofacial criteria (brachycephaly, turribrachycephaly, or midface retrusion). According to their classification, our case could be considered as a "possible" GHLS based on these postnatal criteria. However, alopecia and trigeminal neuralgia are unfortunately neither suitable for antenatal diagnosis nor autopsy at an early gestational age. Alopecia was initially thought to be a form of aplasia cutis congenital, but this diagnosis has been refuted in more recently published cases in which

scalp biopsies demonstrate the presence of underdeveloped "vellus-like" pilosebaceous follicles more likely related to temporal triangular alopecia [9]. The morphology of pilosebaceous follicles being not accessible to fetal autopsy before 25 weeks, this prevents the identification of temporal triangular alopecia in early termination of pregnancy. Similarly, we tried to assess the vagus nerve and trigeminal ganglion on autopsy, but we were unable to identify these structures, probably due to the feticide procedure and early gestation [16]. Considering that GLHS is the most common syndrome associated with RES and that our case presents seven anomalies frequently to constantly encountered in GLHS, this diagnosis is likely. We therefore believe that after the exclusion of a genetic cause and in the absence of ultrasound finding compatible with a VACTERL syndrome, the presence of RES and distinctive craniofacial anomalies are suggestive of GLHS diagnosis and that this syndrome should be considered as "possible," according to the criteria of Rush et al. [8], in front of such an association in prenatal. Although a final diagnosis might not be possible before birth, antenatal counseling should focus on the risk of intellectual disability, ataxia, and behavioral disorders.

Statements of Ethics

This research was conducted ethically in accordance with the Declaration of Helsinki. Written informed consent was obtained from the patient for publication of this case report and any accompanying images. According to the Swiss law on human research, case reports do not require the approval of an ethics commission for publication.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

No funding source was secured for this research.

Author Contributions

L.P. performed the ultrasound examinations, conducted the literature research, and wrote the first draft of the manuscript. W.R. performed the ultrasound examinations, gave care to the mother, and wrote the first draft of the manuscript. E.D. performed the autopsy, contributed to the figures, and critically revised the manuscript. F.G. and I.A. provided genetic counseling, interpreted the exome sequencing, and critically revised the manuscript. S.L. provided neurodevelopmental counseling, participated to the interpretation of data, and critically revised the manuscript. Y.V. performed the ultrasound examinations and supervised the first draft of the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material. Further inquiries can be directed to the corresponding author.

References

1 Schell-Apacik CC, Cohen M, Vojta S, Ertl-Wagner B, Klopocki E, Heinrich U, et al. Gomez-Lopez-Hernandez syndrome (cerebello-trigeminal-dermal dysplasia): description of an additional case and review of the literature. Eur J Pediatr. 2008;167(1):123–6.

2 Muñoz R MV, Santos AC, Graziadio C, Pina-Neto JM. Cerebello-trigeminal-dermal dysplasia (Gomez-Lopez-Hernandez syndrome): description of three new cases and review. Am J Med Genet. 1997;72(1):34–9.

3 Lindsay F, Anderson I, Wentzensen IM, Suhrbier D, Stevens CA. Genetic evaluation including exome sequencing of 2 patients with Gomez-Lopez-Hernandez syndrome: case reports and review of the literature. Am J Med Genet. 2020;182(4):623–7.

4 Ishak GE, Dempsey JC, Shaw DWW, Tully H, Adam MP, Sanchez-Lara PA, et al. Rhombencephalosynapsis: a hindbrain malformation associated with incomplete separation of midbrain and forebrain, hydrocephalus and a broad spectrum of severity. Brain. 2012;135(Pt 5):1370–86.

5 Gomez MR. Cerebellotrigeminal and focal dermal dysplasia: a newly recognized neurocutaneous syndrome. Brain Dev. 1979;1(4):253–6.

6 Lopez-Hernandez A. Craniosynostosis, ataxia, trigeminal anaesthesia and parietal alopecia with pons-vermis fusion anomaly (atresia of the fourth ventricle). Report of 2 cases. Neuropediatrics. 1982;13(2):99–102.

7 Fernandez-Jaen A, Fernández-Mayoralas DM, Calleja-Pérez B, Muñoz-Jareño N, Moreno N. Gomez-Lopez-Hernandez syndrome: two new cases and review of the literature. Pediatr Neurol. 2009;40(1):58–62.

8 Rush ET, Adam MP, Clark RD, Curry C, Hartmann JE, Dobyns WB, et al. Four new patients with Gomez-Lopez-Hernandez syndrome and proposed diagnostic criteria. Am J Med Genet. 2013;161A(2):320–6.

9 Bowdin S, Phelan E, Watson R, McCreery KM, Reardon W. Rhombencephalosynapsis presenting antenatally with ventriculomegaly/hydrocephalus in a likely case of Gomez-Lopez-Hernandez syndrome. Clin Dysmorphol. 2007;16(1):21–5.

10 Brocks D, Irons M, Sadeghi-Najad A, McCauley R, Wheeler P. Gomez-Lopez-Hernandez syndrome: expansion of the phenotype. Am J Med Genet. 2000;94(5):405–8.

11 Sukhudyan B, Jaladyan V, Melikyan G, Schlump JU, Boltshauser E, Poretti A. Gomez-Lopez-Hernandez syndrome: reappraisal of the diagnostic criteria. Eur J Pediatr. 2010;169(12):1523–8.

12 Gomy I, Heck B, Santos AC, Figueiredo MSL, Martinelli CE Jr, Nogueira MPC, et al. Two new Brazilian patients with Gomez-Lopez-Hernandez syndrome: reviewing the expanded phenotype with molecular insights. Am J Med Genet. 2008;146A(5):649–57.
13 Perrone E, D'Almeida V, de Macena Sobreira NL, de Mello CB, de Oliveira AC, Burlin S, et al. Gomez-Lopez-Hernandez syndrome: a case report with clinical and molecular evaluation and literature review. Am J Med Genet. 2020;182(7):1761–6.
14 de Mattos VF, Graziadio C, Machado Rosa RF, Lenhardt R, Alves RPM, Trevisan P, et al. Gomez-Lopez-Hernandez syndrome in a child born to consanguineous parents: new evidence for an autosomal-recessive pattern of inheritance? Pediatr Neurol. 2014;50(6):612–5.
15 Krajden Haratz K, Oliveira Szejnfeld P, Govindaswamy M, Leibovitz Z, Gindes L, Severino M, et al. Prenatal diagnosis of rhombencephalosynapsis: neuroimaging features and severity of vermian anomaly. Ultrasound Obstet Gynecol. 2021;58(6):864–74.
16 Pasquier L, Marcorelles P, Loget P, Pelluard F, Carles D, Perez MJ, et al. Rhombencephalosynapsis and related anomalies: a neuropathological study of 40 fetal cases. Acta Neuropathol. 2009;117(2):185–200.
17 Tan TY, McGillivray G, Goergen SK, White SM. Prenatal magnetic resonance imaging in Gomez-Lopez-Hernandez syndrome and review of the literature. Am J Med Genet. 2005;138(4):369–73.