

Co-occurrence of Gomez-Lopez-Hernandez syndrome and Autism Spectrum Disorder: Case report with review of literature

Bakur Kotetishvili¹, Malkhaz Makashvili^{2,*}, Michael Okujava^{3,4}, Alexandre Kotetishvili¹, Tamar Kopadze⁵

¹B.Kotetishvili Psycho-Neurological Clinic, Tbilisi, Georgia;

²Faculty of the Art and Sciences, Ilia State University, Tbilisi, Georgia;

³Research Institute of Clinical Medicine, Tbilisi, Georgia;

⁴Faculty of Natural Sciences and Engineering, Ilia State University, Tbilisi, Georgia;

⁵European University, Tbilisi, Georgia.

Summary

We report on Gomez-Lopez-Hernandez syndrome (GLHS) in a Caucasian patient, Georgian, 36 months, male, only child born to non-consanguineous parents. There were no similar cases in the family and among close relatives. MRI study confirmed rhombencephalosynapsis (fusion of cerebellar hemispheres in combination with the agenesis of cerebellar vermis) and mild dilation of the lateral ventricles. Other main findings are bilateral parieto-temporal alopecia and brachiturricephaly (broad skull shape and tower-like elongation of the cranium in the vertical axis), low-set posteriorly retracted ears, strabismus (in the right eye), hypotonia (Beighton scale score – 6) and ataxia (trouble maintaining balance). Patient has no signs of trigeminal anesthesia, no recurrent, painless eye infections, corneal opacities and ulcerated wounds on the facial skin and buccal mucosa were observed. Based on the scientific literature we suggest a finding of brachiturricephaly in addition to rhombencephalosynapsis and bilateral alopecia sufficient to put a diagnosis of GLHS. Patient did not speak, disregarded guardians and clinician addressing him, did not make eye contact, was restless and occasionally displayed aggression and self-injurious behavior. These symptoms confirm the earlier diagnosis of Autism Spectrum Disorder (ASD). Therefore, the current study describes a case of co-occurrence of GLHS and ASD.

Keywords: Rhombencephalosynapsis, alopecia, brachiturricephaly, Gomez-Lopez-Hernandez syndrome, autism

1. Introduction

Gomez-Lopez-Hernandez syndrome (GLHS) is characterized by so called "GLHS triad" - rhombencephalosynapsis, trigeminal anesthesia and partial bilateral alopecia of the scalp. Rhombencephalosynapsis denotes brain malformation, mainly expressed in agenesis of cerebellar vermis and fusion of the cerebellar

hemispheres. Rhombencephalosynapsis is observed not only in the case of GLHS, but as an isolated phenomenon as well as in combination with other brain malformations (1). Symptoms, concomitant to GLHS triad, are hydrocephalus, craniosynostosis, midfacial hypoplasia and low set ears, as well as bilateral corneal opacities, ocular hypertelorism-telescanthus, strabismus, clinodactyly of fifth fingers, short stature and intellectual impairment (2-15).

The studies of GLHS are limited in number. To our knowledge, a total of 36 cases of GLHS have been described since the first reports of this clinical condition by Gomez (12) and Lopez-Hernandez (14). Symptomatology of GLHS varies from patient to patient (2-15) and further case studies are important to complete the clinical description of this disease.

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*Address correspondence to:

Dr. Malkhaz Makashvili, Faculty of the Art and Sciences, Ilia State University, Cholokashvili st. 3/5, Tbilisi 0113, Georgia.

E-mail: malkhaz_makashvili@iliauni.edu.ge

2. Case Report

Anamnesis: Patient, J.K. (initials are changed), male, Georgian, Caucasian, only child born to non-consanguineous parents. Parents are in good health and there were no similar cases in the family nor among close relatives. Parents do not confirm the incidence of marriage between relatives in their ancestors. J.K. was delivered via Caesarean section, planned beforehand on the mother's demand. Weight at birth – 3.360 kg, length – 52 cm, head circumference - 37 cm. Bilateral parieto-temporal alopecia and brachiturriccephalic dismorphism as well as low-set ears were observed in the first months after birth (Figure 1). Congenital mild hydronephrosis, open foramen ovale and mild deficiency of the tricuspid valve, as well as strabismus were diagnosed one week after birth. J.K. was treated for hydronephrosis. Second examination at the age of 12 months confirmed cessation of cardiological and nephrological complications. At the age of three months J.K. was surgically treated for inguinal hernia. At the age of 5 months, he started to display involuntary head shaking, mainly in posterior direction and increased tension of lower shoulder muscles. EEG examination did not reveal signs of epileptiform activity. EEG parameters were found to fall into age standards. Transfontanel ultrasound revealed dilation of lateral ventricles and longitudinal fissure. At the age of 32 months, J.K. was diagnosed as having Autism Spectrum Disorder (ASD). Diagnostic procedure was performed according to DSM-V criteria and with the use of ADOS-2 and M-CHAT-R™ as additional instruments for completing ASD diagnosis.

The current study: In May 2018, at the age of 36 months J.K. was admitted to the clinic. Weight at the day of admission - 15.300 kg, height - 87 cm and head circumference 48.2 cm. Patient underwent clinical and MRI examination. MRI was performed on 3T scanner (Magnetom Verio, Siemens): T2-(tse), T1-(fl), FLAR, EPI). Pulse sequences in the axial, sagittal and coronal plane were used. Motor development, sensitivity of trigeminal nerve as well as behavior displayed in the clinic were evaluated.

We did not mention any changes in the clinical status of J.K. in the follow up study (June-July 2018). Behavior of J.K. remained unchanged as well.

Parents signed informed consent for publication of the photographs of J.K. in a scientific periodical. Study was conducted in accordance with Declaration of Helsinki principles and has approved by the Ethic Commission of the Georgian Association of Child Neurologists and Neurosurgeons, Tbilisi, Georgia. The results obtained in the current study are summarized in Table 1.

3. Discussion

Absence of cerebellar vermis and fusion of cerebellar

hemispheres, as well as bilateral scalp alopecia are described in all 36 cases of GLHS (see for review 2,9). The current study provides one more description of rombencephalosynapsis and bilateral alopecia in a GLHS sufferer. This is another argument that rombencephalosynapsis and bilateral alopecia represent obligatory symptoms of GLHS. Since it is principal to decide if the presence of trigeminal anesthesia is obligatory for GLHS diagnosis, the data of the literature concerning this issue is summarized in the Table 2.

Authors propose the presence of trigeminal anesthesia and/or bilateral alopecia to complete the diagnosis of GLHS (4). Trigeminal anesthesia, however, was not present in some studies of GLHS. For example, out of four patients only one was found to display trigeminal numbness in (7), one patient out of two was diagnosed as having trigeminal numbness in (3), no signs of trigeminal anesthesia have been revealed in five patients with GLHS (5) and we report on another case of the absence of trigeminal anesthesia in GLHS.

According to (7) "Rhombencephalosynapsis and scalp alopecia are considered obligate criteria for diagnosing GLHS, while trigeminal anesthesia in conjunction with the two obligate criteria represents a diagnosis of GLHS and as such should stand alone as a separate criterion". At the same time, the finding of brachiturriccephaly in addition to rhombencephalosynapsis and bilateral alopecia is considered sufficient to make a diagnosis of GLHS (7). Skull malformation, mainly brachiturriccephaly, is described in most cases of GLHS (see for example 2,7-9). The current study reports on another case of the tower-like deformation of the skull of brachiturriccephalic character. In our opinion, taken together, the data suggest trigeminal anesthesia is not obligatory for diagnosing GLHS in the case of combined rhombencephalosynapsis, alopecia and brachiturriccephaly.

Malformation of the corpus callosum in GLHS is an inconsistent finding: dysgenesis of the corpus callosum in GLHS sufferers is described in (8), thin corpus callosum was revealed in one case of GLHS (6), while other studies do not report on abnormality of this structure in the case of GLHS (4,11). Corpus callosum in J.K. is of normal size and thickness. Arching of the truncus of the corpus callosum (see Figure 1) should be due to the overall cranial and cerebral dismorphism. The finding of the dilation of the lateral ventricle in the current study confirms the presence of ventricular enlargement in GLHS (3). Other brain malformations, described in GLHS sufferers are absence of the septum pellucidum and a thin cortex (3), but not observable in the current study.

As for the law set years, this symptom does not seem obligatory for GLHS, as it is not apparent in some patients with GLHS. For example, authors (5) observed displacement of ears in four out of six patients with GLHS. Strabismus represents a symptom, concomitant

Table 1. Symptoms, observed in the clinical and MRI examination

Symptoms observed	Comments
Craniofacial features:	
Brachiturriccephaly	Broad skull shape and tower-like elongation in vertical axis (Figure 2)
Alopecia	Bilateral parieto-temporal patch of alopecia (Figure 2)
Displaced ears	Low set, posteriorly retracted ears (Figure 2)
Strabismus	
MRI examination	
Rhombencephalosynapsis	Agenesis of cerebellar vermis and fusion of the cerebellar hemispheres (Figure 3)
Other MRI findings	Ventriculomegaly- mild dilatation of the lateral ventricles
Neurodevelopment:	
Hypotonia	Beighton scale score - 6
Ataxia	J.K. experiences trouble maintaining balance
Trigeminal sensitivity	Temperature and touch sensation of the facial skin were found preserved. No recurrent, painless eye infections, corneal opacities and ulcerated wounds on the facial skin and buccal mucosa were observed
Behavior, observed in the clinic	J.K. does not speak, disregards guardians and clinician addressing him, does not keep instructions and makes no eye contact. J.K. is restless, wanders around the room, from time to time grabs the newspapers from the table and rips them. J.K. occasionally displays aggression and self-injurious behavior



Figure 1. (A), The lack of hair (alopecia) in the left parieto-temporal area; (B), The lack of hair (alopecia) in the right parieto-temporal area, the head elongated in the vertical axis and the low-set ears; (C), The head elongated in the vertical axis and deformed corpus callosum - CC (MRI, sagittal plane). CC deformation is expressed in arching of the middle part of the CC.

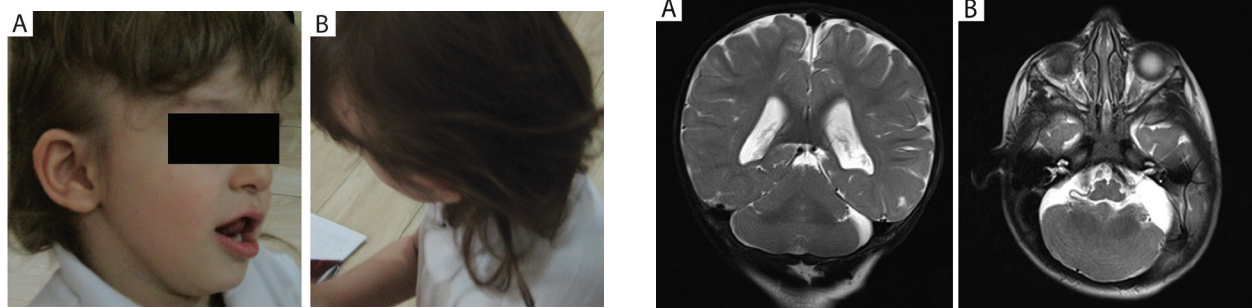


Figure 2. (A), The lack of hair (alopecia) in the right parieto-temporal area and low-set, posteriorly-retracted ears; (B), The lack of hair (alopecia) in the left parieto-temporal area.

Figure 3. Fusion of the cerebellar hemispheres and agenesis of the cerebellar vermis. (A), MRI, T2-weighted image, coronal plane; (B), MRI, T2-weighted image, axial plane.

Table 2. GLHS triad as it is described in the current study and in previous reports on GLHS

Symptoms observed	In the current study	References
Alopecia	observed	observed in 2-15
Rhombencephalosynapsis	observed	observed in 2-15
Trigeminal anesthesia	not observed	not observed in 3,5-7,15; observed in 2,4,7,9, 10,12,14-16.

Digits stand for the number of the manuscript, given in references

to GLHS (2,4,5,7,8,12), however this symptom is not observable in all cases of GLHS (for review see 7,9) and is considered minor craniofacial criteria for diagnosing GLHS (7). We did not observe ptosis in J.K., however it is described in the literature in a few cases of GLHS (5). Similar to the case of J.K., hypotonia and ataxia are mentioned in several reports of GHLS. For example, according to the earlier review of the literature (7) ataxia was described in 73% of patients with GHLS and hypotonia in 77% of GHLS sufferers, while according to a contemporary review (13) the percentage of reports on the presence of ataxia and hypotonia in GHLS patients is 82%.

Cognitive impairment is found in most previously reported patients with GLHS. However, in some cases, cognitive functions are found preserved (for review see 5). Motor restlessness of the GLHS sufferer under our examination is not a new finding since it is observed in other studies of GLHS (4,10). Authors report on psychiatric problems such as hyperactivity, depression, self-injurious behavior and bipolar disorder in patients with GLHS (3,10,15). Co-occurrence of schizophrenia with GLHS is reported as well (11). J.K. was diagnosed as having ASD. On the one hand, we did not find reports on the co-occurrence of ASD and GLHS in the available literature. On the other hand, there are some neurodevelopmental and genetic disorders, which GLHS and ASD may have in common. Cerebellar malformation deserves special attention in this respect. Neocerebellar vermal lobules VI and VII were found to be significantly smaller in patients with autism spectrum disorder (17,18) and atrophy of the vermis is observed in autism sufferers (20). Malformation of cerebellar structures is believed to play a role in intellectual impairment in autism sufferers (18,20,21). Autism was diagnosed in a patient with partial rhombencephalosynapsis (22). Chromosomal mutations in particular cases of rhombencephalosynapsis are associated with autism (23). Evidently, cerebellar malformation is responsible for autistic symptomatology. In our opinion, the current case study suggests rhombencephalosynapsis in GLHS is a structural reason for the development of Autistic Spectrum Disorder in Gomez-Lopez-Hernandez syndrome sufferers.

The genetic background for GHLS is not clear (for review see 4). Similar to some GLHS sufferers (3,4,13,15) and in contrast to some other GLHS patients (3,8,9), J.K. is born to nonconsanguineous parents. At the same time, his parents do not have genetic abnormalities and they do not have witness to a case of marriage between relatives in their ancestors. We hope that these facts may be helpful in further consideration of the role of inheritance in the development of GLHS.

4. Conclusion

Clinical and MRI examination of the patient, male, 36 months, born to non-consanguineous parents revealed

rhombencephalosynapsis, bilateral parieto-temporal alopecia and brachiturricephaly. The patient has no signs of trigeminal anesthesia. Based on the scientific literature we suggest a finding of brachiturricephaly in addition to rhombencephalosynapsis and bilateral alopecia sufficient for a diagnosis of GLHS. Concomitant symptoms are dilation of the lateral ventricles, low-set posteriorly retracted ears, strabismus, ataxia and hypotonia. Patient was diagnosed to have severe symptoms of ASD. Therefore, the current study describes a case of co-occurrence of GLHS and ASD.

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