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SHORT REPORT

Gomez-Lopez-Hernandez syndrome (cerebello-trigeminal-dermal dysplasia): description of an additional case and review of the literature

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Abstract Gomez-Lopez-Hernandez syndrome is a very rare genetic disorder with a distinct phenotype (OMIM 601853). To our knowledge there have been seven cases documented to date. We report on an additional male patient now aged 15 8/12 years with synostosis of the lambdoid suture, partial scalp alopecia, corneal opacity, mental retardation and striking phenotypic features (e.g., brachyturricephaly, hypertelorism, midface hypoplasia and low-set ears) consistent with Gomez-Lopez-Hernandez syndrome. In early childhood the patient demonstrated aggressive behavior and raging periods. He also had seizures that were adequately controlled by medication. Magnetic resonance imaging (MRI) revealed rhombencephalosynapsis, i.e., a rare fusion of the cerebellar hemispheres, also consistent with Gomez-Lopez-Hernandez syndrome. In addition a lipoma of the quadrigeminal plate was observed, a feature not previously described in the seven patients reported in the literature. Cytogenetic and subtelomere analyses were inconspicuous. Microarray-based comparative genomic hybridization (array-CGH) testing revealed five aberrations (partial deletions of 1p21.1, 8q24.23, 10q11.2, Xq26.3 and partial duplication of 19p13.2), which, however, have been classified as normal variants. Array-CGH has not been published in the previously reported children. The combination of certain craniofacial features, including partial alopecia, and the presence of rhombencephalosynapsis in the MRI are suggestive of Gomez-Lopez-Hernandez syndrome. Children with this syndrome should undergo a certain social pediatric protocol including EEG diagnostics, ophthalmological investingation, psychological testing, management of behavioral problems and genetic counseling.

Keywords Cerebello-trigeminal-dermal dysplasia · Behavioral problems · Partial scalp alopecia · Rhombencephalosynapsis · Quadrigeminal plate lipoma

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Introduction

Gomez-Lopez-Hernandez syndrome is a very rare genetic disorder first described in 1979 by Gomez [4] in a girl aged 4 1/2 years and in 1982 by Lopez-Hernandez [6] in two female patients aged 10 years and 11 years, respectively. To date, seven cases have been documented in total [1, 7]. Reported clinical findings included mental retardation, partial scalp alopecia in the parietal and occipital region, asymmetrical skull due to craniosynostosis, gait ataxia, facial anesthesia and secondary corneal opacities and a distinct facial appearance including low-set ears, midfacial hypoplasia, hypertelorism and

Table 1 Comparison of the phenotype of the literature cases and our case (+: trait is present; −: trait is absent; ?: not-informative, i.e., trait was described neither as present nor as absent in the patient)

Trait	Patients							
	1	2	3	4	5	6	7	8
Asymmetrical skull	+	+	+	+	+	+	+	+
Partial scalp alopecia	+	+	+	+	+	+	+	+
Midfacial hypoplasia	+	+	+	+	+	+	+	+
Hypertelorism	+	+	+	+	−	+	+	+
Antimongoloid eye axis	−	+	−	?	−	+	−	+
Low-set ears	+	+	+	+	+	+	+	+
Clinodactyly of the fifth fingers	?	+	+	+	+	+	+	−
Short stature	−	+	+	+	+	+	+	−
Corneal opacities	+	+	+	+	+	+	+	+
Corneal and facial anesthesia	+	+	+	+	+	+	+	+
Muscular hypotonia	+	?	?	?	?	?	+	+
Gait ataxia	+	+	+	+	+	+	?	+
Cerebellar/ brainstem anomaly	?	+	+	?	+	+	+	+
Other brain anomalies	?	+	−	+	+	−	+	+
Mental retardation	+	+	+	+	+	−	+	+
Seizures	?	?	?	?	?	?	+	+
Behavioral problems	?	?	?	?	?	?	+	+

Patient 1: Gomez MR, Brain and Development, 1, 253–256, 1979
Patient 2: López-Hernández A., Neuropediatrics, 13, 99–102, 1982
Patient 3: López-Hernández A., Neuropediatrics, 13, 99–102, 1982
Patient 4: Muñoz M.V. et al., Am J Med Genet, 72, 34–39, 1997
Patient 5: Muñoz M.V. et al., Am J Med Genet, 72, 34–39, 1997
Patient 6: Muñoz M.V. et al., Am J Med Genet, 72, 34–39, 1997
Patient 7: Brocks D. et al., Am J. Med Genet, 94, 405–408, 2000
Patient 8: our case

clinodactyly of the fifth finger (compare Table 1). Neuroradiological studies including magnetic resonance imaging (MRI) revealed rhombencephalosynapsis in three patients and brainstem hypoplasia in three additional cases. Other findings like brain atrophy, moderate hydrocephalus, hypoplasia of the cerebellum and an arachnoid cyst were also reported in selected cases. Cytogenetic analyses were performed in five cases with normal results.

Clinical report

The index patient is the fourth child of his single mother. The boy was delivered after an uneventful pregnancy at the 37th gestational week. His birth length (49 cm; p 50) and his birth weight (2,330 g; <p 25) were normal. His head circumference (31 cm) was below the normal range (<p 10). He had feeding problems in the neonatal period, and both a synostosis of the lambdoid suture and a brachyturricephaly were observed. Additionally, a cerebellar hypoplasia was suspected on transcranial ultrasonography. The boy's further development was delayed. In early childhood the patient demonstrated behavioral problems with aggressive behavior and periods of raging. He also had seizures, which were adequately controlled by antiepileptic medication.

Both at the age of 3 8/12 years (Fig. 1) and at the age of 15 8/12 years (Fig. 2) he presented as a cooperative mentally retarded boy with distinct dysmorphic features. These included brachyturricephaly, a flat profile, a high, broad forehead, partial scalp alopecia in the parietal and occipital region, hypertelorism, antimongoloid eye axis, low-set, broad ears, an inverted mucous upper lip, a lanky build and long fingers and toes (compare Table 1). At the age of 15 8/12 years his height (173.5 cm; p 50) was normal, while his weight (71.7 kg; <p 10) and his head circumference (49.5 cm; <p 3) were below the normal range.

At the age of 3 5/12 years cranial magnetic resonance imaging (MRI) was performed. Rhombencephalosynapsis with fusion of the cerebellar hemispheres and absence of the vermis was noted. In addition, a small lipoma of the quadrigeminal plate was discovered (Fig. 3). The remainder of the MR study was reported as normal.

Cytogenetic and array-CGH results

Chromosome analysis and subtelomere fluorescence in situ-hybridization (FISH) yielded normal results. To investigate the patient's genomic DNA for submicroscopic aberrations, we used a whole genome tiling path BAC array consisting of 36,000 BAC clones. The patient's and reference DNA

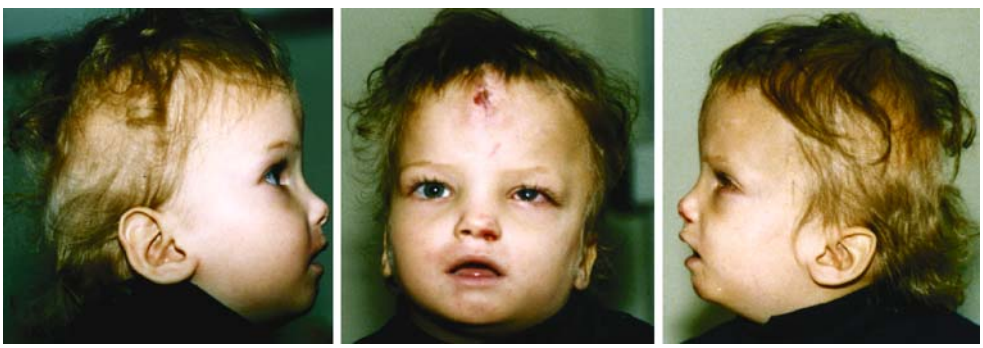

Fig. 1 Patient at the age of 3 8/12 years

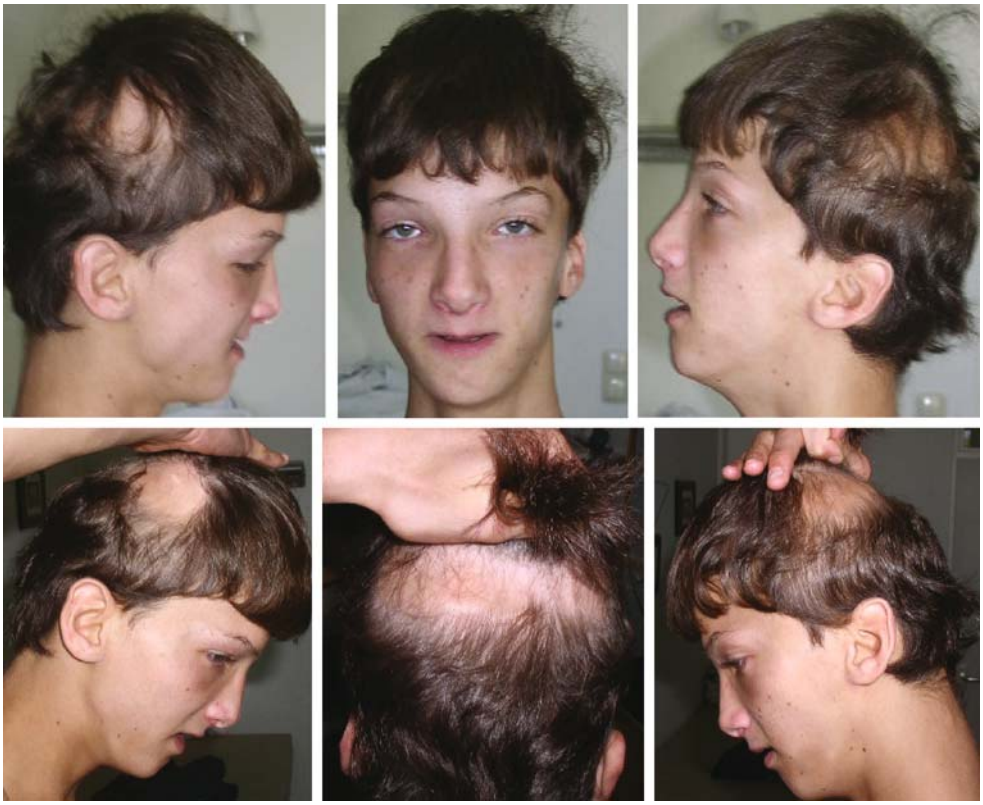

Fig. 2 Patient at the age of 15 8/12 years

were labeled using the Bioprime CGH labeling kit (Invitrogen) and hybridized on the array (Slide-Booster, Implen). Analysis and visualization were performed with CGHPRO software [2]. Copy number changes were determined by a conservative log2ratio threshold (gain ≥0.3; loss ≤−0.3). Profile deviations consisting of ≥ three neighboring BACs are considered as genomic aberrations.

We detected five aberrations: partial deletions of 1p21.1, 8q24.23, 10q11.2, Xq26.3 and partial duplication of 19p13.2. However, all of these aberrations have been classified as genomic variants [3]. According to today's state of knowledge these variants are of no pathogenetic relevance (Fig. 4).

Discussion

Gomez-Lopez-Hernandez syndrome was first described by Gomez [4] and López-Hernández [6]. The syndrome has a distinct phenotype including asymmetrical skull, partial scalp alopecia, corneal opacity, corneal and facial anesthesia, ataxia and some dysmorphic features. Cerebellar anomalies including rhombencephalosynapsis have been described in three patients (Table 1). Quadrigeminal plate lipoma as observed in our patient has not been described in the seven patients with Gomez-Lopez-Hernandez syndrome previously reported in the literature.

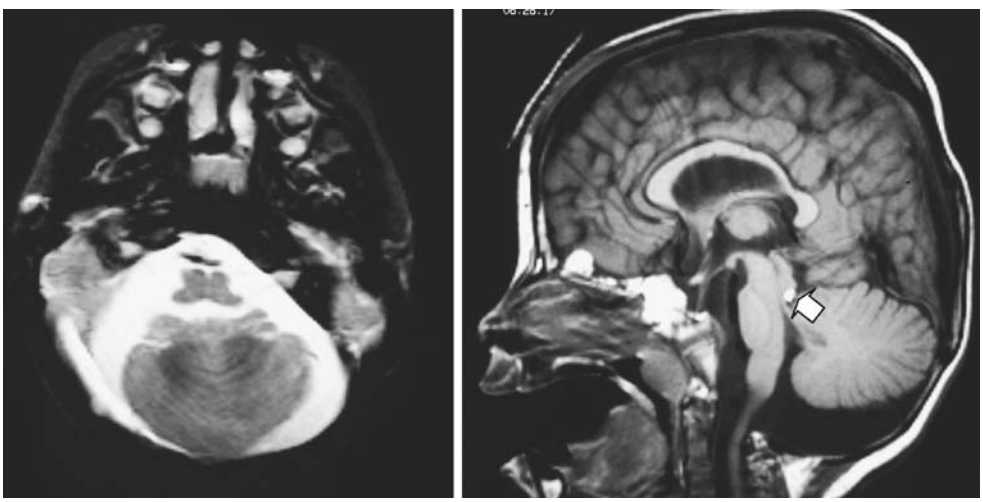

Fig. 3 Cranial magnet resonance imaging of the patient showing rhombencephalosynapsis and a small lipoma at the lower border of the quadrigeminal plate (arrow)

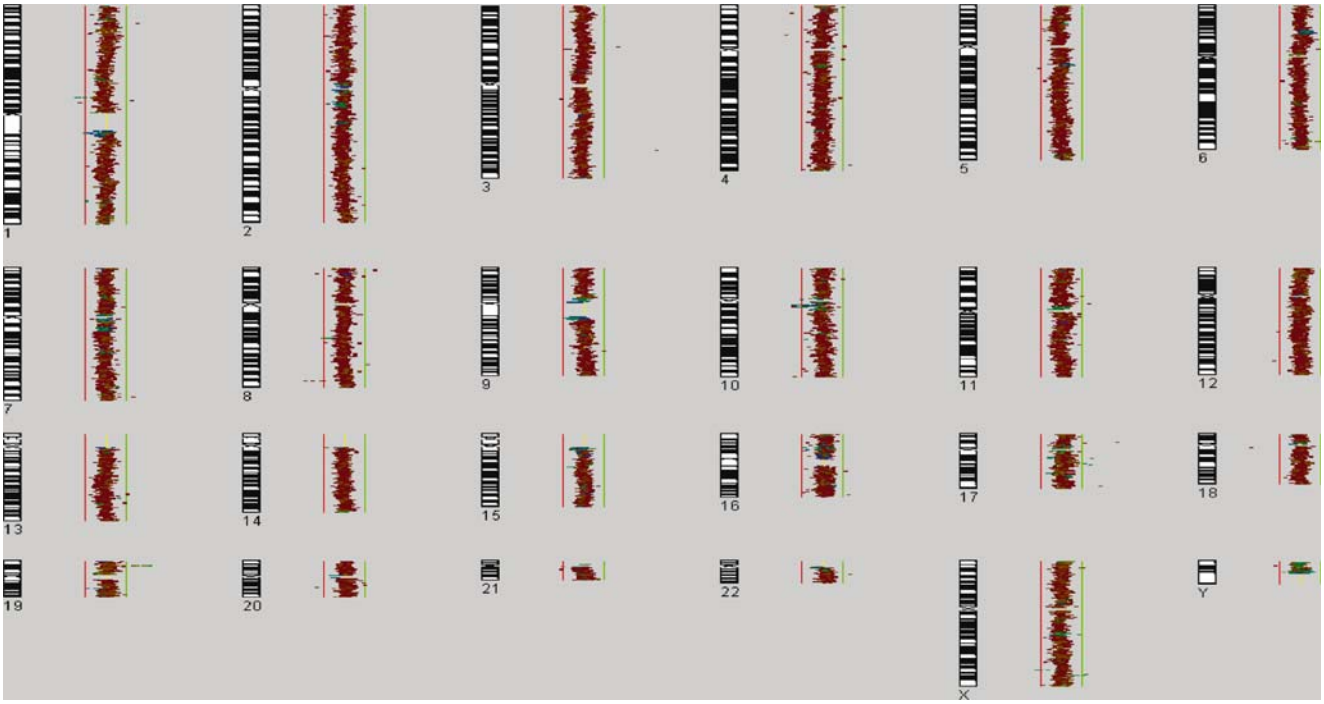

Fig. 4 Array-CGH profile in our patient. Five aberrations were detected: partial deletions of 1p21.1, 8q24.23, 10q11.2, Xq26.3 and partial duplication of 19p13.2. However, all of these aberrations can be classified as genomic variants according to today's state of knowledge (database of genomic variants; http://projects.tcag.ca/variation/)

It was postulated by Gomez in 1979 and 1987 [4, 5] that the syndrome is due to disturbances in the embryonic development of the ectoderm, which gives rise to the alar plate of the rhombencephalon, the overlying epidermis and the trigeminal placodes.

Cytogenetic analyses performed in five literature cases as well as in our patient were inconspicuous. In addition, subtelomere FISH was inconspicuous in our patient. High-resolution array-CGH analysis, which has not been reported in the previously published cases, revealed five aberrations in our patient: partial deletions of 1p21.1, 8q24.23, 10q11.2, Xq26.3 and partial duplication of 19p13.2, which have to be considered variants of no pathogenetical relevance according to today's state of knowledge. Thus, Gomez-Lopez-Hernandez syndrome may on the one hand be caused by mutations below the detection limit of the 36 k BAC array. On the other hand, it may be caused by a combination of aberrations-while each of the aberrations in and by itself is considered a normal variant, they may together be causative for the distinct phenotype observed. Additional studies are necessary to further elucidate the biological bases of Gomez-Lopez-Hernandez syndrome.

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