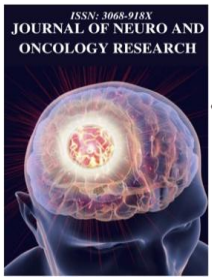

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Case Report

Brain Abnormalities in a Boy with the Goldenhar-Gorlin Syndrome Spectrum and 19p13.2 Microduplication

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Abstract

Background: Oculo-Auriculo-Vertebral Spectrum (OAVS)/Goldenhar-Gorlin syndrome is primarily characterized by extraneurological features that vary in severity, including vertebral and renal anomalies. In addition, patients with this condition often exhibit varying degrees of intellectual disability, behavioral abnormalities and language impairment. There are few reports of neuroimaging findings in these patients and genetic investigations have shown inconsistent results. Methods and Results: We present the case of a child who exhibited all the extraneurological features of the syndrome, except for vertebral and renal involvement. The patient presented with neurodevelopmental delay and peculiar language impairment. Interestingly, neuroimaging revealed anterior dysplasia of the corpus callosum and dysmorphism of both anterior hippocampi. Notably, the patient also had microduplication at 19p13.2, which has not yet been reported in association with this condition. Conclusions: Though microdeletions at 19p13.2 are occasionally found in other similar syndromic conditions, such as Malan syndrome, microduplications have never been associated with Goldenhar-Gorlin syndrome. In the present case microduplications have never, they notably accompany previously unreported callosal and hippocampal abnormalities.

Keywords: Microduplication; Oculo-Auriculo-Vertebral Spectrum (OAVS); Goldenhar-Gorlin; Corpus Callosum; Language Defects

Introduction

Oculo-Auriculo-Vertebral Spectrum (OAVS)/Goldenhar-Gorlin syndrome is a rare congenital condition causing hemifacial microsomia, as well as abnormal development of the eyes, ears and jaw. Vertebral and renal abnormalities are often present. Rarely, global developmental delay and mild intellectual and language disabilities are observed [1]. The child described here exhibited all of the primary extraneurological features of OAVS, except for vertebral and renal anomalies. He presented with hypotonia, moderate intellectual impairment, learning disabilities and peculiar speech and language delays. Genetic testing revealed a microduplication of the short arm of chromosome 19 (19p13.2). Magnetic Resonance Imaging (MRI) of the brain showed anterior callosal dysplasia and mild dysmorphism of both anterior hippocampi. Region 19p13.2 is also the site of microdeletions that may occur in individuals with Malan syndrome, also known as Sotos-like syndrome or Sotos syndrome [2]. Individuals with Malan syndrome share some phenotypic and developmental features with patients with OAVS. However, their clinical presentations and neuroimaging findings differ [2,3]. The presence of a rare 19p13.2 microduplication in a child exhibiting OAVS features and displaying unusual neuroimaging results may expand the range of conditions associated with OAVS.

Case Presentation

This child's pregnancy, delivery and perinatal periods were all uneventful. He first presented at age ten. Upon examination, he exhibited short stature, hemifacial microsomia, bilateral microtia with atresia of the external auditory canal and preauricular skin tags, mandibular hypoplasia with microretrognathia, labiopalatoschisis, hypospadias and mesocardia with anomalous drainage of the right superior vena cava and an absent vena anonima. Despite the absence of ocular dermoids and vertebral or renal anomalies, he was placed in the OAVS/Goldenhar-Gorlin syndrome spectrum due to these anomalies. Blood karyotyping by array Comparative Genomic Hybridization (array CGH) revealed a microduplication on the short arm of chromosome 19 (19p13.2). Interestingly, this copy number variant was considered a polymorphism because the mother had the same microduplication yet was neurologically normal. Computed Tomography (CT) scans of the auditory anatomy showed a normal inner ear, an atretic external auditory canal and auricles, a smaller-than-normal tympanic cavity and an abnormal tympanic chain. The incus-hammer joint was fused and adhered to the lateral wall of the left tympanic cavity. The mastoids showed no pneumatization. Brainstem Auditory Evoked Responses (BAERs) testing revealed slowed mesencephalic conduction and delayed wave V latency. The patient underwent surgery to reconstruct the outer ears and auditory canals. A prosthetic device was also implanted to enhance sensitivity to and perception of acoustic stimuli. Neurologically, the child presented with diffuse hypotonia, reduced muscle strength, clumsy motor responses to stimuli and impaired fine motor skills. Deep tendon responses were poor or absent and plantar responses were flexor. There was no ataxia or dystonic or dyskinetic movements. Cranial nerves were normal except for horizontal strabismus and difficulty swallowing. The child experienced episodes of sudden pallor and blurred vision without loss of consciousness. These episodes were attributed to a cardiovascular abnormality. Electroencephalographic (EEG) recordings revealed bilateral temporo-occipital slow alpha activity and fast, low-voltage dysrhythmia in other regions when the child was awake. The near absence of K-complexes, spindles and central spikes during deep sleep suggested severe disorganization, though not an epileptogenic pattern. Key features of the syndrome included neuropsychomotor impairment and an estimated IQ between 80 and 82%. Speech development was delayed, with the first words appearing after 16 months. Subsequent language development was characterized by phonemic errors and limited semantic production. Only a few simple, standard sentences were acquired. There was no evidence of symbolic thinking or abstraction. He had a moderate learning disability that impaired his ability to perform basic ascending and descending number sequences, as well as simple addition and subtraction. His working memory was also limited; he had difficulty remembering a sequence of three numbers after a few minutes of distraction. A brain MRI was performed using a 1.5T device. T1-weighted, T2-weighted and Fluid-Attenuated Inversion Recovery (FLAIR) images were obtained. Overall, the lateral ventricles appeared reduced in volume, shortened posteriorly and irregularly indented anteriorly by the enlarged head of the caudate nucleus (Fig. 1). The general cortical convolution pattern appeared normal. Although myelination was normal, the hemispheric White Matter (WM) volume was slightly reduced. The Corpus Callosum (CC) was highly abnormal. It was diffusely shortened, especially in the body and splenium. The head, genu and primordial rostrum were abnormally large and irregularly shaped. Notably, the beaked segment of the rostrum was unrecognizable or entirely absent. The shortened splenium exhibited nearly normal morphology (Fig. 1). Both anterior hippocampi exhibited small supernumerary cortical sulci that extended into abnormally deep vertical collateral and subiculum fissures. These sulci resulted in an anomalous cortical tract with excessively small, irregular microconvolutions. It was difficult to distinguish the parahippocampus, subiculum, Ammon's horn and dentate gyrus (Fig. 2).

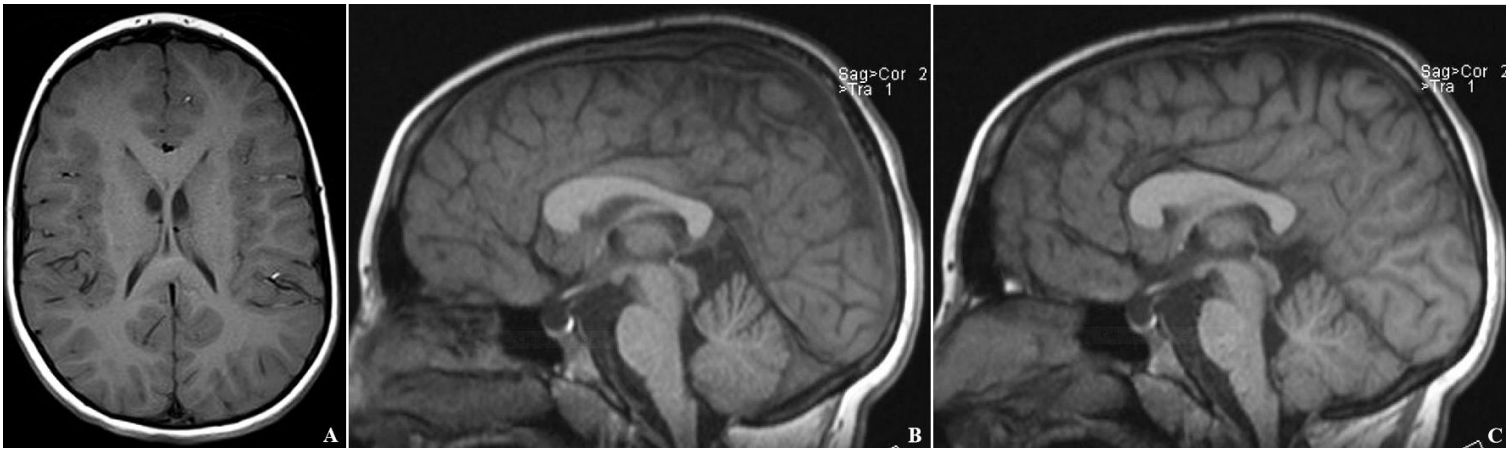

Figure 1: The CC and lateral ventricles. MR images. The lateral ventricles are diffusely reduced in volume and the trigone and posterior horns are shortened, as a consequence of the abnormal CC (A, axial T1). Only the callosal posterior body and

splenium have nearly normal morphology; the anterior body, head and genu are completely dysplastic. The rostrum is barely recognizable and its horizontal beaked segment is absent. The lamina rostralis and reuniens are also absent (B and C, sagittal T1).

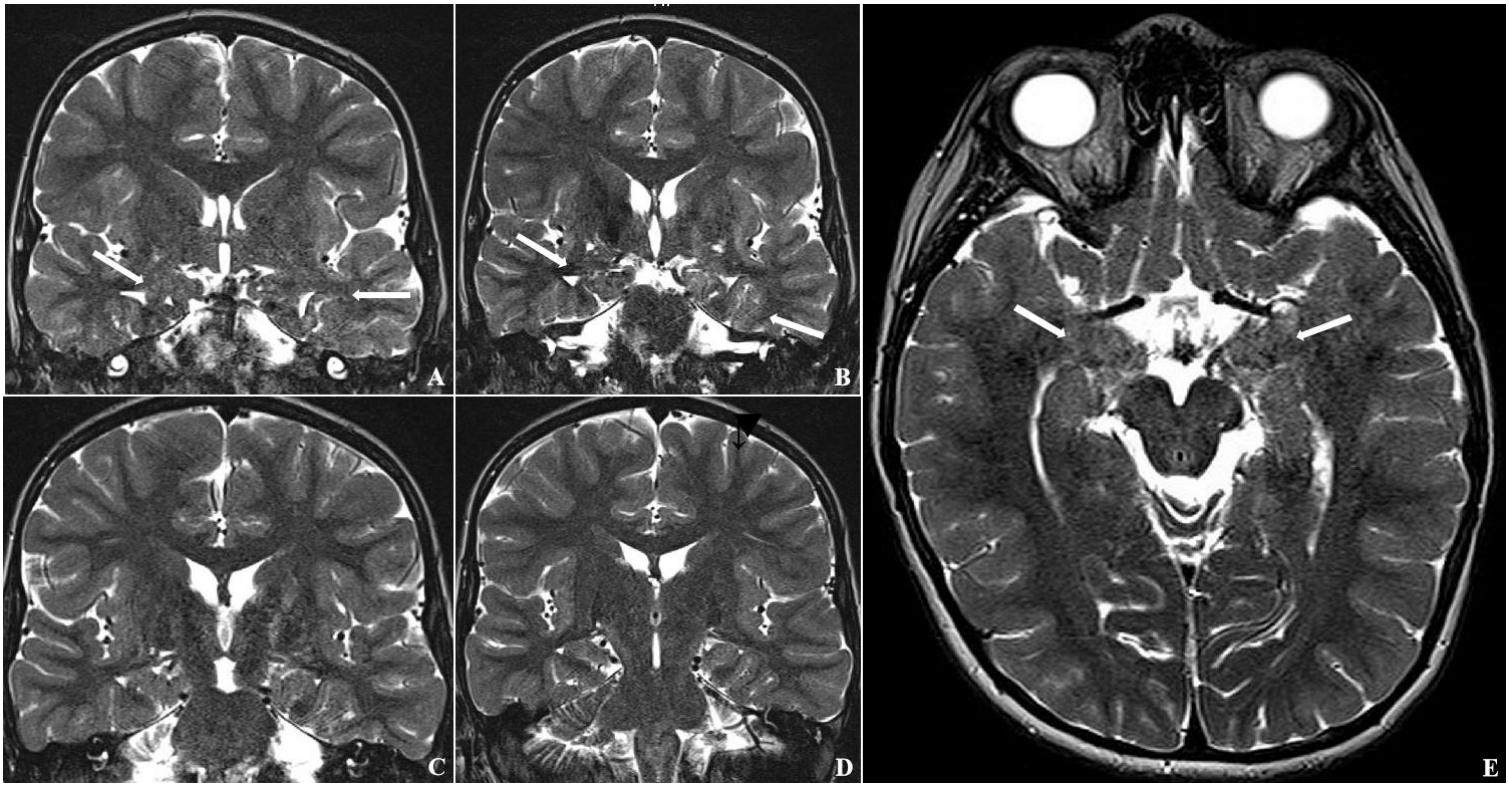

Figure 2: The hippocampi. MR images. The morphology of both hippocampi is less abnormal in the posterior sections. Further anteriorly, the parahippocampus, subiculum, Ammon's horn and dentate gyrus are difficult to identify due to the abnormal penetration of the collicular and subicular fissures of the inferior-medial temporal lobe. This results in abnormal folding, hypoplasia and cortical transformation into many very small convolutions (full white arrows)(coronal A-D and axial E, T2 turbo SE).

Discussion

Brain abnormalities such as occipital encephalocele, hydrocephalus (with or without aqueductal stenosis), Arnold-Chiari malformation, Dandy-Walker malformation, an absent or abnormal septum pellucidum, cerebral hypoplasia, cortical dysplasia, microcephaly, asymmetric lateral ventricles, caudal regression, encephalocele, holoprosencephaly, callosal lipoma and CC hypoplasia or agenesis have been incidentally associated with OAVS [4-9]. However, callosal dysgenesis alongside hippocampal abnormalities and 19p13.2 microduplication has never before been reported in patients with this condition. Typically, callosal growth in humans occurs in an antero-posterior direction, with the rostrum being the last part to form [10,11]. The development of the human CC depends largely on the most superficial cortical layers, particularly the early neurons of the frontal cortical plate. These neurons extend an irregular apical dendrite to the pial surface and a slender axon to the underlying white matter. These axons develop in lateral-medial and rostral-caudal directions, ensuring proper CC formation and connections [12-14]. The callosal specification of superficial cortical neurons is controlled by transcription factors, particularly the special AT-rich Sequence-Binding Protein 2 (SATB2) gene. This is evident in the severely hypoplastic or absent CC observed in human SATB2-Associated Syndrome (SAS) [15]. Additionally, some guidance molecules act as repulsive or attractive factors, directing axons across the midline to the appropriate contralateral cortical plate. Studies of neuroimaging in various malformative conditions have modified the traditional timing parameters of CC development. These studies have revealed that rostral fibers may develop before splenium fibers and may already be present by the time the genu matures. Embryologically, the lamina rostralis plays a critical role. It extends the beaked segment of the rostrum posteriorly and horizontally, connecting it to the lamina terminalis just adjacent to the underlying anterior commissure. The lamina terminalis incorporates the lamina rostralis and the lamina reuniens. In fact, the lamina rostralis itself originates from the embryonic lamina terminalis [16]. The lamina rostralis develops before the

genu and must horizontalize for the subsequent normal development of the callosal body and splenium. If the lamina rostralis retains its primitive vertical orientation, the posterior callosal body and splenium remain underdeveloped. The hippocampal commissure also contributes to CC development. Its fibers originate from the hippocampal primordium and partially cross the midline within the lamina terminalis as they travel alongside the primitive lamina reuniens and anterior commissure. At the same time, axons from the frontal cortical plate cross the midline. This convergence substantially contributes to the early formation of the rostrum. Defective development of the hippocampal commissure has been shown to result in callosal agenesis [17]. In this child, the splenium and the posterior one-third of the CC were shortened, though otherwise, their morphology was rather normal. In contrast, the anterior third, particularly the genu and rostrum, showed significant enlargement and dysplasia. Notably, the beaked rostrum was absent and the lamina rostralis segment was unrecognizable. Additionally, the fornix bent too vertically at the anterior commissure in the lamina terminalis region. The absence of the rostral beak lamina may have prevented the proper antero-posterior development of the callosal body. Consequently, axons from the frontal cortical plate and the hippocampal primordium became entangled and thickened in the most anterior CC.

Many studies have investigated the role of the CC in human language development in patients with complete or partial callosal agenesis. These studies aimed to localize different language defects to specific areas of the structure [18,19]. Some researchers have proposed that callosal axons originating from the temporal and inferior frontal cortex support syntactic processes that appear to be lateralized to the left hemisphere. Others have suggested that axons originating from the more medial temporo-frontal cortex subserve semantic processes [20]. Additionally, patients with an abnormal posterior CC should exhibit defective interaction between syntactic and prosodic information during language processing [19]. Other researchers have suggested that the splenium plays a critical role in the structural network that supports spoken language acquisition and that stuttering, dyslexia and speech sound disorders in children may result from a significantly reduced size and volume of the CC, especially in its anterior third [21-24]. However, no studies have addressed speech problems specifically related to callosal abnormalities affecting the rostrum and genu. Since this child with OAVS had more impaired speech and language skills than intellectual abilities, anterior callosal dysgenesis may have prevented proper phonemic and semantic production, as well as abstract symbolic reasoning. All of these seem to require anterior CC integrity [22-24]. Nevertheless, the ability to speak basic sentences may have been preserved due to the lesser involvement of the middle and posterior CC [20,21]. Additionally, since the hippocampus is involved in mental processing and memory, abnormalities in this region may contribute to speech and language impairments, as well as memory difficulties, in children.

Up to 90% of individuals with Sotos syndrome have deletions in the 19p13 region. Malan syndrome (also known as Sotos type 2 or Sotos-like 2 syndrome) and Marshall-Smith syndrome are allelic and may be caused by microdeletions in the 19p13.2 region [2,3]. OAVS/Goldenhar-Gorlin syndrome shares features with Malan syndrome, including hypotonia, strabismus, intellectual disability, learning impairment and behavioral fragility. However, patients with Malan syndrome also exhibit body overgrowth, macrocephaly, a marfanoid habitus, long fingers, scoliosis, pectus excavatum and a distinctive facial features. They also have normal neuroimaging or a small callosal body [3]. The child reported here, however, had a microduplication of the same region, not a microdeletion. Very few patients with a 19p13.2 microduplication and a Sotos-like phenotype have been reported. Lehman, et al., described a three-generation family in which nine members exhibited a Sotos-like phenotype, suggesting a causal role for the microduplication in this phenotype [25]. However, only individual III-5 had a brain MRI showing an enlarged vestibular aqueduct and individual III-2 had a CT scan showing a pituitary microadenoma. Trimouille, et al., recruited nine patients with an unspecified 19p13 microduplication and focused on the duplicated NFIX gene and its role in Sotos syndrome type 2 [26]. Micaglio, et al., reported an interesting case of a 20-year-old male patient with a 19p13.2 microduplication [27]. The patient presented with macrocephaly, severe neurodevelopmental delay, an absence of speech, behavioral abnormalities, ventricular dilatation and a thin CC on a brain MRI. Interestingly, the patient's mother had the same duplication but did not exhibit craniofacial abnormalities or neurological deficits. As with the child described here, it is important to note that manifestations of identical duplications can vary greatly, even among family members. Indeed, it is well known that patients with CC agenesis may be asymptomatic. Unfortunately, the mother of the patient reported here declined neuroimaging. A complete list of duplicated genes is unavailable because a detailed genetic investigation was not possible at the time. However, the duplication of the DNMT1 gene may be of interest. Indeed, DNMT1 is located at 19p13.2 and plays a critical role in embryonic development, chromatin structure, neuronal survival, the cell cycle and cellular epigenetic regulation [28]. Furthermore, DNMT1 has notably been associated with mental and behavioral disorders, particularly schizophrenia, due to its interaction with the reelin (RELN) gene in neurotrophin signaling [29].

Conclusion

In conclusion, the 19p13.2 microduplication in our patient is notable for its phenotypic similarity to OAVS rather than to Malan or Sotos-like syndromes. The presence of features characteristic of OAVS/Goldenhar-Gorlin syndrome, novel neuroimaging findings indicating peculiar callosal dysplasia and hippocampal dysmorphisms and the occurrence of the rare 19p13.2 microduplication in the reported patient may expand the clinical spectrum of OAVS and the potential expression of this associated copy number variant.

Conflict of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

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Acknowledgement

None.

Data Availability Statement

Not applicable.

Ethical Statement

This study was conducted in accordance with the ethical standards of the Helsinki Declaration of the World Medical Association. Furthermore, the manuscript did not need the approval of the Ethical Committee of our University Administration as this is not a requirement for the publication of a single case provided that it is of definite interest to the scientific community (Regulations of the Ethical Committee of "Area Vasta Emilia Nord", Italy, approved on September 22, 2020).

Informed Consent Statement

Informed consent was verbally obtained from the mother and patient anonymity preserved.

Authors' Contributions

Conception and design, interpretation of the data: E.D.G., M.S. The drafting of the paper: E.D.G. Revision for intellectual content: M.S., L.R.B. All the authors gave the final approval of the version to be published. E.D.G. and M.S. agree to be accountable for all aspects of the work.

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