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Case Report

Expanding the Clinical Spectrum of De Novo 19p13.3 Microdeletion: A Case Report

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Abstract

Background Interstitial microdeletion 19p13.3 is a copy number variant defect characterized by neurodevelopmental disorders, dysmorphic features, and multiple congenital anomalies. Patients with this condition exhibit intellectual disability, attention deficit disorder, delayed language development, inappropriate behavior, hypotonia, scoliosis, and minor brain abnormalities.

Methods and Findings: Here, we present the case of a young male patient with ideomotor dyspraxia, spatial discrimination deficits, and impaired fine motor skills. Neuroimaging revealed lateral ventricular dilatation, corpus callosum thinning, and left hippocampal dysplasia. The patient also experienced a unique focal seizure, and electroencephalographic recordings were highly suggestive of transient benign epilepsy with centro-temporal spikes. Conclusion: This patient's findings have not been reported before. They contribute to a better understanding of the clinical features of this rare condition. Genes in the deleted terminal fragment of the short arm of chromosome 19 may contribute to structural and functional defects.

Keywords: Microdeletion; Chromosome 19; Copy Number Variant; Hippocampus; Epilepsy; Benign Epilepsy with Centro-Temporal Spikes (BECTS)

Introduction

The 19p13.3 microdeletion syndrome is a poorly defined clinical condition. Affected patients may present with various symptoms, including failure to thrive in utero and after birth, feeding and digestive difficulties, strabismus or myopia, conductive or sensorineural hearing loss, cardiac and renal defects, multiple spinal anomalies, hypotonia, motor and behavioral disorders, speech delays, learning disabilities, and rare seizures [1-6]. Magnetic Resonance Imaging (MRI) of the brain has been performed on a few patients and has revealed undefined changes in the hemispheric white matter and thinning of the Corpus Callosum (CC) [2,4]. We report on a young male patient who exhibited most of the phenotypic features of the disorder. However, he exhibited previously unreported abnormalities, including peculiar neuropsychological deficits and transient Electroencephalographic (EEG) features of Benign Epilepsy with Centro-Temporal Spikes (BECTS). He also had abnormal dilatation of the lateral ventricles, left hippocampal dysplasia with slight hypoplasia of the entire left temporal lobe, a retrovermian cyst, and diffuse callosal thinning, as seen on an MRI scan. These brain abnormalities may contribute to the general neurological and mental impairment. Some of the deleted genes may cause structural brain abnormalities and clinical impairments.

Clinical Presentation and Methods

This patient was born at term to healthy, unrelated parents, and the perinatal period was uneventful. During his early years, he exhibited delayed development of motor, intellectual, and behavioral skills. Follow-up EEG recordings revealed a spike-and-wave epileptogenic focus in the left fronto-centro-temporal area. This focal anomaly persisted for several years until it normalized shortly after his only febrile seizure at age ten. Fig. 1 This pattern is very similar to that of Benign Epilepsy with Centro-Temporal Spikes (BECTS).

Based on his EEG findings, he was prescribed daily low-dose oral carbamazepine, which was discontinued after he remained seizure-free for two years. The unique febrile seizure he experienced at age ten was described as a secondary generalized focal seizure with loss of consciousness, tonic-clonic arm movements, gaze deviation, drooling, and cyanosis. At that time, a neurological examination revealed an Occipitofrontal Circumference (OFC) of 55 cm, diffuse hypotonia and hypotrophy, muscle weakness, gait disturbance with lateral oscillations (though no true ataxia), severe right-convex S-shaped scoliosis, and severe ideomotor dyspraxia. Brain MRIs performed at ages ten and sixteen revealed abnormal dilatation of the lateral ventricles, primarily in the parietal-occipital region, as well as thinning of the CC, diffusely reduced hemispheric white matter, a retrovermian arachnoid cyst, and left hippocampal dysplasia with temporal lobe hypoplasia. The hippocampal abnormality primarily affected the parahippocampal and subiculum compartments, causing the entire structure to appear immature, or "fetal". Notably, the subiculum sulcus was nearly absent, which disrupted the normal folding of adjacent regions, maintaining a developmental stage of approximately four to five fetal weeks [7,8]. Additionally, the temporal lobe on the same side was underdeveloped, with slightly irregular folding of the inferior temporal and entorhinal cortex Fig. 2.

Brainstem Auditory Evoked Potentials (BAERs) revealed a mild conduction defect, whereas Evoked Spinal Somatosensory Potentials (ESSPs) were normal. During neuropsychological testing, the child performed well on tasks involving arithmetic, memory, visual naming, and short-term working memory. The worst results were seen in fine motor skills and movements requiring difficult ideomotor organization. Writing was possible only in block letters with defects in spatial organization. Lateral recognition of self and examiner, as well as digital recognition, were also impaired. Tasks and instructions were carried out hastily, resulting in poor ideomotor sequencing. For example, graphic symbols were superimposed on the writing, often altering its size and morphology. While reading, parts of words were superimposed or deleted, making them unintelligible. These symptoms resemble those observed in Attention Deficit Hyperactivity Disorder (ADHD). His behavior was often described as hetero- but not self-aggressive, with frequent mood swings ranging from deep anxiety and social isolation to excessive outbursts. A physical examination at the age of ten revealed an unusually tall stature, an OFC of 55 cm (more than 2 SD), a high forehead, hypotelorism with midline fusion of the eyebrows, and hypertrichosis. His ears were slightly low-set, and his fingers were exceptionally long, suggesting a marfanoid habitus. There were no cardiac or renal abnormalities, but a 3.2 cm hepatic angiomatous mass was present. Genetic analysis using array-Comparative Genomic Hybridisation (a-CGH) revealed a de novo microdeletion of 657 kb at 19p13.3, affecting at least 25 coding genes.

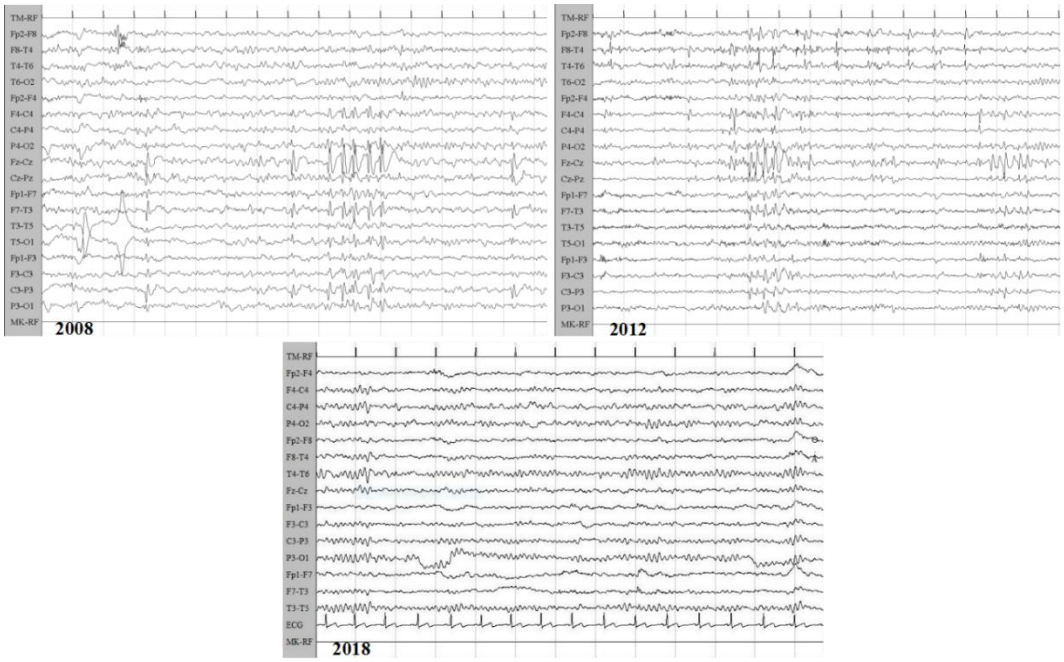

Figure 1: EEG recording progression. The first EEG recording in the year 2008 (age 4) showed focal fronto-centro-temporal irritation on the left side. Four years later, the left focal irritation appeared partially attenuated, yet extended controlaterally; note the association of low amplitude, rhythmic bifocal spikes in the right fronto-central regions. At the age of 14 years (year 2018), the EEG recording was completely normalized.

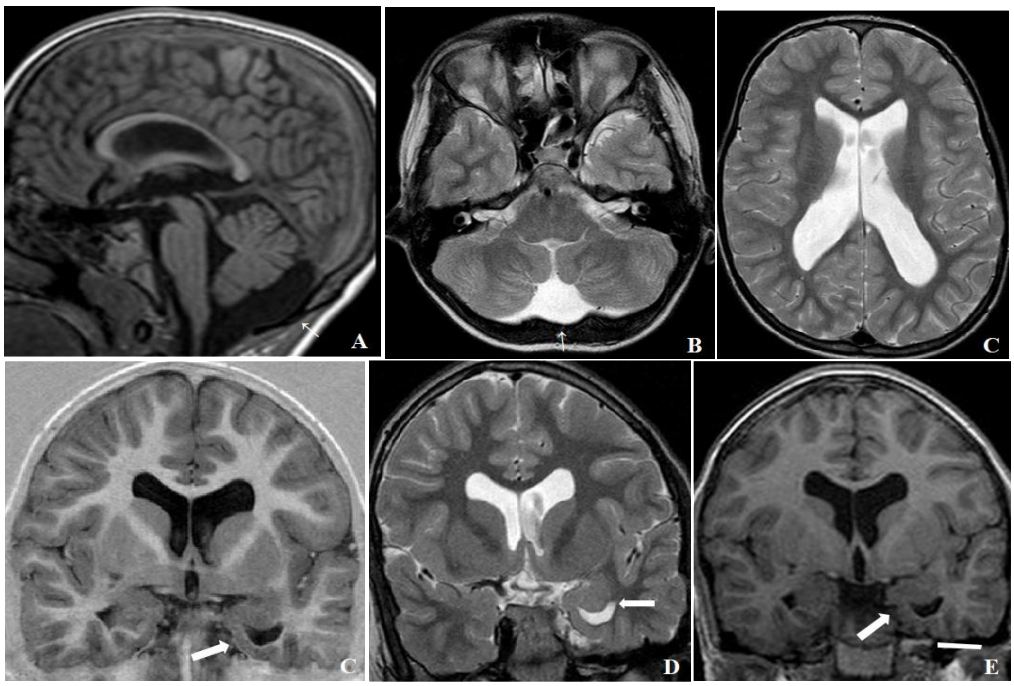

Figure 2: MRI results. Neuroimaging performed at 10 and 16 years of age showed essentially unchanged abnormalities. In the posterior fossa, the only abnormality was the presence of a voluminous retrovermian arachnoid cyst (small white arrows) (A, sagittal T1-weighted; B, coronal T2-weighted). The pathologic square-shaped lateral ventricles were diffusely and rather symmetrically enlarged, especially the frontal horns (B, coronal T2-weighted; C, axial T2-weighted). The left hippocampus showed an essentially absent subiculum fissure with abnormal uniform horizontalization of the parahippocampus and subiculum and progressive alteration of Ammon's horn folding (white arrowheads) (D and E, FLAIR T2-weighted; F, FLAIR T1-weighted); the left temporal lobe was smaller than the contralateral one, and the inferior temporal and entorhinal cortex also showed rather abnormal folding.

Discussion

Neurological and behavioral abnormalities reported in patients with the 19p13.3 microdeletion include impaired gross motor skills, hypotonia, defects in hand-eye coordination and fine motor skills, delayed speech development, dyspraxia and learning disabilities. Social behavior is characterized by anxiety and aggression [1-6]. Seizures are rarely described [2,4-6]. Neuroimaging has revealed undefined changes in the hemispheric white matter and thinning of the CC [4-6]. This patient differs from those in previous reports. His neuroimaging revealed hypoplastic hemispheric white matter, abnormal dilatation of the lateral ventricles, a retrovermian arachnoid cyst, a peculiar left hippocampal abnormality associated with temporal lobe hypoplasia, and a BECTS-type transient EEG pattern. The hippocampus is widely recognized as a highly epileptogenic region, particularly when malformed. Due to its connections with the median and anterior thalamic nuclei, the prefrontal cortex, and the frontal lobe, the hippocampus is also involved in functions such as fine motor skills, reading, writing, and behavioral and social stability. This patient exhibited impairment in all of these functions. The diffuse thinning, or hypoplasia, of the Corpus Callosum (CC) may depend on defective formation of the more superficial cortical layers. Under normal conditions, the neurons in these layers, particularly in the frontal cortex, project their axons through the developing CC to the contralateral cortex. These axons play an essential role in processing afferent input and producing efferent output, including that responsible for motor abilities [9]. In addition, only normal hippocampal development can significantly contribute to proper CC formation via the hippocampal commissure [8]. The EEG findings and clinical course were both suggestive of BECTS, which is generally considered to be free of structural brain anomalies. Additionally, seizures associated with BECTS are generally not accompanied by fever; however, this child experienced a single focal secondary generalized seizure alongside fever. Notably, sophisticated MRI techniques have revealed subtle structural brain abnormalities in patients with BECTS [10]. However, developmental abnormalities of the hippocampus, such as those found in this patient, have never been reported before. The left hippocampal anomaly in this child appears to be a developmental arrest rather than a "true" malformation [11,12]. In this context, the subiculum plays a critical role. Located between the hippocampus proper and the parahippocampal region, the subiculum represents the anatomical transition between Ammon's horn and the entorhinal cortex. It is also the primary anatomical output of neural activity originating from the hippocampus. At the same time, it interacts with and processes epileptic discharges, which in turn modify it [11,13]. In this patient, the underdeveloped subiculum may have improved in terms of connectivity and function over time. This would have been impossible if the subiculum had been severely malformed. Some of the genes deleted from the 19p13.3 region are essential for brain development and function. The Palm gene promotes dendritic and neuronal branching by extending filipodia, and filipodia are precursors of developing synapses in hippocampal neurons [14]. The CDC34 gene facilitates the binding of ubiquitin, derived from the E1 complex, to E2 and E3 ligases. This regulates the stability and function of the entire protein synthesis and degradation system [15]. The FGF22 gene has been shown to be negatively correlated with IL-1β in the serum of people with depression. Treatment with FGF22 reduces IL-1β and reverses cell apoptosis in hippocampal neurons. These findings support the inflammatory hypothesis of depression and the possibility of reversing the condition by increasing FGF22 activity [16]. The POLRMT gene plays a critical role in maintaining proper mitochondrial biogenesis. Of particular interest for the boy reported here, affected patients typically present with early-onset moderate to severe global developmental delay, mild to severe intellectual disability, hypotonia/muscle weakness, speech delay, and focal seizures during childhood [17]. The HCN2 gene stabilizes the membrane potential, controls proper hyperpolarizing and depolarizing inputs, and facilitates synaptic integration and modulation of rhythmic neuronal oscillatory activity. Indeed, the HCN1 gene is the most abundant channel of this class in the human brain. Individuals with HCN1 mutations tend to develop a wide spectrum of seizure disorders, ranging from benign febrile seizures to severe genetic Generalized Epilepsy with Febrile Seizures plus (GEFS+) or catastrophic neonatal and infantile epileptic encephalopathy [18]. Interestingly, defects in the HCN2 gene have recently been proposed as a potential cause of epileptic seizures, as the loss of HCN2 in adult mice results in loss of the CA1 pyramidal neuron layer via apoptosis [19]. Therefore, the patient's single focal seizure with fever and EEG abnormalities may have been induced by a left hippocampal abnormality and HCN2 deletion.

Conclusion

In conclusion, the patient's medical presentation and history are likely the result of impaired complex neuronal functional machinery during brain development and thereafter. This case report shows that searching for subtle, focal brain structural abnormalities in copy number variants can provide insights into the causes of intellectual, language, behavioral, and epileptic defects.

Conflict of Interests
The authors declare that they have no conflicts of interest.

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Ethics Approval Statement
This study was conducted in accordance with the ethical standards of the Helsinki Declaration of the World Medical Association. 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).

Author Contributions
Conceptualization: E.D.G.; P,B.; O.C. Data collection and analysis: E.D.G.; M.S.; E.S.; S.M.; E.C. Data curation: P.B.; O.C. Investigation: P.B.; O.C.; E.S.; E.C.; I.S. Writing-original draft: E.D.G.; L.R.B. Writing-review and editing: All authors.

Consent Statement
The informed consent has been obtained and the patient anonymity preserved.

Data Availability Statement
Data and Materials are available from the authors upon reasonable request.

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