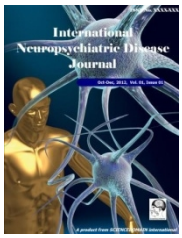

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Association of Corpus Callosum Agenesis with Mental Retardation and Attention Deficit Hyperactivity Disorder

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Authors' contributions

Author RV designed the study, supervised the data collection and managed the literature searches. SM collected the data and wrote the first draft of the manuscript. Author MS analyzed the data and edited the manuscript. Author PK has supervised data collection and have contributed significantly to the revised drafts.

Case Study

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ABSTRACT

Aims: Anomalies of the corpus callosum have been associated with varied brain and somatic malformations. It has been associated with diverse genetic causes with identifiable syndromes. We aim to report a case of corpus callosal agenesis (CCA) associated with mental retardation and hyperactivity.
Presentation of case: We report case of a 7 year old boy having CCA, abnormal facial morphological features, mental retardation and attention deficit hyperactivity disorder (ADHD), devoid of any chromosomal rearrangements or somatic malformations known to be associated with corpus callosal changes.
Discussion: Symptoms in CCA are often related to concurrent migrational disorders, not to the callosal anomaly itself. Although multiple genetic etiologies have been associated, no single gene has been proved to be implied in all cases of CCA.
Conclusion: This case highlights importance of recognizing mental retardation and ADHD as a presentation of isolated CCA which may occur without any known

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chromosomal malformation.

Keywords: Corpus callosum; agenesis; mental retardation; hyperactivity.

1. INTRODUCTION

Available literature suggests that anomalies of the corpus callosum, including agenesis (absence) and hypogenesis, may be associated with a variety of other brain and somatic malformations. It is regarded as a heterogeneous condition, for which several different genetic causes with identifiable syndromes are acknowledged. We report here on the unusual findings in a case of a 7 year old boy with abnormal facial morphological features in conjunction with features of mental retardation and attention deficit hyperactivity disorder (ADHD), having complete absence of corpus callosum devoid of any chromosomal rearrangements or somatic malformations known to be associated with corpus callosum changes. Such an alliance has never been reported as per our knowledge. A common etiology of this association is uncertain, but a currently undetermined genomic component might have contributed to the disease.

2. PRESENTATION OF CASE

The patient, a 7 year old boy, was the first child of non-consanguineously married mother (at 30 years age). He was normally delivered at 39 weeks, devoid of any perinatal distress, with a birth weight of 2½ kg. There was no history of substance abuse in his mother, prior or during the pregnancy. By 4 months of age, low body weight and short stature were noticeable in him. He had late frontal/central head fusion (at 9 months age) with delayed developmental milestones including walking and speaking which were not present until 18 months of age. The patient's family had no history of seizures, and other neurological disorders.

He had no difficulties in playschool. In kindergarten, he had difficulty in learning alphabets and numbers. His parents noticed him to be more disorganized and inattentive compared to his elder brother at same age. Even though parents often had to repeat instructions, he left tasks partially-finished. Teachers would complain that he would not sit still on his seat during the class, but rather roam about and disturb other students. He presented to child psychiatry clinic with these symptoms since 2 years. During interview he couldn't sit still and constantly shifted position. He would play with cloth buttons, ran about in the room or play with articles lying around.

The physical examination showed that he had parietal bossing, medial sparing of eyebrows, epicanthal folds, ear lobes posited laterally and posteriorly, broad nasal bridge, prominent columella, hypertelorism, small jaw, flat feet and short stature. There were three creases in his palms. There were neither anomalies of finger or nail nor any abnormal muscle tone.

Blood tests showed normal levels of blood cell count, C-reactive protein, glucose, electrolytes, creatinine, liver/kidney/thyroid functions, and homocysteine. Sex hormonal tests identified normal levels of prolactin, luteinizing hormones, follicular stimulating hormone, and estrogen levels. Examination of fundus did not show any sign of raised intracranial tension or abnormal deposits. Electrocardiogram, electroencephalogram, cerebrospinal fluid analysis, and ultrasound abdomen reported no abnormality.

He showed deficits in adaptive functioning in almost all areas, especially in the area of communication, on Vineland Social Maturity Scale [1]. On Bender Gestalt test [2], his copying phase reproductions earned him a score of 40 (extremely low) that assigned a T score of 10. He could not recall any of the gestalts. His performance on Colored Progressive Matrices test was erratic with poor comprehension [3]. His Intelligence Quotient (IQ) was estimated to be approximately 43 on Stanford Binet Scale of Intelligence [4].

The patient reported scores of ‘always’ or ‘often’ on more than 6 items on both inattention and hyperactivity section of ADHD rating scale – parent version [5].

The patient was subjected for contrast enhanced computerized tomography/magnetic resonance imaging brain scan which revealed complete absence of corpus callosum and parallel lying lateral ventricles with small & pointed frontal horns and disproportionately enlarged occipital horns suggesting colpocephaly (Figs. 1-4). Third ventricle was dilated and displaced superiorly with splitting of internal cerebral veins. There was no abnormal area of parenchymal/meningeal enhancement on post contrast images. Imaging findings were suggestive of complete agenesis of corpus callosum. The blood chromosomal analysis revealed normal male karyotype (46, XY) with no numerical or structural chromosomal anomalies detected at the level of banding resolution of 450-550 with GTG banding technique (G bands by Trypsin and Giemsa). No abnormality was detected on genetic analysis of both parents.

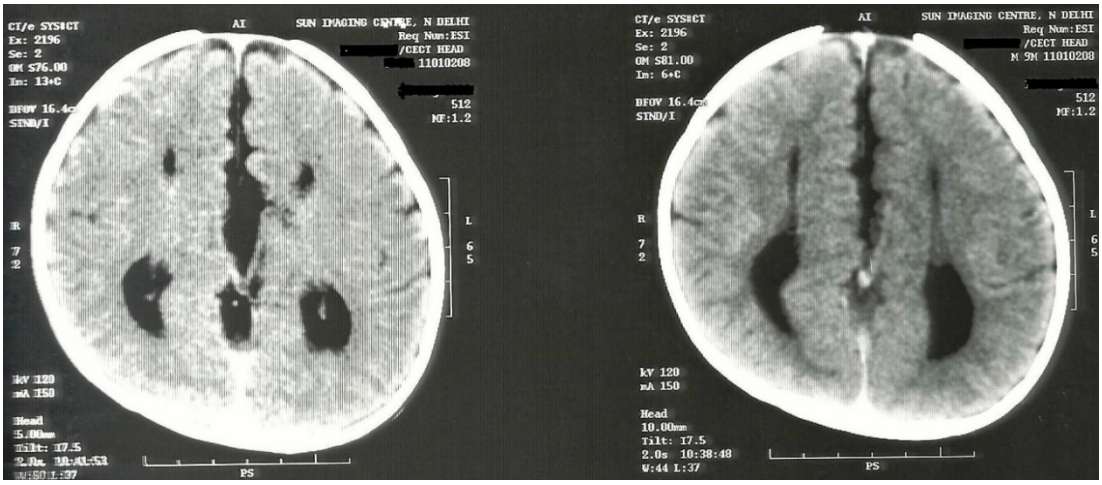

Fig. 1. Axial images of Contrast Enhanced Computerized Tomography (non-ionic) scans of head showing seperation of bodies of lateral ventricles with parallel configurations, dilatation of occipital horns, and relatively small bilateral frontal horns.

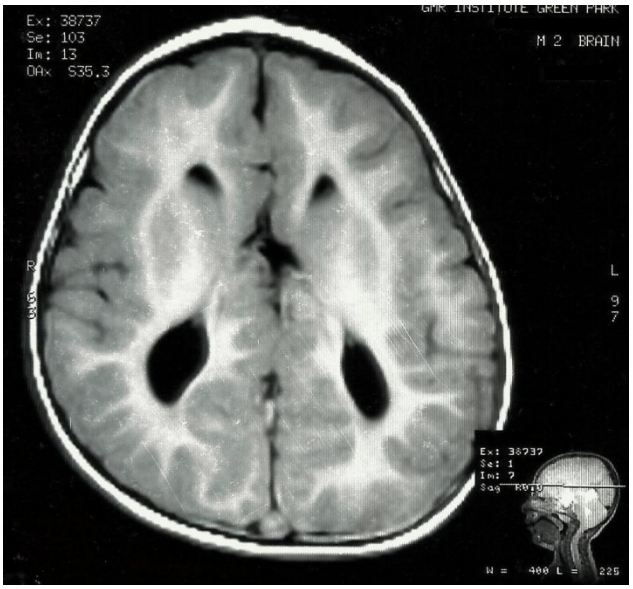

Fig. 2. Axial image of Magnetic Resonance Imaging (T1 weighted) scan of head showing corpus callosal agenesis with seperated lateral ventricles having parallel configuration.

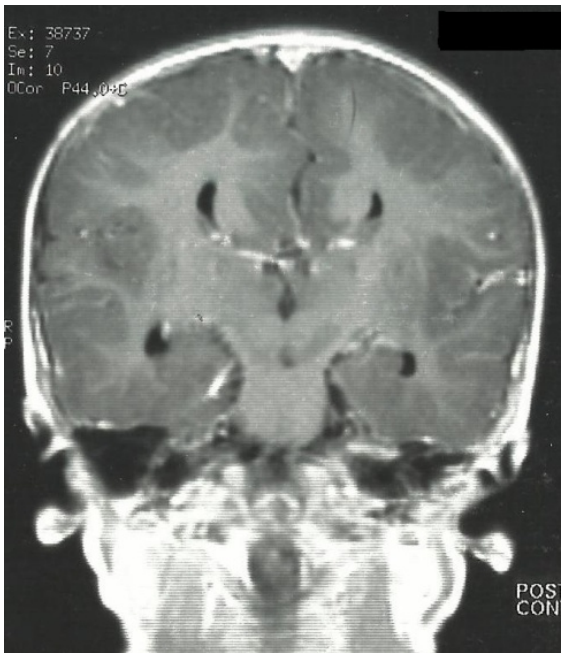

Fig. 3. Coronal image of post contrast Magnetic Resonance Imaging brain scan showing agenesis of corpus callosum.

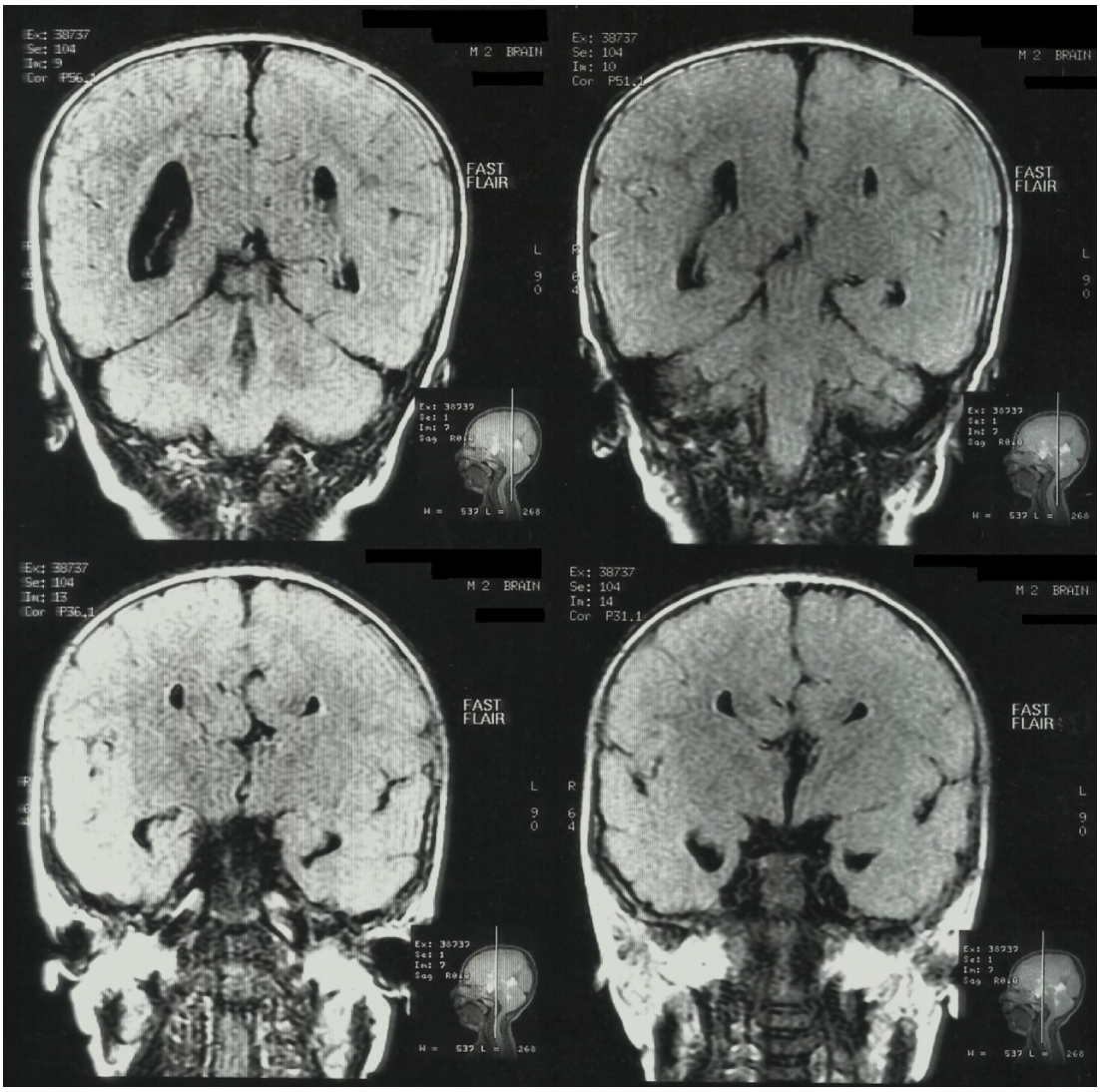

Fig. 4. Coronal images of Magnetic Resonance Imaging (FLAIR) brain scan showing agenesis of corpus callosum with evidence of culpocephaly.

3. DISCUSSION

Corpus Callosum Agenesis (CCA) is one of the most common congenital brain malformation observed in humans. The estimated prevalence of CCA in the general population is 3-7 per 1000 birth, while in children with developmental disabilities it is 2-3 per 100, affecting males and females with equal frequency [6]. It is a disorder of midline prosencephalic development, together with agenesis of septum pellucidum, affecting the commissural plate. Literature suggests that partial or complete callosal agenesis is caused by insults that arrest formation of callosal embryologic precursors (lamina reuniens, sulcus medianus telencephali medii, massa commissuralis) between 8 & 20 wks of gestation [7].

Malformation of the corpus callosum is frequently associated with other congenital brain anomalies, like Chiari II malformation, Dandy-Walker malformation, interhemispheric cysts, anomalies of cortical development, cephaloceles and midline facial anomalies [7,8]. Isolated CCA is per se asymptomatic, with the symptomatology mainly determined by the associated cerebral malformations. [4]. When symptoms (seizures or developmental delay) are present, they are related to concurrent migrational disorders, not to the callosal anomaly itself. CCA is commonly associated with: 1) complex brain malformative diseases leading to severe neuropsychiatric deficit; 2) other neurodevelopmental diseases, including autism, without a well defined role of CCA in the etiology of the disorder; 3) apparently benign conditions, with IQ in normal range but having relevant neuropsychological deficits [9]. These include impairment of abstract reasoning, problem solving, comprehension of syntactic and linguistic pragmatics, and category fluency [10,11]. Parents have reported of problems like feeding or sleep issues, elimination problems and unusual tolerance for pain [12].

Initially symptoms were believed to be a consequence of hemispheres' disconnection [13]. But the current understanding implies that CCA leads to abnormal microstructure and reduced volume of the Ventral Cingulum Bundle causing abnormalities in intrahemispheric white matter tracts [13]. Authors also incriminate reduction in number of Van Economo neurons, large spindle-shaped neurons localized to anterior cingulated cortex and fronto-insular cortex, in patients with CCA [14].

The possible genetical etiology of CCA has been studied both in mouse models [15] and in humans [16]. Anomalies of the corpus callosum often present as a part of chromosomal (trisomy 8, 13, 18, or 21) as well as X-linked syndromes (XXY, 45X). Additional chromosomal abnormalities associated with CCA include: duplication of 8p23 and alterations of 1p36, 1q42−43, and 6qter [17,18]. No single gene has been proven to be implied in all patients with CCA [18]. Environmental factors like ethanol may also play a role as evidenced by the fact that CCA is a relatively common feature of Fetal Alcohol Syndrome [19]. A complex interplay of genes and environmental mechanisms seems to be associated.

Studies have observed that the circuits that control attention are smaller and less active in individuals with ADHD than in controls [20]. These circuits include the parts of the prefrontal cortex that control working memory, alerting, and response inhibition. It is possible that CCA has mediated a deficit in the circuitry manifesting the ADHD symptoms and had led to a global effect on brain mitigating low intelligence. While the presence of mental retardation and ADHD in our case could be an incidental co-occurrence with CCA, there is also a possibility that isolated CCA might influence brain development and lead to low IQ, attention deficits and hyperactivity. Future research should involve detailed screening of large population cohort with isolated CCA to verify previous claims of associated asymptomatology.

4. CONCLUSION

Agenesis and hypoplasia of corpus callosum represent a heterogeneous array of brain disorders and are among the most common brain malformations. They are associated with increased risk of premature birth, are more common with advanced maternal age and are frequently part of a complex, multisystem disorder. This case highlights importance of recognizing mental retardation and ADHD as a presentation of isolated CCA.

CONSENT

All authors declare that 'written informed consent was obtained from the patient's parents for publication of this case report and accompanying images.

ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki."

COMPETING INTERESTS

Authors declare that no competing interests exist.

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