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Coexistence of Neurodevelopmental Disorders (ASD, ADHD) and Neurological Malformations: A Case Study

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Abstract **Case Report**

***Introduction*:** The association of neurodevelopmental disorders and neurological malformations in children is a complex and relatively under-documented phenomenon. Autism spectrum disorder (ASD) and attention deficit hyperactivity disorder (ADHD) can coexist with structural anomalies such as Chiari malformation type 1 (CM-I) and primitive empty sella syndrome (primary ESS). This co-occurrence raises important questions about pathophysiological mechanisms, diagnostic challenges, and therapeutic approaches. We propose to explore this issue through this clinical case. ***Case Report*:** We report here the case of a 6-year-old boy, followed in child psychiatry since the age of 3 for ASD. The child presents with language disorder, lack of pointing and gaze fixation, hyperactivity, agitation crises, and sleep disturbances. Brain imaging revealed CM-I and primary ESS. ***Discussion*:** Several hypotheses regarding the links between neurological malformations and neurodevelopmental disorders are discussed in the light of the literature, explaining the role of the cerebellum, associated structures, and cerebral hemispheres in the pathophysiology of neurodevelopmental disorders such as ADHD and ASD. ***Conclusion*:** The coexistence of neurological malformations, notably CM-I and primary ESS, and neurodevelopmental disorders such as ASD and ADHD is still under-documented in the literature. Further studies are necessary for a better understanding of these links, which could shed light on the etiopathogenesis of these complex cases, to ensure better management of these children and improve their quality of life.

Keywords: Autism Spectrum Disorder, Attention Deficit Hyperactivity Disorder, Primary Empty Sella Syndrome, Chiari Malformation Type 1.

INTRODUCTION

Neurodevelopmental Disorders and Neurological Malformations

Neurodevelopmental disorders are a set of conditions that typically manifest early during the developmental period. They are characterized by developmental deficits that result in personal, social, academic, or occupational impairment. These disorders include intellectual disabilities, communication disorders, autism spectrum disorder (ASD), attention deficit hyperactivity disorder (ADHD), specific learning disorders, and motor disorders. (APA, 2013)

Autism Spectrum Disorder (ASD)

ASD is characterized by persistent deficits in communication and social interactions observed across various contexts. These include deficits in social reciprocity, non-verbal communicative behaviors used during social interactions, and the development, maintenance, and understanding of relationships. In addition to social communication deficits, the diagnosis of ASD requires the presence of restricted or repetitive patterns of behavior, interests, or activities. (APA, 2013)

Attention Deficit Hyperactivity Disorder (ADHD)

ADHD is defined by debilitating levels of inattention, disorganization, and/or hyperactivity-impulsivity. During childhood, ADHD often overlaps with disorders typically considered as "externalizing," such as oppositional defiant disorder and conduct disorder. ADHD often persists into adulthood, leading to social, academic, and occupational impairment. (APA, 2013)

Chiari Malformation Type 1 (CM-I)

CM-I is a morphological anomaly encompassing several syndromic entities, with CM-I being the most common. It involves the descent of the cerebellar tonsils more than 5mm through the foramen magnum (Knafo *et al*., 2021). This anomaly is often

discovered incidentally during brain imaging (CT or MRI). While frequently asymptomatic, it can manifest with occipital headaches, neck pain, dizziness, and vision disturbances (Gilmer *et al*., 2017). Neuroimaging studies estimate the prevalence of CM-I to be about 4% in the pediatric population (Sari., 2021).

Primary Empty Sella Syndrome (ESS)

Primary ESS is characterized by partial or complete absence of the pituitary gland in the sella turcica, mainly due to a deficiency in the development of the sellar diaphragm with an arachnoid herniation into the pituitary fossa leading to pituitary displacement (Sainedane., 2013). In most cases, primary ESS is discovered incidentally during brain imaging. It is often asymptomatic, but may present with headaches, neurological symptoms (dizziness, syncope, cranial nerve palsies, seizures, benign intracranial hypertension), ophthalmic symptoms (blurred or double vision, transient visual loss, visual field defects), cerebrospinal fluid rhinorrhea, endocrine symptoms, and psychiatric symptoms such as anxiety, depression, psychotic disorders, and schizophrenia (Sandeini, De Marini, Shields, Ferreri).

The coexistence of neurological malformations and neurodevelopmental disorders is sparsely documented in the literature. We discuss this association and its particularities through a clinical case.

Clinical Case

This is a 6-year-old boy, the eldest of two siblings, born from a non-consanguineous marriage. He was born at term following a pregnancy complicated by gestational diabetes, with a medically assisted vaginal delivery. In terms of neurodevelopment, he achieved early walking at 9 months, followed by the emergence of a few words which later regressed. He attained bladder control, but not bowel control.

He has been followed in child psychiatry since the age of 3 for autism spectrum disorder (ASD), without notable improvement despite interventions including speech therapy, psychomotor therapy, and Applied Behavior Analysis (ABA) therapy. His parents brought him for a child psychiatry consultation due to language disorder, absence of pointing and gaze fixation, hyperactivity, agitation episodes, and sleep disturbances. Screening with the M-CHAT revealed a high risk of ASD (score of 9), while the Conners' Parent Rating Scale indicated significant ADHD symptoms.

Comprehensive investigations were conducted. Brainstem Auditory Evoked response (BAER) testing and an electroencephalogram (EEG) were normal. A Cranial CT scan revealed an empty sella turcica appearance and a posterior cranial fossa showing a tonsillar ptosis of 6.2mm. MRI confirmed the presence of the pituitary gland and stalk along with tonsillar ptosis. The neurosurgeon diagnosed Chiari Malformation Type 1 (CM-I), clarifying that this anomaly did not explain the observed symptoms. No surgical intervention was indicated, and a follow-up in child psychiatry was recommended. Blood tests, including thyroid, renal, lipid, and hepatic panels, were performed and returned normal. An endocrinological assessment is underway to explore the hypothalamic-pituitary axis. A clinical examination requested by the pediatric neurologist did not reveal any signs of an organic or genetic syndrome.

The final diagnosis is ASD associated with ADHD, along with CM-I and primary empty sella syndrome (ESS).

Discussion

We report the case of a child with neurodevelopmental disorders: autism spectrum disorder (ASD) and attention deficit hyperactivity disorder (ADHD), along with neurological malformations: Chiari malformation type 1 (CM-I) and primary empty sella syndrome (ESS). This association has been rarely described in the literature.

Jayarao *et al*., (2015) studied a sample of 125 children, identifying 9 cases with both ASD and CM-I. They concluded that this association may coexist and be underdiagnosed. Osuagwu *et al*., (2016) described the case of a 10-year-old boy with ASD, ADHD, and CM-I. Voltisa. (2018) reported the case of a 15-year-old boy with CM-I, associated with psychiatric disorders, including global developmental delay, autistic traits, hyperactivity, behavioral issues, and obsessive-compulsive disorder. The author suggested that mixed psychiatric symptoms and developmental delay might be a more frequent comorbidity in CM-I than previously thought.

Previously considered almost exclusively involved in coordinating voluntary movements, the cerebellum is now recognized for its expanding role in modulating higher cognitive functions. Numerous studies in adults have confirmed the cerebellum's involvement in processing higher brain functions such as intelligence, language, complex social functions, perceptual, linguistic, visuospatial, cognitive, and affective functions, as well as procedural and declarative memory. These roles have also been evidenced more recently in developing children.

Consequently, in Chiari malformation, the hypothesis is that compression of the posterior fossa structures could negatively affect the functioning of these cerebellar structures. This malformation can induce intracranial hypertension and hydrocephalus, which can damage neural tissue through ischemic and mechanical forces (Voltisa,. 2018).

Gonzales and Campa-Santamarina. (2018) demonstrated the existence of possible deficits or anomalies in the executive cognitive functions of patients with Chiari Malformation Type 1 (CM-I). These patients were affected in processes of inhibition and self-control as well as in their ability to focus attention and maintain a line of thought and action. According to Koziol and Barker (2013), patients with CM-I exhibit behavioral disorders with alterations in executive functions, verbal fluency, abstract thinking, and working memory (Voltisa,. 2018).

In the context of ADHD, cerebellar anomalies, particularly volumetric reduction, are among the earliest reported observations (Stoodley,. 2014). The severity of symptoms correlates with the degree of reduction in the volume of the posterior vermis and overall cerebellum. Alterations in cerebellar structure and functional connectivity have also been documented (Stoodley, 2014; Ivanov *et al*., 2014).

Through a clinical case study, Osuagwu *et al*., (2006; 2016) highlighted the link between ASD and cerebellar anomalies as well as associated structures. They emphasized the neurobiological connection between ADHD and ASD, particularly due to the cephalocranial disproportion of neural tissues observed in CM-I, also present in ASD. Documented brain abnormalities in ASD include enlargements of the cerebral hemispheres, cerebellum, and caudate nucleus (Stanfield, 2008). Altered cranial growth with increased brain volume during childhood, associated with abnormal neural networks, has also been described in ASD, suggesting that the compressed posterior cranial fossa in our patient could be due to a mechanism similar to that responsible for their ASD (Piven *et al*., 1996).

Structural and functional imaging studies have demonstrated alterations in brain volumes in ADHD, leading to dysfunctions in fronto-subcortical circuits, manifesting as agitation and inattention observed in our patient (Cortese *et al*., 2012). More specifically, functional MRI has differentiated connectivity patterns according to the ADHD subtype: altered cerebellar connectivity in the combined type, versus changes in the cingulo-frontoparietal networks in the predominantly inattentive type (Saad *et al*., 2020).

An important limitation of the current literature is the absence of studies analyzing the link between ADHD and the different types of Chiari malformations. It would be pertinent to study how the severity of each condition influences the other. Furthermore, examining the timeline of the onset of cerebellar malformations and ADHD could help clarify the causal relationship between these two conditions (Dubow *et al*., 2020).

Although historically few pieces of evidence have been found to demonstrate a link between primary empty sella syndrome (ESS) and psychiatric disorders, we report here our case associating primary ESS with ASD and ADHD. Similar cases have also been reported by other researchers.

Girdhar *et al*., (2020) described three cases associating primary ESS with psychiatric disorders such as psychosis and anxiety disorder. In all three cases, the empty sella turcica was an incidental finding during brain imaging (MRI) performed to rule out an organic cause. Bardoloi *et al*., (2018) also reported three cases associating primary ESS with psychiatric disorders such as unspecified psychosis, ADHD, oppositional defiant disorder (ODD), psychosis and postpartum depression, intellectual disability disorder, unspecified neurodevelopmental disorders, and social anxiety disorder. In their article, Bardoloi *et al*., suggested that primary ESS, often an incidental finding, might reflect deficits in the development of midline brain structures. These anomalies, including cavum septum pellucidum, are associated with various neuropsychiatric and neurodevelopmental disorders. Thus, primary ESS is proposed as a potential indicator of these deficits. However, the direct association between primary ESS and neurodevelopmental disorders such as ASD or ADHD remains hypothetical and is not conclusively demonstrated in this article, necessitating further research to clarify these links.

CONCLUSION

Through our case, we highlight the importance of thorough neuroradiological investigations in children presenting with mixed psychiatric symptoms and developmental delay. A coordinated multidisciplinary approach, including child psychiatrists, pediatric neurologists, and neurosurgeons, is essential to optimize the management of these complex patients. This integrated approach allows for regular monitoring of development and continuous adaptation of therapeutic interventions. Although the current review of scientific literature on the coexistence of neurological malformations and neurodevelopmental disorders remains inconclusive, longitudinal prospective studies are needed to better understand these associations and improve the quality of life of these children through personalized and multidimensional care.

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