Scholars Academic Journal of Biosciences
Abbreviated Key Title: Sch Acad J Biosci
ISSN 2347-9515 (Print) | ISSN 2321-6883 (Online)
Journal homepage: https://saspublishers.com

OPEN ACCESS

Child Psychiatry

Autism Spectrum Disorder and Role of the Inflammatory Theory: A Case Report

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DOI: 10.36347/sajb.2023.v11i10.007 | **Received:** 14.09.2023 | **Accepted:** 20.10.2023 | **Published:** 24.10.2023

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Abstract **Case Report**

In this case study, an 8-year-old child from a consanguineous marriage with a complicated pregnancy due to maternal preeclampsia and a normal delivery experienced developmental delays, language problems, social challenges, and other autism spectrum disorder (ASD) symptoms. The child underwent various diagnostic tests, including the M-CHAT, ADI, and ADOS, which all supported an ASD diagnosis. Despite receiving psychomotor, speech, and ABA therapy, the child showed gradual improvement in language skills but continued to exhibit behavioral issues such as irritability, anger outbursts, and sleep disturbances. After experiencing a febrile episode with tonsillitis, followed by knee pain, walking difficulties, chest pain, and shortness of breath, the child was diagnosed with acute rheumatic fever and received corticosteroid therapy, resulting in significant clinical improvement in language, facial expressions, social interactions, and a renewed ASD assessment. The discussion focuses on the potential environmental factors contributing to ASD, emphasizing the role of shared environmental factors in twin studies and genetic factors. The study explores the inflammatory response as a possible common pathway for ASD development, particularly in cases where preeclampsia during pregnancy and its associated inflammation affect the mother and, subsequently, the placenta or fetus. Abnormal angiogenesis and elevated levels of soluble tyrosine kinase 1 (sFlt-1) are discussed as potential factors contributing to fetal neurodevelopmental abnormalities. The text also highlights the role of corticosteroid therapy in improving ASD symptoms, with references to previous studies showing positive responses to corticosteroid treatment in ASD patients. The impact of medications like prednisone and pregnenolone on ASD symptoms and their mechanisms of action, including potential modulation of GABA A receptors, is mentioned. In conclusion, the case study suggests a potential link between prenatal factors, including preeclampsia and inflammatory responses, and the development of ASD. It also points to the positive impact of corticosteroid therapy on ASD symptoms in some cases, highlighting the need for further research in this area.

Keywords: consanguineous marriage, complicated pregnancy, normal delivery, ASD diagnosis.

INTRODUCTION

Autism Spectrum Disorder (ASD) is a complex condition characterized by the involvement of multiple organs and systems. The 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM) defines the autism spectrum as a broad group of heterogeneous neurodevelopmental disorders characterized by symptoms such as abnormalities in social interaction, both verbal and non-verbal communication difficulties, and repetitive and stereotyped patterns of behavior and interests [1]. Recent epidemiological studies in the United States have reported a prevalence of ASD in up to 1 in 54 children at 8 years old [2].

Historically, ASD has primarily been described as a neurofunctional alteration. However, an increasing body of evidence suggests that, in addition to known neurobehavioral characteristics, there have been observed inflammatory, structural, and tissue alterations at various levels [3]. The objective of this article is to describe how inflammatory processes could represent one of the etiopathogenic mechanisms involved in this disorder.

CLINICAL OBSERVATION

This involves an 8-year-old child from a consanguineous marriage, with a complicated pregnancy due to maternal preeclampsia, and a normal delivery with no incidents during the neonatal period. In the child's personal history, there is a history of recurrent sore

throat. The developmental history was marked by a delay in language and toilet training. The patient did not make eye contact, was intolerant to noise, had limited social interactions, exhibited stereotypies, and had restricted interests. These symptoms prompted the parents to seek consultation at the clinic. The patient underwent a battery of tests, including the M-CHAT, ADI, and ADOS, all of which supported a diagnosis within the autism spectrum. The patient received psychomotor and speech therapy, as well as ABA therapy. The clinical course showed gradual improvement in language acquisition but persistence of behavioral issues such as irritability, anger outbursts, and sleep disturbances. Several months later, the patient experienced a febrile episode with erythematous-pultaceous tonsillitis. Fifteen days later, the patient developed knee pain and walking difficulties, followed by precordial chest pain and shortness of breath. Due to these symptoms, the patient was admitted to the pediatric ward, and a diagnosis of acute rheumatic fever was made, leading to corticosteroid therapy at a dose of 1 mg/kg/day. Eight months later, the patient was evaluated in child psychiatry, showing significant clinical improvement with improved language, expressive facial expressions, smoother social interactions, and a renewed ADOS assessment within the autism spectrum.

DISCUSSION

While several pieces of evidence suggest a hereditary component to ASD, recent large-scale studies suggest that the heritability of ASD plays a relatively minor role, highlighting the central role of shared environmental factors in twin studies (Hallmayer et al., 2011). Furthermore, even with recent advancements in whole-genome linkage studies, the identification of candidate genes involved in ASD appears to account for only 10 to 20% of ASD cases (Abrahams and Geschwind, 2008). Therefore, attention has shifted to understanding the environmental factors contributing to the etiology of ASD (Berg, 2009) and how these factors may interact with predisposing alleles during a critical window of neurological development.

The significant heterogeneity in ASD may, in part, be related to various environmental factors and the period of in utero and early postpartum exposure. Despite the diversity of potential causal agents, it appears likely that these environmental challenges converge on common pathways. One candidate fulfilling these requirements is the host's inflammatory response. Research in recent decades has shown how the immune system can affect brain function and how the brain can regulate the immune system through neural and hormonal pathways (as reviewed in Besedovsky and Rey, 2007). In the case of developmental disorders like ASD, the neuroimmune system could affect not only function but also development, leading to long-term alterations and disorders (also discussed in Patterson, 2002).

The patient in our study had a history of maternal preeclampsia, and it has been demonstrated that the inflammatory response, when triggered during pregnancy, can originate from the mother and subsequently induce inflammation in the placenta or fetus (as discussed in Stolp and Dziegielewska, 2009). Similarly, an environmental or genetic factor could affect the newborn's inflammatory response, thereby altering postnatal brain development (Adams-Chapman and Stoll, 2006). Supporting this hypothesis, recent in silico analysis of ASD revealed that genes previously linked to ASD interact at the level of immune signaling pathways, suggesting that mutations in these genes may alter the regulation of immune cell signaling during development (Ziats and Rennert, 2011).

The biological effects of preeclampsia and high blood pressure during pregnancy on the developing brain confirm a potentially causal role in neurodevelopment. Neuroimaging in children exposed to preeclampsia has shown differences in regional brain volumes, abnormal connectivity, decreased vascularization, and intra-cerebral inflammatory processes [5, 6]. Given that abnormal vascular growth and function are central to the proposed pathogenesis of preeclampsia, it is reasonable to assume that abnormal angiogenesis could also affect the fetus.

Specifically, the levels of soluble tyrosine kinase 1 (sFlt-1), a decoy receptor for proangiogenic placental growth factor and vascular endothelial growth factor, are elevated in mothers with preeclampsia throughout pregnancy and in the umbilical cord blood of newborns at birth [7-9]. Inducing the expression of sFlt-1 produces a preeclampsia phenotype in animal models, and early clinical trials in humans suggest that its removal can improve maternal hypertension, end-organ function, and extend pregnancy, thus reinforcing its causal role in preeclampsia development [10, 11]. Elevated sFlt-1 levels may, in turn, induce abnormal angiogenesis in the fetus by reducing available circulating levels of placental growth factor [12, 13].

Studying potential anomalies in cerebral vascularization in patients with neurodevelopmental disorders and the evidence of associations between proangiogenic and antiangiogenic factor levels in newborns and abnormal neurodevelopment would help validate these proposed mechanisms. Similarly, preeclampsia is associated with maternal inflammation. Biological markers of inflammation during pregnancy could strengthen the suggested link between maternal inflammation and neurodevelopmental outcomes in offspring [14].

The clinical improvement of the child in our study after corticosteroid therapy raises several questions about the role of this molecule in ASD. It is worth noting that corticosteroids are anti-inflammatory drugs that inhibit the secretion of pro-inflammatory mediators,

modify the activity of T lymphocytes, and may also interfere with microglial activation [15]. A retrospective study with oral prednisone treatment (2 mg/kg/day for 9-12 months) assessed ASD patients using the Clinical Language Status Questionnaire (CLSQ), frequency-modulated auditory evoked response (FMAER) testing, and EEG. In the treated group (20 participants), 9 out of 14 electrode measures of FMAER at 4 Hz showed statistically significant changes, particularly at the left posterior lower temporal electrode (TP9). No differences were observed in the control group (24 untreated subjects). The steroid-treated group also showed a significant increase in average CLSQ scores after therapy [16].

Shenoy *et al*., [17] reported a response to corticosteroid therapy in a case of ASD comorbid with an autoimmune syndrome. The patient was treated with various oral prednisolone regimens, at an average dose of 0.5 mg/kg per day. The ASD symptoms gradually improved over the year following corticosteroid therapy. In a similar study, a child who experienced language and behavioral regression at 22 months of age (later diagnosed with pervasive developmental disorder) received prednisone (2 mg/kg/day) for 28 weeks. The observed results included improved speech, enhanced responsiveness to verbal communication, better social interactions, and reduced motor stereotypies [18].

Mordekar *et al*., [19] reported 2 patients diagnosed with ASD who were also treated with corticosteroids, showing similar clinical improvement under prednisone treatment (2 mg/kg per day). The first patient exhibited speech recovery by the 11th day of treatment. The second subject, receiving the same dose for one week, demonstrated progressive speech improvement over a 48-month period.

In the 1990s, several studies were conducted using ORG 2766, a synthetic analogue of adrenocorticotropic hormone (ACTH) (4-9). However, ORG 2766 lacks substantial steroidogenic activity and may exert its effects through interaction with endogenous opioid systems [20, 21]. Another open study using pregnenolone, a neurosteroid, showed improvements in patients with ASD. Considering that this medication did not alter cortisol levels, the authors suggested that pregnenolone may act by modulating GABA A receptors, thereby modifying the excitation/inhibition balance in key neural systems [22, 23].

CONCLUSION

In light of recent findings, autism research is increasingly focused on environmental factors. Remarkably, most proposed perinatal factors seem to converge towards the activation of the immune system. As discussed here, cytokines appear to play an essential role in behavior programming and have the ability to access the brain at different stages of life to influence development and brain function. Identifying critical periods, specific cytokines involved, and, most importantly, how these factors affect the brain's architecture is essential for the development of prevention and curative treatment strategies.

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