Clinical Psychopharmacology and Neuroscience - Manuscript Submission

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- Title: Autism Spectrum Disorder in a Child with Megalencephaly-Capillary Malformation-Polymicrogyria Syndrome: A Case Report
- Running Title: Autism Spectrum Disorder and Megalencephaly-Capillary Malformation-Polymicrogyria Syndrome
- Article Type: Case Report
- KeyWords: autism, Megalencephaly-Capillary Malformation Syndrome, genetic

Abstract

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by deficits in social communication and social interaction as well as repetitive behaviors and restricted interests. The genetic mechanism underlying ASD is as complex and heterogeneous as the clinical presentation of the disorder itself. Megalencephaly-Capillary Malformation Syndrome (MCAP) is a rare genetic disorder that is associated with mutations in the ADGRV1 and PIK3CA genes. To the best of our knowledge, there is only one case report in the literature that documents the coexistence of MCAP and ASD. In this case study, we present the case of a 14-year-old girl diagnosed with both ASD and MCAP who was admitted to our clinic. Diagnosing ASD in patients with genetic syndromes can be challenging due to pre-existing cognitive and medical issues. This case underscores the importance of regular child psychiatry follow-ups for children with genetic syndromes to ensure timely and accurate diagnosis of ASD.

Keywords: Autism, Megalencephaly-Capillary Malformation Syndrome, genetic

Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by deficits in social communication and social interaction associated with restricted interests and repetitive behaviors, affecting approximately 1 in 36 individuals according to recent data (1). While the primary cause of ASD remains unknown in most cases, it has been reported that 5-10% of ASD cases may be linked to known genetic causes through monogenic syndromes such as Fragile X syndrome, Rett syndrome, Tuberous Sclerosis and Angelman syndrome (2,3,4). Investigating the association between ASD and these genetic syndromes is particularly valuable for understanding the genetic mechanisms underlying ASD and for developing targeted therapeutic strategies. It may also be important to expand our knowledge of the autistic symptomatology profile within a syndrome, as there may be different ASD phenotypes associated with each genetic syndrome (5, 6).

Megalencephaly-capillary malformation-polymicrogyria syndrome (MCAP) is a rare genetic syndrome primarily caused by mosaic mutations in the PI3K-AKT pathway (7). The syndrome is characterized by a range of clinical features including primary megalencephaly, cutaneous capillary malformations, connective tissue dysplasia, postaxial anomalies such as syndactyly and polymicrogyria (8). In addition to megalencephaly, other structural abnormalities of the brain have been reported in children with MCAP, including ventricular enlargement, cerebral/cerebellar asymmetry, and white matter changes (9). As a result of all these changes, children with MCAP are at greater risk of neurocognitive impairment and neurological

abnormalities than the general population (7). The presence of vascular abnormalities such as capillary malformations increases their susceptibility to certain cerebrovascular events (10). Furthermore, the complex interaction of neurological and vascular abnormalities makes these patients particularly susceptible to medication-related side effects (11).

The present case report describes a child diagnosed with ASD and MCAP who presented to our outpatient clinic. Although the Macrocephaly-Capillary Malformation Network notes that autism may be observed in some individuals with MCAP, to our knowledge, there is only one other case report of the coexistence of MCAP and ASD in the literature (12, 13).

Case Report

A 14-year-old girl with a prior diagnosis of MCAP presented to the child and adolescent psychiatry outpatient clinic with complaints of anxiety and difficulties in attention and concentration. The psychiatric interview revealed that the patient experienced intense anxiety about her own and her parents' health, along with a significant need for constant companionship, resulting in distress when separated from her mother. Her psychiatric history included previous pharmacological interventions prescribed by neurologist, specifically escitalopram, 10 mg for 2 weeks at the age of 7, discontinued because of severe nosebleeds, and sertraline, 50 mg for 1 month at the age of 13, discontinued because of increased menstrual bleeding. In both cases, the bleeding symptoms resolved when the medication was discontinued. Psychiatric assessment revealed significant impairments in social-emotional reciprocity and limited nonverbal communication characterized by poor eye contact and a dysprosodic tone of voice. It was reported that the patient had limited interest in peers, difficulty in adapting behaviour to social contexts, and an unusually quick tendency to be friend with people she had just met. Motor stereotypies such as hand flapping, walking on tiptoe and echolalia were noted. In addition, the

patient had excessively focused, restricted and age-inappropriate interest in football and politics and abnormal responses to sounds.

Her medical history was significant for MCAP, including epilepsy, limb abnormalities and intracranial bleeding (7). She was diagnosed with MCAP at around six months of age, with genetic testing revealing mutations in the ADGRV1 and PIK3CA genes. She continued to receive regular oncology follow-up due to increased risk of Wilms tumor and used orthoses for her limb abnormalities (14).

Her psychometric evaluation revealed borderline mental capacity (IQ:75). A detailed psychiatric assessment was also carried out, including administration of the Childhood Autism Rating Scale (CARS) and the Revised Child Anxiety and Depression Scale (RCADS). On the CARS, the patient scored 36.5, indicating mild to moderate autism. The RCADS revealed mild to moderate anxiety, with specific scores of 14 for separation anxiety and 6 for generalised anxiety, while no significant depressive symptoms were reported. Based on the presenting symptoms and these assessment results, the patient was diagnosed with ASD and separation anxiety disorder. Psychoeducation was provided to both the patient and her family. Given the mild to moderate severity of the anxiety symptoms and a history of bleeding associated with two different SSRIs, non-pharmacological behavioural interventions were recommended as the primary approach.

At our institution, all patients are required to complete a written informed consent form at the time of admission. This form includes a provision allowing the use of anonymised clinical data for academic, educational and publication purposes. In addition, the patient and her parents

were verbally informed about the preparation of this case report and gave their consent for its publication.

Discussion

This case report describes a child with both MCAP and ASD, highlighting the complex association between genetic syndromes and neurodevelopmental disorders (6).

MCAP is a rare genetic syndrome associated with mutations in the ADGRV1 and PIK3CA genes and is part of the PIK3CA-related overgrowth spectrum (PROS) (15). Previous reports have suggested that cognitive impairments such as intellectual disability and learning difficulties are common in MCAP (7). Although autistic features have been identified in other PROS spectrum disorders, documentation of ASD specifically in MCAP patients remains limited (16). A review of the literature reveals only one case report, published by John and Rao in 2021, in which the co-occurrence of ASD and MCAP in a seven-year-old boy has been documented. The PIK3CA gene implicated in MCAP is known to play a role in neural development and synaptic function, areas that are also being investigated in the pathophysiology of ASD (17). In addition, the extensive brain abnormalities seen in MCAP, particularly those affecting white matter integrity and cerebral connectivity, may predispose individuals to neurodevelopmental disorders such as ASD (18). These factors may help to establish a causal relationship between MCAP and ASD. This case report highlights ASD in a child with MCAP and aims to encourage further research to explore different presentations and diagnoses to understand the genetic mechanisms of ASD.

In this case, the patient was diagnosed with ASD at the age of 14 during a psychiatric evaluation. The identification of ASD in patients with genetic syndromes can be challenging due to the

presence of pre-existing cognitive and behavioural problems (6). Overlapping problems in genetic syndromes, such as social anxiety or communication difficulties, often mask or mimic symptoms of autism (19). Neurological abnormalities in these children typically result in their being seen by neurologists rather than child psychiatrists, which can result in a delay or missed diagnosis of ASD (7). Furthermore, a failure to recognise obsessive behaviours and developmental fears associated with ASD can result in patients being misdiagnosed with anxiety disorders or OCD (7). In the presented report, the patient's sensitivity to noise and repetitive questioning were misidentified as an anxiety disorder, resulting in ineffective treatment efforts. Therefore, routine child psychiatric assessment of children with certain genetic syndromes is essential to ensure timely and accurate diagnosis.

In addition, this report highlights the importance of careful monitoring when prescribing antidepressants to patients with additional medical comorbidities. Psychotropic medications including selective serotonin reuptake inhibitors (SSRIs) have been reported to increase the risk of bleeding, such as nose, gastrointestinal or increased menstrual bleeding (20-24). On particular SSRIs have been reported to cause abnormal bleeding due to their effects on platelet aggregation (20,21). This risk is particularly relevant in patients with underlying conditions that may predispose them to bleeding diathesis (24). Given the potential vascular malformations associated with MCAP, the risk of bleeding may be further increased. Comprehensive clinical assessment and multidisciplinary approache are essential in the management of these complex cases.

This case report adds to the literature the co-occurrence of ASD with various genetic syndromes and highlights the need for clinicians to consider the potential for comorbid neurodevelopmental disorders in these syndromes. Further research is required to elucidate the

genetic and neurobiological mechanisms underlying this comorbidity and to understand the pharmacogenomic variations associated with this syndrome.

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