Case Report

EP400-Related Neurodevelopmental Disorder Presenting With Autism Spectrum Disorder: A Case Report

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Abstract

Introduction: Autism Spectrum Disorder (ASD), a neurodevelopmental disorder, is one of the most prevalent mental health disorders in children and young adults. Earlier detection of ASD may allow for timely intervention and improved outcomes. Testing for abnormalities of biomarkers (e.g., genes, cytoarchitecture) reliable screening methods. The EP400 variant has been found in individuals with neurodevelopmental delays and epilepsy.

Case: A young patient presented with social and behavioral issues and academic difficulties suggestive of ASD. Due to failures of multiple treatments, genetic testing was performed, and he tested positive for EP400.

Discussion: The presence of the EP400 variant in the discussed case is in parallel with the findings of earlier research correlating EP400 with neurodevelopmental delays and epilepsy.

Conclusion: Studies with larger samples are required given the limited research analyzing an association between EP400 and neurodevelopmental disorders. Due to the potential association between genetic variants and autism spectrum disorder, we recommend genetic testing in individuals with ASD.

Introduction

Autism, formerly classified as a pervasive developmental disorder, is a neurodevelopmental condition characterized by narrow interests, repetitive behaviors, and impairment in social interactions and communication skills. In 2013, autism was integrated into Autism Spectrum Disorder (ASD) by the Diagnostic and Statistical Manual of Mental Disorders [1]. In the United States, approximately one in 31 children aged eight years is diagnosed with ASD [2]. The prevalence rate has increased in this cohort from 0.9 percent (one in 110 children) in 2006 to 3.2 percent in 2022 [2]. The diagnosis rate of ASD in adults has increased by 450 percent from 2011 to 2022 [3]. However, cases of ASD are likely underreported: older adults may not have been screened in their childhood if diagnostic tools did not exist, and females with ASD have historically been mis-or undiagnosed [3]. Thus, the true prevalence rate of ASD is likely to rise if such cases are accounted for.

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The climbing incidence rate of ASD among individuals in the US emphasizes the need for prompt screening and diagnostic approaches in conjunction with the expansion of specialized healthcare services [3]. The mean age of ASD diagnosis is around four to five years, which is typically after the abnormal behavior becomes evident and delayed developmental milestones concern caregivers [4]. In infants, atypical gaze metrics and orienting patterns have been associated with ASD. However, behavioral manifestations have lower specificity and may vary across individuals with ASD, limiting their utility for timely detection and intervention.

Early diagnosis and timely management of ASD are associated with better functional outcomes and reduced healthcare costs [4]. Cost-effective analyses indicate that children who receive early interventions demonstrate developmental gains and require fewer supportive measures over time compared to counterparts diagnosed at later ages (consequently resulting in cost savings) [4]. The multifaceted benefits of early diagnosis and intervention necessitate the investigation into reliable and specific biomarkers and the development of reliable screening tools.

Various genetic and neurobiological factors contribute to the complicated nature of ASD. As such, tools specifically created to pinpoint these biomarkers may exhibit improved accuracy and precision compared to earlier methods. Magnetic resonance imaging (MRI) can detect early neuroanatomical changes such as cerebrospinal fluid (CSF) volume, white matter, brain volume, etc., with high sensitivity (88%) and specificity (95%) in 6-12-month-old infants. Despite the reliability of MRI as a screening method, it is neither used commonly in the ASD diagnostic process nor a cost-effective option. Genetic testing is a cheaper (make sure this is accurate), ubiquitous technique frequently implemented in the diagnosis of other neurodevelopmental disorders. Genetic testing for copy number variations (CNVs) has identified abnormalities in 7-10% of ASD cases [5]. de novo gene variants are associated with neurodevelopmental disorders (NDDs) and implicated in ASD, developmental delay, and severe epilepsy [6].

One such gene, EP400, encodes chromatin remodelling ATPase and dysregulates downstream gene expression. [7]. EP400 deficiency results in expression of NDD/epilepsy related genes, including dose-sensitive genes [7]. It is mainly expressed in inhibitory neurons during early brain development and in excitatory neurons at the mature stage [7]. The temporal expression of genes is associated with the onset and outcome of illness [7]. Though further investigation is required to substantiate the role of EP400 within the scope of neurology and psychiatry, research has suggested an association among EP400, NDD, and epilepsy.

We present a case of a young male who presented to our clinic for behavioral and emotional regulation and was diagnosed with autism spectrum disorders level I without any mood impairments and tested for EP400 variants.

Case

A 14-year-old white male, “Luke,” presented to an urban community clinic to address his complicated psychiatric problems. One year prior to this visit, he was diagnosed with depression and had received care from psychiatrists through a number of medication trials. Despite a regimen of paroxetine, sertraline, divalproex sodium, and escitalopram, his mood dysregulation still was not properly managed. Further, he became sexually aggressive upon initiating the medications and his parents reported that he expressed passive suicidal ideation. He attended an elementary school for six months but was expelled for anger issues and behavioral disturbances.

Luke’s behavioral history was notable for compulsive, unregulated shopping urges and desires. If his desires were not met, he became angry and used manipulative techniques (i.e., threats of self-harm or harm to family members) until he was satisfied. He also displayed episodes of physical aggression towards his family members, followed by expressing affection and remorse.

On Luke’s mental status examination, he appeared monotonous while speaking, anxious, and depressed. His mood was labile, with rapid shifting between high and low levels. He endorsed passive suicidality during his visit again. Based on the history and clinical presentation, presumptive diagnoses of autistic disorder, disruptive mood dysregulation disorder, and bipolar disorder were ruled out.

Given Luke’s history of autism spectrum disorder and treatment resistance to numerous psychiatric medications, chromosomal analysis/genetic testing was recommended. Buccal swab samples were analyzed for small sequence variants, mitochondrial genome, structural variants, and short tandem repeats. The test identified the EP400 gene variant in addition to other non-pathological variants.

At the six-month follow-up evaluation, Luke showed partial improvement. He stated a reduction in mood instability and anxiety. He was capable of performing adequately in individual teaching but had difficulties participating in school-based learning. He was treated with lamotrigine 250 mg, bupropion 300 mg, and extended-release amphetamine-dextroamphetamine 30 mg.

Discussion

This case is a classical presentation consistent with autism spectrum disorder (ASD), emotional dysregulation, and behavioral disturbances, prompting genetic evaluation that identified the EP400 variant. Normally, EP400 encodes the E1A-binding protein ep400, which is expressed during the early stages of life [7]. The ep400 protein is one of the core subunits of the histone acetyltransferase complex, regulating the expression of selected genes. Beyond ep400, abnormal EP400 variants truncate or disrupt the stability of numerous other proteins [7]. Several genes encoding components of the histone acetyltransferase complex have been linked to NDDs with and without seizures [7]. The severity of the phenotype is directly related to the extent of damage to the variants [7]. In animal models, EP400 alteration expressed lethality with complete penetrance, embryonic growth arrest, and neural tube defects [7].

This study presents a case with multiple psychiatric manifestations besides autism spectrum disorder and a defect present in the EP400 gene. Our case is consistent with a prior small-scale study suggesting a possible association between EP400 variants, neurodevelopmental disorders, and epilepsy [7]. Currently, the pathogenic variant of EP400 is not associated with a specific disease in the Online Mendelian Inheritance in Man® (OMIM®) database and is classified as uncertain for EP400-related disorders [8].

Earlier identification of pathogenic variants such as EP400 may facilitate diagnosing ASD and timely therapeutic, educational, and social interventions [9]. Such strategies may reduce the long-term developmental/social sequelae and economic burden associated with ASD. We question the prevalence of this genetic alteration if it should be considered as a diagnostic tool, and if it can positively impact the management of symptoms for these patients.

Our study is intrinsically limited in sample size: we present only one example of both the presence of autism spectrum disorder and an EP400 gene defect. Larger, more robust studies are recommended to determine the real-world impact of this genetic defect in the general population. Further, we strongly endorse future investigations into the neurobiological and developmental markers of ASD and other psychiatric conditions, especially those that examine the utility of genetic testing as an aid to early intervention.

Conclusion

We report the case of a patient with a previous diagnosis of autism spectrum disorder who presented with mood dysregulation, anxiety, and attention deficit symptoms. Despite initial treatments with anxiolytics, antidepressants, and antipsychotics, medication trials were unsuccessful. A genetic test detected a defect on EP400, a gene related to autism, neurodevelopmental delays, and epilepsy.

Given the implications of autism spectrum disorder, early identification and intervention are critical. Further research with a larger sample size is required to understand the role of EP400 in neurodevelopment and its association with ASD and other neuropsychiatric conditions.

Ethical Review and Consent

Formal ethical approval was not required for this study under local and institutional regulations. Written informed consent was obtained from the patient to publish this case.

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