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UNMASKING AUTISM IN A GENETIC SYNDROME: A FIVE-YEAR DEVELOPMENTAL TRAJECTORY EMPHASIZING REEVALUATION AND COLLABORATION

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Abstract

Accurately identifying autism spectrum disorder (ASD) in children with co-occurring rare genetic conditions presents significant diagnostic challenges, particularly when early developmental features overlap with syndrome-specific phenotypes. This case report expands upon a longitudinal case of a child with SATB2-associated syndrome (SAS) who demonstrated an evolving clinical presentation, including late regression and a marked decline in social communication between ages 2 and 7. The paper highlights how early social strengths, profound speech delays, and motor impairments initially obscured ASD symptomatology, leading to a preliminary diagnosis of global developmental delay. Comprehensive reevaluation in later childhood revealed clear ASD features, emphasizing the necessity of ongoing monitoring for diagnostically complex children. The report underscores the critical role of multidisciplinary teams in differentiating ASD from genetic-syndrome-related behaviors and in providing integrated assessments across developmental domains. Additionally, it discusses how genetic diagnoses such as SAS influence prognosis, guide intervention planning, and support family access to resources. This case study illustrates the importance of combining genetic, developmental, and behavioral perspectives to improve diagnostic accuracy and optimize long-term outcomes for children with rare genetic disorders and co-occurring ASD.

Keywords: *SATB2-associated syndrome, autism spectrum disorder, regression, developmental delay, genetic disorders.*

1. Introduction

Autism spectrum disorder (ASD) is a complex neurodevelopmental condition characterized by persistent deficits in social communication and restricted, repetitive behaviors (American Psychiatric Association, 2022). The U.S. Centers for Disease Control and Prevention estimates a prevalence of approximately 1 in 36 children (Maenner et al., 2020), highlighting the growing importance of accurate and timely diagnosis. Early identification allows access to evidence-based interventions that can significantly improve adaptive functioning, language acquisition, and quality of life (Kodak & Bergmann, 2020). However, diagnosis is often complicated when ASD co-occurs with other neurogenetic syndromes. Children with chromosomal microdeletions or single-gene conditions frequently display overlapping cognitive and behavioral symptoms that mimic ASD but arise from distinct etiologies (Zarate et al., 2021). Misattributing behaviors to one disorder alone can delay or obscure appropriate interventions. Glass Syndrome, also known as *SATB2*-associated syndrome (SAS), is a rare genetic disorder caused by alterations in the "*SATB2*" gene (Zarate & Fish, 2017). The first known case of SAS was identified in 1989 by Dr. Ian Glass, who diagnosed a 16-year-old boy with a genetic deletion on chromosome 2 (specifically 2q32.2-q33.1 microdeletion). At that time, Dr. Glass named the condition "Glass Syndrome," based on his identification of the chromosomal deletion as the cause (Glass et al., 1989).

SATB2-associated syndrome (SAS) exemplifies this challenge. The condition shares several features with ASD, including social-communication difficulties, repetitive movements, and variable intellectual impairment, yet also exhibits distinctive social warmth and a characteristically cheerful demeanor (Zarate & Fish, 2017). Understanding when autism represents a true comorbidity versus part of the SAS behavioral phenotype remains an active area of research.

2. SATB2-associated syndrome and ASD: Overlapping phenotypes and diagnostic challenges

SATB2-associated syndrome is a rare genetic condition caused by pathogenic variants or deletions involving the SATB2 gene. SAS is associated with intellectual disability, severely limited or absent speech, craniofacial anomalies, feeding difficulties, dental abnormalities, hypotonia, motor delays, and a behavioral phenotype often described as “friendly” or “jovial” (Zarate & Fish, 2017). Autism-like features, including stereotypies, irregular social engagement, sensory behaviors, and repetitive actions, have been reported in nearly half of individuals with SAS (Bissell et al., 2022; Zarate et al., 2021).

These overlapping symptoms pose significant diagnostic challenges. Early in development, limited speech, delayed milestones, and motor impairments may be attributed solely to the genetic syndrome rather than ASD. Conversely, some children with genetic disorders exhibit social strengths that mask emerging ASD features. In this case study, the child’s initial presentation at age 2 showed bright affect, eye contact, symbolic play, and cooperative engagement, leading clinicians to diagnose global developmental delay without ASD. Overlap in symptomatology can obscure early autistic traits or create diagnostic overshadowing, where impairments are misattributed to the genetic syndrome alone.

A second complicating factor involves late regression, an area with limited research in SAS. Regression in ASD typically appears before age 3 (Boterberg et al., 2019). In this child, regression emerged later and appeared intertwined with the developmental trajectory of SAS. This pattern underscores the necessity of considering both genetic etiology and neurodevelopmental profiles simultaneously.

3. Case presentation

A male child was initially brought to a university-affiliated Child Development Center at 2 years 10 months due to concerns regarding delayed communication and motor development. He was born at term following an unremarkable pregnancy and delivery. Early developmental history was notable for markedly delayed gross-motor milestones; he did not achieve independent walking until 19 months and exhibited hypotonia, poor balance, and frequent falls. These difficulties prompted physical therapy prior to referral. Speech and language development was significantly limited, with no meaningful word production in either language spoken at home. At the time of the initial evaluation, he was receiving multidisciplinary early intervention services, including speech, occupational, and physical therapy. His family history included a first-degree relative diagnosed with autism spectrum disorder. He resided with both parents and a younger sibling. Initial chromosomal microarray results were reported as normal.

A comprehensive developmental and diagnostic assessment was completed using the Autism Diagnostic Interview–Revised (ADI-R), the Autism Diagnostic Observation Schedule, Second Edition (ADOS-2), and the Adaptive Behavior Assessment System, Third Edition (ABAS-3). Findings were most consistent with global developmental delay rather than autism spectrum disorder. Scores fell well below ASD diagnostic thresholds (ADI-R = 13; ADOS-2 comparison score = 1; ABAS-3 composite = 60). Clinically, he demonstrated a number of social strengths, including consistent eye contact, smooth separation from caregivers, and eager participation in play-based tasks. He used nonverbal communication strategies—such as open-hand pointing and waving—paired with eye gaze, and he engaged in early symbolic play routines. His affect was bright and socially engaged throughout the session. Although motor delays were evident, including a wide-based gait and drooling, these challenges did not limit his ability to participate meaningfully in the evaluation.

At approximately 4 years of age, repeat genetic testing identified a non-recurrent microdeletion at 2q33.1 involving the SATB2 gene, establishing a diagnosis of SATB2-associated syndrome (SAS). When the child returned for reevaluation at 7 years 2 months, caregivers reported increasing concern regarding stagnation of developmental progress and a noticeable loss of previously acquired social and communicative abilities. A second evaluation was conducted using the same standardized measures. Results showed substantial worsening across domains (ADI-R = 47; ADOS-2 comparison score = 8; ABAS-3 composite = 46). Direct observation revealed the absence of eye contact, lack of vocalizations, markedly restricted affect, and persistent repetitive object manipulation. Cooperative and pretend play were no longer observed, and distress sounds had replaced purposeful communication attempts. Motor difficulties persisted, including hypotonia, drooling, and a wide-based gait. Physical maturation highlighted craniofacial and dental findings characteristic of SAS, including a high-arched palate and dental crowding. Based on the convergence of behavioral observations, test findings, and parent report, the child met DSM-5-TR criteria for autism spectrum disorder (Level 3) and Severe Intellectual Disability at the time of follow-up.

4. The importance of ongoing assessment and longitudinal monitoring

For children with rare genetic disorders or diagnostically complex presentations, a single evaluation rarely captures the full developmental picture. Instead, ongoing assessment across multiple time points is critical. Developmental trajectories can change rapidly, and new symptoms may emerge as demands increase with age.

In this case study, the divergence between the two evaluation periods was striking. Initial assessment at age 2 revealed social strengths and emerging play behaviors, whereas the follow-up at age 7 demonstrated profound loss of social communication, absence of expressive language, flat affect, and prominent repetitive behaviors. Without longitudinal reassessment, the diagnosis of ASD would have remained unrecognized and untreated.

Ongoing assessment serves several purposes:

1. Capturing Regression or Plateauing Skills

Developmental regression is a red flag for both ASD and certain genetic syndromes. Regular evaluations enable early detection and clarification of whether regression is global, domain-specific, or behaviorally driven.

2. Differentiating ASD from Global Developmental Delay or Intellectual Disability

As children age, developmental expectations shift and discrepancies become more apparent. The loss of eye contact, social overtures, and symbolic play at age 7 clearly differentiated the child from peers with static developmental delays.

3. Monitoring Adaptive Functioning

Adaptive skill assessments (e.g., ABAS-3) are crucial for refining diagnoses, identifying intellectual disability, and tailoring support services. In this case, adaptive scores declined significantly, signaling increasing functional impairment.

4. Updating Treatment Needs

As diagnostic clarity increases, intervention plans must be recalibrated. Longitudinal evaluation ensures treatments remain aligned with developmental needs.

5. Multidisciplinary teams in the evaluation of complex cases

Children with rare genetic conditions require broad, collaborative evaluation to ensure diagnostic accuracy. Multidisciplinary teams typically include: Clinical psychology (diagnosis of ASD, intellectual functioning, adaptive behavior); Speech-language pathology (communication profile, feeding concerns); Occupational therapy (sensory processing, fine motor skills, adaptive functioning); Physical therapy (gross motor delays, gait abnormalities); Developmental pediatrics (overall medical evaluation); Medical genetics (genetic testing, interpretation, counseling); and Neurology (if seizures, tone abnormalities, or regression occur).

In this specific case report, collaboration between psychology and speech-language pathology yielded critical information at both time points. Genetic testing later revealed SAS, which reframed interpretation of early developmental signs. Without interdisciplinary input, clinicians risk diagnostic overshadowing or incomplete conceptualization of the child's needs.

- Multidisciplinary assessment provides a comprehensive developmental and behavioral profile. Such team-based assessment is cross-disciplinary, offering perspectives that detect subtle deficits. Using multiple skilled examiners from different disciplines would theoretically improve the ability to differentiate between ASD symptoms and genetic-syndrome traits, which in turn could increase the diagnostic confidence for families and service providers. Finally, multidisciplinary teams can provide unified and detailed recommendations for intervention and family support. Such collaboration is now recognized as essential in complex neurodevelopmental evaluations, particularly when genetic disorders are suspected or confirmed.

6. Clinical and research implications

This case highlights several broader implications for clinical practice:

1. Genetic Testing Should Be Standard. As recommended by ASD clinical guidelines, genetic testing is essential in evaluating children with developmental delays or intellectual disability. Yet many children do not receive it (Moreno-De-Luca et al., 2020), resulting in missed diagnoses and suboptimal treatment plans.

2. Dual Diagnoses Require Nuanced Interpretation. ASD and genetic syndromes can co-occur; the presence of one does not exclude the other. Clinicians must remain cautious not to over-attribute delays to genetic conditions or assume ASD alone explains the child's presentation.

3. Longitudinal Data Are Critical. Without reevaluation, this child's significant regression and ASD symptoms would have been missed. Timely reassessment should be an expected component of care.

4. More Research Is Needed on Regression in Genetic Syndromes. Very few studies describe regression in SAS. Detailed case reports such as this one help build a foundation for future research and syndrome-specific guidelines.

7. Conclusion

This case illustrates the diagnostic complexity of ASD when co-occurring with SATB2-associated syndrome. The case demonstrates how genetic findings reshape diagnostic understanding, how late regression can alter developmental trajectories, and how multidisciplinary teams play a vital role in accurate diagnosis and comprehensive care. Ongoing assessments are essential for capturing emerging symptoms, refining diagnoses, and guiding evolving treatment needs. Children with dual diagnoses require individualized, intensive, and interdisciplinary intervention plans that account for both ASD and genetic-syndrome-specific features.

By integrating genetic, developmental, behavioral, and adaptive information, clinicians can better support children with complex neurodevelopmental profiles and improve long-term outcomes. This case contributes meaningful data to the limited SAS literature and reinforces the necessity of genetic testing, multidisciplinary collaboration, and sustained evaluation for children with rare disorders and suspected ASD.

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