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Case report

Expanding the spectrum of *SATB2*-associated syndrome: a case with hearing loss and enlarged perivascular spaces

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Abstract

SATB2-associated syndrome (SAS) is a rare neurogenetic disorder characterized by intellectual disability, absent or limited speech, craniofacial and dental anomalies, and behavioral disturbances. While most cases are associated with normal hearing, some may present with atypical features.

We describe an 8-year-old male with global developmental delay, absent verbal language, autism spectrum disorder, and bilateral moderate sensorineural hearing loss. Dysmorphic facial features and neuroimaging findings of enlarged perivascular spaces were also identified. Whole-exome sequencing ultimately revealed a heterozygous pathogenic *SATB2* variant (c.1285C>T; p.Arg429*), confirming SAS.

This case expands the phenotypic spectrum of SAS by reporting a rare association with sensorineural hearing loss and enlarged perivascular spaces. It emphasizes the importance of considering SAS in patients with global developmental delay and syndromic features and supports the utility of exome sequencing in achieving a definitive diagnosis.

Keywords

Enlarged perivascular spaces, Glass syndrome, neurogenetic, SAS, *SATB2*, sensorineural hearing loss.

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Introduction

SATB2-associated syndrome (SAS, Glass syndrome, OMIM 612313) is a rare neurogenetic disorder first reported in 1989 [1, 2]. It is caused by alterations in the *SATB2* (special AT-rich sequence binding protein) gene on chromosome 2, which can occur through various mechanisms including point mutations, intragenic deletions or duplications, translocations, and larger chromosomal deletions [3]. SAS is estimated to account for approximately 0.3% of individuals with unexplained developmental delay or intellectual disability. It is characterized by developmental delay or intellectual disability with absent or limited speech, craniofacial anomalies, dental and palatal abnormalities, behavioral issues, and skeletal anomalies [4].

Case presentation

The patient is a male born at 37 weeks' gestation via cesarean section, with a birth weight of 2.860 kg (30th centile), length of 48 cm (50th centile), and head circumference of 35 cm (66th centile). He was the first of twins born from a dichorionic diamniotic twin pregnancy. The pregnancy was uncomplicated, and family history was noncontributory. Early development was marked by significant delays, including a social smile at 6 months and independent ambulation at 20 months. From an early age, he was referred to local early intervention services and benefited from therapeutic interventions such as speech therapy, occupational therapy, physical therapy, and psychomotricity. Despite these early interventions, verbal language was not acquired, and functional communication was achieved through the use of the Picture Exchange Communication System (PECS), initiated at 6 years of age.

At 2 years of age, auditory brainstem and steady-state responses revealed bilateral moderate sensorineural hearing loss, with thresholds of 50 dB in the right ear and 55 dB in the left. At age 3, autism spectrum disorder (ASD) was diagnosed based on the *Autism Diagnostic Observation Schedule, Second Edition* (ADOS-2), with core features including restricted interests, stereotyped behaviors, poor eye contact, and episodes of aggressive outbursts.

Dysmorphic features included a long face, downslanting palpebral fissures, a depressed nasal bridge with bulbous tip, and multiple dental diastemata. Brain magnetic resonance imaging (MRI) performed at age 3 (**Fig. 1**) showed mildly enlarged perivascular spaces in the peritrigonal regions. Myelination was age appropriate. The brain parenchyma, brainstem, and posterior fossa demonstrated normal morphology and signal characteristics. The cochleovestibular structures were morphologically normal. Electroencephalography was normal.

Additional investigations included a normal karyotype (46,XY), negative *FMR1* testing, and unremarkable metabolic screening. Array comparative genomic hybridization (array-CGH) and multiplex ligation-dependent probe amplification (MLPA) studies for microdeletions/duplications were also normal.

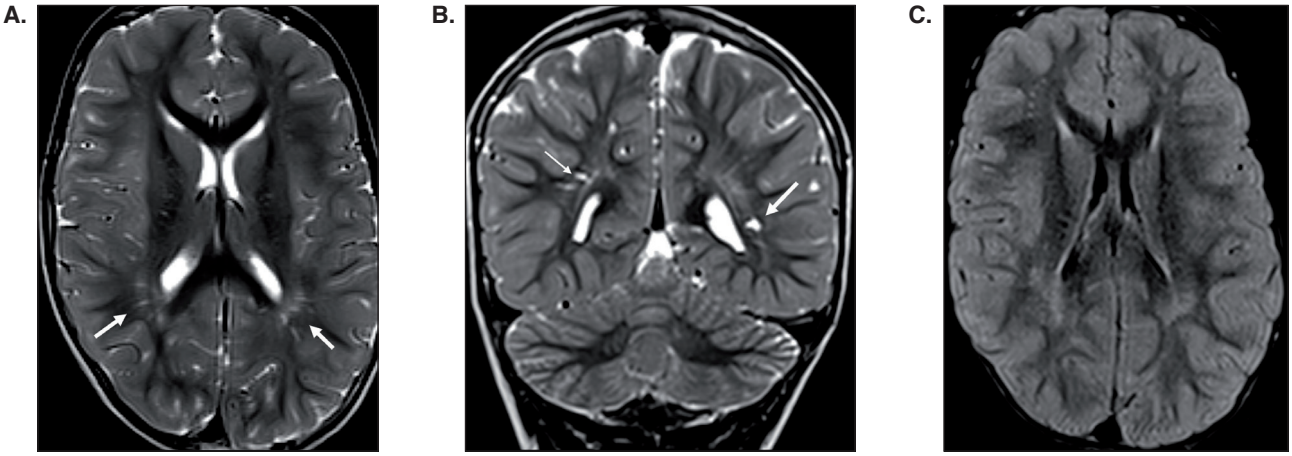

Figure 1. Axial T2-weighted (**A**), coronal T2-weighted (**B**), and axial T2 FLAIR (**C**) images show mildly enlarged perivascular spaces in the peritrigonal regions (arrows).

At 8 years of age, whole-exome sequencing identified a heterozygous pathogenic variant in the *SATB2* gene (NM_015265.3): c.1285C>T (p.Arg429*), a nonsense mutation predicted to introduce a premature stop codon at amino acid position 429. This variant is absent from population databases (Genome Aggregation Database). Segregation analysis confirmed that the variant occurred *de novo*, supporting its pathogenicity and confirming the molecular diagnosis of SAS. His twin brother was clinically healthy, with normal growth, neurodevelopment, and no dysmorphic features. Genetic counseling was provided to the family.

Discussion

SAS is caused by pathogenic variants in the *SATB2* gene, which plays a critical role in craniofacial development, cortical neuron differentiation, and osteoblast function. Skeletal involvement is a recognized component of SAS, reflecting the role of *SATB2* in osteoblast differentiation and bone development. Although the overall frequency of musculoskeletal abnormalities is variable, osteopenia and osteoporosis appear to occur with relatively higher frequency, particularly in individuals with point mutations. Current recommendations emphasize the importance of monitoring bone health, especially during late childhood and adolescence. In our patient, formal assessment of bone mineral density was not performed; however, this aspect warrants clinical attention during follow-up [5-7].

The patient's absence of verbal language and reliance on PECS is consistent with the core feature of severely impaired speech in SAS. SATB2 is a transcription factor critical for cortical development, particularly in brain regions involved in speech and language, including the cortical plate and callosal projection neurons. Mutations in *SATB2* disrupt neuronal development and connectivity, especially in areas related to expressive language [8, 9]. As a result, individuals with SAS often rely on alternative communication methods, such as sign language or augmentative and alternative communication (AAC) devices [10]. Although difficulties with chewing, pharyngeal phase dysphagia, and sialorrhea are commonly reported in this population, our patient did not present with any of these manifestations [11].

Behavioral findings in this case, including restricted interests, stereotypies, poor eye contact, and aggressive outbursts, fulfilled the diagnostic criteria for ASD, which is frequently reported in individuals with SAS [12, 13]. The overlap between SAS and ASD underscores the importance of considering genetic testing in children with atypical ASD presentations, particularly when accompanied by additional syndromic features.

Sensorineural hearing loss, as observed in this patient, is a rare finding in SAS. Review of whole-exome sequencing data did not identify pathogenic variants in genes commonly associated with hereditary hearing loss, and neuroimaging demonstrated normal cochleovestibular anatomy, reducing the likelihood of an alternative etiology. A preliminary analysis by the *SATB2* Gene Foundation reported that approximately 94% of individuals with SAS have normal hearing, highlighting the rarity of this manifestation [14].

While neuroimaging findings in SAS are often nonspecific, including delayed myelination or white matter abnormalities, these features were not present in our patient [15]. Instead, brain MRI revealed multiple enlarged perivascular spaces, particularly in the peritrigonal regions. Enlarged perivascular spaces have previously been reported in individuals with SAS, mainly in cases involving large deletions; however, their occurrence in association with a *SATB2* point mutation is noteworthy and may further expand the neuroimaging spectrum of the disorder [2]. Whether this finding represents an incidental observation or a rare imaging feature of SAS remains to be clarified. The use of MRI is particularly valuable, especially in the absence of cleft palate, as it allows detailed assessment of subtle anatomic variations that may underlie velopharyngeal dysfunction [16].

The patient's diagnostic journey highlights the challenges of identifying SAS using conventional genetic testing methods. The diagnosis was ultimately established through whole-exome sequencing, which identified a heterozygous nonsense variant in *SATB2* (c.1285C>T; p.Arg429*). This variant results in a premature stop codon at position 429 of the amino acid sequence, which is predicted to lead to loss of normal protein function through nonsense-mediated mRNA decay (NMD) or production of a truncated, likely nonfunctional protein, and has been previously reported as pathogenic according to the American College of Medical Genetics and Genomics [17-19].

Conclusion

This report highlights the need to include SAS in the differential diagnosis of syndromic neurodevelopmental disorders, especially when accompanied by craniofacial dysmorphism, language impairment, and behavioral features suggestive of autism. The identification of rarely reported features,

such as hearing loss and enlarged perivascular spaces, contributes to a broader understanding of the clinical spectrum associated with *SATB2* mutations. Raising awareness of SAS can lead to better recognition, support, and family counseling.

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Informed consent

Written informed consent was obtained from the patient's parents for the publication of this case report and any accompanying images. They were informed that personal identifiers would not be disclosed and confidentiality would be maintained.

Declaration of interest

The Authors declare that there is no conflict of interest. No financial or material support was received for the preparation of this manuscript.

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