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Early intervention and sibling imitation in autism spectrum disorder: A twin case report with exploratory SNP analysis

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Abstract

We present a fraternal twin case study that underscores the importance of early diagnosis and targeted intervention in autism spectrum disorder (ASD), demonstrating the potential for substantial symptom reduction or even loss of diagnosis. Despite shared genetics and environment, the twins showed markedly different outcomes: Patient 1 exhibited substantial improvement, and no longer met ASD criteria, while Patient 2 progressed more slowly. Notably, Patient 1 displayed negative imitation, mirroring behaviors of his more severely affected twin. Genetic analysis of Patient 2 revealed ASD-associated variants (*CNTNAP2* rs7794745 A/T, *NRP2* rs849563 T/G, and *OXTR* rs2254298 G/G), which are implicated in neuronal development, synaptic pruning, and social cognition. These findings highlight the influence of sibling dynamics in multi-affected families and underscore the need for larger cohort studies to clarify the role of these polymorphisms in ASD within the Azerbaijani population.

Keywords: Autism, imitation, early intervention, SNPs

INTRODUCTION

Autism spectrum disorder (ASD) is a complex neurodevelopmental condition characterized by social, communication, and behavioral challenges.[1] Early detection is crucial, as timely, intensive therapy can greatly improve outcomes.

ASD has a complex etiology, with heritability estimated at 70–90% in monozygotic and up to 20% in dizygotic twins.[2] Fraternal twins are more likely to both be diagnosed with autism than non-twin siblings, likely due to shared prenatal factors.[3] However, symptoms often differ between them, highlighting the need for individualized care. Twin studies thus provide a valuable model for examining genetic and environmental interactions in early ASD diagnosis and intervention.

Nearly all chromosomes have been linked to ASD at some point.[4] As of March 2025, the SFARI database lists over 1,200 autism-associated genes, including *NRP2*, *OXTR*, and *CNTNAP2*, all linked to various molecular pathways relevant to the disorder.

The following case studies explore early intervention outcomes in dizygotic twins with ASD, focusing on sibling interactions and examining SNP variations in *NRP2*, *OXTR*, and *CNTNAP2* genes.

CASE REPORT

The dizygotic twin boys, born in 2020 to consanguineous parents (mother 43 year, father 56 year), were conceived via artificial insemination and delivered prematurely at 36 weeks by C-section. Their maternal history included hereditary speech delays, and two older siblings had severe genetic conditions, both died in early childhood.

Both twins exhibited delayed mental and physical development from the early stages of

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development, confirmed by a physician. The children were not breastfed and have not received any vaccinations to date. They had lacked social interaction, displayed sensory issues, had no speech, exhibited tics, and struggled with following commands, like "come here", "sit down" (Table 1). Patient 1 occasionally engaged in limited peer play, while Patient 2 avoided peer interactions entirely. Patient 1 was observed to have a relatively large head; however, no significant abnormalities were detected through neurological assessment. Patient 2 had gastrointestinal issues until 18 months and reduced eye contact. Sonographic evaluations at 1–2 months revealed no pathological findings.

At age three, the children were referred to the Narinj Psychology Centre for evaluation. A multidisciplinary team diagnosed both with ASD

Table 1: Main behavioral characteristics and clinical features of fraternal twin cases with autism spectrum disorder

	Patient 1	**Patient 2**
Sex	Male	Male
Term/preterm	Preterm	Preterm
Parent consanguinity	Yes	Yes
Language skill	No	No
Personal/social skills	Equivalent to 1 years	Equivalent to 18 months
Fine motor skills	Equivalent to 1 years	Equivalent to 18 months
Large motor skills	Equivalent to 18 months	Equivalent to 23-24 months
Sitting	Achieved at 8-9 months	Achieved at 6-7 months
Start walking	Achieved at 17-18 months	Achieved at 14 months
GARS score	93	115
Hearing problem	Yes	No
Sleep problem	No	No
Eating problems	No	Yes
Vestibular sensitivity	Yes	Yes
Sensory processing disorder	Yes	Yes
Stereotyped utterance	Yes	Yes
Eye contact	Normal	Occasional
Response to name	Occasionally	No
Play with peers	Yes	No
Swing	No	No
Obsessed with spinning things	Yes	No
Overreacting to changes	Yes	No
Indifference to pain	No	No
Smells everything	No	No
Repetitive behaviors	Yes	Yes
Echolalia	No	No
Unusual sounds	No	Yes
Cognitive	Limited	Limited
Tiptoe walking	No	Yes
Self-care skills	Fully dependent	Fully dependent
Hypersensitivity	Yes	Yes
Hyperactivity	Mild	Mild
Aggression towards others	No	Yes
Epileptic focus	Yes	Yes
Intellectual disability	No	No

GARS score, Gilliam Autism Rating Scale score

based on DSM-5 criteria. They exhibited minimal tongue and lip movement, weak chewing, and an inability to blow. Patient 2 presented with more severe symptoms, with a Gilliam Autism Rating Scale (GARS) score of 115, while Patient 1 had score of 93. Both showed moderate hyperactivity, object gnawing, tiptoe walking, aggression, self-injury, and frequent laughing.

Therapy began in November 2023 at three years and one month, consisting of parental training, educational techniques, and medication. Both children received three weekly sessions each of behavioral, sensory integration therapy, along with regular speech and language therapy. The applied behavioral strategies incorporated prompting, modeling, and skill generalization. Treatment included Cortexin (10 injections) and Pantogam (30 mg/kg/day for four months).

Following therapy, both children exhibited a notable reduction in ASD symptoms. Patient 1 showed significant improvement, with reduced stereotypical behaviors, enhanced emotional and social interactions, improved cognition, and emerging speech. Although his vocabulary is still limited, it continues to expand noticeably each day. His food selectivity resolved, and he became more engaged with peers. Therapists observed that some of his behaviors closely resembled those of his twin, suggesting imitation rather than solely intrinsic autistic traits. After 32 behavioral and 50 sensory therapy sessions, Patient 1 no longer met the criteria for autistic disorder, with his GARS score dropping from 93 to 65, and kindergarten enrollment was recommended.

Patient 2 demonstrated reduced object gnawing and self-injury but minimal progress in speech and social interactions, with his GARS score improving to 85.

Genetic screening for three SFARI-listed genes was performed using buccal swabs and PCR-RFLP method. The rs779475 polymorphism of the *CNTNAP2* gene, the rs849563 polymorphism of the *NRP2* gene, and the rs2254298 polymorphism of the *OXTR* gene were analyzed in both cases. Patient 1 had A/A for *CNTNAP2*, T/T for *NRP2*, and G/G for *OXTR*. Patient 2 had A/T for *CNTNAP2*, T/G for *NRP2*, and G/G for *OXTR*.

DISCUSSION

This fraternal twin case study emphasizes the critical role of early diagnosis and comprehensive intervention in ASD, highlighting the individuality of each case despite shared genetic and environmental factors, such as gestation, birth experience, and family environment. One twin (Patient 1) showed significant improvement, achieving age-appropriate emotional development and social interactions, and no longer met ASD criteria. In contrast, the other twin (Patient 2) exhibited slower progress, though still showed a reduction in symptoms, as reflected in improved GARS scores. These outcomes reinforce the growing evidence that early, targeted interventions can significantly reduce or even reverse ASD symptoms, as demonstrated in previous studies.[5]

As part of the standard therapeutic regimen at the Autism Center where the twins were treated, they received Cortexin and Pantogam, medications commonly prescribed in Commonwealth of Independent States (CIS) countries, including Azerbaijan. Following this regimen, reductions in spontaneous vocalizations and stereotypical behaviors were observed, particularly in Patient 1. Previous studies have reported beneficial effects of Cortexin and Pantogam on cognitive impairment, especially in children with ADHD, speech delays, and perinatal central nervous system lesions, with significant improvements in cognitive function tests among children aged 3–4 years.[6,7] Notably, positive effects in autistic children have also been documented in clinical reports from Ukraine, where these medications were used to support cognitive function, attention, and speech development in ASD patients.

A key finding is the observation of negative imitation, where Patient 1's behaviors seemed influenced by the more severely affected twin (Patient 2). Therapists noted that certain behaviors in Patient 1 mirrored those of Patient 2, suggesting they were acquired through passive observation or environmental exposure rather than inherent autistic traits. While imitation of older autistic siblings by typically developing younger children is well-documented,[8] cases of an autistic twin adopting behaviors from a more severely affected sibling remain rare. This highlights the need to account for sibling dynamics in ASD assessment and intervention, particularly in families with multiple affected children, as these influences may shape symptom expression and complicate diagnosis.

Genetic analysis of both cases revealed variants linked to ASD risk according to previous researches. Specifically, Case 2's genotypic profile - A/T for *CNTNAP2* rs7794745, T/G for *NRP2* rs849563, and G/G for *OXTR* rs2254298 - aligns with studies suggesting these genotypes contribute to ASD susceptibility. All three SNPs

are well-documented common variants. As parental DNA samples were not available, the inheritance status of these variants in the twins could not be directly determined. However, in our parallel analysis of 18 unrelated ASD cases with parental samples, all three variants were found to be transmitted from parents (unpublished observations for *CNTNAP2* rs7794745 and *OXTR* rs2254298).[9] These results suggest that the variants observed in the twins are generally inherited rather than occurring as *de novo* mutations.

CNTNAP2, key in neuronal development, has 18 autism-linked mutations in ClinVar, with the rs7794745 A/T genotype identified as an ASD risk factor in the Chinese Han population.[10] *NRP2* is involved in neuronal function and synaptic pruning. The TG genotype observed in Case 2 has been linked to a higher autism risk compared to TT in Chinese and Iranian populations.[11,12] OXTR, vital for social cognition, has several SNPs linked to ASD in family and population-based studies. The rs2254298 SNP shows population-specific associations: the A allele is linked to autism in Chinese and Japanese cohorts, while the G allele, found in both twin cases, is associated with ASD in Caucasians.[13] These findings suggest that, further research with larger cohorts is needed to clarify the role of these polymorphisms in ASD in Azerbaijan. Additionally, advanced parental age and consanguinity in the twins' family may have contributed to ASD, as both are recognized risk factors in prior studies.[14,15]

This case adds to the emerging body of data on early diagnosis and timely intervention, highlighting the importance of personalized treatment, considering environmental factors like sibling imitation, and the need for a multidisciplinary approach, including speech therapy, behavioral analysis, and pharmacotherapy, to optimize outcomes.

A key limitation of this case report is the restricted scope of the genetic testing, which covered only a limited set of SNPs, while hundreds of autism-associated SNPs and copy number variants have been reported. Thus comprehensive approaches such as whole-exome or whole-genome sequencing, combined with larger cohort studies, will be necessary to provide a more complete understanding of the genetic architecture of ASD in the Azerbaijani population. Additionally, *in silico* prediction of variant function could provide further insights into the biological impact of the identified SNPs and should be incorporated in future studies.

DISCLOSURE

Ethics: Informed consent was obtained from the patient.

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Conflict of interest: None

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