ATR-X Syndrome mimicking Down syndrome: A diagnostic challenge with psychiatric implications

"X-linked alpha thalassemia mental retardation (ATR-X) syndrome" is a genetic disorder with an estimated global prevalence of 1–9 per 1,000,000 individuals. It is inherited in an X-linked recessive manner (Xq21.1) affecting males. Profound developmental delay, facial dysmorphias, genital abnormalities, severe intellectual disability, limited language abilities, seizures, skeletal abnormalities, muscle tone disturbances, and gastrointestinal issues characterize ATR-X syndrome.[1,2]

Down syndrome, caused by trisomy 21, is a relatively common genetic disorder with a global prevalence of 5–6 per 10,000 individuals. It manifests with intellectual disability, developmental delay, language impairment, epilepsy, early-onset dementia, congenital heart defects, atlantoaxial instability, simian crease, low-set ears, epicanthic folds, a flat nasal bridge, flat occiput, up slanting palpebral fissures, recurrent respiratory tract infections, and autoimmune disorders.[3,4]

Here, we present the case of a 1-year-old boy who was initially suspected of having Down syndrome due to his clinical features but was ultimately diagnosed with ATR-X syndrome. To the best of our knowledge, this is the first reported case of ATR-X syndrome mimicking a Down syndrome phenotype.

A 1-year-old male child was referred to the Psychiatry OPD due to the developmental delay. The child exhibited delayed milestones, absence of neck control, lack of bi-dexterous grasp and monosyllabic speech, two episodes of severe pneumonia, and characteristic dysmorphic features, including a depressed nasal bridge, low-set dysplastic ears, antimongoloid slant of the eyes, right-sided undescended testis, single transverse palmar creases bilaterally, hypotonia, clinodactyly, axial hypotonia, appendicular hypertonia, brisk deep tendon reflexes in all four limbs, and poor eye contact.

The child was born at term to non-consanguineous parents via spontaneous vaginal delivery, with a birth weight of 3 kg. The child cried immediately after birth and was exclusively breastfed at the time of evaluation. The prenatal anomaly scan revealed features suggestive of Down syndrome. He exhibited significant developmental delays, including absent neck holding, standing, and walking, delayed social smile (at five months), babbling at 10 months of age, and a lack of disyllabic speech. Pincer grasp and recognition of the mother were present. He had been hospitalized twice at 6 and 9 months due to severe pneumonia. No significant family history of psychiatric disorder or family history present.

An MRI of the brain revealed mild diffuse atrophy, periventricular white matter changes. The initial suspicion was global developmental delay (motor and cognitive) with quadriplegia, possibly due to trisomy 21. Genetic investigations, including a muscular dystrophy and congenital myopathy gene panel, "Spinal Muscular Atrophy (SMN1/SMN2) deletion/duplication analysis," and copy number sequencing for aneuploidy detection, were negative. Subsequent Exome Plus sequencing identified a hemizygous pathogenic variant in exon 9 of the ATRX gene, confirming ATR-X syndrome. Physiotherapy and speech therapy were planned, and parental counseling was conducted regarding prognosis and management.

This case underscores the importance of comprehensive genetic testing in suspected cases of Down syndrome with atypical features. Standard karyotyping and advanced genetic analysis, such as whole-exome sequencing, play a crucial role in differentiating ATR-X syndrome from other neurodevelopmental disorders.[5]

As they grow, children with ATR-X syndrome may experience significant intellectual developmental delays, exhibit autistic behaviors, and develop more severe seizures compared to those with Down syndrome.[1,3]

Accurate diagnosis is crucial for individualized management. Children with ATR-X syndrome require early intervention, specialized speech and occupational therapy, and behavioral management for hyperactivity, aggression, obsessive-compulsive symptoms, mood instability, and self-injurious behavior, as ATR-X syndrome shows more severe psychiatric symptoms. In contrast, individuals with Down syndrome are generally more sociable. Misdiagnosis can lead to unnecessary investigations while overlooking key ATR-X-specific complications, including severe hypotonia, feeding difficulties, and urogenital anomalies.[1] Also, this will help in proper genetic counseling, parental expectations, and family therapy, as the misdiagnosis of Down syndrome might have shaped parental expectations. However, upon receiving the correct diagnosis of ATR-X syndrome, parents may face significant emotional and psychological challenges. Unlike Down syndrome, which

has well-established support systems, ATR-X syndrome is much rarer, leaving families with fewer resources and greater uncertainty.

This case highlights the critical role of genetic testing in differentiating ATR-X syndrome from Down syndrome, particularly in patients presenting with overlapping phenotypic features. Prenatal genetic screening and karyotyping should be emphasized to facilitate early diagnosis and appropriate parental counseling. This case further broadens the phenotypic spectrum of ATR-X syndrome, demonstrating its potential to mimic Down syndrome features. Future research is required in this domain.

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Conflicts of interest
There are no conflicts of interest.

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