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CASE REPORT

A CHILD WITH X LINKED INHERITED INTELLECTUAL DISABILITY

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ABSTRACT

X-linked intellectual disability, also known as X-linked mental retardation, is a neurodevelopmental disorder caused by a gene defect on the X chromosome. While more than 100 genes have been linked to X linked intellectual disability, the genetic aetiology of intellectual disability remains unknown in approximately half of the cases. Intellectual disability often co-occurs with other conditions like epilepsy and autism spectrum disorder.

X-linked 98-related intellectual disability syndrome is a rare neurodevelopmental disorder due to Neurite extension and migration factor gene mutation characterised by global developmental delay, intellectual disability, and language delay, with or without autistic features. Distinctive characteristics include coarse facial features, a protruding tongue, and behavioural abnormalities such as excessive tantrums and intrusiveness.

The case study presented involves a child with a stop-gain variant in the Neurite extension and migration factor gene presenting with autism spectrum disorder, specific learning disability and behavioural abnormalities with interesting phenotypic features.

INTRODUCTION

X-linked intellectual disability (XLID) refers to a generalised neurodevelopmental disorder caused by a gene defect on the X chromosome. More than 100 genes have been proposed to be associated with XLID.[1] Intellectual disability disorder (IDD) co-occurs with several other conditions, such as sensory impairments, epilepsy, and autism spectrum disorder.[2] Factors contributing to ID include genetic mutations, metabolic disorders, chromosomal anomalies, prenatal exposure to toxins or nutritional deficiencies, and disruptions in early brain development.[1] The NEXMIF gene is crucial for neuronal morphogenesis, migration, and synapse formation.[5] Mutations in this gene broaden the phenotype to include a syndromal form of disease with symptoms beyond intellectual disability, such as language and motor delay, social deficits, motor stereotypies, and hypotonia.[6,7] Intellectual disability(ID) is more common in men; the genetic explanation of this sex asymmetry is incompletely understood.[3]

This study aimed to report unappreciated clinical features of the NEXMIF gene mutation, a rare neurodevelopmental disorder characterised by global developmental delay and intellectual disability with autistic features.

CASE REPORT

A 9-year-old child first born to a consanguineously married couple with insignificant perinatal events was thriving well till nine months of age. He was noted to have a lack of neck holding by nine months of age, with subsequent delay pointed out in all domains. Around two years of age, he developed seizures, a generalised tonic-clonic type. This led to hospitalisation, where a thorough clinical examination exposed hypotonia, ataxia, unstable gait, intellectual disability, language-predominant global developmental delay, behavioural abnormalities such as tantrums and violent behaviour, with dysmorphic features of coarse facial features, hooded eyelids and protruding tongue. (Fig 1 and 2). He was diagnosed as an autism spectrum disorder with a specific learning disability. His workup for seizures, including electroencephalogram and magnetic resonance imaging (MRI) of the brain, was unremarkable. He had repeat seizures at five years of age, for which he was started on sodium valproate, and risperidone was used to treat his autistic disorder-related disruptive behaviour. Considering his clinical features of intellectual disability and behavioural abnormalities with dysmorphism, a microdeletion syndrome was suspected, and a whole exome was done. A denovo stopgain variant; c. 1441C>T in exon 3 of the NEXMIF gene observed in a hemizygous state

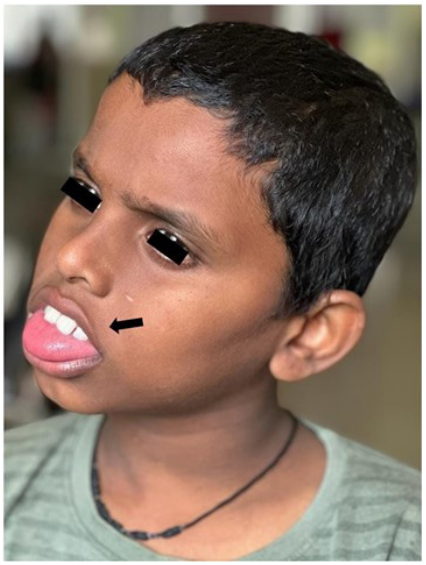

Figure 1:Photograph of the index child showing open hypotonic mouth with a protruding tongue (Black arrow)

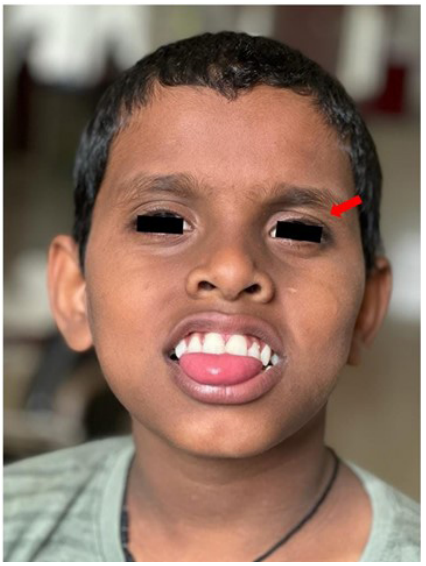

Figure 2:Photograph of the index child showing hooded eyelids (Red arrow)

with X-linked dominant inheritance. Thus, diagnosed with X-linked 98, Intellectual developmental disorder. His Behavioural abnormalities were managed through a combination of behavioural therapies and pharmacological interventions, a physiotherapy regimen to improve muscle tone and coordination. He is currently free of seizures and can walk independently but requires assistance with daily tasks.

DISCUSSION

NEXMIF is one of the genes implicated in XLID. The NEXMIF gene, which stands for Neurite Extension and Migration Factor, has been the focus of research due to its association with various neurological and developmental disorders. The NEXMIF gene, located on the X chromosome, encodes the neurite growth-directed factor, which plays a crucial role in neuronal morphogenesis, migration, and synapse formation.[5] Pathogenic variants in the NEXMIF gene have been linked to intellectual disability, autism spectrum disorder, and epilepsy.[6] Recent studies have highlighted the clinical spectrum of NEXMIF pathogenic variants, with reports of patients from Indian kindreds exhibiting language-predominant developmental delay and later onset of epilepsy.[7] Hooded eyelids, abnormal ear placement, and open hypotonic mouth are a few described phenotypic features that can be noted in our case.[6]

As demonstrated by the clinical case provided, recent evidence has expanded our understanding of the NEXMIF mutations. This broader phenotype now includes a syndromic manifestation of the disease, which involves a range of symptoms beyond intellectual disability. For instance, in the case presented, the child experienced delays in both language and motor development. In addition, social deficits, motor stereotypies and hypotonia were present. Distinctive physical characteristics of protrusion of the tongue with hooded eyelids and behavioural problems such as excessive tantrums, inappropriate screaming and intrusiveness, as noted in our case, have been reported.[3] Due to financial constraints, there was a delay in performing the mutation analysis in our case.

In conclusion, the NEXMIF gene is a key player in neurodevelopment, and its mutations have been linked to various neurological and developmental disorders. Further research in this field is necessary to elucidate the full impact of NEXMIF gene mutations and to develop targeted interventions for individuals affected by these mutations.

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