Section: Psychiatry

Case Series

# UNRAVELING DIVERSE SYNDROMES ASSOCIATED WITH INTELLECTUAL DISABILITY: A CASE SERIES

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***Received*** *: 10/06/2026*
***Received in revised form*** *: 23/07/2026*
***Accepted*** *: 08/08/2026*

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**DOI:** 10.70034/ijmedph.2026.3.391

**Source of Support:** Nil,
**Conflict of Interest:** None declared

**Int J Med Pub Health**
2026; 16 (3); 2453-2457

**ABSTRACT**

**Background:** Rare genetic syndromes are a significant cause of intellectual disability (ID), characterised by overlapping neurological, behavioural, and developmental features that complicate diagnosis. This series presents the clinical and genetic spectrum of syndromic ID in a tertiary psychiatric setting.

**Case Series:** Eight children with syndromic ID underwent comprehensive clinical, developmental, neuroimaging, and genetic assessments. Diagnoses included Aicardi-Goutières syndrome, Alexander disease, Dandy-Walker syndrome, Hurler syndrome, neuronal ceroid lipofuscinosis type 2, Nicolaides-Baraitzer syndrome with Blepharophimosis-Impaired Intellectual Development Syndrome, Zimmermann-Laband syndrome type 2, Smith-Magenis syndrome, and Tuberous Sclerosis Complex type 2. All subjects exhibited developmental delay and intellectual disability; other features, such as epilepsy, behavioural issues, dysmorphisms, motor impairment, and brain abnormalities, varied among them. Genetic testing identified pathogenic variants, facilitating precise diagnosis and management.

**Discussion:** The heterogeneity of intellectual disability has a genetic basis, particularly in severe cases. Advancements in chromosomal microarray analysis and next-generation sequencing have enhanced diagnostic accuracy, early intervention, and genetic counselling. Despite differing molecular aetiologies, common features include developmental delay, epilepsy, cognitive impairment, motor disturbances, and behavioural problems. Integrating clinical evaluation, neuroimaging, and genetic testing is essential for accurate diagnosis. Early genetic confirmation supports prognosis, monitoring, management, and reproductive decision-making. The limited availability of Indian data underscores the importance of this series in highlighting the need for increased awareness and access to genetic diagnostic services.

**Conclusion:** This series underscores the clinical and genetic heterogeneity of syndromic ID, emphasising the importance of comprehensive evaluation, imaging, and molecular testing to facilitate early diagnosis, optimal management, and improved outcomes.

**Keywords:** Genetic Syndromes, Intellectual Disability, Case Series.

## INTRODUCTION

Intellectual disability (ID) is a neurodevelopmental disorder characterised by significant limitations in intellectual functioning and adaptive behaviour, with onset during developmental stages. Affecting between 1% and 3% of the population, it results in lifelong disability with medical, psychological, social, and economic implications for individuals, families, and healthcare systems. A substantial proportion of childhood intellectual disabilities are attributable to genetic disorders, and advancements in chromosomal and sequencing technologies have enhanced the diagnosis of rare syndromic etiologies. Early detection is essential for appropriate treatment, assessment of prognosis, genetic counselling, and rehabilitation.[1-4]

Several rare genetic syndromes—including Aicardi-Goutières syndrome, Alexander disease, Dandy-Walker syndrome, Hurler syndrome, neuronal ceroid lipofuscinosis, Nicolaides-Baraitser syndrome, Smith-Magenis syndrome, and Tuberous

Sclerosis Complex—often present with intellectual disability of varying severity, together with neurological, behavioural, psychiatric, and multisystem manifestations. Although each syndrome has distinct molecular and clinical features, considerable overlap in developmental delay, epilepsy, behavioural disturbances, and cognitive impairment often poses diagnostic challenges, particularly in resource-limited settings. Comprehensive clinical evaluation, supplemented by neuroimaging and molecular genetic testing, is therefore crucial for establishing an accurate diagnosis and guiding syndrome-specific management.[2,5-8]

This case series describes eight children with diverse genetic syndromes associated with intellectual disability who presented to a tertiary care psychiatry outpatient department. By highlighting their clinical features, neurodevelopmental profiles, neuroimaging findings, and genetic diagnoses, this series aims to raise awareness of these uncommon syndromes among psychiatrists and paediatricians, emphasise the value of genomic investigations in children with unexplained intellectual disability, and contribute to the limited literature from India on the psychiatric and developmental manifestations of rare genetic disorders.

**1. AICARDI-GOUTIERES SYNDROME 2 (ENCEPHALOPATHY WITH BASAL GANGLIA CALCIFICATION):** A 4-year-old boy was brought to the psychiatric outpatient department at Government General Hospital, Vijayawada, by his parents. His main issues included delayed motor and speech development, difficulty recognising people, and breathing difficulties with bluish skin discolouration. He had a history of maternal hypothyroidism. Born at term via LSCS after a third-degree consanguineous marriage, he cried immediately after birth and weighed 3.2 kg. Developmental delays were observed across all milestones. Physical examination revealed a weight of 13.15 kg, height of 84 cm, head circumference of 48.2 cm, and a single café-au-lait spot. Notable findings included dystonic postures of the upper limbs, hypertonia (predominantly on the right), ankle clonus, neck flexor weakness, axial muscle weakness, and severe intellectual disability. Genetic analysis identified a homozygous missense mutation in exon 7 of the RNASEH2B gene, and neuroimaging indicated demyelination. Management included cognitive enhancers such as Piracetam, nutritional supplements such as iron, lysine, folic acid, vitamin B12, and Methylcobalamin, and physiotherapy.

**2. ALEXANDER DISEASE:** A 7-year-old boy was brought by his parents to the psychiatry outpatient department at Government General Hospital, Vijayawada, with concerns about developmental delay, including difficulties with walking and speaking. He is the second child of non-consanguineous parents, with an uneventful perinatal history. There is no family history of similar conditions. On general examination, his weight is 16 kg, height is 95 cm, and head circumference is 56 cm. The child exhibits dolichocephaly with frontal bossing. Intelligence testing revealed severe intellectual disability. Brain MRI shows diffuse, bilateral, symmetrical white matter abnormalities, primarily in the frontal lobes. Additionally, there are signal abnormalities and patchy diffusion restriction in both basal ganglia, indicating leukodystrophy, likely Alexander disease. Genetic testing identified a heterozygous missense mutation in exon 4 of the GFAP gene on chromosome.[17]

**3. DANDY-WALKER SYNDROME:** A 5-year-old male child was brought by his parents to the psychiatric outpatient department at Government General Hospital, Vijayawada, presenting with developmental delay, increased head circumference, and bluish skin discolouration during crying. Maternal antenatal history was unremarkable. The child was delivered at full term via caesarean section to consanguineous parents, cried immediately postnatally, and weighed 2.5 kg. He experienced cyanotic spells with limb spasms during crying and had recurrent respiratory infections. Clinical examination revealed short stature, macrocephaly, a depressed nasal bridge, low-set ears, prominent frontal bossing, a wide anterior fontanelle, ambiguous genitalia, and cyanosis involving both central and peripheral regions. He exhibited gait abnormalities and hypertonia in all four limbs, with muscle strength graded 5/5. Reflexes (biceps, triceps, brachialis, knee, ankle) were graded 2+ bilaterally. Plantar reflexes were flexor bilaterally, and the right corneal reflex was absent. Sensory function was intact. Intelligence testing revealed severe intellectual disability. Two-dimensional echocardiography revealed congenital cardiac anomalies, including hypoplastic right heart syndrome, pulmonary atresia, a large ostium secundum atrial septal defect with right-to-left shunt, moderate tricuspid regurgitation, and a patent ductus arteriosus supplying the confluent branch pulmonary arteries. Magnetic resonance imaging of the brain demonstrated Dandy-Walker malformation with communicating hydrocephalus. The patient was managed with catheter-based procedures for congenital heart defects, including PDA closure, and a shunt operation for hydrocephalus.

**4. HURLER SYNDROME (MUCOPOLYSACCHARIDOSIS TYPE 1):** A 7-year-old girl was brought to the Psychiatry outpatient department at Government General Hospital in Vijayawada with difficulty walking and speaking. She is the eldest of two children, born to parents in a third-degree consanguineous marriage. Her mother's perinatal history was uneventful. Her younger sister has arthrogryposis multiplex congenita. General examination showed that she weighs 13.15 kg, measures 84 cm in height, and has a head circumference of 49.5 cm. She presents with

short stature, coarse facial features, corneal clouding, a depressed nasal bridge, low-set ears, a short neck, stubby fingers, a distended abdomen, joint stiffness, and contractures in both legs. Abdominal examination revealed hepatomegaly. She was diagnosed with moderate intellectual disability. Investigations revealed a homozygous missense mutation in exon 7 of the IUDA gene. Her vitamin D3 levels were low, and she had elevated TSH with low T3. Echocardiography showed mitral valve prolapse with mild regurgitation. Treatment included enzyme replacement therapy with L-iduronase 0.58 mg/kg weekly and oral T4 (thyroxine) 25 mcg daily.

**5. NEURONAL CEROID LIPOFUSCINOSIS -2 (CLN2) WITH SPINOCEREBELLAR ATAXIA -7:** A 15-year-old girl presented to the outpatient Psychiatry Department at Government General Hospital, Vijayawada, with concerns about delayed developmental milestones, progressive cognitive deterioration, recurrent seizures, and difficulties with speech and ambulation. She was born to parents in a third-degree consanguineous marriage and has a family history of similar conditions affecting a younger sister and a paternal cousin. No other significant familial history was documented. Physical examination revealed a weight of 44 kg, a height of 130 cm, and a BMI of 26.09 kg/m². Neurological evaluation identified gait imbalance, lateral gaze nystagmus, dysarthria, increased muscle tone, and hyperreflexia. Brain MRI revealed mild atrophy of the cerebrum and cerebellum. Electroencephalogram (EEG) demonstrated occasional generalised spike-and-wave and slow-wave discharges, predominantly on the right side. IQ assessment indicated profound intellectual disability. Genetic testing uncovered a homozygous missense mutation in exon 8 of the TPP1 gene (Chr 11: g: 6637576 C>G; with 86X coverage), specifically a C.1045G>C transition resulting in a P.Ala349Pro substitution, inherited in an autosomal recessive pattern. Management started her on low-dose carbamazepine and levetiracetam, along with muscle-strengthening exercises. At the two-week follow-up, mild improvement was noted, and dosages were adjusted. The patient continues with routine follow-up and remains stable.

**6. NICOLAIDES-BARAITSER SYNDROME (NCBRS), BLEPHAROPHIMOSIS-IMPAIRED INTELLECTUAL DEVELOPMENT SYNDROME (BIS), AND ZIMMERMANN-LABAND SYNDROME 2 (ZLS2):** A 6-year-old girl presented to the outpatient Psychiatry Department at Government General Hospital, Vijayawada, with seizures beginning at 6 months, accompanied by global developmental delay and distinctive facial features—including hooded eyelids, a bulbous nose, boggy cheeks, a grimacing smile, a low anterior hairline, large ears, and tapering fingers—alongside hypertrichosis, joint laxity, microcephaly, speech impairment, and mild generalised hypotonia. Whole-exome sequencing (WES) identified three variants of uncertain significance: two heterozygous frameshift deletions in the SMARCA2 gene at Chr9:2039789 and Chr9:2039786, both in Exon 4, associated with Nicolaides-Baraitser syndrome (NCBRS) and Blepharophimosis-Impaired Intellectual Development Syndrome (BIS); and a heterozygous missense mutation in ATP6V1B2 at Chr8:20072375, linked to Zimmermann-Laband syndrome type 2 (ZLS2). Parental testing revealed unaffected parents at the SMARCA2 loci, indicating de novo mutations. WES detected the variants, which were confirmed by Sanger sequencing and evaluated for inheritance. Additional assessments included EEG, brain MRI, audiology, ophthalmology, skeletal survey, and developmental evaluations. As there is no cure for these chromatinopathies, care is supportive and multidisciplinary, involving psychiatry, neurology, genetics, and developmental therapies. Seizures often require multiple anti-seizure medications, which may yield only partial responses. Therapeutic interventions, including speech, occupational, and physical therapies, address developmental delays, while genetic counselling facilitates family planning and prognosis. Regular monitoring for associated skeletal, ocular, and behavioural issues is recommended.

**7. SMITH-MAGENIS SYNDROME:** A 9-year-old boy presented to the outpatient psychiatry department of Government General Hospital, Vijayawada, with delayed ambulation, unclear speech, microcephaly, and poor growth since birth. The parents reported frequent biting, self-injurious behaviour, hyperactivity, restlessness, and difficulty maintaining concentration. He was the firstborn of non-consanguineous parents with no family history of comparable conditions. The mother's perinatal history was unremarkable. He was born with a ventricular septal defect. On clinical examination, he was short in stature (115 cm) with a head circumference of 48 cm. He had a broad, square face, deep-set eyes, a flat nasal bridge, and a prominent mandible. Musculoskeletal findings included hypotonia, brachydactyly, and pes planus. An IQ assessment revealed mild intellectual disability. Brain MRI demonstrated bilateral periventricular T2- and FLAIR-hyperintense signals in the deep white matter, consistent with periventricular leukomalacia. An enlarged cerebrospinal fluid space posterior to the cerebellum on the left suggested a cisterna magna. Blood analyses for copy number variations, uniparental disomy, or loss of heterozygosity showed no significant regions of LOH. Chromosomal microarray analysis identified a male karyotype with a deletion at 17p11.2, consistent with Smith-Magenis syndrome.

**8. TUBEROUS SCLEROSIS COMPLEX– 2:** A 7-year-old girl, born to unrelated parents, exhibited delayed developmental milestones, including an inability to roll over, along with multiple ash-leaf

macules, flexor spasms lasting four to five days, and complex partial seizures lasting one to two days, beginning at six months of age. IQ assessment indicated severe intellectual disability. Electroencephalograms (EEGs) showed abnormal activity during wakefulness and sleep, suggestive of a generalised seizure disorder, with a subsequent EEG suggesting a potential parieto-occipital seizure onset. Magnetic resonance imaging (MRI) scans revealed small, nodular, isointense grey matter foci near the subependymal area of the lateral ventricles, consistent with subependymal grey matter heterotopia or hamartomas. The child is suspected of having tuberous sclerosis and has undergone genetic testing, which identified a heterozygous nonsense mutation in exon 34 of the TSC2 gene (chr16: g.2084597C>T; depth: 126x), resulting in a premature stop codon at amino acid position 1459 (p.Arg1459Ter; ENST0000219476.9).

## DISCUSSION

Intellectual disability (ID) is a complex neurodevelopmental disorder, with genetic factors accounting for nearly fifty per cent of severe cases. Developments in chromosomal microarray and sequencing technologies have enhanced diagnostic accuracy for children presenting with unexplained delay and intellectual disability, thereby facilitating early detection, management, and genetic counselling. Our case series highlights the extensive phenotypic spectrum of rare syndromes associated with intellectual disability, including leukodystrophies, lysosomal storage disorders, chromatin-remodelling syndromes, and neurocutaneous disorders, underscoring the importance of integrating clinical evaluation, neuroimaging, and molecular testing into routine diagnostic protocols.[3-5,8]

The syndromes described in this series exhibited considerable overlap regarding developmental delay, epilepsy, motor impairment, behavioural abnormalities, and cognitive dysfunction, despite their distinct underlying genetic defects. Aicardi-Goutières syndrome, Alexander disease, and neuronal ceroid lipofuscinosis primarily manifested with progressive neurological deterioration, whereas Hurler syndrome demonstrated multisystem involvement attributable to lysosomal enzyme deficiency. Smith–Magenis syndrome and Nicolaides–Baraitser syndrome were characterised by prominent behavioural disturbances and dysmorphic features, while tuberous sclerosis complex and Dandy–Walker syndrome presented with epilepsy and structural brain abnormalities. These observations are consistent with prior reports indicating that epilepsy, neurodevelopmental delay, and behavioural manifestations constitute common clinical features across numerous rare genetic syndromes associated with intellectual disability.[9-15]

The widespread adoption of genomic technologies has transitioned diagnostic procedures from a phenotype-based approach to one supported by genotypic information for precise diagnosis. Early molecular confirmation not only elucidates the aetiology but also informs surveillance strategies for potential complications, offers prognostic guidance, facilitates prenatal diagnostic procedures, and enables timely multidisciplinary interventions, including developmental therapies, behavioural management, rehabilitation, and disorder-specific treatments such as enzyme replacement therapy for mucopolysaccharidosis type I. Due to the rarity of these disorders and the limited data available from India, this case series contributes to the existing body of literature by emphasising the varied presentations of syndromic intellectual disability within psychiatric practice and underscores the significance of heightened awareness and improved access to genetic testing in tertiary healthcare settings.

## CONCLUSION

This case series highlights the remarkable clinical and genetic heterogeneity of rare syndromes associated with intellectual disability and underscores the importance of considering syndromic aetiologies in children presenting with developmental delay, epilepsy, dysmorphic features, and behavioural abnormalities. A multidisciplinary approach, integrating detailed clinical assessment, neuroimaging, and advanced molecular genetic testing, is essential for accurate diagnosis, enabling syndrome-specific management, genetic counselling, and informed family planning. Reporting such rare cases from India enriches the existing literature, enhances clinician awareness, and emphasises the need for wider access to genomic diagnostic services for the early identification and optimal management of children with syndromic intellectual disability.

**Financial support and sponsorship:** Nil
**Conflicts of interest:** Nil

## REFERENCES

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 5th ed., Text Revision (DSM-5-TR). Washington, DC: American Psychiatric Association; 2022.
2. World Health Organization. International Classification of Diseases 11th Revision (ICD-11): Disorders of Intellectual Development. Geneva: WHO; 2022.
3. Moeschler JB, Shevell M; Committee on Genetics. Comprehensive evaluation of the child with intellectual disability or global developmental delays. Pediatrics. 2014;134(3):e903-e918.
4. Srivastava S, Love-Nichols JA, Dies KA, et al. Meta-analysis and multidisciplinary consensus statement: Exome sequencing is a first-tier clinical diagnostic test for individuals with neurodevelopmental disorders. Genet Med. 2019;21(11):2413-2421.
5. Wright CF, McRae JF, Clayton S, et al. Making new genetic diagnoses with old data: Iterative reanalysis and

reporting from the Deciphering Developmental Disorders Study. Genet Med. 2018;20(10):1216-1223.
6. van Karnebeek CDM, Stockler S. Treatable inborn errors of metabolism causing intellectual disability: A systematic review. Mol Genet Metab. 2012;105(3):368-381.
7. Ellison JW, Rosenfeld JA, Shaffer LG. Genetic basis of intellectual disability. Annu Rev Med. 2013;64:441-450.
8. Vissers LELM, Gilissen C, Veltman JA. Genetic studies in intellectual disability and related disorders. Nat Rev Genet. 2016;17(1):9-18.
9. Crow YJ, Manel N. Aicardi-Goutières syndrome and the type I interferonopathies. Nat Rev Immunol. 2015;15(7):429-440.
10. Messing A, Brenner M. Alexander disease. Handb Clin Neurol. 2018;148:693-700.
11. Clarke LA. Mucopolysaccharidosis type I. GeneReviews®. University of Washington, Seattle; updated 2023.
12. Mole SE, Williams RE, Cotman SL. Neuronal ceroid lipofuscinoses. GeneReviews®. University of Washington, Seattle; updated 2024.
13. Elsea SH, Girirajan S. Smith–Magenis syndrome. Eur J Hum Genet. 2008;16(4):412-421.
14. Sousa SB, Abdul-Rahman OA, Bottani A, et al. Nicolaides-Baraitser syndrome: Delineation of the phenotype. Am J Med Genet A. 2009;149A(8):1628-1640.
15. Northrup H, Aronow ME, Bebin EM, et al. Updated International Tuberous Sclerosis Complex Diagnostic Criteria and Surveillance Recommendations. Pediatr Neurol. 2021;123:50-66.