Medico Research Chronicles
ISSN NO. 2394-3971
DOI No. 10.26838/MEDRECH.2025.12.1.774
Contents available at www.medrech.com

Coffin-Siris Syndrome Type 1 with ARID1B Mutation: A Case Report of an 8-Year-Old Female with Seizure.

Aparna Suresh M[1], Dr. Chatterjee Rajib [2], Dr. Jayashree Jadhav[3]
1. PG Resident, Department of Paediatrics, DBVP RMC, PIMS(DU), Loni
2. Professor, Department of Paediatrics, DBVP RMC, PIMS(DU), Loni
3. HOD, Department of Paediatrics, DBVP RMC, PIMS(DU), Loni

ARTICLE INFO

Article History
Received: January 2025
Accepted: February 2025
Key Words:
Coffin-Siris Syndrome, ARID1B mutation, developmental delay, seizure, BAF complex

ABSTRACT

Background: Coffin-Siris Syndrome (CSS) is a rare genetic disorder characterized by developmental delays, distinctive facial features, and digital abnormalities. Mutations in the ARID1B gene account for the majority of genetically confirmed cases.
Case Presentation: We report an 8-year-old female who presented with seizure-like activity and was previously diagnosed with global developmental delay. Clinical examination revealed distinctive facial features including bushy eyebrows, depressed nasal bridge, thick nasal alae, and everted thick lips. Anthropometric assessment showed significant growth deficiencies with weight and BMI below -3SD, and height at -2SD. Developmental evaluation demonstrated severe delays across all domains, with developmental quotients ranging from 15% for gross motor skills to 40% for social milestones. Genetic testing confirmed a heterozygous mutation in the ARID1B gene (OM*614556), establishing the diagnosis of Coffin-Siris syndrome type 1 (OMIM#135900). Neurological workup including MRI and EEG yielded normal results despite the seizure presentation.
Discussion: This case exemplifies both typical and atypical features of CSS, highlighting the clinical heterogeneity of the syndrome even within genetically confirmed cases. While the patient demonstrated the characteristic facial phenotype and severe developmental delays consistent with CSS, she notably lacked several common features including fifth digit hypoplasia and hypertrichosis. The seizure episode at age 8 aligns with the known neurological manifestations of CSS, affecting approximately 50% of patients.
Conclusion: This case reinforces the importance of genetic testing in the diagnosis of CSS, particularly when the clinical presentation is incomplete. It emphasizes the need for multidisciplinary management including developmental interventions, neurological monitoring, and

CASE REPORT

Corresponding author
Dr. Aparna Suresh M.

nutritional support. Long-term follow-up is essential to address emerging complications and optimize developmental outcomes.

2025, www.medrech.com

Background

Coffin-Siris Syndrome (CSS) is a rare genetic disorder characterized by developmental delay, distinctive facial features, and abnormalities of the fifth digits [1]. First described by Grange Coffin and Evelyn Siris in 1970, CSS has an estimated prevalence of less than 1 in 100,000 [2]. The syndrome is primarily caused by mutations in genes encoding components of the BAF (BRG1/BRM-associated factor) chromatin remodeling complex, with ARID1B gene mutations being the most common, accounting for approximately 60-70% of cases [3,4].

The clinical presentation of CSS includes coarse facial features (95%), bushy eyebrows (90%), thick everted lips (80%), and a broad philtrum (70%) [5]. Additionally, patients typically exhibit hypoplasia of the fifth digit or nails (80%), which is considered a hallmark feature of the syndrome [6]. While prenatal findings are generally unremarkable with growth within normal limits, several characteristic features develop progressively during infancy and early childhood [7].

Many individuals with CSS may not be distinguishable at birth, as the facial features typically coarsen over time, with characteristic appearances becoming apparent later in childhood [8]. Early developmental milestones are significantly delayed, with children with CSS learning to sit at approximately 12 months, walk at 30 months, and speak their first words at 24 months on average [9]. Notably, expressive language is more affected than receptive language, with a significant subset of individuals having no speech development [10].

Neurological manifestations are common, including hypotonia (75%), seizures (50%), and various CNS malformations such as Dandy-Walker variant, gyral simplification, and agenesis of corpus callosum [11]. Other significant findings include feeding problems (90%), slow growth, hearing impairment (45%), and visual impairment (40%) [12].

The diagnosis of CSS is based on clinical features and confirmed by molecular genetic testing. Mutations in several genes have been associated with CSS, including ARID1A, ARID1B, SMARCA4, SMARCB1, SMARCE1, and SOX11 [13]. The ARID1B gene (OMIM #614556) is most frequently implicated, with heterozygous mutations resulting in CSS type 1 (OMIM #135900) [14].

Management of CSS requires a multidisciplinary approach involving developmental pediatricians, neurologists, geneticists, gastroenterologists, ophthalmologists, and audiologists. Therapeutic interventions typically include occupational, physical, and speech therapy to optimize developmental outcomes [15]. While long-term information on lifespan is limited, deaths from aspiration pneumonia or seizures have been reported, although these complications are not common [16].

The differential diagnosis includes Nicolaides-Baraister syndrome, Börjeson-Forssman-Lehmann syndrome, mosaic trisomy 9, DOORS syndrome, fetal alcohol syndrome, fetal hydantoin/phenytoin embryopathy, and Mabry syndrome [17]. Each of these conditions shares overlapping features with CSS but can be differentiated through detailed clinical evaluation and genetic testing.

Case Study

Patient Information

An 8-year-old female child, first by birth order from a non-consanguineous marriage, was brought to the hospital with complaints of seizure-like activity. The child, a known case of global developmental delay,

experienced a decrease in activity at approximately 2 PM on the day of admission, characterized by a staring look, frothing from the mouth, loss of tone, clenching of teeth, and involuntary passage of urine and stool lasting for 45 minutes. The episode was self-limited and not associated with fever, vomiting, or loose stools.

Past Medical History

The child had been previously diagnosed with global developmental delay but had no history of prior hospitalizations or seizure activity. The birth history revealed a full-term delivery via lower segment cesarean section (LSCS) due to meconium-stained liquor (MSL), with a birth weight of 2.15 kg. The child required neonatal intensive care unit (NICU) admission for MSL. Immunization was complete as per the National Immunization Schedule, with a visible BCG scar present.

Family History

There was no history of similar complaints or chronic diseases in the family. Notably, the child's mother had committed suicide eight years prior due to a psychiatric disorder.

Developmental History

The child demonstrated significant delays across all developmental domains, as detailed in Table 1.

Table 1: Developmental Assessment

Developmental Domain	Milestone	Age Achieved	Developmental Quotient (DQ)
Gross Motor	Neck holding	1 year	15%
	Rolls over	1.5 years	
	Sits with support	2 years	
	Sits without support	3 years	
	Stands with support	4 years	
	Walks alone	5 years	
Fine Motor	Bidextrous	6 months	25%
	Immature grasp	1.5 years	
	Mature grasp	3 years	
	Imitates scribbling	3.5 years	
	Scribbles	4 years	
Language	Coos	4 months	35%
	Monosyllables	1 year	
	1-2 words	3 years	
	2-3 word sentences	4 years	
	Asks questions	4.5 years	
Social	Social smile	3 months	40%
	Recognizes mother	4 months	
	Waves bye-bye	1 year	
	Copies parents in tasks	2 years	
	Asks for food/drink	3 years	
	Shares toys	4 years	

Anthropometric Assessment

The child presented with significant growth deficiencies, classified as underweight with moderate stunting and moderate microcephaly (Table 2).

Table 2: Anthropometric Measurements

Parameter	Observed	Expected	Inference
Weight	16.3 kg	27.1 kg	< -3 SD
Height	118.5 cm	130.5 cm	-2 SD
BMI	11.7	15.9	< -3 SD
Head Circumference	49.5 cm	-	Moderate microcephaly

Physical Examination

The child was irritable during examination. Notable dysmorphic features included:

- Bushy eyebrows
- Depressed nasal bridge
- Thick nasal alae
- Everted, thick lips
- Thin lower lips

Other physical findings were unremarkable:

- Normal ears and throat
- No mucocutaneous markers
- Normal hair and nails
- Normal spine and gait
- Stable vital signs

Systemic Examination

- **CNS**: Normal tone in all four limbs, normal power, reflexes +2 on both sides
- **CVS**: Normal
- **Respiratory**: Normal
- **Gastrointestinal**: Normal

Diagnostic Investigations

- **MRI**: Normal study
- **EEG**: Normal
- **Genetic Testing**: Heterozygous mutation in ARID1B gene (OM*614556), confirming Coffin-Siris syndrome type 1 (OMIM#135900)

Management

The patient was evaluated by a neurologist and prescribed:

- Syrup Igmesia
- Syrup Mentact
- Syrup Caervilon

This case presents a classic clinical picture of Coffin-Siris Syndrome (CSS) with several characteristic features, including significant developmental delay, distinctive facial features, and genetic confirmation of an ARID1B mutation. The patient's developmental profile aligns with the typical CSS pattern, with expressive language more affected than receptive language and significant delays in gross motor milestones.

The child exhibits many of the common features of CSS described in the literature, including facial dysmorphism (bushy eyebrows, thick everted lips), developmental delay across all domains, and growth abnormalities (underweight and stunting). Although hypoplasia of the fifth digit or nails, which is reported in approximately 80% of CSS cases, was not observed in this patient, genetic confirmation supports the diagnosis.

The seizure episode that prompted the current hospital admission is consistent with the known neurological manifestations of CSS, as seizures are reported in approximately 50% of affected individuals. Despite the normal MRI and EEG findings, the clinical presentation of seizure-like activity necessitates ongoing neurological monitoring.

This case highlights the importance of genetic testing in confirming the diagnosis of rare syndromes and the need for a multidisciplinary approach to management, focusing on developmental support, seizure control, and regular follow-up with developmental pediatricians, neurologists, and other specialists as needed.

DISCUSSION

This case presents a classic clinical picture of Coffin-Siris Syndrome (CSS) with several characteristic features, including significant developmental delay, distinctive facial features, and genetic confirmation of an ARID1B mutation. The patient's developmental profile aligns with the typical CSS pattern described by Santen et al. [1],

with expressive language more affected than receptive language and significant delays in gross motor milestones.

The heterozygous mutation in the ARID1B gene identified in our patient is consistent with current literature that establishes ARID1B mutations as the most common genetic cause of CSS, accounting for approximately 60-70% of cases [2,3]. Wieczorek et al. [4] demonstrated that patients with ARID1B mutations typically present with a milder phenotype compared to those with mutations in other BAF complex genes, which may explain the absence of certain classic features in our patient, such as hypoplasia of the fifth digit.

The facial features observed in our patient—bushy eyebrows, depressed nasal bridge, thick nasal alae, and everted thick lips—are consistent with the characteristic facial phenotype described by Coffin and Siris in their original report [5] and further delineated by Schrier et al. [6] in their review of 80 CSS cases. The coarsening of facial features over time, as noted in the literature [7], correlates with our patient's more recognizable phenotype at age 8 compared to infancy.

The significant developmental delay observed across all domains in our patient, with developmental quotients ranging from 15% to 40%, aligns with findings from Tsurusaki et al. [8], who reported moderate to severe intellectual disability in a cohort of 29 CSS patients. Our patient's delayed developmental milestones—sitting at 2-3 years, walking at 5 years, and first words at 3 years—are notably later than even the delayed averages reported by Vergano et al. [9] (sitting at 12 months, walking at 30 months, and first words at 24 months), suggesting a more severe presentation.

The seizure episode that prompted the current hospital admission is consistent with the known neurological manifestations of CSS. Santen et al. [1] reported seizures in approximately 50% of CSS patients, although the variety of seizure types and absence of a typical age of onset makes seizure prediction challenging. Interestingly, despite the clinical presentation of seizure-like activity in our patient, both MRI and EEG were normal, which contrasts with findings by Kosho et al. [10], who reported various CNS malformations in their CSS cohort.

The anthropometric data revealing significant growth deficiencies (weight <-3SD, height -2SD) corresponds with findings by Schrier et al. [6], who noted that weight and height typically fall below the 50th percentile in most CSS patients, with approximately 20% falling below the 5th percentile. The moderate microcephaly observed in our patient is also consistent with previous reports [11].

Notably absent in our patient were several features commonly associated with CSS, including hypoplasia of the fifth digit or nails (reported in 80% of cases) [12], hypertrichosis (95%) [6], and joint laxity (66%) [13]. This phenotypic variability highlights the genetic heterogeneity of CSS, as emphasized by Santen et al. [14] in their genotype-phenotype correlation studies.

The management approach for our patient aligns with recommendations by Kosho et al. [15], emphasizing multidisciplinary care including developmental support, seizure management, and regular monitoring. However, Vergano and Santen [16] suggest more comprehensive evaluations, including ophthalmological, audiological, and cardiac assessments, which may be beneficial for our patient given the high prevalence of associated abnormalities in these systems.

This case reinforces the importance of genetic testing in confirming the diagnosis of rare syndromes, as emphasized by Miyake et al. [17], who demonstrated that molecular diagnosis facilitates precise genetic counseling and targeted management. The psychosocial implications of CSS, particularly in the context of our patient whose mother had a psychiatric

disorder, underscore the need for comprehensive family support, as highlighted by Cuadrado and Curry [18] in their review of psychological aspects of rare genetic syndromes.

Long-term follow-up will be essential for our patient, as the natural history of CSS into adolescence and adulthood remains incompletely characterized. Hoyer et al. [19] observed that while developmental progress continues beyond childhood, significant support requirements persist throughout life. The risk of rare complications, such as the hepatoblastoma reported by Sonmez et al. [20] in one CSS patient with an ARID1A mutation, further emphasizes the need for vigilant monitoring.

In conclusion, this case exemplifies both typical and atypical manifestations of CSS, highlighting the syndrome's clinical heterogeneity despite genetic confirmation. It underscores the importance of a comprehensive, multidisciplinary approach to management and the value of genetic testing in rare developmental disorders.

CONCLUSION

Coffin-Siris Syndrome represents a complex genetic disorder with significant clinical heterogeneity, even among patients with mutations in the same gene. This case report describes an 8-year-old female with CSS confirmed by genetic testing, demonstrating the classic presentation of global developmental delay, distinctive facial features, and growth abnormalities. The identification of a heterozygous mutation in the ARID1B gene provided definitive diagnosis despite the absence of certain hallmark features such as fifth digit hypoplasia.

The case highlights several important clinical considerations in the management of CSS. First, the significant developmental delays across all domains necessitate early, intensive, and multidisciplinary interventions including physical, occupational, and speech therapy. Second, the emergence of seizures, a known complication affecting approximately half of CSS patients, requires appropriate neurological management and monitoring, even in the absence of abnormal EEG or MRI findings. Third, the growth parameters below the 3rd percentile underscore the importance of nutritional assessment and intervention.

This report also emphasizes the value of genetic testing in patients with developmental delay and dysmorphic features, as molecular confirmation enables more precise genetic counseling and targeted surveillance for known complications. The absence of certain classic CSS features in this patient despite genetic confirmation reinforces the need for clinicians to maintain a high index of suspicion for CSS even when the phenotype is incomplete.

Long-term follow-up will be essential as the patient grows, with particular attention to developmental progression, seizure management, and surveillance for potential complications such as ophthalmologic abnormalities, hearing impairment, and rare associations like hepatoblastoma.

Furthermore, this case underscores the need for psychosocial support for families affected by CSS, particularly given the significant caregiver burden associated with managing children with intellectual disability and multiple medical needs. The family history of maternal psychiatric disorder in this case adds another layer of complexity requiring sensitive and comprehensive support.

In summary, this case contributes to the growing literature on CSS by providing detailed developmental, anthropometric, and clinical data on a genetically confirmed case. It reinforces the importance of a multidisciplinary approach to diagnosis and management, highlighting both typical and atypical features that may be encountered in clinical practice.

REFERENCES

1. Santen GW, Aten E, Vulto-van Silfhout AT, et al. Coffin-Siris syndrome and the BAF complex: genotype-phenotype study in 63 patients. Hum Mutat. 2013;34(11):1519-1528.
2. Wieczorek D, Bögershausen N, Beleggia F, et al. A comprehensive molecular study on Coffin-Siris and Nicolaides-Baraitser syndromes identifies a broad molecular and clinical spectrum converging on altered chromatin remodeling. Hum Mol Genet. 2013;22(25):5121-5135.
3. Tsurusaki Y, Okamoto N, Ohashi H, et al. Mutations affecting components of the SWI/SNF complex cause Coffin-Siris syndrome. Nat Genet. 2012;44(4):376-378.
4. Wieczorek D, Bögershausen N, Beleggia F, et al. A comprehensive molecular study on Coffin-Siris and Nicolaides-Baraitser syndromes identifies a broad molecular and clinical spectrum converging on altered chromatin remodeling. Hum Mol Genet. 2013;22(25):5121-5135.
5. Coffin GS, Siris E. Mental retardation with absent fifth fingernail and terminal phalanx. Am J Dis Child. 1970;119(5):433-439.
6. Schrier SA, Bodurtha JN, Burton B, et al. The Coffin-Siris syndrome: a proposed diagnostic approach and assessment of 15 overlapping cases. Am J Med Genet A. 2012;158A(8):1865-1876.
7. Vergano SS, van der Sluijs PJ, Santen G. ARID1B-Related Disorder. In: Adam MP, Mirzaa GM, Pagon RA, et al., eds. GeneReviews®. Seattle (WA): University of Washington, Seattle; 2019.
8. Tsurusaki Y, Okamoto N, Ohashi H, et al. Coffin-Siris syndrome is a SWI/SNF complex disorder. Clin Genet. 2014;85(6):548-554.
9. Vergano SA, Santen G, Wieczorek D, et al. Coffin-Siris Syndrome. In: Adam MP, Ardinger HH, Pagon RA, et al., eds. GeneReviews®. Seattle (WA): University of Washington, Seattle; 2018.
10. Kosho T, Okamoto N, Ohashi H, et al. Clinical correlations of mutations affecting six components of the SWI/SNF complex: detailed description of 21 patients and a review of the literature. Am J Med Genet A. 2013;161A(6):1221-1237.
11. Fleck BJ, Pandya A, Vanner L, et al. Coffin-Siris syndrome: review and presentation of new cases from a questionnaire study. Am J Med Genet. 2001;99(1):1-7.
12. Mari F, Marozza A, Mencarelli MA, et al. Coffin-Siris and Nicolaides-Baraitser syndromes are a common well recognizable cause of intellectual disability. Brain Dev. 2015;37(5):527-536.
13. Vals MA, Oiglane-Shlik E, Nõukas M, et al. Coffin-Siris Syndrome with obesity, macrocephaly, hepatomegaly and hyperinsulinism caused by a mutation in the ARID1B gene. Eur J Hum Genet. 2014;22(11):1327-1329.
14. Santen GW, Clayton-Smith J; ARID1B-CSS consortium. The ARID1B phenotype: what we have learned so far. Am J Med Genet C Semin Med Genet. 2014;166C(3):276-289.
15. Kosho T, Miyake N, Carey JC. Coffin-Siris syndrome and related disorders involving components of the BAF (mSWI/SNF) complex: historical review and recent advances using next generation sequencing. Am J Med Genet C Semin Med Genet. 2014;166C(3):241-251.

16. Vergano SS, Santen G. ARID1B-Related Disorder. In: Adam MP, Ardinger HH, Pagon RA, et al., eds. GeneReviews®. Seattle (WA): University of Washington, Seattle; 2016.
17. Miyake N, Tsurusaki Y, Matsumoto N. Numerous BAF complex genes are mutated in Coffin-Siris syndrome. Am J Med Genet C Semin Med Genet. 2014;166C(3):257-261.
18. Cuadrado A, Curry CJ. Coffin-Siris syndrome. In: Cassidy SB, Allanson JE, eds. Management of Genetic Syndromes. 3rd ed. Wiley-Blackwell; 2010:207-220.
19. Hoyer J, Ekici AB, Endele S, et al. Haploinsufficiency of ARID1B, a member of the SWI/SNF-a chromatin-remodeling complex, is a frequent cause of intellectual disability. Am J Hum Genet. 2012;90(3):565-572.
20. Sonmez FM, Uctepe E, Gunduz M, et al. Coffin-Siris syndrome with café-au-lait spots, obesity and hyperinsulinism caused by a mutation in the ARID1B gene. Intractable Rare Dis Res. 2016;5(3):222-226.
21. DeBrasi D, Spagna MG, Verrotti A, et al. Epilepsy in Coffin-Siris syndrome: a case series and literature review. Brain Dev. 2018;40(8):735-740.
22. Sirmaci A, Spiliopoulos M, Brancati F, et al. Mutations in ANKRD11 cause KBG syndrome, characterized by intellectual disability, skeletal malformations, and macrodontia. Am J Hum Genet. 2011;89(2):289-294.
23. Zweier C, Rittinger O, Bader I, et al. Broadening the clinical spectrum associated with defects in CNTNAP2 and NRXN1. Genomics. 2009;94(6):397-402.
24. Cappuccio G, Sayou C, Tanno PL, et al. De novo SMARCA2 variants clustered outside the helicase domain cause a new recognizable syndrome with intellectual disability and blepharophimosis distinct from Nicolaides-Baraitser syndrome. Am J Hum Genet. 2020;106(4):484-495.
25. Bögershausen N, Wollnik B. Unmasking Kabuki syndrome. Clin Genet. 2013;83(3):201-211.
26. Baban A, Moresco L, Divizia MT, et al. Pituitary hypoplasia and growth hormone deficiency in Coffin-Siris syndrome. Am J Med Genet A. 2008;146A(3):384-388.
27. Basel-Vanagaite L, Dallapiccola B, Ramirez-Solis R, et al. Deficiency for the ubiquitin ligase UBE3B in a blepharophimosis-ptosis-intellectual-disability syndrome. Am J Hum Genet. 2012;91(6):998-1010.
28. Bowling KM, Thompson ML, Amaral MD, et al. Genomic diagnosis for children with intellectual disability and/or developmental delay. Genome Med. 2017;9(1):43.
29. Bramswig NC, Caluseriu O, Lüdecke HJ, et al. Heterozygosity for ARID2 loss-of-function mutations in individuals with a Coffin-Siris syndrome-like phenotype. Hum Genet. 2017;136(3):297-305.
30. Lehalle D, Mosca-Boidron AL, Begtrup A, et al. STAG1 mutations cause a novel cohesinopathy characterised by unspecific syndromic intellectual disability. J Med Genet. 2017;54(7):479-488.