CASE REPORT

A newborn with coffin-siris syndrome

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Abstract

Coffin-Siris syndrome (CSS) is a rare congenital genetic syndrome, a multisystem disease related to congenital abnormalities, that manifests with abnormal features, causes repeated infections and is associated with developmental delays. Here, we report a newborn male with CSS from Baoding in the Hebei Province of China.

Keywords: Coffin-Siris syndrome; newborn; rare disease.

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Introduction

Coffin-Siris syndrome (CSS) is a rare congenital genetic syndrome, a multisystem disease related to congenital abnormalities with abnormal features, developing repeated infections and associated with developmental delays. The typical manifestations are hypoplasia of the distal phalanx or fifth finger/toenail, obvious facial features (large eyebrows, broad nose, wide mouth, hirsutism), microcephaly, organ dysfunction, and various degrees of developmental or cognitive impairment.[1,2]

Coffin-Siris syndrome (CSS) is caused by mutations in the human BRG1-related factor (BAF) chromatin-remodelling complex (also known as the SWI/SNF-A complex) gene.[3,4] The SWI/SNF complex is an evolutionarily conserved chromatin remodelling complex that plays an important role in epigenetic regulation and the regulation of several genes. The main mutations of the SWI/SNF gene are concentrated in catalytic subunits and regulatory subunits, including ARID1A, ARID1B, SMARCA4, SMARCB1, SMARCE1 and SOX11.[5-10] Among them, ARID1B is located at the 6q25.3 region of the chromosome, with a total length of approximately 433 kb and contains 24 exons. The mutation types of this gene include nonsense mutations or stop mutation, frameshift mutations, splicing mutations, and exon deletions. All mutation reports lead to protein truncation.[5-8]

Here, we report a new born male with CSS. He belonged to Baoding in the Hebei Province of China. The study was conducted under the recommendations of Baoding Children's Hospital ethics committee (No 202059).

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Case Report

The patient was a full-term male born on 18. September, 2020 and admitted to Baoding Children's Hospital 30 hours later with cyanosis following feeding. The physical examination results were as follows: temperature 36.8°C; pulse, 130 beats/min; respiration 46 breaths/min; blood pressure 88/75 mmHg and weight 2.94 kg. He had a normal development with a medium nutritional condition and a poor mental performance. The crying was vigorous with a hoarse voice and a normal rhythm and steady breathing. The whole body showed no rash, yellowness or bleeding points. No cyanosis was observed around the mouth. The three depressions of inhalation were negative. The anterior fontanel was flat with little tension (size: 1 cm×1 cm). The pupils were bilaterally round with a normal light reflex and no yellow staining in the sclera. The throat showed resistance with pharyngeal congestion. Harsh breath sounds with no rales were audible in both lungs. The heart rate was 130 beats/min with normal rhythm and sounds. The umbilical cord ligation end was dry and clean with a flat abdomen showing no visible peristaltic waves, and normal bowel sounds. Neither the sucking reflex nor rooting reflex were elicited. The embrace reflex was weak with a positive grasping reflex and a weak positive tongue spatula test.

The child had a hoarse voice, intermittent sputum in the throat and laryngeal oedema. Apnoea, cyanosis, upper airway obstruction, auscultation and laryngeal squeal conduction emerged after stimulation. The results of electronic bronchoscopy showed that during crying inhalation, the laryngeal chamber narrowed, the epiglottis slightly swelled, and the diameter of the airway narrowed, which was less than 1/3 of the diameter of the lumen. Therefore, congenital airway dysplasia was diagnosed. As the tracheal mucosa was rough and swollen, with attached white sticky secretions, so endobronchial inflammation was suspected. A diagnosis of neonatal hypocalcaemia was made since he had a lower blood calcium level test on admission (blood calcium: 1.62 mM; free calcium 0.87 mM). He was diagnosed with neonatal tetany since his percutaneous oxygen saturation decreased to approximately 70% intermittently, accompanied by limb shaking, perioral cyanosis and neonatal hypocalcaemia. His skin showed yellow staining on the second day, combined

with higher total bilirubin and indirect bilirubin (blood total bilirubin 5.88 mg/dL, direct bilirubin 0.56 mg/dL, indirect bilirubin 5.32 mg/dL) (Table), and the yellow discolouration disappeared 14 days later, so he was diagnosed with neonatal jaundice. After admission, his blood 25-hydroxyvitamin D was 11.5 μg/L, which was lower than normal (12 μg/L), so vitamin D deficiency was diagnosed. He was diagnosed with bilateral subependymal

Table: Laboratory findings reported during therapy for the newborn with CSS.

Laboratory findings	2020/9/18	2020/9/19	2020/9/24	2020/9/26	2020/10/5	2020/10/14	2020/10/20	Normal range
Haematologic								
White blood cell, $\times 10^9$/L	-	16.31	8.68	-	-	-	9.36	Birth：9.0-30.0 7d：5.0-21.0 14d：5.0-20.0
Red blood cell, $\times 10^{12}$/L	-	4.17	3.59	-	-	-	3.27	1d:5.8 3d:5.6 7d:5.2 14d:5.1
Lymphocytes, %	-	25.6	42.2	-	-	-	51.1	Birth：2.0-11.0 7d：2.0-17.0 14d：2.0-17.0
Red blood cell volume, %	-	39.3	34.8	-	-	-	30.1	1d:58 3d:55 7d:54 14d:52
Haemoglobin, g/L	-	139	122	-	-	-	104	1d:140-220 3d:138-218 7d:140-200 14d:138-198
Platelets, ×109/L	-	299	301	-	-	-	337	1d:100-260 3d:80-320 7d:100-300
Neutrophils, %	-	64.0	39.8	-	-	-	27.5	Birth：6.0-26.0 7d：1.5-10.0 14d：1.0-9.5
Biochemical	-	-	-	-	-	-	-	
AST, U/L	25.9	47	-	-	-	-	22	Birth-7d:boy30-100, girl 24-95 8-30d:22-71
ALT, U/L	10.4	12.6	-	-	-	-	16.0	Birth-7d:6-40 8-30d:boy10-40,girl8-32
Total protein, g/dL	5.539	4.82	-	-	-	-	4.94	Birth:4.6-7.0 7d:4.4-7.6 1-3month:3.64-7.38
Albumin, g/dL	13.48	3.25	-	-	-	-	3.62	Birth:3.2-4.8 7d:2.9-5.5 1-3month:2.0.-4.46
Globulin, g/dL	1.91	1.57	-	-	-	-	1.32	2.0-3.0
Albumin/globulin ration	1.8	2.1	-	-	-	-	2.7	1.5-2.5
Urea, mM	3.71	3.65	-	-	-	-	1.85	1-12h:1.34-4.01 -12h:1.5-10.52 -48h:2.17-12.86 -72h:2.17-12.36
Serum Creatinine, mg/dL	0.646	0.769	-	-	-	-	0.271	Newborn:0.799-1.4
CK-MB, ng/mL	82.3	58	-	-	-	-	32	0-24
Creatinine kinase, IU/L	508.5	1286	-	-	-	-	142	5-8h:214-1175 24-33h:130-1200 72-100h:87-725 Adult:5-130
LDH, IU/L	350.9	499	-	-	-	-	219	Birth:4.84-8.37 1d-1month:3.09-6.75
Total bilirubin, mg/dL	2.37	5.88	-	-	-	-	1.16	2.0-19.0
Direct bilirubin, mg/dL	0.76	0.56	-	-	-	-	0.55	0-0.4
Indirect bilirubin, mg/dL	1.62	5.32	-	-	-	-	0.61	0.1-0.76

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Laboratory findings	2020/9/18	2020/9/19	2020/9/24	2020/9/26	2020/10/5	2020/10/14	2020/10/20	Normal range
Glucose, mg/dL	89.09	56.4	-	-	-	-	113.09	Term infant:30.9-60.0 1d:50.9-90.9 Child:60.1-100.1
25-Hydroxyvitamin D, μg/dL	1.15	1.15	-	-	-	0.87	-	2-10
Blood gas analysis								
PH	7.41	-	-	-	-	-	7.38	0-11h:7.22-7.41 12h-28d:7.33-7.47 2month-3year:7.35-7.46
PaO_2, mmHg	95	-	-	-	-	-	95	0-11h:45.8-70.2 12h-28d:49.0-72.5 2month-3year:59.3-105
$PaCO_2$, mmHg	34.5	-	-	-	-	-	50.1	0-11h:32.9-48.3 12h-28d:29.8-42.5 2month-3year:28.9-40.0
K^+, mEq/L	3.43	-	-	-	-	-	4.35	1-12h:5.3-7.3 -24h:5.3-8.9 -48h:5.2-7.3 -72h:5.0-7.0
Na^+, mEq/L	141	-	-	-	-	-	138	1-12h:124-156 -24h:132-159 -48h:134-160 -72h:139-162
Cl^-, mEq/L	105	-	-	-	-	-	103	1-12h:90-111 -24h:87-114 -48h:92-114 -72h:93-112
iCa_2^+, mEq/L	0.87	-	-	-	-	-	1.21	3-24h:1.07-1.27 -48d:1.0-1.17 ≥3d:1.12-1.23
HCO_3^-, mEq/L	21.5	-	-	-	-	-	29.2	0-11h:15.6-25.2 12h-28d:17.8-26.1 2month-3year:18.2-24.3
AG(K^+)	14.2	-	-	-	-	-	10.1	
BE, mM	-2	-	-	-	-	-	3. 9	1-11h:-9.8-0.3 12h-28d:-6.6-2.4 2month-3year:-5.8-0.1
Lac, mM	1.9	-	-	-	-	-	0.8	0-2.0
Calcitonin, pg/ml	-	-	0.9	-	12.7	-	-	Boy:3-26 Girl:2-17
Thyroid function								
Tetraiodothyronine (T4), ug/dl	-	-	4.98	-	4.89	5.45	-	Birth:6.9-16.7 24-48h:11-23 1-4week:9-18
Triiodothyronine (T3), ug/dl	-	-	63.57	-	57.34	78.52	-	Birth:217 24h-1week:89-256 2week:250 4week:114-189
Thyroid stimulating hormone (TSH), ulU/ml	-	-	5.67	-	3.62	4.84	-	Birth:3-22 24h:17.3±3 48h-1week:12.8±1.9 2week-4week:<1-10
Free triiodothyronine (FT3), pmo1/L	-	-	3.15	-	2.87	3.96	-	2.5-15.0
Free tetraiodothyronine (FT4), pmo1/L	-	-	14.25	-	11.98	14.5	-	8.37-29.6
Coagulation function								
PT, S	-	-	-	15.8	-	11.6	-	Term infants:13-20 Adult time： 1week
APTT, S -	-	-		57	-	36.4	-	Term infants:55±10 Adult time： 2-9month
TT, S	-	-	-	15	-	17.7	-	Term infants:10-16 Adult time： a few days
Fipinogen FIB, mg/dL	-	-	-	113	-	169	-	200-400
D-dimer, mg/L	-	-	-	0.95	-	0.107	-	0-0.256

Abbreviation: PaO_2, urinary oxygen tension; $PaCO_2$, carbon dioxide tension gradient; K, potassium; Na, sodium; Cl, chloride; Ca, calcium; HCO_3, bicarbonate; AG, anion gap; BE, base excess; APTT, activated partial thromboplastin time; PT, prothrombin time.

haemorrhage (absorption period) and patent foramen ovale (2.2 mm, EF 75%) according to the intracranial and cardiac colour ultrasound results.

After admission, he received respiratory support, including BiPAP respiratory support (9/21-9/24, 10/1-10/7), NCPAP respiratory support (10/7-10/8), oxygen inhalation (9/19-9/21, 10/8-10/12), and chamber oxygen inhalation (9/24-10/12, 10/13-10/18). The compound brain peptide ganglioside was injected at an intravenous point to nourish the brain cells; penicillin and ceftazidime were administered to prevent infection; oxycephalosodium (IV, 9/27-10/9), budesonide, ipratropium bromide, and acetyl cysteine atomization (9/19-9/25) were used to reduce airway inflammation and phlegm; calcium carbonate D3, alfacalciferol drops were administered and oral or tube feeding was performed to treat hypocalcaemia; red blood cells were infused to treat anaemia and improve the oxygen carrying capacity. He received oral or tube feeding, oral intervention and blue light therapy. After treatment for 32 days, endobronchial inflammation, neonatal hypocalcaemia, neonatal tetany, neonatal anaemia and neonatal jaundice were clinically alleviated and congenital airway dysplasia improved. His vital signs remained stable (Figure 1). He underwent genetic testing at the age of 24 days using next-generation sequencing, which was validated for his parents using Sanger sequencing. The ARID1B gene had a heterozygous mutation (Figure 2).

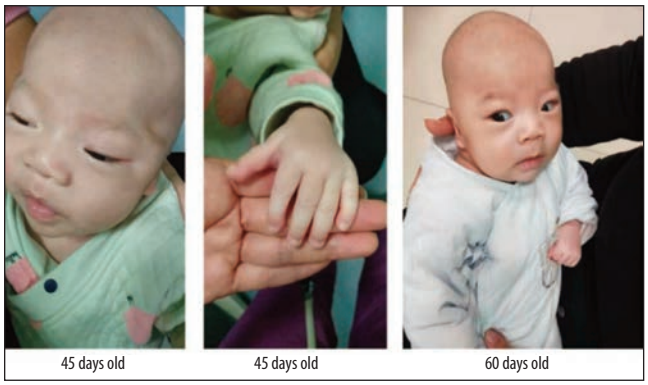

Figure-1: Patient features.

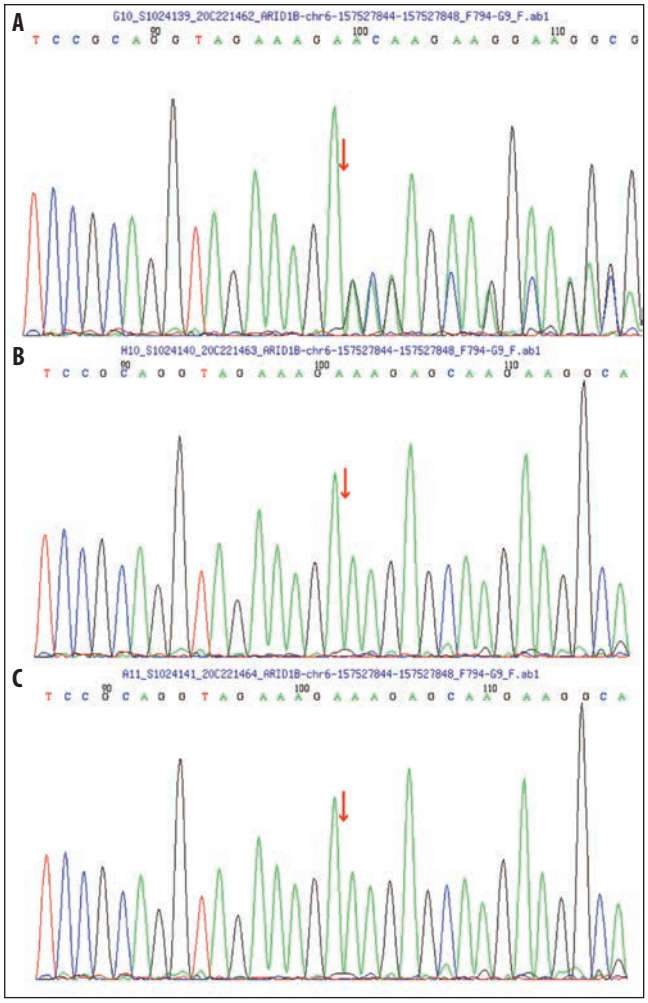

Figure-2: The family analysis results. (A) Child. (B) Father. (C) Mother.

Discussion

This study reported a newborn male with CSS from China. He had a de novo heterozygous mutation in the ARID1B C gene. 5570_5573delAAGA (p. K1857Sfs*17).[7,8] There was no variation in the site for the father and mother, which was verified by Sanger sequencing. At present, there is no effective treatment for Coffin-Siris syndrome, and symptomatic treatment is generally used to treat the corresponding symptoms. The main symptoms of this child were cyanotic attacks and upper airway obstruction. During hospitalisation, non-invasive respiratory support was provided to improve the symptoms. The above symptoms of the child were gradually relieved after treatment, and the child was weaned from the ventilator. The patient was discharged from the hospital after escort training. In the coming period, the patient's development regarding nutrition, exercise, language, hearing, vision and emotional cognition was regularly evaluated, and comprehensive rehabilitation treatment was provided according to the evaluation results. The child still showed laryngeal stridor and dyspnoea when crying and drinking milk. The laryngeal stridor disappeared at approximately 4 months age, and the dyspnoea disappeared at approximately 12 months. In addition, this disease requires prenatal testing and genetic counselling for pregnant women with an identified pathogenic variant in a high-risk family member. Molecular biological diagnosis is recommended for those who have the above phenotypes without a clear aetiology. The prognosis of this disease is that patients may die from aspiration pneumonia or epilepsy in infancy. There is no information on the life

expectancy of CSS patients, and further research is needed to better understand the prognosis of CSS patients.

Conclusion

Early diagnosis and treatment in the initial stage of CSS is beneficial for patients and their families.

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Conflict of interest: None.

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References

1. Sonmez FM, Uctepe E, Gunduz M, Gormez Z, Erpolat S, Oznur 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: 222-6.
2. Vasileiou G, Vergarajauregui S, Endele S, Popp B, Büttner C, Ekici AB, et al. Mutations in the BAF-Complex Subunit DPF2 Are Associated with Coffin-Siris Syndrome. Am J Hum Genet 2018; 102: 468-79.
7. Vasko A, Drivas TG, Schrier Vergano SA. Genotype-Phenotype Correlations in 208 Individuals with Coffin-Siris Syndrome. Genes (Basel) 2021; 12: 937.
3. Filatova A, Rey LK, Lechler MB, Schaper J, Nuber UA. Mutations in SMARCB1 and in other Coffin-Siris syndrome genes lead to various brain midline defects. Nat Commun 2019; 10: 2966.
4. Nixon KCJ, Rousseau J, Stone MH, Sarikahya M, Campeau PM. A Syndromic Neurodevelopmental Disorder Caused by Mutations in SMARCD1, a Core SWI/SNF Subunit Needed for Context-Dependent Neuronal Gene Regulation in Flies. Am J Hum Genet 2019; 104: 596-610.
5. Ellegood J, Petkova S, Kinman A, Qiu L, Lerch J. Neuroanatomy and behavior in mice with a haploinsufficiency of AT-rich interactive domain 1B (ARID1B) throughout development. Mol Autism 2021; 12: 25.
6. Gorokhova S, Mortreux J, Afenjar A, Bitach T, Missirian C. Significant contribution of intragenic deletions to ARID1B mutation spectrum. Genet Med 2019; 21: 2654-5.
7. Sluijs V, Eline P, Ruivenkamp, Claudia AL, Santen, Gijs WE. The ARID1B spectrum in 143 patients: from nonsyndromic intellectual disability to Coffin-Siris syndrome. Genet Med 2019; 21:1295-307.
8. Pagliaroli L, Trizzino M. The Evolutionary Conserved SWI/SNF Subunits ARID1A and ARID1B Are Key Modulators of Pluripotency and Cell-Fate Determination. Front Cell Dev Biol 2021; 9: 643361.
9. Ding Y, Chen J, Tang Y, Chen LN, Yao RE, Yu T, et al. Identification and functional analysis of novel SOX11 variants in Chinese patients with Coffin-Siris syndrome 9. Front Genet 2022; 13: 940776.
10. Wang X, Wu H, Sun H, Wang L, Chen L. ARID2, a Rare Cause of Coffin-Siris Syndrome: A Clinical Description of Two Cases. Front Pediatr 2022; 10: 911954.