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Title

Incomplete Shone's complex as a rare cardiac manifestation of Coffin–Lowry syndrome: a case report

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Abstract

Background: Coffin-Lowry syndrome is a rare X-linked genetic disorder caused by pathogenic variants in the *RPS6KA3* gene, characterized by distinctive craniofacial features, skeletal abnormalities, and neurodevelopmental impairment. Although cardiac involvement has been reported in Coffin-Lowry syndrome, it most commonly manifests as cardiomyopathy or valvular insufficiency. To the best of our knowledge, Coffin-Lowry syndrome has not been associated with obstructive left-sided congenital heart diseases including an incomplete Shone's complex.

Case presentation: We report a case of a 2-month-old boy who, on cardiac evaluation, was found to have coarctation of the aorta, a bicuspid aortic valve with severe stenosis, a parachute-like mitral valve with mild subvalvular stenosis, consistent with an incomplete Shone's complex, and marked left ventricular hypertrophy. The patient underwent successful corrective surgery for

coarctation of the aorta and aortic valve stenosis, with follow-up revealing moderate residual aortic valve stenosis and mild residual valvular dysfunction. Genetic testing identified a maternally inherited microduplication of the X chromosome p22.12 region, encompassing several 5' exons of the *RPS6KA3* gene.

Conclusions: This case suggests that obstructive left-sided congenital heart diseases including an incomplete Shone's complex may represent a previously unrecognized cardiac manifestations of Coffin–Lowry syndrome, thereby expanding the cardiovascular phenotype of this rare condition. Recognition of this association may have implications for early diagnosis, genetic evaluation, and long-term cardiac surveillance in affected patients.

Keywords

Coffin-Lowry syndrome; CLS; Shone's complex

Background

Coffin-Lowry syndrome (CLS; OMIM # 303600) is a rare X-linked genetic disorder caused by pathogenic variants in the *RPS6KA3* gene. CLS is characterized by intellectual disability, craniofacial anomalies, short stature, puffy tapered fingers, hypotonia and skeletal malformations (1). There are a few reported cases of cardiac abnormalities in patients with CLS including left ventricular noncompaction cardiomyopathy, restrictive cardiomyopathy, mitral regurgitation and dilated cardiomyopathy (1–6). While cardiac involvement is a known component of the CLS phenotype, obstructive left-sided heart lesions, in particular incomplete Shone's complex, have not been reported in CLS. Incomplete Shone's complex is itself a rare congenital heart condition (7). It refers to the presence of two or three – but not all four – of the obstructive left-sided cardiac lesions that define classic (complete) Shone's complex (8). The four characteristic

components of complete Shone's complex are supralvalvar mitral ring (SVMR), parachute mitral valve (PMV), subaortic stenosis (subAS), and coarctation of the aorta (CoA) (9). Here, we report a case of CLS associated with incomplete Shone's complex, a combination that, to the best of our knowledge, has not been previously described. Written informed consent for publication of the clinical information and photographs was obtained from the parents.

Case presentation

A 2-month-old boy presented with tachypnea, tachycardia, and poor feeding. He was born at term with a birth weight of 3.3 kg. On the initial examination, the heart rate was 166 beats per minute. The cardiac exam revealed a grade 3 systolic murmur audible throughout the precordium. Femoral pulses were absent, and blood pressure measurements demonstrated systemic hypertension (118/93 mmHg) in the upper extremities with a marked upper-lower limb gradient, with systolic blood pressure in the lower extremities up to 42 mmHg lower than in the upper extremities. Transthoracic echocardiography revealed coarctation of the aorta, a bicuspid aortic valve with severe aortic stenosis (echocardiographically estimated peak systolic gradient 100 mmHg; echocardiographically estimated mean gradient 59 mmHg), and a parachute-like mitral valve with mild subvalvular stenosis, findings consistent with incomplete Shone's complex. Additionally, marked left ventricular hypertrophy was observed. Echocardiogram demonstrated hypertrophic cardiomyopathy, with an interventricular septal diastolic diameter Z-score of +2.6 and a left ventricular posterior wall diastolic diameter Z-score of +3.0. Left ventricular systolic function was preserved (EF 77%), whereas diastolic function was impaired. Computed tomography (CT) angiography demonstrated that the coarctation of the aorta involved the aortic isthmus, with the narrowest segment measuring 3.5 mm in diameter, located 10 mm distal to the origin of the left subclavian artery. Following diagnosis, the patient underwent

median sternotomy with end-to-arch anastomosis for repair of the coarctation of the aorta and aortic valve commissurotomy for severe aortic stenosis. The postoperative course was uncomplicated; however, metoprolol therapy was initiated to manage paradoxical hypertension following CoA correction. At 7-month follow-up, the aortic arch was of appropriate caliber; however, moderate residual aortic valve stenosis persisted (echocardiographically estimated peak systolic gradient 60 mmHg; echocardiographically estimated mean gradient 38 mmHg), accompanied by mild aortic regurgitation. The PMV was associated with mild stenosis (echocardiographically estimated mean gradient ~ 4.3 mmHg). The left ventricle demonstrated marked hypertrophy (Z-score +3.0), hyperdynamic systolic function (EF ~75%), and persistent diastolic dysfunction, with an elevated E/E' ratio (~21). Metoprolol therapy was continued and ongoing follow-up with a pediatric cardiologist was recommended. His gross motor milestones were as follows: he sat unsupported at 10 months and walked independently at 12 months. At 13 months, his growth parameters were within normal limits: weight 11 kg (75th–85th percentile), length 78 cm (50th–75th percentile), and head circumference 48 cm (85th–95th percentile), based on the WHO Child Growth Standards. During subsequent genetic evaluation, craniofacial features included hypertelorism, thickened lower eyelid folds, short, curved nose with broad columella, thick alae nasi, thick nasal septum, micrognathia, retrognathia, large, dorsally rotated ears, nipple hypertelorism and large, puffy hands and feet (Fig. 1). Genomic DNA was obtained from venous blood using the phenol-chloroform extraction method. Genotyping array was performed using HumanCytoSNP-12 BeadChip (Illumina Inc., San Diego, CA, USA) according to manufacturer procedures. Genotyping results were analysed using GenomeStudio Genotyping Module v2.0 (Illumina Inc.). A hemizygous 428 kb microduplication encompassing the first seven exons of the *RPS6KA3* was identified in a patient [Xp22.12(20193514-20621530)x2;

hg38] by single nucleotide polymorphism (SNP) genotyping array analysis, confirming CLS. The microduplication was inherited maternally; the mother was noted to have short stature.

Discussion and Conclusions

CLS is a rare genetic disorder, estimated to occur in approximately 1:50 000 to 1:100 000 people (1). The severity of CLS can vary significantly, even within the same family. However, CLS is most commonly characterized by intellectual disability, craniofacial anomalies and skeletal malformations. Intellectual disability is characterized by cognitive impairment and is objectively assessed by measuring IQ, which typically ranges from 15 to 60 (1). Typical facial features include orbital hypertelorism, downward-slanting palpebral fissures, epicanthic folds, large and prominent ears, thick everted lips, and a thick nasal septum with anteverted nares (1), which are seen in our patient. A potential early feature of CLS is the presence of short puffy tapered fingers. As for skeletal malformations, about 80% of CLS patients have kyphosis or scoliosis and pectus carinatum or pectus excavatum (1). It is also important to note that these patients tend to be of small stature. Some less commonly observed symptoms include neurological manifestations as sensorineural hearing loss, stimuli triggered drop attacks and seizures (1).

The interpretation of the identified *RPS6KA3* microduplication requires careful consideration. CLS is primarily associated with loss-of-function variants in *RPS6KA3*, resulting in reduced or absent kinase activity (1). However, partial and whole-gene duplications involving *RPS6KA3* have also been reported in individuals with CLS or related neurodevelopmental phenotypes, suggesting that duplications may occasionally disrupt gene function rather than cause a simple dosage increase (10,11). In particular, previously described *RPS6KA3* microduplications have been associated with reduced transcript levels and a loss-of-function mechanism (11). In the

present case, the duplication encompasses the first seven exons of *RPS6KA3* and was identified in a patient with a phenotype highly consistent with CLS, including characteristic craniofacial features and large, puffy hands and feet. Taken together, the clinical phenotype and previously reported pathogenic *RPS6KA3* duplications support the clinical relevance of this finding (11). A limitation of this case is that additional genomic and transcriptomic analyses, such as long-read sequencing and RNA sequencing, were not performed, which would have provided further insight into the structure and functional impact of the identified genetic variant.

Cardiac anomalies are a rare feature of CLS, most often presenting as mitral regurgitation, which occurs in only 15% of patients (1,2,5,6). There are a few reports of structural cardiac changes in CLS, with these changes appearing as cardiomyopathies (2–4). However, an incomplete Shone's complex, accompanied by severe aortic stenosis, marked left ventricular hypertrophy, and hypertrophic cardiomyopathy with impaired diastolic function, as seen in our patient, has not been reported in CLS so far (Table 1).

Table 1. Genetic and clinical data of CLS and known heart malformations

Reference	Genetic variant	Heart phenotype
This study	arr(hg38)Xp22.12(20193514_20621530)x2	Coarctation of the aorta, a bicuspid aortic valve, severe aortic valve stenosis, a parachute like mitral valve with associated mild subvalvular stenosis consistent with an incomplete Shone's complex and left ventricular hypertrophy
Massin MM et al., 1999, Acta Paediatr (2)	<i>RPS6KA3</i> variant c.1293G>A (p.Gly431Asp) in exon 15	Dilated cardiomyopathy with recurrent left ventricle failure and mitral valve insufficiency due to short chordae and annular dilation
Facher JJ et al., 2004, Am J Med Genet A (3)	<i>RPS6KA3</i> variant c.1428_1430delTAT in exon 16	Restrictive cardiomyopathy with severe bi-atrial enlargement, moderate mitral and tricuspid regurgitation, and elevated filling pressures

Martinez HR et al., 2011, Am J Med Genet A (4)	<i>RPS6KA3</i> variant c.1000-2A>G in intron 12	Restrictive cardiomyopathy with pulmonary hypertension, left ventricle noncompaction, severe mitral/tricuspid regurgitation, and bi-atrial dilation
Yoshida T et al., 2015, Gen Thorac Cardiovasc Surg (5)	<i>RPS6KA3</i> variant consistent with Coffin–Lowry syndrome (variant not specified)	Severe mitral valve regurgitation with shortened chordae and papillary muscles, enlarged mitral annulus, tricuspid regurgitation, and hypoplastic ascending aorta
Wakami T et al., 2022, Asian Cardiovasc Thorac Ann (6)	<i>RPS6KA3</i> variant consistent with Coffin–Lowry syndrome (variant not specified)	Severe mitral valve regurgitation with enlarged annulus and papillary muscles attached to the basement of the left ventricle, moderate tricuspid regurgitation

The cardiac phenotype in our patient also included a bicuspid aortic valve, a congenital anomaly frequently associated with Shone's complex. Other reported associated anomalies include atrial and ventricular septal defects, patent ductus arteriosus, and interrupted aortic arch (12). Our patient presented with tachypnea, tachycardia, and poor feeding, which are the most typical symptoms of Shone's complex. Other non-specific symptoms include nocturnal cough, failure to thrive and fatigue (13). In Shone's complex, mitral valve obstruction occurring early in embryonic development is thought to be the initial pathological event, resulting in an underdeveloped left ventricular cavity and subsequently causing varying degrees of left ventricular outflow tract obstruction and aortic coarctation (8). Congenital heart defects often emerge early in fetal development, typically between 2 and 7 weeks of gestation, which is when the heart undergoes essential structural formation (14,15). These cardiac structural abnormalities are not necessarily caused by genetic factors, as they can also result from environmental influences, including teratogenic exposures, or other unknown factors during early fetal development (14). Based on the clinical history, the patient had no prenatal exposure to any known cardiac teratogens.

This case highlights an uncommon presentation of CLS associated with obstructive left-sided congenital heart disease consistent with incomplete Shone's complex. While cardiac manifestations in CLS have been reported infrequently and are typically limited to cardiomyopathies or valvular insufficiency, the combination of coarctation of the aorta, bicuspid aortic valve with severe stenosis, and parachute-like mitral valve observed in our patient has not previously been described. Although a causal relationship cannot be definitively established, this finding expands the known cardiovascular phenotype of CLS and suggests that careful cardiac evaluation may be warranted in affected patients, particularly during early infancy.

List of abbreviations

RPS6KA3: ribosomal protein S6 kinase A3

CLS: Coffin-Lowry syndrome

SVMR: supralvalvar mitral ring

PMV: parachute mitral valve

subAS: subaortic stenosis

CoA: coarctation of the aorta

CT: computed tomography

EF: ejection fraction

WHO: World Health Organization

SNP: single nucleotide polymorphism

IQ: intelligence quotient

Declarations

Ethics approval and consent to participate

We confirm that all methods were performed according to the Declaration of Helsinki.

Consent for publication

Written informed consent was obtained from the patient's parents for publication.

Availability of data and materials

Data is provided within the manuscript.

Competing interests

The authors declare that they have no competing interests.

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None.

Authors' contributions

SS and BB acquired the patient's clinical data and images. GG wrote the main manuscript and prepared tables and figures. SS and BB reviewed the manuscript. All authors edited and approved the final manuscript.

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Figure legends

Figure 1. Clinical photograph of the patient showing dysmorphic facial features (a), photograph of the patient's hand demonstrating the characteristic large, puffy appearance (b), CT demonstrating coarctation of the aorta (c, red arrow), echocardiographic images revealing a parachute mitral valve with submitral stenosis (d, e), two-dimensional image of a parachute mitral valve (f), stenosis of the parachute mitral valve (g) and severe aortic valve stenosis (h) with a bicuspid aortic valve (i).

