Cardiology in the Young

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Nicolaides–Baraitser syndrome in a patient with hypertrophic cardiomyopathy and *SMARCA2* gene deletion

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Brief Report

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Abstract

Nicolaides–Baraitser syndrome is a rare, neuro-developmental disorder caused by heterozygous pathogenic variants in the *SMARCA2* gene, involved with chromatin regulation. Cardinal features include intellectual disability, short stature, microcephaly, triangular facies, sparse hair, brachydactyly, prominent interphalangeal joints and seizures. Genetic testing demonstrated a loss within *SMARCA2* at 9p24.3 inclusive of basepairs 2094861_2141830 (hg19) in our patient. This case highlights a child with Nicolaides–Baraiter syndrome, a *SMARCA2* gene deletion and a novel association of hypertrophic obstructive cardiomyopathy.

Case presentation

A baby boy was born at full term, the product of non-consanguineous parents. A diagnosis of intrauterine growth restriction was made antenatally, and he weighed 2.3 kg at birth. He had an uncomplicated delivery with no respiratory distress and normal vital signs. However, he was noted to have significant feeding difficulties and a harsh grade 3/6 systolic murmur in the early neonatal period. Nasogastric tube feeding was initiated and an echocardiogram was carried out within the first week of life to investigate. This demonstrated situs solitus with normal cardiac connections and severe hypertrophic obstructive cardiomyopathy with asymmetric hypertrophy and dynamic intracavity obstruction. The pulmonary valve was mildly dysplastic with no significant gradient. Propranolol therapy was initiated at a dose of 1 mg/kg three times a

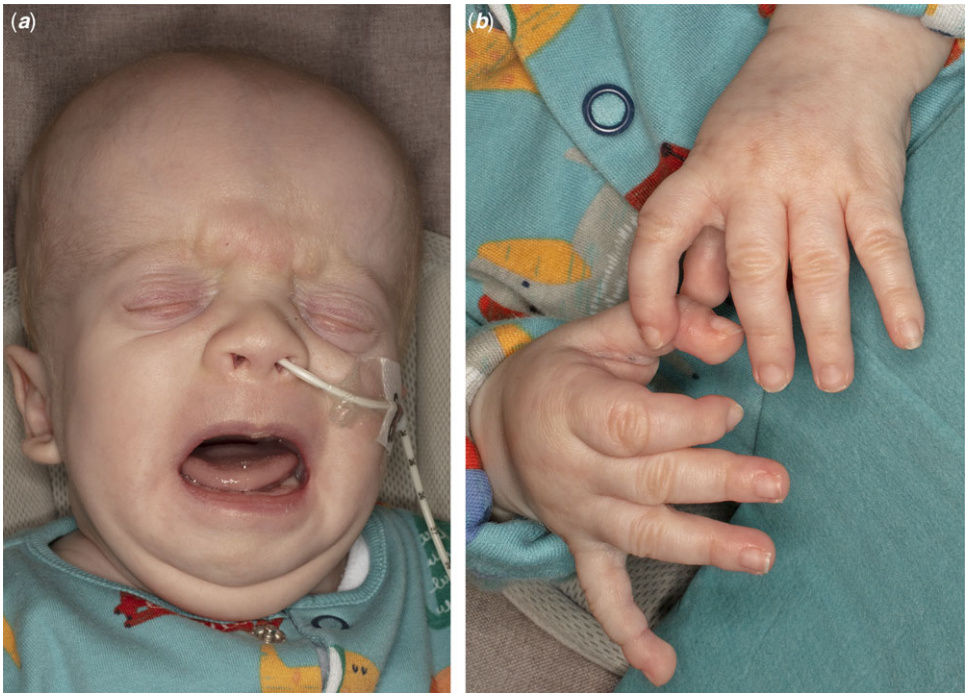

Figure 1. (***a***) Clinical photograph of child with Nicolaides–Baraitser syndrome, demonstrating coarse facial features with a triangular-shaped face, sparse hair and downward slanting palpebral fissures. (***b***)Characteristic hand features including brachydactyly and prominent interphalangeal joints.

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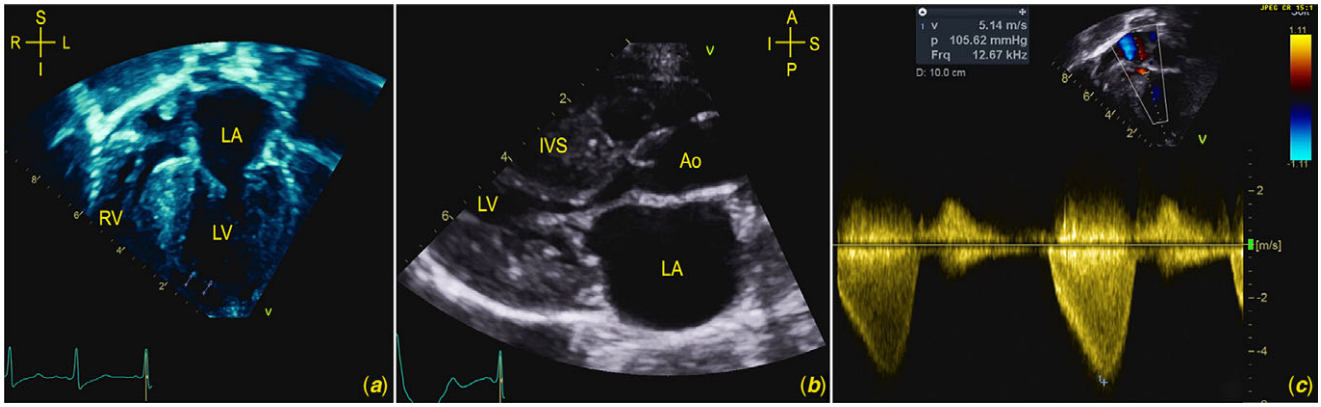

Figure 2. (***a***) Four chamber transthoracic echocardiogram demonstrating severe obstructive hypertrophic cardiomyopathy. (***b***) Parasternal long axis view showing severe asymmetric septal hypertrophy with left ventricular outflow tract obstruction. (***c***) Doppler velocity imaging demonstrating 105 mmHg gradient across the left ventricular outflow tract.

day. A follow-up echocardiogram at 3 weeks of age revealed a gradient of 90 mmHg across the left ventricular outflow tract.

Clinically, the patient was noted to have a number of dysmorphic features (Fig 1). He had a small chin with a triangular-shaped face, sparse hair and downward slanting palpebral fissures. There was no family history of cardiomyopathy, congenital heart disease or any inherited condition. Given the pattern of cardiac involvement, a Noonan syndrome genetic panel was carried out which was negative. Further genetic testing in the form of array comparative genomic hybridisation (60k Agilent Sureprint G3) demonstrated a loss within *SMARCA2* at 9p24.3 inclusive of basepairs 2094861_2141830 (hg19). Both parents tested negative for this variant. The characteristic phenotypical features in association with this gene deletion confirmed the diagnosis of Nicolaides–Baraitser syndrome. Our patient also had a metabolic work-up, an MRI brain and an abdominal ultrasound which were normal.

The patient remains under regular cardiology follow-up. He slowly gained weight with the introduction of fortified expressed breast milk and nasogastric tube top-up feeds. He continues on propranolol therapy. Echocardiogram at 6 months of age demonstrated an interventricular septal end diastolic measurement of 2.1 cm which correlates to a *Z* score of +24. The peak systolic gradient of left ventricular outflow tract obstruction measured 105 mmHg (Fig 2). There was evidence of systolic anterior motion of the mitral valve. A Holter monitor demonstrated normal sinus rhythm with less than 1% premature ventricular complexes. He is also under the care of ophthalmology as he had congenital glaucoma.

Discussion

The *SMARCA2* gene, also known as hBRM, is located on chromosome 9p24.3 and contains 38 exons. It encodes the core ATPase catalytic subunit of the main human BRM-associated factors complex which belongs to the SWI/SNF group of protein complexes.[1] These complexes regulate gene expression via chromatin remodelling. Chromatin is the complex of DNA and proteins used to package long strains of DNA into more complex structures. Chromatin remodelling is a way of regulating gene expression. Loosely packed DNA allows for higher levels of gene expression, whereas more tightly packed DNA reduces gene expression. SWI/SNF proteins achieve this by repositioning or removing nucleosomes. The SMARCA2 gene provides energy to the SWI/SNF complex for this process using ATP. SWI/SNF complexes regulate gene expression in many different processes including cell growth and division, and DNA repair and replication.

Table 1. Recognised cardiac findings in Nicolaides–Baraitser syndrome

Atrial septal defect
Pulmonary artery stenosis
Coarctation
Patient ductus arteriosus
Double aortic arch

Nicolaides–Baraitser syndrome was first described in 1993 but has only recently been well delineated.[2] At least 50 mutations in the *SMARCA2* gene have been identified and associated with Nicolaides–Barrister syndrome. Almost all of these mutations are a missense or loss of function single nucleotide variants in the *SMARCA2* gene. Interestingly, our patient was found to have the less frequently described deletion within the *SMARCA2* gene. All of the identified mutations occur in the region of the *SMARCA2* gene which encodes the ATP binding region. The resulting altered protein cannot bind to ATP and therefore cannot provide energy to the SWI/SNF complex for chromatin remodelling. Loss of function of the SWI/SNF complexes results in multi-systemic complications, since these complexes regulate gene expression in a large number of processes throughout the body.

Phenotypically, the main features of Nicolaides–Baraitser syndrome include typical triangular facies, sparse hair, microcephaly, severe intellectual disability, epilepsy, short stature, brachydactyly and prominent interphalangeal joints. Other abnormalities including ophthalmological, audiological and gastrointestinal have been identified. In a complete analysis of all confirmed cases (61) in 2014, 6 were found to have cardiac involvement. Atrial septal defects, patent ductus arteriosus, double aortic arch, mild pulmonary stenosis, mild self-resolving left ventricular hypertrophy, mild aortic coarctation and tracheal compression of the trachea by the brachiocephalic trunk were all described (Table 1).[3] However, to our knowledge, we report the first case of hypertrophic obstructive cardiomyopathy in a patient with confirmed Nicolaides–Baraitser syndrome.

This is the first report of hypertrophic cardiomyopathy occurring in the setting of Nicolaides–Baraitser syndrome. Although the hypertrophic cardiomyopathy gene panel was negative in this patient, one may postulate that loss of function of the *SMARCA2* gene may be associated with the development of hypertrophic

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cardiomyopathy in this patient. This report highlights the need to assess for cardiomyopathy in Nicolaides–Baraitser syndrome.

Conclusion

This is the first case to our knowledge which describes hypertrophic obstructive cardiomyopathy in association with Nicolaides–Baraitser Syndrome. As the phenotype of this rare disease is still being described, we hope this case will add to the current available knowledge in the literature.

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Conflicts of interest. None.

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