Cardiology in the Young

cambridge.org/cty

Shone's complex in a patient with chromosome 9q34.3 deletion (Kleefstra syndrome)

Utkarsh Kohli[1,2]

[1]Department of Pediatric Cardiology, Division of Pediatrics, St. John Hospital and Medical Center, Detroit, MI, USA and [2]Assistant Professor of Pediatrics, Division of Pediatric Cardiology, Department of Pediatrics, University of Chicago School of Medicine, Chicago, IL, USA

Brief Report

Cite this article: Kohli U. (2019) Shone's complex in a patient with chromosome 9q34.3 deletion (Kleefstra syndrome). *Cardiology in the Young* **29**: 249–251. doi: 10.1017/S104795111800210X

Received: 27 August 2018
Revised: 18 October 2018
Accepted: 5 November 2018
First published online: 26 December 2018

Key words:
Chromosome 9q34.3 deletion; Shone's complex; Kleefstra syndrome

Author for correspondence:
U. Kohli, MD, Assistant Professor of Pediatrics, Department of Pediatric Cardiology, Division of Pediatrics, University of Chicago, 5481S Maryland Avenue, RM-C104E, MC 4051, Chicago, IL 60637, USA. Tel: 773-702-6172; Fax: 773-702-2319; E-mail: ukohli@peds.bsd.uchicago.edu

Abstract

Kleefstra syndrome (chromosome 9q34.3 deletion) is a rare genetic disorder with less than 110 patients reported till date. We report a 4-month-old Caucasian girl with Kleefstra syndrome and Shone's complex, an association which has not been previously reported. Surgical planning for patients with Kleefstra syndrome and complex CHD can pose challenges due to an uncertain natural history and a risk of post-operative pulmonary hypertension.

Case report

A 4-month-old Caucasian girl was detected to have hypoplastic left ventricle, moderately enlarged right ventricle with mild right ventricular dysfunction, severely hypoplastic arch, and a conoventricular ventricular septal defect on a fetal echocardiogram performed at 24 weeks' gestation. She was closely followed *in utero* with frequent fetal echocardiograms and was delivered at 36 weeks' gestation. Notable findings on examination included intrauterine growth restriction, hypotonia, hypertelorism, and slight midfacial hypoplasia. Postnatal echocardiogram showed aortic arch hypoplasia with coarctation of aorta (Fig 1), parachute mitral valve with mitral stenosis where chordal insertion was predominantly into posteromedial papillary muscle, left ventricular outflow tract narrowing, and borderline left ventricle (Shone's complex) (Fig 2), a moderate-sized conoventricular ventricular septal defect which was partially filled in with aneurysmal tricuspid valve tissue and a moderate-sized atrial septal defect. She had a stormy neonatal course and required intubation and inotropic support in the setting of severe right ventricle dysfunction and low cardiac output. She, however, rapidly improved and underwent palliation with patent ductus arteriosus stenting and bilateral pulmonary artery bands on day 12 of life. The post-operative period was complicated by atrial arrhythmias which were controlled with digoxin and hypertension which eventually improved. Additional problems included feeding difficulty which gradually improved permitting her to be discharged after a month. Her other problems include bilateral hydronephrosis, oral food aversion requiring nasogastric feeding, and milk protein allergy.

A chromosomal microarray was sent after birth and revealed a large region (3.7 Mb) of loss of genomic material at 9q34.2q34.3 locus, which is associated with Kleefstra syndrome.

She is currently doing well and gaining weight. Her most recent echocardiogram shows a patent ductal stent, appropriately restrictive bilateral pulmonary artery bands, mild left ventricle dysfunction, and mild-to-moderate right ventricle dysfunction. Given the current echocardiographic findings and uncertain long-term prognosis, she is not deemed to be a suitable candidate for single-ventricle palliation or heart transplant. A decision regarding offering the family biventricular repair will be taken soon after discussion with the surgical team.

Discussion

Kleefstra syndrome, also known as chromosome 9q chromosome subtelomeric deletion syndrome (STDS), is a rare genetic syndrome which is characterised by a loss of genetic material on the long arm of chromosome 9 (9q34.3). Less than 110 cases of Kleefstra syndrome have been reported till date.[1] This syndrome is characterised by severe developmental delay, learning disability, hypotonia, microcephaly, seizures, and CHD. The first patient with this syndrome was reported in 1994 by Shimmenti *et al.*[2] This male infant had characteristic facial and skeletal features and supraventricular tachycardia because of a concealed accessory pathway. Since then, several cases have been reported and the associated cardiac abnormalities include ventricular septal defects, atrial septal defects, tetralogy of Fallot, pulmonary hypertension, hypoplastic

CAMBRIDGE UNIVERSITY PRESS

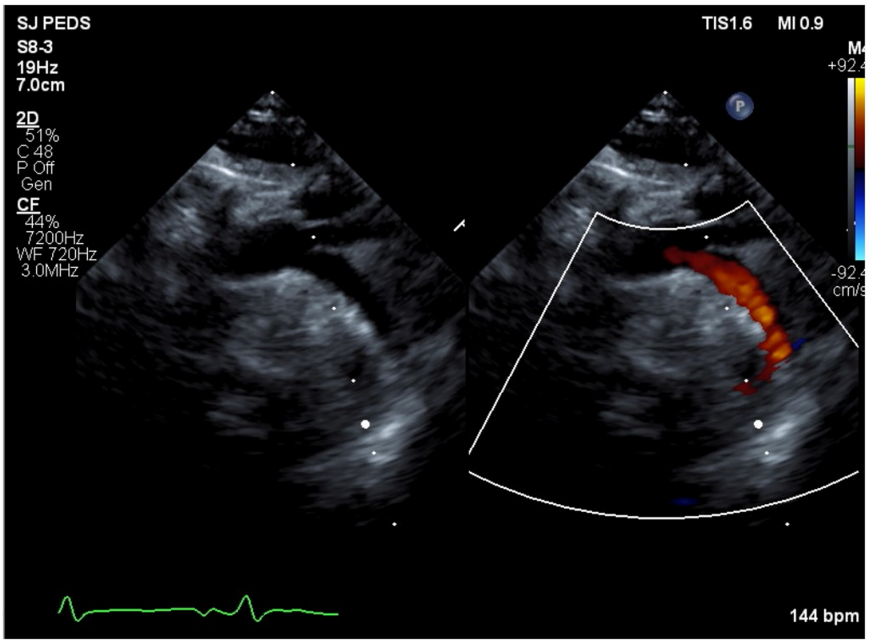

Figure 1. Hypoplastic aortic arch with retrograde flow in diastole is seen in suprasternal sagittal view.

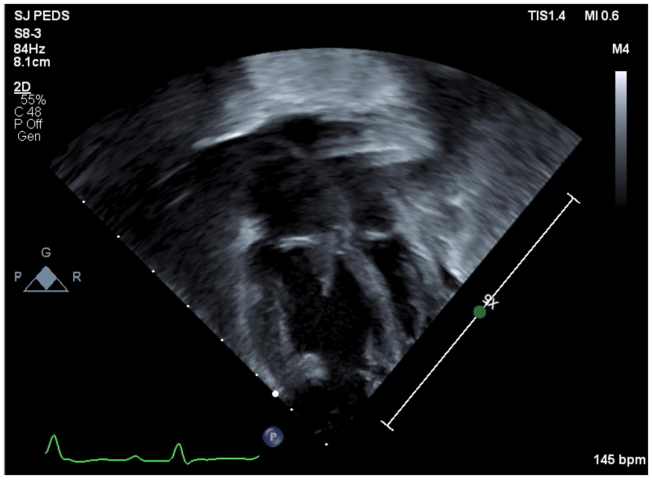

Figure 2. Hypoplastic left ventricle, which is almost apex forming, is noted in apical four-chamber view. The right ventricle appears moderately dilated and moderately hypertrophied. The mitral valve appears moderately hypoplastic.

pulmonary arteries, coarctation of aorta, hypoplastic left heart syndrome, and double-outlet right ventricle.[1,3–10] Association of this syndrome with Shone's complex, as seen in our patient, has not been reported. Cardiac abnormalities are noted in approximately 41–50% of affected individuals.[1,11,12]

Kleefstra syndrome is caused by haplo-insufficiency of euchromatic histone methyltransferase-1 gene (*EHMT1*), a gene whose protein product (Eu-HMTase1) is a histone H3 Lys 9 (H3-K9) methyltransferase. H3-K9 histone methylation is restricted to the euchromatin of mammals and functions to silence individual genes. Deletion size does not correlate with the severity of the 9q STDS since patients with mutations in *EHMT1* are as severely affected as those with sub-microscopic deletions.[11] A majority (85%) of cases of Kleefstra syndrome are accounted for by microdeletions.[9]

Surgical management of patients with Kleefstra syndrome and complex CHD poses a challenge as insufficient information is available about the natural history of this syndrome. However, a 43-year-old woman has been reported with this syndrome,[13] suggesting that a select group of patients with this syndrome and complex CHD could be candidates for complex procedures such as univentricular repair and cardiac transplantation. An additional problem that has been reported in these patients after complete repair of cardiac defects is persistent pulmonary hypertension which carries a poor long-term prognosis.[9] Surgical planning in our patient is further complicated by the presence of biventricular dysfunction. The Pediatric Advanced Care Team was consulted soon after birth and continues to be involved in the care of our patient.

To conclude, Kleefstra syndrome is a rare genetic disorder which is often associated with CHD. To the best of our knowledge, association of this syndrome with Shone's complex has not been reported. However, there is a single report of association with hypoplastic left heart syndrome, which includes some of the abnormalities seen in Shone's complex. Surgical planning in these patients, those with complex CHD, can be quite difficult due an uncertain long-term prognosis and a risk of post-operative pulmonary hypertension.

Acknowledgements. None.

Financial Support. This research received no specific grant from any funding agency, or from commercial or not-for-profit sectors.

Conflicts of Interest. None.

Ethical Standards. Informed consent was obtained from all individual participants included in the report. This report does not include any human or animal experimentation.

References

1. Campbell CL, Collins RTII, Zarate YA. Severe neonatal presentation of Kleefstra syndrome in a patient with hypoplastic left heart syndrome and 9q34.3 microdeletion. Birth Defects Res A Clin Mol Teratol 2014; 100: 985–990.

https://doi.org/10.1017/S104795111800210X Published online by Cambridge University Press

2. Schimmenti LA, Berry SA, Tuchman M, Hirsch B. Infant with multiple congenital anomalies and deletion (9) (q34.3). Am J Med Genet 1994; 51: 140–142.
3. Ayyash H, Mueller R, Maltby E, Horsfield P, Telford N, Tyler P. A report of a child with a deletion (9)(q34.3): a recognisable phenotype? J Med Genet 1997; 34: 610–612.
4. Neas KR, Smith JM, Chia N, et al. Three patients with terminal deletions within the subtelomeric region of chromosome 9q. Am J Med Genet A 2005; 132A: 425–430.
5. Cormier-Daire V, Molinari F, Rio M, et al. Cryptic terminal deletion of chromosome 9q34: A novel cause of syndromic obesity in childhood? J Med Genet 2003; 40: 300–303.
6. Iwakoshi M, Okamoto N, Harada N, et al. 9q34.3 deletion syndrome in three unrelated children. Am J Med Genet A 2004; 126A: 278–283.
7. Penacho V, Galán F, Martín-Bayón TA, et al. Prenatal diagnosis of a female fetus with ring chromosome 9, 46,XX,r(9)(p24q34), and a de novo interstitial 9p deletion. Cytogenet Genome Res 2014; 144: 275–279.
8. Guterman S, Hervé B, Rivière J, Fauvert D, Clement P, Vialard F. First prenatal diagnosis of a 'pure' 9q34.3 deletion (Kleefstra syndrome): a case report and literature review. J Obstet Gynaecol Res 2018; 44: 570–575.
9. Okur V, Nees S, Chung WK, Krishnan U. Pulmonary hypertension in patients with 9q34.3 microdeletion-associated Kleefstra syndrome. Am J Med Genet A 2018: https://doi.org/10.1002/ajmg.a.38852.
10. Noruzinia M, Ahmadvand M, Bashti O, Salehi Chaleshtori AR. Kleefstra syndrome: the first case report from Iran. Acta Med Iran 2017; 55: 650–654.
11. Stewart DR, Kleefstra T. The chromosome 9q subtelomere deletion syndrome. Am J Med Genet C Semin Med Genet 2007; 145: 383–392.
12. Willemsen MH, Vulto-van Silfhout AT, Nillesen WM, et al. Update on Kleefstra syndrome. Mol Syndromol 2012; 2: 202–212.
13. Verhoeven VM, Egger JI, Vermeulen K, van de Warrenburg BP, Kleefstra T. Kleefstra syndrome in three adult patients: further delineation of the behavioral and neurological phenotype shows aspects of a neurodegenerative course. Am J Med Genet A 2011; 155A: 2409–2415.

https://doi.org/10.1017/S104795111800210X Published online by Cambridge University Press