Coronary arteriopathy in a patient with Noonan phenotype: Case report

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ABSTRACT

Noonan syndrome (NS) is a pleomorphic genetic disorder. Up to 50-80% of individuals have associated congenital heart disease. The scope of cardiac disease in NS is quite variable depending on the gene mutation. The most common forms of cardiac defects include pulmonary stenosis, hypertrophic cardiomyopathy (HCM), atrial septal defect and left-sided lesions. Amongst the rare vascular abnormalities few case reports have been mentioned about coronary artery lesions apart from sinus of Valsalva aneurysm, aortic dissection, intracranial aneurysm. This is a case report a rare case of asymptomatic coronary artery aneurysm in a young male with NS. There is lack of unified protocol for the screening, diagnosis, treatment, and follow-up of coronary artery disease in patients with NS. We conclude, echocardiography is sufficient in most cases in children. But a CT scan is appropriate in adults or when other lesions are suspected.

Keywords: Coronary arteriopathy, Noonan phenotype, Noonan syndrome, RASopathy

INTRODUCTION

A subset of RASopathy, Noonan syndrome (NS), is a pleomorphic genetic disorder with up to 50%–80% of individuals estimated to have congenital heart disease.[1] Although sporadic, NS can be familial. Several gene mutations cause the disease, and the PTPN11 gene is involved in about half of the cases. These mutations alter the RAS-mitogen-activated protein kinase (MAPK) cell signaling pathway, which is involved in cell proliferation, migration, and differentiation.[2]

The scope of cardiac disease in NS is quite variable depending on the gene mutation. The most common forms of cardiac disease include pulmonary stenosis, hypertrophic cardiomyopathy (HCM), atrial septal defect, and left-sided lesions. Vascular abnormalities include sinus of Valsalva aneurysm, aortic dissection, intracranial aneurysm, and rarely, coronary artery lesions.[3-7] However, the prevalence, management, and prognosis of these lesions have not been reported.

To our knowledge, this is the first case report from India of an adult NS with a coronary artery aneurysm.

CASE REPORT

A 27-year-old male visited a general physician for generalized fatigue. On clinical examination – he was found to have short stature, broad chest, wide-spaced nipple, pectus excavatum, ptosis, webbed neck, and cryptorchidism. With the abovementioned dysmorphism, he was suspected to be a Noonan phenotype [Figure 1] and sent to our institute for cardiac evaluation.

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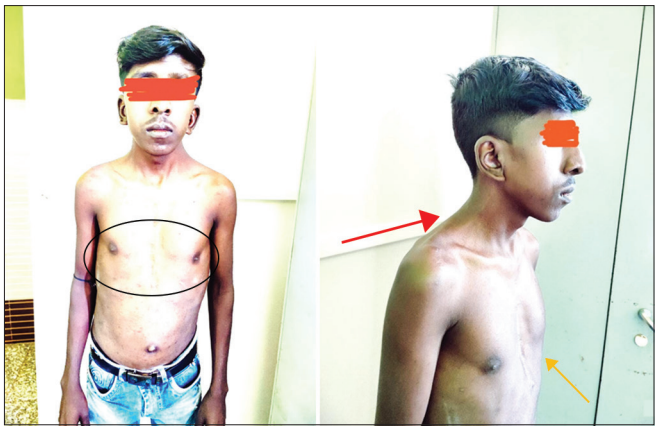

Figure 1: Facial dysmorphism, short stature, broad chest, wide-spaced nipple (black arrow), pectus excavatum (orange arrow), webbed neck (red arrow)

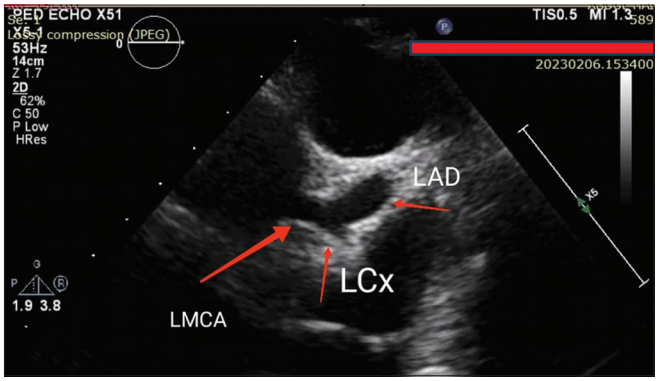

Figure 3: Significantly dilated left coronary artery system. LMCA: Left main coronary artery, LAD: Left anterior descending, LCx: Left circumflex

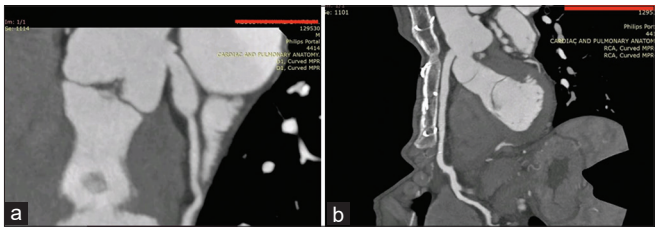

Figure 5: Computed tomography – Coronary angiography showing aneurysmal left (a) and right-sided coronary arterial system (b)

He did not reveal any significant past history of medical, surgical, or specific cardiac symptoms. His vitals were within normal limits. On cardiovascular system examination, S1 and S2 were normal. There was a Grade III/VI ejection systolic murmur in the pulmonary area. His electrocardiogram revealed a heart rate of 75 beats/min, sinus rhythm, northwest axis deviation, and poor R wave progression in the left precordial leads [Figure 2].

A two-dimensional echocardiography revealed moderate pulmonary valvular stenosis with a peak and mean gradient of 48 mmHg and 22 mmHg, respectively. There

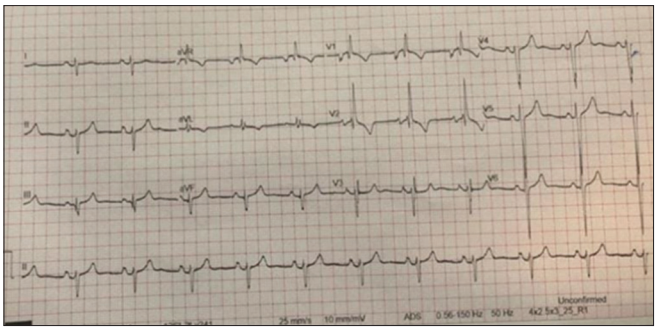

Figure 2: Electrocardiogram – Northwest axis deviation, poor R wave progression in left precordial leads

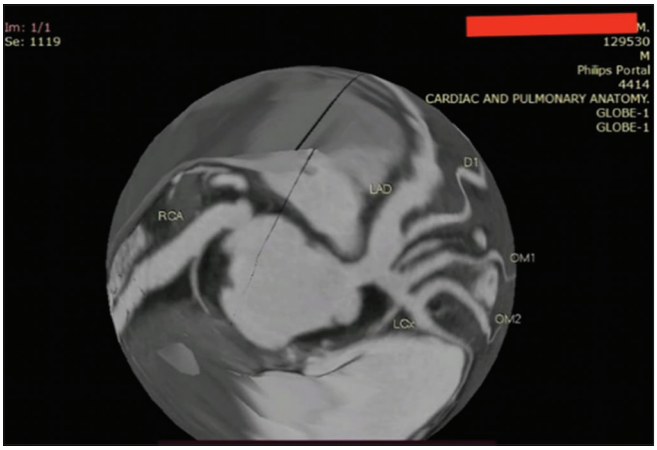

Figure 4: Computed tomography coronary angiography – Spider view showing dilated left anterior descending and right coronary artery. LAD: Left anterior descending, LCx: Left circumflex, RCA: Right coronary artery

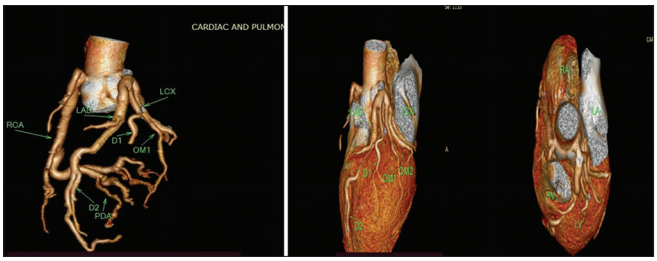

Figure 6: Three-dimensional multiplanar reconstruction reconstruction showing dilated coronary arterial system. LAD: Left anterior descending, LCx: Left circumflex, RCA: Right coronary artery, PDA: Posterior descending artery, RV: Right ventricular, LV: Left ventricular, RA: Right atrial, LA: Left atrial

was a significantly dilated left coronary artery system with a left main coronary artery – 6.6 mm (+6.82 Z), left anterior descending artery 8.3 mm (+14.12 Z), and left circumflex artery – 4.6 mm. The right coronary system was not well visualized [Figure 3]. Interatrial septum and interventricular septum were intact. The left ventricular outflow tract was unobstructed. There was no ventricular hypertrophy. The biventricular function was normal.

Computed tomography (CT) coronary angiography was planned for better delineation of coronary anatomy. It

revealed aneurysmal dilatation with a beaded appearance of bilateral coronary arteries in their proximal course [Figures 4-6]. And valvar pulmonary stenosis with poststenotic dilatation of the pulmonary artery.

In view of the lack of standardized treatment, this patient was managed on the lines of management of coronary artery aneurysm in Kawasaki disease (KD). The patient was started on anti-platelet therapy with aspirin and anti-coagulation therapy with warfarin with sequential international normalized ratio (INR) monitoring (Target INR – 2–2.5).

DISCUSSION

Coronary artery involvement is infrequent among NS patients. Among the literature available, so far, around 15 cases of coronary aneurysm/ectasia have been reported, mainly in adults.[8-12] There is a lack of unified protocol for the screening, diagnosis, treatment, and follow-up of coronary artery disease in patients with NS.

Pathophysiology of coronary arteriopathy

The cause of coronary involvement in NS remains unclear. The PTPN11 gene encodes Src homology protein-tyrosine phosphatase 2 domain-containing phosphatase 2 (SHP2), which positively regulates RAS-MAPK signaling and regulates cell fate determination.[2] It was speculated that the PTPN11 mutations cause the excess activity of SHP2, resulting in the vulnerability of arterial walls.[13] Unknown inflammatory triggers may result in the expansion of the coronary artery because of its vulnerability.

HCM may contribute to the formation of a coronary artery aneurysm. Parietal stress generated by cardiac muscle on the arterial wall can reduce the systolic flow, with the weakening of the arterial wall.

Screening for coronary arteriopathy

Patients with coronary arteriopathies are often asymptomatic. In addition, it is difficult to detect these by transthoracic echocardiography; indeed, it is mainly the proximal part of the coronary artery that can be explored in adults.[14] Although there are three case reports of coronary involvement in the pediatric population of NS (one of whom was only 3 years old), these coronary involvements are more often diagnosed in adolescence or adulthood.[9] In children, echocardiography is usually sufficient. However, a CT scan is appropriate in adults or when other lesions are suspected. Similarly, when pulmonary valvar stenosis needs dilatation, coronary angiography could be performed at the same time.

Medical and surgical management

Medical management is not consensual. Treatment may be like the treatment of coronary aneurysm seen in KD. Whether or not and how long antiplatelet and/or anticoagulant therapies should be prescribed are questions under consideration, especially when coronary artery aneurysms are found incidentally.

Serum elevation of P-selectin, beta thromboglobulin, and platelet factor 4 has been shown in patients with isolated coronary ectasia, suggesting an increase in platelet activation.[15] Other authors recommend the use of preventive anticoagulation with Vitamin K antagonists to reduce the risk of coronary thrombosis. However, no prospective study has been conducted on these therapeutics for the prevention of thrombosis in aneurysmal coronary arteries.[16]

Among case reports described in medical literature, a few patients were treated with a coronary artery bypass graft but always associated with another heart defect repair.[5-7,17]

Prognosis and complications

In rare cases, artery dilation can lead to dissection, rupture, thrombosis, distal embolization, pericardial tamponade, or fistula formation. The prevalence of these complications is still unknown, and there is no recommended follow-up to detect them. Regardless of coronary abnormalities, the presence of an associated congenital heart lesion should, however, be managed because it may have an impact on quality of life.[18]

CONCLUSIONS

Coronary arteriopathy causing coronary aneurysm/ectasia is a rare manifestation in adult patients with NS, and there is a lack of standardized screening and management protocol for such patients. Further, prospective studies in children, adolescents, and adults are needed to understand the long-term prognosis better and improve the management and outcome of these patients.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Linglart L, Gelb BD. Congenital heart defects in Noonan syndrome: Diagnosis, management, and treatment. Am J Med Genet C Semin Med Genet 2020;184:73-80.
2. Tartaglia M, Gelb BD. Noonan syndrome and related disorders: Genetics and pathogenesis. Annu Rev Genomics Hum Genet 2005;6:45-68.
3. Calcagni G, Baban A, De Luca E, Leonardi B, Pongiglione G, Digilio MC. Coronary artery ectasia in Noonan syndrome: Report of an individual with SOS1 mutation and literature review. Am J Med Genet A 2016;170:665-9.
4. Delhaas T, Mühler EG. Proximal left coronary artery occlusion in a 15-year-old boy with Noonan syndrome and hypertrophic cardiomyopathy. Pediatr Cardiol 2003;24:67-9.
5. Fujimoto N, Nakajima H, Sugiura E, Dohi K, Kanemitsu S, Yamada N, *et al.* Bilateral giant coronary aneurysms in a 40-year-old male with Noonan syndrome caused by a KRAS germline mutation. Int J Cardiol 2014;173:e63-6.
6. Gulati GS, Gupta A, Juneja R, Saxena A. Ectatic coronary arteries in Noonan syndrome. Tex Heart Inst J 2011;38:318-9.
7. Hakim FA, Gruden JF, Panse PM, Alegria JR. Coronary artery ectasia in an adult Noonan syndrome detected on coronary CT angiography. Heart Lung Circ 2013;22:1051-3.
8. Loukas M, Dabrowski M, Kantoch M, Ruzyłło W, Waltenberger J, Giannikopoulos P. A case report of Noonan's syndrome with pulmonary valvar stenosis and coronary aneurysms. Med Sci Monit 2004;10:S80-3.
9. Mauro DM, Flors L, Hoyer AW, Norton PT, Hagspiel KD. Development of bilateral coronary artery aneurysms in a child with Noonan syndrome. Pediatr Radiol 2016;46:422-5.
10. Nomura Y, Yanagi S, Kono Y, Kamimura J, Nishi J, Yoshinaga M, *et al.* Bilateral coronary artery dilatation in a child with Noonan syndrome. Jpn Circ J 2000;64:481-3.
11. Ogihara Y, Fujimoto N, Ohashi H, Yamamoto N, Ito H, Mitani Y, *et al.* Case of Noonan syndrome with an expanding coronary arterial aneurysm. Circ Cardiovasc Imaging 2019;12:e009429.
12. Ramaiah AK, Das JK, Shetty KR. Ectatic coronary arteries in a patient with Noonan syndrome on transoesophageal echocardiography. Ann Card Anaesth 2014;17:139-40.
13. Tartaglia M, Mehler EL, Goldberg R, Zampino G, Brunner HG, Kremer H, *et al.* Mutations in PTPN11, encoding the protein tyrosine phosphatase SHP-2, cause Noonan syndrome. Nat Genet 2001;29:465-8.
14. Krzanowski M, Bodzoń W, Dimitrow PP. Imaging of all three coronary arteries by transthoracic echocardiography. An illustrated guide. Cardiovasc Ultrasound 2003;1:16.
15. Yasar AS, Erbay AR, Ayaz S, Turhan H, Metin F, Ilkay E, *et al.* Increased platelet activity in patients with isolated coronary artery ectasia. Coron Artery Dis 2007;18:451-4.
16. Devabhaktuni S, Mercedes A, Diep J, Ahsan C. Coronary artery ectasia – A review of current literature. Curr Cardiol Rev 2016;12:318-23.
17. Ringle A, Rousse N, Toledano M, Lemahieu JM, Domanski O, Godart F, *et al.* Surgical management of giant coronary aneurysms in Noonan syndrome. Int J Cardiol 2016;221:107-9.
18. Karsenty C, Maury P, Blot Souletie N, Ladouceur M, Leobon B, Senac V, *et al.* The medical history of adults with complex congenital heart disease affects their social development and professional activity. Arch Cardiovasc Dis 2015;108:589-97.