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Brief Report

Bilateral multiple pulmonary arteriovenous fistulas and duplicated renal collecting system in a child with Noonan's syndrome

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Abstract Noonan's syndrome involves the association of multiple congenital abnormalities, with a variety of cardiac defects. We describe here the association of Noonan's syndrome with multiple pulmonary arteriovenous fistulas and bilateral duplicated renal collecting systems. To the best of our knowledge, this is the first reported case of an association of the Noonan phenotype with pulmonary arteriovenous fistulas.

Keywords: Arteriovenous malformation; renal anomaly; Noonan phenotype

Noonan's syndrome is relatively common, being inherited genetically as an autosomal dominant disorder with variable penetrance. It is defined by a characteristic phenotype, comprising congenital cardiac malformations, ocular defects, and mild mental retardation.[1] We describe here a 14-year-old boy with multiple characteristics of the Noonan phenotype, but also with multiple pulmonary arteriovenous fistulas, and bilateral duplicated renal collecting systems. As far as we are aware, this combination has not previously been reported.

Case report

A 14-year-old male patient was referred to our department for the evaluation of moderately reduced exercise tolerance and cyanosis. His family history was unremarkable. Physical examination revealed bilateral simian creases, hypertelorism, epicanthal folds, low-set malrotated ears with skin tags, a webbed neck, a low posterior hairline, and pectus carinatum, all of these being consistent with the clinical diagnosis of Noonan's syndrome. Operation scars for undescendent testicle and left sided inguinal hernia were also observed. The patient was 133.3 centimetres tall, less than the 5th centile, and weighed 29 kilograms, again less than the 5th centile. On cardiovascular examination, cyanosis and clubbing of the fingers, together with normal auscultatory findings, were present. Saturation of oxygen, measured with the pulse oxymeter, was 87%. Complete blood count showed polycythaemia. Hepatic and renal function tests were within the normal range, as were the electrocardiogram and the chest radiograph. No pathological findings were observed by transthoracic echocardiographic examination. To account for the cyanosis, we performed contrast echocardiography, injecting agitated saline solution in a peripheral vein. The bubbles were detected in the left atrium, showing a right-to-left shunt through the lungs. These findings raised the possibility of pulmonary arteriovenous fistulas. A chest computerized tomography was performed, but revealed no pathological finding. Still believing that pulmonary arteriovenous fistulas might be present, we proceeded to cardiac catheterization to elucidate the diagnosis. The pulmonary angiogram demonstrated a vascular network, with multiple fistulas in both lungs (Fig. 1). The angiographic study also showed a bilateral duplicated collecting system during the urographic phase (Fig. 2). Abdominal ultrasonography failed to reveal any other

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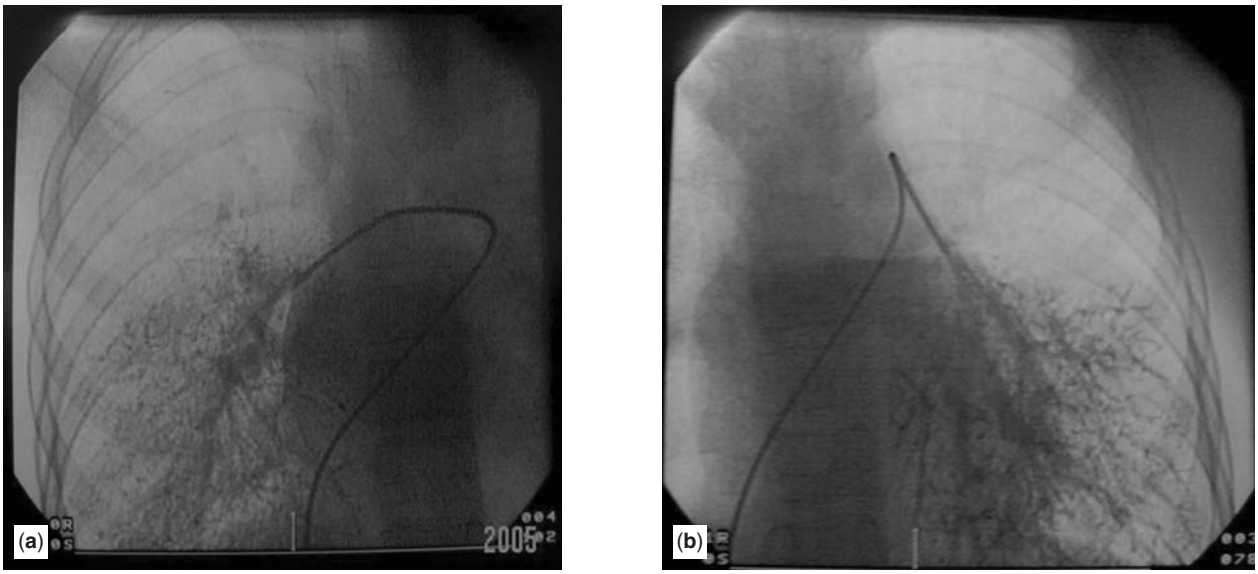

Figure 1.
*Anteroposterior view of selective pulmonary angiograms, showing bilateral multiple pulmonary arteriovenous fistulas after (**a**) right and (**b**) left pulmonary arteriography.*

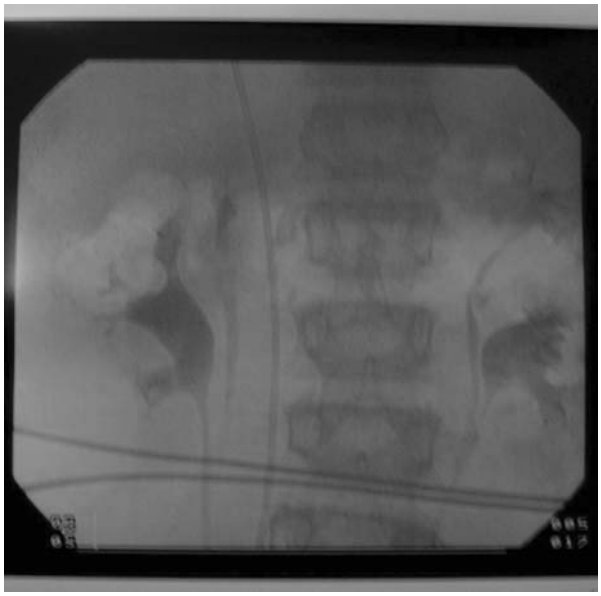

Figure 2.
Anteroposterior view of the urographic phase, showing bilateral duplicated renal collecting systems.

pathology except the presence of bilateral duplication of the renal collecting system. Interventional embolisation was not performed, nor surgery, because of the diffuse nature of the lesions.

Discussion

Pulmonary arteriovenous fistulas are characterized by right-to-left shunts of variable magnitude, the effect of these communications depending on the size of the vessels involved. If the anastomoses affect peripheral arterioles and venules, a small telangiectasia will result, and it usually remains small, not causing haemodynamic alterations in the pulmonary circulation. If larger veins and arteries are affected, or if massive involvement of the pulmonary capillaries takes place, an increase in the size of the vessels may occur,[2] resulting in severe haemodynamic alterations. Arterial desaturation of oxygen, cyanosis, clubbing of the fingers, and polycythemia may occur, secondary to the intrapulmonary shunt.[3]

The pulmonary arteriovenous fistulas may be congenital or acquired. The congenital form is usually associated with hereditary haemorrhagic telangiectasia,[3] or Rendu-Osler-Weber syndrome. Some studies, together with the scientific division of the Hereditary Hemorrhagic Telangiectasia Foundation International, Inc., reached a clinical consensus on the diagnostic criterions for this disease, stating that 4 criterions should be sought, namely epistaxis, telangiectasias, visceral lesions, and a compatible familial history. The diagnosis of Rendu-Osler-Weber disease is established if 3 of the above criterions are present. If less than 2 criterions are present, the diagnosis of the disease is very unlikely, even though children of parents affected should be considered at risk due to the fact that the penetrance varies with age. The clinical investigation of our patient showed only one of the cited criterions, which was pulmonary telangiectasia, making the diagnosis of Rendu-Osler-Weber syndrome unlikely. Acquired pulmonary arteriovenous fistulas have been reported in association either with severe hepatic disease,[4] or with cavopulmonary

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anastomotic procedures, such as the Glenn operation.[5] Besides these, few cases of pulmonary arteriovenous fistulas secondary to patency of the venous duct have been reported.[6]

Laboratory examination of our patient did not show any hepatic dysfunction. To investigate the presence of patency of the venous duct, we performed an abdominal ultrasonogram, but found no evidence suggesting portosystemic shunting. Transthoracic echocardiography was also within normal limit. When we put all these things together, we ask whether the pulmonary arteriovenous fistulas are a manifestation of Noonan's syndrome, or are their presence in our patient a mere coincidence? Although various vascular abnormalities[7] have been reported in Noonan's syndrome, pulmonary arteriovenous fistulas presenting with cyanosis and dyspnoea during exertion, to the best of our knowledge, have not thus far been described.

The cardinal features of Noonan's syndrome are unusual facies, congenital cardiac disease,[8] short stature, and chest deformity. The syndrome occurs in either a sporadic or autosomal dominant fashion. Recently, using new information provided by the human genome project, the gene on chromosome 12, called PTPN11, regulating the product of a protein named SHP-2, was identified. SHP-2 is a protein essential in several intracellular single transduction pathways that control a number of developmental processes. This suggests that PTPN11 is involved in the control of cell growth, differentiation, migration, and apoptosis.[1,9] Thus, a kind of connective tissue defect due to PTPN11 mutations could explain the wide range of clinical features observed in Noonan's syndrome, including vascular abnormalities such as arteriovenous fistulas.

In Noonan's syndrome, anomalies of the genitourinary system are known to occur, but are not clinically significant. Interestingly, besides pulmonary arteriovenous fistulas, our patient also had bilateral duplicated renal collecting systems, which have been reported in a few previous cases with Noonan's syndrome.[10]

Conclusion

Taken together, therefore, we suggest that the findings support the hypothesis that a vasculitic process has been superimposed on the connective tissue defect associated with Noonan's syndrome. Furthermore, since the pathogenesis of the condition remains unclear, our experience stresses the need to look carefully for abnormalities co-expressed in Noonan's syndrome.

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