To the Editor: Noonan syndrome (NS) is a common genetic multisystem disorder caused by aberrant signal flux through mitogen-activated protein kinase (Ras-MAPK) and has an estimated prevalence of 1 in 1000–2500. [1] It was characterized by Jacqueline Noonan, who reported nine patients with pulmonary valve stenosis, small stature, hypertelorism, mild intellectual disability, webbed neck, undescended testes, and skeletal malformations. [2] The lymphatic disorders are rare, it can happen at any age but most instances happen at birth, which are known to be particularly associated with NS, though it has not been well characterized to date. Gene mutations identified in individuals with the NS, regulate impertinently the Ras/MAPK signal transduction pathway and they can currently explain 70% of the NS cases. Therefore, it is very important for genetic counseling and life management. [2]

Here, we reported a rare Noonan syndrome 9 patient in Asian with significant, persistent and progressive bilateral lower limb dysplasia.

A 9-year-old girl from a non-consanguineous Chinese parents was diagnosed clinically with Noonan syndrome at the Beijing Children’s Hospital in 2016. She was admitted because of chronic bilateral lower limbs lymphedema and shortness for 6 years. Six years ago, she was found to be suffering from left lower limb lymphedema without obvious cause, accompanied by local skin pyrexia, redness, and blisters. At the same time, parents found her shorter than other same age girls, but did not pay much attention because of her atrial septal defect (ASD) and a ventricular septal defect (VSD) after birth. Eight months later, her right lower limb developed edema, and gradually spread to the vulva. Then she was taken to my hospital for further treatment. She had a heart operation when she was 1 year old. Physical examinations showed her height of 115 cm, the weight of 21 kg, below the third percentile. She had hyperpigmentation of the whole body, curly hair, low posterior hairline, prominent forehead, hypertelorism with down-slanting palpebral fissures, low-set posteriorly rotated ears with a thickened helix, bilateral ptosis, protruding eyes, thick lips, and broad and webbed neck. Her thorax was broad with wide-spaced nipples, reaching to 14.5 cm. Non-pitting edema of the bilateral lower limb, with more severe signs below the knees, coarse skin, dark, scattered blue subcutaneously. Edema and pigmentation of major labia were also seen and lack of any pubic hair (Figure 1).

During the hospital stay, chromosomes were normal (46, XX) and sex-determining region of Y chromosome (SRY) was negative. No abnormalities were seen in the ultrasound examination of lower limb vein. However, bilateral lower limbs lymphatic imaging showed primary lymphatic dysplasia and bilateral lower limbs were lymphoma and the left venous angle was not visible. The girl had mild mental retardation present with poor school grades.

The patient was diagnosed with Noonan Syndrome and for further precision classification, we sent her sample to Genetic and Metabolic Central Laboratory, Guangxi Maternal and Child Health Hospital. We got the reported pathogenic heterozygous c.800T>A (p.M267K) of Rho guanine nucleotide exchange factor 2 (SOS2) in this patient. It is a reported mutation, [3] getting characterized as Noonan type 9.
After diagnosis, symptomatic treatments and nutritional support were initiated for the patient and she was advised to have more rest, wear an elastic bandage, and do more rehabilitation training for her different symptoms. Growth hormone therapy was not suggested after getting the SOS2 mutation report.

Noonan syndrome can be sporadic or familial. *De novo* mutations are more common, found in about 60% of the cases.[2] The characteristics of the facial and skeletal muscle system are important factors in the accurate diagnosis of Noonan syndrome. So far, the NS patients reported in mainland China were only a description of the clinical phenotype, no genotyping and not found very remarkable when compared to existing literature. We did not find any report on lymphoedema. Lymphedema secondary disorder of lymph vessel formation is reported in less than 20% of Noonan syndrome patients. Some of the characteristics of this condition include - webbed neck, low-set ears, low hairline and ptosis may be related to in-utero edema.[4]

We reported the 9-year-old Noonan syndrome girl here who matched the specific appearance, her bilateral lower limbs edema and vulva lymphedema. This situation appeared in the first decade, which is a rare case and is reported only in two cases of one family by an American doctor Miller,[5] a 27-year-old man and his mother. He first noted edema of both legs below his knees at age of 16 years. Evaluation at that time showed chronic edema of the legs, bilateral pes cavus. His mother had a history of chronic leg edema since the age of 7 years. Her leg edema is not painful and does not interfere with her ambulation. No other case has been reported till now. Our case is the second recorded report of this complexity.

To date, 13 genes have been identified that relate to Noonan syndrome in the same pathway and genetic mutations are identifiable in more than 70% of the patient.[6] Noonan syndrome 1–10 named base on the gene. Over half of Noonan syndrome cases are caused by gene defects in protein tyrosine phosphatase, non-receptor type 11 (*PTPN11*). SOS1 mutations account for about 13% of the cases, KRAS

Figure 1: Characteristic facial features of the patient with Noonan syndrome. (A and B) The proband’s webbed neck, low posterior hairline, bilateral ptosis, curly hair, low set ears, prominent forehead, convex and bloodshot eyes and thick lips. (C) The patient bilateral lower limb lymphedema accompanied by local pyrexia, redness, and blisters. (D) Vulva edema.
proto-oncogene (KRAS) accounts for under 5%, and other genes (NRAS, BRAF, MAP2K1, RRAS, RASA2, A2ML1, SOS2, LZTR1) reported mutations in under 1% cases (http://www.hgmd.cf.ac.uk/docs/login.html).

Yamamoto et al.[3] first reported five patients from 3 unrelated families with SOS2 mutation caused Noonan syndrome-9. To date, the identified variants, p.M267K, M267R, T376S and T264K were located in the Dbl homology (DH) domain of SOS2, where the SOS1 mutations that were also identified, suggesting that these mutations could be pathogenic.[7] In this study, a reported pathogenic heterozygous SOS2 gene c.800T<A (p.M267K) was identified, confirmed as Noonan syndrome-9[3] and it is a rare case reported in Asians.

Approximately, 50% to 70% of individuals with NS have short stature.[5] Birth weight and body length are typically normal, but there is a subsequent deceleration of height and weight to the third centile or less. The mean delay of bone age is less than 2 years. In a small subgroup of patients with NS, tumor risk is increased and is associated with specific mutations of Ras-MAPK pathway genes. Similar to tumourigenesis, all genes responsible for RASopathies (developmental syndromes of Ras/MAPK pathway dysregulation) that have been described so far, cause dysregulation of the Ras/MAPK pathway by increasing extracellular signal-regulated kinase (ERK) signaling, either by gain-of-function mutations in RAS genes and RAS-GEFs, such as PTPN11 and SOS1, or by loss-of-function mutations in GTPase activating proteins, such as NF1.[10] SOS1 and SOS2 are homologous, so NS with variants in SOS2 might lead to tumourigenesis. However, according to a recent study,[6] which included 13 prepubertal NS children who received long-term recombinant human growth hormone (rhGH) therapy (rhGH subcutaneously at a dose of 50 to 75 μg/kg/day for 6 days a week for at least 3 years) were safe and effective at improving height, growth velocity, and serum insulin-like growth factor-1 (IGF-1) levels. While, we suggest to do the gene test before GH treatment to avoid this rare type, and it could be safer or use GH carefully with patients having this mutation. That is the meaning of precision medicine for the safety of the patient.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for 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.

Acknowledgements

We gratefully thank the patient’s family for their great and persistent cooperation.

Funding

This study was supported by a grant from the National Key Research and Development Program of China (No. 2016YFC0901505).

Conflicts of interest

None.

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