CASE REPORT

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PTPN11 c.853T>C (p.Phe285Leu) mutation in Noonan syndrome with chylothorax

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ABSTRACT

Recent advances in molecular and genetic approaches have identified a number of genes responsible for Noonan syndrome (NS). However, there has been limited analysis of the genotype-phenotype correlation of NS patients. Here, we report the case of a Japanese patient with NS possessing a c.853T>C (p.Phe285Leu) mutation in the gene encoding protein-tyrosine phosphatase, nonreceptor-type 11 (*PTPN11*). To clarify genotype-phenotype correlations, the accumulation of data on the clinical course of patients with genetically confirmed NS is important. We summarized the cases with mutations at *PTPN11* position 285 and found that c854T>C (p.Phe285Ser) is the most common mutation at this position. In these reports, although little is mentioned about the genotype-phenotype correlation, two patients with NS possessing the *PTPN11* c854T>C (p.Phe285Ser) mutation accompanied by chylothorax are described. There is still a lack of detailed information about the phenotype associated with the c.853T>C (p.Phe285Leu) mutation observed in this case. More research is needed to better understand these cases.

Keywords: Noonan syndrome, chylothorax, genotype-phenotype, *PTPN11*, c.853T>C (p.Phe285Leu)

Abbreviation:
NS: Noonan syndrome

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INTRODUCTION

Noonan syndrome (NS) is an autosomal dominant disorder involving multiple congenital malformations.[1] Recent advances in molecular and genetic approaches have identified a number of genes responsible for this condition. Missense mutations in the gene encoding protein-tyrosine phosphatase, nonreceptor-type 11 (*PTPN11*), account for approximately 50% of NS cases.[2] The genotype-phenotype correlation in NS has been widely analyzed but the variant site-specific correlation remains poorly understood.[3] *PTPN11* c.853T>C (p.Phe285Leu) (rs397507531) is a

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known pathogenic mutation located in exon 7 but the detailed clinical course associated with it is unknown.[4-7] Herein, we report a case of NS associated with this mutation.

CASE REPORT

A male infant was born as a first child to healthy, nonconsanguineous parents at 35 weeks and 4 days of gestation. His birth weight was 1,452 g. At 21 weeks of gestation, massive chylothorax was observed. At 23–24 weeks of gestation, thoracoamniotic shunting was performed, which was removed at birth. Physical examination revealed a peculiar face with a prominent forehead, droopy eyelids, micrognathia, low-set ears, webbed neck, funnel chest, and cryptorchidism. Heart ultrasound examination revealed good wall motion and no signs of pulmonary stenosis, hypertrophic cardiomyopathy, or other heart anomalies. CT examination revealed the presence of hypoplasia of the sternum and ribs. He was mechanically ventilated for 15 days. Enteral feeding was started from the first day, and his weight gain was good with human milk fortifier and medium-chain triglyceride oil. When the total water intake reached 150 ml/kg/day at 42 days of age, recurrence of the chylothorax occurred (Fig. 1). Pleural fluid analysis showed that white blood cells, lymphocytes, triglycerides, and Rivalta's reaction were 55,900/μL, 98%, 2364.1 mg/dL, and positive, respectively. At the age of 54 days, the subject's feeding was changed to medium-chain triglyceride formula and he received octreotide for the treatment of chylothorax. At

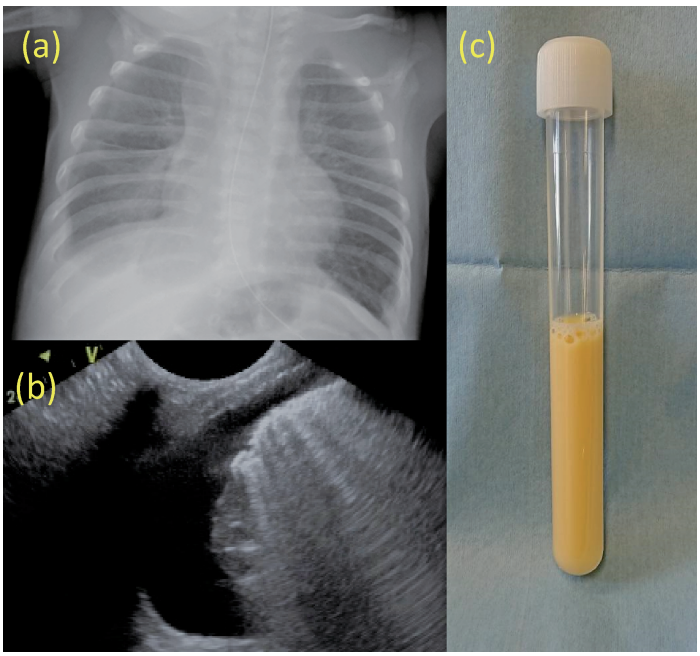

Fig. 1 At the age of 42 days, the patient had chylothorax on the right side

Fig. 1a: X-ray examination. Right and subpulmonic effusion. Decreased lung volume. Diffuse hazy opacities in the right lung were consistent with chylothorax and atelectasis.

Fig. 1b: Ultrasonogram. Examined from the intercostal space above the right axillary line. Accumulation of the pleural effusion.

Fig. 1c: Pleural fluid analysis. Thoracentesis was performed, and 10 ml of pleural fluid was drained.

63 days of age, furosemide and spironolactone were administered for the treatment of chylothorax. The patient was discharged at 5 months of age with no re-accumulation of the chylothorax after reducing the dose of octreotide.

After written informed consent was obtained, next-generation sequencing analysis of genes associated with NS (*PTPN11*, *SOS1*, *RAF1*, *KRAS*, *NRAS*, *HRAS*, *RIT1*, *BRAF*, *MAP2K2*, *MAP2K1*, *CBL*, and *SHOC2*) from peripheral blood lymphocytes detected a *PTPN11* c.853T>C (p.Phe285Leu) mutation.

DISCUSSION

Chylothorax is an important complication of NS; therefore, presentation of the clinical course with medical management is clinically informative. To clarify genotype-phenotype correlations, the accumulation of data on the clinical course of patients with genetically confirmed NS is important.

NS associated with *PTPN11* c.853T>C is very rare; however, this mutation is reported in the literature in individuals affected by Noonan or Noonan-like syndrome.[4-7] Other mutations similar to c.853T>C (p.Phe285Leu) have also been reported: c.853T>A (p.Phe285Ile),[8] c854T>C (p.Phe285Ser),[1,2,5,8-17] c854T>G (p.Phe285Cys),[5] and c.855T>G (p.Phe285Leu).[18] We summarized the cases with mutations at *PTPN11* position 285 and found 4, 3, 18, 1, and 1 cases with c.853T>C (p.Phe285Leu), c.853T>A (p.Phe285Ile), c854T>C (p.Phe285Ser), c.854T>G (p.Phe285Cys), and c.855T>G (p.Phe285Leu), respectively (Table 1). The majority of mutations are c.854T>C, making the mutational hotspot at *PTPN11* position 285. Two cases of chylothorax associated with mutation at *PTPN11* position 285 have been reported. However, the phenotypic differences among those with different mutations at *PTPN11* position 285 have not yet been reported. Moreover, in previous reports, little was mentioned about the genotype-phenotype correlation.

Information about the genotype-phenotype association of different mutations at a particular site could be useful in a clinical context.[19] For example, the p.Asn308 mutation in the *PTPN11* gene was most prevalent in Japanese NS patients and hearing loss was not noted in those with p.Asn308 mutation.[1] Some specific mutations of *PTPN11* were found to be associated with hypertrophic cardiomyopathy (p.Tyr279, p.Thr468, and p.Gln510 mutations),[20] juvenile myelomonocytic leukemia, and myeloproliferative disease (p.Thr73 mutation).[21] Chylothorax of NS may be related to the presence of genetic factors. Yaoita et al was found in 8 of 13 (62%) *RIT1*-positive NS patients with chylothorax, which was significantly more frequent than in other genes.[22] Chylothorax of *PTPN11*-associated NS has been noted in previous reports; the molecular changes include c.182A>C (p.Asp61Ala),[23] c.218C>T (p.Thr73Ile),[24] c.417G>C (p.Glu139Asp),[25] c854T>C (p.Phe285Ser),[10,11] and c.1507G>C (p.Gly503Arg).[26] These reports describe two patients with NS possessing the *PTPN11* c854T>C (p.Phe285Ser) mutation accompanied by chylothorax[10,11]; one patient died 9 h after birth due to hypoplasia of the lungs.[10] The case in this report involves a rare patient with NS possessing *PTPN11* c.853T>C (p.Phe285Leu) with chylothorax for which information on the clinical course is available. Although it is difficult to draw definitive conclusions on the genotype-phenotype correlation based on a few case reports, our findings provide very important clinical information for patients with *PTPN11* pathogenic variants.

Table 1 *PTPN11* p.Phe285 mutations in Noonan syndrome

Author	Country	Race	cDNA	Phenotype
Our case	Japan	Mongoloid	c.853T>C	**chylothorax**, facial phenotype, funnel chest, webbed neck, cryptorchidism
Tartaglia et al[4]	USA	NA	c.853T>C	NA
Aoki et al[5]	Japan	Mongoloid	c.853T>C	NA
Lee et al[6]	USA	Caucasoid	c.853T>C	NLS, PS, low bone density
Jafarov et al[7]	USA	Caucasoid	c.853T>C	cherubism
Ferrero et al[8]	Italy	NA	c.853T>A	facial phenotype, SS, PS, bleeding diathesis (3 cases)
Kosaki et al[9]	Japan	Mongoloid	c.854T>C	facial phenotype, SS, PS, webbed neck, cubitus valgus, oligomenorrhea, DD
Shoji et al[1]	Japan	Mongoloid	c.854T>C	SS, atrial septal defect, PS, DD
Schlüter et al[10]	Germany	NA	c.854T>C	**chylothorax**, hypoplasia of lungs, cystic hygroma, right ventricular hypertrophy
Baldassarre et al[11]	Italy	NA	c.854T>C	**chylothorax**, SS, HCM, PS, JMML,
Essawi et al[12]	Egypt	Caucasoid	c.854T>C	NA
Ferrero et al[8]	Italy	Caucasoid	c.854T>C	NA
Bertola et al[13]	Brazil	NA	c.854T>C	NA
Levaillant et al[14]	France	NA	c.854T>C	Costello syndrome, facial phenotype, hypoplastic tricuspid and pulmonary valves, one single pulmonary sigmoid, cryptorchidism, hydronephrosis
Athota et al[2]	India	NA	c.854T>C	NA (4 cases)
Cizmarova et al[15]	Slovakia	Caucasoid	c.854T>C	NA (2 cases)
Kiper et al[16]	Turkey	NA	c.854T>C	NA (2 cases)
Yoshida et al[17]	Japan	Mongoloid	c.854T>C	NA
Aoki et al[5]	Japan	Mongoloid	c.854T>C	NA
Aoki et al[5]	Japan	Mongoloid	c.854T>G	NA
Hung et al[18]	Taiwan	Mongoloid	c.855T>G	NA

NLS: Noonan-like/multiple giant cell lesion syndrome
SS: short stature
PS: pulmonary stenosis
HCM: hypertrophic myocardiopathy
DD: developmental delay
JMML: juvenile myelomonocytic leukemia
NA: not available

CONCLUSION

In summary, we report the case of a patient with chylothorax caused by *PTPN11* c.853T>C (p.Phe285Leu) mutation complicated by NS. There is still a lack of detailed information about the phenotype associated with the c.853T>C (p.Phe285Leu) mutation observed in this case. More research is needed to better understand these cases.

AUTHOR CONTRIBUTION

DW wrote the first draft of this manuscript.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

ETHICAL STANDARD AND INFORMED CONSENT

We received ethical committee approval from our hospital and informed consent from the patient's parents. Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

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