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Case Report

Late-onset Lymphedema and Protein-losing Enteropathy with Noonan Syndrome

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Abstract. Noonan syndrome is characterized by facial dysmorphology, congenital heart disease and growth failure. Although it is also accompanied by deranged lymph-vessel formation, protein-losing enteropathy (PLE) with Noonan syndrome is rarely reported. We report clinical information about a boy with Noonan syndrome and late-onset lymphedema and PLE after standing for long periods of time during athletic practice sessions. The boy recovered from lymphedema and PLE after administration of 2.5 g of albumin followed by resting and raising his legs. They did not recur after he began walking again. Standing for long periods of time congested the lymph stream at the abdominal lymph vessel, whose formation is frequently disturbed in Noonan syndrome, and the increased pressure caused lymphedema and PLE. PLE is one of the clinical manifestations of Noonan syndrome.

Key words: Noonan syndrome, lymphedema, protein-losing enteropathy, growth hormone

Introduction

Noonan syndrome is characterized by facial dysmorphology (low set of ears, hypertelorism, downward eyeslant and epicathic fold), growth failure and congenital heart anomalies such as pulmonary stenosis and atrial septum defects (1). Lymphedema is a clinical manifestation accompanying Noonan syndrome. It is attributed to hypoplasia or dysplasia of lymph vessels. Lymphedema with Noonan syndrome reportedly occurs in the neonatal and later period (2, 3).

Although protein-losing enteropathy (PLE) occurs in post-cardiac operations, such as the Fontan operation, inflammatory bowel syndrome, connective tissue diseases and parasitic disease (4–9), PLE with Noonan syndrome is rarely reported (10).

We treated a 13-yr-old boy with Noonan syndrome accompanied by late-onset lymphedema, hydrocele testis and PLE during growth hormone treatment for growth failure.

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Case Report

A 13-yr-old boy with prior diagnosis of Noonan syndrome based on characteristic facial deformation and congenital heart anomaly (pulmonary stenosis and atrial septum defect)

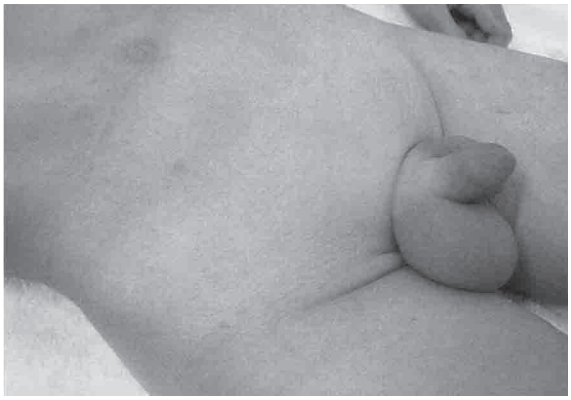

Fig. 1 Distinctive features of our patient. Edema of the lower abdomen and hydrocele testis were observed.

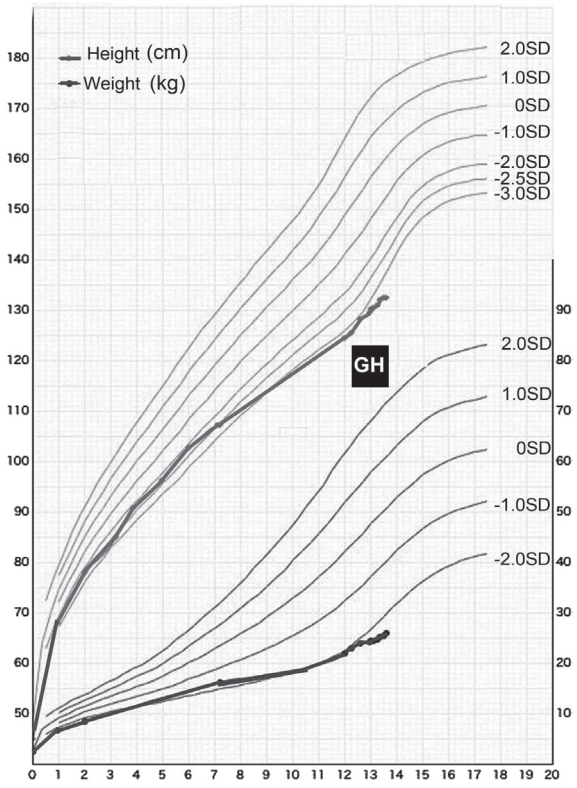

Fig. 2 Growth charts of our patient. Growth hormone treatment was started at the age of 12 yr of age.

came to our hospital complaining of edema of his leg in September 2007. He also presented edema of his lower abdomen and hydrocele testis (Fig. 1). He had no tenderness on his abdomen and legs and was diagnosed as having lymphedema. His consciousness was clear. His blood pressure was 86/40 mmHg and his heart rate was 70/min. His height was 132.5 cm (–3.6 SD) and his weight was 27.6 kg (–2.2 SD). His weight had increased by 1.4 kg within 1 wk before coming to the hospital. His Tanner pubertal stage was G_2P_1. His testicular volume was 8 ml bilaterally. He had not suffered from diarrhea. No polyuria or oliguria was observed. Before coming to our hospital, he practiced hard for athletic meets and stood for long periods of time each day.

In regard to his past history, neuroblastoma was suspected at 6 mo of age because the level of urinary vanillylmandelic acid (u-VMA) was high, although MRI and RI testing identified no tumor. An operation for pulmonary stenosis and atrial septum defect was conducted at 6 yr of age. For his short stature, he was monitored by our hospital from 6 yr of age. His growth chart is shown in Fig. 2. At 12 yr of age (height, 124.7 cm, –3.21 SD; weight, 22.1 kg, –2.1 SD), he was diagnosed as having growth hormone deficiency (IGF-1, 158 ng/ml; peak value of serum growth hormone after provocation; insulin, 5.3 ng/ml; clonidine, 5.2 ng/ml). Growth hormone treatment was started after informed consent was obtained from his parents. His endocrinological data at start of growth hormone treatment was as follows: TSH, 4.68 μU/ml; free T4, 1.23 ng/dl; FSH, 22.1 mIU/ml; LH, 1.5 mIU/ml; and testosterone, 13.9 ng/ml. His testicular volume reached the pubertal level soon after starting growth hormone treatment. His amount of food intake and food preference were not altered before and after start of growth hormone treatment. During growth hormone treatment, asymptomatic hypoproteinemia was found after an athletic meet in 2006 (Fig. 3). Without specific therapy, his serum protein level recovered to a normal level.

He was admitted to our hospital for examination of the cause of lymphedema and

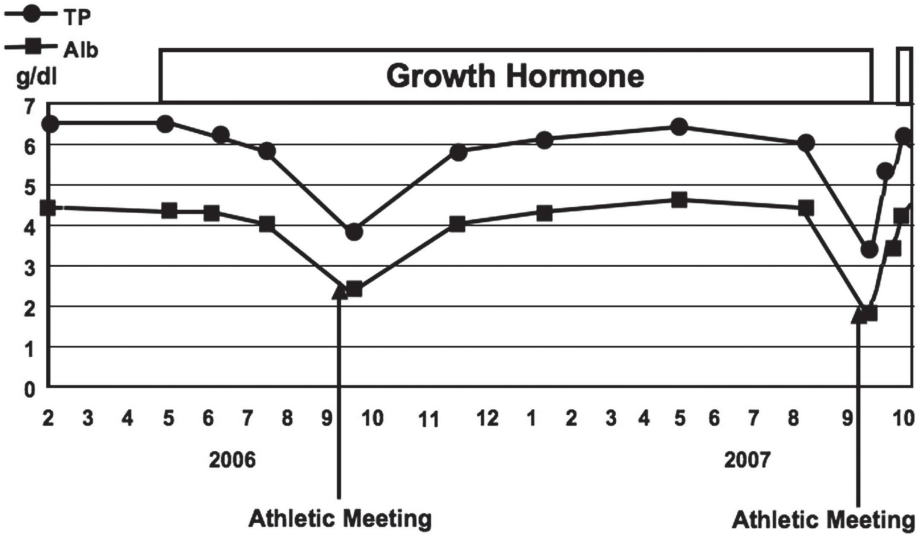

Fig. 3 Clinical courses during 2006–2007. Hypoproteinemia worsen after athletic meets in 2006 and 2007.

Table 1 Results of laboratory testing at admission

WBC	4.32×10^3 /μl	TP	3.2 g/dl	Urine	
Neu	74.3 %	Alb	1.8 g/dl	Specific Gravity	1.004
Mon	8.2 %	AST	19 IU/l	pH	7.0
Ly	14.2 %	ALT	15 IU/l	Protein	(–)
Eos	3.1 %	LDH	137 IU/l	Glucose	(–)
Bas	0.3 %	CHE	179 IU/l	Blood	(–)
Hb	14.3 g/dl	T-cho	143 mg/dl	Ketone	(–)
RBC	5.4×10^6 /μl	UA	3.0 mg/dl	Leukocyte	(–)
MCV	81 fl	UN	12.5 mg/dl	Urobilinogen	(+ –)
MCH	26.4 pg	CRTN	0.53 mg/dl	Nitrite	(–)
MCHC	32.5 %	NA	139 mEq/l		
PLT	214×10^3 /μl	K	3.8 mEq/l	U-TP	5.6 mg/dl
		CL	109 mEq/l	U-CRTN	13.1 mg/dl
		Ca	7.8 mg/dl	U-NAG	<1.4 U/l
				U-β2MG	<0.05 mg/dl
PT	10.9 sec	IgG	139.5 mg/dl	VMA	6.5 mg/mg·Cr
APTT	37.4 sec	IgA	25.4 mg/dl		
Fibg	387 mg/dl	IgM	46.6 mg/dl		
TT	43 %	C3	84.0 mg/dl		
AT III	105 %	C4	46.6 mg/dl	Stool	
PLG	65 %	CH50	34 U/ml	Oil red staining	Negative
D-dimer	0.5 μg/ml	CRP	0.01 mg/dl	Parasitic eggs	Negative
Protein C	75 %	β2MG	1.77 mg/l		
Protein S	62 %	NSE	15.02 ng/ml		

TT, thrombotest; AT III, antithrombin III; PLG, plasminogen; β2MG, β2microglobuline; NSE, neuron-specific enolase; NAG, N-acetyl-β-D-glucosaminidase; VMA, vanillylmandelic acid.

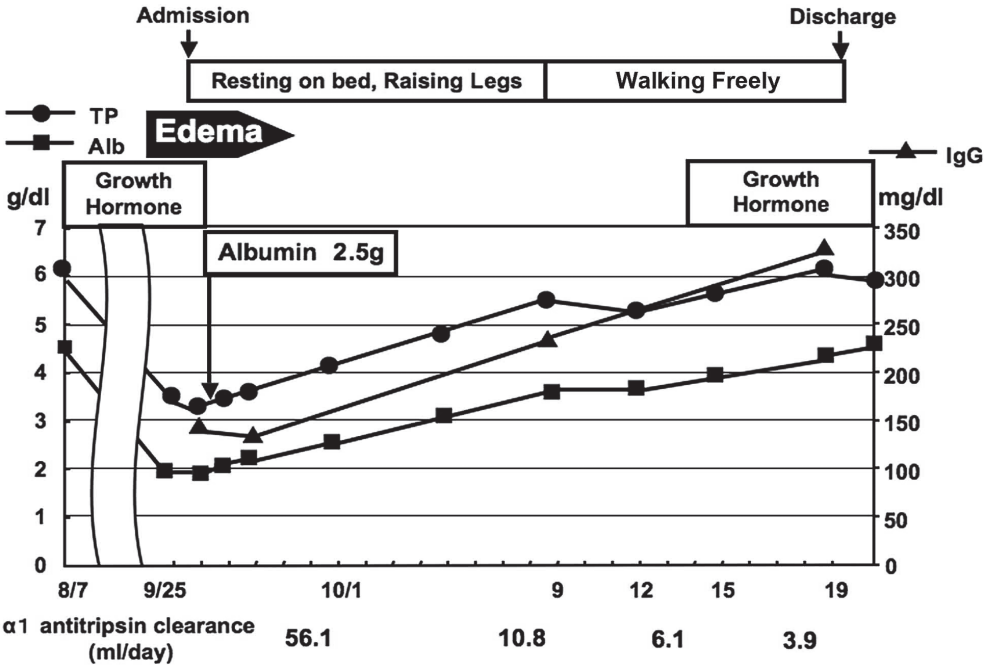

Fig. 4 Clinical courses during and around admission.

hypoproteinemia. Laboratory testing on admission (Table 1) showed hypoproteinemia, hypoalbuminemia and hypoimmunoglobulinemia. Urinary analysis revealed no proteinuria. No hypereosinophilia reflecting parasitic diseases or eosinophilic gastroenteropathy was found. The level of serum neuron-specific enolase (NSE) and u-VMA were within the normal ranges. His stool was solid, not diarrheal. Oil red staining excluded fatty stool. No parasitic eggs were found in his stool. Abdominal CT imaging showed edematous intestine. Neither abdominal nor femoral deep venous thrombosis was found by MRI angiography. No tumor mass was revealed by CT and MRI. Small amounts of pleural fluid and ascites were identified by MRI. No cardiac enlargement was found by chest roentgenogram. Echocardiography showed that his cardiac function was normal and that he did not have right ventricular failure or constrictive pericarditis.

Soon after admission, 2.5 g of albumin was injected into him; he was made to rest in bed and to raise his legs to maintain his blood pressure (Fig. 4). Growth hormone treatment was stopped because of its fluid retention effects. On day 2, 99mTc-human serum albumin (HSA) scintigraphy on showed protein loss from the small intestine at 6 h (Figs. 5-(A) and 5-(B)). Because his level of α1 anti-trypsin clearance on day 5 was elevated (56.1 ml/d), he was diagnosed as having PLE.

His serum total protein and albumin levels increased each day after admission. On day 6, 99mTc-HSA scintigraphy identified no protein loss during an 8-h period (Figs. 5-(C) and 5-(D)). His level of α1 anti-trypsin clearance on day 13 was normal (10.8 ml/d).

Although he was allowed to start walking on day 14 and growth hormone treatment was restarted on day 19, his serum total protein and albumin levels continued to rise. His level of α1 anti-trypsin clearance did not elevate again (day 18; 6.1 ml/d, day 23; 3.9 ml/d). He was discharged from the hospital on day 24. Hypoproteinemia and lymphedema did not recur after discharge from our hospital for 1 yr.

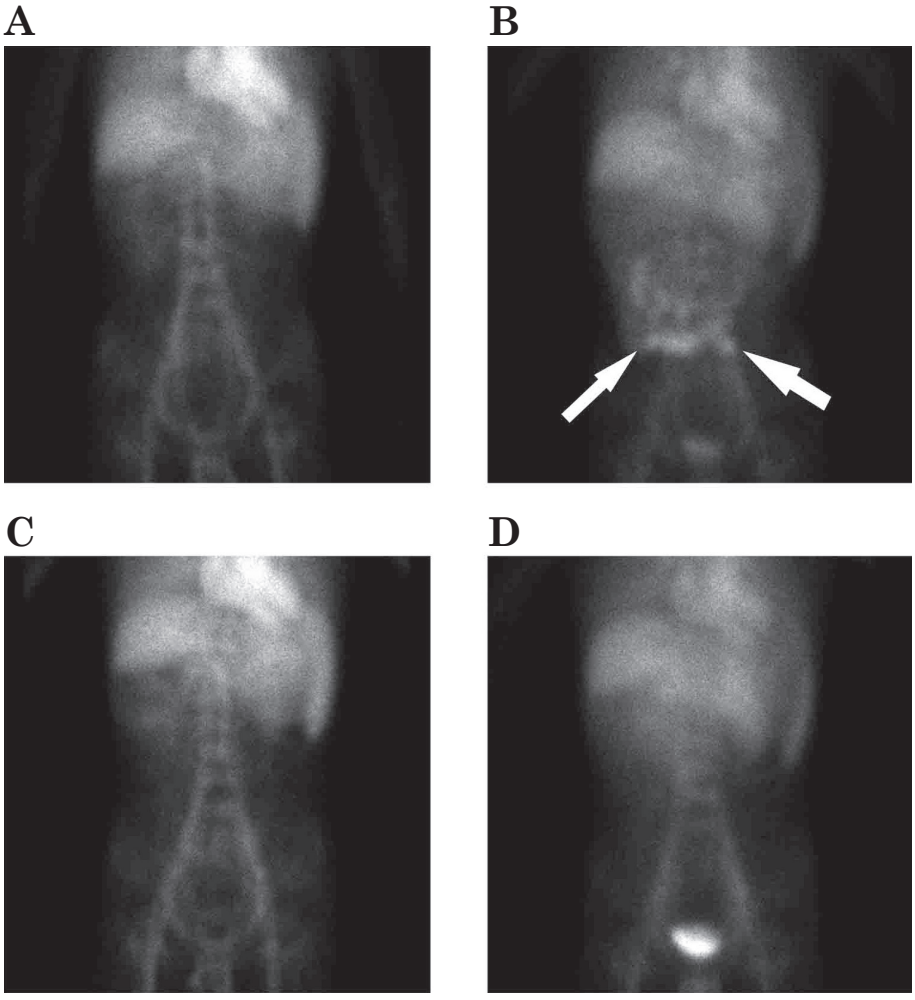

Fig. 5 Results of 99mTc-human serum albumin scintigraphy on day 2 (A, 5 min after injection; B, 6 h after injection) and day 6 (C, 5 min after injection; D, 8 h after injection). White arrows indicate protein loss from the small intestine.

Discussion

Disorder of lymph vessel formation is frequently reported with Noonan syndrome (11, 12). Although lymphedema secondary to disorder of lymph vessel formation is reported in up to 20% of Noonan syndrome patients (3), PLE is rarely reported with Noonan syndrome (10).

Our patient received growth hormone treatment for short stature. Recent reports showed that growth hormone treatment does not increase any severe adverse event in Noonan syndrome (13, 14). PLE during growth hormone therapy has not been reported in Noonan syndrome. Our patient also showed asymptomatic hypoproteinemia and hypoalbuminemia after athletic meet in the year prior to admission (Fig. 3). Although growth hormone treatment had not been discontinued, hypoproteinemia and hypoalbuminemia have not continued. Therefore, growth hormone treatment does not seem to be the main trigger of his lymphedema and PLE.

Although a fat-rich, low-protein diet aggravates PLE, our patient did not prefer this

kind of food. Alteration of the amount of food intake or food preference was not observed after start of growth hormone therapy. He received no specific therapy for PLE, such as protein-rich, low-fat diet therapy, during admission, and the amount and composition of his food intake were not altered before and after admission. So, in this case, food was considered to have had little effect on the occurrence of PLE.

Lymphedema and PLE that accompany constrictive pericarditis or that occur after cardiovascular surgery, such as the Fontan operation, are commonly reported (4, 5). These are attributed to an elevated central venous pressure (CVP). Although our patient also underwent a cardiac operation for atrial septum defect and pulmonary stenosis, an echocardiogram did not indicate right ventricular failure or constrictive pericarditis before or after start of the growth hormone treatment. Recent reports show that growth hormone treatment does not increase adverse effects on cardiac muscle mass in Noonan syndrome (15, 16). Therefore, operation and cardiac disorders are also not presumed to have caused his lymphedema and PLE in this patient.

No tumors, such as neuroblastoma and lymphoma, that occasionally cause PLE (17, 18) were found in the present patient.

Our patient practiced hard for athletic meets and stood for long periods of time each day before coming to our hospital (Fig. 3). Standing for long periods of time congested the lymph stream and increased the pressure in lymph vessels. Although lymphangiography and lymphoscintigraphy were not conducted on this patient, dysplasia and hypoplasia of lymph vessels originating from Noonan syndrome might have contributed to congestion of the lymph stream. These were considered to cause defluxion of lymph into interstitial tissues of the legs, lower abdomen and intestine, which caused lymphedema and PLE.

Recently, genetic mutations in the genes organizing the RAS-ERK MAPK pathway were found to be causative candidates of Noonan syndrome (19–22). The MAPK pathway is activated by VEGFR3, an important component for lymphangiogenesis (23). Although the genotype-phenotype correlation is not fully understood in Noonan syndrome, the severity of disorder in lymph vessel formation might differ according to the genetic mutation. In addition, the severity of the disorder in lymph vessel formation might engender different clinical symptoms of Noonan syndrome: asymptomatic or lymph edema only or both lymphedema and PLE, as well as early onset or late onset.

In conclusion, Noonan syndrome might be accompanied by PLE. Asymptomatic hypoproteinemia attributable to PLE, as our patient showed, might be more common in patients with Noonan syndrome than previously thought. Therefore, more attentions to the clinical symptoms such as lymphedema and hydrocele testis, and the serum levels of total protein and albumin should be paid in patients with Noonan syndrome.

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