Newly-identified symptoms of left renal vein entrapment syndrome mimicking orthostatic disturbance

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Original article

Background: **In addition to the urinary abnormalities, symptoms of left renal vein entrapment between the aorta and superior mesenteric artery (left renal vein entrapment syndrome, LRVES) may include abdominal and flank pain as well as chronic fatigue. We investigated various LRVES symptoms in this study.**

Methods: **In 53 pediatric LRVES patients treated at our department, 22 had a score of 5 points or higher on orthostasis. Initial evaluation of LRVES by abdominal ultrasonography showed a stenotic-to-prestenotic vein diameter ratio of 0.2 or less. Definitive diagnosis was made by computed tomography and magnetic resonance angiography. Cortisol, catecholamine (CA), and brain natriuretic peptide (BNP) were also measured.**

Results: **The frequency of LRVES was 2.5 times higher in girls than in boys. Low or very low body mass indexes were seen in both sexes. The most common initial finding was urine abnormalities, followed by dizziness and malaise. In 6 patients, orthostasis precluded school attendance. Ten patients had orthostasis scores above 12. Patients unable to attend school had either low levels of plasma or urinary cortisol. Midodrine significantly decreased orthostasis scores. Some patients required treatment with fludrocortisone. Plasma CA, renin, and BNP levels were all normal.**

Conclusions: **Locally excessive venous pressure may cause reversible adrenal dysfunction with transitory Addisonian symptoms. Children with cryptogenic malaise or severe orthostasis should be evaluated for LRVES.**

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Key words: **abdominal and flank pain;**
dizziness;
hematuria;
nutcracker syndrome;
pre-stenotic dilation;
proteinuria

Introduction

In left renal vein entrapment syndrome (LRVES), compression and stenosis occur as it courses through the acute angle formed descending aorta (Ao) and the origin of the superior mesenteric artery (SMA). Resulting congestion of the left renal vein (LRV) and venous plexuses of the left pelvic and ureteral mucosa as well as the renal parenchymas caused various urinary abnormalities.[1] Despite absence of anatomic abnormalities, compression can arise when the level of the adipose tissue separating the two arteries from the LRV is reduced.[1] LRVES therefore is most frequent in thin adolescents. Most often, the syndrome presents as urinary abnormalities seen upon mass screening with urine tests at school. However, it sometimes manifests as gross hematuria after intense exercise or prolonged forward bending position.[1]

The pathogenesis of hematuria in stenosis of the LRV involves congestion and ultimately perforative hemorrhage of the renal calyx or ureter.[1,2] Proteinuria is caused by congestion in LRV stenosis when increased intrarenal venous pressure decreases renal plasma flow volume, which increases vascular resistance in the efferent arteries; this glomerular abnormality may lead to proteinuria when the hydrostatic pressure exceeds the capacity of glomerular barrier function to result in protein leakage.[2-5] Thus, changes in glomerular microcirculation may induce protein leakage despite absence of microscopically visible glomerular capillary wall injury.[2-5] However, increased thickness of the glomerular basement membrane (GBM) due to the

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unequivocal radiolucent widening of the lamina rara interna was frequently observed in LRVES patients by electron microscopy.[6]

Ultrasonography has been performed as the initial test.[7] To make a definitive diagnosis, pressure differences between the inferior vena cava (IVC) and LRV were measured during left renal venography, and hematuria was confirmed through selective left ureteral catheterization using a cystoscope.[8] More recently, contrast-enhanced computer tomography (CT), magnetic resonance angiography (MRA), and three-dimensional CT (3D-CT) have been employed.[9] Other than those, measurement of peak systolic velocity at the stenotic portion of the LRV may also be a parameter for detecting LRVES.[10]

Symptoms of this disorder include urinary abnormalities such as hematuria and/or proteinuria, and mild abdominal and flank pain. Recent studies reported patients with symptoms resembling those of chronic fatigue syndrome or with orthostatic disturbance (OD) of the blood pressure.[11,12] The prognosis of this disorder is favorable. Growth-related thickening of retroperitoneal adipose tissue and collateral drainage to the IVC from the LRV can decrease the LRV pressure, and relieve urinary abnormalities.[1,2] On the other hand, persistent compression was reported to result in chronic LRV hypertension, reversing flow in veins related to the LRV to adversely affect renal, adrenal, and gonadal functions.[13] In this study, we investigated symptoms and pathogenesis of LRVES in 53 patients diagnosed in the Department of Pediatrics at Kinki University.

Methods

Subjects

Of the 53 patients diagnosed with LRVES in our department, 22 scored 5 points or higher according to the diagnostic criteria for OD (6 boys and 16 girls).[14]

Diagnosis of LRVES

Patients with the ratio of diameters of the distended to the narrowed portions of LRV being 5:1 (Fig. 1, b/a ≤0.2) were diagnosed tentatively with LRVES. These patients then underwent contrast-enhanced CT, 3D-CT and/or MRA for a definitive diagnosis. In some patients, left renal venography was performed to confirm collateral drainage or flow reversal and to measure pressure differences between the IVC and LRV. However, since physiologic evaluations by venography with measurement of pressure gradients or peak velocity (PV) of LRV were not done in all patients, the diagnosis of LRVES in our patients was largely dependent on the morphologic findings by imaging examinations.

Diagnosis and semi-quantification of OD

The diagnostic criteria for OD included major and minor symptoms. Major symptoms included frequent dizziness, nausea, syncope on standing, episodes of nausea during bathing or upon hearing and seeing disagreeable things, palpitations or shortness of breath, and difficulty in waking up or discomfort on arising in the morning. Minor symptoms included facial pallor, anorexia, severe abdominal pain, general malaise or fatigue, and motion sickness. Findings scored similarly to minor symptoms included pulse pressure reduction (16 mmHg or more) upon standing, a 21 mmHg or greater decrease in systolic blood pressure upon standing, an increase in pulse (21 or more beats per minute) upon standing, and a 0.2 mV or greater decrease in Th or other changes upon standing during electrocardiography. The diagnosis of OD was based on the criteria described by Tanaka et al.[14] In brief, each individual having 3 major symptoms or 2 major symptoms plus one or more minor symptoms was clinically diagnosed as having OD. Each major symptom was counted as 2 points, and each minor symptom or finding as 1 point. The severity of OD in each patient was scored as the sum of points assigned for each symptom. Regarding the criteria by Tanaka et al,[14] patients scored 5 points or higher were regarded as having OD.

Endocrinologic tests

Plasma cortisol, renin, and brain natriuretic peptide (BNP) were determined in blood collected after overnight fasting. Urinary cortisol was determined using first-voided morning urine samples, and was expressed as a cortisol/creatinine ratio (μg/gCr). For blood and urinary catecholamines (CA), 3 fractions representative adrenaline, noradrenaline, and dopamine, were measured. Blood collection was taken after patients rested for 30 minutes. Plasma and urinary parameters were measured at least 5 times. Values were expressed as mean ± standard deviation (SD).

Immunofluorescent staining

Immunofluorescent staining was carried out according to the previously described method.[15] In brief, 3-μm thick frozen renal sections were incubated with fluorescein-labeled anti-human immunoglobulin (Ig) A, IgG, complement components C3, C1q, and C4 (purchased from Cosmo Bio, Tokyo, Japan), and observed under an immunofluorescent microscope (Nikon, Tokyo, Japan).

Statistical analyses

We employed the Mann-Whitney *U* test. *P* values below 0.01 were considered statistically significant.

Results

Diagnostic imaging

Typical images of LRVES are shown in Figs. 1-4. Ultrasonography was performed first. Patients with a ratio of diameters ≤0.2 between stenotic and pre-stenotically dilated LRV (Fig. 1; b/a, arrows) were diagnosed tentatively with LRVES. A definitive diagnosis was performed with contrast-enhanced CT, 3D-CT, or MRA. In these patients, an LRV stenosis or defect (Figs. 2-4) and pre-stenotic dilation (Fig. 2) were observed. In 3 of the patients with severe OD symptoms, pressure differences between the IVC and LRV were measured during left renal venography (Fig. 4b). Patients 1, 2 and 5 showed pressure differences of 8, 3 and 5 mmH_2O, respectively, which meet the criterion of a pressure difference of 2 mmH_2O or more. The association of superior mesenteric artery syndrome was excluded by the findings of contrast-enhanced CT or MRA in all patients.

Physical status and signs at time of detection

Findings are summarized in Table 1. Among OD patients, body mass index (BMI) was in the 50th percentile or lower in boys and 85% percentile or lower in girls. In 10 patients, it was in the 50th percentile or lower. In 2 patients, BMI was below -2.0 SD, suggesting emaciation. The most common presenting signs and symptoms were hematuria and/or proteinuria in 11 patients, followed by dizziness in 5 and persistent malaise in 2. Severe OD symptoms interfered with school attendance in 6 patients. Eight patients were brought to our hospital with OD symptoms or inability to attend school, and subsequent urinalyses only disclosed urinary abnormalities. Furthermore, 4 patients had no urinary abnormalities. Both flank and abdominal pain were noted in 4 patients, flank pain alone in 7, and abdominal pain alone in 6. Neither flank nor lumbar pain was present in 5 patients. In addition, testicular varices were found in 2 boys and dysmenorrhea was observed in 7 girls. Kidney biopsy was performed in 10 patients showing proteinuria exceeding 0.5 g/day and/or gross hematuria. In these patients, significant mesangial increase, diffuse thickening of GBM together with tubulointerstitial alterations were not observed by light microscopy. No immunoglobulin or complement deposition was seen. There were no significant differences in BMI, age at first OD symptom, and the severity of urinary abnormalities between LRVES patients with or without OD symptoms. However, the prevalence of flank pain and/or abdominal pain was more prominent in patients with OD symptoms than that in patients without OD symptoms (P<0.01).

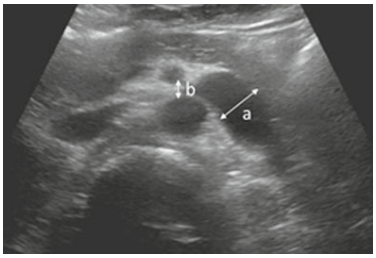

Fig. 1. Ultrasonographic findings in left renal vein entrapment syndrome (LRVES). Marked dilation of the left renal vein (LRV) is evident. A ratio of stenotic LRV diameter (b) to pre-stenotically dilated LRV diameter (a) less than 0.2 (1:5) suggests LRVES.

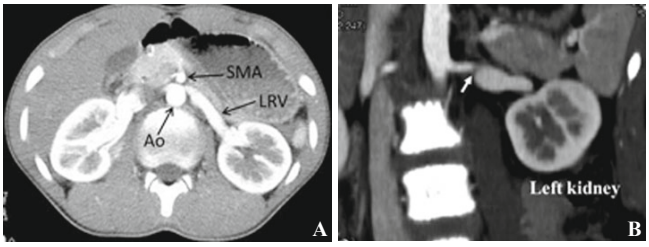

Fig. 2. Contrast-enhanced CT discloses stenosis of the left renal vein between the aorta and superior mesenteric artery (**A**). Stenotic (→) and pre-stenotically dilated sites are evident (**B**).

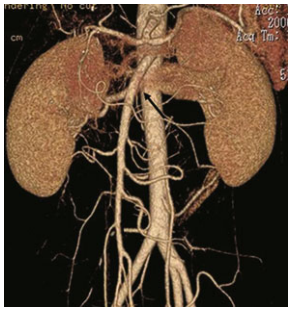

Fig. 3. 3D-CT showing dilation of the left renal vein prior to stenosis between the aorta and superior mesenteric artery (arrow).

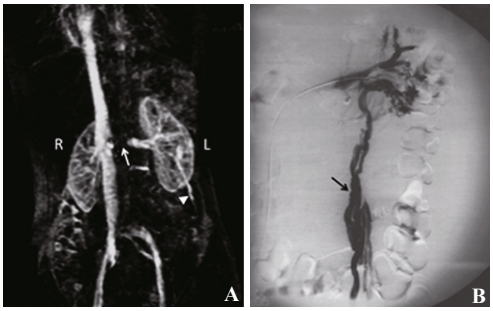

Fig. 4. Additional imaging. MRA (**A**) showing a defect in the stenotic site (→) and flow reversal (arrowhead). Renal venography (**B**) showing dilation and enlargement of intrarenal veins and flow reversal (arrow).

OD symptoms

The symptoms observed in LRVES patients are listed in Table 2. Ages at diagnosis of OD ranged from 7 to 23 years, with a mean of 12.8 years. The most common symptoms were frequent dizziness in 20 patients, followed by nausea upon bathing or hearing/seeing disagreeable things in 17, nausea on standing or syncope in 15, general malaise and fatigue in 15, palpitation or shortness of breath in 14, difficulty in waking up or discomfort in the morning in 12, facial pallor in 11, anorexia in 10, severe abdominal pain in 10, headache in 10, motion sickness in 10, and increased pulse (21 beats per minute or more) on standing in 2. No pulse pressure reduction of 16 mmHg or more was seen on standing; 21 mmHg or greater decrease in systolic blood pressure on standing; a 0.2 mV or greater decrease in Th or other on standing during electrocardiography. At time of diagnosis, OD scores ranged from 5 to 16 points (mean: 10.77). Ten patients showed an OD score of 12 points or higher. Of these patients, 6 were unable to attend school. In most patients, symptoms such as difficulty waking up in the morning and dizziness precluded school attendance. However, one patient often was absent from school because of psychosocial factors and could not establish good friendship; this led to secondary psychosomatic symptoms such as nausea after attending school.

Mean systolic and diastolic blood pressures at the diagnosis of OD were 102.84±9.2 and 58.64±7.6 mmHg, respectively. Mean pulse pressure was 44.2±4.9 mmHg. Blood pressure was lower than normal for the Japanese at 14.1 years (100 to 120/50 to 70 mmHg),[16] the median age of the subjects. The mean blood pressure in 31 LRVES patients without OD symptoms was 112.38±18.9/60.3±11.4 mmHg.

Changes in clinical symptoms and urine findings after drug therapy

Pretreatment OD scores ranged from 5 to 16 points, with a mean of 10.41 points. In these patients, drug therapy with midodrine hydrochloride or amedinium methylsulfonate was carried out. Dizziness subsided, and the mean OD score was 7.91, showing a significant decrease (P=0.0068). However, effects of drug therapy on frequency and grade of abdominal and flank pain varied among patients, showing no particular tendency. Before drug therapy, urine abnormalities were noted in 18 patients (proteinuria in 7, hematuria in 9, and both in 2). After drug therapy, 5 patients showed such abnormalities (proteinuria in 3, hematuria in 1, and both in 1).

The mean systolic and diastolic blood pressures before drug therapy at the time of OD diagnosis were 102.84±9.2 and 58.64±7.6 mmHg, respectively.

Table 1. Patient's profiles

Patient, *n* (gender)	Age at diagnosis of LRVES (y)	Age at 1st OD symptom (y)	1st symptom of OD or LRVES	Urinary abnormalities	Abdominal pain/ flank pain	BP (mmHg)	BMI	OD score pre/ post treatment	Renal biopsy
1 (F)	14	14	School phobia/fainting	Macro H	+/-	93/52	18	13/11	+
2 (F)	22	15	School phobia	Proteinuria	+/+	88/48	15	16/13	+
3 (F)	12	12	School phobia	None	-/+	101/64	18	15/12	ND
4 (F)	13	13	School phobia	None	-/+	109/64	15	14/12	ND
5 (M)	17	12	School phobia	Proteinuria	-/+	97/50	15	13/5	+
6 (F)	11	11	School phobia	Proteinuria	+/-	98/55	23	13/11	+
7 (F)	15	16	Fainting	Micro H	+/-	100/53	23	10/10	ND
8 (F)	13	13	Fainting	Micro H	-/+	100/57	17	11/8	+
9 (M)	15	15	Proteinuria	Proteinuria	+/+	108/60	19	10/10	ND
10 (F)	12	12	Fainting/fatigue	None	+/-	90/56	14	14/9	ND
11 (F)	23	23	Macro H	Micro H	-/-	94/48	15	9/7	+
12 (F)	8	7	Macro H	Macro H	-/-	128/78	22	12/10	+
13 (F)	10	10	Micro H	Micro H/proteinuria	+/-	101/62	16	5/4	+
14 (M)	24	13	Proteinuria	Proteinuria	-/+	100/62	16	8/6	ND
15 (F)	12	9	Micro H	Micro H	-/-	115/66	15	12/8	ND
16 (M)	14	12	Proteinuria/micro H	Proteinuria/micro H	+/-	113/59	16	7/4	+
17 (M)	11	13	Micro H	Micro H	-/+	110/65	15	5/3	ND
18 (F)	13	10	Fainting/fatigue	Proteinuria	+/+	106/60	19	14/8	ND
19 (F)	14	17	Micro H	Micro H	-/-	96/47	19	7/5	ND
20 (F)	17	17	Severe fatigue	None	-/-	103/63	19	10/6	ND
21 (F)	13	12	Severe fatigue	Proteinuria	-/+	99/58	16	9/5	+
22 (M)	13	14	Macro H	Macro H	+/+	110/64	16	10/7	ND

The 6 patients whose school attendance was affected are grouped together. LRVES: left renal vein entrapment syndrome; OD: orthostatic disorder; BP: blood pressure; BMI: body mass index; H: hematuria; F: female; M: male; ND: not done.

The mean pulse pressure was 44.2±4.9 mmHg. The mean systolic and diastolic blood pressures during drug therapy were 107.8±6.5 and 62.7±6.69 mmHg, respectively. The mean pulse pressure was 45.05±5.17 mmHg (P=0.706). Although blood pressures increased by administration of midodrine hydrochloride or amedinium methylsulfonate, the change was not significant.

Cortisol, CA and BNP levels and renin activity in patients in whom severe OD made them difficult to attend school

Plasma and urinary concentration of cortisol (mean±SD) in each patient with school attendance problem, as well as averages for those without school attendence problem, are shown in Fig. 5. In patients 1 and 6, plasma cortisol was at the lower limit of the normal range (10 μg/dL) at several measurement points. On the other hand, in patients 3, 4 and 5, median plasma cortisol concentration on point measurement was within the normal range, but variability was marked in urinary cortisol. In patients whose plasma cortisol concentration was consistently low (patients 1 and 2), severe OD symptoms persisted. In those with marked variability in urinary cortisol, OD symptoms deteriorated when the concentration was low. In LRVES patients with OD who could attend school, no such tendency was noted. In patients 1 to 5, fludrocortisone acetate at 0.05 to 0.1 mg/day was given orally when OD symptoms deteriorated in association with low cortisol. Treatment resulted in relief of symptoms. No abnormalities were noted in plasma or urinary CA, plasma renin, or plasma BNP in any patient. Furthermore, variability over time was within the physiologic range.

Table 2. Frequency of symptoms mimicking OD found in (left renal vein entrapment syndrome (LRVES) patients

Symptoms in LRVES patients enrolled in this study	Number of patients
Frequent dizziness	20
Nausea upon bathing or hearing/seeing disagreeable things	17
Nausea on standing or syncope	15
General malaise and fatigue	15
Palpitation or shortness of breath	14
Difficulty in waking up or discomfort in the morning	12
Facial pallor	11
Anorexia	10
Severe abdominal pain	10
Headache	10
Motion sickness	10
Increased pulse (21 beats per minute or more) on standing	2

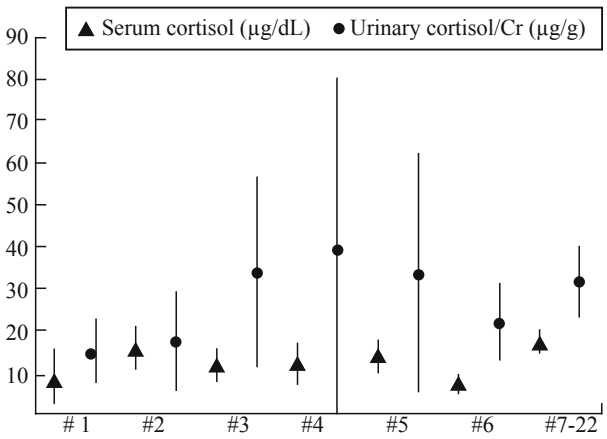

Fig. 5. Serum and urinary cortisol for the 6 patients with school attendance problems and 16 without such problems. Symbols are means; bars indicate SD.

Discussion

The LRV, which is 3 times longer than the right renal vein, drains into the IVC to the right of the Ao. The acute angle formed at the origin of the SMA is only 2 to 3 mm distant from where the LRV crosses the Ao.[1,2] This angular configuration is reflected in an alternative name for the syndrome, Nutcracker syndrome. When adipose tissue between the Ao and SMA is reduced, the LRV can be compressed, therefore LRV pressure increased. Veins flowing into the LRV such as adrenal, gonadal, lumbar, and hemiazygous veins dilate and show flow reversal.[1,2,17] For the purpose of diagnosis, ultrasonography is performed initially. LRV compression and venous dilation then are evaluated using contrast-enhanced CT and MRA.[7-9] When LRV blood flow is examined using color Doppler ultrasonography, blood flow velocity is reduced, often showing a flat pattern.[13] Takebayashi et al[18] found that the sensitivity and specificity of Doppler ultrasonography were 78% and 100%, respectively; they concluded that LRVES may exist in either non-distended or distended LRVs because blood flow can be normal in a distended LRV and ultrasound assessment is incomplete without assessment of collateral venous flow. Evaluation of the PV ratio may also be a potential way for estimating the severity of LRVES.[10] However, variable PVs may be highly dependent on the position of the patient, and thus PV ratios may be more predictive.[2] Intravenous pyelography (IVP) discloses compression of the renal pelvis and ureter related to the development of collateral veins. Compression of the LRV, development of collaterals, and a significant increase in pressure difference between LRV and IVC can be confirmed by angiography. However, LRV pressure may not be increased after enlargement of

collateral drainage.[1,2,8] Therefore, the final diagnosis of LRVES should be made by both physiologic and morphologic findings. Since the diagnosis of LRVES in our patients was largely dependent on the morphologic findings, physiologic evaluation might be absolutely necessary to make definitive diagnosis of LRVES in future.

LRVES has been considered a possible etiological factor for idiopathic renal hemorrhage. Recent studies have reported that this syndrome causes proteinuria.[13,19] Although its prevalence is unclear, a survey in Japan found stenosis of the LRV between the SMA and Ao with pre-stenotic dilation in approximately 11% of fifth- and sixth-year elementary school children.[12] A subsequent study suggested an association with testicular varices and proteinuria with orthostasis.[20,21] According to the report by Takahashi et al,[8] the prevalence of testicular varices is 16.2% in children aged 6 to 19 years. Several studies suggested the involvement of LRVES in 50% or more of children with testicular varices.[8,13] LRVES was observed ultrasonographically in all children with 3+ or higher proteinuria associated with orthostasis. Analysis of urine samples collected selectively using a ureteral catheter demonstrated that excessive urinary protein arose from the left kidney.

Additional symptoms of this disorder include mild abdominal and/or flank pain.[1,2] Although the precise mechanisms causing abdominal and/or flank pain in LRVES patients remain still unclear, a decreased blood flow caused by the continuous vasoconstriction of the small arteries located on the renal cortex is a considerable reason.[21] However, a recent study in children also suggested an association with chronic fatigue syndrome or chronic fatigue.[11] We reported some children with LRVES in whom psychosocial factors made daily living difficult.[12] In the present study, we investigated symptoms and courses in children with LRVES who had been followed up in our department. LRVES is frequent in the adolescents. In our series, BMI did not exceed the standard value in any child, and some children showed a BMI below -2 SD. Mean age at diagnosis was 14.1 years, which is consistent with previously reported findings.[1] Although the severity of OD symptoms varied, 22 (41.5%) of the 53 patients showed an OD score of 5 points or higher, often reflecting regarding dizziness. Patients with severe OD symptoms often had difficulty in attending school. When drug therapy was given to activate the autonomic nervous system, OD symptoms often lessened significantly. However, some patients did not respond to this therapy. Abdominal or flank pain often subsided but did not disappear completely. Drug therapy increased the blood pressure, but not to a statistically extent. Also, many patients showed urinary improvement. A modest increase in basal blood pressure was associated with LRV-pressure reduction related to improvement in blood flow from the LRV to the IVC via activation of the autonomic nervous system by drugs. Better neural responses to postural change may be involved in the mechanism.

Persistent inflammatory or posture-related LRVES may cause chronic LRV hypertension despite development of collateral veins, thus affecting autonomic function via abnormalities in adrenal hormone secretion. The renal renin-aldosterone system, water excretion, and changes of the right renal venous pressure were related to variations in IVC pressure.[11] In some children of this study, plasma cortisol was consistently low, while other children showed marked variability in urinary cortisol (SD), despite median plasma cortisol concentration within the normal range. We speculated that, in these patients, in addition to low basal blood pressure and decreased overall blood flow related to blood trapping in the LRV, such cortisol changes might exacerbate OD symptoms. Worsening of OD symptoms was noted when urinary cortisol was low. Therefore low oral doses of fludrocortisone acetate (0.05 to 0.1 mg/day) were given to these patients for maintaining sufficient blood cortisol. Since a small number of patients were analyzed in this study, our findings remain speculative, therefore a large-scale study of this therapy would be desirable. In some children, symptoms subsided within a few weeks. In these patients, an increase in venous pressure between the LRV and IVC induced flow reversal in the left adrenal vein, causing reversible adrenal hypofunction that lowered urinary cortisol. Transient symptoms resembling those of Addison's disease could be induced. When this occurs repeatedly, OD symptoms may deteriorate. However, some patients in our study did not show abnormalities in plasma cortisol despite a high OD score, and others had no marked changes in the OD. This suggests that the adrenal reserve capacity differs markedly between individuals. Shin et al[22] reported that administration of aspirin to patients with chronic fatigue symptoms associated with nutcracker phenomenon lessened the symptoms. However its efficacy seemed to be varied in each individual.

With respect to LRVES treatment, follow-up is continued in most patients when concomitant symptoms such as urinary abnormalities and abdominal pain are mild. However, when severe abdominal or flank pain persists, or when gross hematuria continues, definitive treatment may be required. In surgical treatment, the LRV is divided and then reconstructed 2 to 3 cm inferiorly, avoiding from the SMA.[23,24] Dilation of the stenotic site with a balloon catheter or intravenous stent insertion has been tried recently. These procedures could reduce urinary abnormalities, malaise, and school

difficulties in some patients.[9] In many patients, LRVES subsides spontaneously as collateral routes develop.[25] In patients with severe OD symptoms, autonomic nerve activation and/or therapy with fludrocortisone acetate may be effective. Most importantly, detailed examination is needed in children who cannot attend school and complain of general malaise with or without obvious OD symptoms.

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Competing interest: None declared.
Contributors: Koshimichi M wrote the first draft of this paper. All authors contributed to the intellectual content and approved the final version. Takemura T is the guarantor.

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