【 CASE REPORT 】

Chronic Hypercapnic Respiratory Failure in an Adult Patient with Silver-Russell Syndrome

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Abstract:
 A 31-year-old woman who was clinically diagnosed with Silver-Russell syndrome (SRS) in childhood was admitted with complaints of dyspnea. She had hypercapnic respiratory failure accompanied by nocturnal hypoventilation. Computed tomography revealed systemic muscle atrophy and superior mesenteric artery syndrome; however, the bilateral lung fields were normal. She was treated with nocturnal noninvasive positive pressure ventilation and showed improvement of respiratory failure. In this case, loss of methylation on chromosome 11p15 and maternal uniparental disomy of chromosome 7, which are the common causes of SRS, were not detected. This is a rare case of adult SRS manifesting as chronic hypercapnic respiratory failure.

Key words: Silver-Russell syndrome, hypercapnic respiratory failure, nocturnal hypoventilation, noninvasive positive pressure ventilation, superior mesenteric artery syndrome

Introduction

Silver-Russell syndrome (SRS) is a rare but well-recognized condition associated with prenatal and postnatal growth retardation and is clinically diagnosed on the basis of a combination of characteristic features (1-3). The clinical diagnosis of SRS is defined as meeting at least four of the six criteria from the Netchine-Harbison clinical scoring system (NH-CSS): (i) prenatal growth retardation, (ii) postnatal growth retardation, (iii) relative macrocephaly at birth, (iv) a protruding forehead, (v) body asymmetry, and (vi) feeding difficulties and/or a low body mass index (BMI) (4). The most common molecular mechanisms are loss of methylation on chromosome 11p15 (11p15LOM; seen in 30-60% of patients) and maternal uniparental disomy of chromosome 7 [upd (7) mat; seen in 10% of patients] (5-7). However, the molecular cause remains unknown in a substantial proportion of patients.

Although the prevalence of SRS is estimated to range from 1:30,000 to 1:100,000 (1), the true prevalence is unknown because of the heterogeneity of symptoms and severities in patients with SRS. Most individuals with SRS are not routinely followed up; therefore, very little information exists in the literature regarding the long-term natural history of SRS.

We herein report an adult case of SRS with associated hypercapnic respiratory failure treated with noninvasive positive pressure ventilation (NPPV).

Case Report

A 31-year-old woman presented to our hospital with dyspnea. The patient was born at 39 weeks via normal vagi-

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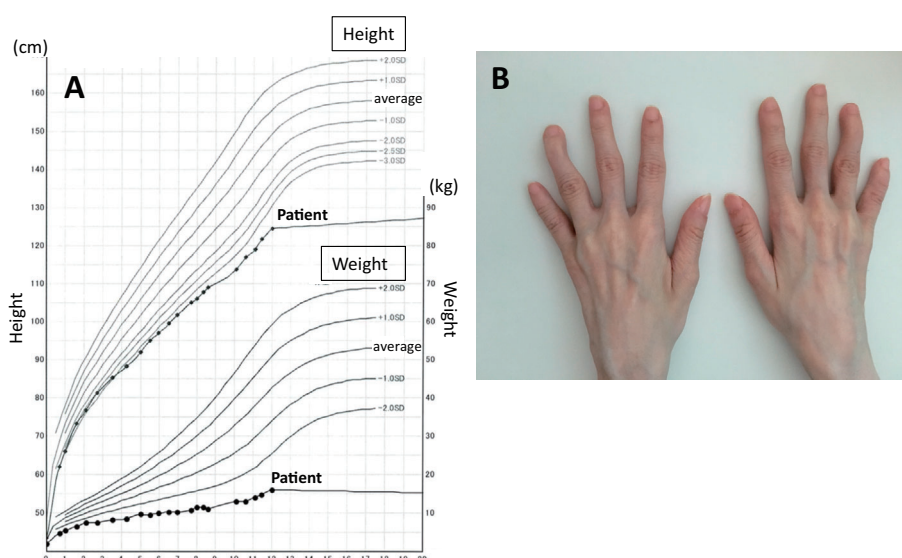
Figure 1.   Physical characteristics of the patient. (A) The growth curve showing that catch-up growth was not observed in childhood. (B) Hands at 31 years old showing brachydactyly of the fifth fingers.

nal delivery to healthy parents without a family history of a congenital disease. However, she was small for her gestational age at birth; her length was 43.5 cm (-3.2 SD), weight was 2,014 g (-3.0 SD), and occipitofrontal circumference was 29 cm (-3.0 SD). She was clinically diagnosed with SRS at 9 years of age based on her postnatal growth failure (Fig. 1A) and several clinical features associated with SRS, including body asymmetry, scoliosis, foot anomalies, and fifth-finger brachydactyly (Fig. 1B). Although anabolic steroids were used to promote her growth for two years, she showed no catch-up growth. She stopped visiting the hospital from 12 years old.

During childhood and adolescence, she was able to eat orally three times a day without any abdominal symptoms, such as abdominal distension, nausea, or vomiting. Nevertheless, she was unable to gain weight, and her weight at 20 years old was only 18 kg, the largest recorded in her life. In her 20s, she noticed morning headaches. She gradually preferred to eat low-calorie foods and decreased the number of meals to twice a day owing to repeated diarrhea and vomiting after eating. At 31 years old, she complained of difficulty breathing and was admitted to our hospital.

At the time of admission, her height, weight, and BMI were 131 cm (-5.2 SD), 15.5 kg (-5.9 SD), and 9 kg/m^2, respectively. Her clinical features met four of the six NH-CSS criteria, and she was diagnosed with SRS. The patient was afebrile, normotensive, mildly tachycardic (heart rate, 98 beats/min), and tachypneic (respiratory rate, 24 breaths/min) with an oxyhemoglobin saturation [measured via pulse oximetry (SpO$_2$) in the sitting position] of 97% on ambient air. However, the SaO$_2$ measured via an arterial blood gas analysis (ABG) was 93% in the supine position (Table), suggesting that the arterial oxygen level was lower in the supine than the sitting position. Chest auscultation was normal. She had different left and right foot lengths, scoliosis, and fifth-

finger brachydactyly; these were indicative of musculoskeletal dysplasia. A neurologic examination showed a significantly symmetric face, body muscle atrophy, decreased muscle tone, and reduced deep tendon reflexes. Her manual muscle testing (right/left) results were as follows: trapezius 4/4, deltoid 4/4, biceps 4/4, triceps 4/4, iliopsoas 4/4, quadriceps femoris 4/4, hamstrings 4/4, and a negative Gower's sign. Regarding laboratory tests, her serum creatine phosphokinase, white blood cell count, and C-reactive protein levels were normal. Her growth hormone and insulin-like growth factor 1 levels were also within normal limits. However, her serum brain natriuretic peptide level was elevated to 61.8 pg/mL (normal <18.4 pg/mL). Although diabetes complications are frequent among adult patients with SRS (8, 9), her blood glucose and glycosylated hemoglobin levels were normal.

Electrocardiography revealed sinus tachycardia, but no signs of right ventricular (RV) hypertrophy. Although an echocardiogram showed no signs of either right atrium/RV enlargement or RV hypertrophy, the estimated tricuspid regurgitation pressure gradient was elevated to 35 mmHg, suggesting mild pulmonary hypertension. The patient's exercise capacity was examined using the 6-minute walk test (6 MWT) under ambient air. Her physiological responses to the 6MWT were a heart rate of 114 (baseline)/119 (maximum) beats per min and an SpO$_2$ of 96% (baseline)/92% (nadir). The distance completed in the 6MWT was 248 m, indicating reduced exercise tolerance. Chest radiography and chest computed tomography (CT) (Fig. 2A, B) showed systemic muscle atrophy, thoracic deformation, and small lung volumes with an otherwise normal lung parenchyma. Pulmonary function tests revealed a severe restrictive ventilatory defect, with a vital capacity of 0.40 L (16% of the predicted value). Her maximal inspiratory and expiratory pressures were 38% and 77% of the predicted values, respectively,

Table. Changes in Blood Gas Analysis Variables.

	On admission	Day 5	Day 6	Day 12	Day 13	Day 17	Day 18	Day26	Day 27
Patient events		CO$_2$ narcosis				Pneumonia			
NPPV setting									
Mode	ventilator-free	ventilator-free	S/T		S/T		S/T		S/T
IPAP (cmH$_2$O)			4		8		12		12
EPAP (cmH$_2$O)			3		3		4		4
Pressure support (cmH$_2$O)			1		5		8		8
Rise time (msec)			150		150		150		150
Oxygen supplementation (L/min)			0		0.5		0.5		0
Blood gas analysis (in supine position)									
pH	7.353	7.335		7.459		7.377		7.406	
PaCO$_2$(mmHg)	63.4	71.8		54.9		72.3		59.4	
PaO$_2$(mmHg)	68.6	60.9		69.9		62.1		151.5	
cHCO$_3$-(mEq/L)	36.1	37.4		38.1		41.6		36.4	
SaO$_2$(%)	93.7	90.6		96.3		91.5		99.3	
A-aDO$_2$(mmHg)	1.88	-0.92		11.2					

EPAP: expiratory positive airway pressure, IPAP: inspiratory positive airway pressure, NPPV: non-invasive positive pressure ventilation, S/T: spontane-ous-timed
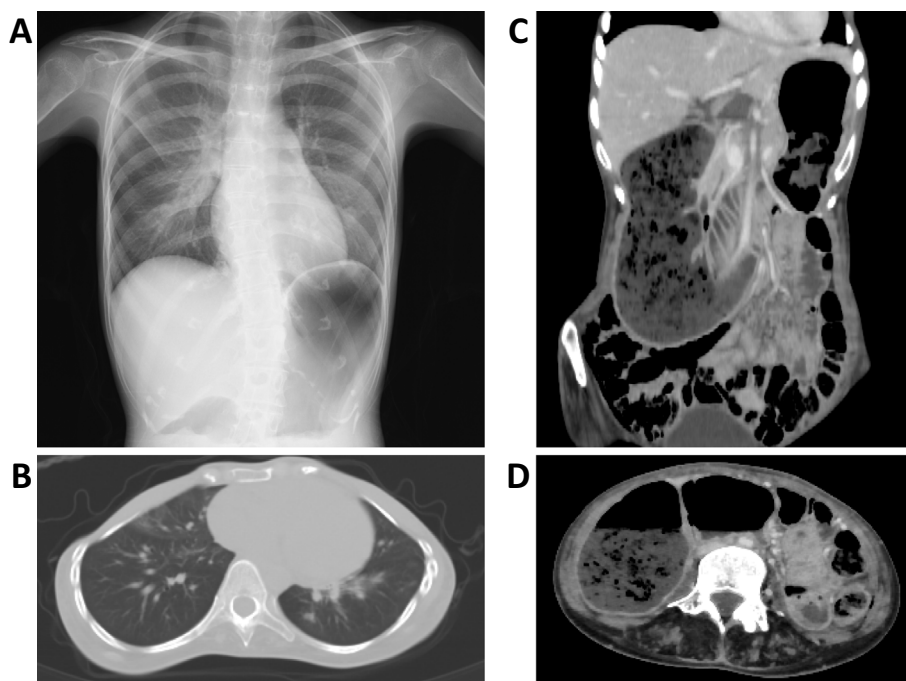

Figure 2. Radiographic and computed tomography (CT) findings of the patient on admission. (A) Chest radiography at the time of admission revealing whole-body muscle atrophy, scoliosis, and gastric dilatation. (B) CT of her chest showing thoracic deformation and small lung volumes. (C, D) Coronal (C) and axial (D) views of abdominal CT showing that her stomach and proximal duodenum were dilated and filled with gas and fluid.

which signified her remarkably reduced respiratory muscle strength. The patient's ABG in ambient air was indicative of chronic hypercapnia (pH 7.353, PaCO$_2$ 63.4 mmHg, PaO$_2$ 68.6 mmHg, and HCO$_3$- 36.1 mEq/L), and her alveolar-arterial oxygen gradient was within normal limits (Table). Nocturnal pulse oximetry revealed that her 3% oxygen de-saturation index (ODI) was 14.19/h, and the total time spent with an oxygen saturation of <88% was 5 hours and 25 minutes (70.6% of the total recorded time), suggesting severe nocturnal hypoventilation (Fig. 3A). She had not taken any medications that induced depression of ventilation. We considered the cause of her symptoms to be hypercapnic
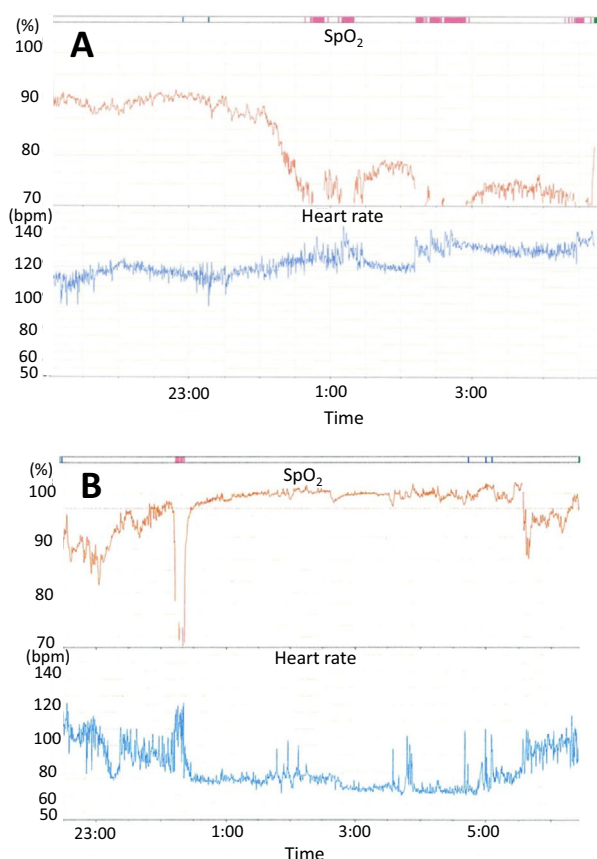
Figure 3. **Nocturnal pulse oximetry findings in the patient. (A) Nocturnal pulse oximetry before noninvasive positive pressure ventilation (NPPV) showing severe oxygen desaturation accompanied by tachycardia. There were few saw-tooth patterns on oxygen desaturation waveforms, suggesting that nocturnal hypoxia in this patient was caused by hypoventilation rather than sleep apnea. (B) Nocturnal pulse oximetry during NPPV therapy showing improvement in her nocturnal hypoxemia and tachycardia. SpO$_2$: percutaneous oxygen saturation**

ventilatory failure due to nocturnal alveolar hypoventilation.

On day 5 after admission, she fell unconscious with carbon dioxide narcosis and began nocturnal NPPV therapy for alveolar hypoventilation. The bi-level positive airway pressure setting was started with a weak pressure, considering her small body type, and adjusted according to her clinical examination findings, SpO$_2$, and ABG (Table). On day 17 after admission, she developed aspiration pneumonia after breakfast and had to be placed on oxygen. Finally, her PaCO$_2$ level decreased to 59.4 mmHg with the use of NPPV. In addition, her 3% ODI improved to 3.63/h, and the total time with a saturation <88% decreased by 33 minutes (7.06% of the total recorded time) (Fig. 3B). On day 26 after admission, the combined use of oxygen supplementation at night was stopped since her PaO$_2$ was as high as 150 mmHg.

However, she complained of abdominal distension and nausea during NPPV therapy. Contrast-enhanced CT (Fig. 2C, D) of the abdomen revealed a grossly dilated

stomach and duodenum, with an abrupt narrowing of the duodenum behind the superior mesenteric artery (SMA). Based on these findings, we diagnosed the patient with SMA syndrome. We started her on conservative therapies, including posture changes, dietary changes, and intravenous nutrition support. After treatment, her symptoms improved, and intravenous nutrition was discontinued. Finally, her nocturnal hypoxemia improved without supplemental oxygen using NPPV. After discharge, she continued to use nocturnal NPPV at home.

With written informed consent from the patient and her mother, and approval by an ethics committee, we performed methylation analyses for two differentially methylated regions (DMRs) responsible for SRS (the *H19/IGF2*: IG-DMR at the 11p15 imprinted region and *MEST*:alt-TSS-DMR on chromosome 7) (10). However, the methylation levels of these DMRs were normal. Next, we attempted to identify the molecular cause through a whole-exome analysis of the patient, her mother, and her older sister. The method was applied to all mutations in the Human Genetic Variation Database predicted to match her clinical features (11). As one of the potential responsible genes, the variant G529A and A177T mutation in exon 6 of the *ALPL* gene was found to be homozygous in the patient; however, the same variant was identified as heterozygous in her mother. In this case, the relationship between the *ALPL* gene mutation and her growth delay was unclear.

Discussion

This was the first case in which NPPV was effectively used to treat hypercapnic respiratory failure in an adult patient with clinically diagnosed SRS. One retrospective study identified mild sleep-disordered breathing (SDB) in 74% of children with SRS, and most children with SRS presented obstructive sleep apnea, possibly due to narrowing of the airways and lymphoid organ hypertrophy (12). In the present case, polysomnography (PSG) was preferred for the evaluation of the SDB type; however, we could not perform diagnostic PSG because the patient developed carbon dioxide narcosis and it was difficult to withdraw NPPV. Although the occurrence of obstructive sleep apnea could not be ruled out, her nocturnal hypoventilation was considered to be the main type of SDB, as suggested by the oxygen desaturation pattern that lacked saw-tooth waveforms of nocturnal pulse oximetry.

The cause of respiratory failure in this case may have been chronic respiratory muscle weakness due to the patient's severe growth delay. We consider her growth delay and malnutrition likely to have been caused by SRS, and the secondary SMA syndrome accelerated the muscle atrophy. Digestive problems and malnutrition occur in over 70% of patients with SRS (13). Failure to thrive in children with SRS is considered likely to be due to a combination of factors, including poor appetite, feeding difficulties, and gastrointestinal problems (1). SMA syndrome is a digestive condi-

tion characterized by the extraluminal compression of the duodenum by the SMA and the abdominal aorta and is attributed to the loss of the mesenteric fat pad. Most patients present with chronic abdominal symptoms, including nausea and vomiting, postprandial abdominal pain, and anorexia (14). The resulting weight loss further decreases the intervening space surrounding the duodenum. In addition, chronic obstruction can result in significant distention of the stomach, which can trigger a vicious cycle in which the mesenteric root along with the SMA is further displaced posteriorly (15). The present patient had symptoms of chronic abdominal fullness, nausea after eating, anorexia, and significant gastric distension on chest radiography. Although SRS is known to be associated with digestive problems or malnutrition, including severe gastroesophageal reflux (13), there have been no reports on the complications of SMA syndrome related to SRS. We should therefore pay attention to the complications associated with SMA syndrome due to long-term failure to thrive in adult cases of SRS.

SRS is a not only a clinically but also a genetically heterogeneous disease. While an underlying molecular cause can be identified in around 60% of patients clinically diagnosed with SRS (5), the etiologies are not detected in approximately 40% of patients (16). We detected a homogeneous *ALPL* gene mutation using a whole-exome analysis in this case. An *ALPL* gene mutations is reported as a causative mutation for hypophosphatasia, which is a systemic skeletal disorder resulting from a tissue-nonspecific alkaline phosphatase deficiency (17, 18). This enzyme plays an important role in the growth and development of bones and teeth. Although the present patient did not satisfy the clinical criteria for hypophosphatasia, the *ALPL* gene mutation may have had some effect on her growth.

The present patient had muscle atrophy and mild muscle weakness, which are atypical findings of SRS (19). Although congenital neuromuscular diseases were considered as differential diagnoses, she had a normal musculoskeletal system in her childhood. Furthermore, her muscle weakness was mild and symmetrical, even as an adult. Therefore, we speculated that the cause of her muscle atrophy was long-time malnutrition. However, there may have been other hidden genetic abnormalities that caused hypotonia and muscle atrophy. It is possible that she had structural abnormalities in the regions containing promoters and enhancers that could not be identified by an exome analysis. Very little information exists in the literature about the long-term course of SRS. Most patients with SRS are not routinely followed up, and the small number of reported adults have had few severe medical problems. However, careful observation from childhood is necessary in patients where SRS is clinically suspected, as these patients have an increased risk of developing chronic respiratory failure or heart vascular disease due to severe growth delay. In addition, nocturnal alveolar hypoventilation cannot be detected with daytime SpO$_2$ alone; therefore, the diagnosis is likely to be missed in childhood.

When patients complain of an early morning headache or fatigue, it is important to screen for hypercapnia by ABG or for hypoventilation by night pulse oximetry. At present, there are very few reports on SDB associated with SRS, so further studies are necessary.

The authors state that they have no Conflict of Interest (COI).

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