Orthodontic Treatment in Conjunction with Twin-bock Treatment and Growth Hormone Therapy in Silver Russell Syndrome

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Silver-Russell syndrome (SRS) is a very rare genetic disorder characterized by intrauterine growth retardation, short stature, and typical craniofacial abnormalities including micrognathia. While growth hormone (GH) therapy in children with SRS significantly improves somatic growth, functional orthopedic treatment can also be effective in adolescents with mandibular deficiency. We report the effects of Phase 1 functional orthopedic treatment of a twin-block appliance in conjunction with GH administration in a 9-year-old boy with GH deficiency and SRS, and the result of the subsequent Phase 2 orthodontic treatment.

Key words:*Silver-Russell syndrome, growth hormone, twin-block appliance*

INTRODUCTION

Silver-Russell syndrome (SRS) is a very rare genetic disorder of unknown etiology—possibly related to chromosome 7 and 11p15.5.[1] The syndrome was first independently reported by Silver in 1953, and by Russell in 1954.[2,3] SRS is characterized by intrauterine growth retardation, low birth weight, proportionately short stature, growth deficiency, early pubertal development, body asymmetry, low-set ears, fifth-finger clinodactyly, and other characteristics.[4-6] Growth rate is normal, but the average adult height without growth hormone (GH) therapy is 151.2 cm (-7.8 SD) for males and 139.9 cm (-9 SD) for females.[7]

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Typical craniofacial abnormalities with SRS include a small triangular face, decreased posterior facial height, a small mandible with short ramus, downturned corners of the mouth ("shark's mouth"), and a prominent forehead. The dental assessment includes microdontia, high-arched palate, and severe crowding secondary to micrognathia.[7,8] SRS is primarily diagnosed by the identification of consistent clinical features.

Human GH therapy in children with SRS significantly improves somatic growth, even in the absence of GH deficiency.[9] The administration of human GH seems to induce the cartilage-mediated growth of the mandibular condyle.[10]

To treat the patient with SRS, we accomplished Phase 1 functional orthopedic treatment with a combination of a twin-block appliance, GH administration, and a subsequent Phase 2 orthodontic treatment.

Diagnosis and etiology

A 9 year and 1 month old boy was referred by a pediatrician due to severe anterior crowding. The chief complaint from his parents was upper anterior protrusion and severe lower crowding. The patient's height was 113.3 cm (below the 3rd percentile of a normal Korean boy's growth chart) with a normal upper to lower segment ratio, and his weight was 23 kg (10~25 percentile). The patient was born at 39 weeks, weighing 1.9 kg. His father, mother, and elderly sister's heights were 170 cm, 159 cm, and 162 cm, respectively. There was no report of a history of endocrine system genetic defects in the family.

A thyroid function test demonstrated a total T3 of 142.6 ng/dL (normal 60-181 ng/dL), free T4 of 1.36 ng/dL (normal 0.89-1.76 ng/dL), and TSH of 1.08 μU/mL (normal 0.35-5.5 μU/mL). The IGF-1 level was 74.9 ng/mL (normal 74-551 ng/mL), and the peak GH level in an insulin tolerance test was 6.56 ng/ml. A GH stimulation test with clonidine showed that the GH level at maximum was 8.49 ng/mL. The boy's bone age at 8.5 years was 7 years (delay of

bone age was 1.5 years). The sellar MRI indicated that the size and shape of his pituitary gland was normal and there was no evidence of adenoma.

Low birth weight and a proportionate short stature could be attributed to intrauterine growth retardation. There was no evidence of body asymmetry, and he lacked fifth-finger clinodactyly. A craniofacial evaluation showed he had a small triangular face, a prominent forehead, low-set ears, "shark's mouth," a small mandible, and upper lip protrusion. Intraoral examination revealed severe lower anterior crowding, narrow upper and lower arch, excessive anterior overjet, and deep overbite (Figs. 1 and 2). Cephalometric findings showed a Class II skeleton with large ANB difference, a retrusive chin, convex profile, decreased posterior facial height, short ramus, severely proclined maxillary incisors, and the eruption of his permanent teeth was delayed with normal root development (Fig. 3).

The patient was diagnosed with SRS and partial GH deficiency.

Treatment objectives

The treatment objectives were to (1) stimulate mandibular growth during twin-block therapy in conjunction with GH administration; (2) relieve the locked occlusion by slow buccal expansion during Phase 1 orthopedic treatment; (3) improve facial profile and lip seal; and (4) create space for alignment and accomplish a functional occlusion through Phase 2 comprehensive orthodontic treatment.

Fig 1. Pretreatment facial and intraoral photographs

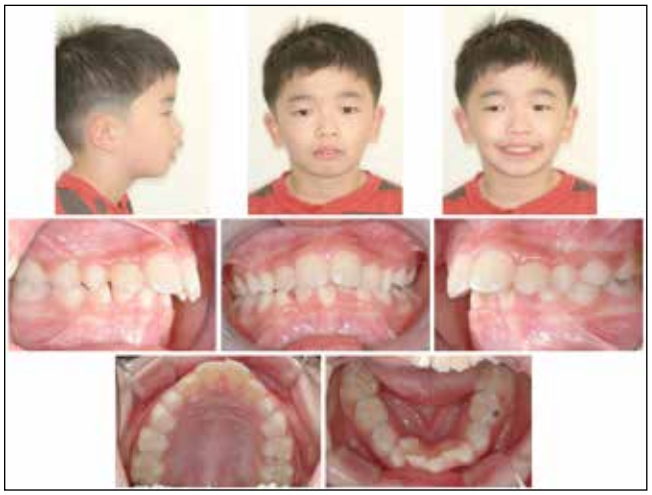


Fig 2. Pretreatment study models

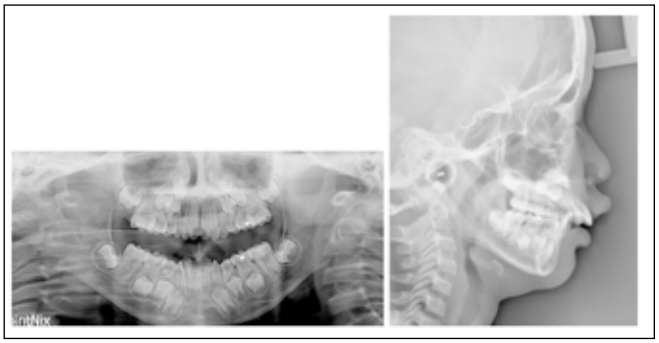
Treatment progress

From the age of 9 years and 1 month, the recombinant human growth hormone (Eutropin, LG Life Science, Korea) was administered for 4 years as a subcutaneous dose of 0.3 mg/kg/wk. At 2 years and 6 months into treatment, the boy's pubertal growth and bone age had progressed rapidly. At this point, gonadotropin-releasing hormone analogue (GnRHa, Triptorelin 3.75 mg) was injected intramuscularly at 4-week intervals to treat the delayed bone age. Thyroid hormone and glycated hemoglobin (HbA1c) were normal when monitored at 3- to 6-month intervals. His IGF-1 level was 74.9 ng/mL (normal 74-551 ng/mL) at the start of GH treatment, 329 ng/mL at 0.5 years of treatment, 508 ng/mL at 2 years of GH treatment, and 724 ng/mL at 3 years of GH treatment. During the four years of GH therapy, the boy's height increased 8.3 cm in the first year, 8.4 cm in the second year, 9.5 cm in the third year, and 5.4 cm in the fourth year, and his weight increased by 2 kg, 5 kg, 6.5 kg, and 4.5 kg, respectively (Fig. 4).

A twin-block appliance with a buccal expansion screw was delivered to stimulate mandibular growth. The construction bite was recorded at baseline to monitor a desired 5 mm mandible advancement. The Patient was instructed to wear the appliance for 12 to 16 hours a day. After 11 months of the first application, the twin-block appliance was reconstructed with 4 more millimeters of mandibular advancement. To unlock the occlusion and relieve the anterior crowding, slow buccal expansion in both arches was also achieved during the twin-block treatment. After another 9 months of a second application, the anterior overbite and overjet were reduced and the facial profile was improved by the significant growth of the mandible. Buccal expansion in both arches was achieved, relieving the arch length discrepancy. (Figs. 5 and 6) Cephalometric analyses demonstrated that the mandible had grown sufficiently within the normal range of ANB difference. The severely proclined maxillary incisors were spontaneously corrected and finished within the normal range. And the anteroposterior position of mandibular incisors was well maintained. There was no evidence of anterior displacement of the mandibular condyle or rotational growth of the mandible (Figs.7, 11, and Table). This appliance was maintained as a retainer for 12 months before the start of Phase 2 orthodontic treatment.

Phase 2 treatment was started at the age of 12 years and 1 month. We used a 0.018-in slot straight bracket system with an 0.016-in heat-activated NiTi archwire, 0.017 x 0.025-in heat-activated NiTi archwire, and 0.017 x 0.025-in TMA archwire sequentially. The alignment in both arches was completed by mild arch expansion

Fig 3. Pretreatment radiographs



and interproximal reduction without the extraction of premolars. Although the impaction of maxillary canines is not related with SRS,[11] in this case the maxillary left canine was impacted and its orthodontic traction was done after closed flap surgery. After Phase 2 treatment, lingual fixed retainers were bonded and removable Hawley retainers were delivered in both arches.

Fig 4. Height growth curve during growth hormone treatment

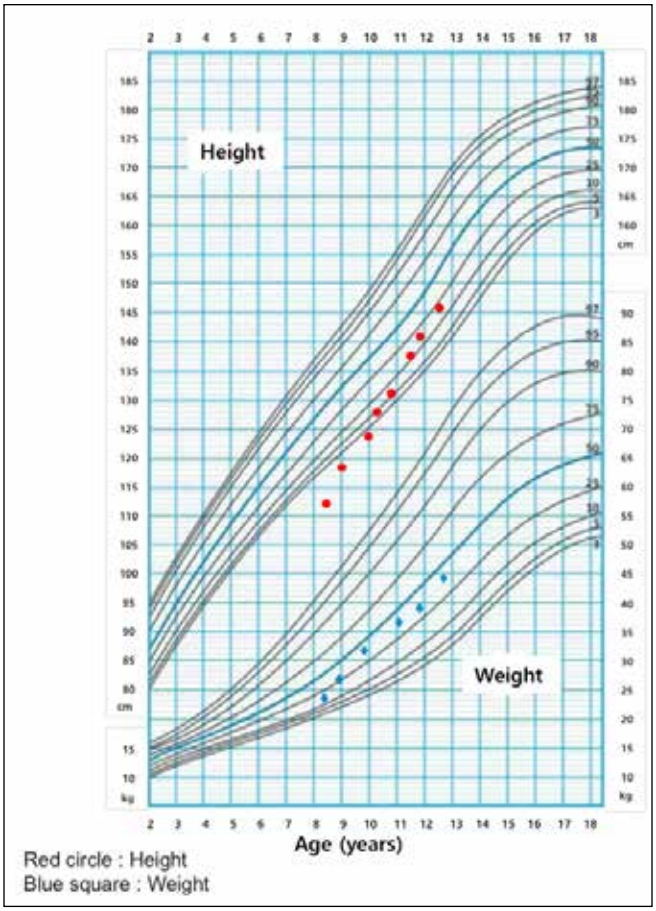


Fig 5. Facial and intraoral photographs after Phase 1 treatment

Fig 6. Study models after Phase 1 treatment

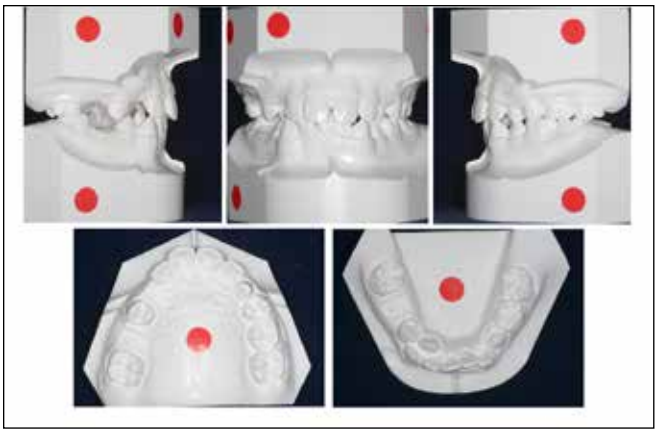


Fig 7. Radiographs after Phase 1 treatment

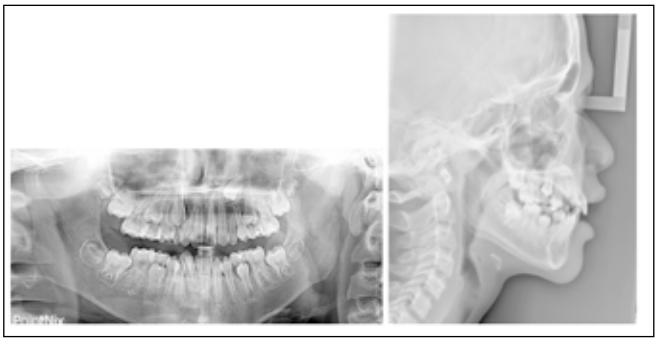


Table. Cephalometric measurements

Measure-ment	Norm	Pretreatment	After Phase I tx	Posttreatment
SNA (°)	82.0	82.6	83.6	82.8
SNB (°)	80.0	74.9	78.9	79.1
ANB (°)	2.0	7.7	4.7	3.7
Wits (mm)	-1.0	2.2	-1.1	-1.9
SN–MP (°)	32.0	35.2	35.6	34.5
FH–MP (°)	24.0	26.4	26.1	25.2
LFH(ANS-Me/N-Me)(%)	55.0	56.0	57.1	57.6
U1–SN (°)	104.0	115.8	102.6	104.4
U1–NA (mm)	4.0	8.0	3.6	5.1
IMPA (°)	90.0	92.7	94.5	95.8
L1–NB (mm)	4.0	5.4	6.4	7.3
U1/L1 (°)	131.0	116.3	127.3	125.3
Upper lip to E plane (mm)	-4.0	6.0	4.5	3.0
Lower lip to E plane (mm)	-2.0	3.0	4.8	3.0

Treatment results

Posttreatment facial photographs demonstrated that the lower third of facial profile was significantly improved. The protrusion of the upper lip was somewhat reduced, and the lower lip position has been improved. Posttreatment intraoral photographs demonstrated that the highly impacted maxillary left canine was successfully aligned, surrounded with good periodontal support and that a functional occlusion was achieved. Both arches were well coordinated and the dental midline was also corrected (Figs. 8 and 9). A panoramic radiograph showed normal root development of the maxillary left canine and root parallelism throughout the whole dentition. Lateral cephalograms were superimposed and revealed that there was significant skeletal, dental, and soft tissue improvement (Figs. 10, 11, and Table).

Phase 1 and Phase 2 treatments took 20 months and 28 months, respectively, and the interim period between the two Phases was 12 months.

Fig 8. Posttreatment facial and intraoral photographs

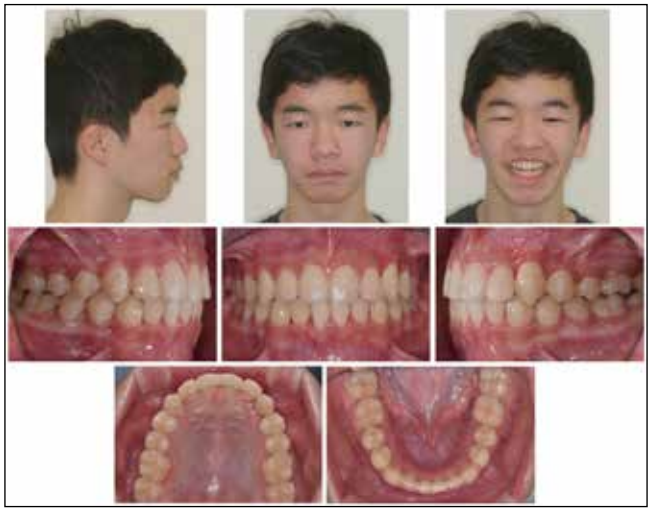
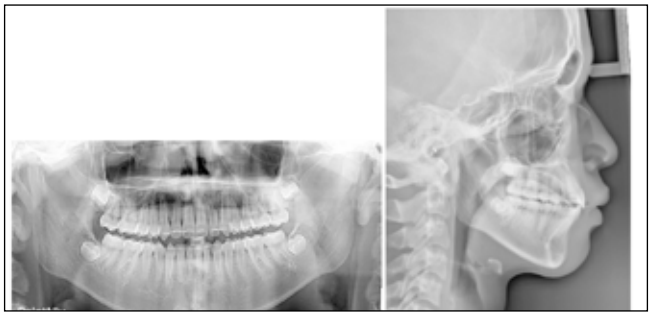


Fig 9. Posttreatment study models

Fig 10. Posttreatment radiographs



DISCUSSION

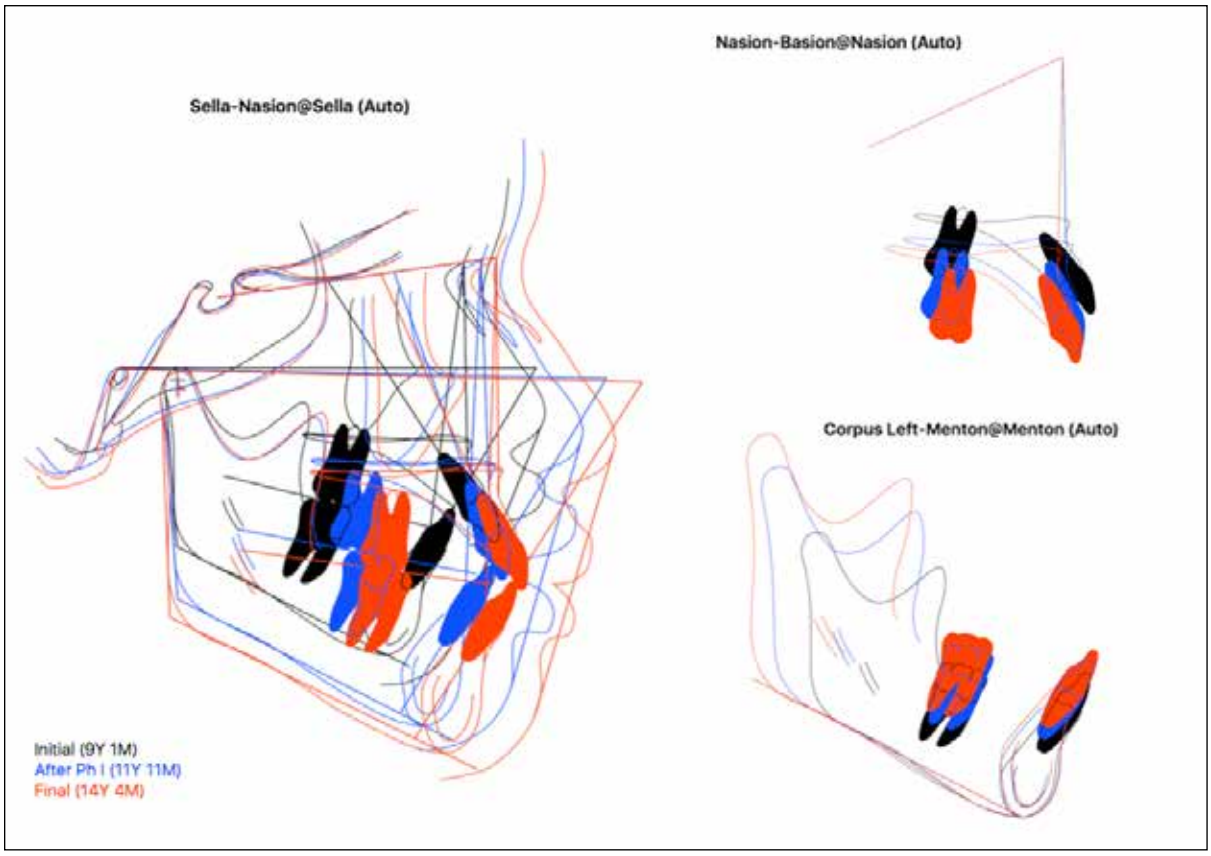
SRS is a uniform malformation syndrome and under-diagnosed genetic disorder. The meaningful genetic tests are limited due to the unknown cause of SRS. Chromosome abnormalities have been reported, but a consistent pattern of genetic abnormalities in SRS is not present. Therefore, SRS is mainly diagnosed by clinical implications of pre- and post-natal growth restriction and typical craniofacial manifestations based on only two reports (1953 and 1954).[2,3] Although one of the most important diagnostic criteria of SRS is unique craniofacial morphology, the rare occurrence of SRS tends to be overlooked in the field of dentistry. SRS is characterized by severe intrauterine growth retardation and further loss of weight and height during infancy and early childhood caused by eating difficulties. The first major component of the diagnosis of SRS is severe intrauterine growth retardation and shortness of stature.

GH treatment strongly facilitates somatic growth—stature, long bones, etc. The Recombinant GH is a currently accepted growth-promoting drug for children born small relative to their gestational age, including children with SRS.[12] SRS might not always be accompanied with GH deficiency.[13] Instead, it might be rather due to a lack of receptor sites for GH or increased GH resistance with normal GH secretion. The patient in this report was diagnosed with SRS with partial GH deficiency. It was observed that his height increased incrementally during the four years of GH treatment. However, Rakover *et al* mentioned that many children with SRS still do not achieve normal stature even with GH therapy.[9]

The second major component of the diagnosis of SRS is unique craniofacial morphology. Bergman et al found that the children with SRS showed deviations in their facial proportions such as a retro-positioned, and steeply inclined maxilla and mandible, and a proportionally larger anterior facial height in relation to their posterior facial height. Since their skull size compared with the face seemed to be normal, he hypothesized that there was a lack of catch-up growth, even in the face.[11]

Kisnisci *et al* reported that a small mandible in SRS was corrected by distraction osteogenesis for arch broadening and mandibular advancing surgery after the completion of growth.[14] If the mandibular growth can be stimulated by the use of a functional appliance in conjunction with GH treatment, it is assumed that Phase 2 orthodontic treatment could be simplified and possibly allow for the avoidance of jaw surgery later. Davies *et al* reported that the growth of the mandible in Turner's syndrome was stimulated by a functional appliance in conjunction with GH treatment.[15] Several case reports showed that GH treatment affects the growth of the mandible more than the growth of the maxilla during

Fig 11. Cephalometric superimposition pretreatment, after Phase 1 treatment, and posttreatment



orthodontic treatment.[16,17] Although the effect of GH on craniofacial bony components is poorly understood, it is believed that GH treatment primarily affects craniofacial regions where cartilage-mediated growth occurs and in regions that adapt to cartilage growth, particularly in the mandibular ramus.[15,18,19]

Pretreatment IGF-I levels may have a role in predicting responsiveness to GH and IGF-I monitoring as a tool for dose optimization may be useful in those children receiving GH treatment.[20] Suzuki *et al* noted that the local injection of IGF-I stimulates the condylar growth of the mandible in mature rats.[21] The IGF-I level in acromegaly patients was significantly elevated with increased secretion of GH.[22] Interestingly, the IGF-I level in our patient was significantly increased during twin-block treatment and GH administration. It may be postulated that the significant growth of our patient's mandible might be attributed to an elevation of the IGF-I level due to the GH treatment. However, it cannot be asserted that the elevated IGF-I level during GH treatment would accelerate the mandibular growth by twin-block appliance. Further research should be conducted to support the role of IGF-I level for mandibular growth.

With our patient, lateral cephalometric superimposition and corresponding measurements revealed that the amount of skeletal change was greater than that of the dentoalveolar change. The ANB difference was significantly decreased by the mandibular growth, which occurred at the mandibular ramus as well as in the mandibular body. After Phase 1 treatment, the interincisal angle was obtuse and the mandibular incisors were somewhat uprighted. This may be explained as favorable dental compensation due to catch-up growth of the mandible.

Singleton *et al* reported that the greatest treatment effect and catch-up was seen in rats with the lowest relative maturity whereas more mature measures showed less growth response to GH replacement.[23] Some clinicians showed that twin-block therapy was more effective during or slightly after the onset of the pubertal peak in growth velocity.[24,25] In our case, the twin-block therapy was started at the age of 9 years 1 month, maintained until after pubertal growth peak, and stopped at the age of 11 years 11 months. The bone age of the patient exceeded chronological age in the middle period of the twin-block therapy. After Phase 1 treatment of twin-black appliance and GH administration, the ANB value was reduced from 8 degrees to 5 degrees and facial profile was improved from 16 degrees to 11 degrees. We assume that the mandibular growth would have been sufficiently stimulated by GH treatment despite the use of functional appliance therapy at an early age. Like Bergman's hypothesis, we speculate that children with SRS might have a lack of catch-up growth in their faces including their mandibles, but not their genetic undergrowth. Because of his facial change, the mechanics of Phase 2 treatment of our patient was simplified without a need to remove his premolars or to pursue any other surgical approaches. However, the total treatment period was extended due to a prolonged Phase 1 treatment.

Davies *et al* showed that there was a normal pubertal growth spurt in SRS children similar to that of healthy children.[26] Rakover *et al* demonstrated that the onset age of puberty was just about normal in children with SRS.[9] However, Wollmann *et al* reported that early or precocious puberty was present in less than 10 percent of SRS cases.[7] Our patient also showed precocious puberty during the prolonged GH treatment and GnRHa was subsequently

administered to delay his bone maturation and pubertal growth. Further research might be required to assess the effective timing of twin-block therapy in conjunction with GH treatment.

With SRS, there is severe crowding in the mandibular arch, secondary to the small mandible, but there is no evidence of delayed eruption of permanent dentition, congenital missing teeth, or delayed dental maturity.[11] Ioannidou-Marathiotou *et al* reported that the mandibular arch width was normally developed by expansion treatment during late mixed dentition.[27] The development of arch width in growing children might not be disturbed by SRS. We conducted slow buccal expansion in both arches during twin-block treatment and GH therapy. Arch expansion was sufficient to relieve the arch length discrepancy and the normal eruption of the teeth occurred spontaneously without other disturbance or delay. It is not clear whether the arch expansion was also stimulated by the GH treatment. Kotilainen *et al* reported that there was delayed tooth development in 19 SRS patients, although great variation was seen.[28] Ito et al stated that GH therapy in idiopathic short-statured children had a significant influence on acceleration or gain in stature, but it did not have a significant influence on tooth formation.[29] Bergman *et al* demonstrated that SRS might have tendencies towards a delay in tooth eruption, but no delay of dental maturation and root formation.[11] Although the impaction of a maxillary left canine was found in our patient, it is considered to be merely delayed eruption due to the retained primary maxillary left canine. After extraction of the primary canine and forced eruption, the impacted canine showed a normal eruption pattern.

CONCLUSION

We provided twin-block treatment in conjunction with GH administration in a boy with SRS. His height was significantly increased by GH administration and his mandibular growth was sufficiently promoted by the twin-block treatment. As a result, this early combination treatment of an SRS case simplified the mechanics of Phase 2 orthodontic treatment, eliminating the need to remove premolars or have additional orthognathic surgery later.

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