Clinical Case Report

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Craniofacial anomalies associated with spondyloenchondrodysplasia

Two case reports

Seok Woo Hong, MD[a], Kyung-Hoe Huh, DDS, PhD[b], Jeong Keun Lee, DDS, PhD[c], Jeong-Hyun Kang, DDS, PhD[d,*]

Abstract

Rationale: Spondyloenchondrodysplasia (SPENCD) is an autosomal recessive skeletal dysplasia by biallelic mutations in *ACP5* gene encoding tartrate-resistant acid phosphatase (TRAP). The extra-osseous phenotype of SPENCD is pleiotropic and involves neurological impairment and immune dysfunction. Dentofacial abnormalities and orofacial symptoms in SPENCD patients have been little discussed in the literature.

Patients concerns: Herein we present clinical and radiological data regarding 2 siblings with SPENCD. Both patients exhibited short stature, cervical platyspondyly, growth disturbances with multiple skeletal deformities of the wrist, and systemic lupus erythematosus related autoimmunity. They experienced prolonged pain in the temporomandibular joint (TMJ) area and exhibited delayed dental development. One patient presented with midface hypoplasia, retrognathic mandible, and anterior openbite. Computed tomographic images demonstrated delayed spheno-occipital synchondrosis, obtuse cranial base angle, overdeveloped and anteriorly displaced sphenoidal sinuses, and compressed ethmoidal sinuses.

Diagnosis: The genetic analysis revealed heterozygous for a missense mutations at *ACP5* in both probands.

Interventions: Routine follow-up with conservative treatment were conducted for 12 months.

Outcomes: The elder sister's orofacial pain was relieved but the boy showed sustained masticatory and cervical muscle pain and TMJ arthralgia which had changed in accordance with systemic condition. No further teeth eruption or skeletal growth was observed in 2 siblings during the follow-up period.

Lessons: These findings extend the phenotypic spectrum of SPENCD and indicate that compromised endochondral ossification and the loss of TRAP activity may affect altered dentofacial development and orofacial symptoms.

Abbreviations: CT = computed tomography, JIA = juvenile idiopathic arthritis, SLE = systemic lupus erythematosus, SPENCD = spondyloenchondrodysplasia, TRAP = tartrate-resistant acid phosphatase.

Keywords: ACP5, skeletal dysplasia, spheno-occipital synchondrosis, spondyloenchondrodysplasia, tooth eruption

1. Introduction

Spondyloenchondrodysplasia (SPENCD) is a rare autosomal recessive skeletal dysplasia featured by the presence of endochondromatous nonossifying metaphyseal and spondylar lesions.[1,2] Endochondromatous lesions predominantly develop within the pelvis and long bones but these could also occur in other areas of endochondral growth.[3] Dorsally accentuated platyspondyly with disturbances in ossification and significantly short stature are the main clinical characteristics of SPENCD.[4] The extra-osseous phenotype of SPENCD is pleiotropic and involves neurological impairments such as spasticity, intracranial calcification, and mental retardation and immune dysfunctions including Sjogren syndrome, renal failure, vasculitis, and systemic lupus erythematosus (SLE) like pathologies.[4–7]

Owing to advances of genetic technology, genetic etiology of SPENCD was revealed. SPENCD is caused by biallelic mutations in *ACP5* gene, which encodes tartrate-resistant acid phosphatase (TRAP).[8] TRAP plays a role in the dephosphorylation of osteopontin, which is known to affect osteoclast activity and type I interferon production.[9] The loss of TRAP activity in SPENCD patients results in increased serum osteopontin levels and abnormal osteoclast activity, leading to impaired cartilage resorption and bone dysplasia.[8] Elevated type I interferon levels due to increased osteopontin levels alter immune regulation, leading to the development of SLE like phenotype.[8,9]

Several studies have reported the skeletal, immunological, and neurological aspects of SPENCD.[1,3–7,10] However, the craniofacial manifestations of SPENCD in terms of the pathophysiology of

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[a] Department of Orthopedic Surgery, College of Medicine, Ewha Womans University, [b] Department of Oral and Maxillofacial Radiology, School of Dentistry and Dental Research Institute, Seoul National University, [c] Department of Oral and Maxillofacial Surgery, [d] Clinic of Oral Medicine and Orofacial Pain, Institute of Oral Health Science, Ajou University School of Medicine, Suwon, Korea (ROK).

[*] Correspondence: Jeong-Hyun Kang, Clinic of Oral Medicine and Orofacial Pain, Institute of Oral Health Science, Ajou University School of Medicine, 164, Worldcup-ro, Yeongtong-gu, Suwon, Gyeonggi-do 16499, Korea (ROK) (e-mail: irene85@snu.ac.kr).

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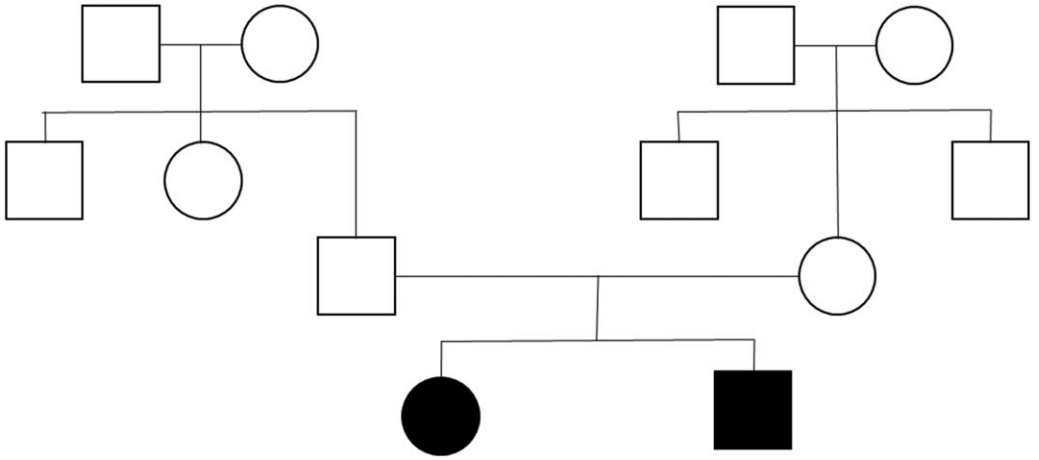

Figure 1. Pedigree of 2 cases with SPENCD included in the present study. SPENCD = spondyloenchondrodysplasia.

this rare disorder are poorly documented in the literature. Herein we present clinical and radiological data regarding 2 siblings with SPENCD who were born to non-consanguineous parents. We aimed to present the maxillofacial abnormalities and orofacial symptoms associated with the pathophysiology of SPENCD and to share the diverse aspects of this pleiotropic entity.

2. Case presentation

The cases in this report were from 2 patients of the Temporomandibular joint (TMJ)· Orofacial Pain Clinic, Ajou University Dental Hospital, between May 2017and May 2018. The probands were 13-year-old boy and 16-year old his elder sister who were born from their unaffected nonconsanguineous parents (Fig. 1). The ethical approval of research protocol was approved by the Institutional Review Board of the University Hospital (#AJIRB-MED-EXP-17–457). The patients and their parents agreed an approval for the publication of the cases under anonymized conditions.

2.1. Case 1

The 13-year-old boy presented malocclusion, delayed teeth eruption, and midface hypoplasia. He complained of bilateral preauricular pain, headache and myalgia in the masticatory and cervical muscles. All symptoms had begun approximately 4 years prior. He was 125.4 cm tall (− 6 SD), weighed 43 kg, and showed mental retardation.

The boy had presented with short stature, choreic movement, severe headache, hypertension, hematuria, and multiple arthralgia in the elbows, knees, wrists, fingers, ankles, and lumbar spine when he was 6 years old. Elevated levels of C-reactive protein, decreased complement levels (C3 and C4 proteins), and positive reactions to autoimmune antibodies including antinuclear antibody and anti-dsDNA had been detected. Following kidney biopsy, the condition was diagnosed as class IV lupus nephritis (Table 1). He was clinically diagnosed as SPENCD with systemic lupus erythematous (SLE) based on radiographic and clinical findings, 7 years of age. Piroxicam, prednisolone, azathioprine, gabapentin, and topiramate had been prescribed to control arthralgic pain and headache. Furthermore, mycophenolate mofetil, atenolol, and enalapril had been commended to control hypertension and renal failure caused by lupus nephritis.

When the boy presented in our clinic, he complained of severe pain and exhibited a limited range of mouth opening. He experienced pain on palpation in several masticatory and neck muscles, bilaterally. He showed severe growth disturbances, skeletal dysplasia, immune depressions, and dentofacial anomalies. Hand and wrist radiograph series revealed growth disturbance and endochondromatous nonossifying metaphyseal and spondylar lesions. Delayed carpal ossification, decreased radial height and radial inclination, irregular border of distal radial metaphysis with enchondroma, distal ulnar metaphyseal enchondroma, and ulnar negative variance, representing altered length proportion between ulna and radius were detected (Fig. 2). He exhibited slower eruption of permanent teeth, with delay of approximately 3 years, compared to his chronological age (Fig. 3). Lateral cephlometric radiograph and facial computed tomographic (CT) images showed abnormal morphology of cervical vertebra and cranio-mandibular development. Cervical platyspondyly, skeletal retrognathic (ANB = 7.25°) relationships with anterior openbite, obtuse cranial base angle (N-S-Ba = 147.9°, +3.4 SD), and short cranial base (N-S = 63 cm, −4.3 SD) were detected (Fig. 4). Axial CT images revealed delayed spheno-occipital synchondrosis, overdeveloped and anteriorly displaced sphenoidal sinuses, and compressed ethmoidal sinuses (Fig. 5). As part of the diagnostic work up, genetic testing was conducted. Whole exome sequencing performed and

Table 1

Patient's features with SPENCD.

			Skeletal			Neurological			Immunological					
	Age	Gender	Short stature	Metaphyseal dysplasia	Platyspondyly	Intracranial calcification	Spasticity	Developmental delay	Antinuclear positivity	Anti ds-DNA positivity	C3	C4	SLE	Renal failure
Case 1	13	Male	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Decrease	Decrease	Yes	Yes
Case 2	16	Female	Yes	Yes	Yes	No	No	No	Yes	Yes	Decrease	Decrease	Yes	No

C3 = complement component 3, C4 = complement component 4, dsDNA = double stranded DNA, SLE = systemic lupus erythematosus, SPENCD = spondyloenchondrodysplasia.

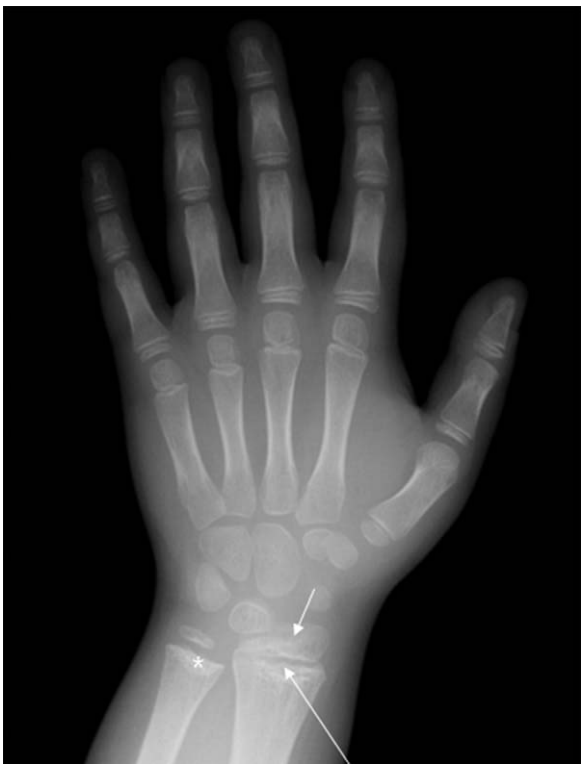

Figure 2. Hand and wrist radiographs demonstrating growth disturbances with multiple skeletal deformities of the wrist in Case 1. Delayed carpal ossification, decreased radial height and radial inclination (short arrow), irregular border of distal radial metaphysis with enchondroma (long arrow), and distal ulnar metaphyseal enchondroma (asterix).

the boy and his elder sister were found to be compound heterozygous for a missense mutations at *ACP5*, c.449T>A (p.Val150Glu, V150E) and c.136C>T (p.Arg46Trp, R46W). The former variant was considered novel when it was found in Exome Aggregation Consortium database (http://exac.broadinstitute.org) and Human Gene Mutation Database (http://www.hgmd.cf.ac.uk/ac/index.php).

Conservative management was instituted, including habit control and exercise, but a stabilization splint could not be applied due to delayed eruption. A routine follow-up was conducted for 12 months, and no further teeth eruption or skeletal growth was observed during this period. Levels of the masticatory and cervical muscle pain and TMJ arthralgia had changed in accordance with his systemic condition. Relapse followed by worsening of facial symptoms was noted when he stopped steroid therapy owing to hypertension. Orthodontic treatment was carefully considered but his parents declined it owing to the medication, masticatory muscle pain, and arthralgic pain in the TMJs. His parents are aware of prognosis of his disease and have consented to continue with the conservative treatment in order to control symptoms originating from the orofacial areas.

2.2. Case 2

The 16-year-old girl who was elder sister of case 1 complained of bilateral preauricular pain and headache which had begun approximately 3 years previously. She was 144.2 cm tall (− 3 SD) and weighed 40 kg. Similar to her brother, she had shown involuntary hand movements, pain in the lumbar and thoracic spine, and severe headache at the age of 10 years (Table 1). Elevated levels of C-reactive protein and decreased levels of C3 and C4 proteins had been detected along with positive reactions to autoimmune antibodies (Table 1). She was clinically diagnosed with SPENCD with SLE at the age of 10 years. She had complained of intermittent severe thoracic and lumbar pain and was prescribed with corticosteroids and infliximab.

When she presented in our clinic, she complained of pain on palpation in preauricular area, bilaterally. Panoramic radiograph showed approximately 3 to 4 years delay in dental maturation. Hand and wrist radiograph series revealed diffuse sclerotic changes in the radiocarpal joint. Lateral cephalometric radiograph revealed cervical platyspondyly and CT images revealed no significant skeletal problems. A genetic analysis test was performed and the heterozygous for a missense mutations at *ACP5*, c.449T>A (p.Val150Glu, V150E) and c.136C>T (p.Arg46Trp, R46W) as same as her younger brother.

Conservative management was instituted, including habit control, exercise, and a stabilization splint. Her TMJ arthralgia was relieved after 1 month, but no further dental or skeletal growth was observed during 12 month follow-up period. In addition, no relapse in the thoracic and lumbar pain was noted during the treatment period.

3. Discussion

SPENCD, a clinically heterogeneous disease which encompasses diverse conditions, including skeletal dysplasia, immune dysregulation, and neurological impairments is caused by biallelic *ACP5* mutation.[1,3,4,8,11] Abnormal osteoclast activity and increased serum levels of type I interferon in SPENCD patients may cause aberrations in the endochondral ossification process and autoimmune phenotypes.[8,11] Compromised endochondral ossification and dysregulated immunological functions may induce orofacial

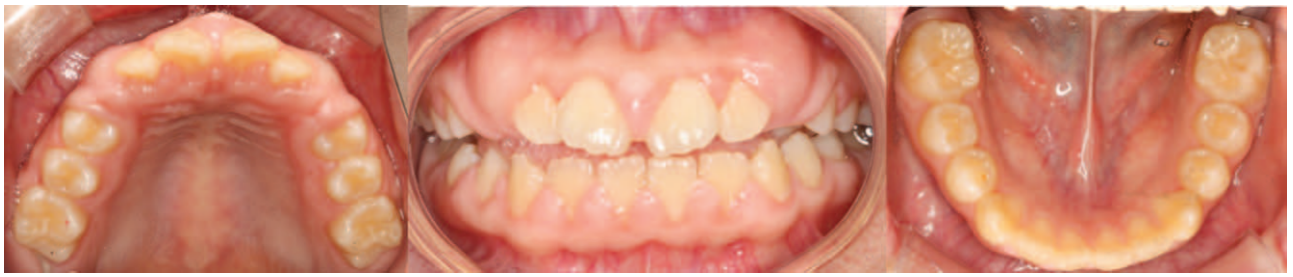

Figure 3. Intraoral photographs of the boy (Case 1) demonstrating delayed teeth eruption and anterior openbite tendency.

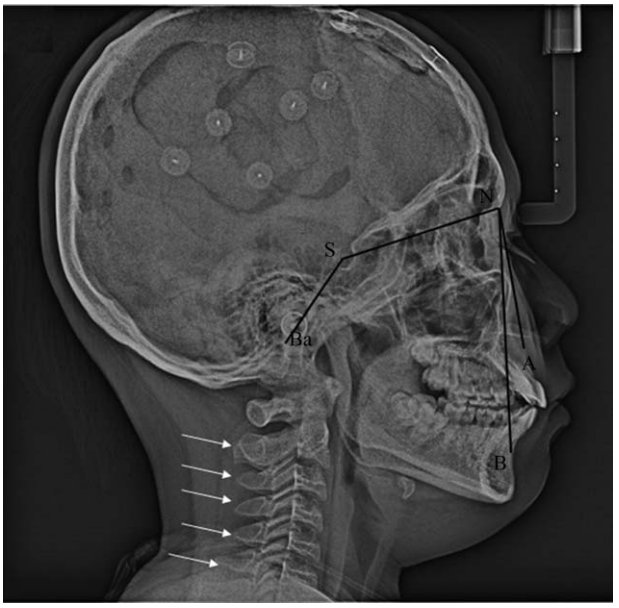

Figure 4. Lateral cephalometric radiographs of the boy (Case 1). Cervical platyspondyly (arrows), skeletal retrognathic (ANB = 7.25°) relationships, obtuse cranial base angle (N-S-Ba = 147.9°) and short cranial base (N-S = 63 cm) were detected. S = Sella, N = Nasion; A point, deepest point on the curvature of the premaxilla between the anterior nasal spine and the crest of the maxillary alveolar process; B point, the greatest point of concavity of the mandible between infradentale and Pogonion, Ba = Basion.

pain and cause abnormal dentofacial growth, unique facial profiles, and malocclusion. However, clear associations among the pathophysiology of SPENCD, orofacial pain, and dentofacial abnormalities have not been documented so far.

Short stature, cervical platyspondyly, growth disturbance with multiple deformities of the wrist, and autoimmunity are regarded as main clinical features of SPENCD,[1,3,4] and these were observed in both probands in the present study. Interestingly delayed spheno-occipital synchondrosis, obtuse cranial base angle, overdeveloped and anteriorly displaced sphenoidal sinuses, and compressed ethmoidal sinuses were observed in the boy. Unlike other craniofacial bones which are mostly formed through intramembranous ossification, spheno-occipital synchondrosis is a major cartilaginous growth site in the cranium and acts as principal growth center of the basicranium. Endochondral bone growth in spheno-occipital synchondrosis is associated with the primary displacement of the sphenoid and occipital bones.[12] The interior of the sphenoid bone becomes hollow to form a sizable sphenoid sinus after displacement.[12] Delayed synchondrosis due to the inhibition of endochondral ossification may lead to development of a short and flat posterior cranial base. Obtuse cranial base angle creates a downward and forward positions of the nasomaxillary complex, which may rotate the mandible downward and backward to form a retrognathic skeletal relationship and overdeveloped and anteriorly displaced sphenoidal sinuses.[12] Displaced sphenoidal sinuses would inhibit ethmoidal sinus development. Previous studies already reported dysmorphic facial profiles in patients with SPENCD, such as prominent premaxilla and retrognathia.[3] Altered cranial base development may cause midface hypoplasia and prominent premaxilla. Similar facial patterns have been observed in patients with achondroplasia and metatrophic dysplasia which is also characterized by alteration in endochondral ossification.[13,14]

Delayed dental development was observed in both patients. SPENCD is caused by biallelic mutations in *ACP5* gene, which encodes TRAP. TRAP is known to play a role in osteoclast activity in the alveolar bone.[15] During dental development, TRAP-positive osteoclasts were found around tooth–bone interface and remove bone as the tooth germ expanded.[15] Alteration in TRAP activity mediated by *ACP5* mutations may influence on tooth development and tooth eruption which may prevent normal dental maturation and occlusion.

Both patients have experienced bilateral TMJ arthralgia and multiple joint pains. Although the pediatric rheumatologist had not reached a diagnosis of juvenile idiopathic arthralgia (JIA), it might be suspected in these cases on the basis of their symptoms. Previous reports have showed co-existence of JIA and SPENCD[5] and the presence of pain and functional impairment of TMJ in patients with JIA has also been reported.[16] Therefore,

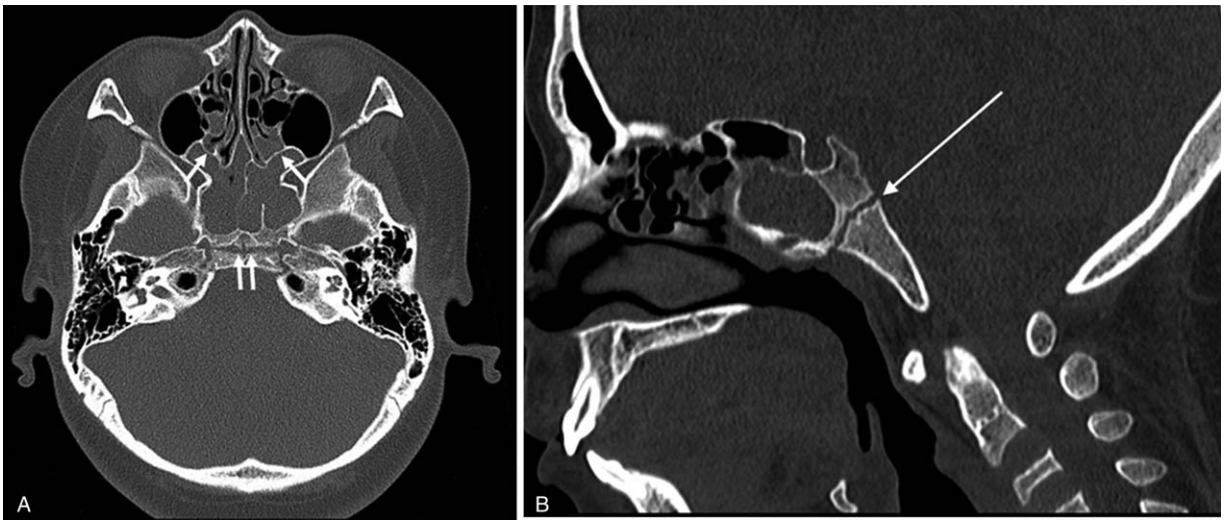

Figure 5. CT images of Case 1 (A) Axial computed tomographic (CT) image demonstrating delayed spheno-occipital synchondrosis (double arrow), overdeveloped and anteriorly displaced sphenoidal sinuses (arrows), and compressed ethmoidal sinuses. (B) Sagittal CT image demonstrating delayed spheno-occipital synchondrosis (long arrow).

preauricular pain in patients with SPENCD might considered as products of autoimmunity.

In summary, here we present craniofacial manifestations of SPENCD in 2 young patients on the basis of genetic, radiographic, and clinical data. Previous reports have focused upon the immunological and neurological aspects, but sparse reports have investigated dentofacial abnormalities in patients with SPENCD. Since not enough cases of SPENCD have been reported, the treatment protocol of growth disturbances or dentofacial anomalies have not been established. The patient with greater severity of SPENCD showed more severe dentofacial anomaly. This would imply that the dentofacial manifestations might be related with the pathophysiology of SPENCD. Including steps of evaluating dental and craniofacial growth as well as orofacial pain in diagnostic work up of SPENCD is necessary. On the basis of findings of this study, we further recommend interdisciplinary approach of patient management including pediatric radiologist, rheumatologist, orthopedic surgeon, and dentist. Finally this may eventually help improve quality of life among patients with SPENCD.

Author contributions

Conceptualization: Seok Woo Hong, Kyung-Hoe Huh, Jeong Keun Lee, Jeong-Hyun Kang.
Data curation: Jeong-Hyun Kang.
Investigation: Kyung-Hoe Huh, Jeong Keun Lee.
Supervision: Jeong-Hyun Kang.
Writing – original draft: Seok Woo Hong.
Writing – review & editing: Jeong-Hyun Kang.
Jeong-Hyun Kang orcid: 0000-0001-7124-8693.

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