

Five-year follow-up outcomes of comprehensive rehabilitation in Korean siblings with cerebral, ocular, dental, auricular, skeletal anomalies (CODAS) syndrome

A case report

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Abstract

Rationale: Cerebral, ocular, dental, auricular, skeletal anomalies (CODAS) syndrome is a very rare multisystem disorder, which shows malformations of the central nervous system, ears, eyes, teeth, and skeleton that was first reported in 1991. Only a few cases that sporadically occurred have been reported worldwide. The research investigating the pathogenesis and patterns of CODAS inheritance is still ongoing. There is no satisfactory treatment for this rare genetic disease yet. Due to the lack of curative medical treatment, rehabilitation could play a major role in treatment for genetic disease.

Patient concerns: To our best knowledge, the 2 children described in this study are the only CODAS syndromes siblings reported in the world so far. These Korean siblings show highly distinctive features consisting of developmental delay, cataracts, vulnerability to tooth decay, epiphyseal dysplasia, and anomalous ears.

Diagnoses: CODAS syndrome.

Interventions: Comprehensive long-term rehabilitation treatment during 5 years.

Outcomes: We report on the progress of the comprehensive long-term rehabilitation treatment at 5-year follow-up. Their fine motor and language skills development improved similarly to that of same-aged children. We observed the positive effect of rehabilitation on the quality of life.

Lessons: The therapy of genetic disorders is challenging for pediatric neurologists and pediatric physiatrists. We suggest that rehabilitation is the best treatment currently available for this genetic disease that yields satisfactory therapeutic effect.

Abbreviations: CODAS = cerebral, ocular, dental, auricular, skeletal anomalies, DDST = the Denver developmental screening test, FSIQ = Full Scale Intelligence Quotient, GMFCS = Gross Motor Function Classification System, K-WISC-IV = Korean Wechsler Intelligence Scale for Children Fourth Edition, LONP1 = LON peptidase 1, MRI = magnetic resonance imaging.

Keywords: CODAS syndrome, developmental disabilities, rehabilitation

1. Introduction

The first report that described cerebral, ocular, dental, auricular, skeletal anomalies (CODAS) syndrome was published by Shebib et al in 1991. The component of the CODAS syndrome consisted

of cerebral (mental retardation), ocular (early onset cataract), dental (delayed eruption of the teeth), auricular (outer ear malformation), and skeletal (dysplasia) anomalies.^[1] Only 12 patients have been reported with CODAS worldwide until now. Currently, CODAS has been proposed to be accompanied by a wide range of clinical features and symptom severity. The pathogenesis and patterns of inheritance that influence CODAS syndrome have not been clearly investigated. As the interest in the characteristics of the CODAS syndrome in the field of molecular genetics has gradually increased, Dikoglu et al identified mutations in the mitochondrial protease gene LONP1.^[2] The first Korean CODAS siblings (cases 2 and 3) were among the 7 children in this genetic study above. This case report is about the rehabilitation effect of the previously published “cases 2 and 3” siblings. There is no research about the effect of interventions such as rehabilitation for CODAS. Although in genetic disorders recovering to their normal condition is impossible, the patients can have regular examinations for surgery, rehabilitation therapy, education, and complications to maximize the quality of life by receiving proper early treatment. The siblings received comprehensive rehabilitation services, such as physical, occupational, and speech therapies. We report the detailed characteristics and significant follow-up rehabilitation outcomes of these

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siblings with this congenital syndrome. The comprehensive rehabilitation services improved motor and cognitive impairments, maximized functional abilities and would maintain independence what parents wanted best. The patients' parents have consented for publication of the case details and the images.

2. Case report

2.1. Case 1

This 10-year-old boy was born at term (36 + 5 weeks) with a birth weight of 3230 g to healthy Korean parents of non-consanguineous marriage. No remarkable family history and perinatal problems were noted. At birth, the mother and father were aged 30 and 32 years, respectively, and the boy was healthy except for physiological jaundice. His face showed a flat nose with anteverted nares without any ear abnormalities.

At the age of 2 months, his parents noticed a white spot on his pupil and he did not make eye contact. He was diagnosed with cataract at the age of 80 days. When he was 24 months old, artificial lenses were used for both eyes. He had strabismus and nystagmus. His tooth came out a little later and was vulnerable to teeth cavities. He had no hearing impairment, but mild speech delay and dysarthria were noted. He had problems with cognitive functioning, such as attention and learning.

He had a developmental delay, especially in the gross motor milestones. He started to stand without any support at 16 months. He began to walk several steps without any assistance at 18 months. He had truncal ataxia, and his balance function and posture stability decreased. Magnetic resonance imaging (MRI) at aged 24 months revealed cerebellar atrophy (Fig. 1). He started to receive comprehensive rehabilitation – physical, occupational, and speech-language therapies.

The strategies for physical rehabilitation were to facilitate proximal stability, to do core exercise, stretching and strengthening exercise, pelvic movement training, knee grading movement training, dynamic standing balance training, progressive gait training, and to educate home program.

In occupational therapy, to promote proximal stability and body scheme, to facilitate sensory interaction (vibration, balance, tactile stimulation using a swing, and a balance ball) and to promote independent activities of daily living were used. The strategies for speech rehabilitation were to communicate through

structured play for articulation therapy, to do oral mechanism exercise with phonation (lip: risorius muscle, tongue: range of motion exercise, strengthening exercise), to read sentences with appropriate speed and loudness and to maintain maximal phonation time.

The developmental level was that of 16 to 20 months at age 3 years. Overall, the development level was low in most areas (gross and fine motor development, and expression language and personal-social skills) other than the receptor language skills. At 5 years old, he had severe right knee pain accompanied by knee flexion contracture and genu valgum. MRI showed discoid meniscus in his right knee. Additionally, he had knee arthroscopic operation and a series of surgical corrections of the bilateral genu valgum (Fig. 2).

For 7 years, he has received continuous rehabilitation therapies. Regarding the complex occupational therapy, the upper extremity sensory, motor function, and coordination in both hands improved. However, his trunk stability, gait pattern, and body balance were not improved, and he was easily fatigued even though physical therapy has been provided. This was because he has ataxia of definite cerebellar atrophy and bilateral knee pain due to genu valgum. In the standing posture, anterior pelvic tilt, hip joint flexion, and lumbar hyperlordosis were noted due to hip extensor muscle weakness (Fig. 3.).

The Denver developmental screening test, 2nd edition (DDST – II)^[3] was regularly performed to track the boy's progress over time. The DDST follow-up result is shown in Table 1. He was at class II on the Gross Motor Function Classification System (GMFCS)^[4] at age 10 years. This means he could walk indoors and outdoors, hold the rail, and climb the stairs, but running and jumping were difficult.

At 5 years old, the assessment of the Korean Wechsler Intelligence Scale for Children Fourth Edition (*K-WISC-IV*)^[5] was conducted. Full-Scale Intelligence Quotient (FSIQ) was 70 (2.2%) that was classified as borderline, mild intellectual impairment. At 6 years old, attention-deficit hyperactivity was noted. Methylphenidate treatment was used for symptom relief. His dosage was increased to 20 mg as appropriate. He went to the general education elementary school with special public support. Other nonspecific symptoms were rhinitis and skin hemangioma.

2.2. Case 2

A 6-year-old girl, the younger sister of the first Korean CODAS syndrome (case 1) case underwent radiographic imaging at 4

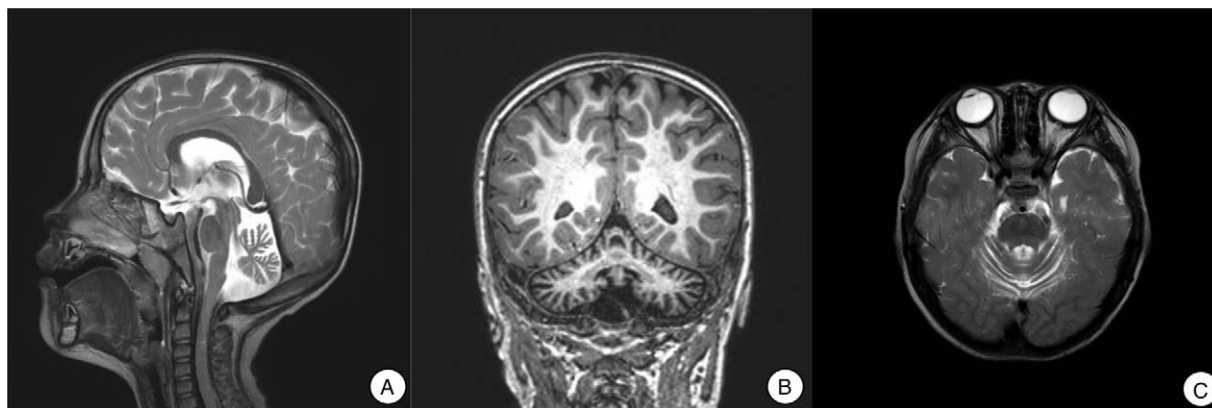


Figure 1. The MRI images of the brain in three orthogonal planes at the age of 24 months showing atrophy in the cerebellum. (A) Sagittal T2 weighted image. (B) Coronal 3D-T1 weighted image. (C) Axial T2 weighted image.

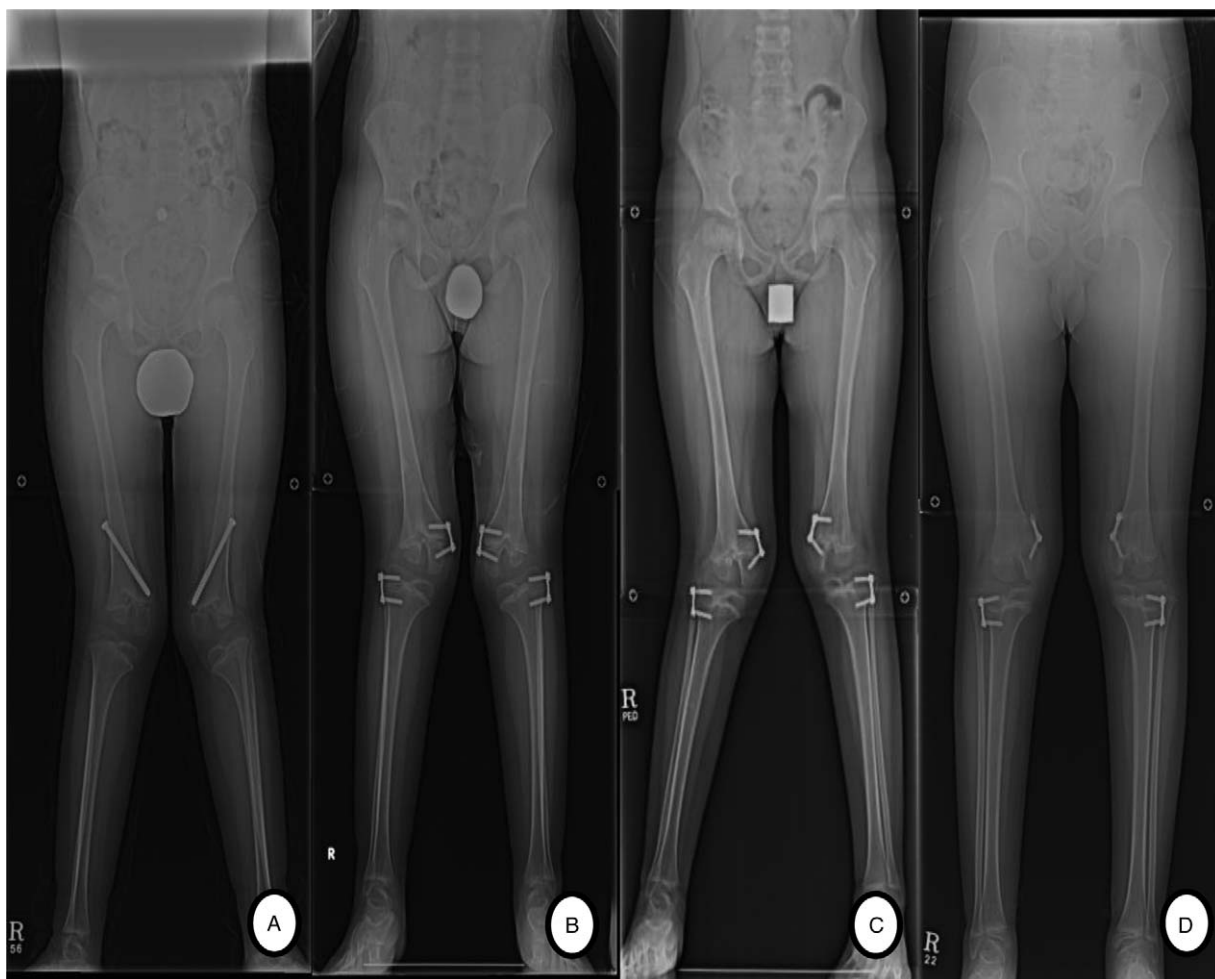


Figure 2. Lower extremity standing AP x-rays showing genu valgum at 7 (A), 8 (B), 9 (C), and 10 (D) years old. For correction of genu valgum deformity, the knee joints are fixed with screws.

months old to check if she had the same disorder as her brother. The radiograph revealed a generalized epiphyseal dysplasia. At 4 months old, ultrasound of both the hips was performed. Epiphyseal ossification was delayed with flat acetabular margins, which induced significant posture instability. Her unstable hips were treated with hip abduction brace for 3 months.

She was diagnosed with cataracts at 6 months old. At 23 months old, an artificial lens was placed on the left eye first. Mild anomalies of the external ears and membrane-like skin projection in the triangular fossa of the ears (without overfolded and crumpled ears) were noted. She had several decayed teeth accompanied with delayed teeth eruption (Fig. 4.).

At 6 and 23 months old, MRI scans were performed, which showed relatively normal findings. However, MR images taken at 46 months were suspected of mild bilateral cerebellar atrophy (Fig. 5.).

She had delayed milestones, especially with respect to motor and language development. She had bilateral genu valgum due to epiphyseal dysplasia.

She began to receive comprehensive rehabilitation at 10 months old. The strategies for physical rehabilitation were to facilitate proximal stability, normal movement, symmetric

posture and movement, to train progressive gait and to educate home program.

In occupational therapy, to offer various activities in the sitting position, to facilitate bilateral hand coordination activities, eye-hand coordination, dexterity, cognition, and independent activities of daily living were used. The strategies for speech rehabilitation were to imitate words included difficult vowels, 2 syllables of the vowel, and to promote the use of everyday verbs and articulation and phonological development.

Early and intensive rehabilitation contributed to remarkable, improved outcomes in most areas, except for motor development. DDST was followed up (Table 2).

She was classified as class III on the GMFCS at 6 years old. This meant that she could walk indoors or outdoors on a level surface with a walking aid. The Preschool Receptive-Expressive Language Scales at 6 years and 9 months (81 months) old were consistent with that of 66 months in the domain of expression and 64 months for comprehension. The result was more than a year delayed in contrast to that for her current age. At 5 years old, her FSIQ was 62 (0.5%), which was classified as mild mental retardation level. In terms of other nonspecific symptoms, she had rhinitis and vitiligo.



Figure 3. The general and radiographic appearance. (A) The general appearance at 8 years old (case 1). Lateral and frontal photographs demonstrating forward bending at the level of the hip joints, anterior pelvic tilt, lumbar hyperlordosis, and genu valgum. (B) The radiographic appearance at 9 years old. The whole spine AP and lateral images showing delay in ossification of the capital femoral epiphyses and lumbar hyperlordosis.

3. Discussion

These siblings are the first familial cases diagnosed with CODAS syndrome worldwide, to our knowledge. They had the same LONP1 mutation (E476A; P749S). Shebib et al (1991) described a 3-year-old girl with a syndrome involving various inborn anomalies characterized by cerebral, ocular, dental, auricular, and skeletal abnormalities and denominated by the acronym CODAS syndrome.^[1] Since it is a rare disease, only a few more reports have been published in the next 25 years.^[6–8] Dikoglu et al suggested that LON peptidase 1 mutations are responsible for the CODAS phenotype and that the clinical spectrum is larger than the typical form described in case reports. The authors agree that the spectrum may be expanded further in the near future.^[2]

In these siblings, evidences of hypotonia, coronal clefts, hearing loss, and organ dysfunction were not observed in contrast to that with other CODAS children. Particularly, they

had only mild phenotypes of auricular, dental problems of cerebral, ocular, dental, auricular, and skeletal anomalies. They had a developmental delay with respect to motor and cognitive performance. They had gross motor delay due to epiphyseal dysplasia, cerebellar atrophy, and/or pain. Epiphyseal dysplasia is the primary cause of delayed motor development; however, noteworthy rehabilitation outcomes were observed after a comprehensive rehabilitation. Their fine motor and language skills development improved similarly to that of same-aged children.

Designing an appropriate therapy for genetic disorders is challenging for pediatric neurologists and physiatrists (who specialize in children rehabilitation). Given the difficulties to decide appropriate type of gene therapy and its timely therapy, they must decide the treatment and management strategies to improve particular signs and symptoms associated with the disorder based on limited information. Therefore, pediatric neurologists and physiatrists recommend rehabilitation therapy based on the patient’s symptoms. However, no available concrete evidence is convincing enough to show its clinical benefits in these patients.

Reports on the rehabilitation effectiveness in congenital disorders such as a qualitative interview for Noonan syndrome and a survey study on the rehabilitation for Charcot Marie Tooth disease are limited.^[9,10]

Although no systematic research on rehabilitation has been conducted, patients should be encouraged to perform physical activities for the improvement of their quality of life. We followed up on these siblings with CODAS syndrome for 5 years and

Table 1
DDST follow up result of 1st case at the age of 5years, 8 years, and 10 years.

Real age	5 yr 8 mo	8 yr 1 mo (97 mo)	10 yr 8 mo
Personal-social (evaluated age)	40 mo	54 mo	54 mo
Fine motor (evaluated age)	5 yr 8 mo	Over 6 yr	Over 6 yr
Language (evaluated age)	5 yr 8 mo	Over 6 yr	Over 6 yr
Gross motor (evaluated age)	10 mo	15 mo	18 mo

*DDST = The Denver developmental screening test.



Figure 4. Case 2 patient has mild anomalies of the external ears, membrane-like skin projection (white arrow) in triangular fossa in the ears (A) and several decayed teeth accompanied with delayed teeth eruption (B).

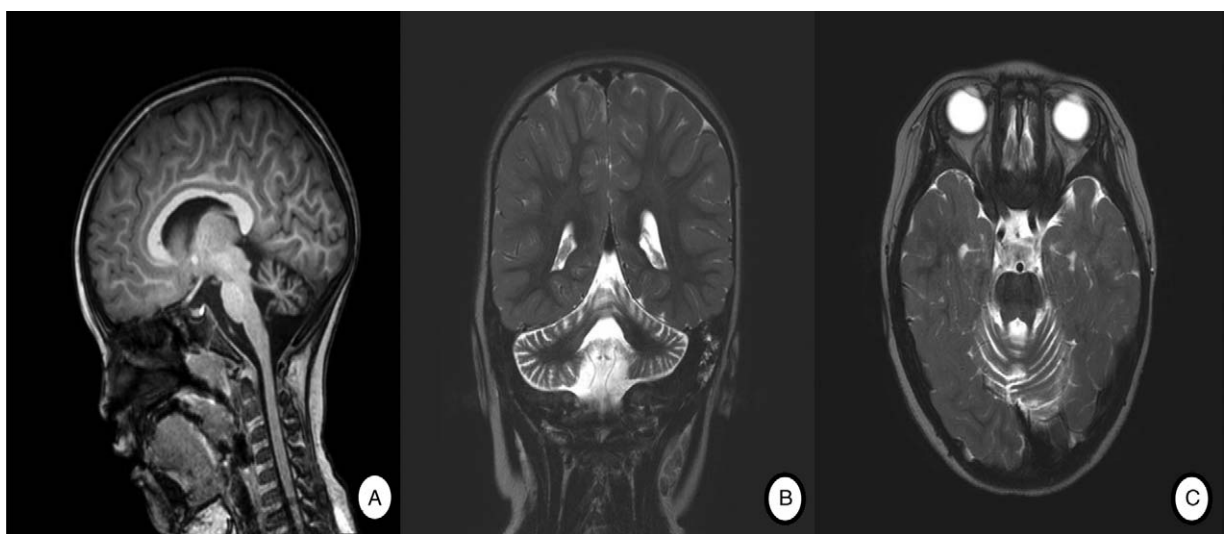


Figure 5. The MRI images of the brain in three orthogonal planes at 4 years old showing mild prominence of folia of both cerebellar hemispheres that is suspicious of mild both cerebellar atrophy. (A) Sagittal T2 weighted image. (B) Coronal T2 weighted image. (C) Axial T2 Weighted image.

Table 2**DDST follow up result of 2nd case at the age of 10 months, 4 years, and 6 years.**

Real age	10 mo	4 yr 5 mo (53 mo)	6 yr 9 mo
Personal-social (evaluated age)	9 mo	33 mo	42 mo
Fine motor (evaluated age)	9 mo	4 yr 5 mo (53 mo)	6 yr
Language (evaluated age)	6 mo	4 yr (48 mo)	5.5 yr
Gross motor (evaluated age)	10 mo	12 mo	15 mo

*DDST = the Denver developmental screening test.

observed the positive effect of rehabilitation on the quality of life. Their parents wanted their children to grow up as independent individuals in the society.

Until now, most genetic disorders, unfortunately, cannot be cured. These disorders often affect many body systems, and as a result, the children with genetic disorders have a developmental delay in many areas. We recommend that young children with genetic disorders are encouraged at the time of diagnosis to undergo comprehensive, intensive rehabilitation in order to achieve better outcomes.

Author contributions

Conceptualization: Seung Don Yoo, Young Rok Han, Dong Hwan Kim, Seung Ah Lee.

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Supervision: Seung Don Yoo.

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Writing – original draft: Seung Don Yoo, Young Rok Han, Dong Hwan Kim, Seung Ah Lee.

Writing – review & editing: Seung Don Yoo, Young Rok Han, Dong Hwan Kim, Seung Ah Lee.

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