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Long-Term Clinical Course of a Korean Patient with Chronic Neuropathic (type III) Gaucher Disease

Jun Hwa Lee

Department of Pediatric Neurology, Samsung Changwon Hospital, Sungkyunkwan University School of Medicine, Changwon, Korea

Gaucher disease (GD) is an autosomal recessive inborn error of metabolism resulting from a deficiency in β-glucocerebrosidase (GBA) activity that leads to the accumulation of glucocerebroside in macrophages in multiple organs, such as the bone marrow, liver, spleen, and brain. GD can be classified into three clinical types: type 1 (non-neuropathic form, OMIM #230800); type II (acute neuropathic form, OMIM #230900); and type III (chronic neuropathic form, OMIM #231000). Type III is the subacute form of neuropathic GD. The best available treatment for GD is long-term enzyme (imiglucerase) replacement therapy (ERT) performed every two weeks. This report describes the long-term clinical course of a patient with type III GD who was treated with ERT for 18 years.

Key words: Gaucher disease, Neuropathic, Clinical course, Korean

CASE REPORT

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Correspondence to: Jun Hwa Lee
Department of Pediatrics, Samsung Changwon Hospital, Sungkyunkwan University School of Medicine, 158 Paryong-ro, Masanhoewon-gu, Changwon 51353, Korea
Tel: +82-55-233-5310
Fax: +82-55-233-5329
E-mail: ljh3643@hanmail.net, ljh3643@skku.edu

ORCID
Jun Hwa Lee: https://orcid.org/0000-0001-9717-3677

INTRODUCTION

Gaucher disease (GD) is the most prevalent lysosomal disorder, and it results from mutation of beta-Glucosidase (GBA1) gene causing a deficiency in glucocerebrosidase activity, leading to accumulation of glucocerebroside in lysosomal macrophages. GD is a rare, pan-ethnic, autosomal recessive, genetic disease that involves multiple organs, such as the bone marrow, liver, spleen, and brain [1-3]. GD can be classified into three clinical types: type 1 (non-neuropathic form, OMIM #230800); type II (acute neuropathic form, OMIM #230900); and type III (chronic neuropathic form, OMIM #231000), which is the subacute form of neuropathic GD. The best available treatment for GD is long-term enzyme (imiglucerase) replacement therapy (ERT) performed every two weeks. This report describes the long-term clinical course of a patent with type III GD who was treated with ERT for 18 years.

CASE DESCRIPTION

A 20-year-old female patient with GD visited our pediatric outpatient center for ERT. She was born full term via spontaneous vaginal delivery with a birth weight of 4.0 kg to healthy nonconsanguineous Korean parents. Her family history included an older brother with suspected GD who died of status epilepticus at age 23, which was four years prior to presentation. The other family members had no history of metabolic disorders or neurologic diseases (Fig. 1). The patient showed normal development until 12 years of age when she first complained of leg pain.

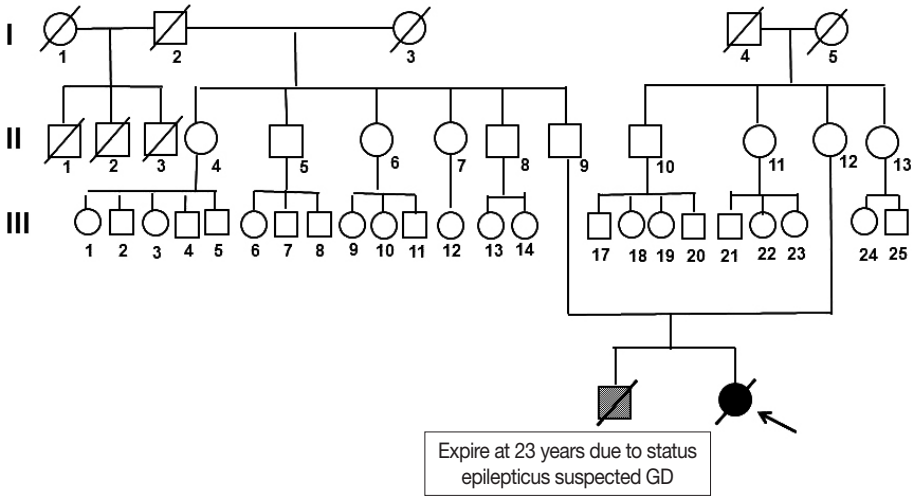

Fig. 1. Family pedigree of the patient with Gaucher disease. The solid circle represents the patient (proband), and the square represents her older brother, a suspected GD patient who expired with status epilepticus at age 23.

Fig. 2. Serial photographs of the patient. She had a normal development and lived an almost normal life except for intermittent seizures. However, at 27 years of age, her seizures worsened, and she required multiple antiepileptic medications. The disease slowly progressed until she was quadriplegic with sluggish speech and altered mental status. She was bedridden after age 30.

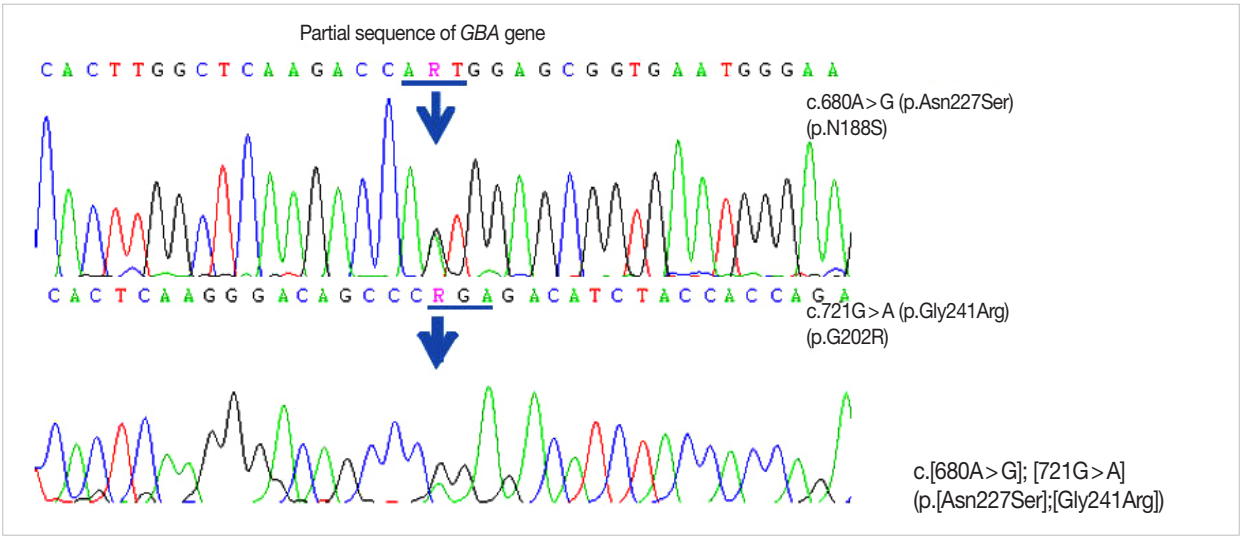

Fig. 3. Sanger sequencing analysis for the GBA gene. The patient was confirmed to have p.N188S and p.G202R mutations in the GBA gene mutation test, findings consistent with GD.

The initial suspicion was osteomyelitis, and she was treated with antibiotics. However, the leg pain progressed, and she developed bilateral hip pain. She was subsequently treated with medication for rheumatoid arthritis until age 18, although her symptoms waxed and waned. Her elder brother died due to status epilepticus when she was 16 years old.

At 18 years of age, the patient developed hepatosplenomegaly and seizures with eyeball deviation as well as generalized tonic-clonic type of seizures. Treatment with antiepileptic drugs, such as valproic acid and topiramate, was unsuccessful, and she underwent tests for an accurate diagnosis at a tertiary hospital. The patient was found to have Gaucher cells in the bone marrow and decreased leukocyte GBA activity (1.32 mM/hr/ng protein, reference range: 5.11-11.32), and she was finally diagnosed with GD. She received ERT at age 20, and the bone pain and hepatosplenomegaly significantly improved. The laboratory evaluation revealed: hemoglobin 12.3 g/dL, hematocrit 35.9%, WBC 4,300/mm^3, platelets 177,000/mm^3, segment neutrophil 65.1%, eosinophil 2.1%, basophil 0.1%, lymphocyte 27.9%, monocyte 1.5%, immature cell 0%, GOT/GPT 11/9 IU/L, calcium 9.3 mg/dL, phosphorus 2.9 mg/dL, BUN/Cr 8.2/0.7 and PT/aPTT 13.8/45.5 seconds. Brain MRI findings were non-specific. Electroencephalography (EEG) showed focal epileptiform discharges from right temporo-occipital or left occipital areas. Abdominal MRI findings at age 21 were normal shape and size of liver and spleen.

Except for uncontrolled intermittent seizures, she lived an almost normal life until the age of 27. However, the myoclonic seizures worsened despite the use of multiple antiepileptic medications, such as zonisamide, clobazam, pregabalin, Levetiracetam and phenobarbital. Over time, the disease slowly progressed, and she had abnormal eye movements (such as supranuclear gaze palsy), quadriplegia, sluggish speech and altered mental status despite continued ERT (Fig. 2). A GBA gene mutation test found that she had a heterozygote p.N188S and p.G202R genotype mutations (Fig. 3). Although she had been using ambroxol chaperon therapy with starting dose ranging from 1.5 mg/kg/day up to 24 mg/kg/day in combination with ERT treatment since age 37 and 5 months to improve her neurological symptoms, she was repeatedly hospitalized and discharged due to infectious diseases such as pneumonia and sepsis. She died of septic shock and pneumonia at age 38 and 4 months.

DISCUSSION

GD is a rare, pan-ethnic, autosomal recessive, lysosomal storage disorder resulting from a beta-Glucosidase (*GBA1*) gene defect. Patients with GD have a glucocerebrosidase enzyme deficiency and an increased accumulation of glycolipid glucocerebroside inside cell lysosomes. GD involves multiple organs, such as the bone marrow, liver, spleen, eyes and brain, so affected patients generally exhibit various clinical symptoms. To date, there are nearly 460 known mutations in the *GAB1* gene [1-3]. The incidence rate in the general population varies from approximately 1 in 40,000 to 1 in 60,000 births, and is

as high as 1 in 800 births among Ashkenazi Jews [4].

GD can be classified into three clinical types: type 1 (non-neuropathic form), type II (acute neuropathic form), and type III (chronic neuropathic form). Among the three types, type 1 is the most common and is characterized by a wide variety of clinical symptoms ranging from asymptomatic to severe manifestations. The most common symptoms are anemia, thrombocytopenia, splenomegaly and/or hepatomegaly, and potentially severe bone involvement. Type 1 GD carries a particularly high risk of hematologic diseases such as multiple myeloma, Parkinson's disease, and some solid cancers. Its treatment includes enzyme replacement therapy or substrate reduction therapy [1,4]. Type 2 GD is the most severe and progressive form, and patients manifests symptoms prenatally or in the first month of life and die in the first year of life [5]. Type 3 GD, known as chronic neuropathic disease, is a milder but chronically progressive variant that is characterized by hepatosplenomegaly, anemia, thrombocytopenia, bone alterations and central neurological manifestations, including seizure, myoclonic epilepsy, and progressive neurodegeneration [2,6,7]. Type 3 GD also has ocular features and gaze abnormalities, including saccadic eye movement abnormalities, corneal clouding, ocular deposits and pigmentary changes in the macula [8, 9]. Although the main treatment for GD is ERT, it is not effective for neurological symptoms. Ambroxol in combination with ERT has been suggested as a promising therapy for patients with Type 3 GD [10].

According to a report of 20 Korean patients with GD (11 type 1, two type 2, and 7 type 3), most patients presented with hepatosplenomegaly, thrombocytopenia, and short stature, and atypical symptoms included B cell lymphoma, protein-losing enteropathy, and hydrops fetalis. In the same study, the neuropathic group manifested variable neurological features, such as seizures, tremor, gaze palsy and hypotonia at age 8.7 ± 4.3 years. L444P was the most common mutation. N188S and G202R variants that are known to be retained in the endoplasmic reticulum, is also amenable to chemical chaperoning. The L444P variant is not chaperoned by any of the active site-directed molecules tested, likely because this mutation destabilizes a domain distinct from the catalytic domain [11].

The patient in the present case had typical type 3 GD clinical symptoms, and despite 18 years of ERT treatment and 1 year of ambroxol chaperone therapy, her neurological symptoms did not improve. She expired with pneumonia and sepsis.

This study was approved by the Institutional Review Board of Samsung Changwon Hospital (IRB study #SCMC 2019-01-007).

CONFLICT OF INTEREST

There are no potential conflicts of interest relevant to this article.

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I would like to thank my patient's parents for agreeing to this study, and I express my deepest condolences for the patient.

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Torticollis Management Using the Customized Soft Neck Collar in CATCH 22 Syndrome Combined with Klippel-Feil Anomaly: A Case Report

Myung-Hoon Moon, Soo-Yeon Kim

Department of Rehabilitation Medicine, Pusan National University School of Medicine and Research Institute for Convergence of Biomedical Science and Technology, Pusan National University Yangsan Hospital, Yangsan, Korea

CATCH 22 syndrome is rare genetic disease that has various manifestations. Cervical vertebral anomaly, such as Klippel-Feil anomaly, is frequently observed in the patients with CATCH22 syndrome. We present the case of an 11-year-old female patient with CATCH22 syndrome and Klippel-Feil anomaly who had been treated torticollis using the customized soft neck collar. During the patient's first visit to our clinic, she presented with low ear set, skull deformity, intellectual disability, and tilting of the head to the left by approximately 25 degrees. Imaging studies revealed multisegmental fusion and C3 hemivertebrae of the cervical spine and left thoracic scoliosis at T4 with 50 degrees of Cobb's angle. We instructed passive stretching and applied the customized soft neck collar we invented. The ipsilateral aspect of the neck collar is designed to provide vertical support between the clavicle and mandibular angle and is adjustable in height. The Velcro was attached to the neck collar at the point of contact with the ipsilesional mandibular angle, which provides negative sensory feedback, inducing her to tilt neck to the contralesional side. We applied the neck collar for 2 hours a day. After 1 year of treatment, her neck inclination angle improved from 25 to 10 degrees. Providing negative sensory feedback using the customized soft neck collar can be one of the treatment options of postural management in patients with torticollis in cases of CATCH 22 syndrome combined with Klippel-Feil anomaly.

Key words: CATCH 22, Klippel-Feil syndrome, Torticollis, Orthotic device

CASE REPORT

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Correspondence to: Soo-Yeon Kim
Department of Rehabilitation Medicine, Pusan National University Yangsan Hospital, Pusan National University School of Medicine, 20 Geumo-ro, Mulgeum-eup, Yangsan 50612, Korea
Tel: +82-55-360-4250
Fax: +82-55-360-4251
E-mail: drkimsy@gmail.com

ORCID
Myung-Hoon Moon: https://orcid.org/0000-0001-7464-4317
Soo-Yeon Kim: https://orcid.org/0000-0001-5679-0126

INTRODUCTION

CATCH 22 syndrome is characterized by cardiac defects, abnormal facial features, thymic hypoplasia, cleft palate, and hypocalcemia, which are associated with the deletion of chromosome 22q11. Since DiGeorge syndrome, velo-cardio-facial syndrome, and conotruncal anomaly face syndrome are all due to the microdeletion in chromosome 22q11, CATCH 22 syndrome encompasses these syndromes [1]. A deletion in chromosome 22q11 is the genetic basis of the most common interstitial deletion syndrome, the 22q11 deletion syndrome in humans, with an incidence of 1 in 4,000–5,000 births [2]. According to the literature, patients with this syndrome are associated with a high incidence of various types of relatively mild cognitive deficits, including learning difficulties, which is sometimes combined with mild learning disability and attention deficit hyperactivity disorder [3].

Klippel-Feil syndrome (KFS) is another rare disease that was initially described by Klippel and Feil [4], and its prevalence is reported to be approximately 1:40,000–42,000 births in the literature [5]. The genetic etiology of KFS is still unclear and had been reported heterogeneously, but defect of the notochord and its signaling with insufficient separation of the cervical vertebrae are considered the

main underlying causes [6]. Partial or complete fusion of two or more cervical vertebrae is the key feature of KFS, frequently associated with further osseous and non-osseous manifestations such as low posterior hairline, torticollis, brevicollis, basilar impression, atlanto-occipital fusion, scoliosis, facial asymmetry, Sprengel's deformity, and other genitourinary, central nervous, and cardiopulmonary system anomalies [7].

There have been a few case reports suggesting genetic association between the CATCH22 syndrome and KFS, but the correlation between two syndromes has not yet been clearly revealed. Nevertheless, cervical vertebral anomaly is frequently observed in both syndromes [8-10]. Since spinal growth originates from the superior and inferior endplates of each body, congenital vertebral malformation with asymmetric shape causes unbalanced vertebral growth. The rate of deterioration and severity of the final deformity vary according to the type and location of the anomaly [11]. Generally, as congenital scoliosis due to vertebral anomaly is typically inflexible, bracing is known to be unresponsive in these cases. Thus, observation is usually indicated in mild congenital scoliosis that does not require surgical treatment [12].

Here, we present a case of torticollis managed using customized neck collar in a female patient with both CATCH22 syndrome and Klippel-Feil anomaly.

CASE REPORT

An 11-year-old female patient was referred to our clinic for torticollis by her pediatricians. She was the firstborn child of a healthy 35-year-old mother and father. She was delivered via cesarean section due to fetal distress after 39 weeks of gestation and weighed 2,180 g. There was no family history of genetic diseases.

At birth, her pediatrician performed chromosome analysis because of her low ear set, skull deformity, and C3 cervical hemivertebrae found on brain magnetic resonance imaging. The test result showed deletion of 22q11, and she was diagnosed with CATCH22 syndrome. Echocardiogram revealed tricuspid atresia combined with several cardiac anomalies. A few days after her birth, cyanosis was observed, and the symptom worsened over time. Her thoracic surgeon planned to perform Fontan surgery, the first step of which was to perform main pulmonary artery banding when the patient was 3 months old. As planned, bidirectional cavopulmonary correction was performed when she was 4 years old, and extracardiac conduit Fontan procedure was finally performed when she was 6 years old.

During her first visit in our outpatient department, she presented with the head rotated and tilted to the left, approximately 25 degrees (Fig. 1A), and prominent Adam's sign was observed on the left posterior upper back. The patient reported

Fig. 1. (A) The angle of inclination of the head on the coronal plane is approximately 25 degrees before treatment. (B) The angle of inclination has improved to 10 degrees after 1 year of treatment. In both pictures, long vertical lines are at the midline of her body, and the short ones are at the midline of her head.

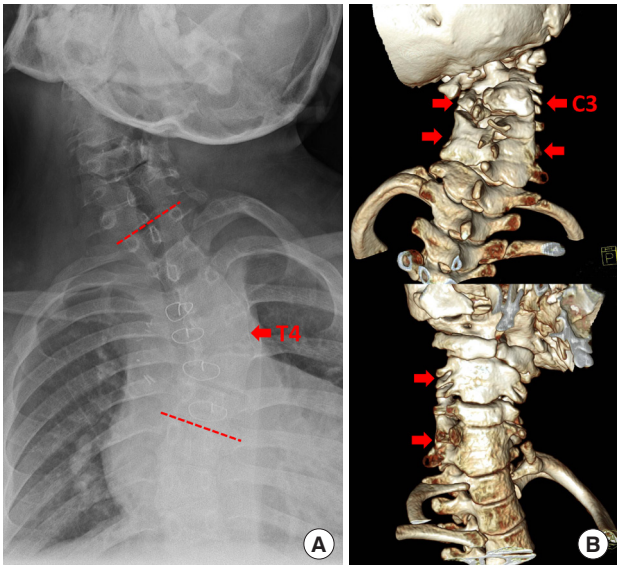

Fig. 2. (A) Plain radiography reveals left thoracic scoliosis at T4 with 50 degrees of Cobb's angle. (B) Three-dimensional computed tomography representing C3 hemivertebrae and multisegmental fusion, C4 to C6, of the cervical spine (indicated by arrows).

Fig. 3. (A) A customized soft neck collar. The Velcro is attached to the site of contact with the mandibular angle at the tilted head side (arrow). The neck collar is adjustable in height. (B) Because of the discomfort caused by the Velcro, the patient tilted her neck to the contralesional side.

cosmetic problems and neck pain due to the abnormal head posture. Plain film radiography and three-dimensional computed tomography (3D CT) scans to obtain an accurate assessment of her spine according to her current age were performed. Her cervicothoracic X-ray revealed left thoracic scoliosis at the T4 vertebral body with 50 degrees of Cobb's angle and right cervical scoliosis due to vertebral malformation (Fig. 2A), and 3D CT scan revealed right lateral C3 hemivertebrae accompanied with multisegmental fusion of the cervical spinal vertebral bodies, C4 to C6, which implied the possibility of KFS (Fig. 2B). Together with her pediatricians, we decided to perform whole exome sequencing to establish the diagnosis, but genetic evidence of KFS was not found.

Since she was unable to fully cooperate with the exercise instruction due to her intellectual disability, we decided to apply the customized soft neck collar specifically tailored to correct torticollis (Fig. 3A). The ipsilateral aspect of the neck collar is significantly designed to provide sufficient vertical support between the clavicle and mandibular angle and is adjustable in height. Additionally, the rough surface was intentionally made by attaching the Velcro to the neck collar at the point of contact with the ipsilesional mandibular angle. This made the patient felt uncomfortable, inducing her to tilt her neck to the opposite side of the lesion, as a negative sensory feedback (Fig. 3B). We applied the neck collar for 2 hours a day and instructed active stretching exercise of the ipsilateral neck muscles and active strengthening exercise of the contralateral neck muscles.

The angle of inclination of her head was measured at each visit in our outpatient clinic, and the neck collar was modified sequentially to fit between the ipsilateral clavicle and mandibular angle according to the improvement of neck motion. After 1 year of treatment, her neck inclination angle improved from 25 to 10 degrees (Fig. 1B). As the abnormal head posture was corrected, cosmetic problems and neck pain were also improved. She and her families were satisfied with the outcome of the treatment.

DISCUSSION

Generally, the initial treatment of juvenile and adolescent idiopathic scoliosis is observation with regular X-ray checkup. It is known that scoliosis with Cobb's angle of 30 degrees or more has a risk of progression into adulthood, and scoliosis with Cobb's angle of 50 degrees or more is certainly going to progress into adulthood [13]. Thus, if there are more than 10 degrees of progression per year or if there is a high risk of progression, nonsurgical treatments, including bracing, stretching, and exercise, are recommended, and surgical treatment is indicated in patients with more than 50 degrees of Cobb's angle [13]. Contrary to idiopathic scoliosis, nonsurgical treatment of congenital scoliosis is rarely recommended because congenital curves, in most cases, are inflexible and unresponsive to bracing, which can cause secondary deformation of the thoracic cage if these are applied forcibly [14]. Surgical procedure is considered depending on the amount and rate of progression and the expected progression of each deformity type [15].

In this case, the child had hemivertebrae of the C3 vertebral body and thoracic scoliosis with approximately 50 degrees of Cobb's angle, which were indications for surgical treatment. However, the patient had an intellectual disability due to CATCH 22 syndrome; hence, difficulty in postoperative care was expected. Therefore, we tried to treat the patient's torticollis by performing nonsurgical treatment as much as possible to improve her quality of life. Bracing was eliminated from our treatment option because it is not effective in treating scoliosis due to congenital vertebral anomaly and difficulty in application of bracing in cervical lesion. Instead, we instructed the patient's family to assist the patient in performing ipsilesional neck muscle stretching and tried to encourage her to perform active strengthening exercise of the contralesional neck muscle. Due to her intellectual disability, it was impossible for her to perform exercise herself. Hence, we designed a customized soft neck collar that fits between her ipsilesional mandibular angle

and clavicle. Moreover, we attached the Velcro to the site of the neck collar that touched the mandibular angle; hence, the patient felt uncomfortable, considered a negative sensory feedback. Thus, the patient tilted her neck to the opposite side.

During her early visits in our clinic, her neck showed a very limited range of motion with an inclination angle of 25 degrees. It was so inflexible that it did not change with active stretching, and we almost considered it a muscular contracture. However, after 1 year of treatment with passive stretching and active strengthening exercise via negative sensory feedback, the neck inclination angle improved from 25 to 10 degrees. Furthermore, her cosmetic problem and persistent neck pain improved. She and her family were satisfied with the result. There has been no report on the management of cervical torticollis, which is a manifestation of congenital anomaly, by providing negative sensory feedback using the customized soft neck collar. The neck collar is a tailor-made novel device that we specifically invented.

The treatment continued afterward, but no further improvement has been observed because the muscular portion had been improved by consistently wearing the customized soft neck collar, but not the underlying bony deformity. Unexpected problems, such as skin irritation and mental stress of the child, have also been observed during the treatment. Despite these fundamental limitations, providing negative sensory feedback using the customized soft neck collar is considered a valuable treatment option because it improves the quality of life of children with cervical scoliosis due to a congenital anomaly that does not require surgery.

CONCLUSION

Providing negative sensory feedback using the customized soft neck collar can be considered one of the treatment options of postural management in patient with torticollis in CATCH22 syndrome combined with Klippel-Feil anomaly.

CONFLICT OF INTEREST

No competing financial interests exist.

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