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【 CASE REPORT 】

Oculo-dento-digital Dysplasia Presenting as Spastic Paraparesis Which Was Successfully Treated by Intrathecal Baclofen Therapy

Akiko Shinya[1,2], Makoto Takahashi[1], Nozomu Sato[2], Yoichiro Nishida[2], Akira Inaba[1], Motoki Inaji[3], Takanori Yokota[1] and Satoshi Orimo[1]

Abstract:
A 42-year-old man with a history of migraine and bilateral syndactyly presented with numbness of the extremities and shaking legs, which thus prevented him from working as a carpenter. A neurological examination revealed spastic paraparesis with pathological reflexes on all four extremities. Oculo-dento-digital dysplasia (ODDD) was suspected based on his medical history and characteristic facial appearance including small eye slits, thin mouth, and pinched nose with anteverted nostrils. Genetic tests revealed a gap junction alpha 1 (*GJA1*) gene mutation and confirmed the diagnosis of ODDD. His spastic paraparesis was resistant to oral antispastic medication, however, his symptoms successfully improved after the initiation of intrathecal baclofen therapy, which thus allowed him to return to work.

Key words: oculo-dento-digital dysplasia, intrathecal baclofen therapy, spastic paraplegia

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Introduction

Oculo-dento-digital dysplasia (ODDD) is a hereditary disorder caused by a mutation of the gap junction alpha 1 (*GJA1*) gene encoding the connexin 43 protein (Cx43) (1, 2). ODDD patients show a wide variety of symptoms comprising mainly of craniofacial, ocular, dental, and digital anomalies, which are often recognized as facial dysmorphism (3). One-third of ODDD patients develop neurological complications including spastic paraparesis (4); however, these are rarely their primary symptoms and it is a highly under-recognized disease among neurologists. In addition, conventional treatments for spastic paraparesis in ODDD patients with oral muscle relaxants offer limited efficacy. We herein present a case of newly diagnosed ODDD - with characteristic facial appearances, syndactyly, and magnetic resonance imaging (MRI) findings as effective clues for diagnosis - who first presented to the neurological department complaining of spastic paraparesis and was successfully treated with intrathecal baclofen (ITB) therapy.

Case Report

A 42-year-old man consulted our department with numbness of the fingers and toes and shaking legs. He was the youngest of three children born to healthy unrelated parents. Neither his parents, who were alive and healthy at 66 and 71 years of age, nor his 44- and 43-year-old siblings had any neurological disorders or dysmorphisms. At birth, he had syndactyly of his fourth and fifth fingers bilaterally and underwent a separation procedure at an early age. He completed high school, and was working as a carpenter at the time of his visit. He had a history of migraines that began in his thirties. Three years before consultation, he complained of having shaky legs when climbing down ladders or straining his feet to lift heavy objects as a carpenter. The shaking in his legs gradually worsened and began to interfere with his work. On the morning of the consultation, he experienced numbness in his extremities before the examination.

[1]Department of Neurology, Kanto Central Hospital, Japan, [2]Department of Neurology and Neurological Science, Tokyo Medical and Dental University, Japan and [3]Department of Neurosurgery, Tokyo Medical and Dental University, Japan
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Correspondence to Dr. Makoto Takahashi, mt.awakenings@gmail.com

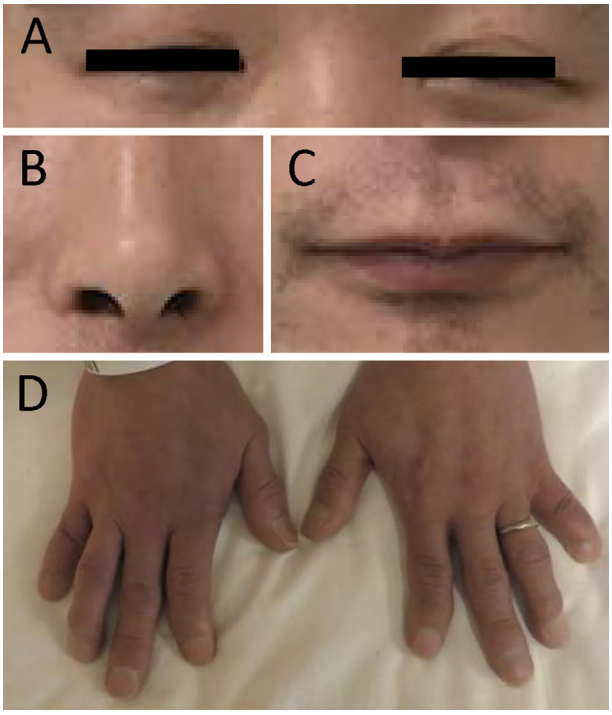

Figure 1. Photographs of a patient showing the classical traits of ODDD. (A) Small eye slits. (B) A pinched nose with anteverted nostrils. (C) A thin mouth, hypoplastic alae nasi, and sparse, fine, curly hair. (D) Symmetrical post-operational scars from bilateral syndactyly of the fourth and fifth fingers. ODDD: oculo-dento-digital dysplasia

Distinctive features in his facial appearance were noticeable, such as having small eye slits, a thin mouth, hypoplastic alae nasi, a pinched nose with anteverted nostrils, and sparse, fine hair (Fig. 1A-C). Physical examination revealed a deformation of the fingers and symmetrical post-operational scars from bilateral syndactyly of the fourth and fifth fingers (Fig. 1D). Toenails on both his feet were bristled and deformed. A neurological examination revealed spastic paraparesis with ankle clonus. An exaggeration of patellar and Achilles tendon reflexes as well as pathological reflexes, including Waltenberg, Chaddock, and Babinski reflexes, were present. Sensory findings showed paresthesia as a tingling sensation in the distal extremities beyond the elbows and knees. Light touch, cold, and pain sensations as well as vibration and position sensations were within the normal range.

Laboratory tests of the patient's serum and cerebrospinal fluid were unremarkable. Motor and sensory peripheral nerve conduction results were normal. Motor-evoked potentials showed almost no reaction in the limbs suggesting marked pyramidal tract disturbance, while somatosensory-evoked potentials by stimulation of all four extremities showed delayed latencies suggesting demyelination of sensory nerves in the central nervous system (Fig. 2). Brain MRI revealed symmetrical hyperintensities in the subcortical white matter and the brainstem on T2-weighted images (T2-WI) (Fig. 3A, B, white arrows). In addition, T2-WI hypointensities of the basal ganglia and the region surrounding the precentral and postcentral gyri were identified Fig. 3C, white arrows). Computed tomography scans showed bilateral calcifications of the globus pallidus and hyperostosis cranii (Fig. 3D). Hand and foot X-rays showed bilateral clinodactyly and brachymesophalangy (Fig. 3E, F). A general examination, neurological findings, and imaging findings suggested ODDD; thus, a sequencing analysis of the *GJA1* gene was performed, revealing a heterozygous mutation of c.412 G>A (p.Gly138Ser) (Fig. 4). This confirmed the diagnosis of ODDD.

The patient's main concern being spastic paraparesis, he was initially treated with oral medications such as clonazepam, dantrolene sodium hydrate, and baclofen - to no avail - thus ITB was our next choice. For pre-assessment, changes in spasticity and occurrence of side effects (weakness and urinary retention) were recorded after manually injecting several different volumes of ITB. Each dose was given once every 24 hours. After his first dose at 50 μg, his ankle clonus diminished after four hours; at 75 μg, the clonus subsided after two hours. Finally, at 100 μg, the clonus completely vanished and his leg dullness eased after four hours; he could walk more smoothly and sit without leg tremors. As for side effects, residual urine increased to up to 410 mL after inducing baclofen, compared to 120 mL before treatment. The patient then underwent surgery for ITB-pump implantation. After some adjustments, at 140 μg/day the spasticity including clonus and gait disturbance subsided enough for the patient to restart his job. Although he did not develop symptoms of urinary retention postoperatively, the dose of baclofen was reduced if he developed constipation. After over three years of continuous outpatient consultations, he has been able to continue to work normally with 210 μg/day of baclofen.

Discussion

In this report, we first emphasize the importance of a swift and correct diagnosis of ODDD with spastic paraparesis, without which providing appropriate clinical intervention becomes difficult. While the ocular, dental, and digital dysmorphisms that compose ODDD's name accurately describes the first impression of patients with the disease, MRI scans and gene testing can confirm the diagnosis. Second, to provide a satisfactory and sustainable treatment for spastic paraplegia in ODDD, we used ITB therapy.

ODDD is a rare genetic disorder characterized by dysmorphisms such as syndactyly and a unique facial appearance including small eye slits, thin mouth, hypoplastic alae nasi, pinched nose with anteverted nostrils, and sparse, fine hair - all of which were identified in our patient (2, 3, 5). These external features are important clues indicating possible ODDD. In addition, patients with ODDD may initially consult a neurologist with neurological symptoms, which have been reported to be present in up to a third of patients with ODDD, such as slowly progressive spastic paraparesis

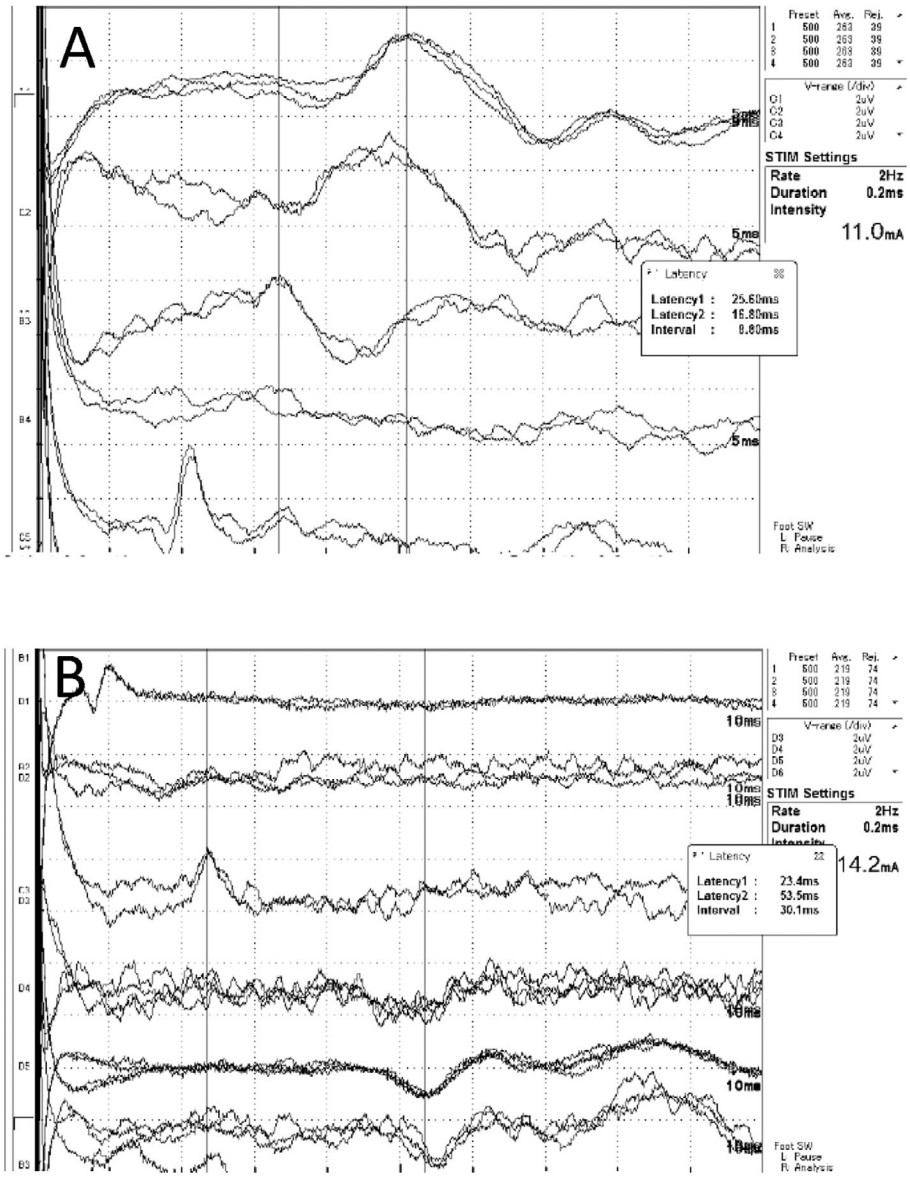

Figure 2. The patient's SEP. (A) SEP from the right medial nerve and (B) right tibial nerve showed delayed latencies (A: N13=16.8, N20=25.6; B: N22=23.4, P38=53.5) and elongated CCT (A: 8.80; B: 30.1). The approximate normal ranges (average to +3 SD) are N13: 12.7-15.0, N20: 18.6-21.5, N22: 20.0-24.4, P38: 36.9-44.4; CCT for the medial nerve: 5.9-7.3; CCT for the tibial nerve: 16.9-21.8. CCT: central conduction time (expressed in ms), SEP: somatosensory evoked potential (expressed in ms)

associated with MRI abnormalities and spastic bladder, which are among the most common (4). Abnormal findings on brain MRI in ODDD patients, including high-intensity lesion in white matter, basal ganglia, and brainstem and low-intensity lesion surrounding the precentral and postcentral gyri on T2-WI image, have been reported (4).

When a patient is suspected of having ODDD, a sequencing analysis of the *GJA1* gene (6q22-23) can help in making a final diagnosis. More than 70 mutations have been found in *GJA1*, a gene encoding the Cx43 protein, which functions as a channel in the gap junction in its hexamer form (1, 2). Most known mutations are dominant missense mutations resulting in a mutant Cx43 and the loss of function of the gap junction. In our case, the mutation, c.412G>A, was found in a hotspot encoding the intracellular loop that is known to be a pH-dependent binding site for the Cx43 carboxyl terminus and affects channel closure (1). This mutation has already been reported in the dental and dermatology fields (6, 7) but, to our best knowledge, this is the first report on this mutation that focused on the neurological findings. Since some of the responsible mutations in ODDD have a high penetrance and exhibit marked intra- and inter-familial phenotypic variability (1, 5), a gene analysis is recommended when ODDD is suspected. In our case, because the parents and two brothers showed no symptoms of ODDD to date, we suspect that our patient was the first in his family to have this mutation. However, it is possible that one of the parents could have been a carrier of the mutation with very

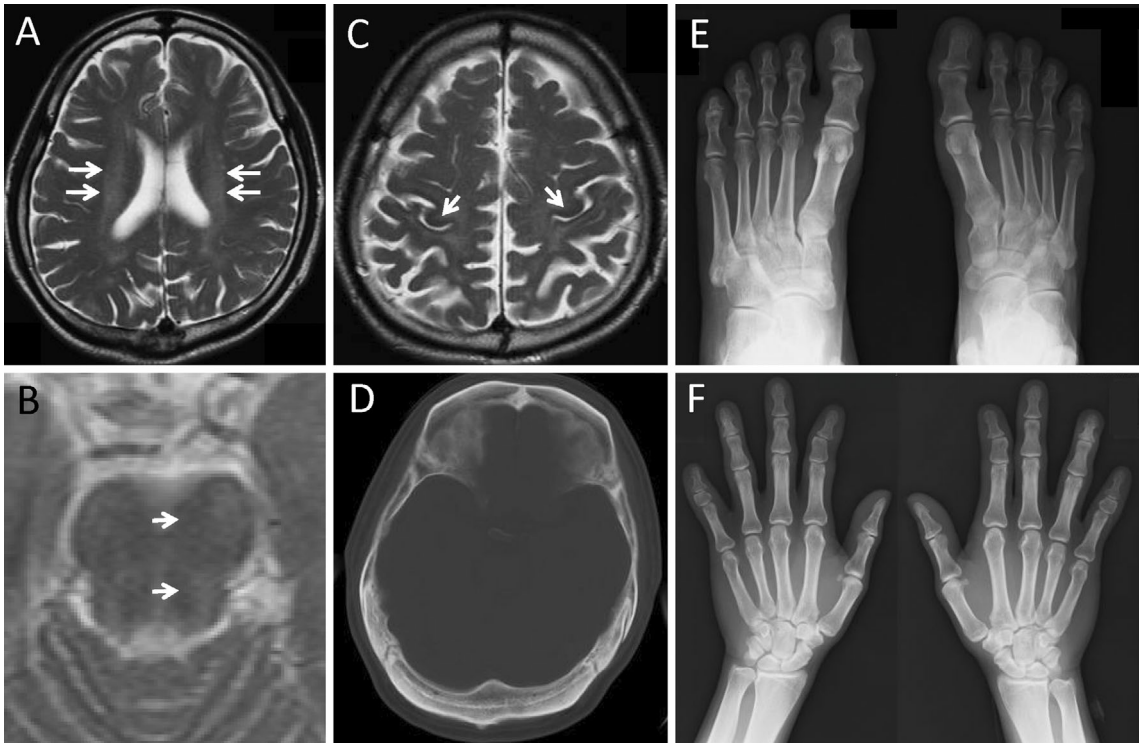

Figure 3. **The patient's imaging results. (A, B) Brain MRI revealed symmetrical T2-WI hyperintensities in the subcortical white matter and the brainstem (white arrows). (C) T2-WI hypointensities (white arrows) around the precentral and postcentral gyri. (D) Computed tomography scans showed hyperostosis cranii. X-rays of the extremities showed symmetric clinodactyly of the second fingers, camptodactyly of the second and fifth fingers, and hypoplasia of the intermediate phalanxes in his hands (E), and missing intermediate phalanxes in his feet (F). MRI: magnetic resonance imaging, T2-WI: T2-weighed image**

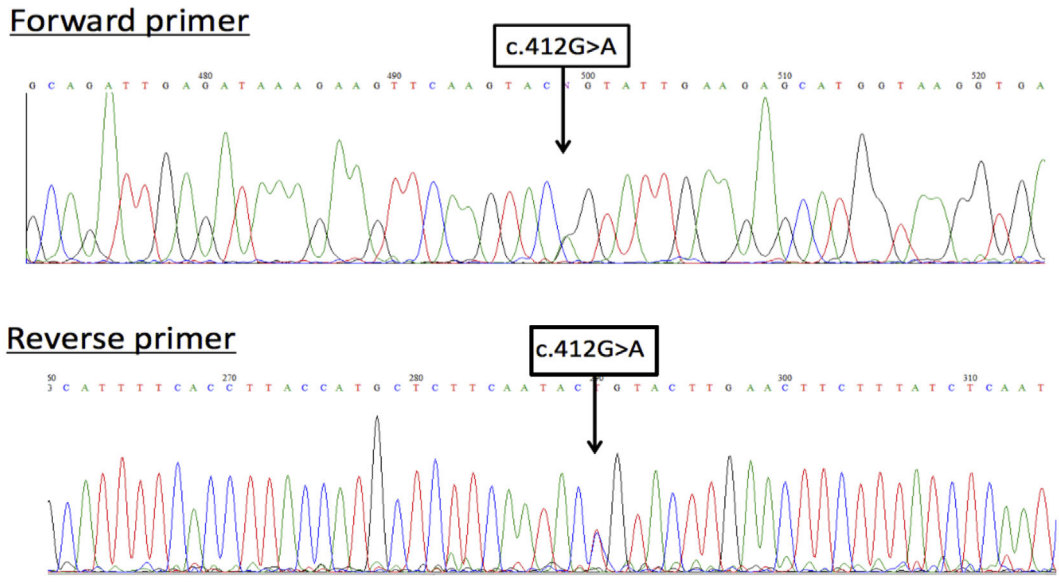

Figure 4. **A sequencing analysis showed an identical heterozygous mutation, c.412G>A (p.Gly138Ser), in the *GJA1* gene (6q22-23). GJA1: gap junction alpha 1**

mild signs or symptoms, because they did not undergo DNA testing or neurologic examinations.

ITB therapy has been used to treat hereditary diseases such as hereditary spastic paraplegia and Friedrich's ataxia; however, to the best of our knowledge, none have considered its application to ODDD. The patient in this case had to climb stairs and ladders or walk on unstable narrow surfaces while holding heavy objects in his work as a carpen-

ter, but the ankle clonus made his legs tremble and destabilized him in such situations. Sitting on a low surface or squatting in a position that extended his Achilles tendons also made his legs tremble and destabilized him so that his feet seemed to be fidgeting all the time. ITB was administered because the effects of oral muscle relaxants were insufficient. The intervention and subsequent adjustment of the baclofen dosage during outpatient visits successfully diminished his spastic paraplegia, thus enabling him to not only climb stairs, ambulate, and stand more stably but also to sit more comfortably and calmly, thereby allowing the patient to return to work.

Baclofen [β-(4-chlorophenyl)-γ-aminobutyric acid] is a recognized treatment option for spasticity of any etiology. It is a gamma-aminobutyric acid (GABA) agonist that resets the imbalance of supraspinal inhibitory and excitatory inputs in spastic patients via GABA B receptors (5). Although oral baclofen has evinced clinical benefits in many spastic patients, it does not cross the blood-brain barrier well. Furthermore, its equal distribution across spinal and supratentorial compartments may cause severe side effects (5). As a solution, performing ITB via implanted pumps was introduced to directly and continuously deliver the drug to the site of action, reducing the required dosage and consequently the risk of adverse effects. Multiple reports show that ITB therapy has yielded a good functional improvement and long-term adherence to treatment for spasticity (8-11).

Urinary retention, constipation, muscle weakness, and catheter-related complications are common side effects of ITB (12). In our case, gradually increasing the injected volume of baclofen reduced some of these. Although careful adjustment is needed for good conditioning, ITB therapy should be considered as a treatment option for ODDD patients with refractory spastic paraparesis.

In conclusion, we described a case of newly diagnosed ODDD with spastic paraparesis successfully treated with ITB. This case report shows that ITB treatment may be an efficient option for spastic paraparesis in patients diagnosed with ODDD.

Informed consent for publication of this report, including pictures and genetic test result, was obtained from the patient. All procedures performed in this report were in carried out in accordance with the ethical standards of the institutional research committee of Kanto Central Hospital and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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

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