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Treatment of *ZC4H2* Variant-Associated Spastic Paraplegia with Selective Dorsal Rhizotomy and Intensive Postoperative Rehabilitation: A Case Report

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Selective dorsal rhizotomy (SDR) has been used to treat children with spastic cerebral palsy (CP), and its beneficial effect on quality of life and ambulation has been confirmed in long-term follow-up studies. However, the role of SDR in the treatment of spasticity in patients with hereditary spastic paraplegia (HSP) and related disorders is not well-established. Here, we report the first patient with the *ZC4H2* variant who underwent SDR to treat spastic paraplegia. Abnormal gait was discovered during a regular checkup at the age of 3 years and 9 months, and she was diagnosed with spastic paraplegia. She was heterozygous for the *ZC4H2* variant and underwent SDR at the age of 5 years and 11 months, which alleviated the spasticity. The patient underwent inpatient postoperative rehabilitation for 4 months and continued outpatient physiotherapy after discharge. The Gross Motor Function Measure-88 score and maximum walking speed decreased transiently 1 month postoperatively, but gradually recovered, and continuously improved 6 months postoperatively. SDR and postoperative intensive rehabilitation were effective in improving motor and walking functions up to 6 months after surgery, although long-term follow-up is needed to draw conclusions.

Keywords: Gross Motor Function Measure; hereditary spastic paraplegia; selective dorsal rhizotomy; SPG16; *ZC4H2*
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Introduction

Selective dorsal rhizotomy (SDR) has been used to treat children with spastic cerebral palsy (CP) for more than three decades (Josenby et al. 2012, 2015; Dudley et al. 2013; Park et al. 2017a). It has a beneficial effect on quality of life and ambulation, particularly in Gross Motor Function Classification System (GMFCS) Groups I-III with spastic diplegia, as confirmed in long-term follow-up studies (Josenby et al. 2012, 2015; Dudley et al. 2013; Park et

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al. 2017b).

Hereditary spastic paraplegia (HSP), a spectrum of genetically and clinically heterogeneous neurodegenerative disorders, is characterized by progressive lower limb weakness and spasticity (Shribman et al. 2019; Meyyazhagan and Orlacchio 2022). Currently, no definitive treatment exists for HSP (Shribman et al. 2019; Meyyazhagan and Orlacchio 2022). Although several studies have investigated the role of SDR in HSP patients, its effectiveness in the management of HSP-related spasticity remains unclear (Gump et al. 2013; Kai et al. 2014; Sharma et al. 2016; Buizer et al. 2017; Park et al. 2021). Here, we present a case of spastic paraplegia attributed to the *ZC4H2* variant, which demonstrated improvement in motor function and gate after SDR and 6 months of postoperative rehabilitation.

Case Presentation

Preoperative clinical course

A girl aged 6 years and 8 months had been born by cesarean section due to breech presentation after 38 weeks of pregnancy from non-consanguineous Japanese parents. She had no asphyxia. The birth weight, body length, and head circumference were 2,996 g (−0.2 SD), 48.0 cm (0.0 SD), and 35.0 cm (+1.54 SD), respectively. No family history of neurological disorders was noted. Early development was unremarkable.

Abnormal gait was discovered during a regular checkup at the age of 3 years and 9 months, and she was referred to our hospital. Scores on the modified Ashworth scale, the Babinski sign, and exaggerated deep tendon reflexes of the lower extremities indicated spastic paraplegia. Her developmental quotient was 84 [motor domains (locomotion 46, manipulation 96), social domain and ADL 100, and cognition domains (words 68, words comprehension 91)]. Brain magnetic resonance imaging findings were unremarkable. She had short big toes, and radiographs indicated shortening of the first metacarpal and metatarsal bones. She was started on outpatient physiotherapy at 4 years and 11 months old when she had an equinus spastic gait and was unable to run. She could go up and down stairs without using handrails.

We conducted family-based whole-genome sequencing, as described previously (Takayama et al. 2021; Saito-Hakoda et al. 2023), to establish a molecular diagnosis. The patient and her family provided informed consent for next-generation sequencing and publication of this case report. This study was approved by the Ethics Review Boards of Miyagi Children's Hospital and Tohoku University Hospital. We identified a *de novo* heterozygous variant in *ZC4H2,* c.592C>T, p. (Arg198Trp) [NM_018684.4], which was confirmed by Sanger sequencing and classified as "pathogenic" according to the American College of Medical Genetics and Genomics guidelines (PM1 + PM2 + PM5 +PP2 + PP3 + PP5). No other pathogenic variants were detected. The *ZC4H2* variant is the causative gene of spastic paraplegia: SPG16 (Meyyazhagan and Orlacchio 2022).

She attended a local kindergarten before SDR at 5 years and 8 months and was able to walk independently. However, handrails were required when going up and down stairs, suggested worsening. She had no heel contact during the stance phase of the equinus gait. Clearance during the swing phase was insufficient, and her toes often rubbed against the floor.

SDR

She underwent SDR at Okinawa Prefectural Nanbu Medical Center and Children's Medical Center at 5 years and 11 months old. The dorsal root amputation rate was 21% on the right side (L2: 0%, L3: 0%, L4: 33%, L5: 20%, S1: 50%, S2: 25%) and 18% on the left side (L2: 0%, L3: 0%, L4: 0%, L5: 25%, S1: 60%, S2: 25%). Amputation of the S2 dorsal root was performed after evaluating pudendal nerve components, for which individual dorsal root action potentials from the S1-S3 roots were recorded by electrical stimulation of the clitoral nerve skin region as described previously (Deletis et al. 1992). She was transferred to our hospital for intensive postoperative rehabilitation 1 month after SDR and acute phase rehabilitation. The spasticity in the lower limbs disappeared at this time, except in the hip adductors. Heel contact was observed while walking, and internal rotation gait was reduced. Support of the lower limbs decreased, and the patient required walking hand-in-hand with her mother. The Modified Ashworth Scale score improved, deep tendon reflexes decreased, and clonus became negative. No significant change in the range of motion of the lower limb joints was observed (Table 1).

Methods

Motor and walking functions were evaluated before SDR and every month from 1 to 6 months postoperatively. Motor function was evaluated using the Gross Motor Function Measure-88 (GMFM-88) (Russell et al. 1989; Adair et al. 2012). Walking was evaluated using the 10-m walk test (10MWT) (Graham et al. 2008). We also videotaped the gait and confirmed it in the frontal and sagittal planes. Furthermore, we performed the 6-minute walk test (6MWT) (Kuettel et al. 2022) and the Timed Up and Go Test (TUG) (Podsiadlo and Richardson 1991) every month starting 1 month after surgery. TUG measures the time(s) it takes to get up from a chair, walk 3 m, touch a wall, and sit back down in the chair. Finally, we conducted the Canadian Occupational Performance Measure (COPM) (Cusick et al. 2007; McColl et al. 2023) at the time of admission (1 month after surgery) and at discharge (4 months after surgery), to set goals and evaluate the effectiveness of inpatient rehabilitation (Table 2).

Based on these needs, goal-oriented rehabilitation was performed; physiotherapy was performed four or five times a week (40 min/session), and occupational therapy was performed two or three times a week (40 min/session). In

Table 1. Changes in Modified Ashworth Scale (MAS), deep tendon reflexes, clonus, and range of motion (ROM) of the lower limb joints after Selective Dorsal Rhizotomy (SDR).

	Before SDR Right/Left	1 month after SDR Right/Left
MAS		
Hip abduction (with hip and knee flexed)	1+/1+	1/1
Knee extension	3/3	0/0
Knee flexion	1/1+	0/0
Ankle dorsiflexion (with knee flexed)	2/2	0/0
Ankle dorsiflexion (with knee extended)	2/3	0/0
Ankle plantar flexion	1/1	0/0
Deep tendon reflexes		
Patellar tendon reflex	3+/3+	+/+
Achilles tendon reflex	3+/3+	−/−
Clonus		
Ankle clonus	+/+	−/−
ROM of the lower limb joints (°)		
Hip extension	−5/−10	−5/−10
Hip abduction (with knee extended)	30/25	30/30
Hip internal rotation	20/30	30/30
Hip external rotation	30/20	20/15
Popliteal angle	50/60	40/45
Knee extension	−5/0	−5/−5
Ankle dorsiflexion (with knee flexed)	20/20	25/25
Ankle dorsiflexion (with knee extended)	10/10	20/15

Table 2. Comparisons of Canadian Occupational Performance Measure (COPM) at the time of admission and discharge.

Needs	Importance	Admission (1 month after SDR) Performance/Satisfaction	Discharge (4 months after SDR) Performance/Satisfaction
Walking inside the hospital without holding hands	10	2/2	10/10
Going up and down stairs independently	8	1/2	10/10
Climbing over a 5 to 6 cm step without support	10	1/2	10/10
Standing up from the floor	10	1/2	8/8
Changing clothes and shoes in about 5 minutes	10	4/2	8/8
Walking and carrying a school lunch tray with dishes on it	10	1/2	8/8
Opening a sachet of jam	8	1/2	8/8
Pinching food with chopsticks	10	5/5	8/10
		Average 2.0/2.4	Average 8.8/9.0

When the COPM was performed at the time of hospital transfer, eight needs were identified, including walking, climbing steps, standing up, and Activities of Daily Living (ADL). Although it is necessary to narrow down the needs to a maximum of five, we judged that the needs raised by the mother were specific and meaningful and indicative of reasonable goals for this case.
SDR, Selective Dorsal Rhizotomy.

addition, the patient performed ward rehabilitation (walking practice, stair climbing practice, standing/sitting practice, and ADL practice such as changing clothes and using the toilet) while hospitalized every day with nurses. She continued receiving outpatient physiotherapy once a month (40 min/session) at 4 months postoperatively. Her body weight/height at the initiation of physiotherapy, at the time of SDR, and 6 months postoperatively were 17.1 kg/100.4 cm, 17.3 kg/104.8 cm, and 20.0 kg/109.3 cm, respectively.

Results

The preoperative GMFM-88 score of this patient was 87%, which dropped to 82% but gradually improved to the preoperative level by 4 months after surgery (Fig. 1A). It was 89% at 6 months after surgery. Scores for dimensions A (lying and rolling), B (sitting), C (crawling and kneeling),

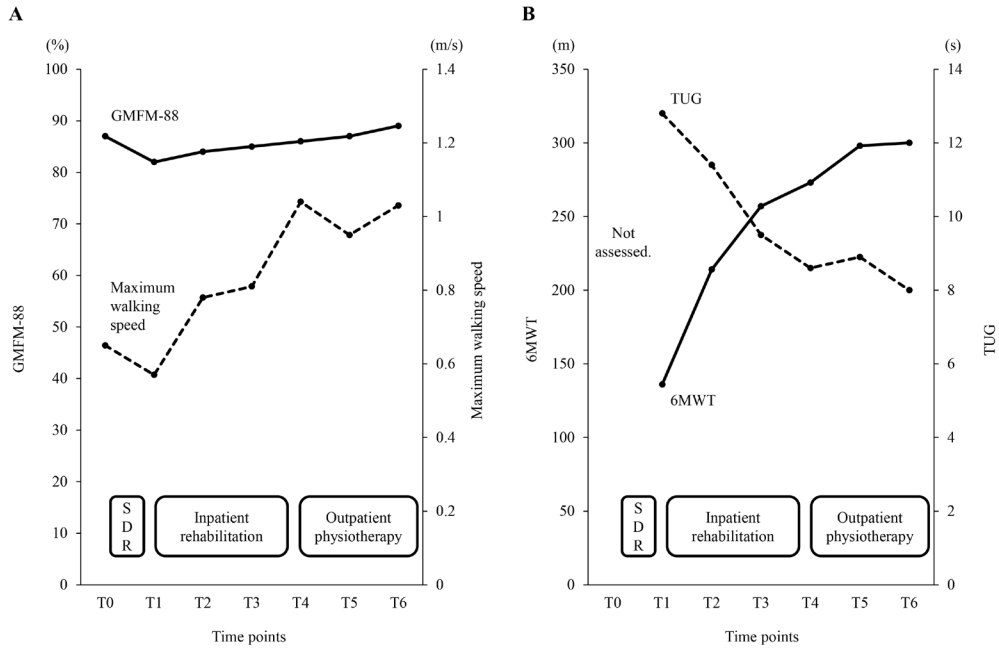

Fig. 1. Timeline and changes in (A) Gross Motor Function Measure-88 (GMFM-88) and maximum walking speed, and (B) The Timed Up and Go Test (TUG) and 6-minute walk test (6MWT).
(A) The preoperative GMFM-88 score for this patient was 87%, which initially decreased to 82% but gradually recovered to the preoperative level by 4 months after surgery. At 6 months after surgery, it reached 89%. The maximum walking speed, calculated using the 10MWT, demonstrated significant improvement from 0.65 m/s preoperatively to 1.03 m/s at 6 months postoperatively. (B) TUG and 6MWT revealed an improved walking speed and dynamic balancing and reduced fatigability after surgery. SDR, Selective Dorsal Rhizotomy; T0, before SDR; T1, 1 month after SDR (transferred to our hospital); T2, 2 months after SDR; T3, 3 months after SDR; T4, 4 months after SDR (discharged from our hospital); T5, 5 months after SDR; T6, 6 months after SDR.

D (standing) and E (walking, running, and jumping) were recorded preoperatively and at 1, 3, and 6 months postoperatively (A: 96-96-96-96, B: 98-90-98-98, C: 95-90-90-98, D: 85-72-79-82, and E: 63-61-63-69). The GMFM-66 score, calculated using the GMAE-2 free software, was 68.5 preoperatively and 67.4 at the 6-month postoperative evaluation. Maximum walking speed calculated using the 10MWT improved 2 months after surgery and continued to improve 6 months postoperatively from 0.65 to 1.03 m/s. The actual measured time required was 15.41 s before surgery and 9.72 s 6 months postoperatively. In addition, the 6MWT and the TUG, evaluated at 1 to 6 months postoperatively, also showed substantial improvement (Fig. 1B).

The COPM performance level improved by 6.8, and the satisfaction level improved by 6.6, after versus before admission (Table 2). As a change in the COPM of ≥ 2 is considered a clinically important change (McColl et al. 2023), the amount of change in this case was remarkable. Preoperative motor regression in stair climbing demonstrated postoperative improvement, as indicated in COPM.

Balance stabilized when walking, and there were fewer situations where she had to walk hand in hand, not only inside the hospital but also outdoors. Her mother said, "After the surgery, she no longer hated going for walks."

She enrolled in elementary school 6 months postoperatively, where she was able to walk approximately 800 m from her home to school with her guardian. Internal rotation was reduced, toes and knees were facing straight in the direction of movement, and single-leg standing was stable. The heel contacted the ground initially. Hip extension at the end of the stance increased, and the take-off by plantar flexion of the ankle became stronger. The swinging motion due to hipflexion during the swing phase became stronger, and foot clearance improved.

Discussion

Reports of SDR for patients with HSP and related genetic disorders causing spastic paraplegia have been limited compared with reports for CP: 4 (Kai et al. 2014), 4 (Sharma et al. 2016), 1 (Gump et al. 2013), 2 (Buizer et al. 2017), and 37 (Park et al. 2021) patients have been reported. Among them, genetic diagnoses were done in 34 patients, and SPG 3 and SPG 4 were the most common gene variants. No reports are available regarding patients with the *ZC4H2* variant (Lohkamp et al. 2020). *ZC4H2* encodes the zinc-finger C4H2-type containing protein (ZC4H2); mutations in this gene lead to a spectrum of neurological disorders known as ZC4H2-associated rare disorders (ZARDs) (Frints et al. 2019). ZARDs manifests as a complex array of neurological features, including hyperreflexia, arthrogryposis, distal muscular weakness, club foot, and camptodactyly. SPG16, an X-linked spastic paraplegia,

is a type of ZARD (Meyyazhagan and Orlacchio 2022). A recent study demonstrated a potential link between ZARDs and TRPV4-pathies, a broad spectrum of disease phenotypes caused by mutations in the *TRPV4* gene (Vangeel et al. 2020).

Park et al. (2021) investigated changes in spasticity and postoperative walking function in 37 HSP patients who underwent SDR at an average age of 14.7 years (range: 2-45 years). When a follow-up study (mean: 3.8 years, range: 0-33 years) was conducted, four patients reported worsening of spasticity, and six reported a decline in walking function. The remaining 73% of patients maintained their level of ambulation. It is necessary to evaluate spasticity as well as motor and walking functions over the long term, taking into consideration the possibility of worsening of spasticity and functional decline.

In the present patient, spasticity of the lower limbs was reduced by SDR. Motor function was temporarily reduced after surgery, but gradually recovered and continued to improve until 6 months postoperatively, as indicated by the GMFM-88, 10MWT, 6MWT, TUG, and COPM.

This patient showed only a 2-point improvement on the GMFM-88 at 6 months postoperatively. It is difficult to interpret the change in this score, as the minimally clinically important difference (MCID) of the GMFM-88 has not been reported for HSP. Furthermore, no significant improvement was observed in the GMFM-66 score at 6 months postoperatively. Although the ability to lower oneself to the floor with free arms (dimension D) remained unchanged, scores for climbing stairs (dimension E) demonstrated improvement, consistent with the findings of COPM. Regarding MCID, a study was performed to measure MCID in 25 patients with HSP (21 adults and 4 children, 17 were SPG4) using timed functional tests, including the 10MWT, TUG, and 6MWT, which revealed no difference at the 18-month follow-up (Cubillos-Arcila et al. 2022); this reflects the difficulty of setting the MCID in patients with HSP because of very slow motor evolution. In contrast, as shown in the 10MWT, 6MWT, and TUG results, a significant change in walking speed was detected at 6 months postoperatively in this patient, indicating that an evaluation with multiple scales is important in addition to the GMFM-88/66 to interpret the functional changes after SDR in children with a high preoperative GMFM-88/66 score.

Children with CP require intense rehabilitation for a certain time after SDR. Some reports recommend that intensive and specific physiotherapy should be emphasized during the first postoperative year (Nicolini-Panisson et al. 2018). This patient received outpatient physiotherapy once per month after discharge from the hospital. However, it may be necessary to reconsider the use of home-visit rehabilitation and reevaluate the use of the COPM.

As in cases of CP, appropriate selection criteria are needed to establish the efficacy of SDR for patients with HSP and related disorders. Park et al. (2021) recommended that patients suitable for SDR should have "uncomplicated" HSP, i.e., be free from epilepsy, cognitive impairment, and peripheral neuropathy, aged 2-50 years at the time of evaluation, and have neurological abnormalities limited to the lower extremities (Park et al. 2021). As the genes causing HSP are heterogeneous and clinical evolution varies, a genetic diagnosis may be needed to select the best spasticity treatment and rehabilitation approach for each case.

In conclusion, we report the first patient with the *ZC4H2* variant who underwent SDR to treat spastic paraplegia. SDR and postoperative intensive rehabilitation were effective in improving motor and walking functions up to 6 months after surgery, although long-term follow-up is needed to draw conclusions.

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Conflict of Interest

The authors declare no conflict of interest.

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