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Intrathecal Baclofen Therapy Improves Refractory Status Dystonicus in Neuro-hepatic Wilson's Disease: A Case Report

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Abstract

Wilson's disease is an autosomal recessive disorder of copper metabolism. A current unresolved issue is the worsening of neurological symptoms during the initial treatment phase, particularly with chelation therapy. This phenomenon, termed "early neurological worsening," is attributed to the rapid mobilization and redistribution of copper during treatment initiation. We report the case of a 10-year-old boy, with neuro-hepatic Wilson's disease who developed treatment-refractory generalized dystonia, which improved with intrathecal baclofen therapy. The patient experienced walking discomfort 5 months before referral to our hospital, with rapid progression to dysphagia and a 3 kg weight loss. Initially, he presented with dystonia, including foot inversion. Wilson's disease was diagnosed based on physiological, clinical, and imaging findings, with confirmation of a homozygous mutation in the *ATP7B* gene. The patient was treated with trientine hydrochloride, followed by zinc monotherapy. Despite appropriate chelation therapy, dystonia progressed to severe axial torsion involving the trunk. His condition deteriorated to status dystonicus, with high-grade fever, elevated creatine phosphokinase levels, and dehydration, requiring midazolam sedation. These symptoms were attributed to "early neurological worsening." A trial of intrathecal baclofen injection provided symptom relief, leading to the implantation of a baclofen pump, which significantly reduced the status dystonicus. At discharge, the patient had a modified Rankin Scale score of 5. Three years later, although wheelchair-dependent, his oral intake and speech are progressively improving with training. This is the first reported case of status dystonicus in Wilson's disease successfully treated with intrathecal baclofen, highlighting its potential as a viable treatment option for Wilson's disease-associated debilitating dystonia.

Keywords: Wilson's disease, intrathecal baclofen, status dystonicus, dystonia

Introduction

Wilson's disease (WD) is an autosomal recessive disorder of copper metabolism caused by abnormal copper accumulation in multiple organs, such as the liver, brain, cornea, and kidneys.[1)] It is caused by mutations in the *ATP7B* gene, which encodes a copper-transporting adenosine triphosphatase. Although WD is one of the few inherited metabolic diseases manageable with early diagnosis and treatment, it poses significant challenges, including "early neurological worsening," which often occurs shortly after the initiation of chelation therapy, and is characterized by a rapid deterioration of neurological symptoms. This condition occurs in 11% of patients with WD undergoing chelation therapy, with over 60% of cases reported to be reversible.[2,3)] However, in rare and severe instances, it may result in death due to complications associated with immobilization.[2,4)] Dystonia is a relatively common and poten-

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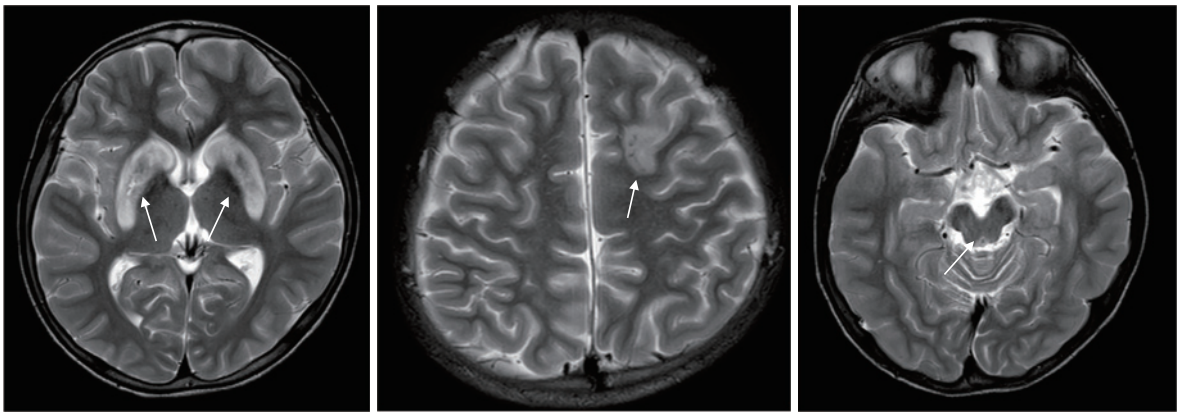

Fig. 1 Magnetic resonance imaging of the brain.
A; Abnormal high T2 signal in the bilateral basal ganglia (Arrow) .
B; Abnormal high T2 signal in the left frontal cortex (Arrow) .
C; Abnormal high T2 signal in the midbrain (around aqueduct of the midbrain) .
T2: type 2

tially severe neurological symptom in WD. Stereotactic brain surgery, including deep brain stimulation (DBS), has been rarely employed for the treatment of dystonia secondary to WD, and only a single case involving intrathecal baclofen (ITB) therapy has been previously documented. Herein, we report the first case of ITB therapy for status dystonicus in a patient with WD.

Case Report

A previously healthy 10-year-old boy experienced discomfort while walking because of inward rotation of his left leg, leading to frequent stumbling, 5 months prior to being referred to our hospital. There was a gradual decline in his appetite, and he started missing school. He visited a nearby clinic, and his symptoms were initially diagnosed as a psychogenic reaction; however, he was re-examined by a local pediatrician for the worsening of symptoms. The boy was admitted to the pediatric department of our hospital for further examination. Based on the following investigations and clinical findings, a definite diagnosis of WD was made: dystonia of legs, sluggish speech, hypertonia, abnormal liver function, low serum ceruloplasmin (8.6 mg/dL; baseline 66-130) and elevated urinary copper (227 μg/L; baseline <36) levels, chronic hepatitis pattern on ultrasonography, abnormally high type 2 signal in the bilateral basal ganglia, midbrain, and frontal cortex on magnetic resonance imaging (shown in Fig. 1), and Kayser-Fleischer rings in cornea on slit lamp examination. Genetic testing revealed a homozygous mutation in the *ATP7B* gene. Early neurological worsening is a reported phenomenon where neurological symptoms deteriorate following the initiation of copper chelation therapy.[2-5] In this case, zinc monotherapy was initially used, followed by trientine hydrochloride, as an additional chelation therapy, to prevent early neurological worsening. Despite carefully managed treatment that reduced free copper levels, a key indicator of treatment efficacy, to the target level (5-15 μg/dL), the patient's neurological symptoms worsened. One and a half months after the initiation of treatment he became bedridden, unable to eat because of increased muscle tone. Moreover, vocal communication became challenging due to dysarthria. His creatine phosphokinase (CPK) level became elevated (1,664 IU/L; baseline 62-287), and the patient developed a fever of >38°C with complaints of severe myalgia throughout his body due to generalized muscle tension. Administration of trihexyphenidyl, baclofen, dantrolene, eperizon, and diazepam proved ineffective in relieving the symptoms, and the patient's condition progressed to prestatus dystonicus. Dystonia is one of the intractable neurological symptoms of WD's, and in severe instances, it may result in death.[4] Despite the successful progression of copper chelation therapy for the underlying WD, the exacerbation of neurological symptoms indicated the need for intensive symptomatic management of dystonia. Consequently, ITB therapy was initiated, with a trial ITB administration of 25 and 50 μg intrathecal injection. Even at 25 μg, the abnormal dystonic postures improved; however, due to persistent severe muscle tone, a trial with 50 μg was also conducted, which resulted in muscle relaxation and pain relief, and the patient reported enhanced comfort; therefore, the ITB pump (Synchromed II, Medtronic Inc., Minneapolis, MN, USA) implantation was planned. The catheter was placed at the C6 level to relieve general symptoms. We initiated baclofen administration with 25 μg/day by a continuous infusion. The dosage was gradually increased by 15% per dose. One week after therapy initiation; at 126 μg/day of baclofen, CPK levels became normal,

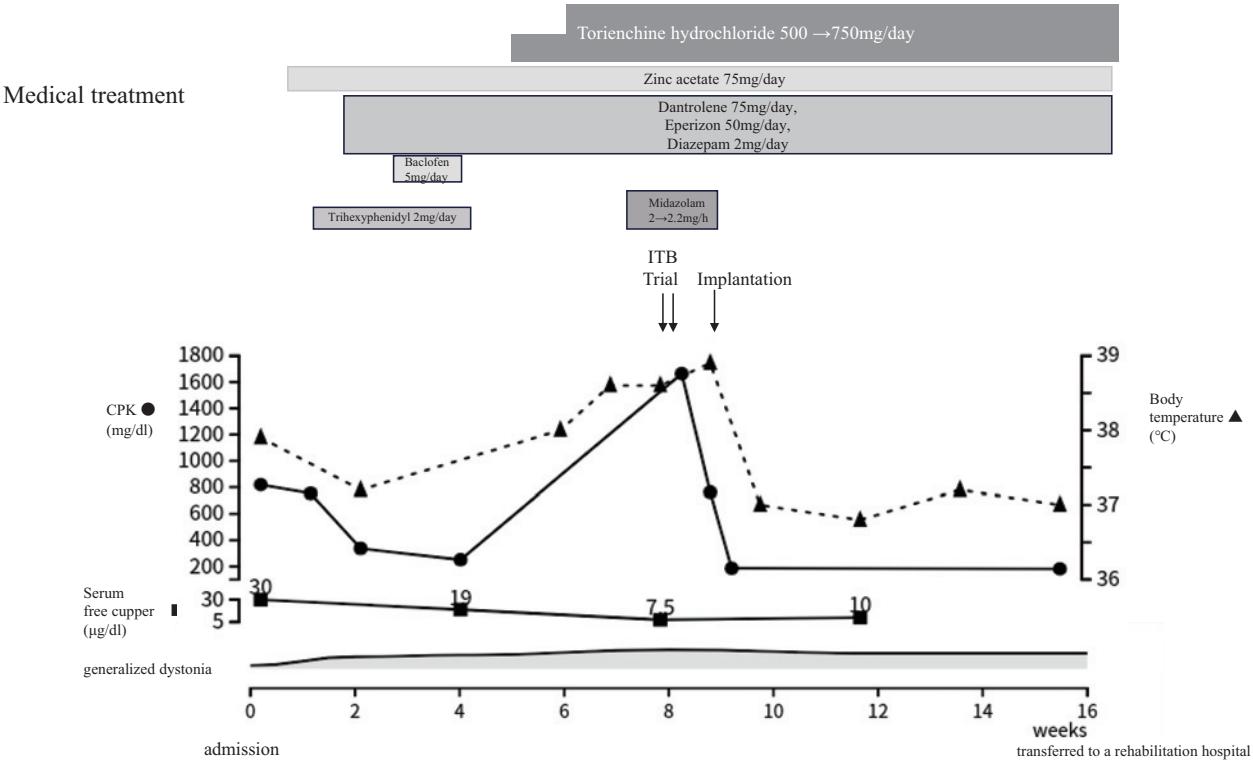

Fig. 2 Clinical course.

and the fever subsided rapidly. Rehabilitation, which was previously difficult due to increased muscle tone, was resumed, and the patient's comfort level increased. Two months after the ITB implantation, the patient was transferred to another hospital for further rehabilitation and treatment of WD. A summary of the clinical course is illustrated in Fig. 2. His final modified Rankin Scale score was 5 and the Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS), was 71/120 before treatment, and 63/120 at discharge from our hospital.

Remarkably, 3 years later, with a daily dose of 256 μg of baclofen administered in flex mode, which includes bolus dosing, the patient has shown good progress. Despite being wheelchair-dependent, his oral intake and his speech are steadily improving with training.

Discussion

Neurological manifestations of WD vary, with dysarthria, dystonia, tremors, parkinsonism, and ataxia being prevalent symptoms,[6-10] which can be subtle, and possibly masked by more prominent symptoms.[11] Treatment with chelating agents and/or zinc salts typically results in clinical improvement. However, neurological symptoms appear to be less responsive to treatments compared with hepatic symptoms. Neurological worsening that occurs shortly after the initiation of treatment of WD[2-4,6,12] is referred to as "early neurological worsening." Patients undergoing chelation therapy typically report this early neurological worsening. This is based on the hypothesis that copper gets deposited in brain tissue due to rapid changes in copper metabolism after copper chelation therapy, and studies indicate that neurological symptoms are often exacerbated when initially treated with the chelating agent D-penicillamine.[5] In Japan, treatment of cases with severe neurological symptoms is started with zinc acetate, and when chelation therapy is chosen, trientine hydrochloride rather than D-penicillamine is recommended.[13] However, similar worsening has also been reported in patients undergoing zinc salt therapy.[12] The pathophysiology underlying early neurological worsening remains poorly understood and controversial. In our case, the neurological symptoms rapidly worsened despite adequate treatment (careful chelation therapy preceded by zinc preparation). Litwin et al.[2] identified the initial neurological presentation as a factor of neurological worsening, which was also observed in our case.

Dystonia is a common neurological manifestation of WD, affecting 11%-65% of patients, and is considered one of the most severe and refractory symptoms.[2,9,14,15] Classified as secondary dystonia, it results from structural damage, primarily in the basal ganglia. Stereotactic surgery for involuntary movements in WD has been reported in very few cases.[16-20] The intervention has been reported as a therapeutic approach for WD tremors through targeting the ventralis intermedius nucleus of the thalamus or pos-

terior subthalamic area, demonstrating favorable outcomes of >80% tremor reduction.[17-19] However, globus pallidus internus-targeted stereotactic surgery for dystonia with WD is rare,[17,20] with an average improvement of 7.8% on the BFMDRS, which is not a satisfactory outcome. Recently, Grana et al.[21] reported a case demonstrating a 5-month effectiveness of ITB for secondary dystonia in the chronic phase of WD. In our case, we chose ITB for the following reasons: first, limited effectiveness of stereotactic surgery for WD-related secondary dystonia; second, significant morphological changes in the basal ganglia; and third, the patient's severe condition, necessitating a faster therapeutic response compared to DBS. Two months postoperatively, our patient's BFMDRS improvement rate at discharge was 11%. The low improvement rate was because BFMDRS is relatively insensitive to clinically meaningful changes, such as axial dystonia, vocalization and communication, fine motor skills, and hand dexterity and swallowing, as described by Sidiropoulos et al.[20] In addition, patients with WD, including ours, have relatively fixed dystonia,[16] which may be another reason for the difficulty in assessing WD dystonia using the BFMDRS. The BFMDRS is commonly used for the quantitative assessment of primary torsion dystonia in adults; however, it does not distinguish between abnormal postures and movements caused by dystonia and those resulting from non-dystonic symptoms. Additionally, its test items evaluate the influence of dystonia on functional activities, regardless of whether dystonia is the primary cause of functional impairment in the affected body segment or activity.[22] The distinguishing features of our report are its demonstration of the effectiveness of ITB in treating dystonic status and the long-term observation over a 3-year follow-up.

In summary, while neurological symptoms associated with WD often improve with appropriate treatment, dystonia remains one of the most severe and treatment-resistant manifestations. Given the lack of evidence-based guidelines for WD-related dystonia, surgical options must be explored on an individual basis. Although over 60% of cases of early neurological worsening are reported to be reversible, extremely severe symptoms can be life-threatening. ITB warrants further investigation as a potential treatment option for status dystonicus associated with WD.

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Author Contributions

Sae Yamanaka: Data acquisition, Writing - original draft. Tomoko Hanada: Conceptualization, Investigation, Resources, Data acquisition, Writing - review & editing. Chihiro Yonee: Conceptualization, Investigation. Takuichiro Higashi: Data acquisition. Manaka Matsunaga: Data acquisition, Investigation. Shinsuke Maruyama: Data acquisition, Supervision. Ryosuke Hanaya: Conceptualization, Supervision.

Informed Consent

Consent was obtained from the patient's family.

Data Availability Statement

Anonymized data not published in this article will be made available upon request from the corresponding author.

Disclaimer

Author Ryosuke Hanaya is one of the Editorial Board members of the Journal. This author was not involved in the peer-review or decision-making process for this paper.

Conflicts of Interest Disclosure

All authors have no conflict of interest.

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