

News Release

Title

New treatment for intractable neurological disease! Effect of levodopa on pathological gait in Dravet syndrome is validated with a randomized crossover trial using three-dimensional gait analysis.

Key Points

- Dravet syndrome is a refractory developmental epileptic encephalopathy characterized by convulsive status epilepticus during fever. Patients with Dravet syndrome also exhibited various symptoms including intellectual disability and progressive gait disturbance.
- We evaluated the efficacy of levodopa for pathological gait in Dravet syndrome with a randomized crossover trial based on quantitative evaluation using three-dimensional gait analysis.
- The present study with nine participants showed that levodopa significantly improved the Gait Deviation Index (a comprehensive index of gait), 6-minute walking distance, and the results of balance test.
- Subgroup analysis revealed that levodopa was more effective in younger participants with a higher baseline gait performance. This finding suggests that levodopa treatment may be beneficial in younger people with Dravet syndrome.

Summary

Prof. Jun Natsume (corresponding author), Dr. Takeshi Suzuki (first author), Dr Yuji Ito and Prof. Yoshiyuki Takahashi of the Department of Pediatrics, Nagoya University Graduate School of Medicine (Dean: Hiroshi Kimura, MD, PhD), Dr. Tadashi Ito and Dr Koji Noritake of Aichi Prefectural Mikawa Aoitori Medical and Rehabilitation Center for Developmental Disabilities have proposed that levodopa is effective and tolerable treatment for pathological gait in patients with Dravet syndrome.

Dravet syndrome is a designated intractable disease with a prevalence of 1 in 20,000 to 40,000 people. In addition to seizures, which are the central symptom of the disease, patients with Dravet syndrome present with intellectual disability and progressive gait disturbance. Although gait disturbance significantly affects the quality of life, there has been no established treatment for this condition. The study group led by Prof. Natsume

quantitatively evaluated the gait of patients with Dravet syndrome using three-dimensional gait analysis and conducted a randomized crossover trial for validating effect of levodopa on pathological gait. levodopa significantly improved the Gait Deviation Index (a comprehensive index of gait), 6-minute walking distance, and the results of balance test.

These results will not only provide support for patients who experience difficulty in walking, but will also lead to a better understanding of the pathophysiology of movement disorders in Dravet syndrome, which remains largely unknown.

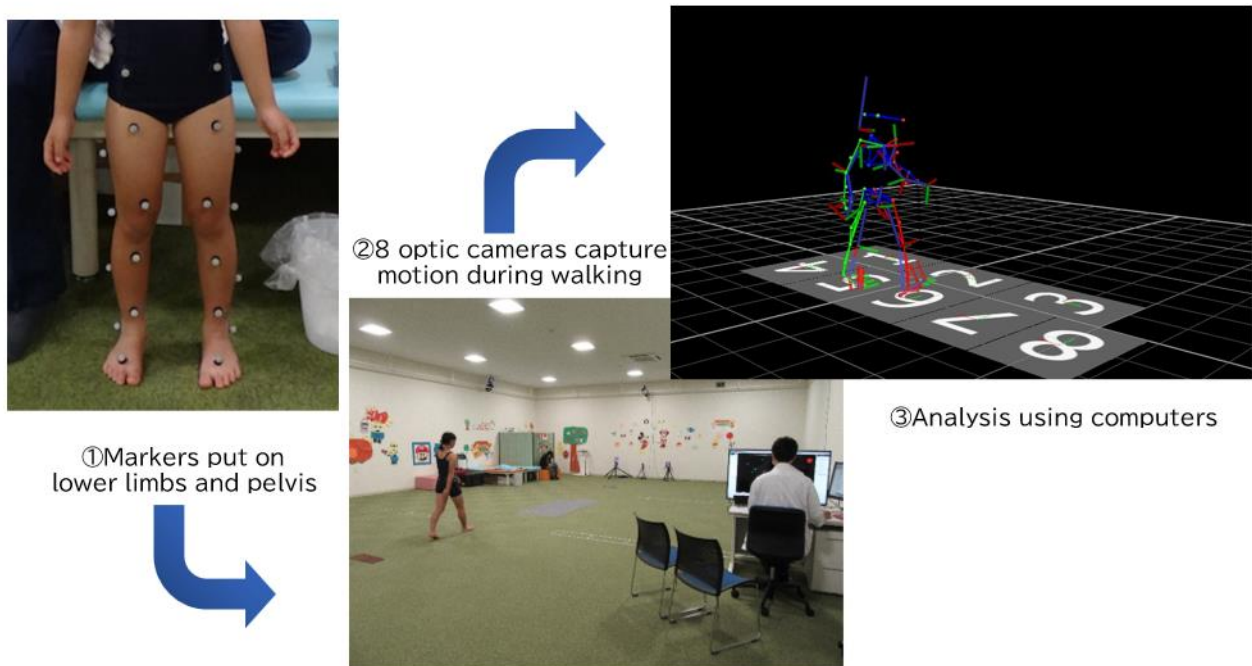
Research Background

Dravet syndrome is a rare developmental and epileptic encephalopathy characterized by the onset of febrile or afebrile seizures, often of long duration, during the first year of life, followed by multiple additional seizures and slowing of developmental and cognitive skills. Gait disturbance is one of the most significant problems for people with Dravet syndrome and caregivers because the ability to walk is important for activities of daily living and quality of life. Currently, there are few established treatments for pathological gait in people with Dravet syndrome. One case report pointed to the possible effectiveness of levodopa for Parkinsonian gait in an adult woman with Dravet syndrome. However, randomized controlled trials have not been conducted to assess the effectiveness of levodopa for gait abnormalities in Dravet syndrome.

Three-dimensional gait analysis of spatiotemporal data, kinematics, and kinetics is a reliable way to evaluate gait quantitatively. (Figure 1) Recently, 3DGA was used to assess specific gait characteristics and improve therapeutic outcomes in pediatric neurological diseases and cerebral palsy.

Based on this background, the present randomized crossover unblinded study was to evaluate quantitatively the improvement in pathological gait associated with the administration of levodopa using 3DGA.

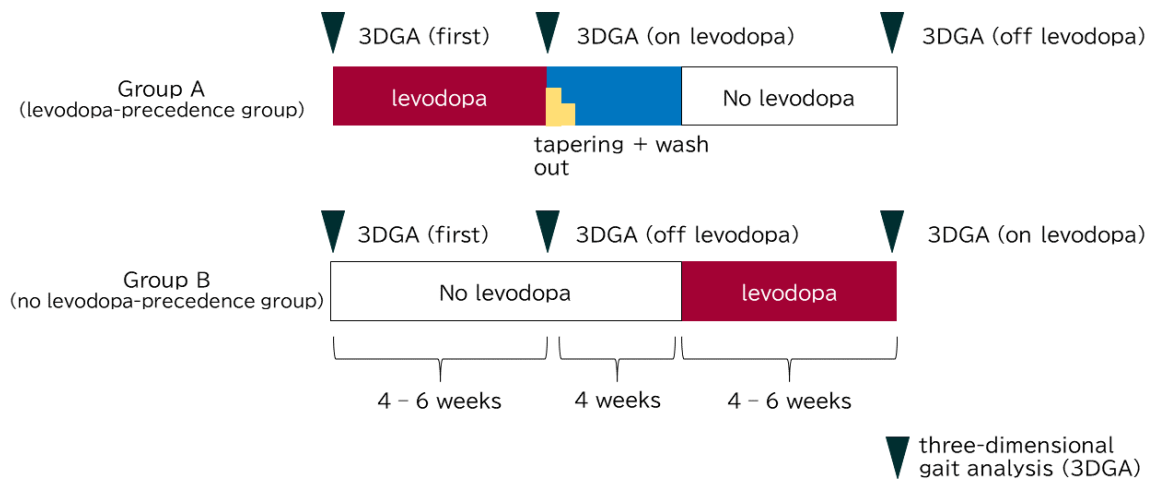
(Figure 1)



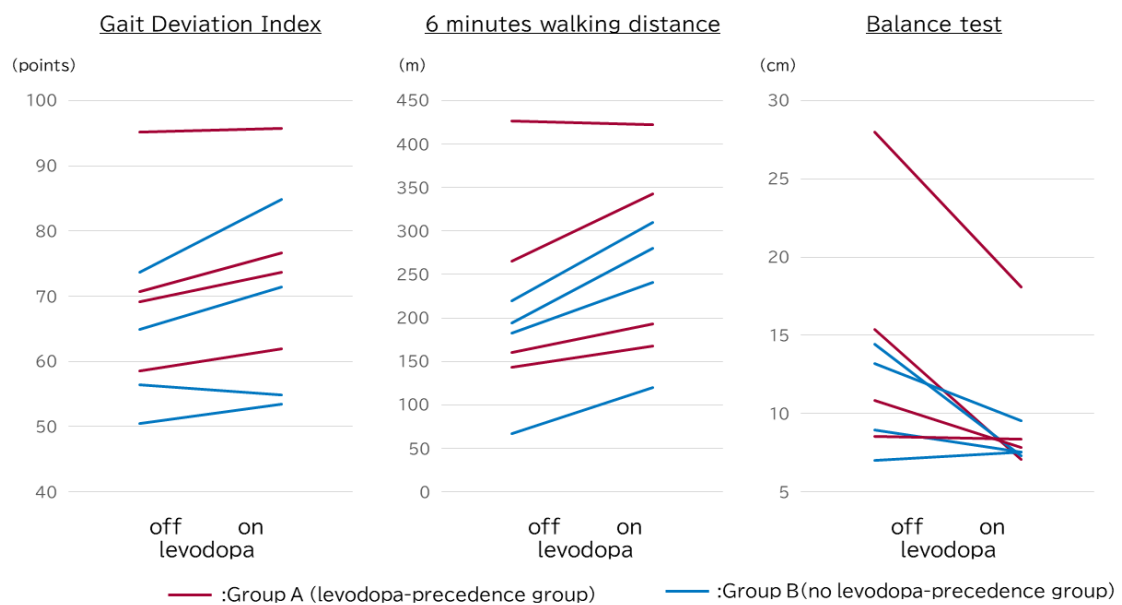
Research Results

Nine individuals with Dravet syndrome, aged 6–20 years, participated in a crossover study of levodopa and were randomly assigned to the levodopa precedence or no levodopa precedence group. (Figure 2) Levodopa was administered at 5 mg/kg per day (<60 kg body weight) or 300 mg per day (>60 kg body weight) for 4–6 weeks. Evaluation using a mixed-effects model showed statistically significant improvements in the Gait Deviation Index, a comprehensive index of gait, 6-minute walk distance, and balance test results on levodopa. (Figure 3) Subgroup analysis revealed that levodopa was more effective in younger participants with a higher baseline gait performance. There were no significant adverse events, except for one patient who discontinued medication due to fever with no known causal relationship to the drug. In conclusion, levodopa may be an effective and well-tolerated treatment for gait disturbance in Dravet syndrome.

(Figure 2)



(Figure 3)



Research Summary and Future Perspective

Levodopa can now be presented as a treatment option for patients with Dravet syndrome who experience difficulty walking. In addition, it is expected to help elucidate the pathophysiology of movement disorders in Dravet syndrome, which has been unclear to date. In the future, we would like to work on the search for the optimal dosage and the evaluation of long-term efficacy and safety, which could not be done in this study.

Publication

Takeshi Suzuki, Jun Natsume, Yuji Ito, Tadashi Ito, Koji Noritake, Fumie Kinoshita, Tatsuya Fukasawa, Takeshi Tsuji, Kazuya Itomi, Hirokazu Kurahashi, Kazuo Kubota, Tohru Okanishi, Shinji Saito, Hideshi Sugiura, Hirohisa Watanabe, Yoshiyuki Takahashi, and Hiroyuki Kidokoro
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