


SHORT RESEARCH ARTICLE

Decreased homovanillic acid and 5-hydroxyindoleacetic acid levels in the cerebrospinal fluid of patients with Dravet syndrome with parkinsonism

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Abstract

Dravet syndrome (DS) is an early onset, developmental, and epileptic encephalopathy characterized by drug-resistant seizures and multiple comorbidities. It has been reported that in adulthood, it may be accompanied by parkinsonism, but the pathogenesis of this condition remains unclear. We performed dopamine transporter single-photon emission computed tomography (DAT SPECT) and measured monoamine metabolite levels in the cerebrospinal fluid (CSF) in two adult patients with DS who developed parkinsonism around the age of 30 years. DAT SPECT showed no abnormalities in either patient, whereas CSF tests revealed significant decreases in the levels of homovanillic and 5-hydroxyindoleacetic acids. One patient with severe symptoms was treated with levodopa–carbidopa, which improved parkinsonism manifestations. The other patient initiated treatment with a low dose and has been continuing the treatment without any reported side effects. In conclusion, CSF testing can detect a decrease in dopamine synthesis and may be useful in monitoring the efficacy of levodopa treatment in patients with DS and parkinsonism.

Plain Language Summary: Dravet syndrome (DS) is an early onset, developmental, and epileptic encephalopathy. DS can lead to the development of parkinsonism in adulthood, a clinical syndrome characterized by tremor, slowed movements, and rigidity. Although parkinsonism is a significant issue for patients, its underlying pathology has not yet been elucidated. In this study, we confirmed that the levels of monoamine metabolites in the CSF were low in two patients, potentially shedding light on the pathology involved.

KEYWORDS

dopamine transporter, levodopa, monoamine metabolites, single-photon emission computed tomography

1 | INTRODUCTION

Dravet syndrome (DS) is an early onset, developmental, and epileptic encephalopathy characterized by drug-resistant seizures and multiple comorbidities.¹ The seizure onset typically occurs between 3 and 9 months of age. After early, repeated, and febrile seizures, patients experience multiple seizure types, particularly convulsive, myoclonic, and absence seizures that are frequently triggered by fever and drug resistance.² Development appears normal at seizure onset; however, from the second year of life, children suffer cognitive and behavioral impairments, and subsequently, most patients exhibit mild to severe intellectual disability.² In adulthood, the number of epileptic seizures decreases, and fever no longer triggers seizures in some cases.^{3,4} In DS, epileptic seizures gradually subside, but gait disturbance progresses from childhood and parkinsonism emerges, especially in adulthood.^{5–7} Up to 57% of adult patients with DS have parkinsonian gait.⁸ Parkinsonism is a symptom of Parkinson's disease and several other neurodegenerative disorders. Parkinsonism impairs the activities of daily living and has a serious impact on daily life, as the degree of dependence on caregivers increases over time.⁹ Therefore, parkinsonism is an important problem for many patients with DS and their caregivers. However, its underlying pathogenesis has not yet been elucidated. As Parkinson's disease is caused by the degeneration of dopaminergic neurons and a decrease in dopamine synthesis, dopamine transporter single-photon emission computed tomography (DAT SPECT) and measurement of monoamine metabolites in the cerebrospinal fluid (CSF) are typically performed.^{10–12} However, DAT SPECT in patients with parkinsonism associated with DS has been rarely reported,^{13,14} and CSF monoamine metabolites were measured in only one case report.¹⁴ To evaluate the function of dopaminergic neurons and assess the level of dopamine synthesis, we performed DAT SPECT and measured CSF monoamine metabolite levels in two adult patients with DS who presented with parkinsonism. One patient was treated with levodopa-carbidopa. Here, we describe these two cases and discuss their pathogenesis.

2 | CASE REPORTS

Case 1 was a 29-year-old woman who manifested a typical clinical course of DS and was later diagnosed genetically. At the age of 4 months, she developed seizures after she had been bathed. She subsequently had a difficult course with repeated status epilepticus, mainly when she had fever or was bathing. She had many seizures, predominantly on one side of the body, as well as

Key points

- Two adult patients with Dravet syndrome (DS) developed parkinsonism at approximately 30 years of age.
- CSF tests in both patients revealed decreased levels of monoamine metabolites.
- Declined dopamine synthesis may cause parkinsonism in DS.
- Thus, parkinsonism may improve with levodopa administration.

generalized seizures. Gradually, in addition to convulsive seizures, she developed other types of seizures, including focal impaired awareness and myoclonic seizures, and was diagnosed with DS based on the course of illness in early childhood. Genetic testing revealed a heterozygous missense variant in *SCN1A*, NM_001165963.3: c.1262T>C (p.Val421Ala). Although this variant is registered as having uncertain significance in Clinvar ([https:// www.ncbi.nlm.nih.gov/clinvar/](https://www.ncbi.nlm.nih.gov/clinvar/)), different variants at the same amino acid position (p.Val421Met) have been reported as pathogenic or likely pathogenic in the Clinvar and HGMD databases (<https://www.hgmd.cf.ac.uk/ac/index.php>). In addition, the mutation in this case has not been reported in the general population, and its pathogenicity prediction scores (SIFT: deleterious, Polyphen2_HVAR: probably damaging, CADD: 27.7) suggest its pathological potential. Thus, the variant was considered the cause of the disease. According to the American College of Medical Genetics and Genomics and the Association of Molecular Pathology guidelines (ACMG/AMP guidelines),¹⁵ this variant was classified as having uncertain significance (PM2, PM5, and PP3). The seizures were resistant to various anti-seizure medications (ASMs), and psychomotor developmental delays became apparent in early childhood. At the age of 3, she learned to walk unaided, motor function did not regress thereafter, and the number of seizures decreased after school age. As she entered adulthood, the frequency of her epileptic seizures decreased, and status epilepticus became rare, but from around the age of 27, she began to experience walking difficulties (shuffling gait with steps, gait freezing), dropped head, tremors in her limbs and face, hypomimia, sialorrhea, insomnia, and restlessness. At the age of 28, she was admitted to the hospital to investigate the cause of these symptoms. On admission, she had a dropped head, irregular 4–8 Hz tremor in the limbs and face that disappeared during sleep, muscle rigidity, postural instability, shuffling gait with steps, and gait freezing. First, we considered the possibility of drug-induced

parkinsonism and discontinued valproic acid (VPA) and risperidone; however, bradykinesia, rigidity, and tremor persisted, and other symptoms did not improve either. The thyroid function was normal. Brain magnetic resonance imaging (MRI) showed no abnormalities that could cause parkinsonism, such as hydrocephalus or vascular lesions,

but revealed non-specific cerebral atrophy (Figure 1A). DAT SPECT was performed to evaluate the degeneration of dopaminergic neurons. No decrease in the striatal signals was observed (Figure 1C). Summary of the patient's information is available in Table 1. CSF examination was performed to examine the capacity of dopamine synthesis,

FIGURE 1 (A) T1-weighted axial brain MRI image of Case 1. (B) T1-weighted axial brain MRI image of Case 2. In both cases (A, B), non-specific atrophy of the cerebral cortex and white matter was observed. No atrophy was detected in the thalamus or striatum. (C) Dopamine transporter single-photon emission computed tomography (DAT SPECT) scan of Case 1. Striatal ¹²³I-N-ω-fluoropropyl-2β-carbomethoxy-3β-(4-iodophenyl)nortropane binding was high, with specific binding ratios of 10.49 (right) and 9.58 (left). (D) DAT SPECT of Case 2. Striatal ¹²³I-N-ω-fluoropropyl-2β-carbomethoxy-3β-(4-iodophenyl)nortropane binding was high, with specific binding ratios of 9.32 (right) and 9.88 (left). In both cases (C, D), binding ratios were within the normal range.

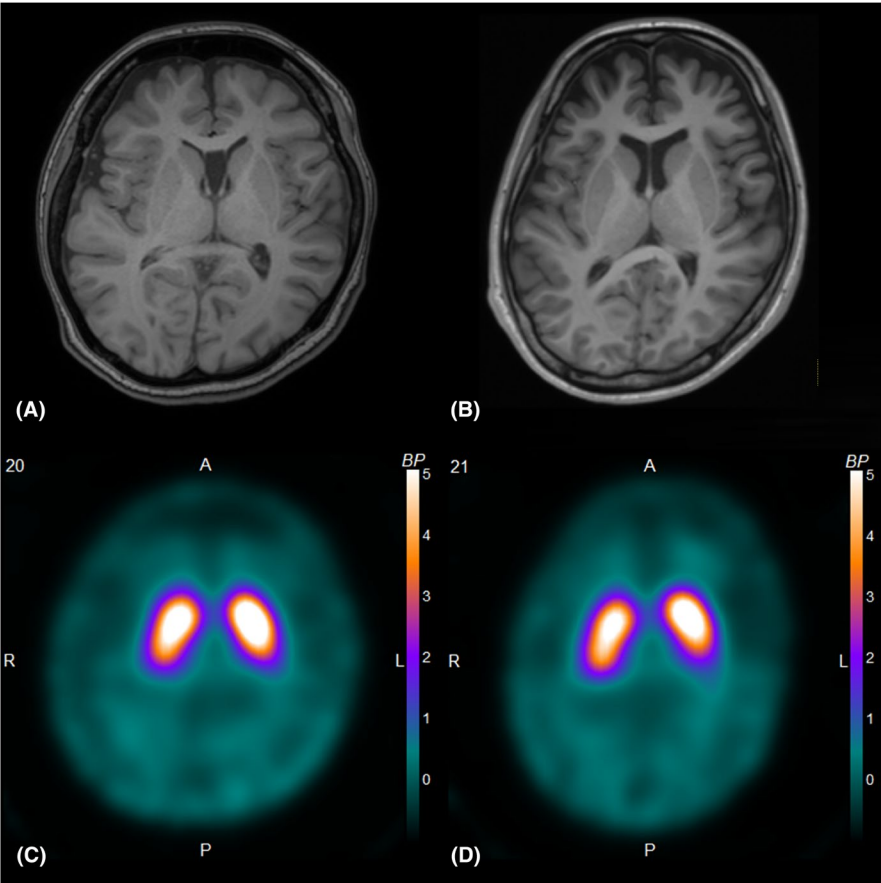


TABLE 1 Clinical data of the two cases.

Parameter	Case 1	Case 2
Age	28 years	33 years
Sex	Female	Female
Motor function	Able to walk on her own	Bedridden
Intellectual disability	Profound	Profound
SCN1A variant	c.1262T>C (p.Val421Ala)	c.5347G>A (p.Ala1783Thr)
Brain MRI	Non-specific cerebral atrophy	Non-specific cerebral atrophy
DAT SPECT	Normal	Normal
Thyroid function	Normal	Normal
Medication (ASM)	LEV, CLB, KBr, LCM	VPA, CLB, ZNS, fenfluramine
Medication (other)	Aripiprazole, Lemborexant	
Treatment of parkinsonism	Levodopa–carbidopa	Levodopa–carbidopa

Abbreviations: ASM, anti-seizure medication; CLB, clobazam; DAT SPECT, dopamine transporter imaging, single-photon emission computed tomography; ID, intellectual disability; KBr, potassium bromide; LCM, lacosamide; LEV, levetiracetam; MRI, magnetic resonance imaging; SCN1A, sodium channel alpha 1 subunit; VPA, valproic acid; ZNS, zonisamide.

and homovanillic acid (HVA) and 5-hydroxyindole acetic acid (5-HIAA) levels were markedly low (Table 2). As this suggested a decrease in dopamine synthesis, a combination of levodopa and carbidopa 150 mg (150 mg levodopa equivalent) was started. When the dose was increased to 400 mg, the dropped head gradually disappeared, and improvements in gait and tremor were observed. Treatment was continued for ~1 year to date, and the effect persisted.

Case 2 was a 33-year-old woman who developed epilepsy during infancy and had a typical clinical course of DS. She developed myoclonus in her right hand at 2 months of age. Thereafter, she repeatedly experienced myoclonus while she was having a bath and developed recurrent generalized convulsions. Gradually, various seizure types were observed. Because seizures were induced by fever, she was clinically diagnosed with DS in early childhood. Subsequently, a heterozygous missense *SCN1A* variant, NM_001165963.3: c.5347G>A (p.Ala1783Thr), was confirmed. The same variant was reported as a disease-causing mutation in DS.¹⁶ According to the ACMG/AMP guidelines,¹⁵ the variant was classified as likely pathogenic (PS1, PM2, and PP3). The seizures were resistant to various ASMs, and psychomotor developmental delays became apparent during early childhood. Frequent seizures continued into adulthood, and a vagus nerve stimulator was placed at the age of 22; thereafter, the seizure frequency slightly decreased. She was able to walk at the age of 1 year and 4 months and learned to run after that. However, her motor function gradually declined, and from her early 20s, she began to experience a dropped neck, slowness of movements, and hypomimia. From around the age of 25, she had difficulty walking unaided and eventually became confined to a wheelchair. Around the age of 30, she began to experience tremors in her face and extremities, and at the age of 33, she was hospitalized to investigate the cause of the tremor. Upon admission, a slightly irregular tremor of the face and upper limbs that occurred continuously during wakefulness was observed. In addition, she had hypomimia, jaw opening, and a dropped head. Therefore, she was diagnosed with parkinsonism. She was taking VPA, but we did not discontinue

it because she had been taking it for many years, and the blood level was stable at 60–80 µg/mL. The thyroid function was normal; brain MRI showed no findings suggestive of the cause of parkinsonism, whereas non-specific cerebral atrophy was observed (Figure 1B). DAT SPECT also showed no decrease in the signal intensity in the striatum (Figure 1D). An overview of the patient's clinical data is presented in Table 1. Low CSF levels of HVA and 5-HIAA were observed (Table 2). We initiated treatment with a low dose of levodopa and carbidopa combination and are evaluating its effectiveness (Table 1).

3 | DISCUSSION

We described two patients with DS who developed gait disorders in their 20s, later presented with tremor and bradykinesia, and were diagnosed with parkinsonism. To evaluate the function of dopaminergic neurons and dopamine metabolism, we performed DAT SPECT and measured monoamine metabolites in the CSF. No abnormalities were detected using DAT SPECT, whereas CSF HVA and 5-HIAA levels were markedly low in both cases.

Our two cases showed normal radiotracer uptake. DAT SPECT results have been previously described in three patients with DS: a 20-year-old male, a 42-year-old female, and a 19-year-old male who presented with parkinsonism. All three patients showed normal radiotracer uptake in the basal ganglia.^{13,14} Normal DAT SPECT findings indicated the absence of degeneration of the presynaptic dopaminergic neurons, excluding the possibility of initial degeneration that was not detected by imaging, suggesting that postsynaptic neurons in the striatum or another system caused parkinsonism.

In Parkinson's disease, a pathological decrease in dopamine synthesis is accompanied by decreases in HVA and 5-HIAA levels in CSF.¹⁷ Therefore, measurements of these monoamine metabolites in CSF may be useful for evaluating the condition of patients with DS who present with parkinsonism. Deuel et al. reported a decrease in HVA, 5-HIAA, neopterin, and tetrahydrobiopterin levels in the CSF of patients with DS and parkinsonism.¹⁴ However, this is the only report in which CSF monoamine metabolites were measured in such patients, and the actual measured values were not reported. In general, CSF monoamine metabolite levels are affected by the method of CSF collection and measurement conditions, and can be reduced secondarily because of epilepsy, convulsions, and other factors.¹⁸ In our cases, the CSF was collected as described by Hyland et al.,¹⁸ and we measured monoamine metabolites by high performance liquid chromatography with fluorescence detection. Our measurement method

TABLE 2 Monoamine metabolite levels in the cerebrospinal fluid in the two cases^a.

Monoamine metabolite	Case 1	Case 2
HVA (145–324 nmol/L ¹⁸)	36.6	79.3
5-HIAA (67–140 nmol/L ¹⁸)	20.4	52.2
MHPG (35–65 nmol/L ¹⁸)	27.7	40.7
3-OMD (<100 nmol/L ¹⁸)	<16	19.1

Abbreviations: 3-OMD, 3-O-methyldopa; 5-HIAA, 5-hydroxyindoleacetic acid; HVA, homovanillic acid; MHPG, 3-methoxy-4-hydroxyphenylglycol.

^aReference values for cerebrospinal fluid test parameters are cited from Ref. [18].

has been confirmed to produce results that were comparable to those by Hyland et al.¹⁹ No epileptic seizures and other causes that can affect the CSF results occurred before the examination; therefore, the measurement results were considered reliable. In both cases, HVA and 5-HIAA levels were significantly lower than the reference values in the published report,¹⁸ and these results strongly support those reported by Deuel et al.¹⁴ Based on the results of the CSF examination in our study and a previous report, we conclude that a decrease in dopamine synthesis may be present at least in some patients with DS, and thus, may be a cause of parkinsonism in them. Additionally, CSF monoamine metabolite levels were lower in Patient 1 than those in Patient 2, with Patient 1 exhibiting more varied and severe parkinsonism symptoms. It is difficult to determine the reasons for these differences conclusively; however, the severity of parkinsonism might have influenced the results. Therefore, similar cases should be investigated at a greater detail in the future.

In Case 1, the administration of levodopa effectively ameliorated tremors and gait disturbance, although previously, the efficacy of levodopa's effect on parkinsonism in patients with DS has been reported as inconclusive.^{5,13} The most recent randomized crossover unblinded trial showed that levodopa improved gait disorders, and its effectiveness was higher in younger than in older patients.²⁰ In another study, levodopa improved walking ability in a 24-year-old patient; however, in two older patients, aged 42 years and 46 years, gait impairment progressed even after starting levodopa.⁶ In parkinsonism in DS, the effect of levodopa varies from case to case, and it is not well understood which patients would respond to levodopa treatment. However, some studies suggested that levodopa may be more effective in younger than in older patients. Wyers et al. mentioned that the vulnerability of the dopaminergic system to aging explains why parkinsonism was only described in adult patients with DS, showing a clear correlation with age.⁷ In the present study, we hypothesize that a decrease in dopamine synthesis might cause parkinsonism in DS: the partial response to levodopa in our Case 1 was likely owing to the relatively young age of the patient and dopamine synthesis impairment. In previous reports, the therapeutic effect may have depended on the patient's age; however, dopamine synthesis could also be an important predictor.

In patients with Parkinson's disease, levodopa treatment can restore the levels of monoamines and their metabolites in the CSF,^{21,22} and there is an inverse correlation between CSF monoamine metabolite concentrations and treatment responsiveness.^{23,24} Measurements of dopamine and monoamine metabolites in DS may be useful for predicting responsiveness to levodopa

treatment. The lack of CSF data in patients with DS who do not have parkinsonism is an important limitation of our study. If we were to observe normal CSF metabolites in patients with DS without parkinsonism, a decrease in dopamine levels may be responsible for parkinsonism in patients with DS.

4 | CONCLUSIONS

Decreased HVA and 5-HIAA levels in Cases 1 and 2 may be important because the underlying cause of parkinsonism in DS may be a decline in dopamine synthesis, which supports the possibility of improvement of parkinsonism with levodopa administration. Levodopa should be attempted in patients with DS and parkinsonism, especially if a decrease in CSF monoamine metabolites is confirmed.

AUTHOR CONTRIBUTIONS

Ryo Sugiyama was involved in the conceptualization, data acquisition, visualization, and writing of the original draft. Takashi Saito was involved in the conceptualization, data acquisition, project administration, supervision, and writing (review and editing). Shota Yoneno was involved in data acquisition. Atsuko Katsumoto was involved in the conceptualization and writing (review and editing). Tomoyuki Akiyama was involved in providing the resources and writing (review and editing). Hirofumi Komaki was involved in project administration and writing (review and editing).

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CONFLICT OF INTEREST STATEMENT

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with these guidelines.

DATA AVAILABILITY STATEMENT

Data supporting the findings of this study are available from the corresponding author upon reasonable request.

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