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Carbamoyl phosphate synthetase 1 deficiency manifested in an adult treated with prednisone for polymyositis, and cured by live-donor liver transplantation

Kazuhiro Yokota [a], Akira Ohtake [b,c,d], Taro Yamazaki [b], Takuma Tsuzuki-Wada [a], Megumi Saito-Tsuruoka [c,d], Takuya Fushimi [e], Kei Murayama [e,f], Yuji Akiyama [a], Toshihide Mimura [a,d,*]

[a] Department of Rheumatology and Applied Immunology, Faculty of Medicine, Saitama Medical University, Saitama, Japan
[b] Department of Pediatrics, Faculty of Medicine, Saitama Medical University, Saitama, Japan
[c] Department of Clinical Genomics, Faculty of Medicine, Saitama Medical University, Saitama, Japan
[d] Center for Intractable Diseases, Saitama Medical University Hospital, Saitama, Japan
[e] Department of Metabolism, Chiba Children 's Hospital, Chiba, Japan
[f] Diagnostics and Therapeutic of Intractable Diseases, Intractable Disease Research Center, Graduate School of Medicine, Juntendo University, Tokyo, Japan

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ABSTRACT

Carbamoyl phosphate synthetase 1 (CPS1) deficiency (OMIM#237300) is a rare inherited disorder due to complete or partial lack of the CPS1 enzyme. Polymyositis is a relatively rare systemic inflammatory autoimmune disease. Here, we report a 59-year-old Japanese woman diagnosed with late-onset CPS1 deficiency during polymyositis treatment. The polymyositis appeared two years before the diagnosis of CPS1 deficiency. Prednisolone (PSL) at 35 mg/day initial dosage, promptly alleviated the symptoms. However, the patient, without apparent cause, suddenly developed confusion progressing to unconsciousness and coma. Upon admission, the patient's plasma ammonia levels were 458 μg/dL (269 μM). Plasma amino acid analysis revealed decreased citrulline levels and elevated glutamine levels. Genetic analysis of *CPS1* (OMIM *608307) showed homozygosity for the likely pathogenic variant c.2397G > A (p.Met799Ile), leading to the diagnosis of CPS1 deficiency. The patient responded to pharmacotherapy and continuous hemodialysis. However, the patient experienced hyperammonemia decompensation events while on pharmacotherapy at home, which were successfully managed with emergency treatment and/or hemodialysis. Subsequently, after liver transplantation, the patient's plasma ammonia levels consistently remained at normal. This case illustrates late-onset CPS1 deficiency manifested in an adult treated with PSL for polymyositis, and the cure of its enzyme deficiency by live-donor liver transplantation.

1. Introduction

Carbamoyl phosphate synthetase 1 (CPS1) deficiency (OMIM #237300), inherited in an autosomal recessive manner, is a rare and the most severe urea cycle disorder [1,2]. This deficiency results in vomiting, reduced appetite, unconsciousness, motor dysfunction, and convulsions, all of which are associated with hyperammonemia [1,2]. The diagnosis is further suggested by the observation of low citrulline and high glutamine levels in plasma and the absence of elevated urinary orotic acid, being confirmed by genetic analysis revealing abnormalities in *CPS1* (OMIM *608307) [1,3].

Polymyositis is a systemic inflammatory autoimmune disease that primarily damages the skeletal muscles, leading to symptoms such as muscle weakness and pain. It can also affect the lungs, heart, and other organs, highlighting the importance of early diagnosis and treatment. Despite an exhaustive search, we have not found reports on *co*-occurrence of CPS1 deficiency with polymyositis.

Here, we report a very rare case that developed in a woman in her late fifties who experienced a sudden coma due to hyperammonemia during the treatment course for polymyositis, which was in remission.

* Corresponding author at: Department of Rheumatology and Applied Immunology, Faculty of Medicine, Saitama Medical University, 38 Morohongo, Moroyama-machi, Iruma-gun, Saitama 350-0495, Japan.
E-mail address: toshim@saitama-med.ac.jp (T. Mimura).

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She was diagnosed with CPS1 deficiency and was saved through living-donor liver transplantation.

2. Case report

A 59-year-old woman unexpectedly experienced confusion in the evening, leading to her family noticing a change in her consciousness. Consequently, she was admitted to our hospital. This patient had no personal or familial history of episodes of loss of consciousness or epilepsy. Her parents were first cousins; however, there was no family history of metabolic diseases or neonatal deaths. This patient had no history of avoiding or self-limiting protein intake. There were no signs of confusion or changes in mental state during menstruation or after giving birth to any of her 2 daughters. The patient had a medical history of osteoporosis. Two years before admission, the patient was diagnosed with polymyositis, characterized by proximal muscle weakness, elevated muscle enzymes, and focal inflammatory cell infiltration observed in the muscle tissue biopsy. Prednisolone (PSL) was initiated at 35 mg/day, leading to a rapid disappearance of symptoms. Consequently, the PSL dosage was gradually reduced to 4 mg/day, maintaining the patient in remission for one year.

At the time of admission, her height was 153 cm, and her weight was 45 kg (body mass index 19.2 kg/m^2). The patient was unconscious, scoring 5 on the Glasgow Coma Scale (eye opening 1, verbal response 1, motor response 3), with a body temperature of 36.2 °C, blood pressure of 155/90 mmHg, pulse rate of 70 beats/min, and respiratory rate of 20 breaths/min. Diminished alveolar breath sounds and low-pitched continuous rales were audible in the patient's chest. Hepatosplenomegaly was not recognized in the abdomen. Neurological examination revealed pendulum-like nystagmus and hypotonia, along with muscle atrophy of both the biceps brachii and quadriceps femoris, with no other abnormalities observed. The urinalysis showed no abnormalities. Arterial blood gas analysis revealed a pH of 7.44, partial pressure of oxygen of 94.2 mmHg, partial pressure of carbon dioxide of 31.3 mmHg, bicarbonate ion level of 21.2 mmol/L, base excess of −2.0 mmol/L, and mildly elevated anion gap of 20 mEq/L. Alanine transaminase, aspartate transaminase, alkaline phosphatase, and gamma-glutamyl transferase were all within the normal range. General blood tests, including biochemical tests for blood sugar, electrolytes, and kidney function, and myogenic enzymes, showed values within the normal range. However, the plasma ammonia level was significantly elevated at 458 μg/dL (269 μM) (normal range: 12–66 μg/dL; 7–39 μM). Additionally, the plasma glutamine level was elevated to 1149.1 nmol/mL (normal range: 418.0–739.8 nmol/mL), while the citrulline level was decreased to 11.7 nmol/mL (normal range: 17.9–48.0 nmol/mL). Furthermore, the C-reactive protein level was 0.1 mg/dL, the erythrocyte sedimentation rate was 20 mm/h, and the antinuclear antibody titer was 1:640 (displaying a cytoplasmic pattern), but myositis-related autoantibodies were all negative. Magnetic resonance imaging of the brain revealed bilateral lesions in the cerebral white matter. The electroencephalogram primarily showed low-amplitude alpha and beta waves, with the absence of three-phase waves. Contrast-enhanced abdominal computed tomography and abdominal ultrasound revealed no abnormalities in the liver or spleen and no intrahepatic portosystemic shunt.

After admission, sugar solution infusion and lactulose via tube/enema were promptly initiated. On the second day of admission, a urea cycle disorder was suspected, and sodium phenylbutyrate (4500 mg/day) and L-arginine (12,000 mg/day) were administered. Sodium benzoate was not used as it is not approved for use in Japan. The patient's plasma ammonia levels decreased rapidly, and her level of consciousness quickly improved (Fig. 1). In addition, the urinary organic acid analysis indicated an absence of orotic acid excretion, suggesting CPS1 deficiency. Subsequently, *CPS1* genetic analysis was performed using peripheral blood leukocytes, and the c.2397G > A (p.Met799Ile) variant was identified in the homozygous state, providing a definitive diagnosis of CPS1 deficiency.

After initiation and continuation of pharmacotherapy (sodium phenylbutyrate (4500 mg/day) and L-arginine (12,000 mg/day)) and a protein-restricted diet (1 g/kg/day of protein), her plasma ammonia level remained below the standard value, leading to her discharge from the hospital on the 60th day of her stay. This patient was receiving glucocorticoid treatment (prednisolone 4.0–7.5 mg/day) during and after hospitalization. However, within a period of one year, she unexpectedly experienced three episodes of hyperammonemia-associated unconsciousness. The events that triggered acute hyperammonemia

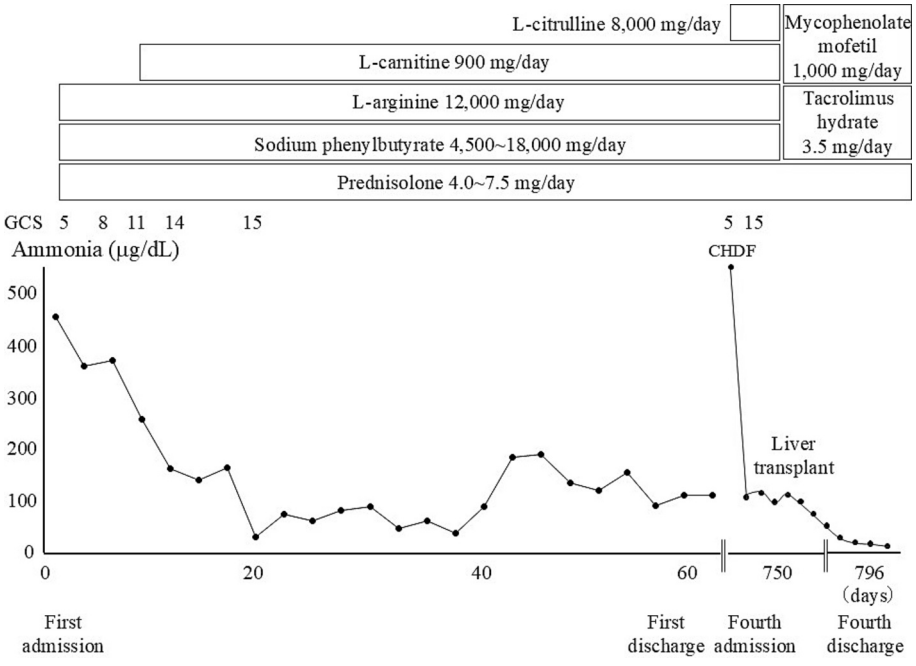

Fig. 1. Medical intervention timeline for the patient.
GCS: Glasgow Coma Scale, CHDF: continuous hemodiafiltration.

were fever, dehydration, diarrhea, acute bronchitis, and acute upper respiratory tract inflammation. Notably, during her fourth admission, her plasma ammonia level increased to 542 μg/dL (318 μM) and was managed with temporary continuous hemodiafiltration (CHDF), nutritional support through a central venous feeding catheter, and the administration of oral citrulline (8000 mg/day). Consequently, her plasma ammonia levels rapidly decreased, leading to a reduction in the frequency of episodes of unconsciousness. However, the central parenteral nutrition catheter could not be removed because of intermittent increases in plasma ammonia levels.

Given the concerns about central nervous system toxicity from prolonged hyperammonemia, a living-donor liver transplantation was performed with the patient's second daughter as the donor 750 days after the patient's first admission to our hospital. The patient demonstrated favorable progress after her liver transplantation and was discharged from the hospital on the 46th day following the surgery. Thereafter, there was no need for continued hyperammonemia treatment including both sodium phenylbutyrate as well as arginine/citrulline, and her plasma ammonia levels consistently remained below the standard values. Following the liver transplant, she has been consistently taking methylprednisolone at a dose of 2.5 mg/day and tacrolimus hydrate at 0.5 mg/day. Now, seven years after the onset of her illness, she continues to live without any recurrence of either CPS1 deficiency or polymyositis.

3. Discussion

CPS1 deficiency presents in two forms: neonatal-onset and late-onset. The neonatal-onset form is characterized by significantly reduced liver CPS1 enzyme activity [4], while the late-onset form is associated with some residual enzyme activity [5]. Neonatal-onset CPS1 deficiency presents with hyperammonemia shortly after birth, leading to potential fatalities or neurological impairment in survivors [6]. Late-onset CPS1 deficiency, which is less likely to be fatal, typically emerges following triggers such as illness, stress, or certain medications [7,8]. Although liver CPS1 activity was not measured in our case, the age of onset and good response to treatment during hyperammonemic crises strongly suggested a late-onset deficiency that developed during the treatment course for polymyositis.

The three intramitochondrial urea cycle deficiencies, which result from loss-of-function inborn errors of *N-acetylglutamate synthase (NAGS)*, *CPS1*, and *ornithine transcarbamylase (OTC)*, share the same clinical presentations and the analytical observation of hyperammonemia, decreased plasma citrulline and elevated plasma glutamine [3,6]. While OTC deficiency can be differentiated from the other two deficiencies by the presence of high concentrations of orotate in the urine, there is no analytical marker to differentiate CPS1 deficiency and NAGS deficiency [3,6]. Only the complete and rapid curative response to administration of N-carbamylglutamate in the case of NAGS deficiency can strongly suggest NAGS deficiency [9]. In practice, genetic diagnosis, i.e. the identification of biallelic variants in the *CPS1* or *NAGS* genes, is considered the gold standard for diagnosis of one or the other of these deficiencies [1,5,9]. In our case, we found no increase in urinary orotate, making us think of CPS1 deficiency or NAGS deficiency. We examined the *CPS1* gene, despite the considerable challenges represented by its large number of exons (38 exons) and of coding bases (4500) [10]. The patient was found to be homozygous for a single-base change causing the predicted amino acid substitution p.(Met799Ile). Mutation Taster made a prediction of disease-causing change. The change has not been reported in the GNOMAD or 1000 Genomes databases that give data for large populations. This server described potential negative effects of this change to alteration in the protein (the effect of the amino acid change itself), and/or to altered splicing, since the base changed is the sixth of exon 20, thus being just six positions downstream from the intron/exon boundary. The search for the mutation in the consanguineous parents (first cousins) proved them to be heterozygous carriers of this change, as it was the case for the two daughters of the patient (a brother of the patient was also tested, but he did not carry this change) (Fig. 2). Thus, the change co-segregates with the disorder as expected for recessive inheritance, and we concluded that this was highly likely the causative change, labeling the patient as suffering from partial CPS1 deficiency.

As mentioned above, the initial diagnostic process is relatively simple, based on biochemical findings. While awaiting the results of genetic testing for a definitive diagnosis, the prognosis of CPS1 deficiency often depends on the timely initiation of emergency treatments like intravenous fluids, intravenous ammonia scavengers, and continuous hemodialysis. Recently, novel compound heterozygous mutations in the *CPS1* gene have been identified through genetic analysis of patients and their families, leading to definitive diagnoses of CPS1 deficiency [1,11,12]. Consequently, we performed *CPS1* genetic analysis on both parents and their family members. The analysis revealed that a newly identified c.2397G > A (p.Met799Ile) variant was homozygous in the patient and heterozygous in the patient's parents, and daughters (Fig. 2). These genetic findings confirmed a definitive diagnosis of CPS1 deficiency in the patient.

In cases of CPS1 deficiency, patients may experience sudden episodes of hyperammonemia despite adequate pharmacotherapy and dietary management, indicating that these treatments alone do not always control these episodes. The prognosis of CPS1 deficiency often depends on the timely initiation of continuous hemodialysis. Although this patient was not provided with emergency home treatment guidelines, we provided the best possible lifestyle guidance at home, including dietary guidance to prevent hyperammonemia, basic infection prevention measures, and encouragement to drink water to prevent dehydration, through a multidisciplinary approach. It is essential to note that cerebral edema can develop due to hyperammonemia when levels exceed 340 μg/dL (200 μM) [13]. In our case, acute episodes were characterized by disturbances in consciousness, with plasma ammonia levels reaching as high as 542 μg/dL (318 μM). After initiating CHDF, no significant complications occurred, and the patient regained consciousness the following day with plasma ammonia levels decreasing to below the standard values (Fig. 1). Therefore, in this case, the swift initiation and effective management of CHDF were critical to save the patient's life and prevent neurological complications.

Liver transplantation is the definitive and recommended treatment for CPS1 deficiency [2,14,15]. Currently, living-donor liver

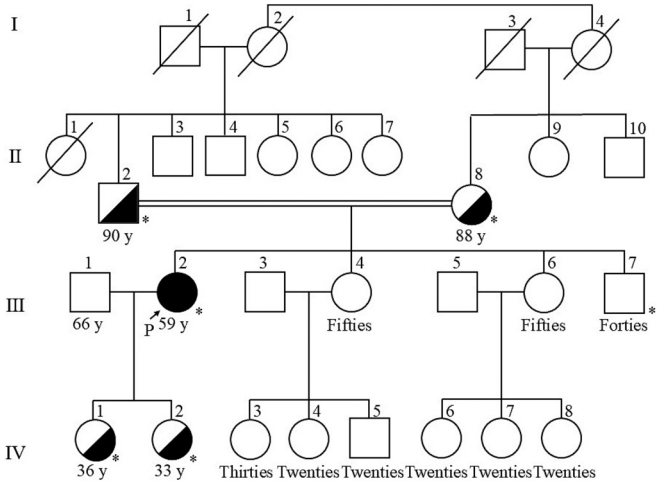

Fig. 2. Pedigree chart of the patient and her family.
The patient's parents carried a heterozygous (NM_001875.5) c.2397G > A (p.Met799Ile) variant in the *CPS1* gene. The patient's daughters were heterozygotes, each with a c.2397G > A variant in the *CPS1* gene. The patient (indicated by the arrow) is homozygous that inherited pathogenic variants from both parents. An asterisk (*) indicates that CPS1 genetic analysis was conducted using peripheral blood leukocytes.

transplantation for urea cycle disorders frequently involves parents who may be heterozygous carriers serving as donors. This approach is advantageous in terms of donor availability. However, this approach entails potential health risks for the donors, necessitating careful execution and obtaining informed consent. In this case, following the transition from acute-to-chronic-phase treatment, we collaborated with the transplant surgery team and prepared meticulously for a living-donor liver transplantation. The transplantation, with the patient's daughter as the donor, was successfully performed 14 months after the initial manifestation of CPS1 deficiency symptoms. This case is notable as it represents the oldest patient with late-onset CPS1 deficiency who has undergone living-donor liver transplantation.

Adult-onset CPS1 deficiency, including that described in our report, has been reported in 13 cases [2,7,8,11,16–22]. Table 1 describes the clinical features of the 13 cases, with the average age at diagnosis being 37.8 years. The distribution was three male cases (23 %) and ten female cases (77 %), indicating a higher prevalence among females. Clinical symptoms varied, but confusion was the most common symptom, affecting six cases (46 %), followed by unconsciousness in three cases (23 %) (data was unavailable for two cases). Twelve cases exhibited low citrulline and high glutamine levels in blood amino acid analysis, highlighting its utility in early diagnosis (data was unavailable for one case). Diagnostic biopsies were performed on the liver in six cases and on peripheral blood leukocytes in two cases. *CPS1* genetic analysis was performed in six cases. Liver transplantation was undertaken in two cases, resulting in 11 survivors and two deaths, achieving a survival rate of 85 %.

In our case, the patient also had polymyositis. There is currently no literature indicating a correlation between polymyositis and CPS1 deficiency, and the genetic pathogenesis suggests no association between CPS1 deficiency and polymyositis. However, it is possible that the loss of muscle volume associated with polymyositis, along with the catabolic effect of glucocorticoids such as PSL, promotes muscle hypercatabolism. In addition, corticosteroids treatment has been shown in the spf-ash mouse model of OTC deficiency to decrease expression of several urea cycle enzymes in the liver, including CPS1 [23]. Thus, a combination of increased protein catabolism and decreased CPS1 expression in the liver, both due to corticosteroids, combined with the reduction of intrinsic CPS1 activity derived from the genetic variant observed, may have promoted the development of hyperammonemia and hyperammonemic crises in situations in which other patent or unnoticed catabolic stresses (fever, infections, trauma, vomiting, increased protein load ingested, etc.) were also in operation.

If corticosteroids are involved in the pathogenesis of the hyperammonemia observed in this patient, it may appear puzzling that the much higher dose of corticosteroids given at the beginning of the polymyositis did not result in earlier manifestations of partial CPS1 deficiency. While we cannot provide a definitive answer for this observation, loss of muscle mass or function might perhaps account for that finding. Striated muscle is an important player in nitrogen metabolism largely via its role in making glutamine [24]. The large share of body weight represented by striated muscle is an important factor in this role. Thus, the decrease in muscle mass with the progression of the polymyositis may have decreased the ability of this additional player to act as a temporal ammonia buffer (as glutamine), thus opening the way to increased likelihood of hyperammonemic crises in situations of urea cycle deficiency and increased catabolic load of ammonia.

In conclusion, we reported a case of late-onset CPS1 deficiency with a

Table 1
Summary of the case reports on adult-onset carbamoyl phosphate synthetase 1 deficiency.

Age/ Sex	Initial symptoms	Plasma ammonia	Plasma citrulline	Plasma glutamine	Hepatic enzyme activity	Diagnostic tissue	*CPS1* Mutation 1	*CPS1* Mutation 2	Outcome	Reference
33/F	Anorexia, nausea, gait ataxia, lethargy	256 (μM)	trace (nmol/mL)	663 (nmol/mL)	5 %	Liver	NA	NA	Alive	(16)
32/F*	Nausea, vomiting	NA	NA	NA	80 %	Liver	NA	NA	Alive	(17)
26/F	Confusion, disorientation, coma, decerebrate posturing, tonic-clinic seizures	1000 (μM)	14 (nmol/mL)	857 (nmol/mL)	<1 %	Liver	NA	NA	Died	(18)
41/F	Headache, confusion, drowsiness, ataxia, slurred speech	520 (μM)	12 (nmol/mL)	800 (nmol/mL)	20 %	Liver	NA	NA	Alive	(19)
31/F	NA	3593 (μg/dL)	34.9 (nmol/mL)	NA	NA	NA	c.634 T > A	c.3308 A > G	Died	(20)
45/F	NA	263 (μg/dL)	2.8 (nmol/mL)	NA	39 %	Liver	ND	ND	Alive	(20)
27/F	Unconsciousness	284 (μg/dL)	5.2 (nmol/mL)	821.1 (nmol/mL)	ND	Liver	ND	ND	Alive	(21)
49/M	Confusion, nausea, myalgia, emotional lability, apathy	157 (μM)	13 (nmol/mL)	1391 (nmol/mL)	28 %	Peripheral blood leukocytes	ND	ND	Alive	(8)
35/F	Agitation, confusion, mystic delusions	224 (μM)	NA	NA	NA	NA	c.259C > T	c.2407C > T	Alive	(22)
53/F	Confusion	375 (μg/dL)	NA	Mild increased	NA	NA	c.2407C > T	ND	Alive	(7)
25/M	Altered mentality after exercise	542 (μM)	7.7 (nmol/mL)	539.1 (nmol/mL)	NA	NA	c.2219G > T	c.3712G > C	Alive	(2)
36/M	Unconsciousness after drinking	844 (μg/dL)	11.3 (nmol/mL)	82.7 (nmol/mL)	NA	NA	c.2549G > A	ND	Alive	(11)
59/F	Confusion, unconsciousness, coma	542 (μg/dL)	11.7 (nmol/mL)	1149.1 (nmol/mL)	NA	Peripheral blood leukocytes	c.2397G > A	ND	Alive	Our case

M, male; F, female; NA, not available; ND, not detectable; *, suspected case.

novel *CPS1* variant that emerged during polymyositis treatment. This case highlights the effectiveness of living-donor liver transplantation as a curative approach for treating late-onset CPS1 deficiency. Given the risk of severe neurological sequelae associated with CPS1 deficiency, it is imperative to consider early liver transplantation and manage treatment using a coordinated, planned approach across relevant medical specialties.

Ethics

All procedures in the present case report complied with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of the World Medical Association. The case was approved by the Institutional Review Board of the Saitama Medical University Hospital (No. 17–139). Written informed consent was obtained from all family members participating in the case report.

Informed consent

Informed consent was obtained from the patient and her daughters for the publication of this case report.

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CRediT authorship contribution statement

Kazuhiro Yokota: Writing – original draft, Visualization, Validation, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Akira Ohtake:** Writing – review & editing, Supervision, Conceptualization. **Taro Yamazaki:** Writing – review & editing, Investigation. **Takuma Tsuzuki-Wada:** Investigation. **Megumi Saito-Tsuruoka:** Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Data curation. **Takuya Fushimi:** Writing – review & editing, Formal analysis. **Kei Murayama:** Formal analysis. **Yuji Akiyama:** Supervision. **Toshihide Mimura:** Writing – review & editing, Supervision.

Declaration of competing interest

We have no conflicts of interest to declare.

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Data availability

No data were used for the research described in the article.

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