■ Clinical commentary

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Epileptic Disorders

ACTH for epileptic spasms in Leigh syndrome with *SLC19A3* mutation can induce status dystonicus

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ABSTRACT

Patients with Leigh syndrome (LS) sometimes develop epileptic spasms (ES). ACTH treatment for ES may be effective without serious adverse events in some patients with LS. Status dystonicus is a life-threatening disorder characterized by an acute exacerbation of generalized dystonia and often develops as a triggered event. The underlying pathophysiology of status dystonicus remains unclear. To our knowledge, there has been no reported case of status dystonicus associated with ACTH treatment. Here, we describe the first reported patient with LS, harbouring compound heterozygous mutations in *SLC19A3* gene, who developed status dystonicus following initial intramuscular injection of a course of ACTH treatment for ES. Stressors can precipitate acute exacerbation in *SLC19A3*-related disorders. Interestingly, in this patient, external discomfort stimuli tended to induce transient hypertonia with opisthotonos. This report suggests that attention should be paid to acute exacerbation of generalized dystonia when ACTH treatment for ES is started in patients with LS, who have dystonia tend to exacerbate transiently by external discomfort stimuli.

Key words: ACTH, epileptic spasms, Leigh syndrome, *SLC19A3*, status dystonicus

Status dystonicus, known as dystonic storm or dystonic crisis, is a rare, life-threatening disorder characterized by an acute exacerbation of generalized dystonia. Mortality has been reported in 10% cases [1]. Early recognition of worsening dystonia may facilitate intervention or prevent progression to status dystonicus [2]. The underlying pathophysiology of status dystonicus remains unclear. However, status dystonicus often develops as a triggered event and all disease associated with basal ganglia lesions should be considered as a potential cause of status dystonicus [3].

Many new pathogenic mutations in *SLC19A3* gene, encoding thiamine transporter type 2, have been reported recently resulting in several age-related neurological phenotypes such as early-infantile Leigh syndrome (LS), childhood biotin-thiamine responsive basal ganglia disease, and adult Wernicke encephalopathy [4]. Stressors, such as fever and mild trauma, can precipitate acute exacerbations in *SLC19A3*-related disorders [5].

LS is an early-infantile-onset mitochondrial disease with extensive genetic heterogeneity. Mutation in *SLC19A3* is detected in approximately 1-12% of patients with LS who undergo genetic analysis [6-9]. Approximately 40% patients with LS develop epilepsy. Epileptic spasms (ES) have been reported in

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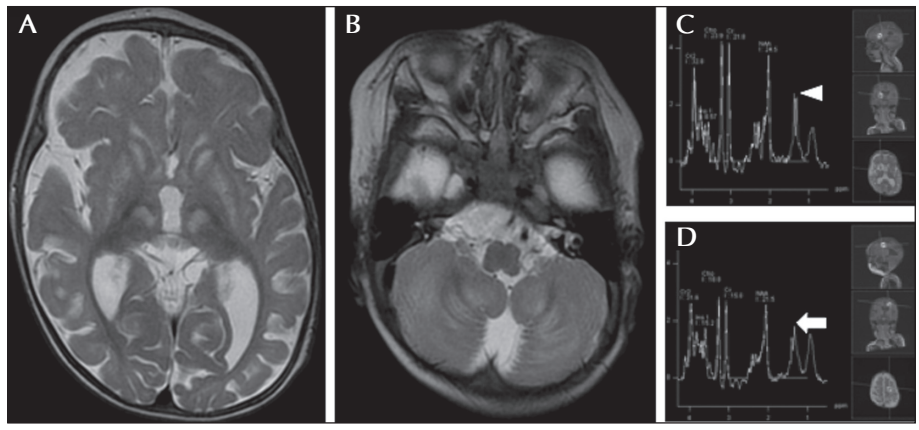
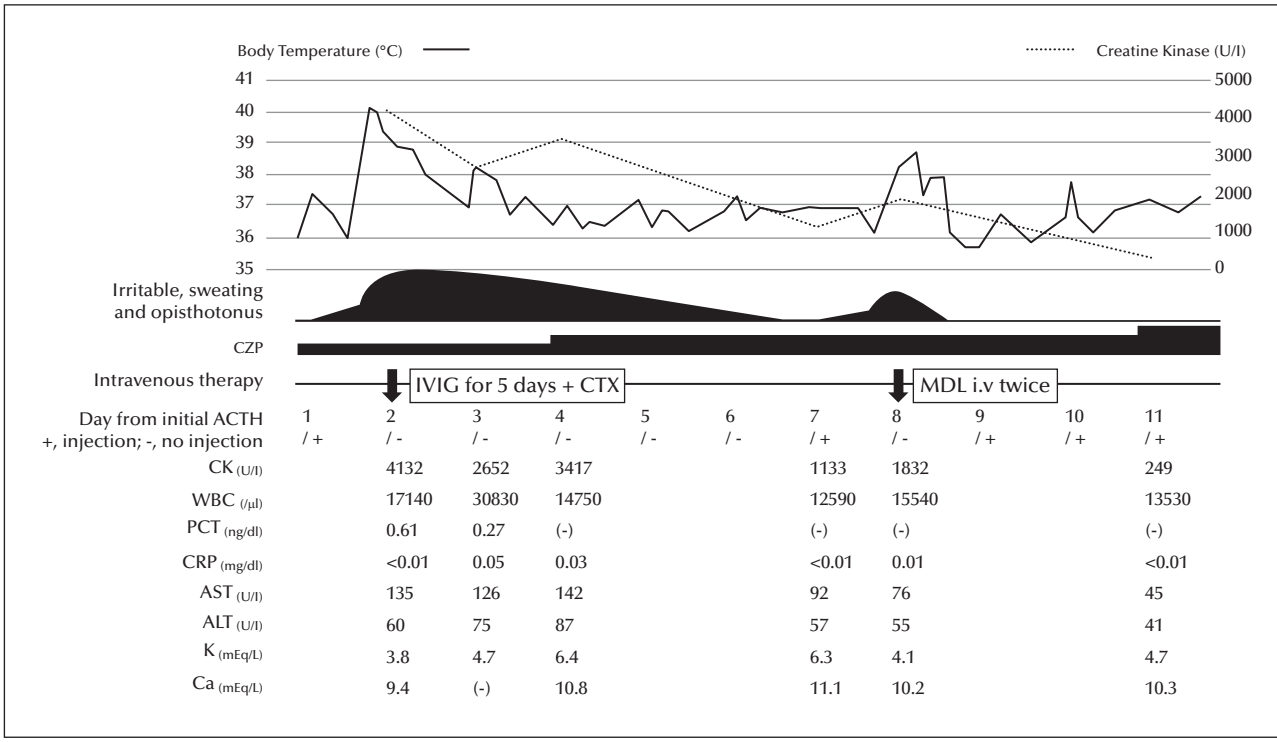
6.1% of these patients [6]. The efficacy of ACTH treatment for ES has been reported without serious adverse events in some patients with LS [10-13].
We report a two-year-old patient with LS with *SLC19A3* mutation who developed ES. ACTH treatment was effective, however, status dystonicus occurred following initial intramuscular injection of the course of ACTH treatment. To our knowledge, there has been no reported case of status dystonicus associated with ACTH treatment.

Case study

A two-year-old Japanese boy was the second child born to healthy, non-consanguineous Japanese parents. His family history was unremarkable. He was delivered at 38 weeks after uncomplicated gestation. By age two months, he had developed smiling and visual tracking, but his oral intake gradually worsened. At age six months, he developed shoulder twitching involving head flexion 1-5 times daily, which occurred repeatedly at an interval of 10-15 seconds, with one whole episode lasting 2-5 minutes. Head lag and axial hypotonia were present, and external discomfort stimuli occasionally induced transient hypertonia with opisthotonos, indicating the presence of pre-existing dystonia. Blood and urine test results were unremarkable: WBC 8,620/µL, CRP <0.01 mg/dL, AST 44 U/L, ALT 32 U/L, LDH 297 U/L, CK 218 U/L, Na 139 mEq/L, K 4.6 mEq/L, Ca 11.0 mEq/L, immunoglobulin (Ig) G 615 mg/dL, IgA 27 mg/dL, and IgM 115 mg/dL except for an elevated serum lactate-to-pyruvate ratio of 34.2 (lactate and pyruvate concentrations: 31.8 mg/dL and 0.93 mg/dL, respectively). CSF analysis revealed no significant findings (lactate and pyruvate concentrations: 14.4 mg/dL and 0.98 mg/dL, respectively). An interictal EEG revealed intermittent diffuse slowing of background activity with multifocal epileptiform discharges, and ictal EEG showed high-voltage generalized slow waves. Transient hypertonia with opisthotonos induced by external discomfort stimuli showed no abnormal electrical activity of the brain on EEG. Brain MRI showed multiple symmetric lesions in the basal ganglia, thalamus, and cerebellum (*figure 1A, B*); magnetic resonance spectroscopy revealed lactate peaks in the basal ganglia (*figure 1C*) and white matter (*figure 1D*).
We diagnosed LS presenting with ES, and initiated treatment with a vitamin cocktail therapy (biotin, coenzyme Q10, thiamine, vitamins C and E, and L-carnitine at 0.5, 5, 10, 100, 10, and 30 mg/kg/day, respectively) for LS. Vigabatrin is one of the first-line treatment options for ES, however, we could not prescribe vigabatrin as an ophthalmologist registered with the Sabril Registration System was absent in our hospital. Thus, clonazepam (CZP, at 0.08 mg/kg/day) was administered for ES and dystonia because CZP has shown a positive effect against dystonia [14]. Four days after starting with these treatments, intramuscular synthetic ACTH treatment (0.014 mg/kg/day for 14 days followed by tapering) was started. However, the patient gradually became irritable at initial ACTH injection. On the day after the injection, he developed fever, excessive sweating, and increasingly frequent hypertonia with opisthotonos. EEG showed no generalized and focal epileptiform discharges during episodes of hypertonia with opisthotonos. Blood test revealed WBC count at 17,140/µL (82% neutrophils), CRP at <0.01 mg/dL, procalcitonin (PCT) at 0.61 ng/mL, and CK at 4,132 U/l (*figure 2*). Myoglobinuria was not measured. Immunochromatographic rapid antigen



■ **Figure 1.** Brain MRI and MRS at six months of age. (A, B) Axial T2-weighted images showing bilateral hyperintense lesions in the basal ganglia, thalamus, and cerebellum. (C, D) A peak of lactate is present in the basal ganglia (arrowhead) and white matter (arrow) on MRS.



■ **Figure 2.** Clinical course in this patient. Four days before starting with ACTH injection, CZP (at an initial dose of 0.02 mg/kg/day, increasing by 0.02 mg/kg/day every week up to 0.08 mg/kg/day) was started. The patient gradually became irritable on Day 1 and 7 after initial intramuscular injection of ACTH treatment (0.014 mg/kg/day). On the day after the injection, he developed fever, excessive sweating, increasingly frequent hypertonia with opisthotonos, and elevated serum level of CK. The level of CRP was normal over the course of ACTH treatment. Intravenous bolus injection of midazolam (0.15 mg/kg) was more effective for his condition including severe generalized dystonia than intravenous immunoglobulin (400 mg/kg/day for five days) and cefotaxime (130 mg/kg/day for three days). Transient subfebrile temperature (37.8 °C) with mild hypertonia at Day 10 after initial ACTH injection may have been associated with pre-status dystonicus triggered by ACTH injection. We considered transient increased body temperature (37.0 to 37.4 °C) to be normal because he occasionally had transient increased body temperature without the presence of other infectious or dystonic symptoms and signs even after the course of ACTH treatment was completed. Blood samples at Days 4 and 7 were obtained by heel prick. CTX: cefotaxime; CZP: clonazepam; IVIG: intravenous immunoglobulin; MDL: midazolam; PCT: procalcitonin.

detection tests for respiratory syncytial virus, influenza A and B virus, adenovirus, and rotavirus were negative. We discontinued ACTH treatment and started intravenous cefotaxime because of the possibility of severe bacterial infectious diseases. Moreover, his general condition gradually worsened, thus we administered intravenous immunoglobulin (IVIG, at 400 mg/kg/day for five days) which has been shown to have a positive effect for both infectious diseases and ES in at least some patients with West syndrome [15]. His condition improved gradually without appearance of other infectious symptoms, such as cough, nasal discharge, vomit, and diarrhea, and he recovered to the same condition as that before starting ACTH treatment. The levels of CRP and PCT were not elevated compared to markedly increased WBC count, and blood, urinary, and nasopharyngeal cultures were negative, which suggested the absence of severe bacterial infectious diseases. ES and interictal EEG abnormalities did not improve after treatment with IVIG. Thus, we considered that it was better to evaluate whether his serious condition was triggered by ACTH injection or not, as ACTH treatment is one of the promising treatment options for ES with LS [10-13]. We restarted ACTH

treatment, however, the same condition developed as before (*figure 2*). We discontinued ACTH treatment again and administered intravenous bolus injection of midazolam (MDL, at 0.15 mg/kg) twice, which was successful. His condition recovered more quickly and dramatically after the second episode than after the first episode. On the day after MDL injection, we restarted ACTH treatment without recurrence of episodes. After five days of restarting with ACTH treatment, ES disappeared and his interictal EEG improved markedly. The course of ACTH treatment was completed without adverse events after MDL injection. Due to hypersecretion, CZP was switched to lamotrigine (LTG, at 3.0 mg/kg/day, with a serum concentration of 2.6 µg/mL) during ACTH tapering, as LTG has shown to be of benefit against mitochondrial toxic effects and is therefore one of the antiepileptic drugs with best tolerability for mitochondrial epilepsy [16]. At age eight months, this patient was discharged with treatment with vitamin cocktail therapy and LTG.

Whole-exome sequencing confirmed compound heterozygous mutations in *SLC19A3*, NM_025243.3: c.958G>C, p.(Glu320Gln), inherited from his mother, and c.74dup, p.(Ser26LeufsTer19), inherited from his father. At age two years, the final diagnosis was LS with *SLC19A3* mutation. The dose of thiamine was increased from 10 to 20 mg/kg/day, and that of biotin from 0.5 to 15 mg/kg/day, with no significant change on his condition beside the cognitive development. At present, aged two years and 11 months, he is bedridden but remains completely free of seizures and dystonia. He is able to smile, perform eye tracking, turn his head, reach for objects, and receive oral feeding.

Discussion

This patient with LS and *SLC19A3* mutation developed ES and responded well to ACTH treatment, but suffered with status dystonicus associated with this treatment. Status dystonicus can be recognized by the following symptoms and signs: increasingly frequent dystonia, fever, tachycardia, hypertension, sweating, autonomic instability, and elevated serum CK [2]. This patient with pre-existing dystonia gradually become irritable at each initial intramuscular injection during the course of ACTH treatment, and in turn presented increasingly frequent hypertonia with opisthotonos, fever, excessive sweating, and elevated serum CK. Although he might have had infectious disease with non-specific viruses, we speculated that his increasingly frequent generalized dystonia induced severe muscular spasms, resulting in fever, excessive sweating, and elevated serum CK. Intravenous MDL was effective for his condition, which prevented permanent deterioration. The clinical course showed that the intramuscular ACTH treatment could have caused acute exacerbation of dystonia and subsequently led to status dystonicus. We would have avoided administering IVIG and started with intravenous MDL if we had suspected status dystonicus as the cause of his serious condition after initial ACTH injection. Malignant hyperthermia, neuroleptic malignant syndrome, and serotonin syndrome were considered as differential diagnoses of his condition [3]. However, we diagnosed status dystonicus based on clinical features including increasingly frequent dystonia and underlying disease associated with basal ganglia lesions [3].

Two patients with *SLC19A3* mutation who were treated with ACTH treatment for ES have been reported: one had opisthotonic posture and the other had no dystonia [17]. The two patients had not developed status dystonicus associated with ACTH treatment. Stressors, such as fever and mild trauma, can precipitate acute exacerbation in *SLC19A3*-related disorders [5]. External discomfort stimuli tended to induce transient hypertonia with opisthotonos in this patient. However, he never developed lasting exacerbation of dystonia. We speculate that ACTH may have affected the duration of exacerbation of dystonia. A possible mechanism for the arising status dystonicus in this patient is that ACTH caused some functional changes in the hypothalamic-pituitary-adrenal axis, allowing the transient exacerbation of dystonia triggered by intramuscular injection to become persistent, leading to status dystonicus. The underlying pathophysiology of status dystonicus is unclear. Moreover, as this is a single case presentation, we cannot draw any definitive conclusions.

Status dystonicus often develops as a triggered event, which has been detected in approximately two thirds of patients with status dystonicus. The main triggers are infection (51.7%), therapeutic adjustment (30%) such as introduction of dopamine-receptor blockers and CZP, and surgical procedure (6.7%) [1]. We speculate that ACTH treatment could trigger acute exacerbation of dystonia, which may lead to status dystonicus in some patients with *SLC19A3* mutation. In this case study, the patient's condition was milder in the second episode than the first. Transient subfebrile temperature (37.8 °C) at Day 10, from initial ACTH injection after the second episode, appeared along with mild hypertonia (*figure 2*), which could be associated with pre-status dystonicus triggered by ACTH injection. This patient may have gradually adjusted to stressors associated with ACTH treatment, preventing status dystonicus a third time.

Benzodiazepines are often used for dystonia [14], and intravenous MDL was dramatically effective for the severe generalized dystonia of our patient. On the

other hand, the introduction of CZP might have facilitated status dystonicus in this patient. Introduction of CZP was reported to trigger status dystonicus in three patients (two primary torsion dystonia and one cerebral palsy) [1]. To our knowledge, there has been no reported case of status dystonicus triggered by the introduction of other benzodiazepines, except CZP. Thus, status dystonicus caused by CZP might involve unique mechanisms that are not shared by other benzodiazepines. However, this is a hypothesis based on our experience of a single case, and further investigation with larger samples will be needed to clarify this aspect.

In conclusion, ACTH treatment for ES can induce status dystonicus as a triggered event in some patients with LS and *SLC19A3* mutation. The efficacy of treatment at early stages may predict long-term seizure outcome in patients who have ES without hypsarrhythmia [18], suggesting that ACTH treatment is one of the possible options for ES at an early stage in patients with LS of unknown genetic aetiology. Thus, attention should be paid to acute exacerbation of dystonia when ACTH treatment for ES is started in patients with LS who have dystonia tend to exacerbate transiently by external discomfort stimuli. ■

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