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Case Report

Lamotrigine-induced DRESS syndrome in a patient with mood disorder and NAGS deficiency: A case report

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Abstract

N-acetyl glutamate synthase (NAGS) deficiency is a very rare autosomal recessive metabolic disease that affects the urea cycle and can cause serious morbidity and mortality. In these cases, mood disorders are rare, and potential side effects are important in the treatment of neurological and psychiatric conditions occurring due to the existing enzyme deficiency. In this study, a case of NAGS deficiency, epilepsy, and mood disorder, as well as drug rash with eosinophilia and systemic symptoms (DRESS) syndrome after lamotrigine use, is presented.

Keywords: N-acetyl glutamate synthase deficiency, DRESS syndrome, Lamotrigine, Mood disorder, Treatment

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INTRODUCTION

Urea Cycle Disorders (UCD) are rare inherited metabolic conditions that impair the efficiency of the urea cycle responsible for the removal of excess ammonia from the body (1). The rarest of UCDs, N-acetyl glutamate synthase (NAGS) deficiency, which was first described in 1981, is an autosomal recessive disorder caused by a homozygous or compound heterozygous mutation in the NAGS gene on chromosome 17q21 17q21.31, with an incidence of less than 1:2 000 000 (2,3). Infants with UCDs with complete enzyme deficiency often present in the neonatal period with hyperammonemic coma and symptoms related to hyperammonemia (4). In neonatal cases, malnutrition or feeding intolerance, vomiting, lethargy, hypertonia and/or hypotonia, seizures and tachypnea, and in later-onset cases, confusion or disorientation, vomiting, behavioral changes, ataxia, lethargy, decreased levels of consciousness, seizures, and hypotonia are among the most common symptoms (5,6). Patients with partial urea cycle enzyme deficiencies with late-onset symptoms may present with chronic encephalopathy, autism, learning disabilities, hyperactivity and self-destructive behaviors, vomiting with changes in level of consciousness, stroke-like attacks, as well as psychiatric symptoms such as episodic psychosis, bipolar disorder, and/or major depression in young people and adults as emphasized in previous studies[1]. It was reported that 47% of patients enrolled in the UCD consortium in the United States of America (USA) were diagnosed with an intellectual disability, 38% were diagnosed with learning disabilities, 20% were diagnosed with attention deficit and hyperactivity disorder (ADHD), and 3% were diagnosed with autism (7). In these patients, mood disorders are rare, and potential side effects are important in the treatment of neurological and psychiatric conditions associated with the existing enzyme deficiency8. Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is a life-threatening delayed drug hypersensitivity reaction which is rare in childhood and has not been previously reported in patients with NAGS deficiency. DRESS syndrome is a reaction to certain drugs, especially anticonvulsant drugs, usually manifested by fever, generalized body rash, and increased eosinophil counts, but its most prominent feature is the systemic response seen in liver function, renal function, or other major organs (8).

In this study, we present a patient with NAGS deficiency, epilepsy, and mood disorder who developed lamotrigine-induced DRESS syndrome. This case highlights the potential vulnerability of individuals with underlying metabolic disorders to severe idiosyncratic drug reactions and underscores the importance of the early recognition and prompt discontinuation of the suspected agent to prevent life-threatening complications.

CASE

F 13-year-old female patient with known NAGS deficiency and epilepsy was referred to us by the pediatric metabolic diseases and nutrition outpatient clinic for mood lability.

It was learned that the patient was born with C/S, weighing 3200 grams. She started walking at 14 months of age, started talking at the age of 2.5 years, and completed toilet training at the age of 2.5 years. She was admitted to the emergency department on the 4th day after her birth with fever, feeding difficulties, and respiratory distress. Hyperammonemia was detected as a result of the tests performed, and she was hospitalized in the neonatal intensive care unit for 15 days with the pre-diagnoses of sepsis, metabolic syndrome, and encephalopathy. The results of the tests of the patient performed in the neonatal period are shown in Table 1. It was learned that the patient with high blood ammonia levels had been on a protein-restricted diet since the age of 6 years, and her blood ammonia levels by years are shown in Figure 1.

Table 1. Laboratory tests and treatment information of the patient

	Neonatal	Adolescent	DRESS
Symptoms	Feeding difficulty Dyspnea Fever Vomiting Lethargy	Convulsions Mood lability Decreased cognitive functions	Skin discoloration, Fever and spots, Enlarged pupil, constantly sleeping
Laboratory Tests	Ammonia: 296.3 (ref: 0-228) AST: 557 U/L (ref: 0-40) ALT: 326 U/L (ref: 0-41) CK: 1283U/L (ref<70) LDH: 5124U/L (ref: 160-500) Severely elevated: Glutamic acid Moderately elevated: Aspartic acid, Tyrosine Phenylalanine Mildly elevated: Serin, Ornithine, Lysine, Methionine, Leucine Liver NAGS enzyme activity: Could not be determined	Ammonia: 26.8 µmol/L (ref: 0-228) Arginine: 69.54 (ref: 45-125) Asparagine: 76.1 µmol/L (ref: 24.90) Phenylalanine: 62 µmol/L (ref: 38-180) Glycine: 421 µmol/L (ref: 149-417) Glutamate: 46.4 µmol/L (ref: 22-131) Glutamine: 518 µmol/L (ref: 333-809) Histidine: 57.28 µmol/L (ref: 41-106) Liver NAGS enzyme activity: Could not be determined	Hb: 12.6 g/dL (ref: 11.5-15), WBC: 5.98x10^3/uL (ref: 4.5-13), Lymphocytes: 0.64x10^3/uL (ref: 1-4.8). Eosinophils: 0.26x10^3/uL (ref: 0.02-0.5), Platelets: 121x10^3u/L (ref: 150-450), AST: 18 U/L (ref<25), ALT: 60 (ref<24), GGT: 43 U/L (ref<33), CK: 57 U/L (ref<145), CR: 0.63 mg/dL (ref: 0.57-0.87), Fibrinogen: 237.7 mg/dL (ref: 70-400), Complement C4: 5.37 mg/dL (ref: 16.00-38.00), Complement C3: 22.90 mg/dL (ref: 79.00-152.00), p-ANCA: negative c-ANCA: negative Anti-dsDNA: negative ANA: negative PCR: HHV 6, Mycoplasma pneumonia, CMV, EBV negative
Treatments	Blood glucose stabilization (approx. 150) Sodium benzoate Carnitine 200 mg/kg B vitamins Coenzyme Q Protein: starting from 0.5 g/kg raised to 2 g/kg Lipid: started at 0.5 g/kg.	Current Treatment Carglumic acid 3600 mg/day Clobazam 30 mg/day Aripiprazole 15 mg/day	Methylprednisolone 32 mg/day
Outcomes	15 days of hospitalization in neonatal intensive care. Advanced tests performed. Discharged after no ammonia elevation was found in her follow-ups.	Blood ammonia concentrations under control. Diagnosed with epilepsy at the age of 12. No epileptic seizures for 10 months. Decreased cognitive functions. Mood lability.	

ALT: Alanine Transaminase, AST: Aspartate Transferase, CK: Creatine Kinase, LDH: Lactate Dehydrogenase, Hb: Hemoglobin, WBC: White Blood Cell, GGT: Gamma Glutamyl Transferase, CR: Creatinine, ANCA: Antineutrophil Cytoplasmic Antibodies, Anti-dsDNA: Anti-Double-Stranded Deoxyribonucleic Acid, ANA: Antinuclear Antibody, PCR: Polymerase Chain Reaction, CMV: Cytomegalovirus, EBV: Epstein-Barr Virus, HHV-6: Human Herpesvirus 6

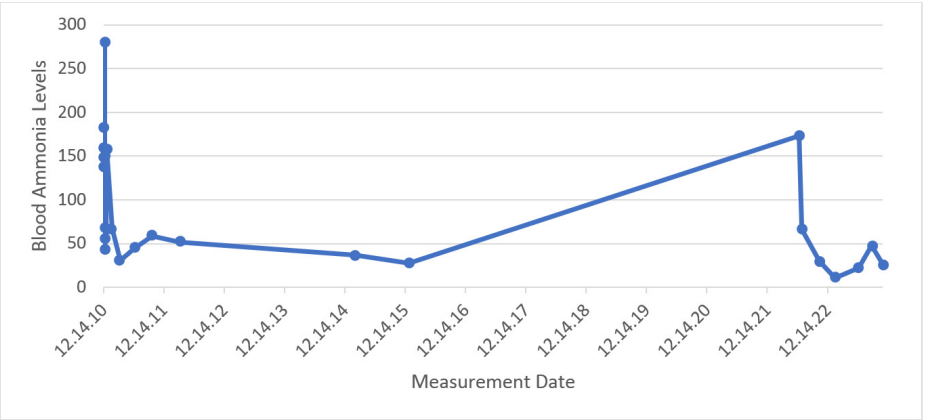

Figure 1. Blood ammonia changes.

The patient, who had no epileptic seizures in the first years of her life had a tonic-clonic seizure at the age of 11 years and was diagnosed with epilepsy, and medication was recommended. Again, at the age of 11, the patient was diagnosed with NAGS deficiency as a result of detailed genetic analysis. The parents of the patients were related, and there was no known metabolic or psychiatric disease in her family.

It was reported that the patient's mood fluctuated approximately every 15 days. During elevated periods, she talked excessively, displayed pressured speech, engaged in excessive spending, showed increased attention to self-care and heightened energy, required less sleep, demonstrated distractibility, and reported racing thoughts (consistent with DSM-5 hypomania criteria, including decreased need for sleep, distractibility, and flight of ideas) (9). Following these days, she had periods of locking herself in her room for a few days, burning incense, and meditating with music all day. During these periods, she no longer enjoyed activities she had previously found pleasurable, preferred to be alone, felt persistently tired, had difficulty falling asleep, struggled to study, and stated that she was unable to sustain her attention (these symptoms were consistent with DSM-5 criteria for a depressive episode, including loss of interest, fatigue, sleep disturbance, and impaired concentration) (9). These complaints had been going on for about 2 years.

Following a comprehensive psychiatric evaluation, the patient was diagnosed with Bipolar II Disorder in accordance with the DSM-5 diagnostic criteria (9).

Two years ago, she was brought to a child and adolescent psychiatrist, she was followed up with a diagnosis of anxiety disorder and received sertraline 100 mg/day for 6 months. Her enthusiasm and energy increased after the sertraline treatment, her family stopped the treatment thinking that she did not benefit from this treatment, and she had not used psychiatric drugs for the last 6 months. The patient had increased aggressive behaviors in the last 2 years and had 1 suicide attempt by wrapping a rope around her neck in 2023. Aripiprazole 5 mg/day was started, and the dose was increased to 10 mg/day after 1 week due to mood lability. Haloperidol 0.5mg/day was started simultaneously. When the patient was referred to us, she was on carglumic acid at 3600 mg/day for her metabolic diagnosis and clobazam at 30 mg/day for epilepsy. It was learned that the patient had tonic-clonic epileptic seizures every month since her first seizure at the age of 11. The patient, who could not use valproic acid (VA) as an anticonvulsant due to the risk of hyperammonemia, was prescribed lamotrigine 25 mg/day in addition to her ongoing treatment for epilepsy by the pediatric neurology clinic. On the 17th day of her lamotrigine treatment, it was learned that she was brought to the emergency department due to skin discoloration, fever and spotting, dilated pupils, and constant sleepiness, and as a result of further examinations and investigations, she was hospitalized in the pediatric allergy and immunology diseases inpatient clinic with the diagnosis of DRESS syndrome.

In 2024, the patient's Wechsler Intelligence Scale for Children-Revised (WISC-R) test revealed an overall intelligence score of 56, and the clinical observation result was "dull-normal intelligence". The results of the brain magnetic resonance imaging performed in 2020 were normal. Electroencephalography (EEG) performed in September 2024 provided normal results.

Clinical Outcome

The blood tests of the patient performed during the diagnosis of DRESS syndrome revealed thrombocytopenia in complete blood count (CBC), slightly elevated alanine aminotransferase (ALT) in liver function tests, normal blood urea nitrogen and creatinine in renal tests, Complement C4: 5.37 mg/dL (ref: 16.00-38.00), Complement C3: 22.90 mg/dL (ref: 79.00-152.00), and negative serum autoimmune antibodies. Human herpes virus 6, mycoplasma pneumonia, cytomegalovirus (CMV), and Epstein–Barr virus (EBV) were not detected. After the reaction, lamotrigine was discontinued, and 32 mg/day methylprednisolone was added to the treatment. The treatment results are presented in Table 1. The patient was hospitalized in the pediatric allergy and immunology inpatient clinic for 2 weeks after the reaction. She was brought to us for follow-up after her discharge. It was observed that nystagmus started in her eyes after the drug reaction. It was learned that she had been calmer and less irritable for the last 4 weeks, but the same complaints started again after lamotrigine was discontinued. During the examination of the patient, lisping was observed in her tongue, and haloperidol was discontinued considering that the condition was due to the haloperidol treatment. The patient is currently on aripiprazole 15 mg/day and is followed up by us at frequent intervals. She had experienced no seizures for 10 months, and her September 2024 EEG examination result was normal.

DISCUSSION

In this article, we present a patient diagnosed with hyperammonemia in the neonatal period, diagnosed with NAGS deficiency at the age of 11 years, had epilepsy and bipolar disorder, and developed DRESS syndrome due to lamotrigine use. To our knowledge, this is the first case report describing a patient with NAGS deficiency who developed DRESS syndrome secondary to lamotrigine. Most patients with NAGS deficiency present early in life, but cases of later onset have also been reported (6,10). In a review of 98 cases of NAGS deficiency reported until 2020, it was stated that 1 case was diagnosed prenatally, 57 cases were diagnosed in the neonatal period, 29 cases were diagnosed post-neonatally, and 5 cases were defined as late onset (6). The most common clinical symptoms in neonatal cases are feeding difficulties, vomiting, lethargy, coma, convulsions, hypertonia/hypotonia, and tachypnea. Common symptoms in later-onset cases include vomiting, confusion, ataxia, lethargy, seizures, and hypotonia (11). In our case, hyperammonemia was detected in the neonatal period, and respiratory distress, feeding difficulty, and vomiting symptoms were present. NAGS deficiency and epilepsy were diagnosed at the age of 11 years, and mood disorder was diagnosed at the age of 12.5 years. Diseases that cause hyperammonemia usually present as severe neurological metabolic problems in the neonatal period or in the first months of life, as in our patient. The patient in our case report was hospitalized in the intensive care unit at the age of 4 days with complaints of fever, moaning, respiratory distress, and feeding difficulties.

In a retrospective cross-sectional study investigating the neurological outcomes of UCD patients (5 cases of NAGS deficiency), the impact of peak ammonia levels and frequency of hyperammonemia episodes on neurological outcomes was emphasized, and patients with abnormal neurological parameters were reported to have a significantly higher mean number of annual episodes of hyperammonemia (12). All four participants (one child and three adults) with NAGS deficiency in a longitudinal study of the Urea Cycle Disorders Consortium (UCDC) performed within the average range of intellectual functioning, and one woman who was not diagnosed until adulthood

was reported to have experienced severe psychiatric problems and cognitive impairment prior to NAGS deficiency diagnosis and treatment (13). Intellectual, adaptive, and behavioral functioning may be impaired in children with UCDs. In a study characterizing the cognitive, adaptive, and emotional/behavioral functioning of 92 children with UCD (33 neonatal onset, 59 late onset), children presenting with neonatal onset were reported to have worse outcomes than those with onset times later in childhood, with about half of the children performing in the intellectual disability range, whereas even in children with late-onset UCDs, evidence of neurocognitive and behavioral impairment was seen, especially in terms of attention and executive functions (4). In the intelligence assessment of our case, a dull-normal level of intelligence was determined. In a review summarizing neuropsychological outcomes among patients with eight types of UCDs (including NAGS deficiency) in reports published from 1980 to 2019, data on cognitive abilities of 1649 individuals were compared before and after 2000, and 556 patients (34%) were in the intellectual disability range. After 2000, the most significant improvement in neuropsychological outcomes was in the NAGS deficiency cases, with the prevalence of intellectual disability decreasing from 50% to 9%, reflecting the effectiveness of *N*-carbamyl glutamate treatment, and the favorable results of some studies suggested that it is possible to prevent or reverse the negative impact of UCDs on neuropsychological functioning (5).

Table 2. Case progress and medication management

Date/Time	Clinical Status	Treatment Initiated / Modified	Dose	Clinical Response
Neonatal Period	Hyperammonemic metabolic decompensation	Protein-restricted diet initiated	-	Clinical stabilization following dietary intervention
Age 11	Diagnosis of NAGS deficiency and epilepsy	Carglumic Acid & Clobazam	3600 mg/ day & 30 mg/day	Initial treatment for metabolic disorder and seizures
Last 2 Years	Increased aggressive behaviors	Not specified	-	Persistent behavioral issue
2023	Suicide attempt	Aripiprazole	5 mg/day	Persistent mood lability
1 Week Later	Mood lability	Aripiprazole (dose increase)	10 mg/day	Continued clinical managemen
Simultaneous	Behavioral symptoms	Haloperidol	0.5 mg/day	Adjunctive treatment
Pediatric Neurology Consultation	VA contraindicated (hyperammonemia risk)	Lamotrigine	25 mg/day	Triggered DRESS Syndrome.
Day 17 (Lamotrigine)	Skin discoloration, fever, dilated pupils, somnolence	Hospitalization / drug discontinuation	-	Diagnosis: DRESS syndrome (admitted to immunology).
Current Status	Post-recovery from DRESS	Aripiprazole (dose adjusted)	15 mg/day	Mood disorder symptoms are under control

A case with NAGS deficiency with psychotic features, which is also rarely reported in the literature, was presented in another study (11). Likewise, in the literature, a female patient who presented with recurrent vomiting attacks, psychotic behaviors, and confusion during adolescence until she was diagnosed with partial NAGS deficiency at the age of 13 was reported (14). In the report of an

adolescent male patient with chronic psychological symptoms starting in late childhood, it was stated that when he was about 9 years old, his conduct started to change, with attention deficit and learning disabilities, episodes of anxiety and irritability, and hand tremors. At 12 years of age, he was admitted to the hospital because of an episode of acute headache, vomiting, and confusion, without fever, and NAGS deficiency was diagnosed in the patient (11).

In a study evaluating a total of 229 UCD patients, it was reported that 35% of the patients had abnormal magnetic resonance imaging (MRI) or computed tomography findings, and 26% had abnormal brain waves (15). Our patient, who did not have seizures in the first years of her life, had a seizure at the age of 11 years and was diagnosed with epilepsy, and mood lability was added to her clinical records. The EEG performed in September 2024 and brain MRI performed in 2020 showed normal results.

In a review of cases with NAGS deficiency in 2020, it was reported that 18% of the cases had consanguinity between the parents (6). In our case, the parents were also related. NAGS deficiency is the only treatable UCD (16). The mainstay of treatment has been the reduction of ammonia through dietary restriction and/or alternative route therapies. This disease can currently be treated using carglumic acid, an N-acetyl glutamate analog, and a low-protein diet when starting treatment (16,17). Approved in 2010 by the FDA, carglumic acid is the treatment of choice for NAGS deficiency (16,18). However, there is insufficient data on the clinical response of these cases and the side effects of the selected drugs in the presence of comorbidities such as epilepsy and mood disorders. For example, a case who developed hyperammonemia due to VA use and was diagnosed with underlying NAGS deficiency was presented (19). In the aforementioned case, when VA treatment was stopped, and the treatment regimen was switched to lamotrigine, it was reported manic symptoms reappeared after the cessation of lamotrigine treatment. Then, VA treatment was restarted with weekly follow-ups after the third weekly visit, as manic symptoms worsened, and concerns about rashes were reported (19). In this case, VA was the only effective therapeutic option and was therefore initiated despite the presence of hyperammonemia. Subsequent diagnostic evaluation revealed a genetically confirmed NAGS deficiency. Following this diagnosis, carglumic acid therapy was started, and it resulted in significant clinical and biochemical improvement (19).

Neuropsychiatric/neurodevelopmental findings are common among the initial symptoms of late-onset UCDs, and serum ammonia levels should be checked in the presence of unexplained or treatment-resistant neuropsychiatric/neurodevelopmental symptoms that emerge during childhood or adolescence (20).

DRESS syndrome usually starts abruptly with maculopapular morbilliform exanthema with a fever of >38°C as of 2–3 weeks after the introduction of the implicated drug (21). It classically occurs 3 weeks–3 months after exposure to a limited number of drugs, mainly anticonvulsants, antibiotics, and sulfonamides (8,22,23). Indeed, the five drugs (carbamazepine, phenytoin, phenobarbital, zonisamide, and lamotrigine) mainly associated with DRESS have not changed significantly over the last 15 years (24). Common pharmacological triggers for pediatric DRESS syndrome include aromatic anticonvulsants, responsible for 50% of cases (mainly carbamazepine, phenytoin, and phenobarbital), antibiotics, responsible for up to 30% of cases (mainly vancomycin, trimethoprim-sulfamethoxazole, and amoxicillin) and, although infrequent, sulfasalazine (4.6%) and nonsteroidal anti-inflammatory drugs (4.6%) (25).

DRESS syndrome is an adverse drug reaction characterized by widespread skin involvement, fever, lymphadenopathy, visceral involvement, and laboratory abnormalities (e.g., eosinophilia, mononucleosis-like atypical lymphocytes) (24,25). A review of 16 case studies of pediatric patients with lamotrigine-induced drug-induced hypersensitivity syndrome (DIHS)/DRESS revealed that DRESS should be considered in patients exhibiting both a dermatological rash and impaired liver function

several weeks after initiating an anticonvulsant medication. It is more common in adults and only rarely seen in children, in whom it is frequently associated with systemic organ involvement, such as liver dysfunction, renal impairment, and interstitial pneumonitis. Myocarditis, thyroiditis, encephalitis, and type 1 diabetes mellitus have also been reported as manifestations of this syndrome (21).

Table 3. RegiSCAR score of our case

Score	-1	0	1	2	Our case
Fever ≥38.5°C	No/U	Yes			0
Enlarged lymph nodes		No/U	Yes		1
Eosinophilia		No/U			0
Eosinophils (×10⁹/L)			0.7–1.49	≥1.5	
Eosinophils if leukocytes <4×10⁹/L			10–19.9%	≥20%	
Atypical lymphocytes		No/U	Yes		0
Skin involvement					
Skin rash extent >50% BSA		No/U	Yes		1
Skin rash suggesting DRESS	Nu	U	Yes		1
Biopsy suggesting DRESS	No	Yes/U			0
Organ involvement					
Liver		No/U	Yes		1
Kidney		No/U	Yes		0
Lung		No/U	Yes		0
Muscle/heart		No/U	Yes		0
Pancreas		No/U	Yes		0
Other organ		No/U	Yes		0
Resolution ≥15 days		No/U	Yes		1
Evaluation of other potential causes					
ANA					
Blood culture					
Serology HAV/HBV/HCV					
Chlamydia/mycoplasma					
If none positive and ≥3 above negative			Yes		1
Total score					6

Additionally, the data suggest adult and pediatric DRESS cases are not significantly different in terms of their clinical manifestations (24). Nevertheless, pediatric DRESS syndrome should be considered when a child presents with fever, maculopapular eruption, lymphadenopathy, eosinophilia, and visceral involvement, and the onset of the symptoms may be delayed (2–6 weeks) or rapid (<15 days) (25). The review of the relevant literature and the experience of these cases suggest that the risk of lamotrigine-associated severe cutaneous adverse reactions is increased when starting lamotrigine treatment at high initial doses, and we recommend practitioners be alerted of the risk of severe cutaneous drug reactions particularly at initial doses greater than 25 mg (23). In our case, DRESS syndrome developed after lamotrigine use, and the patient was hospitalized in the pediatric inpatient clinic. Our patient also developed skin discoloration, fever and spotting, dilated pupils, and constant sleepiness on the 17th day of her lamotrigine treatment. The patient's RegiSCAR score is presented in Table 3 (26).

DRESS syndrome is an acute, severe, and life-threatening disease with a mortality rate of about 10%, but most patients with DRESS have a full recovery (21,23,24,27). Similarly, the early recognition of the

condition and the early withdrawal of allergenic drugs is a very important aspect of the management of DRESS (21). Glucocorticoid therapy is the first-choice treatment, and plasma exchange, intravenous immunoglobulin (IVIG), and immunosuppressant drugs should be considered in cases with multiorgan involvement and life-threatening complications (21). In these cases, like in our case, clinical recovery occurs as a result of ceasing treatment with the implicated drug and providing steroid treatment (8).

CONCLUSION

Patients with NAGS deficiency, as in our case, are prone to serious drug side effects and neuropsychiatric disorders that need to be closely monitored. The timely diagnosis of these patients is important, and treatment should be started immediately to prevent complications. This case highlights lamotrigine-induced DRESS syndrome in a patient with NAGS deficiency, epilepsy, and mood disorder, demonstrating that individuals with underlying metabolic disorders may be more vulnerable to severe idiosyncratic drug reactions. The early recognition of DRESS and prompt discontinuation of the suspected or causative agent are critical to prevent life-threatening complications in this vulnerable population.

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Conflict of Interest

The authors declare that they have no conflict of interests regarding content of this article.

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Ethical Declaration

Informed consent was obtained from the participant and Helsinki Declaration rules were followed to conduct this study.

Authorship Contributions

Concept: SS, PCR, Design: SS, PCR, AYT, DK, Supervising: PCR, GG, AYT, DK, Financing and equipment: SS, PCR,, Data collection and entry: SS, PCR, AYT, GG, DK, Analysis and interpretation: SS, PCR, GG, Literature search: SS, PCR, DK, Writing: SS, PCR, DK, Critical review: PCR, AYT, GG.

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