JPPT | Case Report

High Anion Gap Metabolic Acidosis (HAGMA) After Levetiracetam Administration in an 11-Year-Old Boy With Laminin-α2-Deficiency-Associated Muscular Dystrophy and Epilepsy

Piet Erik Beusker, MD; Doortje Marieke Mehrtens, MD; Eckard Hamelmann, MD; and Georg Classen, MD

Congenital muscular dystrophy type 1A (MDC1A), an autosomal recessive disorder, is one of the most prevalent forms of congenital muscular dystrophy, characterized by the loss of Laminin-α_2 subunit (Merosin). Approximately one-third of affected patients experience epileptic seizures, typically manifesting around 8 years of age, with focal onset and secondary generalization, often with tonic-clonic semiology. Most reported cases show limited or no response to conventional treatment, though a subset responds to valproate or lamotrigine. The efficacy of levetiracetam in these patients remains insufficiently studied. Metabolic acidosis is not listed as a known adverse effect of levetiracetam in the medication's technical information. In this case, an 11-year-old male with MDC1A presented with nocturnal seizure equivalents and was started on levetiracetam therapy. Approximately 24 hours after receiving the loading dose, the patient's condition deteriorated significantly, and severe metabolic acidosis with an elevated anion gap was observed. The patient required transfer to the pediatric intensive care unit and received intensive intravenous hydration and potassium supplementation. Upon discontinuation of levetiracetam, the patient stabilized, and metabolic normalization was achieved within approximately 24 hours. There are very few reports in the literature that also point to the development of a high anion gap metabolic acidosis after levetiracetam administration. The underlying mechanism is hypothesized but not experimentally verified, and a causal relationship remains unproven. Nevertheless, this observation represents a potentially serious adverse event associated with a commonly used medication, warranting heightened clinical awareness. We therefore recommend actively highlighting this and considering safety monitoring based on the individual risk of the patients being treated.

ABBREVIATIONS EEG, electroencephalography; HAGMA, high anion gap metabolic acidosis; *LAMA2*, laminin-α_2

KEYWORDS levetiracetam; high anion gap metabolic acidosis; laminin α_2 deficiency- associated muscular dystrophy; epilepsy

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Information Box

What specific question(s) does this report address?

Could high anion gap metabolic acidosis be an adverse drug reaction caused by levetiracetam?

What does this report add to our current knowledge?

High anion gap metabolic acidosis must be considered as a rare but potentially severe adverse effect after levetiracetam administration, requiring intensive care monitoring and treatment.

Introduction

Laminin-α_2-Deficiency-Associated Muscular Dystrophy. Muscular dystrophy can be distinguished from other neuromuscular disorders by the following 4 mandatory characteristics: it is a primary myopathy with a genetic cause, exhibits a progressive course, and leads to the degeneration and death of muscle fibers at a certain stage of the disease.[1]

According to the German Society for Muscle Diseases, congenital muscular dystrophy type 1A is one of the most common forms of congenital muscular dystrophy. It is caused by mutations in the Laminin-α_2 (*LAMA2*) gene on chromosome 6 at locus 6q22-q23, resulting in a partial or complete absence of merosin (laminin subunit-α_2). Hence, this condition is also referred to as merosin-negative muscular dystrophy. A complete absence of merosin is most commonly observed, leading to disease onset at birth or within the first few months of life. The diagnosis is confirmed

by detecting 2 pathological mutations in the *LAMA2* gene (autosomal recessive inheritance) when clinically suspected. Characteristic features include generalized hypotonia and muscle weakness with ophthalmoplegia, as well as early joint contractures or hypermobility. Serum creatine kinase concentrations are typically markedly elevated (>1000 U/L). As the disease progresses, respiratory insufficiency and difficulties in feeding may also occur. Magnetic resonance imaging of the brain typically shows diffuse changes in the white matter consistent with leukodystrophy. Muscle biopsy reveals muscular dystrophy with merosin deficiency. Cerebral malformations may also occasionally occur. Patients with complete merosin deficiency may achieve the ability to sit independently, although walking ability is rarely attained. Approximately one-third of affected patients, including the case described here, experience epileptic seizures.[2]

The most extensive clinical investigations to date, conducted by Natera-de Benito et al and Geranmayeh et al.[4] observed epilepsy in approximately 36% of patients with a complete absence of the laminin subunit-α_2[3]. The data from these two studies were included in a review by the Department of Clinical and Experimental Medicine at the University of Pisa in Italy, which systematically examined 20 studies on "Epilepsy in *LAMA2*-Related Muscular Dystrophy."[5] A complete absence of merosin led to a significantly earlier onset of seizures compared with a partial absence. The average age at first seizure was 8 years, and, clinically, the seizures typically began focally with pronounced visual and autonomic symptoms, including vomiting. The seizures predominantly presented as generalized tonic-clonic seizures, irrespective of the onset of the disease and merosin expression. In contrast, focal seizures were less common and more frequently associated with cortical malformations. Electroencephalography (EEG) abnormalities mainly were observed bilaterally in the posterior cortical regions.[5]

Overall, there is limited information available on the efficacy of antiseizure drugs in these patients. In most cases described, most treatment approaches were minimally or not effective, while a small subset of patients responded to monotherapy with valproate or lamotrigine or to combination therapy with valproate and ethosuximide or carbamazepine. A correlation between brain structural defects and drug-resistant seizures is suspected, according to the authors of the review, as a smaller extent of cortical malformations was associated with a better response to antiseizure therapy in these patients. Overall, the data and the resulting recommendations for antiseizure therapy in epileptic seizures associated with *LAMA2*-related muscular dystrophy are considered weak due to the low incidence and limited reporting.[5]

Pharmacological Aspects of Levetiracetam. According to the Union Register of Medicinal Products for Human Use of the European Commission and the prescribing information from Sun Pharmaceuticals (as of June 2022), "Levetiracetam Sun 100 mg/mL" is primarily indicated for monotherapy of partial seizures with or without secondary generalization in adults and adolescents aged 16 years and older with newly diagnosed epilepsy. Additionally, it is approved as adjunctive therapy for partial seizures in patients aged 4 years and older. Common side effects include nasopharyngitis, somnolence, headache, fatigue, and dizziness. In children aged 4 to 16 years, vomiting, agitation, mood swings, emotional instability, aggression, abnormal behavior, and lethargy occur more frequently.[6]

The active ingredient levetiracetam belongs to the pharmacotherapeutic group of antiseizure drugs (ATC code: N03AX14) and is a pyrrolidone derivative. The exact mechanism of action is not fully understood. Studies indicate that levetiracetam influences intracellular calcium concentrations, leading to inhibition of calcium influx and a reduction in calcium release. It interacts with synaptic vesicle protein 2A, which is thought to contribute to its antiseizure effects.[6]

Levetiracetam is primarily metabolized through enzymatic hydrolysis, without affecting the cytochrome P450 isoforms in the liver. The main metabolite is pharmacologically inactive. Additional metabolites are produced through hydroxylation and opening of the pyrrolidone ring, while unidentified degradation products account for only 0.6% of the dose. Levetiracetam has minimal effects on certain liver enzymes (CYP1A2, SULT1E1, UGT1A1) but causes slight induction of CYP2B6 and CYP3A4.[6]

The plasma half-life of levetiracetam in adults is approximately 7 ± 1 hours and is not affected by dose, mode of administration, or repeated dosing. Approximately 95% of the administered dose is primarily excreted via urine, with 93% being eliminated within 48 hours. Only 0.3% is excreted through feces. Within the first 48 hours, 66% of the dose is excreted as levetiracetam and 24% as its primary metabolite, indicating glomerular filtration and tubular reabsorption. The elimination correlates with creatinine clearance.[6]

In patients with mild to moderate hepatic impairment, levetiracetam clearance is only slightly affected, but in cases of severe impairment, clearance is reduced by more than 50%. There are no data on intravenous administration in children (4–12 years), but it is assumed that the pharmacokinetics are comparable to oral administration. After oral administration of 20 mg/kg/day in children with epilepsy (6–12 years), the half-life is 6 hours, and total body clearance is approximately 30% higher than in adults. After repeated oral administration (20–60 mg/kg/day), levetiracetam is rapidly absorbed, with peak plasma concentrations occurring after 0.5 to 1 hour. The half-life is approximately 5 hours.[6]

Case Presentation

An 11-year-old male Caucasian patient weighing 35 kg with confirmed Laminin-α_2-deficiency-mediated muscular dystrophy was admitted with newly developed nocturnal cyanosis, oxygen desaturation, and gaze deviation. There were no other relevant preexisting conditions, and the patient was not on any regular medication. No allergies were reported, and there was no infection. Routine laboratory tests, including complete blood count, electrolytes, clinical chemistry, and coagulation parameters, at admission showed no abnormalities except for a previously known elevated creatine kinase concentration of 1020 U/L due to the underlying disease. In previous hospital stays between 2013 and 2021, creatine kinase concentrations fluctuated between 112 and 1584 U/L for this patient. EEG revealed bilateral frontal spike waves, bilateral synchronous spikes, and intermittent generalized slowing, leading us to interpret the nocturnal cyanosis and desaturation as seizure equivalents with hypopnea. Consequently, we initiated seizure-suppressing therapy with levetiracetam. On day 3 of hospitalization, an intravenous loading dose of 30 mg/kg was administered over 30 minutes. On day 4, approximately 12 hours after the loading dose, the patient received the first intravenous maintenance dose of 10 mg/kg over 30 minutes as well. The planned ongoing treatment regimen was 20 mg/kg/day in 2 divided doses. All doses administered were diluted in sodium chloride 0.9%.

Approximately 12 hours after administering the first levetiracetam maintenance dose, the patient's clinical condition deteriorated significantly, with the onset of tachypnea, tachycardia, increased sweating, and polyuria. Initial blood gas analysis revealed severe metabolic acidosis with a pH of 7.27 and a base excess of −19 mmol/L, with compensatory respiratory alkalosis (pCO_2 19 mm Hg). A concurrent hypokalemia of K^+ 3 mmol/L was also noted. Blood gas and electrolyte analysis (Na^+ 140 mEql/L, K^+ 3.06 mEq/L, Cl^- 107 mEq/L, HCO_3^- 12.6 mEq/L) indicated a high anion gap metabolic acidosis (HAGMA; anion gap 23.46 mmol/L). Laboratory evaluations ruled out other causes of HAGMA, such as diabetic ketoacidosis (blood glucose 84 mg/dL, lack of glucosuria), lactic acidosis (lactate 0.7 mmol/L), acute kidney injury (serum creatinine <0.17 mg/dL, blood urea 7 mg/dL), rhabdomyolysis (serum creatine kinase 277 U/L), and sepsis (C-reactive protein 25.1 mg/L, interleukin 6 3.5 pg/mL, procalcitonin 0.06 ng/mL). However, there was marked ketonuria (>80 mg/dL), which may have been influenced by reduced food intake in the preceding days.

The patient was transferred to the pediatric intensive care unit and received intensive intravenous hydration and potassium replacement. In total, the patient received isotonic electrolyte solution (Jonosteril, Fresenius Kabi) 360 mL, potassium chloride 7.45% 40 mL, Ringer's acetate 1320 mL, and pediatric semi-osmolar glucose electrolyte solution (Pediatric Infusion Solution 2, B. Braun Melsungen AG) 380 mL in the first 24 hours, resulting in a total intravenous volume of 60 mL/kg. Additionally, the patient received 4 nasogastric tube feedings (1.3 kcal/mL) of 50 mL each in the first 24 hours. Levetiracetam administration was discontinued immediately after the detection of acidosis. These interventions within the first 24 hours led to normalization of the patient's metabolic state with a pH of 7.43, base excess of −1.5 mmol/L, and potassium 3.8 mEq/L achieved approximately 24 hours later. Owing to persistent EEG changes, an alternative seizure-suppressing therapy with oral valproate 150 mg twice a day (8.5 mg/kg/day) was initiated. This was well tolerated by the patient, allowing for a successive increase to the target dose of 300 mg twice a day (17 mg/kg/day) without complications. Nocturnal hypopnea as a seizure component was observed for the last time 2 days after the start of valproate therapy. During the further observation period, no further seizure equivalents occurred, but residual EEG changes persisted even on day 15 after initiation of therapy. A condensed overview of the relevant events during the inpatient course is shown in the Figure.

The Naranjo score was 7, corresponding to a probable association.[7] To complete the scale, definitions for each of the 10 criteria outlined in the National Institute of Diabetes and Digestive and Kidney Diseases instructions for using the adverse drug reaction probability scale have been used.[8] The criteria and their evaluation in this case are shown in the Table.

Discussion

There are very few reports in the literature that point to the development of a high anion gap metabolic acidosis after levetiracetam administration. A Phase 4 clinical study conducted by eHealthMe, which analyzes

Figure. Extract of relevant events during the hospital stay, including the periods of levetiracetam administration, acidosis, and pediatric intensive care unit (PICU) treatment.

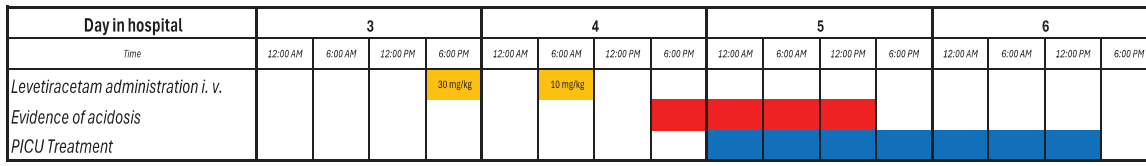

Table. Adverse Drug Reaction Probability Scale.

Question	Yes	No	Do Not Know	Score
1. Are there previous conclusive reports on this reaction?	+1	0	0	1
2. Did the adverse event appear after the suspected drug was administered?	+2	−1	0	2
3. Did the adverse event improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	1
4. Did the adverse event reappear when the drug was readministered?	+2	−1	0	0
5. Are there alternative causes that could on their own have caused the reaction?	−1	+2	0	2
6. Did the reaction reappear when a placebo was given?	−1	+1	0	0
7. Was the drug detected in blood or other fluids in concentrations known to be toxic?	+1	0	0	0
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	0
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	0
10. Was the adverse event confirmed by any objective evidence?	+1	0	0	1
			Total Score: 7	

large Food and Drug Administration data sets with the help of big data-capable artificial intelligence models. It calculates frequencies over time and found metabolic acidosis in 412 of 74,747 patients (0.55%) who reported adverse effects while taking levetiracetam between 2001 and 2024. The majority of affected patients were male (51.1%), with the most common age groups being 20–29 years (25.4%) and 10–19 years (18.9%), the latter including the patient in this case report. Most cases (66.6%) occurred within less than a month of levetiracetam initiation, as was the case in this report.[9] However, caution is warranted in interpreting these data, as they are derived from patient self-reports rather than controlled, scientifically validated studies.

In contrast to the eHealthMe study, which relies on patient self-reporting, the literature contains only 1 similar physician-reported clinical case series involving 3 patients who developed high anion gap metabolic acidosis after levetiracetam administration. The authors postulate that the accumulation of the ketone-like acidic metabolite 2-pyrrolidone-N-butanoic acid might be the underlying mechanism. They support this hypothesis by referencing the incomplete understanding of levetiracetam's mechanism of action and the possibility that the accumulation of this metabolite might contribute to the drug's anticonvulsant effect like the widely used ketogenic diet.[10]

Ultimately, it remains unclear whether the initial administration of levetiracetam in our case was causative for the observed metabolic acidosis. Alternative causes that could, on their own, have caused HAGMA, such as diabetic ketoacidosis, lactic acidosis, acute kidney failure, rhabdomyolysis, and sepsis, were ruled out by the diagnostic report. However, the absence of other clinical factors that could have influenced the previously stable acid-base balance, as well as the more than 400 self-reported adverse events from Food and Drug Administration data, and the similar observations described by Megri et al,[10] suggest a likely causal relationship.[9] Nevertheless, this represents a potentially serious adverse effect of a commonly used medication, indicating a high degree of clinical relevance for this observation. We therefore recommend actively drawing attention to this and considering safety monitoring, including respiratory function and acid-base balance assessment, based on the individual risk of the patients being treated.

Conclusion

This case report documents a rare but potentially severe adverse effect requiring intensive care monitoring and treatment associated with a commonly used medication, underscoring the clinical significance of this observation. Although it remains uncertain whether the initial administration of levetiracetam was the cause of the observed metabolic acidosis in this case, the literature suggests a possible link. The underlying pathophysiological mechanism also remains unclear and warrants further investigation through experimental

preclinical and clinical studies. Nevertheless, it is important to repeatedly highlight the observed condition after levetiracetam administration and to indicate safety monitoring based on the individual risk of the patients being treated.

Article Information

Affiliations. Department of Pediatrics, University of Bielefeld, University Hospital OWL, Children's Center Bethel, Bielefeld, Germany

Correspondence. Dr. Piet Erik Beusker, MD; piet-erik.beusker@evkb.de

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References

1. Kliegman RM, Nelson WE. *Nelson Textbook of Pediatrics*. Volume 2. 21 ed. Philadelphia, PA: Elsevier; 2020.
2. Gesellschaft für Muskelkranke. Kongenitale Myopathien. Accessed August 7, 2024. https://www.dgm.org/muskelerkrankungen/kongenitale-myopathien
3. Natera-de Benito D, Muchart J, Itzep D, Ortez C, González-Quereda L, Gallano P et al. Epilepsy in LAMA2-related muscular dystrophy: an electro-clinico-radiological characterization. *Epilepsia.* 2020;61(5):971–983.
4. Geranmayeh F, Clement E, Feng LH, et al. Genotype-phenotype correlation in a large population of muscular dystrophy patients with LAMA2 mutations. *Neuromuscul Disord.* 2010;20(4):241–250.
5. Salvati A, Bonaventura E, Sesso G, et al. Epilepsy in LAMA2-related muscular dystrophy: a systematic review of the literature. *Seizure*. 2021;91:425–436.
6. Levetiracetam [package insert] . Leverkusen, Germany: *Sun Pharmaceuticals Germany GmbH*. Accessed August 7, 2024. https://ec.europa.eu/health/documents/community-register/2021/20210318151210/anx_151210_en.pdf
7. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther*. 1981;30(2):239–245.
8. *LiverTox: Clinical and Research Information on Drug-Induced Liver Injury*. Bethesda, MD: National Institute of Diabetes and Digestive and Kidney Diseases; 2012.
9. eHealthMe.com. Levetiracetam and Metabolic acidosis - a phase IV clinical study of FDA data. Accessed August 7, 2024. https://www.ehealthme.com/ds/levetiracetam/metabolic-acidosis/
10. Megri MA, Abusnina WA, Bukamur HS, Shweihat YR. Levetiracetam as a cause of high anion gap metabolic acidosis. *Am J Respir Crit Care Med.* 2019;199:A4808.