Journal of Community Hospital Internal Medicine Perspectives

Volume 14 | Issue 3 Article 13

2024

A Rare Case Report of Hypoketotic Hypoglycemia Induced Seizures Due to Secondary Carnitine Deficiency In a 44-year-old Female

Ayrton Bangolo
Department of Medicine. Palisades Medical Center, North Bergen, NJ, USA.0, ayrtonbangolo@yahoo.com

Nicole Tesoro
Department of Medicine. Palisades Medical Center, North Bergen, NJ, USA.

Sonia Onyeka
Department of Medicine. Palisades Medical Center, North Bergen, NJ, USA.

Mary Bangura
Department of Medicine. Palisades Medical Center, North Bergen, NJ, USA.

Rekha Shrestha
Department of Medicine. Palisades Medical Center, North Bergen, NJ, USA

See next page for additional authors

DOI: 10.55729/2000-9666.1279
Available at: https://scholarlycommons.gbmc.org/jchimp/vol14/iss3/13

A Rare Case Report of Hypoketotic Hypoglycemia Induced Seizures Due to Secondary Carnitine Deficiency In a 44-year-old Female

Authors

Ayrton Bangolo, Nicole Tesoro, Sonia Onyeka, Mary Bangura, Rekha Shrestha, Vignesh K. Nagesh, Roua Alrestom, Joshua Rathod, Eugenio L. Gomez, Youssef Laabidi, Imane Laabidi, Conrad Erikson, Aayat Sheikh, Sharon Maria, Mansi Naria, Erwin J. Tabucanon, Juilee V. Dongre, Auda Auda, Mohammed Jurri, Reshma Radhakrishnan, Hisham Alrefai, and Simcha Weissman

CASE REPORT

A Rare Case Report of Hypoketotic Hypoglycemia Induced Seizures Due to Secondary Carnitine Deficiency in a 44-year-old Female

Ayrton Bangolo [a,*], Nicole Tesoro [a], Sonia Onyeka [a], Mary Bangura [a], Rekha Shrestha [a], Vignesh K. Nagesh [a], Roua Alrestom [a], Joshua Rathod [a], Eugenio L. Gomez [a], Youssef Laabidi [a], Imane Laabidi [a], Conrad Erikson [a], Aayat Sheikh [a], Sharon Maria [a], Mansi Naria [a], Erwin J. Tabucanon [a], Juilee V. Dongre [a], Auda Auda [a], Mohammed Jurri [a], Reshma Radhakrishnan [a], Hisham Alrefai [b], Simcha Weissman [a]

[a] Department of Medicine, Palisades Medical Center, North Bergen, NJ, USA
[b] Department of Endocrinology, Endocrines Associates, Louisville, KY, USA

Abstract

Carnitine deficiency is a rare metabolic condition that can result in fasting hypoglycemia. Carnitine deficiency could be primary or secondary to other conditions. Among secondary causes, antiepileptics such as valproic acid have been incriminated. Valproic acid is known to deplete carnitine stores and inhibit the process of β-oxidation. Herein we report the case of a 44-year-old female with epilepsy that presented with breakthrough seizures associated with hypoglycemia despite being on appropriate antiepileptic therapy. The patient was later found to have carnitine deficiency. Discontinuation of valproic acid and supplementation with L-carnitine resolved the patient's hypoglycemia and breakthrough seizures. With this case report, we hope to encourage clinicians to include carnitine deficiency in the differential diagnosis of unexplained hypoglycemia.

Keywords: Seizures, Carnitine, Convulsions, Endocrinology, Adrenal insufficiency, Case report

1. Introduction

Carnitine is an essential amino acid involved in the beta-oxidation of fatty acids. Diet is the primary source of this compound, particularly in red meat and dairy products, but it is also biosynthesized endogenously in the liver and in the kidneys.

Carnitine facilitates the transfer of long-chain fatty acids into muscle mitochondria so the process of beta-oxidation can proceed.[1] Secondary systemic carnitine deficiency is rare and results from severe dietary deprivation or impaired hepatic and renal function. It can sometimes result from a complication of valproate therapy.[2] Valproic acid (VA) is a commonly utilized anti-epileptic drug in the management of outpatient epilepsy and the emergent treatment of seizures. Side effects of VA include hepatotoxicity, pancreatitis, bone marrow suppression, and hyperammonemic encephalopathy. VA also depletes carnitine stores, especially during long-term or high-dose therapy, causing hypoketotic hypoglycemia and other symptoms.[3] We present the case of a young female with hypoglycemic seizures due to carnitine deficiency. This case report has the objective of informing clinicians about this rare cause of fasting hypoglycemia.

2. Case presentation

This is a 44-year-old female with a past medical history of epilepsy and asthma who presented for evaluation of breakthrough seizures. Prior to admission, the patient's anti-epileptic regimen consisted of topiramate and valproic acid. She has been diagnosed with epilepsy since childhood and has

Received 25 June 2023; revised 12 September 2023; accepted 12 October 2023.
Available online 7 May 2024

* Corresponding author at: Palisades Medical Center, North Bergen, NJ, USA.
E-mail address: Ayrtonbangolo@yahoo.com (A. Bangolo).

https://doi.org/10.55729/2000-9666.1279

been on valproic acid for approximately 30 years and topiramate for 27 years. Her last seizure activity was several years prior to our encounter. Other medications include duloxetine 30 mg BID, which the patient takes for anxiety and ibuprofen as needed for back pain.

Despite long-term stability, she experienced a 5–10-min episode of convulsions, hand twisting, and frothing at the mouth, followed by 15 min of unresponsiveness witnessed by her daughter. Emergency Medical Services (EMS) administered 10 mg of versed and transported her to the Emergency Room (ER).

Upon arrival in the ER, she was found to be in a post-ictal state. Her blood glucose (BG) was found to be 61 mg/dL (70–122), dextrose 50% (D50) was administered and Levetiracetam was added to the antiepileptic regimen. One hour after administration of D50, the patient was witnessed to have an additional tonic clonic seizure activity and her BG was found to be 51, she received an additional dose of D50 and was started on dextrose 5% (D5) continuous infusion; endocrinology and neurology were consulted. The hypoglycemic panel was ordered, results of which were unremarkable as reported in Table 1. While on D5, the patient had multiple hypoglycemic seizures requiring D50, Lacosamide was also added to the regimen. The patient underwent further testing including an adrenal challenge test, growth hormone deficiency work-up and a video continuous electroencephalogram which were all unremarkable. The antiepileptics levels were also within normal limits.

Table 1. Summary of diagnostic work-up during hospitalization.

	Laboratory values
Hemoglobin A1C	4.7% (<5.7)
Alanine Transaminase	20 Units per liter (U/L) (7–52)
Aspartate Aminotransferase	19 U/L (13–39)
Blood Urea Nitrogen	8 mg per deciliter (mg/dL) (7–25)
Creatinine	0.49 mg/dL (0.60–1.20)
Sulfonylureas	None detected
Proinsulin	<4.0 pmol per liter (pmol/L) (< or = 18.8)
Insulin	11.3 uIU/mL (< or = 19.6)
Insulin Antibody	<0.4 Unit per milliliter (U/mL) (<0.4)
C-peptide	1.99 ng/mL (0.80–3.85)
BETA-HYDROXYBUTYRATE	0.05 mmol/L (< or = 0.28)
AM basal cortisol	9.8 ug/dL (8.7–22.4)
Cortisol 30 min after Cosyntropin injection	20.8 ug/dL (increase of >7 from baseline)
Cortisol 60 min after Cosyntropin injection	28.8 ug/dL (increase of >7 from baseline)
Adrenocorticotrophic hormone (ACTH)	13 pg/mL (6–50)
Insulin like growth factor 1	75 ng/mL (52–328)
Human growth hormone	0.1 ng/mL (≤7.1 ng/mL)
Total carnitine	**47 nmol/mg Cr (180–412)**
Free carnitine	**6 nmol/mg Cr (77–214)**
Valproic acid level	72 mg/L (50.0–100.0)
Creatine Kinase	43 [iU]/L (30–220)
Ammonia	22 umol/L (16–53)

The patient's episode was further complicated by the fact that initial non-contrast Computed tomography (CT) imaging did not reveal any acute conditions. This makes the case particularly challenging, as both seizures and hypoglycemia persisted despite multiple treatments, and no clear underlying cause could be established even after extensive testing.

A carnitine level was then ordered and revealed a deficiency of free and total carnitine.

The patient's valproic acid was discontinued and she was started on L-carnitine supplementation. The patient's glucose gradually normalized and the D5 infusion was eventually discontinued. The patient remained seizure free and was discharged from the hospital.

3. Discussion

Carnitine plays an important role in the transfer of long-chain fatty acids like valproic acid across the inner mitochondrial membrane for the process of β-oxidation, which is required for energy production during the fasting state. The mechanism behind the breakthrough seizures in this case report lies largely in the lack of ATP production from the dysfunction of the β-oxidation secondary to carnitine deficiency. Therefore, patients with carnitine deficiency may present with hypoketotic hypoglycemia similar to hyperinsulinemia state during fasting.[3]

Secondary carnitine deficiency (SCD) is less severe with respect to its short-term clinical impact and is much more common than Primary carnitine deficiency (PCD).[4] As opposed to PCD which is a genetic disorder, SCD occurs due to, or in association with, other disorders such as liver or kidney disease, defects in fatty acid metabolism, or administration of pharmacological agents such as pivampicillin or valproic acid (VA).[5] Our patient's liver and kidney profiles were within normal limits, and she was not on pivampicillin. The most plausible risk factor for the development of carnitine deficiency was VA, which can cause SCD even at therapeutic range.[6] Our patient was initially presented with fasting hypoglycemic seizures. The work up for hyperinsulinemia and adrenal insufficiency were within normal limits. The free carnitine level as well as the total level were low. Studies have shown that children who were on VA polytherapy or monotherapy had a decrease in the carnitine pool compared to patients on other antiepileptic agents.[7]

VA depletes carnitine stores, especially during long-term or high-dose therapy, via various specific mechanisms: First, VA is a fatty acid that combines with carnitine to form a valproylcarnitine ester, a form of acylcarnitine, that is excreted in urine. However, because this excretion accounts for less than 1% of total acylcarnitine elimination in urine, it is likely that insufficient endogenous carnitine synthesis or a decreased dietary carnitine intake contribute to the depletion. Second, VA causes decreased tubular reabsorption of both free carnitine and acylcarnitine. Third, VA reduces endogenous synthesis of carnitine by blockade of the enzyme butyrobetaine hydroxylase. Fourth, valproylcarnitine inhibits the transport of extracellular carnitine into the cell and the mitochondria. Fifth, VA metabolites prevent regeneration of carnitine stores via *Carnitine Palmityl Transferase 2*.[8] Lastly, as carnitine levels decrease, the half-life of VA is prolonged and further fuels the cycle of metabolic toxicity.[9]

Numerous studies have quoted that acylcarnitine has a neuroprotective effect from preservation of mitochondrial function, avoiding free radical production and excitotoxic pathways. This neuroprotective effect is lost due to the numerous mechanisms that deplete carnitine stores and contributes to the mechanism of breakthrough seizures.[10]

Carnitine supplementation with L-carnitine has shown benefits in patients with SCD.[11–13] The reasonable dose given is 100 mg/kg IV over 30 min (maximum dose 6 g), followed by 50 mg/kg IV (maximum dose 3 g) given every 8 h. Treatment is continued until the clinical signs of SCD resolve. Oral carnitine supplements can be administered prophylactically at a dose of 100 mg/kg per day every 6 h for patients with an acute overdose of VA but no clinical or laboratory signs of toxicity. There are no known side effects attributed to L-carnitine, establishing the excellent tolerance of the supplement.

Supportive care along with benzodiazepines (eg, lorazepam 2 mg IV then repeated every 5–10 min as necessary for refractory seizures) must be given initially while carnitine stores are being replenished. Clinical implications of unresolved hypoketotic hypoglycemia range from confusion and drowsiness to coma and death. But majority of patients with acute VA side effects recover uneventfully.[14,15]

Our patient was started on L-carnitine oral supplementation, she was also advised to avoid hypoglycemia and have frequent meals. VA was discontinued. Her symptoms subsequently improved and was discharged from the hospital seizure free. To date, there are not enough studies that support use of alternative AEDs without causing SCD. There have also been no formal surveillance guidelines for individuals with SCD. However, our patient may be continuously managed using the following screening recommendations suggested by Magoulas, P.L. & El-Hattab (2012): (1) Echocardiogram and electrocardiogram should be done annually or less frequently. If cardiomyopathy is found, she should be referred to cardiology for further management and treatment. (2) Plasma carnitine levels should be obtained and monitored frequently (after two weeks of each dose adjustment) until levels reach within the normal range. Once normalization is reached, periodic plasma carnitine analysis should be obtained annually for adults. (3) CK and liver transaminases measurement can be considered during acute illness.

Our patient should also be referred to a metabolic or genetic specialist so that appropriate management, anticipatory guidance, and genetic counseling can be initiated as soon as possible.[16]

4. Conclusion

Secondary Carnitine deficiency (SCD) is a rare metabolic condition that can result from Valproic Acid (VA) use. Patients who have epilepsy and who are maintained on valproic acid are at risk of subsequent hypoketotic hypoglycemia and associated breakthrough seizures due to the deficiency. Carnitine supplementation can normalize the beta-oxidation process and is a reasonable treatment to patients who get SCD secondary to VA. Early recognition of this rare and yet morbid condition can prevent serious consequences. Further studies should focus on strategies to identify patients at risk for secondary carnitine deficiency and on the development of alternative antiepileptic drugs with reduced risk of developing SCD. With this case report, we hope to encourage clinicians to include SCD in the differential of unexplained fasting hypoglycemia, not associated with hyperinsulinemia.

Author contributions

Ayrton Bangolo searched the literature, wrote, and revised the manuscript. Nicole Tesoro, Sonia Onyeka, Mary Bangura, Rekha Shrestha, Vignesh K. Nagesh, Roua Alrestom, Joshua Rathod, Eugenio L. Gomez, Youssef Laabidi, Imane Laabidi, Conrad Erikson, Aayat Sheikh, Sharon Maria, Mansi Naria, Erwin J. Tabucanon, Juilee V. Dongre, Auda Auda, Mohammed Jurri and Reshma Radhakrishnan revised and edited the manuscript. Simcha Weissman and Hisham Alrefai approved the final version

and are the article's guarantors. All authors certify that they contributed sufficiently to the intellectual content and data analysis. Each author has reviewed the final version of the manuscript and approves it for publication.

Statement of ethics

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

This study protocol was reviewed and the need for approval was waived by the ethics committee at Palisades Medical Center Hackensack Meridian Health.

Funding sources

No funding was received.

Data availability statement

All data generated or analyzed during this study are included in this article.

Conflicts of interest

No potential conflict of interest was reported by the authors.

Acknowledgements

Not applicable.

References

1. Kalantar-Zadeh K, Kopple JD. Chronic renal failure and the uremic syndrome: nutritional issues. In: Lerma EV, Rosner MH, Perazella MA, eds. *Current diagnosis & treatment: nephrology & hypertension*. 2e. New York, NY: McGraw-Hill Education; 2017.
2. Ropper AH, Samuels MA, Klein JP, Prasad S. *Diseases of muscle. Adams and victor's principles of neurology*. 11e. New York, NY: McGraw-Hill Education; 2019.
3. Jun JS, Lee EJ, Park HD, Kim HS. Systemic primary carnitine deficiency with hypoglycemic encephalopathy. *Ann Pediatr Endocrinol Metab*. 2016;21(4):226–229.
4. Reuter SE, Faull RJ, Evans AM. L-carnitine supplementation in the dialysis population: are Australian patients missing out? (Review Article). *Nephrology*. 2008;13(1):3–16.
5. Famularo G, Matricardi F, Nucera E, Santini G, Simone CD. Carnitine deficiency: primary and secondary syndromes. *Carnitine today: Springer*. 1997:119–161.
6. Murphy J, Marquardt K, Shug A. Valproic acid associated abnormalities of carnitine metabolism. *Lancet*. 1985;325(8432):820–821.
7. Opala G, Winter S, Vance C, Vance H, Hutchison HT, Linn LS. The effect of valproic acid on plasma carnitine levels. *Am J Dis Child*. 1991 Sep 1;145(9):999–1001.
8. Lheureux PE, Penaloza A, Zahir S, Gris M. Science review: carnitine in the treatment of valproic acid-induced toxicity - what is the evidence? *Crit Care*. 2005 Oct 5;9(5):431–440.
9. Zeiler FA, Sader N, Gillman LM, West M. Levocarnitine induced seizures in patients on valproic acid: a negative systematic review. *Seizure*. 2016;36:36–39.
10. Okumura A, Kurahashi H, Iwayama H, Numoto S. Serum carnitine levels of children with epilepsy: related factors including valproate. *Brain Dev*. 2019 June;41(6):516–521.
11. Spiekerkoetter U, Lindner M, Santer R, et al. Treatment recommendations in long-chain fatty acid oxidation defects: consensus from a workshop. *J Inherit Metab Dis*. 2009;32(4):498–505.
12. Cederbaum SD, Koo-McCoy S, Tein I, et al. Carnitine membrane transporter deficiency: a long-term follow up and OCTN2 mutation in the first documented case of primary carnitine deficiency. *Mol Genet Metabol*. 2002;77(3):195–201.
13. Kishimoto S, Suda K, Yoshimoto H, et al. Thirty-year follow-up of carnitine supplementation in two siblings with hypertrophic cardiomyopathy caused by primary systemic carnitine deficiency. *Int J Cardiol*. 2012;159(1):e14–e15.
14. Lheureux PE, Hantson P. Carnitine in the treatment of valproic acid-induced toxicity. *Clin Toxicol*. 2009 Feb;47(2):101–111. https://doi.org/10.1080/15563650902752376. PMID: 19280426.
15. Perrott J, Murphy NG, Zed PJ. L-carnitine for acute valproic acid overdose: a systematic review of published cases. *Ann Pharmacother*. 2010 Jul-Aug;44(7–8):1287–1293. https://doi.org/10.1345/aph.1P135. Epub 2010 Jun 29. PMID: 20587742.
16. Magoulas PL, El-Hattab AW. Systemic primary carnitine deficiency: an overview of clinical manifestations, diagnosis, and management. *Orphanet J Rare Dis*. 2012;7:68.