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Case Report

Tramadol Induced Hypoglycemia Masquerading as a Seizure Disorder

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ABSTRACT

Background: Common causes of hypoglycemia include hypoglycemic agents including exogenous insulin and insulin secretagogues, increased endogenous insulin, decline in circulating cortisol, human growth hormone and enzymes required for glucose production as well as hepatic and renal dysfunction.

Case presentation: Patient presented to emergency room with re-current seizures treated with Levetricatem and Topiramate for 10 years with increased frequency of 2-3/week during last 6 months. During ER visits to different hospitals for these episodes, plasma glucose, 1.5-1.8 mM/L and undetectable levels of insulin, C peptide, proinsulin, Insulin antibodies eliminated hyperinsulinemia due to insulinoma, insulin secretagogues as well as exogenous insulin as a cause of hypoglycemia. Normal HGH, ACTH and cortisol responses at onset of hypoglycemia excluded hypopituitarism with HGH and/or ACTH deficiency and primary adrenal insufficiency. Large tumor secreting IGF2 was eliminated by CT scans of chest and abdomen. Hepatic and renal disease as a cause of hypoglycemia were excluded as well by documentation of normal laboratory tests. Tramadol use in high daily dose confirmed by elevated urine levels and total remission of hypoglycemia and seizures following withdrawal of tramadol resulted in documenting this unique presentation of tramadol induced hypoglycemia. We believe lack of suppression of IGF2 in presence of hypoglycemia may indicate role of Tramadol in stimulating production or decreasing metabolism or clearance of IGF2 responsible for onset and perpetuation of hypoglycemia.

Conclusion: A unique presentation of Tramadol induced hypoglycemia masquerading as a seizure disorder probably caused by IGF2 dysregulation.

Keywords: Hypoglycemia; Hyperinsulinemia; Insulinoma; Metabolism

Abbreviations: IGF: Insulin like Growth Factor; ACTH: Adrenocorticotropic Hormone; EEG: Electroencephalography; ECG: Electrocardiogram; eGFR: estimated Glomerular Filtration Rate test; HGH: Human Growth Hormone; TSH: Thyroid Stimulating Hormone

INTRODUCTION

Common causes of hypoglycemia include administration of hypoglycemic agents including exogenous insulin and insulin secretogogues, inappropriate excessive secretion of endogenous insulin by insulinoma or beta cell hyperplasia as well as IGF2 secreting tumors. Alternatively, recurrent hypoglycemia may be induced by decreased secretion of counter regulating hormones including ACTH, cortisol and Human Growth Hormone, lack of enzymes or substrate as well as dysfunction of the organs, e.g. liver, kidney required for glucose production, e. g. Glycogenolysis, gluconeogenesis [1,2]. Herein, we report a patient presenting with recurrent seizures attributed to hypoglycemia induced by Tramadol. Dysregulation of IGF 2 secretion or metabolism induced by Tramadol is suggested as a probable pathophysiologic mechanism of onset of hypoglycemia.

CLINICAL CASE

57 years Caucasian woman presented to ER with reported seizure followed by confusion. Next of kin reported recurrent seizures occurring over past 10 years being treated with Levetiracetam and Topiramate XR. Frequency of seizures progressed to 2-3/weeks in 6 months prior to this visit. She was also receiving Ami-triptyline at bedtime (HS) and Tramadol 50 mg Three Times Daily (TID) 'for neuropathic pain', KCL and spironolactone for hypokalemia attributed to Topiramate. Hypokalemia was also well documented during 'seizure' along with hypoglycemia.

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Physical examination revealed confusion, with no focal neurological deficit, pulse 68/min, BP 114/72 mmHg. Rest of the examination including heart, lungs, abdomen and extremities was unremarkable. Multiple EEG determinations and ECG were normal as well.

Finger stick blood glucose was 2.4 mM/L. Simultaneous plasma glucose was 1.6 mM/L. Other laboratory tests revealed hypokalemia (2.8 mM/L and normal sodium, chloride and HCO_3 as well as normal calcium, phosphorus, serum urea nitrogen, creatinine and eGFR. Liver enzymes including AST, ALT, GGT and Alkaline Phosphatase as well as serum proteins and prothrombin time were normal as well. During observation in emergency room, plasma glucose rose to 8 mM/L on resuscitation with intravenous administration of Dextrose 50%, 50 mL. However, fingerstick blood glucose declined to <3 mM/L within half an hour of resuscitation and the pattern persisted for 4 hours. Therefore, patient was admitted into Intensive Care Unit for observation, while continuing administration of infusion of 10% dextrose and 2000 calories/day diet. During 48 hours, plasma glucose remained between 5-8 mM/L while receiving infusion. However, following discontinuation of infusion, symptomatic hypoglycemia (blood glucose <3 mM/L returned promptly within an hour. Therefore, she was retained for further observation. Further inquiry and examination of records about visits to emergency rooms at different hospitals for a seizure revealed documentation of hypoglycemia and hypokalemia (both plasma glucose and K <3.0 mM/L) as well. Other pertinent laboratory tests at this visit and at another occasion of documented hypoglycemia in a different hospital are shown in Table 1. During this hospitalization, CT scans of chest, abdomen and pelvis conducted because of documentation of circulating IGF2 concentrations failed to show presence of a large bulky tumor known to secrete IGF2. Finally, patient was noted to being administered orally Tramadol 50 mg three times daily for pain as she was receiving as outpatient prior to admission. Urine toxicology screen documented markedly elevated levels of both Tramadol and its metabolite Desmethyltramadol and confirmed chronic Tramadol administration in a relatively high daily dose (Table 1). Tramadol was promptly dis-continued because of well-established documentation of hypoglycemia on administration of 'propoxyphen' an analgesic with a chemical structure similar to Tramadol [3-6]. Blood glucose remained between 4.5-8.0 mM/L at hourly interval for next 4 hours following discontinuation of Tramadol and therefore glucose infusion was terminated. Neither a seizure nor hypoglycemia and hypokalemia ensued during next 48 hours. Therefore, KCL and spironolactone were discontinued and patient was dis-charged. Over the next 6 months, both Levetiracetam and Topiramate XR were discontinued by a neurologist as well because of lack of occurrence of a seizure. Finally, over the last 2 years, patient has been free of seizures and symptoms of hypoglycemia. Plasma glucose, insulin and IGF2 during one of the follow visits were 5.1 mM/L, 6.8 mcU/mL and 556 ng/mL respectively.

DISCUSSION

Herein, we report a patient presenting with recurrent seizures treated with Levetricatem and Topiramate for last 10 years. Frequency of seizures had progressed to 2-3/weeks in 6 months prior to the visit to emergency room. During this and previous another emergency room visit to different hospitals for these episodes, hypoglycemia with Plasma Glucose (PG), 2.5-3.0 mM/L was well documented. Undetectable levels of insulin, C peptide and proinsulin eliminated endogenous hyperinsulinemia due to insulinoma, islet beta cell hyperplasia and insulin secretagogues. Absence of Insulin antibodies in the circulation excluded exogenous insulin as a cause of hypoglycemia as well. Moreover, normal responses of HGH, ACTH and cortisol at the time of hypoglycemia also excluded presence of hypopituitarism with deficiency of HGH and/or ACTH as well as primary adrenal insufficiency. Normal free T4 and TSH concentrations eliminated thyroid dysfunction and CT scans of chest, abdomen and pelvis excluded presence of a large bulky tumor secreting IGF2. Finally, acute or chronic hepatic and/or renal disease as a cause of hypoglycemia was excluded as well by documentation of normal laboratory tests. Thus, almost all disorders well established to cause recurrent hypoglycemia were excluded [1,2].

Possible role of Tramadol in induction of recurrent hypoglycemia was considered because of its chemical structure being similar to another older non-steroidal analgesic 'propoxyphen' known to cause hypoglycemia [3-6]. Moreover, total remission of hypoglycemia and seizures following withdrawal of Tramadol and other anticonvulsants established the diagnosis of Tramadol induced hypoglycemia in this patient. Finally, this report is consistent with the data in the literature [7-17].

Table 1: Pertinent laboratory tests at 2 visits to emergency department with symptoms of hypoglycemia documented by plasma glucose <3 mM/L. Urine levels of tramadol and its metabolite during hospitalization.

Serum level	Unit	Normal range	Visit 1	Visit 2
Blood glucose	mM/L	3.6-7.8	1.8	1.9
Insulin	mcU/mL	2.6-24.9	<0.2	<0.2
C-peptide	ng/mL	0.78-5.19	0.4	0.2
Pro-insulin	pM/L	3.6-22		4.1
cortisol	mcg/dL	3.1-22.4	13.4	11.6
HGH	ng/mL	0.13-9.88	8.3	5.6
ACTH	pg/mL	7.2-63	32	
IGF1	ng/mL	37-208	117	
IGF2	ng/mL	333-967	659	643
insulin antibody	nM/L	<0.02	0	0.01

*Tramadol: 0.834 mg/L (Normal Range: 0.1-0.3); *Desmethyltramadol (metabolite), 9913 ng/mL (Normal <185)

Mechanism of hypoglycemia induced by Tramadol is not well elucidated in previous reports [7-17]. We believe that the onset and perpetuation of hypoglycemia during Tramadol use may be caused by elevated ratio of IGF2/plasma Glucose (368,338) due to lack of suppression of IGF2 in presence of hypoglycemia Table 1 attributed to increased production or decreased metabolism or clearance of IGF2 induced by Tramadol. Total remission of hypoglycemia following Tramadol withdrawal may be attributed to lowering of IGF2/plasma Glucose ratio (109) due to normalization of production as well as metabolism and/or clearance of IGF2.

CONCLUSION

Here is a unique presentation of Tramadol induced hypoglycemia masquerading as a seizure disorder. Moreover, hypoglycemia may be attributed to dysregulation of IGF2 expressed by elevated IGF2/plasma Glucose ratio during Tramadol use. Finally, total remission of hypoglycemia with normalization of IGF2/plasma Glucose ratio on Tramadol withdrawal may add further credence to the role of IGF2 in Tramadol induced hypoglycemia.

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