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CASE STUDY

Neuroendocrine, Autonomic and Metabolic Challenges in Hypermobile Ehlers-Danlos Syndrome: A Case Study on Hypoglycemia in a patient with Craniocervical Instability.

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ABSTRACT

This report presents a compelling case of hypoglycemia in a 20-year-old female with craniocervical instability receiving chronic total parenteral nutrition (TPN). Noteworthy is her intricate history, including Chiari malformation, Hypermobile Ehlers-Danlos syndrome, and tethered cord, complicating the clinical picture.

Following a complex spinal surgery, the patient received postoperative dexmedetomidine for pain relief. Subsequent hypoglycemic episodes prompted meticulous investigations and endocrinology consultations. Discrepancies in TPN infusion rates, nephrology perspective on glycogen depletion due to chronic TPN, and the patient's unique medical history added layers of complexity to the clinical landscape.

Our exploration delves into the multifactorial nature of hypoglycemia in this patient. Chronic TPN alters glucose dynamics, impacting glycogen stores, while dexmedetomidine, known for α2-adrenoceptor activation induced sympatholysis, may contribute to hypoglycemia. Dysfunction of hypothalamic-pituitary axis in patients with craniocervical instability necessitated enhanced scrutiny for the detection of potential central etiologies of hypoglycemia.

Our findings underscore the importance of a multidisciplinary approach, integrating pharmacological insights, nutritional considerations, and the patient's unique medical history, to provide a comprehensive understanding of adverse events in complex clinical scenarios. The dynamic nature of glycemic control in this context warrants careful consideration in clinical decision-making.

Glossary of Items: Total parenteral nutrition (TPN), dextrose 50% in water (D50), dextrose 20% in water (D20), dextrose 10% in water (D10), Adrenocorticotropic Hormone (ACTH), Cytochrome P450 (CYP).

Keywords: Hypoglycemia, Craniocervical instability, Total parenteral nutrition, Dexmedetomidine.

Introduction:

Patients who suffer with hypermobility type Ehlers-Danlos Syndrome (EDS), a progressive connective tissue disorder, suffer from severe neurological manifestations including instability of all levels of the spine[1-6]. The cranial-cervical instability causes compression of the medulla oblongata and resultant dysfunction of the neuroendocrine axis[5-9] and the autonomic nervous system (ANS)[6,10,11].

Disruption of ascending catecholaminergic neuronal pathways, selectively impairs hypothalamus-pituitary-adrenal (HPA) axis systemic-stress responses to homeostatic perturbations like hypoglycemia[12-14]. These responses, governed by overlapping limbic forebrain, hypothalamic, and brainstem circuits, dynamically modulate the contributions of neuroendocrine and autonomic systems based on stressor characteristics[13]. The multifaceted regulation of the HPA stress axis, encompassing sensory-driven "reactive" responses to immediate challenges and limbic-associated "anticipatory" signals even in the absence of overt physiological stress, has potential implications for understanding dysfunction in various diseases[14].

Patients with craniocervical instability and ventral brainstem compression may also experience gastroparesis, contributing to malnutrition[5,6]. Their reliance on chronic total parenteral nutrition (TPN) for nutritional support diminishes the necessity for glycogen storage[15], decreases insulin secretion vital for glucose uptake and storage in the liver[16], ultimately impairing the liver's ability to release glucose as needed.

In this report, we described a case of hypoglycemia in a patient with craniocervical instability receiving chronic TPN. Following a procedure for craniocervical fusion, the patient experienced hypoglycemia, triggering an in-depth examination of contributing factors. Dexmedetomidine infusion for pain relief, discrepancies in chronic TPN administration, and consultations with various medical services, including nephrology and endocrinology, unveiled a multifaceted clinical picture.

Clinical Observation:

The 20-year-old female, diagnosed with EDS, Chiari malformation and tethered cord, presented an intricate surgical history, including posterior fossa decompression, craniocervical fusion, section filum terminale, ventriculoperitoneal shunt placement, and multiple spine surgeries. Her antecedent thoracic fusion surgery was complicated by a postoperative infection, specifically involving methicillin-resistant Staphylococcus aureus and Enterococcus. Her coexisting medical conditions comprise craniocervical instability, neurogenic bladder, postural orthostatic tachycardia syndrome, contracted extremities, gastroparesis, peripherally inserted central catheter, and chronic TPN.

The patient was admitted for an extension of craniocervical fusion and revision of section filum terminale. On postoperative day 1, dexmedetomidine infusion was initiated for pain relief, administered without a loading dose, commencing at a rate of 0.2 mcg/kg/hr and subsequently titrated to 0.7 mcg/kg/hr later in the same evening. The following morning at approximately 10:30 am, the patient displayed mild grogginess, and her capillary blood glucose level measured 29 mg/dL. Hypoglycemia was corroborated by

the morning metabolic panel, indicating a plasma glucose level of 37 mg/dL. The administration of an ampule of dextrose 50% in water (D50) resulted in a rapid and substantial increase in her blood glucose, reaching 121 mg/dL.

Approximately at 12:30 pm, the patient experienced a resurgence of lethargy concomitant with a precipitous decline in blood glucose, receding to 29 mg/dL. An additional ampule of D50 was administered, and verification of TPN line patency was undertaken. The patient was receiving dextrose 20% in water (D20) via TPN at a rate of 83 ml/hr. The nephrology service was consulted to validate the formulation of TPN, ensuring the accurate glucose concentration and absence of insulin. Following the verification of a 50g deficit in the administered TPN relative to the prescribed home dose, its infusion was halted. Simultaneously, the patient was commenced on dextrose 10% in water (D10) at 100 ml/hr., pending the formulation of a fresh TPN solution. Capillary blood glucose monitoring was instituted at two-hour intervals, revealing hypoglycemia for the third instance, notably around 2:30 pm.

The patient was afebrile and normotensive; however, sepsis markers were requisitioned given her history, and an endocrine consult was completed. Sepsis markers were negative, and endocrine recommended a thyroid panel and plasma glucose testing every 4 hours. Notably, the patient exhibited abnormal thyroid function, characterized by diminished levels of thyroid-stimulating hormone (TSH) at 0.2 IU/ml (normal range: 0.4-4.20), free triiodothyronine (T3) below detectable limits (<1.5 pg/ml; normal range: 2.1-4.4), and and a notably diminished total T3 concentration of 42.48 ng/dl (normal range 87-178). Conversely, growth hormone (GH) levels were elevated at 13.1 ng/ml (normal range: 0-10.0), while levels of insulin-like growth factor 1 (IGF-1) and IGF-2 remained within the normal range at 139 ng/ml (normal range 108-384) and 430 ng/ml (normal Range 333-967), respectively. Her baseline pre-operative morning cortisol (13.5 mcg/dL) and adrenocorticotropic hormone (ACTH) (29.4 pg/ml) levels were normal. A comprehensive metabolic panel was done to rule out any liver disease or renal failure that may be contributing to hypoglycemia.

The hospital pharmacy was engaged to conduct a verification of medications and their respective side effect profiles. The singular additions to the patient's existing medication regimen, aside from those administered at home, included vancomycin, piperacillin-tazobactam, and dexmedetomidine. The clinical pharmacist conducted a comprehensive review and actively collaborated with critical care team members concerning the side effect profile of dexmedetomidine, encompassing instances of both hyper- and hypoglycemia. However, neither clinical pharmacists nor critical care providers had been previously informed of such episodes. This occurrence garnered a score of 5 on the Naranjo Algorithm, denoting dexmedetomidine as the probable but not definite cause of hypoglycemia. No evidence of drug-drug interaction was discovered as the underlying cause of hypoglycemia during the medication review.

At 3 pm, the administration of dexmedetomidine ceased, and TPN recommenced with D50 replacing D20 as the base solution, concomitant with D10 administered at a rate of 30 ml/hr. Furthermore, an additional

ampule of D50 was administered. The fifteen-minute assessment revealed a rebound in plasma glucose levels to 86 mg/dL. At 5 pm, capillary blood glucose measured 69 mg/dL, followed by readings of 70 mg/dL at 6 pm, 77 mg/dL at 7 pm, and a plasma glucose level of 94 mg/dL at 8 pm. Overnight blood glucose testing consistently recorded values exceeding 100 mg/dL. Nevertheless, the nephrologist encountered challenges reinstating the patient to her customary TPN regimen, and as a consequence, the patient has persisted on D50 as the base solution subsequent to this episode.

Discussion:

This study presents a case of hypoglycemia occurring in a patient afflicted with craniocervical instability and reliant on chronic TPN. The liver, being the principal organ responsible for glucose homeostasis, plays a pivotal role in storing and releasing glucose to sustain normoglycemia. Glycogen, a complex polysaccharide, serves as the primary reservoir of glucose in the liver, undergoing enzymatic breakdown into glucose when metabolic demands necessitate energy release. The administration of chronic TPN bypasses the physiological route of nutrient absorption, supplying a continuous stream of nutrients and energy directly into the systemic circulation. Consequently, this exogenous nutrient provision diminishes the necessity for glycogen storage within the liver[15]. Furthermore, chronic TPN administration has been associated with diminished insulin secretion[16], an essential hormone facilitating glucose uptake and storage within hepatocytes. This dual effect of chronic TPN administration, comprising reduced reliance on hepatic glycogen stores and diminished insulin secretion, may contribute synergistically to the depletion of glycogen reserves in the liver, compromising the liver's capacity to maintain euglycemia.

In our patient, inability of the nephrology service to restore the patient to her customary TPN regimen post-recovery from the hypoglycemia event is attributed to depleted glycogen stores associated with chronic TPN use and malnutrition. Individuals with craniocervical instability may exhibit dysphagia or gastroparesis[6], conditions that can precipitate malnutrition and subsequent hypoglycemia.

The central endocrine system, encompassing the pituitary and hypothalamus, plays a crucial role in glucose regulation[17,18]. In the context of craniocervical instability due to hypermobile EDS, mechanical stress and potential vascular compromise may directly affect the pituitary gland or hypothalamic-pituitary axis, leading to endocrinopathies[5-9]. Historical observations by Lewitus proposed a link between EDS and hypophyseal dysfunction[9], depicting two distinct presentations—one demonstrating acromegalic indicative of hyperfunction and the other manifesting signs consistent with functional hypopituitarism and hypocortisolism, thus emphasizing the potential involvement of the hypothalamic-pituitary axis in EDS-related endocrine disturbances. Another comprehensive analysis of a cohort comprising 20 consecutive patients diagnosed with cervical medullary syndrome due to a hereditary connective tissue disorder unveiled a case exhibiting coexisting adrenal insufficiency and acromegaly[6].

Evidence from prior studies, including Denko and Bojo, underscores elevated levels of GH, IGF-1 and insulin levels in patients with

hypermobility syndrome associated with EDS[19], revealing a notable pattern of endocrine dysregulation. Notably, our patient exhibited elevated GH levels, while IGF-1 and IGF-2 levels remained within normative bounds. GH is essential for gluconeogenesis and lipolysis, processes that generate glucose and free fatty acids, respectively, crucial during fasting states[20-22]. Dynamic stimulation tests may offer additional insights into the patient's GH status.

Similarly, adrenal insufficiency due to impaired ACTH secretion from the pituitary results in reduced cortisol production. Instances of adrenal insufficiency have been documented, highlighting the broad spectrum of endocrine abnormalities observed in individuals with hereditary connective tissue disorders presenting with craniocervical instability and ventral brainstem compression[5,6]. Cortisol is necessary for gluconeogenesis and for the mobilization of glycogen stores[23,24], and its deficiency can further exacerbate the risk of hypoglycemia. Despite the normal pre-operative cortisol levels, dynamic testing such as an ACTH stimulation test could be considered to assess the adrenal response more comprehensively, especially given our patient's complex medical history.

Disruption of the HPA axis can also affect the release and regulation of thyroid-releasing hormone and TSH, potentially resulting in thyroid dysfunction, as was the case in our patient. Sayed et al. have described secondary hypothyroidism in a patient with EDS[7]. Henderson et al. reported hypothyroidism in 6 of 53 (11%) consecutive patients diagnosed with EDS, who presented with craniocervical instability[5]. The thyroid gland's impact on glucose metabolism is multifaceted, involving modulation of insulin sensitivity and glucose utilization. The incorporation of thyroid function assessment within our patient's diagnostic regimen is consistent with the comprehensive approach necessary for elucidating the etiology of abnormal glucose levels through thorough endocrine evaluation.

Last but not the least, dexmedetomidine, a potent and highly selective α2-adrenoceptor agonist, has been employed for postoperative analgesia following intricate spinal procedures[25-27], mirroring its application in the presented case with our patient. The α2A adrenoreceptor, present on pancreatic β cells, is an important regulator of blood glucose homeostasis and its activation inhibits insulin secretion resulting in hyperglycemia[28,29]. By activating a2-adrenoreceptors within the central nervous system, dexmedetomidine reduces norepinephrine release, thereby resulting in a sympatholytic effect[30]. The hyperglycemic effect of a2-adrenoceptor-mediated inhibition of insulin secretion is cancelled out by hypoglycemic effect of an a2-adrenoceptor-mediated sympathoadrenal inhibition[31]. The Naranjo Algorithm, employed to assess the likelihood of an adverse drug reaction[32], indicated that dexmedetomidine was the probable but not definite cause for hypoglycemia in this patient.

Pharmacogenomics can help predict an individual's response to certain drugs and may answer the question of hypoglycemia associated with dexmedetomidine in this case. Dexmedetomidine undergoes almost complete biotransformation with very little excreted unchanged in urine and feces. Biotransformation involves both direct

glucuronidation as well as cytochrome P450 (CYP) mediated aliphatic hydroxylation[33]. Also note that while the patient had pharmacogenomic testing done, it did not include CYP2A6 which is the major CYP enzyme that participates in the drug's metabolism.

Furthermore, conditions associated with dysautonomia, such as POTS, contracted extremities and neurogenic bladder, underscore the systemic impact of autonomic dysfunction, which can exacerbate the challenges in maintaining glucose homeostasis in this patient population. The interplay of metabolic challenges, HPA axis insufficiency, autonomic dysfunction, and patient's complex surgical history may contribute to the multifactorial nature of hypoglycemia observed in the context of craniocervical instability.

Conclusion:

In conclusion, our investigation into the complex case of hypoglycemia in a patient with craniocervical instability undergoing chronic TPN has illuminated a multifaceted interplay of factors. The alteration of glucose dynamics induced by chronic TPN has significant implications for glycogen stores, while the potential hypoglycemic effects of dexmedetomidine, mediated through α2-adrenoceptor activation and sympatholysis, further compound the intricate nature of this adverse event. The presence of endocrinopathies and dysautonomia in patients with craniocervical instability, underscores the necessity for heightened vigilance among healthcare providers in discerning potential central causes of hypoglycemia within analogous patient populations. This underscores the imperative for a multidisciplinary approach, encompassing pharmacological, nutritional, and medical perspectives, to comprehensively comprehend and address adverse events within complex clinical scenarios.

Conflict of Interest:

None.

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Statement of Authorship:

- Paolo A. Bolognese, MD: This author contributed to the validation of the case report and provided supervision.
- Navdeep S. Nayyar, MD MBA: This author participated in the conceptualization and drafting of the case report.
- Jaclyn N. Amaru, MS PA-C: This author played a role in the retrospective chart review and manuscript preparation.
- June Guo, PharmD BCPS: This author contributed to the retrospective chart review and manuscript preparation.
- Lance Cho, PharmD BCPS: This author contributed to the retrospective chart review and manuscript preparation.
- Sophie Bloom (high school student): This author assisted in the retrospective chart review.
- John B. Biggins, PhD.: This author aided in the preparation of the manuscript.
- Ilene S. Ruhoy, PhD MD: This author contributed to the conceptualization of the case report.

Disclosures:

None declared.

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