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Case Report

Ambiguous Presentations of Pyruvate Dehydrogenase Deficiency: Combined Case Studies

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Abstract: Background: The pyruvate dehydrogenase (PDH) complex is essential in the glycolytic conversion of pyruvate to acetyl-CoA. This reaction helps yield adenosine triphosphate (ATP) – a source for energy. Hence, PDH deficiency will lead to metabolic dysfunction. Case: The case report at hand unearths the perplexing presentation of two genetically predisposed Emirati siblings that were found to be thiamine responsive. Both patients complained of a variety of symptoms at the same age following an episode of gastritis. They undergo extensive laboratory tests and imaging and are initially diagnosed with non-alcoholic Wernicke encephalopathy (WE). Objective: It has come to our attention that this rapidly debilitating condition demonstrates a constellation of seemingly incongruent gastrointestinal and neuropsychiatric manifestations. It is imperative that the peculiarities of this disease be recognized. Because PDH deficiency does not conform to defined diagnostic criteria outlined in evidence-based guidelines, treatment is likely to be delayed. Method: A careful retrospective scrutiny of the patients' initial presentation and peculiar hospital course encourages identification of our limitations in providing efficacious quality care and in hopes of devising a systematic approach for future encounters. Conclusion: Any patient presenting to the emergency department with prolonged vomiting or diarrhea, for example, should be given thiamine as it is safe, inexpensive and may be lifesaving. We herein report two patients with indistinct, yet similar, signs and symptoms.

Keywords: Pyruvate Dehydrogenase Deficiency, Thiamine, Wernicke Encephalopathy

1. Introduction

The PDHA1 and PHDB genes produce proteins that combine to form the enzyme PDH [1]. PDH is an enzyme which catalyzes the breakdown of glucose for energy production [1, 2]. A mutation of either gene results in reduced PDH activity, subsequent lactic acidosis and hyperpyruvatemia [1].

PDH deficiency is particularly perilous as it remains underdiagnosed among children on a global scale. The authors have determined that the degree of symptomatic expression correlates with exposure to biochemical or physiological stressors imposed on the human body. When metabolic activity intensifies, the clinical features of PDH deficiency are more inclined to appear [3].

This concept can be applied to cases of WE. It is the result of a decrease in thiamine reserve – a water-soluble nutrient that is stored in relatively small amounts [4]. While WE is notoriously associated with chronic alcohol misuse, accelerated utilization or excessive loss of thiamine may individually, or in unison, precipitate the underlying disorder.

Literature corroborates the infamous triad of WE: confusion, ophthalmoplegia and ataxia [5]. Patients with PDH deficiency may share similar neurological deficits [6]. Even so, the initial complaints for both metabolic disorders are rather vague and may demand a variety of investigations – most of which will be normal or entirely inconclusive.

The present study highlights the challenges encountered with PDH deficiency patients in terms of deciphering an ambiguous presentation, distinguishing it from suspected

acute non-alcoholic WE, preventing deleterious progression and, lastly, formation of a clinical roadmap that tackles disease.

2. Case Report

A 14-year-old, Emirati female patient complains of persistent nausea for 2 weeks, several episodes of non-bloody vomiting and diarrhea, fatigue, dizziness, proximal muscle weakness, heat intolerance, hand tremors, palpitations, decreased appetite and 10 kg weight loss over 3 months.

Past medical history is notable for unresolving intermittent, cramping abdominal pain. She is on treatment for H. pylori. Inquiry about family history unveils maternal thyroid disease. Gross hand tremors and diffuse thyroid enlargement are appreciated. Muscle power is 4/5 in both proximal lower limbs. Our initial impression is that of a hyperthyroid disorder (possibly Grave's disease) accompanied by a proximal myopathy and dehydration from repeated vomiting and diarrhea.

In the following days, her GCS declines to 8-9, becoming responsive only to painful stimuli. Limbs are flaccid, areflexic with new-onset nystagmus. Vitals remain stable throughout. Head MRI showed sharply symmetrical areas of hyperintensity on FLAIR and T2 weighting affecting the "medial aspects of the thalami…mamillary bodies and…dorsal medulla", consistent with that of acute WE. Parenteral thiamine is initiated. On the 10^{th} day of hospitalization, GCS improves to 15/15, resting hand tremors disappear and patient moves with minimal assistance.

Five years later, patient's 14-year-old brother presents with similar complaints: 6 weeks of progressive muscle weakness, epigastric pain and 5 kg weight loss. He also happens to be on treatment for H. pylori. Symptoms were not preceded by a respiratory tract infection or diarrhea, otherwise. On physical examination, patient seems fatigued. Cranial nerves examination elicits appropriate responses. Spine examination is normal. He struggles to extend both of his hands, and has marginal difficulty standing up. Reflexes of the lower limbs are preserved, otherwise. Sensation is normal, with no numbness or tingling. Patient improves remarkably with thiamine supplementation.

Genomic analysis identifies a homozygote variation for the PDHB gene and heterozygote variations for LRPPRC and ACAD9 genes, making PDH deficiency the main differential. Comprehensive genetic counseling is recommended discuss the implications of these test results.

3. Discussion

Thiamine levels can drop during periods of protracted diarrhea or repeated vomiting, as seen in both patients. When thiamine declines to critically low levels, cell death evokes brain lesions in selected vulnerable regions [7]. The EFNS guidelines on management of acute WE endorse MRI use "to support the diagnosis of acute WE both in alcoholics and non alcoholics" (Level B) [8]. The medial thalami, periaqueductal areas, mamillary bodies are most prone to TD [9]. The MRI results of both siblings strongly corresponded with that of WE. Their response to parenteral thiamine affirms the preliminary diagnosis of WE, yet again.

Disease expression, however, is multifactorial. Predetermined genetics combined with an underlying thyroid disorder or H. pylori gastritis, for example, play a role, especially in adolescents with escalating metabolic requirements. This prompted our search for a genetic component, and a mutation of the PDHB gene was found in both patients.

The presentation of symptomatic patients varies – from lactic acidosis that occurs when a patient is under physiologic stress to deranged infantile brain development [6, 10, 11]. Nevertheless, treatment for acute PDH deficiency and long-term management entail supplementing the following cofactors: thiamine, carnitine and lipoic acid [12]. Some patients are more responsive to thiamine treatment than others [10]. Thiamine has reasonable overall safety (Level B) as validated by the EFNS [8]. Guidelines suggest that thiamine should be given to all at-risk subjects admitted to the ER [8]. This practice would alleviate the symptoms of suspected PDH deficiency (although rare) or WE before MRI retrieval.

Limitations to the approach of this case include:

Viewing the patient's thyroid-function abnormality as an obstacle to overcome separate from its capacity to inflame PDH deficiency or acute WE.

Although the patient regained full recovery courtesy of a teamwork-based strategy that pushed to rule out multiple diagnoses simultaneously, PDH enzyme probing and measuring thiamine levels would have consolidated a diagnosis of PDH deficiency or WE, respectively, early on.

In order to refine acute management tactics for cases of PDH deficiency, we encourage discussion that encompasses the importance of recognizing its vast atypical features, understanding the guidelines put forth for empirical treatment and preventing further detriment, as well as conducting thorough genomic studies. Any patient with relentless vomiting and diarrhea, for example, should be given a trial of intravenous thiamine. Response to supplementation establishes need for continued administration. Attempting to adapt to the recommendations put forward is considered good medical practice and will help minimize the socioeconomic burden of WE. Moreover, we propose training caregivers specifically in regions where subclinical deficiencies are likely to be prevalent.

4. Conclusion

There are two factors which make PDH deficiency an intricate domain: relatively non-specific presentation and genetics. This combined case study serves as exemplary insight into the challenges that may be faced by clinicians with regards to confirming diagnosis and hastening appropriate management.

PDH deficiency exacerbation is a medical emergency that

must not be undermined. Caregivers should have a high index of suspicion for any symptom or underlying medical illness that can provoke acute disease onset. A patient with relentless vomiting and diarrhea, for example, should be given a trial of intravenous thiamine. An adequate 'experimental' dose of thiamine is safe and inexpensive. Response to supplementation determines need for continued administration and will alert us to possibilities of the problem at hand.

Abbreviations

ATP	Adenosine triphosphate
EFNS	European Federation of Neurological Societies
GCS	Glasgow coma scale
PDH	Pyruvate dehydrogenase
TD	Thiamine deficiency
WE	Wernicke encephalopathy

Statement of Ethics

This study conforms to the ethical standards set by the ethical committee at Sheikh Shakhbout Medical City. The patients' guardian consent to the publication of this case.

Conflict of Interest

The authors declare that they have no competing interests.

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