Published in final edited form as:

Mol Genet Metab. 2011 February ; 102(2): 216–217. doi:10.1016/j.ymgme.2010.10.001.

4-Hydroxybutyric aciduria associated with catheter usage: A diagnostic pitfall in the identification of SSADH deficiency

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Abstract

Succinic semialdehyde dehydrogenase deficiency is a slowly progressive to static neurological disorder featuring elevated concentrations of 4-hydroxybutyric acid in body fluids. We present two patients with elevated 4-hydroxybutyric acid in urine which was later shown to be linked to catheter usage.

Keywords

SSADH deficiency; 4-hydroxybutyric acid; Catheter; Diagnostic pitfalls

1. Introduction

Succinic semialdehyde dehydrogenase (SSADH) deficiency (MIM# 271980) was first reported as 4-hydroxybutyric aciduria in 1981 [1]. The clinical presentation is variable and is associated with a late-infantile to early-childhood onset of slowly progressive or static encephalopathy characterized by ataxia, hypotonia, speech disturbance, seizures and variable mental retardation [2]. The diagnosis of SSADH deficiency is entertained in individuals with 4-hydroxybutyric aciduria detected on urine organic acid analysis and is confirmed by assay of SSADH enzyme activity in leukocytes and/or DNA mutation analysis. We describe two young patients with elevated 4-hydroxybutyric acid (gamma-hydroxybutyric acid; GHB) excretion in urine.

2. Patients, material and methods

Patient 1, a 7-week-old girl, was evaluated for metabolic disease because of cholestasis. Patient 2, an 8-day-old girl, had a positive neonatal screening test for maple syrup urine disease (MSUD) with a leucine of 406 $\mu\text{mol/l}$ (nl <400) and valine of 439 $\mu\text{mol/l}$ (nl <400). As part of the diagnostic work-up, urine organic acid analysis was performed in both patients. Because of elevated GHB excretion in the organic acid profile, GHB was quantified in urine and plasma from both patients with a stable isotope dilution gas chromatography-mass spectrometry (GC-MS) method [3]. In patient 1 we further measured succinic semialdehyde (SSA) and dihydroxyhexanoic acid (DHHA) by a stable-isotope

dilution liquid chromatography-tandem mass spectrometry method [4] and a stable isotope dilution GC-MS method [5], respectively (Table 1). Both SSA and DHHA represent additional biomarkers of SSADH deficiency [2]. To confirm SSADH deficiency, enzyme activities in lymphocytes were determined [6].

3. Results and discussion

In the organic acid analysis of patient 1 GHB was clearly elevated but other metabolites often found in affected patients, like threo- or erythro-4,5-dihydroxyhexanoic-acid [7] were absent. Quantification of GHB in urine showed a highly elevated excretion of 245 mmol/mol creatinine; controls <5 mmol/mol creatine. In plasma taken at the same day the GHB concentration was normal 0.35 $\mu\text{mol/l}$; controls 0.24–1.98 $\mu\text{mol/l}$. The levels of DHHA and SSA in urine were normal to slightly elevated, but not consistent with those levels observed in patients with SSADH deficiency. The SSADH activity in lymphocytes derived from patient 1 was also normal (Table 1), ruling out SSADH deficiency. No inborn error of metabolism was found as the cause for the cholestasis in patient 1.

In the urine sample taken at day 8 with a catheter from patient 2 we found increased excretion of GHB in the organic acid analysis, without other metabolites indicating SSADH deficiency. Quantification of GHB in urine showed a highly elevated excretion of 175 mmol/mol creatinine. In plasma taken at the same day the GHB concentration was normal 1.75 $\mu\text{mol/l}$. In follow-up urine samples collected with urine collection bags at the age of 9 and 42 days the GHB levels had normalized. SSADH deficiency was therefore very unlikely. MSUD was excluded in patient 2.

We were subsequently informed that the urine samples with elevated GHB derived from both patients were collected with a Coloplast SpeediCath catheter. We tested different lot numbers of this product and found that the physiological salt solution (in which the catheters are stored in prior to use in patients) for one lot contained a significant concentration of GHB (11 mM). Conversely, other lot numbers of the catheters and physiological salt solutions revealed a much lower GHB concentration (0.05 mM). Further investigation and discussion with the manufacturer revealed that the coating of these catheters normally has small residual amounts of gamma-butyrolactone (GBL) adhered to them, and because of this the catheters are subsequently dried to remove residual GBL. GBL is a major industrial solvent used in the manufacture of many materials, including precursors employed for catheter preparation [www.patentgenius.com/patent/6987191.html; www.freepatentonline.com/EP0214721.html]. GBL is also the prodrug form of GHB [8]. It is impossible, however, to remove all GBL, and these residual amounts of GBL may leak out of the catheter coating into the swelling media during storage. The swelling media is slightly acidic and GBL can be hydrolyzed to GHB. We speculate that in the lot number we tested, and the catheters used for our two patients, the drying process to remove excess GBL was incomplete, resulting in higher concentrations of GHB than normal. Since December 2008 the Coloplast Speedicath catheters have been produced without GBL to avoid this problem.

4. Conclusions

We report another diagnostic pitfall in the diagnosis of SSADH deficiency. GHB elevations in body fluids have previously been shown to result from sedation with GHB, as well as clinical intervention with GHB for narcolepsy, and finally in the instance of illicit consumption of GHB as a recreational drug [8,9]. We now add the use of some catheters to this list of diagnostic challenges in documenting inherited SSADH deficiency.

Acknowledgments

We thank Coloplast A/S Denmark very much for their cooperation and support in publication.

Abbreviations

SSADH	succinic semialdehyde dehydrogenase
GHB	4-hydroxybutyric acid
DHHA	dihydroxyhexanoic acid
SSA	succinic semialdehyde
GBL	gamma-butyrolactone
MSUD	maple syrup urine disease

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Table 1

Metabolite concentrations and SSADH enzyme activity in two patients compared to controls.

	Patient 1	Patient 2	Controls
GHB (urine, mmol/mol creatinine)	245	1 ^a) 175 2 ^b) 1.7 3 ^c) 0.5	0.09–5.0
GHB (plasma, μ mol/l)	0.36	1.75	0.24–1.98
DHHA (urine, mmol/mol creatinine)	0.26	n.a.	0.10–3.7
SSA (urine, mmol/mol creatinine)	4.3	n.a.	0.35–2.1
Enzyme activity (pmol/(min mg protein))	788	n.a.	342–1509

n.a.—not available.

^aCollected at day 8 with a catheter.^bCollected at day 9 with a urine collection bag.^cCollected at day 42 with a urine collection bag.