of skeletal and neurological symptoms. Little is known about the mechanism of neurologic involvement, but it may result from inefficient hydrolysis of vitamin B6 (pyridoxal 5'-phosphate, PLP), which is involved in neurotransmitter synthesis and is markedly elevated in HPP. However, it remains unknown what PLP levels are in the cerebrospinal fluid (CSF) of patients with HPP. We report two cases: (1) one with pre- and post-treatment CSF PLP levels and (2) one with pre-treatment CSF PLP and neurotransmitter levels.

Case 1: A 30-year-old woman with extensive fracture history presented with seizure-like activity. Laboratory evaluation while on no B6 supplementation was notable for low ALP (14 U/L, ref: 40-150), high plasma PLP (362 mcg/L, ref: 5-50), and high CSF PLP (16 mcg/L), with a low CSF/plasma PLP ratio (0.04, ref: 0.1-0.7[1]). Genetic testing showed a pathogenic variant of TNSALP (Het c.1133A>T, p.Asp378Val, rs 121918008). After initiation of enzyme replacement therapy (ERT), her plasma and CSF PLP levels normalized to 6.3 and 1.4 mcg/L, respectively, with a ratio of 0.23. She reported improvement in energy level and seizure-like activity after several months of ERT.

Case 2: A 34-year-old man with no history of skeletal pathology presented with diffuse musculoskeletal pain, weakness, and loss of sensory function attributed to generalized peripheral neuropathy. Laboratory evaluation while on no B6 supplementation was notable for low ALP (23 U/L), high plasma PLP (496 mcg/L), and high CSF PLP (17 mcg/L) with a low CSF/plasma ratio (0.03). CSF neurotransmitter levels were also low, including 5-hydroxyindoleacetic acid (40 nmol/L, ref: 67-140) and homovanillic acid (115 nmol/L, ref: 145-324). Genetic testing showed heterozygous expression of a catastrophic frameshift mutation of TNSALP (c.662del, p.Gly221Valfs*56). ERT is being considered at this time.

Conclusions: We report the novel findings that in these patients with HPP:

1. CSF PLP levels are markedly elevated, though to a much lesser extent than plasma levels. Elevated CSF/plasma ratios suggest that transport of PLP and its metabolites across the blood brain barrier may be impaired in HPP.
2. Decreased CSF neurotransmitter levels, as seen in our patient, may contribute to neurologic symptoms of HPP.
3. Enzyme replacement therapy normalized both CSF and plasma PLP in case 1. Further studies are needed to understand how these changes affect patient symptoms and prognosis.

Citation:

1. Albersen, M., et al., *Vitamin B-6 vitamers in human plasma and cerebrospinal fluid*. Am J Clin Nutr, 2014. **100**(2): p. 587-92

Pediatric Endocrinology

PEDIATRIC ENDOCRINE CASE REPORTS II

Cross-Reactivity of Human Insulin and Insulin Analogues in Human Insulin Immunoassay Complicates Case of Medical Child Abuse

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Cross-Reactivity of Human Insulin and Insulin Analogues in Human Insulin Immunoassay Complicates Case of Medical Child Abuse

Background: Measurement of insulin levels with human insulin immunoassays is important in the investigation of hypoglycemia; however, cross-reactivity with insulin analogues complicates clinical assessment.

Clinical Case: A 2-month-old male presented with hypoglycemia. Initial tests were consistent with hyperinsulinemic hypoglycemia: low serum glucose (29 mg/dL, n 70 to 99), elevated insulin (90.1 mU/L, n 3.0 to 19.0), suppressed beta-hydroxybutyrate (0.16 mmol/L, n 0.02 to 0.27), and suppressed free fatty acids (0.27 mmol/L, n 0.50 to 1.60). C-peptide level resulted undetectable (<0.1 ng/mL, n 0.8 to 3.5) raising suspicion for exogenous insulin administration. History revealed an older brother with type 1 diabetes mellitus treated with insulins glargine and lispro. Only one caregiver was present in the hospital, who denied knowledge of exogenous insulin administration. Hypoglycemia persisted despite placement of a continuous 1:1 sitter, high-dose intravenous glucose (glucose infusion rate up to 21.6 mg/kg/min), and treatment with diazoxide. A repeat insulin measurement with the Roche Diagnostics assay specific for human insulin was performed on a critical sample and resulted elevated (13.9 uIU/L, n 2.6 to 24.9), suggestive of endogenous insulin. However, an extensive study of commercial human insulin immunoassays by Heurtault *et al*., including the Roche Diagnostics assay, has demonstrated cross-reactivity with insulin analogues and their metabolites [1]. Given persistent concern for exogenous insulin administration, the patient's caregiver was asked to leave the bedside for an extended period of time which resulted in normoglycemia. Diazoxide and dextrose-containing IV fluids were discontinued. Patient maintained normoglycemia for the remainder of the admission and was discharged in the care of child protective services.

Conclusions: Cross-reactivity exists in human insulin immunoassays with insulin analogues and their metabolites complicating the determination of endogenous versus exogenous insulin as the cause of hyperinsulinemic hypoglycemia. It is important to know the cross-reactivity of the assay used if a diagnosis of surreptitious insulin administration is suspected. Separation of patient and possible perpetrators and involvement of child protective services is essential in suspected cases of exogenous insulin administration. Evaluation in cases where self-injection of insulin is suspected may be more difficult to decipher, and inclusion of c-peptide measurement at the time of hypoglycemia is critical.

Reference: [1] Heurtault B, Reix N, Meyer N, et al. Extensive study of human insulin immunoassays: promises and pitfalls for insulin analogue detection and quantification. Clin Chem Lab Med. 2014; 52:355-362.