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Holocarboxylase synthetase deficiency pre and post newborn screening

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ABSTRACT

Holocarboxylase synthetase deficiency is an autosomal recessive disorder of biotin metabolism resulting in multiple carboxylase deficiency. The typical presentation described in the medical literature is of neonatal onset within hours to weeks of birth with emesis, hypotonia, lethargy, seizures, metabolic ketolactic acidosis, hyperammonemia, developmental delay, skin rash and alopecia. The condition is screened for by newborn screening (NBS) tandem mass spectroscopy by elevated hydroxypentanoylcarnitine on dried blood spots. Urine organic acid profile may demonstrate elevated lactic, 3-OH isovaleric, 3-OH propionic, 3-MCC, methylcitric acids, and tiglylglycine consistent with loss of function of the above carboxylases. Here we describe a cohort of patients, 2 diagnosed pre-NBS and 3 post-NBS with broad differences in initial presentation and phenotype. In addition, prior to the advent of NBS, there are isolated reports of late-onset holocarboxylase synthetase deficiency in the medical literature, which describe patients diagnosed between 1 and 8 years of life, however to our knowledge there are no reports of late-onset HCLS being missed by NBS. Also we report two cases, each with novel pathogenic variants HCLS, diagnosed at age 3 years and 21 months respectively. The first patient had a normal newborn screen whilst the second had an abnormal newborn screen but was misdiagnosed as 3-methylcrotonylcarboxylase (3-MCC) deficiency and subsequently lost to follow-up until they presented again with severe metabolic acidosis.

1. Introduction

Holocarboxylase synthetase (HCLS) deficiency is an autosomal recessive disorder of biotin metabolism resulting in multiple carboxylase deficiency. It has an incidence of around 1/200,000 live births. HCLS is responsible for covalently linking biotin to propionyl-CoA carboxylase, 3-methylcrotonyl-CoA carboxylase (3-MCC), pyruvate carboxylase and acetyl-CoA carboxylase (see Fig. 1) [1,2]. Failure to attach biotin causes reduced activity of these biotin-dependent carboxylases and results in multiple carboxylase deficiency. The typical presentation described in the medical literature is of neonatal onset within hours to weeks of birth with emesis, hypotonia, lethargy, seizures, metabolic ketolactic acidosis, hyperammonemia, developmental delay, skin rash and alopecia [1]. Left untreated, infants will progress to profound metabolic acidosis, cerebral edema, coma and death. Prior to the advent of universal newborn screening (NBS) in the United States, age of onset was used to differentiate between HCLS deficiency and biotinidase deficiency, with biotinidase deficiency generally presenting after 3 months [3]. The mainstay of treatment for HCLS deficiency is free biotin supplementation in an effort to alleviate the symptoms of the enzyme deficiency or prevent symptoms from developing in asymptomatic individuals.

NBS in the United States is a public health initiative which includes screening, diagnosis, follow-up and management of inborn errors of metabolism identified at birth. The mainstay of testing for inborn errors of metabolism, (as opposed to other genetic conditions such as cystic fibrosis or congenital heart disease), involves tandem mass spectroscopy analysis of analytes such as amino acids, acylcarnitines and multiplex enzyme analysis on dried blood spots. Abnormal levels will flag newborns for subsequent confirmatory testing and referral to a metabolic specialist. HCLS deficiency is screened for through the detection of elevated hydroxypentanoylcarnitine (C5-OH). Urine organic acid profile may demonstrate elevated lactic, 3-OH isovaleric, 3-OH propionic, 3-MCC, methylcitric, and tiglylglycine consistent with loss of function of the above carboxylases. HCLS is caused by pathogenic variants in HLCS (21q22.1) which result in loss of function, through either reduced activity or absent activity of the holocarboxylase synthase enzyme [3].

The natural history of HCLS in the medical literature describes this condition as clinically severe often with significant intellectual disability and frequent hospitalizations with profound metabolic acidosis. Here we describe a cohort of patients, 2 diagnosed pre-NBS and 3 post-NBS with broad differences in initial presentation and phenotype. In addition, prior to the advent of universal NBS, there are isolated reports of late-onset holocarboxylase synthetase deficiency in the medical literature, which describe patients diagnosed between 1 and 8 years of life

Abbreviations: 3-MCC, 3-methylcrotonyl-CoA carboxylase; ACP, acylcarnitine profile; DOL, day of life; HCLS, holocarboxylase synthetase; NBS, newborn screen.

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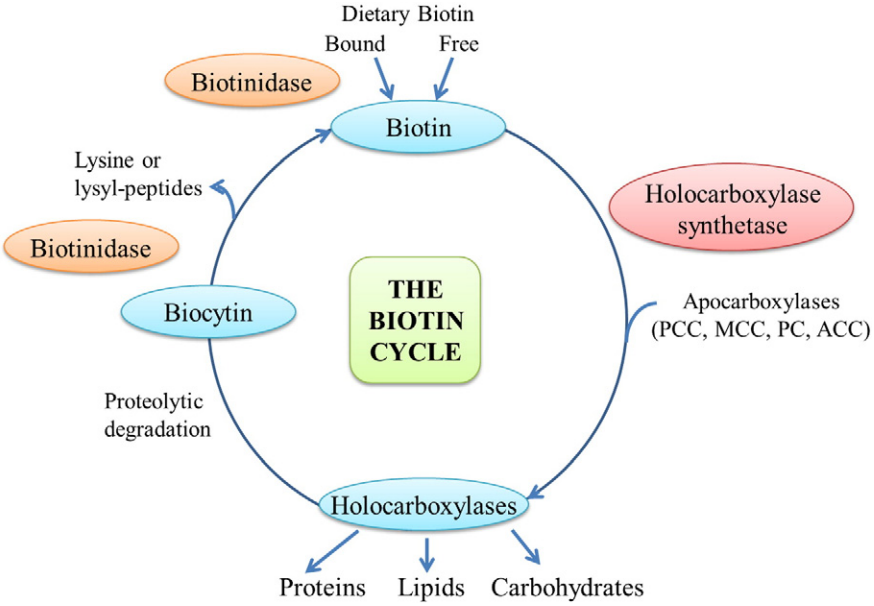

Fig. 1. The biotin cycle. Holocarboxylase synthetase covalently links biotin to the biotin-dependent carboxylases, propionyl-CoA carboxylase (PCC), 3-methylcrotonyl-CoA carboxylase (MCC), pyruvate carboxylase (PC), and acetyl-CoA carboxylase (ACC).

[2,4–6], however to our knowledge there are no reports of late-onset HCLS being missed by NBS. Also we report two cases, each with novel pathogenic variants HCLS, diagnosed at age 3 years and 21 months respectively. The first patient had a normal newborn screen whilst the second had an abnormal newborn screen but was misdiagnosed as 3-methylcrotonylcarboxylase (3-MCC) deficiency and subsequently lost to follow-up.

2. Materials and Methods

2.1. Case 1

Case 1 is now a 5 year old female who was born to a 24-year-old G1P1 via normal vaginal delivery. Pregnancy had no complications except minor gestational diabetes that did not require treatment and no adverse exposures were reported. The patient's NBS was performed in Illinois and was normal. She had been healthy until age 2 years 6 months when she presented to the ER with an episode of emesis and lethargy. She received IV fluids, recovered rapidly and was subsequently discharged, with no biochemical testing being performed at this time.

She represented at age 3 years with 2 days of emesis, tachypnea, and anion gap metabolic acidosis with pH 7.1 (Normal 7.35–7.45), bicarbonate 11.1 mmol/l (normal 20–28), elevated lactate 5.6 mmol/l (Normal <3), ketosis (beta-OH butyrate 5 mmol/l, normal <0.3) and elevated ammonia 90 mmol/l (normal <48).

Biochemical labs on the day of admission (see Table 1) demonstrated normal plasma amino acids, acylcarnitine profile with multiple

Table 1
Biochemical & molecular results.

	Age at presentation	Initial presentation ACP C3 (normal 0–870 mmol/l) C5-0H (normal 0–110 mmol/l)	Initial presentation organic acids elevations	HCLS sequencing & Del/Dup	Metabolically stable clinic follow-up ACP C3 (normal 0–870 mmol/l) C5-0H (normal 0–110 mmol/l)
Case 1	3 years 6 months	C0 – 30 C3 – 10,257 C5-OH – 540	• 3-OH butyric • 3-OH isovaleric • 3-OH propionic • 3-Methylcrotonylglycine • Acetoacetic • Lactic • Tiglylglycine	• Heterozygous c.1993C>T (p.R655X) in exon 8 • Novel heterozygous c.500A>C (p.Y167S) in exon 2	C0 – 42 C3 – 1017 C5-OH – 18
Case 2	24 months	CO – 42 C3 – 17,298 C5-OH – 2659	• 3-OH isovaleric • 3-OH propionic • 3-Methylcrotonylglycine • Lactic • Methyl citric	• Novel heterozygous c.1532A>T (p.N511I) in exon 6 • Novel heterozygous c.2078G>C (p.G693A) in exon 9	C0 – 44, 29, 13, 21, NR C3 – 26,560, 7719, 7690, 5366, 2570 C5-OH – 2267, 2446, 1922, 982, 700
Case 3	18 days	C3 – elevated C5-OH – elevated	• 3-OH isovaleric acid • 3-OH propionic • 3-Methylcrotonylglycine • Methylcitrate	• Novel heterozygous c.1693C>T (p.R565X) • Novel heterozygous c.977G>A (p.G326E)	C0 – 38, NR, NR, NR C3 – 3705, 960, 1520, 730 C5-OH – 411, 770, 360, 260
Case 4	4 months	C3 – elevated C5-OH – elevated	NR	NR - HCS enzyme in lymphoblasts showed no activity	C0 – 22 C3 – 602 C5-OH – 36
Case 5	5 months	NR	• 3-OH isovaleric • 3-Methylcrotonoylglycine	• Novel heterozygous c.1710C>G (p.N570K) • Novel heterozygous c.1519+5G>A	C0 – 24 C3 – 558 C5-OH – 68

Key: ACP–acylcarnitine profile, NR–no result available.