Molecular Genetics and Metabolism Reports 1 (2014) 176–183

Contents lists available at ScienceDirect

Molecular Genetics and Metabolism Reports

journal homepage: http://www.journals.elsevier.com/molecular-genetics-and-metabolism-reports/

Case Report

Lysinuric protein intolerance presenting with multiple fractures

Jennifer E. Posey [a], Lindsay C. Burrage [a,*], Marcus J. Miller [a], Pengfei Liu [a], Matthew T. Hardison [a], Sarah H. Elsea [a], Qin Sun [a], Yaping Yang [a], Alecia S. Willis [a], Alan E. Schlesinger [b], Carlos A. Bacino [a], Brendan H. Lee [a,c]

[a] Department of Molecular and Human Genetics, Baylor College of Medicine, One Baylor Plaza, Suite R814, Houston, TX 77030-3411, USA
[b] Department of Pediatric Radiology, Texas Children's Hospital, 6701 Fannin, Suite 470, Houston, TX 77030, USA
[c] Howard Hughes Medical Institute, Houston, TX, USA

ARTICLE INFO

Article history:
Received 17 December 2013
Received in revised form 19 March 2014
Accepted 19 March 2014
Available online 18 April 2014

Keywords:
Lysinuric protein intolerance
Osteoporosis
Bone fractures
SLC7A7

ABSTRACT

Lysinuric protein intolerance (LPI) is a rare autosomal recessive inborn error of metabolism caused by mutations in *SLC7A7*, which encodes a component of the dibasic amino acid transporter found in intestinal and renal tubular cells. Patients typically present with vomiting, diarrhea, irritability, failure to thrive, and symptomatic hyperammonemia after protein-rich meals. Long-term complications may include pulmonary alveolar proteinosis, renal disease, and osteoporosis. We present a 5-year-old male who was followed in our skeletal dysplasia clinic for 3 years for multiple fractures, idiopathic osteoporosis, and short stature in the absence of typical features of LPI. Whole exome sequencing performed to determine the etiology of the osteoporosis and speech delay identified a nonsense mutation in *SLC7A7*. Chromosome microarray analysis identified a deletion involving the second allele of the same gene, and biochemical analysis supported the diagnosis of LPI. Our patient's atypical presentation underscores the importance of maintaining a high index of suspicion for LPI in patients with unexplained fractures and idiopathic osteoporosis, even in the absence of clinical symptoms of hyperammonemia after protein rich meals or other

Abbreviations: CMA, chromosomal microarray analysis; LH3, lysyl hydroxylase 3; LPI, lysinuric protein intolerance; WES, whole exome sequencing.

* Corresponding author at: Baylor College of Medicine, Texas Children's Hospital Clinical Care Center, 6701 Fannin St. Suite 1560, Houston, TX 77030, USA.

E-mail addresses: jp042803@bcm.edu (J.E. Posey), burrage@bcm.edu (L.C. Burrage), marcus.miller@bcm.edu (M.J. Miller), pengfeil@bcm.edu (P. Liu), mhardison@ncpmr.com (M.T. Hardison), sarah.elsea@bcm.edua (S.H. Elsea), qsun@bcm.edu (Q. Sun), yapingy@bcm.edu (Y. Yang), willa36@labcorp.com (A.S. Willis), aeschles@texaschildrenshospital.org (A.E. Schlesinger), cbacino@bcm.edu (C.A. Bacino), blee@bcm.edu (B.H. Lee).

http://dx.doi.org/10.1016/j.ymgmr.2014.03.004

systemic features of classical LPI. This case further demonstrates the utility of whole exome sequencing in diagnosis of unusual presentations of rare disorders for which early intervention may modify the clinical course.

1. Introduction

Lysinuric protein intolerance (LPI, OMIM # 222700) is an autosomal recessive inborn error of metabolism associated with mutations in *SLC7A7*, the gene encoding solute carrier family 7 (amino acid transporter light chain), member 7 [1,2]. This protein binds to solute carrier family 3 (amino acid transporter heavy chain), member 2, to form the heterodimeric $y + L$ cationic amino acid transporter which transports arginine, lysine, and ornithine at the basolateral membrane of intestinal and renal tubular cells. In LPI, decreased transporter activity results in low plasma lysine, ornithine, and arginine. It has been proposed that patients manifest with clinical symptoms of urea cycle disorders because of deficiencies of urea cycle intermediates within the cellular compartment.

Classically, patients with LPI develop vomiting and diarrhea after introduction of protein-rich foods. Other presenting features may include failure to thrive, protein avoidance, and neurologic symptoms of hyperammonemia such as lethargy, abnormal behavior, and hypotonia after protein-rich meals. Rare presentations include systemic lupus erythematosus [3–5] or interstitial lung disease [6]. Long-term complications of LPI may include pulmonary alveolar proteinosis, dyslipidemia, hematologic abnormalities, macrophage activation syndrome, renal disease, and osteoporosis. Treatment involves dietary protein restriction and citrulline supplementation to replete urea cycle intermediates. Oral lysine supplementation and nitrogen-scavenging agents have also been used.

In the present report, we describe a 5-year-old male with short stature and speech delay who was followed for idiopathic osteoporosis and fragility fractures. Whole exome sequencing (WES) with chromosomal microarray analysis (CMA) revealed a diagnosis of LPI, demonstrating that idiopathic osteoporosis should raise suspicion for LPI.

2. Case report

2.1. Clinical description

The patient was born to non-consanguineous parents after an unremarkable 37-week gestation. His birth weight was 3.5 kg (25–50th centile), and length was 50.8 cm (50–75th centile). At 1.5 months of age, he exhibited irritability when weaned from breast milk to infant milk-based formula. These symptoms resolved with transition to another milk-based formula.

The patient had an otherwise uneventful course until 14 months of age, when he developed an intermittent limp and had periods in which he reverted from walking to crawling for a single day. At 22 months of age, he sustained a non-displaced right supracondylar fracture following a witnessed fall. At 24 months of age, he fractured his left distal humeral diaphysis also after a fall.

His fragility fractures prompted a skeletal genetic assessment at 26 months of age. Detailed pedigree analysis revealed that he was the only product of the union between his 22-year-old father (Mexican ancestry) and 19-year-old mother (Mexican/Salvadoran ancestry). There was no family history of fragility fractures, dental anomalies, blue sclera, or hearing loss. Physical examination demonstrated a height of 76.1 cm (less than 5th centile), a weight of 10.3 kg (just below 5th centile), and a head circumference of 49 cm (25th–50th centile). Examination was notable for a depressed nasal bridge, prominent cheeks, tented upper lip, mild limping gait, normal skin texture and elasticity, and absence of blue sclera or contractures. Initial investigations revealed mildly elevated phosphorus, normocytic anemia, and elevated alkaline phosphatase (Table 1). A radiographic skeletal survey suggested osteopenia but no wormian bones (Fig. 1). Bone age was consistent with chronological age.