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CASE REPORT

GALACTOSIALIDOSIS IN A NEWBORN WITH A NOVEL MUTATION IN THE *CTSA* GENE PRESENTING WITH TRANSIENT HYPERPARATHYROIDISM

Okulu E[1,*], Tunc G[1], Eminoglu T[2], Erdeve O[1], Atasay B[1], Arsan S[1]

***Corresponding Authors:** Emel Okulu, M.D., Department of Pediatrics, Division of Neonatology, Ankara University School of Medicine, Tip Fakultesi Street, 06620 Mamak, Ankara, Turkey. Tel: +90-312-595-6599. Fax: +90-312-319-1440. E-mail: emelokulu@gmail.com

ABSTRACT

Galactosialidosis is a lysosomal storage disease caused by deficiency of protective protein that is encoded by the cathepsin A (*CTSA*) gene localized on chromosome 20q13.1. Mutations of this gene are the cause of galactosialidosis that result in loss of function of protective protein. Galactosialidosis is an autosomal recessive inherited disease and has been divided into three subtypes based on age of onset and the severity of clinical manifestations. We report an early infantile form of galactosialidosis in a newborn with a novel mutation on the *CTSA* gene.

Keywords: Galactosialidosis; Hyperparathyroidism; Newborn

INTRODUCTION

Galactosialidosis is a lysosomal storage disease caused by deficiency of protective protein/cathepsin A (PPCA). This protein forms a complex with β-galactosidase and α-neuraminidase, and has a distinct protective and catalytic function. Protective protein/cathepsin A is encoded on chrosome 20, and mutations of this gene have been reported. Galactosialidosis is an autosomal recessive inherited disease and has been divided into three subtypes based on age of onset and the severity of clinical manifestations. All three forms of the disease are considered rare, and the most severe form is the early infantile form [1-4]. We herein report a new novel homozygous mutation for the cathepsin A (*CTSA*) gene in a Turkish newborn with galactosialidosis and transient hyperparathyroidism.

Case Report. The female newborn was born at term, by cesarean section because of fetal bradycardia, as the first child of healthy consanguineous parents, with a birth weight of 3050 g (50 percentile) a length of 50 cm (50-75 percentile) and a head circumference of 36 cm (90 percentile). Their first pregnancy had ended in abortion, and the second was terminated with in *utero exitus* at 26 weeks' gestation when cardiomegaly and polyhydroamnios had been detected.

The infant was admitted to the neonatal intensive care unit at another center with respiratory insufficiency on the first day of life. She had convulsions and was referred to our hospital on the fifth day of her life. Physical examination on admission showed a coarse face, hepatosplenomegaly, hypotonia, increased deep tendon reflexes of lower extremities (Figure 1). Laboratory tests revealed anemia [hemoglobin (Hb) 9.0 g/dL], neutropenia [white blood cell (WBC) count 3.920/mm^3], hypocalcemia (6.9 mg/dL; reference range 8.7-10.4 mg/dL), hypophosphatemia (3.48 mg/dL; reference range 4.5-6.5 mg/dL) and elevated alkaline phosphatase (ALP) levels (747.0 U/L; reference range 122.0-473.0 U/L). On further investigation, serum parathormone (PTH) was markedly elevated (676.2 pg/L; reference range 11.0-67.0 pg/L) whereas serum 25-hydroxyvitamin D [25(OH)D] was normal (31.0 ng/mL; reference range 20.0-60.0 ng/mL). Vitamin D_3 (1000.0 U ergocalciferol/day) and calcium (150.0 mg/kg/d) therapies were initiated orally. Although serum calcium and phosphate reached normal levels on following days, the alkaline phosphatase (ALP) level slightly increased (854.0 U/L), PTH remained high (but decreased) (301.0 pg/mL) and serum 25(OH)D was normal (23.3 ng/mL). Abdominal

[1] Department of Pediatrics, Division of Neonatology, Ankara University School of Medicine, Ankara, Turkey

[2] Department of Pediatrics, Division of Pediatric Metabolism, Ankara University School of Medicine, Ankara, Turkey

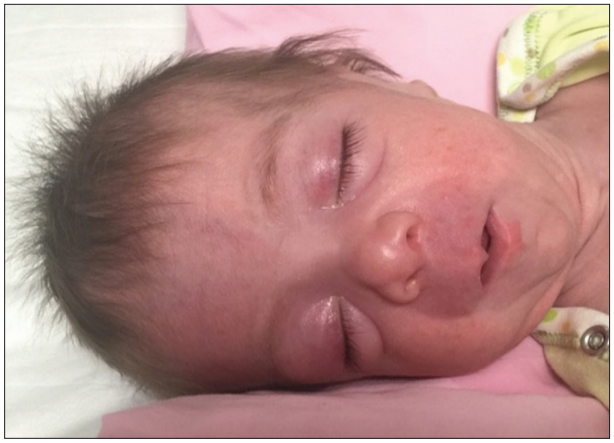

Figure 1. Coarse face of the patient.

ultrasonography demonstrated splenomegaly. An echocardiogram detected ventricular septal defect and pulmonary stenosis. Ophtalmological evaluation revealed albinoid appearance on the maculae.

Clinical and laboratory findings suggested the lysosomal storage disease. The β-galactosidase activity was as low as 5.62 nmoL/h/mL (normal range 85.4 ± 22.7). The activities of other lysosomal enzymes were normal. No mutation on the *GLB1* gene was detected. A homozygous mutation on the *CTSA* gene, p.F191Pfs*39 (c.569_570 delTT) was identified by genetic analysis. Secondary hyperparathyroidism in the infant was resolved biochemically at 5 months of age, but she suffered recurrent aspiration pneumonias and died at 8 months of age. An informed consent was obtained from the family.

DISCUSSION

Galactosialidosis is an autosomal recessive transmitted lysosomal storage disease due to a defect of the protective protein. The protective protein forms a complex with β-galactosidase and α-neuraminidase, and protects these enzymes against excessive proteolytic degradation. Several mutations of the gene encoding this protein have been reported [1-4]. We herein present a newborn infant case with galactosialidosis and transient hyperparathyroidism due to a novel mutation.

There are three phenotypic types of galactosialiodosis that are characterized by the age of onset and clinical symptoms. Early infantile onset is characterized by hydrops fetalis, oedema, organomegaly, coarse facial features, cardiomyopathy, ocular abnormalities, skeletal dysplasia, mental retardion and early death. The late infantile form presents with organomegaly, cardiac involvement and skeletal dysplasia without neurological symptoms. The juvenile/adult form is mainly characterized by neurological signs, skin involvement and long survival. The early infantile form is the most severe form, which may also appear as non immune hydrops fetalis. Specific therapy for galactosialidosis is not available at present [1,5,6]. Our case was the early infantile form presenting with coarse face, organomegaly, seizure, cardiac and ocular abnormalites, and her parents had consanguinity with a history of an in *utero exitus* with hydrops fetalis at 26 weeks' gestation.

The *CTSA* gene encoding the protective protein has been localized on chromosome 20q13.1. Mutations of this gene are the cause of galactosialidosis resulting in the loss of function of protective protein [1,3,7]. A novel homozygous *CTSA* gene mutation at p.F191Pfs*39 (c.569_570 delTT) that gave rise to a frameshift and premature termination codon was defined in our patient.

Primary and secondary hyperparathyroidism are both rare disorders in the neonatal period. Previous reports of neonates and infants with mucolipidosis type II and sialidosis type II have described radiological and biochemical abnormalities compatible with hyperparathyroidism [8-10]. It has been suggested that hyperparathyroidism in these patients can be related to impaired transplacental calcium transport or tissue hypersensitivity to circulating PTH [9-12]. However, the case presented here is the first patient with galactosialidosis exhibiting transient neonatal hyper-parathyroidism. The patient had increased serum PTH and ALP activity, decreased serum phosphorus and calcium, but normal 25(OH)D levels. Secondary hyperparathyroidism persisted in contrast to oral supplemental support up to 5 months of age.

We conclude that galactosialidosis is similar to mucopolysaccharidosis type IV, sialidosis, mucolipidosis type 2, GM1 gangliosidosis should be kept in mind in the presence of coarse facial features in a newborn with organomegaly and hyperparathyroidism. To define the relation on novel mutations and new manifestations, more genetic and clinical investigations of the disease are needed.

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Declaration of Interest. The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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