TJEM TURKISH JOURNAL OF ENDOCRINOLOGY AND METABOLISM

CASE REPORT
Turk J Endocrinol Metab. 2022;26(4):221-223

Novel Mutation in T-Cell Immune Regulator 1: A Case of Adult-Onset Autosomal Recessive Osteopetrosis

ABSTRACT

Osteopetrosis is a rare genetic disorder. Defective osteoclast function causes increased bone mass. It can occur in varying severity from mild forms that are asymptomatic to fatal forms. T-cell immune regulator 1 mutation has been associated with malignant forms of autosomal recessive osteopetrosis. Rarely, mild clinical forms associated with this mutation have been reported in the literature. We present a case of osteopetrosis with a mild clinical course presenting with a fracture, no hematologic and neurological pathologies, and a new T-cell immune regulator 1 mutation. We think that the clinician should keep in mind the differential diagnosis of osteopetrosis in patients presenting with skeletal anomalies, pathological fractures, and increased bone mineral density, even if they do not have neurological or hematological symptoms in early adulthood.

Keywords: Metabolic bone disease, osteopetrosis, pathological fracture

Introduction

Osteopetrosis is a rare genetic disorder. Defective osteoclast function causes increased bone mass.[1] The time of onset of symptoms and physical examination findings differ depending on the type of mutation. Depending on the severity and timing of clinical findings, the autosomal recessive form of osteopetrosis (ARO), which is called malignant, is very severe and often leads to death in early childhood.[1] Severe cases of infantile malignant osteopetrosis may present with bone enlargement, pathological fracture, pancytopenia, cranial neuropathies and hepatosplenomegaly, frequent infections, and bleeding problems.[1,2] In addition, macrocephaly, hepatosplenomegaly, nasal congestion due to sinus malformations, and dental abscess or osteomyelitis may occur.[1]

The symptom range of patients with moderate autosomal recessive osteopetrosis is highly variable. Its symptoms are similar to infantile autosomal recessive osteopetrosis but not as severe and do not appear as early as symptoms in the malignant form of autosomal recessive disease. This form usually becomes clinically significant during the first decade of life. These patients often have pathological fractures and progressive cranial nerve entrapment neuropathies.[3] There are 2 subclasses of autosomal dominant osteopetrosis and these patients are usually asymptomatic in adulthood. Type I autosomal dominant osteopetrosis typically does not have an increased risk of fracture and presents with isolated osteosclerotic thickening of the skull. Type II autosomal dominant osteopetrosis patients usually present with anemia, pathological fracture, or arthritis in adulthood.[3]

The genetic basis of the disease has largely been revealed: mutations in T-cell immune regulator 1 (TCIRG1), CLCN7, OSTM1, SNX10, and PLEKHM1 result in osteoclast-rich ARO, while mutations in TNFSF11 and TNFRSF11A result in osteoclast-poor ARO. In osteoclast-rich ARO, impaired osteoclast endosomal and lysosomal vesicle structure results in inability to resorb bone and mineralized cartilage. Autosomal recessive form of osteopetrosis occurs soon after birth and can be fatal if left untreated. The heterogeneity in the clinical presentation of the disease may cause confusion in the diagnosis.[4] In addition, in ARO disease, there is a loss of function mutation in carbonic anhydrase II (CAII), this mutation leads to the production of defective CAII protein. Therefore, renal tubular acidosis may also be seen in patients.[2,5]

Heterozygous dominant mutations of the CLCN7 gene are found in approximately 70% of patients with ADO type II osteopetrosis. As a result of this mutation, the mutant gene product interacts with the proteins encoded by the normal gene, preventing the function of functional proteins. In approximately 30% of the cases, no mutations are detected in the CLCN7

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Received: July 31, 2022
Accepted: September 26, 2022
Publication Date: December 1, 2022

Cite this article as: Arslan Cellat EG, Akarsu E, Sayiner ZA, Kördüğüm A. Novel mutation in T-cell immune regulator 1: A case of adult-onset autosomal recessive osteopetrosis. *Turk J Endocrinol Metab.* 2022;26(4):221-223.

DOI: 10.5152/tjem.2022.22092

gene sequences. In this case, it comes to mind that other genes play a role in the pathogenesis of this form of osteopetrosis.[2]

In this study, we present a case with a new TCIRG1 mutation associated with ARO diagnosed in adulthood. Written informed consent was obtained from the patient who participated in this study.

Case Presentation

A 26-year-old female patient had sclerotic changes in the bone during the implant surgery performed for a femoral fracture as a result of a fall. There was no consanguinity between the mother and father and there was no history of bone fracture in the family of the patient, who had 1 sibling. The patient, who had no history of chronic disease, had a fracture in the right femur as a result of falling while playing volleyball at the age of 16. The patient did not have a history of other trauma until 4 months ago. A left femur fracture developed as a result of falling while running (Figure 1). In the laboratory examination, serum calcium, phosphorus, albumin, parathyroid hormone, alkaline phosphatase values, and hemogram were in normal range. Parathyroid hormone was 22 ng/L (12-88), 25 hydroxyvitamin D (25(OH)D) was 26 µg/L, and phosphorus was 3.1 mg/dL (2.5-4.5).

Thickening of the skull bone was detected on x-ray examination. No impairment of hearing and vision was detected in the patient. In thorocalumbar computed tomography imaging, there were hyperdense areas at the level of the vertebral corpuscles suggesting an increase in diffuse sclerosis, there was increased sclerosis in bilateral sacroiliac joints and opposing joint surfaces. In bone scintigraphy, focal bone lesions with increased activity uptake were observed in the upper part of the right femoral diaphysis and the middle-upper part of the left femoral diaphysis (Figures 2 and 3). These were compatible with previous fractures. In addition, there was increased bone mineral density in dual-energy x-ray absorptiometry evaluation.

Z-Scores : L1/+5.0, L2/+5.1, L3/+4.1, L4/+3.5

T-Scores : L1/+5.0, L2/+5.0, L3/+4.1, L4/+3.4

Genetic analysis was performed for osteopetrosis. Whole exome sequencing was performed on genomic DNA obtained from affected individual. Human all exon kit next-generation sequencing was conducted with the Illumina Next-generation sequencing platform. In total, 21 285 genes were investigated. Detected variants were interpreted according to the guidelines of the American College of Medical Genetics and Genomics (ACMG). A c.2162T>A (Ile721Asn) homozygous variant was detected in the 18th exon of the TCIRG1 gene. A missense mutation was detected. This variant was associated with the ARO 1 (OMIM: 259700) phenotype and was interpreted as a variant of uncertain (or unknown) significance (VUS) according to the ACMG 2015 criteria.[6] Relatives of the patient were questioned

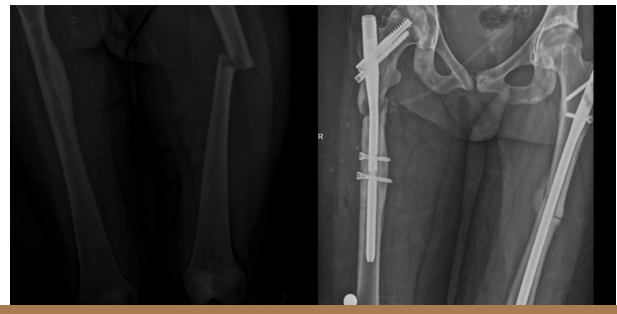

Figure 1. Bilateral non traumatic femur fractures on X-ray examination.

especially among her first- and second-degree relatives in terms of pathological fracture, but no one with a history of fracture was found.

Discussion

The TCIRG1 gene located on human chromosome 11q13.2 contains 22 exons, which encode the a3 subunit of V-ATPase composed of 830 amino acids. V-ATPase is a proton pump, and its function is to send hydrogen ions into the lysosome. When hydrogen ions are sent out from osteoclast, they acidify the cortical environment between the osteoclast and bone tissue and thus bone reabsorption increases.[7] Mutations in TCIRG1 are responsible for approximately 50% of all ARO cases. The vast majority of reported TCIRG1 mutations have been associated with the severe form of the disease.[8] A wide variety of mutations have been described and all these mutations have been linked with similar severe presentation.[9]

Here we present a novel TCIRG1 (c.2162T>A) mutation that causes a mild ARO phenotype. Our case is a case of osteopetrosis, diagnosed at the age of 26 when she presented with a fracture, without hematological and neurological pathologies, and only bone fracture. Our patient had a c.2162T>A (Ile721Asn) homozygous variant in the 18th exon of the TCIRG1 gene. When the ClinVar database was examined, a single case with the current mutation was reported on January 12, 2018, and its clinical significance was evaluated as uncertain.

Sobacchi et al[9] presented an 8-year-old case with mild phenotype to the literature in 2014 due to TCIRG1 mutation. This case was the first example of a mild phenotype due to recessive TCIRG1 mutations in the literature. They showed that the molecular mechanism underlying the mild severity of the case was the incomplete splicing defect: A small amount of correctly spliced mRNA from the mutated alleles was found to prevent the serious effect by producing a small amount of functional protein. Although the case was extremely rare, it did demonstrate that mild forms of TCIRG1-dependent ARO may

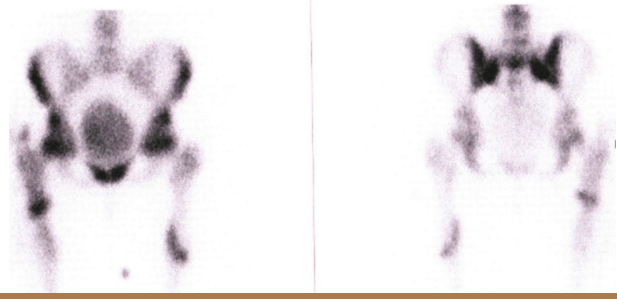

Figure 2. Focal bone lesions with increased activity uptake in bone scintigraphy examination.

MAIN POINTS

- Autosomal recessive osteopetrosis seen during infancy and adolescence tends to cause severe complications.
- It should be kept in mind that although rare, autosomal recessive osteopetrosis can also be seen in adulthood.
- Especially in the presence of pathological fractures and increased mineral bone density, osteopetrosis should be considered even in adults.

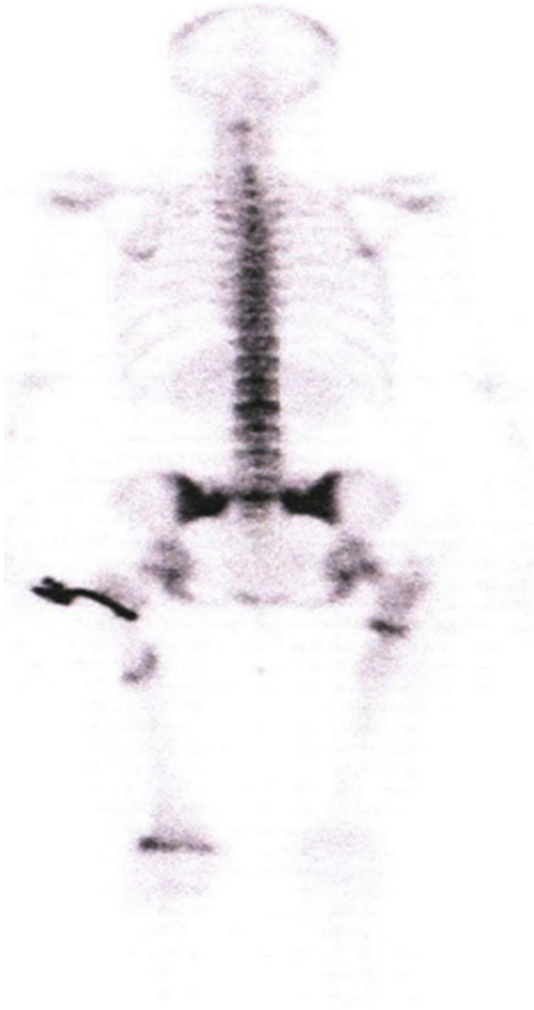

Figure 3. Whole body bone scintigraphy examination.

exist.[9] However, due to the young age of the case and the possibility of worsening of the disease symptoms with age, it will probably be possible to reach definite conclusions after a long follow-up.

Later, Zhang et al[10] presented the first case of TCIRG1-induced osteopetrosis with a mild clinical course observed in the Chinese population in 2017. He was a 24-year-old male patient from a related family, diagnosed based on radiological findings and had no neurological or hematological pathology. It was stated that a homozygous mutation for c.2236+6T>G was detected in TCIRG1 gene Intron 18 in the case. Also, Zirngibl et al[8] identified a novel TCIRG1 (c.G630A) mutation responsible for an unusually mild form of the disease in 2019. Current treatment of osteopetrosis includes fracture repair and stabilization, lifestyle modification, taking precautions to prevent falling high-dose vitamin D supplementation, blood transfusions when necessary, and treatments for the pathology of underlying genetic abnormalities. In severe forms of ARO, allogeneic hematopoietic stem cell transplantation may be recommended.[11]

In this case, we wanted to present the clinical features of a patient with TCIRG1 (c.2162T>A) missense mutation to the literature. In this case, we wanted to draw attention to the fact that the TCIRG1 mutation may rarely have mild forms, except for its association with infantile malignant osteopetrosis. Lifestyle changes and vitamin D supplementation were recommended.

In conclusion, we think that the clinician should keep in mind the differential diagnosis of osteopetrosis in patients who present with skeletal abnormalities, pathological fractures, and increased bone mineral density, even if they do not have neurological or hematological symptoms in early adulthood.

Informed Consent: Written informed consent was obtained from the patient who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – Z.AS., E.A; Design – Z.AS., E.A.; Supervision – Z.AS., E.A, G.E.A.C.; Data Collection and/or Processing – Z.AS., E.A, G.E.A.C. A.K.; Analysis and/or Interpretation – Z.AS., E.A, G.E.A.C.; Literature Review – Z.AS., E.A, G.E.A.C.; Writing – Z.A.S.; G.E.A.C.; Critical Review – Z.AS., E.A, G.E.A.C.; Materials – Z.AS., E.A, G.E.A.C.

Declaration of Interests: The authors declare that they have no competing interest.

Funding: This study received no funding.

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