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Case report

Mild early course of osteogenesis imperfecta type XIV - a case report

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Summary

Introduction. Mutations in TMEM38B gene, which encodes the endoplasmatic reticulum membrane trimeric intracellular cation channel (TRIC) type B, cause osteogenesis imperfecta type XIV. So far there have been only four different pathogenic variants reported in TMEM38B. Clinical features of osteogenesis imperfecta type XIV described in scarce reports include osteopenia, femoral bowing, low trauma fractures, scoliosis, muscular hypotonia and cardiac pathology.

Case report. A 2-month-old male infant was referred to a clinical geneticist office due to bone deformities. The shortening of the limbs was observed during the prenatal ultrasound examination in seventh month of pregnancy. Prenatal cytogenetic analysis was performed from a fetal blood sample and showed normal findings. Neither fetal fractures were observed prenatally, nor any occurred during vaginal labor. During the first clinical exam by the clinical geneticist, discrete rhizomelia and bluish sclerae were observed. Due to the suspicion of skeletal dysplasia, indication for genetic analysis was established. Next generation sequencing panel for skeletal dysplasia showed homozygous deletion of exons 1 and 2 in the TMEM38B gene, confirming osteogenesis imperfecta type XIV. At the follow-up visit performed at 12 months of age, no fractures were reported. Several skeletal deformities were observable: discrete frontal bossing, rhizomelic upper extremities, slightly bowed thighs and shins. The infant achieved normal psychomotor development. A radiographic examination showed bowing of long bones of the lower extremities, without significant osteopenia.

Conclusion. Absence of early fractures is rare in osteogenesis imperfecta type XIV. Relatively mild clinical features of our patient therefore contribute to the understanding of the phenotype of osteogenesis imperfecta type XIV and its relation to the genotype.

Key words: skeletal dysplasia, TMEM38B gene, deletion

Introduction

Osteogenesis imperfecta represents a group of heritable disorders of connective tissue with an estimated prevalence of 1:10.000 to 1:20.000 live births [1]. Main clinical features of osteogenesis imperfecta include bone fragility, recurrent fractures, bone deformities, dentinogenesis imperfecta (DI) and growth deficiency [1]. Also, different extra-skeletal manifestations could be found in these patients, such as blue sclera, hearing loss, joint hypermobility and cardiovascular complications [2]. As of 2021, 20 types of osteogenesis imperfecta have been defined [3]. Types I-IV are autosomal dominant disorders caused by defects in the COL1A1 and COL1A2 genes that encode type I collagen and account for about 75–85% of cases [4, 5]. Rare forms of osteogenesis imperfecta (types V-XXI) are caused by mutations in genes associated with post-translational modification of type I collagen and are mostly inherited in autosomal recessive manner, with exceptions of type V (autosomal dominant) and type XIX (X-linked recessive) [5]. Mutations in TMEM38B gene, which encodes the endoplasmatic reticulum membrane trimeric intracellular cation channel (TRIC) type B, cause osteogenesis imperfecta type XIV [6]. TRIC-B channel is involved in the release of calcium ions from intracellular stores [7, 8]. So far there have been four different pathogenic variants reported in TMEM38B: a deletion in exon 4 found in Saudi Arabians and Israeli Bedouins [6, 9], a point mutations in exon 4 and intron 3 found in Chinese children [10], and a deletion of exons 1 to 2 found in an Albanian child [11]. Clinical features of osteogenesis imperfecta type XIV described in scarce reports include osteopenia, femoral bowing, low trauma fractures, scoliosis, muscular hypotonia and cardiac pathology [6, 9–12].

The aim of our report is to describe a patient with mild phenotype of extremely rare form of osteogenesis imperfecta,

Case report

A 2-month-old male infant was referred to a clinical geneticist office due to bone deformities. The shortening of the limbs was observed during the prenatal ultrasound examination in the seventh month of pregnancy. Prenatal cytogenetic analysis was performed from a fetal blood sample and showed normal finding. No fetal fractures were observed prenatally, nor any occurred during vaginal labor. Body weight at birth was 2800 g, body length was 48 cm, while Apgar score was 9/10. Hearing screening showed a normal finding.

During the first clinical exam by the clinical geneticist, discrete rhizomelia and bluish sclerae were observed. Due to the suspicion of skeletal dysplasia, indication for genetic analysis was established. Family history was negative for skeletal disorders (short stature, deformities or recurrent fractures). Consanguinity was negated by the parents, but could not be excluded due to same ethnic background in relatively small community.

Next generation sequencing panel for skeletal dysplasia was performed at CeGaT laboratory in Tubingen (Germany), and showed presence of homozygous deletion of exons 1 and 2 in the TMEM38B gene (NM_018112.3(TMEM38B):c.454+279_543-5092delinsAATTAAGGTATA). This finding confirmed the diagnosis of osteogenesis imperfecta type XIV.

At the follow-up visit performed at 12 months of age, no fractures were reported. Several skeletal deformities were observable: discrete frontal bossing, rhizomelic upper extremities, slightly bowed thighs and shins. The infant achieved normal psychomotor development. Findings in other organ systems were normal, apart from blue sclera.

A radiographic examination of the upper extremities, spine, pelvis and lower extremities was performed, which showed bowing of long bones of the legs (Figure 1). All bones were of preserved continuity, with no signs

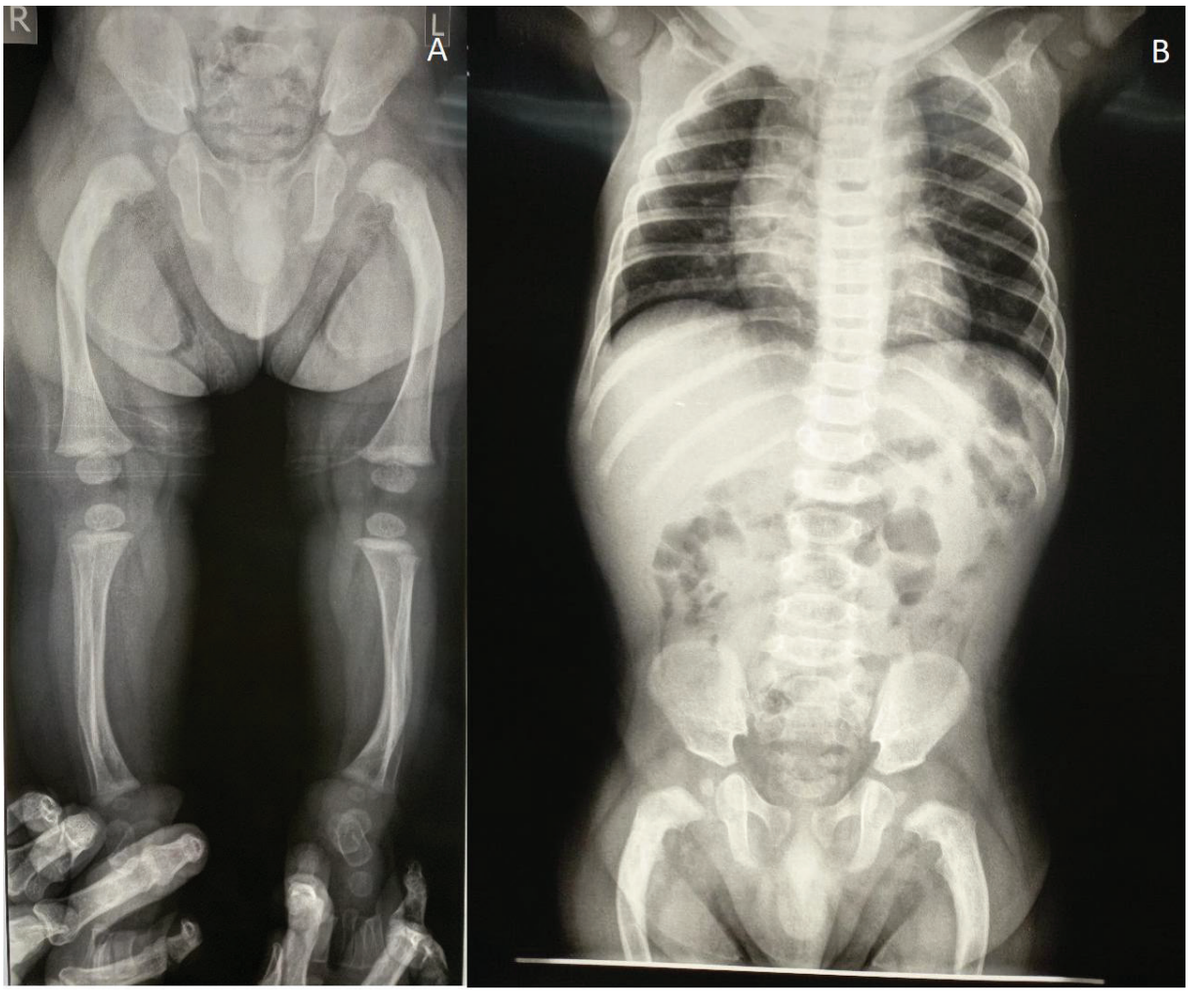

Figure 1. X-ray findings in a male infant with osteogenesis imperfecta type XIV: A. bowed long bones of the legs, B. Femoral bowing without other significant skeletal abnormalities

of fresh or old fractures. Also, radiographs did not show significant demineralization of the skeleton.

Discussion

When compared to the only osteogenesis imperfecta type XIV patient previously reported with the same genotype (homozygous deletion of exons 1 and 2 in TMEM38B), our patient has a milder clinical picture [11]. Namely, a girl of Albanian origin reported by Rubinato et al. had seven fractures already at birth, while our patient did not have any conatal fractures. Also, they did not occur during first year of life. Additionally, our patient did not show significantly reduced bone mineralization. A mild conductive hearing loss that was observed in a previously reported patient with the same genotype was absent in our patient. Additionally, in this Albanian girl bone deformities were not recorded, while the infant boy we are reporting herein has bowed limbs. It is important to note that the girl was diagnosed at the age of 10, and that the examination was preceded by surgical interventions due to numerous fractures, as well as bisphosphonate therapy. Also, fetal ultrasound exam was missing in case described by Rubinato et al. Similarities between these two patients are the normal psychomotor development and absence of cardiac involvement. Both patients

homozygous for deletions of exons 1 and 2 in TMEM38B are of Albanian ethnic background and come from rural communities with possible consanguinity. Differences in fracture incidence between patient reported by Rubinato et al. and our patient could be attributed to the influence of an unknown modifier gene. Data on labor circumstances for the patient from literature [11] are not available, and presence of several fractures could be caused by prolonged vaginal labor or abnormal birth presentation. In our patient no fractures were recorded at birth despite the vaginal labor.

Two patients carrying the aforementioned deletion in heterozygous state have been reported to have British-American and British-German heritage [12]. These patients also displayed normal motor and cognitive development.

Lack of cardiac involvement in patients homozygous for deletions of exons 1 and 2 in TMEM38B could be of importance since different cardiac abnormalities including congenital septal defects, tricuspid regurgitation, non-obstructive hypertrophic cardiomyopathy and early myocardial infarction have been described in more than a third of osteogenesis imperfecta type XIV patients reported by Webb et al. [12].

Blue sclerae are well known sign of inherited connective tissue disorders and one of the hallmarks of osteogenesis imperfecta. Blue sclera was noted at the first clinical geneticist examination of our patient at two months of age. However, this clinical sign is not universal in osteogenesis imperfecta type XIV since several authors report majority of their patients lacking the bluish sclera appearance (China, Israel). Furthermore, the patient with the same homozygous deletion of exons 1 and 2 did not show blue sclera [11]. This difference in comparison to the patient we report could be related to the age of first detailed evaluation.

Low trauma fractures during the first two years of age have been verified in more than 90% of the reported patients with osteogenesis imperfecta type XIV [6, 9–12]. Lack of fractures during infancy observed in our patient seems to be uncommon in this type of osteogenesis imperfecta. However, at least one reported patient homozygous for mutations in TMEM38B remained asymptomatic [12].

Prenatal ultrasound findings were the very first sign of osteogenesis imperfecta type XIV in our patient. Short and bowed extremities, decreased mineralization and prenatal fractures have been reported as the hallmarks of ultrasound exam in fetuses with early onset types of osteogenesis imperfecta [13, 14]. Therefore, such findings of fetal ultrasound screening should prompt genetic evaluation due to high risk of skeletal dysplasia.

Genetic tool employed postnatally in the diagnostics of our patient was the panel for osteogenesis imperfecta and related skeletal dysplasias with decreased bone density provided by CeGaT GmbH, Tübingen, Germany, that sequenced 30 genes of interest, with turnaround time of less than four weeks. A recent study showed whole exome sequencing established a genetic diagnosis in 15.4% of fetuses with skeletal dysplasia. The same study showed that diagnostic yield of prenatal WES was higher for skeletal dysplasia when compared to other indications. Other studies showed even greater benefit from whole exome sequencing employed both in prenatal and postnatal setting, especially if targeted gene panel for skeletal disorders was used [15].

Conclusion

Clinical and radiographic features of our patient contribute to the understanding of the phenotype of very rare type of osteogenesis imperfecta and its relation to the genotype. Early genetic diagnosis provides possibility to plan specific follow-up, treatment strategy and adequate genetic counseling.

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References:

1. Marini JC, Dang Do AN. Osteogenesis Imperfecta. In: Feingold KR, Anawalt B, Boyce A, et al., editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000. [Updated 2020 Jul 26, cited 2022 Aug 5]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK279109/
2. Rossi V, Lee B, Marom R. Osteogenesis imperfecta: advancements in genetics and treatment. Curr Opin Pediatr 2019;31(6):708–15.
3. Deguchi M, Tsuji S, Katsura D, Kasahara K, Kimura F, Murakami T. Current Overview of Osteogenesis Imperfecta. Medicina (Kaunas) 2021;57(5):464.
4. Forlino A, Cabral WA, Barnes AM, Marini JC. New perspectives on osteogenesis imperfecta. Nat Rev Endocrinol 2011;7(9):540–57.
5. Marom R, Rabenhorst BM, Morello R. Osteogenesis imperfecta: an update on clinical features and therapies. Eur J Endocrinol 2020;183(4):R95–R106.
6. Shaheen R, Alazami AM, Alshammari MJ, Faqeih E, Alhashmi N, Mousa N, et al. Study of autosomal recessive osteogenesis imperfecta in Arabia reveals a novel locus defined by TMEM38B mutation. J Med Genet 2012;49(10):630–5.
7. Zhou X, Lin P, Yamazaki D, Park KH, Komazaki S, Chen SR, et al. Trimeric intracellular cation channels and sarcoplasmic/endoplasmic reticulum calcium homeostasis. Circ Res 2014;114(4):706–16.
8. Marini JC, Reich A, Smith SM. Osteogenesis imperfecta due to mutations in non-collagenous genes: lessons in the biology of bone formation. Curr Opin Pediatr 2014;26(4):500–7.
9. Volodarsky M, Markus B, Cohen I, Staretz-Chacham O, Flusser H, Landau D, et al. A deletion mutation in TMEM38B associated with autosomal recessive osteogenesis imperfecta. Hum Mutat 2013;34(4):582–6.
10. Lv F, Xu XJ, Wang JY, Liu Y, Asan, Wang JW, et al. Two novel mutations in TMEM38B result in rare autosomal recessive osteogenesis imperfecta. J Hum Genet 2016;61(6):539–45.
11. Rubinato E, Morgan A, D'Eustacchio A, Pecile V, Gortani G, Gasparini P, et al. A novel deletion mutation involving TMEM38B in a patient with autosomal recessive osteogenesis imperfecta. Gene 2014;545(2):290–2.
12. Webb EA, Balasubramanian M, Fratzl-Zelman N, Cabral WA, Titheradge H, Alsaedi A, et al. Phenotypic Spectrum in Osteogenesis Imperfecta Due to Mutations in TMEM38B: Unraveling a Complex Cellular Defect. J Clin Endocrinol Metab 2017;102(6):2019–28.
13. Tsai PY, Chang CH, Yu CH, Cheng YC, Chang FM. Three-dimensional ultrasound in the prenatal diagnosis of osteogenesis imperfecta. Taiwan J Obstet Gynecol 2012;51(3):387–92.
14. Pajkrt E, Chitty LS. A sonographic approach to the prenatal diagnosis of skeletal dysplasias. Prenat Diagn 2019;39(9):701–19.
15. Zhang L, Pan L, Teng Y, Liang D, Li Z, Wu L. Molecular diagnosis for 55 fetuses with skeletal dysplasias by whole-exome sequencing: A retrospective cohort study. Clin Genet 2021;100(2):219–26.

Blagi rani tok osteogenesis imperfecta tip XIV – prikaz slučaja

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Uvod. Mutacije gena TMEM38B koji kodira trimerički intraćelijski katjonski protein tip B (TRIC) endoplazmatskog retikuluma, uzrokuju autozomno recesivnu osteogenesis imperfecta tip XIV (osteogenesis imperfecta tip XIV). Do sada su opisane svega četiri patogene varijante u navedenom genu. Kliničke karakteristike u malobrojnim radovima o osteogenesis imperfecta tip XIV uključuju osteopeniju, zakrivljenost femura, patološke frakture, skoliozu, mišićnu hipotoniju i promene na srcu.

Prikaz slučaja. Dvomesečno muško odojče je upućeno na pregled kliničkog genetičara zbog deformiteta kostiju. Skraćenje ekstremiteta je bilo vidljivo prilikom prenatalnog ultrazvučnog pregleda u sedmom mesecu gestacije. Prenatalna citogenetička analiza je bila uredna. Nije bilo fetalnih fraktura, niti su se dogodile tokom porođaja. Pri prvom pregledu kliničkog genetičara registruju se diskretna rizomelija i plavičasta prebojenost beonjača. Zbog sumnje na koštanu displaziju sprovedena je genetička analiza panela gena sekvencioniranjem nove generacije i utvrđena je homozigotna delecija egzona 1 i 2 u TMEM38B genu, čime je postavljena dijagnoza osteogenesis imperfecta tip XIV. Na kontrolnom pregledu u uzrastu od 12 meseci, dobija se podatak da nije bilo fraktura. Uočavaju se diskretni koštani deformiteti: naglašeni frontalni tuberi, rizomelični gornji ekstremiteti i lako zakrivljene natkolenice i potkolenice. Dete ima uredan psihomotorni razvoj. Radiografski nalaz je pokazao zakrivljenost kostiju nogu bez značajne osteopenije.

Zaključak. Odsustvo patoloških preloma u ranom uzrastu se susreće kod većine pacijenata sa osteogenesis imperfecta tip XIV. Stoga, blaži klinički tok kod našeg pacijenta doprinosi boljem razumevanju fenotipa ove retke bolesti i njegovog odnosa prema genotipu.

Ključne reči: skeletna displazija, TMEM38B gen, delecija