

Case Report

A Drakou et al. Ann Case Report 14: 508.

DOI: 10.29011/2574-7754.100508

Osteogenesis Imperfecta (OI) Type 2-B or 3: Investigating the Survivorship of a Patient

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Citation: Drakou A, Boutzios G, Koutsogeorgopoulou L, Tzioufas A (2020) Osteogenesis Imperfecta (OI) Type 2-B or 3: Investigating the Survivorship of a Patient. Ann Case Report 14: 508. DOI: 10.29011/2574-7754.100508

Received Date: 19 October 2020; **Accepted Date:** 22 October 2020; **Published Date:** 28 October 2020

Abstract

We present a case of osteogenesis imperfecta where the exact molecular diagnosis was made at 36 years. Based on the severity of the molecular diagnoses obtained in retrospect, the pregnancy would have been terminated. However, our patient survived and thrived in her adult life. The case demonstrates that genotype alone can not predict the phenotype of the patient. Genetic counseling plays a vital role in these situations to integrate prenatal ultrasound and molecular findings.

Case

A 36-year-old woman sought consultation for low bone density. She reported a history of multiple spontaneous skeletal fractures since the 8th day of birth (humeral, rib, femoral and hip) as well as severe scoliosis, poor hearing, blue sclera, and dentinogenesis imperfecta. She is a graduate of the School of Sociology and a current student at the Art School of Acting. To this point, she was treated based on the clinical manifestations according to Sillence classification of Osteogenesis Imperfecta (OI), type 3 (progressively deforming OI) [1]. There was no family history for bone fractures. The patient was mobilizing both with a cane and a wheelchair alternatively. Radiographic investigation revealed severe malformations, some of which had been treated surgically (Figure 1A and B).

Bone mass density (L1-L4) was measured 0.62 g/cm³ with a Z-score of -3.8. Radiographic investigation revealed severe malformations, some of which had been treated surgically (Figure 1A and B). Laboratory tests were all within normal limits. We decided to proceed with genetic testing for OI in order to have a precise molecular diagnosis. The testing revealed a heterogenic mutation with autosomal dominant inheritance in the COL1A2 gene, chromosome 7, exon 46 c.3034GC>A:p. (Gly1012Ser), a defect compatible with OI type 2 as well as OI type 3. Osteogenesis Imperfecta Type 2 is generally considered lethal. According to the provided pedigree, the asymptomatic parents are non-consanguineous, and she has no affected sibling; a de novo gene

mutation was suspected.



Figure 1: Standing Anteroposterior radiograph of the pelvis (A). Anteroposterior radiograph of the left tibia (B).

Discussion

Since 1984 it has been postulated that some babies have a phenotype which is a little less severe with fewer rib fractures (OI type 2-B), and as such, they can show overlap with OI type 3 [2,3]. Additionally, the OI type 3 phenotype does not necessarily equate with progressively deforming OI, and probably only a proportion

of cases with severe deformity and normal sclerae have OI type 3. The distinction between these patients and those with a milder form of perinatally lethal OI type 2 might be difficult [4]. OI types 2 and 3 are dominantly inherited, and most cases are due to heterozygous COL1A1/2 mutations that result in substitutions for glycine. In general, glycine substitutions near the carboxyl-terminal end appear to result in the severest phenotype [5].

Q1. How significant can be a possible misclassification of OI patients prenatal or post-natal?

Q2. How vital is phenotyping of individuals compared to molecular genetic diagnosing, and will molecular techniques such as Next-Generation Sequencing (NGS) decrease the need for phenotyping?

In developed countries, most children's prenatal diagnosis with OI type 2 (by ultrasound and DNA analysis) results in pregnancy termination. Therefore, it becomes imperative to make a precise intrauterine diagnosis of OI type 2 to suggest pregnancy termination [6]. In cases where OI type 2 overlaps with OI type 3, it is challenging to make the diagnosis based solely on the genetic diagnosis. Intrauterine sonographic findings predicting OI's lethality include thoracic circumference below the 5th percentile, abnormal thoracic/abdominal circumference ratio, cardiothoracic ratio, and a markedly sagittal anteroposterior diameter of the thorax.

For our patient, thirty-six years earlier, neither intrauterine sonographic investigation was carried out prenatally nor genetic testing.

Conclusion

Obtaining a precise diagnosis of OI allows expanding our understanding of its molecular landscape, potentially leading to improved personalized care in the future. Acknowledgment of the Phenotypic variability and molecular overlapping of OI types 2 and 3 is of paramount importance in decision making (i.e., termination of pregnancy). This case emphasizes the importance of phenotyping to diagnose, classify, and assess OI's severity because if left to NGS only, our patient would have never come to life.

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