Abstract Title: Syndromic osteogenesis imperfecta with suboptimal response to bisphosphonate caused by WNT1 mutation

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Introduction

Osteogenesis imperfect (OI) is a heritable disorder characterized by recurrent fractures and osteoporosis. Severity varies and traditionally classified in four types according to the expanded Sillence classification. Majority of the OI was caused by pathogenic mutation in COL1A1, COL1A2, leading to autosomal dominant disease. With the advance in genomic technology, mutations were identified in the CRTAP, FKBP10, LEPRE1, PLOD2, PPIB, SERPINF1, SERPINH1, SP7, WNT1, BMP1, TMEM38B and PLS3 genes, accounting for the recessive OI and x-linked OI. We here reported a boy with recurrent fractures, skeletal deformity, short stature, global delay and dysmorphism, who harboured compound heterozygous mutations in WNT1 gene.

Case Report

A full term baby boy born from non consanguineous couple presented with multiple fractures over the long bones on day 4 of life. Antenatal history was unremarkable, non invasive prenatal testing was unremarkable. His birth weight was 3.13kg. Family history was unrevealing. He suffered from recurrent fractures more than 10 times, involving 4 limbs, clavicles and sacrum. Serial X ray showed osteopenia. Blood for calcium, phosphate level were normal. Diagnosis of osteogenesis imperfecta was made and monthly pamidronate was started since 10 months old. However, no significant improvement noted. Apart from skeletal abnormalities, he had an episode of cardiac arrest in neonatal period and found to have supraventricular tachycardiac and wolf-parkinson-white syndrome, and stabilized with propranolol afterwards. He had severe global developmental delay. Physical examination at 17 months old in genetic clinic showed macrocephaly, with head circumference of 51cm (>97%) BW 9.8kg (10-25%), Ht 71cm(2cm<3%). MRI showed no structural brain malformation. He was hyperteloric with downslanting palpebral fissure. He had upsweeping headline and mildly hirsutic. He had general hypotonia, deformed long bone especially the femurs. His teeth showed discoloration and compatible with dentinogenesis imperfecta. Hearing assessment was unremarkable. He still had recurrent fractures about 4 to 5 times per years despite pamidronate infusion. Genetic test done for COL1A1, COL1A2, IFITM5 were negative. In view of features of syndromic OI, microarray and exome sequencing were performed. Whole exome sequencing revealed biallelic variants in WNT1 gene. A heterozygous missense variant in NM_005430.3(WNT1):c.385G>A p.(Ala129Thr) was detected. This variant was reported in the literature to be associated with osteogenesis imperfect (Liu et al., 2016). It is not present in ClinVar, ExAC but in gnomAD [ALL: 0.0016%-EAS: 0.023%]. It is classified as likely pathogenic by ACMG guideline [PS1,PM2]. Another heterozygous missense variant NM_005430.3(WNT1):c.937C>T p.(Arg313Cys) was detected. This variant was not reported in the literature, ClinVar, ExAC, gnomAD and dbSNP database. It is located at the Wnt-1 protein domain that is weakly conserved at nucleotide level and highly conserved at amino acid level. This variant was classified as variant of unclear significance. Parental study showed the two variants are in-trans. Therefore, diagnosis of WNT1 related osteogenesis imperfecta, type XV was made. Pamidronate was withhold due to lack of beneficial effect in WNT1 related OI. The latest assessment was at the age of five and he was on vitamin D and calcium supplement. He attended special child care center, and still unable to walk with no meaningful words. He had astigmatism and hypermetropia with divergent squint cared by ophthalmologist. He had snoring and pending assessment for obstructive sleep apnoea.

Conclusions / Learning Points

Up to our current knowledge, there are 18 types of OI reported in the literatures (Marini et al., 2020). The clinical features of WNT1 related OI includes moderate to severe bone fragility, involving mainly long bone and vertebral bodies. Intellectual disability, brain anomalies and ptosis were commonly observed in some patients (Kuptanon et al., 2018). Molecular diagnosis in OI patients is important, not only for genetic counselling, but also have treatment implications. The use of bisphosphonate in WNT1 related OI is still controversial, studies showed inconsistent results (Pamolo et al., 2014; Rakitie et al., 2017). Further studies on pharmacological treatment of WNT1 related OI need to be conducted before any recommendation or protocol to be implemented.