An infant with Opsismodysplasia and Dilated Cardiomyopathy: A coincidence or an association ?

Muneer Almutairi[1], Mohammed AlMannai[2]
[1]Pediatric Neurology Department, National Neurosciences Institute, King Fahad Medical City - Riyadh (Saudi Arabia).
[2] Section of Medical Genetics, Children's Specialized Hospital, King Fahad Medical City - Riyadh (Saudi Arabia).

Background

Opsismodysplasia (OPSMD: OMIM# 258480) is an extremely rare and severe autosomal recessive skeletal dysplasia that is under the category of severe spondylodysplastic dysplasias. It is characterized by delayed bone maturation and affected patients are identified by a peculiar cranio-facio-skeletal dysmorphism in the form of wide anterior fontanelle, depressed nasal bridge, anteverted nares, and short limbs and feet. Radiologically, they are characterised by severe platyspondyly, squared metacarpals, delayed skeletal ossification, and metaphysical cupping (2,3).

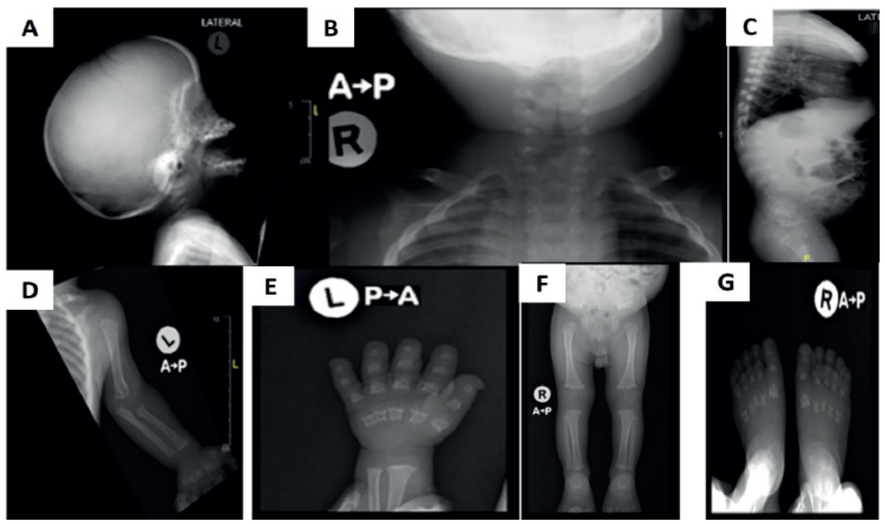
Methods

We present the clinical and radiological features of a 14-month-old boy with a homozygous, likely pathogenic variant in INPPL1 gene c.2627dup (p.Pro977Thrfs*7) consistent with the diagnosis of OPSMD. He also has dilated cardiomyopathy.
To our knowledge Cardiac involvement is an uncommonly reported features of OPSMD.

Case Presentation

A 14 months old boy born full term after uneventful pregnancy by Caesarean section due to face presentation. He developed respiratory distress and found to have congestive heart failure for which he was admitted to NICU for 20 days on mechanical ventilation and required Anti-failure medications.
He subsequently developed gross motor milestones delay with an otherwise appropriate-for-age developmental milestones.
He is the second child of consanguineous parents with unremarkable family history.

On examination, all of his growth parameters lied below 3rd centile. His facial features were coarse, with micromelic upper and lower limbs, in addition to a short trunk. His left eye examination showed a pendular nystagmus in association with generalized truncal and appendicular hypotonia on complete neurological examination. His workup is remarkable for skeletal survey (Fig A-G) in consistence with rhzomelic skeletal dysplasia, high urinary phosphate, Creatine and urinary phosphate/creatinine ratio.Skeletal dysplasia genes panel was sent, and came to be positive for a homozygous likely pathogenic variant in INPPL1 c.2627Dup (p.Pro977Thrfs*7). Parents were carriers for the same variant. We obtained a DCM panel on our patient and he was found to have variants of unknown significance in TTN (c.89711G>A (p.Arg29904His) and c.97099C>T (p.Arg32367Cys)) and MYH6 (c.824T>A (p.IIe275Asn) and c.4505 G>A (p.Arg1502Gln)). The father is a carrier of the two TTN variants, while the mother is a carrier of the two MYH6 variants found in the proband.



Discussion

INPPL1 is highly expressed in skeletal & cardiac muscles (2), and there has been only one reported case of cardiac involvement in patients presenting with OPSMD (4). Furthermore, having variants of unknown sigfance in MYH6 & TTN, and their carrier states in the proband's parents make these variants less likely to be disease causing, but actually do not completely rule out the pathogenicity of these variants given the incomplete penetrance. Also, DCM is not always a monogenic disorder. Therefore, it is not clear if DCM in our patient is a coincidence or a new association with OPSMD, as the full spectrum of OPSMD is yet to be fully understood, especially with a previously reported case of DCM in an OPSMD patient.

Conclusion

Opsismodysplasia is an uncommon form of skeletal dysplasia that should be suspected in the context of short stature with characteristic radiological features. Furthermore, cardiac involvement is a potential phenotypic feature within the spectrum of OPSMD clinical presentations.
Up to now, no definitive therapeutic measure is available, and hence preventive measures are essential in the management of families with affected members.

Acknowledgment

None

Bibliographic References

1. OMIM.
2. Cho SY, Jin DK. Guidelines for genetic skeletal dysplasias for pediatricians. Ann Pediatr Endocrinol Metab 2015;20(4):187–91..
3. Huber C, Faqeih EA, Bartholdi D, Bole-Feysot C, Borochowitz Z, Cavalcanti DP, et al. Exome sequencing identifies INPPL1 mutations as a cause of opsismodysplasia. Am J Hum Genet 2013;92(1):1449..
4. Below JE, Earl DL, Shively KM, McMillin MJ, Smith JD, Turner EH, et al. Whole-genome analysis reveals that mutations in inositol polyphosphate phosphatase-like 1 cause opsismodysplasia. Am J Hum Genet 2013;92(1):137–43..