Camurati-Engelmann Disease: A Case Report

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Abstract

Among the genetic causes of osteosclerosis, Camurati-Engelmann disease is a rare entity. Bhadada et al. have recently reported the first Indian family with genetic confirmation of Camurati- Engelmann Disease (CED) (Bhadada et al., 2014). Here we describe another case of CED with molecular confirmation.

Case Report

A 33-years-old lady presented with gradually progressive pain over both lower limbs since 7 years of age. She had mild headache and gave a history of delayed puberty. There was no significant family history. She was on multiple non-steroidal anti-inflammatory medications without much relief for her symptoms. Positive examination findings included proptosis (Figure 1), a waddling gait and mixed hearing loss in the right ear. Her hemoglobin level was 10.9g% (11-15gm/dl in females), alkaline phosphatase was 240 IU/L (40-125 IU/L) and CPK was 51mg/dl (<145 mg/dl in females). Radiographs revealed bilateral symmetrical hyperostosis of the diaphyses of long bones (Figure 2) with involvement of the skull (Figure 3a & 3b). There was intense tracer activity observed in the skull and long bones in the PET scan. Based on the clinical, radiological and PET scan findings, a diagnosis of Camurati Engelmann was suspected and the mutation analysis was attempted by direct sequencing of all the *TGFβ1* encoding exons which showed a known heterozygous mutation (c.652C>T; p.Arg218Cys) in exon 4, confirming the clinical diagnosis at the molecular level. The patient was started on glucocorticoids and showed significant response symptomatically. Genetic analysis was performed for other available members of her family, including her mother and 5 siblings and none of them were found to harbour the mutation. As her father had expired in a road traffic accident, his genotype could not be ascertained, but there was no history suggestive of any bone disorders in him.

Figure 1 Proptosis seen in the patient.

Discussion

CED is a rare autosomal dominant condition, belonging to the group of craniotubular hyperostoses. The hallmark of this disorder is the cortical thickening of the diaphyses of the long bones. Exophthalmos has been reported by Jiajue et al. as the presenting feature in a milder form of CED (Jiajue et al., 2016). Though our patient never complained of eye problems, proptosis was evident on clinical examination. Generally, CED is caused by mutations in the Transforming Growth Factor β (*TGFβ1*) gene, functionally leading to an increased activity of *TGFβ1* which then disturbs both the osteoclastic resorption and osteoblastic bone formation (Janssens et al., 2006). Majority of the

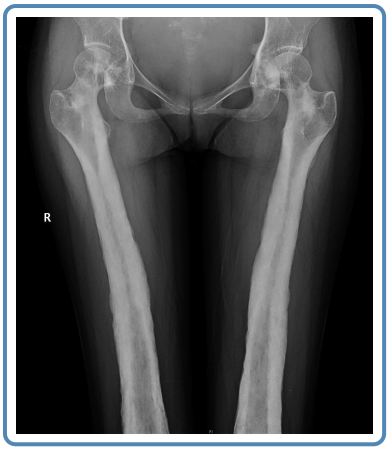
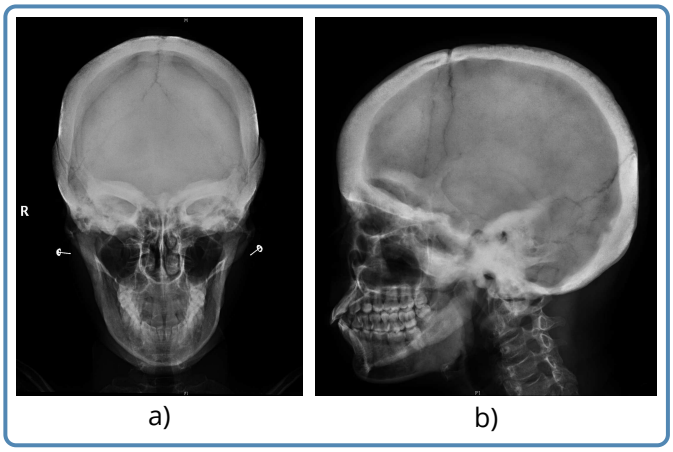


Figure 2 Radiograph shows cortical thickening and hyperostosis of both femora.



a) b)

Figure 3 a&b) Sclerosis of skull is evident in radiographs.

mutations detected in CED are missense mutations in exon 4 and arginine residue at position 218 is considered as a mutation hotspot, accounting for 60% of the mutations (Janssens et al., 2006). Probably Indian kindreds also harbour the same hotspot as evidenced by the present case report and the studies of Bhadada et al. (2014). De novo mutations are not reported so far in CED. Apparent de novo mutations should be considered for non- paternity or maternity (e.g., with assisted reproduction) or undisclosed adoption could also be explored (Wallace & Wilcox, 2015). The proband was the only affected member for our family. The mother and siblings were negative for mutation. However chances of inheritance of the disease from the paternal side could not be ruled out.

Several investigators have described success with corticosteroids in the treatment of CED, in reducing pain and weakness, improving gait, exercise intolerance and correcting anemia (Naveh et al., 1985; Heymans et al., 1998). As our patient also had an improvement in clinical symptoms following prednisolone, we support the literature recommending short term glucocorticoids in the management of CED.

Ours is another Indian case of CED with confirmed molecular diagnosis with a missense mutation in the previously described common position denoting this to be a hotspot region in Indian families similar to other ethnic groups. Molecular testing for this hotspot could be easily offered on a diagnostic basis for young individuals presenting with non specific limb pain and waddling gait for diagnosing CED. This will help to avoid unnecessary evaluation and start steroids to provide symptomatic relief for the patient at the earliest.

References

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