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Clinical report

Reversible prostaglandin-induced cortical hyperostosis in an infant without 3040C →T mutation in *COL1A1*

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Background: A hereditary form of infantile cortical hyperostosis (ICH), known as Caffey disease, was recently found to be caused by a heterozygous 3040C T mutation in the *COL1A1* gene.
Objective: To determine whether a similar mutation was also responsible for a sporadic case of ICH.
Methods: We identified a Thai male infant who was a sporadic case of ICH. He had symmetric cortical hyperostosis of all of his long bones, clavicles, and ribs occurring after a prolonged infusion of prostaglandin E1 (PGE1) for a cyanotic congenital heart disease. Mutation analysis of *COL1A1* was performed in the patient and his parents by restriction enzyme digestion of PCR products.
Results: The particular mutation was not found in our case and in his parents. A follow-up after 15 months demonstrated that the child had normal growth and development. Repeated imaging studies revealed markedly decreased cortical thickenings of the affected bones.
Conclusion: Our findings confirm that PGE1-induced cortical hyperostosis is reversible and does not associate with the *COL1A1* 3040C→T mutation.

Key words: *COL1A1*, infantile cortical hyperostosis, prostaglandin, reversible.

The inherited form of infantile cortical hyperostosis (ICH), Caffey disease, is mimicked by several acquired conditions including prolonged prostaglandin infusion [1-3], hypervitaminosis A [4], and hyperphosphatemia [5]. Prostaglandin E1 (PGE1) is widely used as palliative therapy for patients with various forms of congenital heart disease where survival depends on the patency of the ductus arteriosus [6, 7]. The side effects associated with the use of prostaglandins include apnea, bradycardia, fever, diarrhea, hypotension, skin flushing and edema [8]. It has also been found that prolonged administration of prostaglandin E1 can lead to cortical hyperostosis [2].

Recently, a novel missense mutation in *COL1A1* was identified in all affected individuals with Caffey disease from four unrelated families [9, 10]. They were heterozygous for the identical mutation, a 3040C→T transition resulting in the substitution of an arginine by a cysteine at position 836 (R836C), within the helical domain of the a1 chain of type 1 collagen.

We report a male infant who developed cortical hyperostosis after a prolonged infusion of PGE1 for a cyanotic congenital heart disease. A 3040C→T transition in exon 41 of *COL1A1* was not found. This condition was reversible as demonstrated by decreasing cortical thickening after a 15-month follow-up.

Case report

A 2-month-old male infant was referred to us due to a chest X-ray finding revealing cortical thickening of the clavicles and ribs. He was born full term to non-consanguineous unaffected parents. There was no history of ICH or skeletal dysplasia in the family. He was well at birth. At the age of seven days, he was presented to the referring hospital with poor feeding, respiratory distress and cyanosis. Echocardiography revealed pulmonary atresia with intact ventricular septum. The PGE1 was started initially at a rate of 0.1 μg/kg per min and rapidly reduced to 0.01 μg/kg per min. He also developed pneumonia requiring antibiotics.

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At five weeks old, the patient was referred to our center for further management. PGE1 was continued at 0.05 μg/kg per min. The valvulotomy was performed a week later. One week after the surgery, he did well and the PGE1 was subsequently discontinued. He therefore received PGE1 infusion for a total of six weeks due to his ductus-dependent cyanotic heart disease. At the age of seven weeks, the follow-up chest X-ray was done and revealed cortical thickening of the clavicles and ribs (**Fig. 1a**). Further skeletal surveys revealed extensive involvement of all four extremities (**Fig. 1c, e**). Nevertheless he never developed any swelling or redness of the affected bones during PGE1 therapy. The radiographic findings during a follow-up visit at 17 months of age revealed normal clavicles and ribs with decreased cortical thickening of all four extremities (**Fig. 1b, d, f**). His growth parameters were within the normal ranges.

After informed consent was obtained, genomic DNA from the patient and his parents were analyzed for the 3040C→T transition in exon 41 of *COL1A1* by restriction enzyme digestion of PCR products as previously described [9, 10]. This particular mutation was not detected in this case (**Fig. 2**).

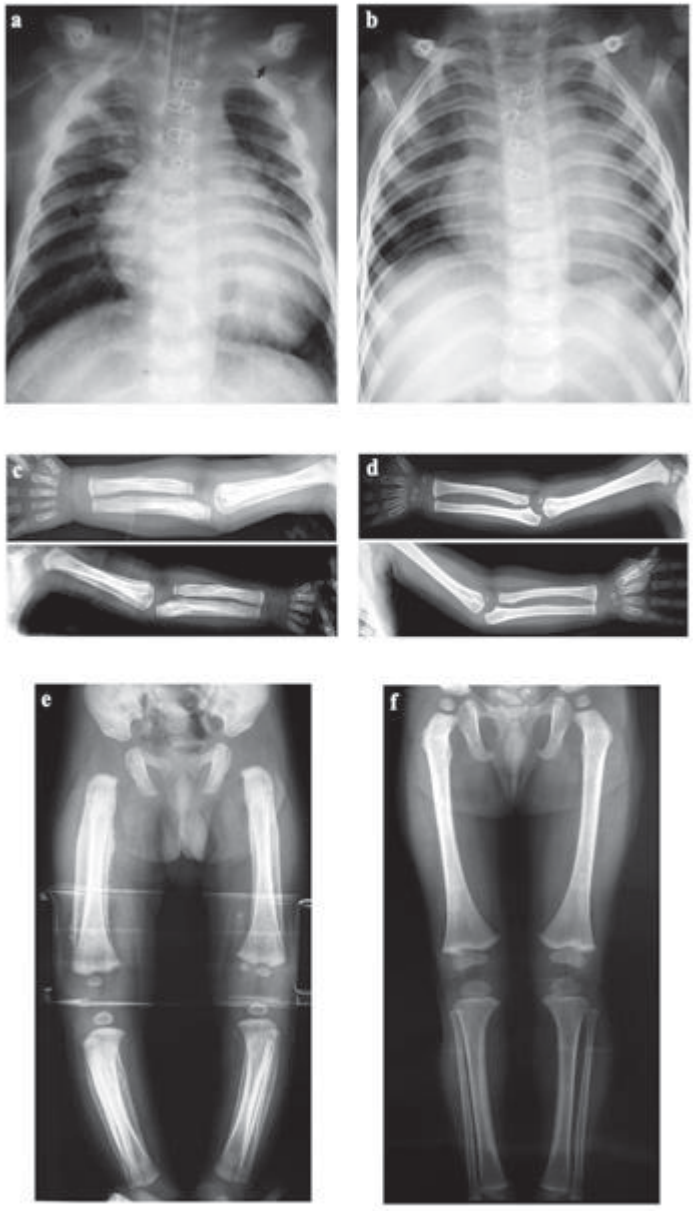

Fig. 1 Radiological features of the patient. Radiographs of the patient showing cortical thickening of (**a**) the clavicles and ribs (arrows) (**c**) the upper extremities (**e**) the lower extremities. After 15 months, the X-ray findings revealed (**b**) normal clavicles and ribs (**d, f**) decreased cortical thickening of all four extremities.

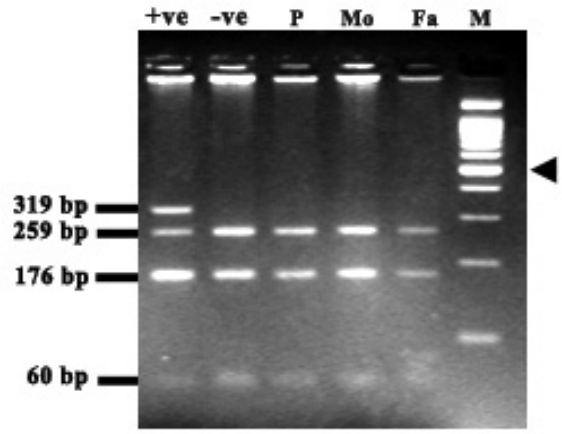

Fig. 2 Mutation analysis. M: 100-bp marker. The 500-bp band indicated by an arrow head. **+ve** control: a patient with Caffey disease. **–ve** control: unaffected control. **P**: patient. Mo: mother. **Fa**: father. Restriction enzyme analysis of PCR products showing the wild type allele with bands of 259, 176 and 60 bp and the mutant allele lacking one of the cleavage sites for the restriction endonuclease *HpyCH4IV* resulting in bands of 319 and 176 bp. The patient with Caffey disease was heterozygous for C→T mutation at nucleotide 3040 of *COL1A1*. Only wild type alleles were detected in our patient and his unaffected parents.

Discussion

In addition to the inherited form of ICH, sporadic cases have also been described. At least some of these cases can be attributed to prostaglandin infusion for treatment of ductal-dependent cardiac lesions [1-3]. The percentage of infants with hyperostosis increases with increasing duration of PGE1 infusion from 42 % at < 30 days to 100 % at >60 days [2]. The bony changes can be seen as early as 9 to 11 days after starting PGE1 [3, 11, 12]. Some patients may develop symptomatic bone tenderness or swelling mimicking osteomyelitis [11, 13]. Our patient remained asymptomatic despite receiving PGE1 infusion for a total of six weeks. Cortical hyperostosis was therefore diagnosed by radiographic findings. This is consistent with the previous studies showing that cortical hyperostosis is a common, often asymptomatic, side effect of prolonged PGE1 infusion [2]. After cessation of PGE1, the cortical thickenings in our case gradually resolved without any medical intervention confirming that this was a benign condition.

Recently the molecular defect of the autosomal dominant form of ICH has been elucidated [9]. The 3040C→T transition (R836C) in exon 41 of *COL1A1* was described in a study of three unrelated kindred from Australia and Canada as well as in our previous study of a Thai family [9, 10]. Although it has been shown that one sporadic case of ICH did not have any demonstrable mutations in *COL1A1* [9], it is possible that other sporadic cases might harbour the R836C mutation. In addition, mutation analysis of the responsible gene may help diagnose Caffey disease and therefore distinguish it from other mimicking conditions leading to an improved genetic counseling. We, therefore, performed a mutation analysis in our patient and his unaffected parents. The 3040C→T transition in exon 41 of *COL1A1* was not detected. This finding further confirmed that the nonfamilial form of ICH induced by PGE1 administration was not associated with the *COL1A1* 3040C→T mutation. Since other areas of the *COL1A1* gene were not included in the study, it is still possible that other variants in the *COL1A1* gene could predispose an individual to ICH after exposure to a medication or other environmental factors.

In conclusion, we present an infant with prolonged PGE1 infusion who developed cortical thickening of all four extremities, clavicles, and ribs without any swelling or tenderness of the affected bones. A follow-up after 15 months demonstrated that the child had normal growth and development with markedly decreased cortical thickening of the affected bones. Mutation analysis performed in our case and his parents failed to detect the 3040C→T transition in exon 41 of *COL1A1*. Our findings confirm that PGE1-induced cortical hyperostosis is reversible and does not associate with the *COL1A1* 3040C→T mutation.

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The authors have no conflict of interest to report.

Author contributions

KS, AT, VS examined the patients and participated in the study design. KS, ST, VS performed mutation analysis. KS and VS analyzed the data, drafted the manuscript and organized the funding.

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