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CASE REPORT

Caffey-Silverman syndrome – a case report of a two-month-old boy with a positive family history

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ABSTRACT

Caffey-Silverman disease is a rare, self-limiting disease of infancy. The onset of the disease is usually sudden, and it is characterised by the following symptoms: irritability and/or fever, painful swelling of soft tissues, and excessive bone formation – typical changes in X-ray. The disease usually occurs in the first six months of the child's life. In most cases, well-researched clinical history, basic laboratory tests, and X-ray imaging are enough to diagnose the disease. We present a case of a two-month-old boy with clinical, radiological symptoms and a positive family history of Caffey-Silverman disease. The baby was admitted to the clinic due to left leg oedema and limitation of mobility in the left hip. In the X-ray, intensive periosteal layering along the mandible and long limb bones was seen. Genetic testing revealed a mutation in the *COL1A1* gene. Although Caffey-Silverman disease is a rare collagenopathy, one should not forget its existence.

KEY WORDS:
COL1A1 gene, Caffey-Silverman disease, infantile cortical hyperostosis.

INTRODUCTION

Caffey-Silverman syndrome, also known as Caffey disease or infantile cortical hyperostosis (ICH), was first described in 1945 by Caffey and Silverman on the basis of certain characteristic bone and radiographic lesions [1–3]. The first case study was presented in 1888 by West, and radiologically documented cases come from Roske (1930) and de Toni (1943) [1, 3].

It is a rare infant disease and occurs in both sexes [4, 5]. Available literature does not provide accurate prevalence of the disease. However, it is known that from the moment of the disease recognition until 1960 there were 100 cases reported, after 1970 an inexplicable decline of the incidence rate was observed, and between 2000 and 2015 20 cases of ICH were described [6]. The scientists are certain that these values are underestimated, since the disease is probably unrecognizable, for the symptoms usually resolve spontaneously in early childhood.

Due to the periods of incidence of ICH there exist acute and subacute phases of the disease. An acute phase starts before 35 weeks of pregnancy, it is characterised by high mortality and is diagnosed during ultrasound scanning of the foetus. Then we can observe polyhydramnion, hepatomegaly, and cortical hyperostosis in the foetus, while a mild case starts after 35 weeks of pregnancy and has a typical course of ICH.

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The symptoms usually occur within first six months of a child's life and resolve until the second year of life [7]. A characteristic symptom of the disease is painful swelling of soft tissues, limited mobility of limbs, high temperature, hyperactivity, irritability, and typical bone lesions seen in X-ray tests [4, 6–8]. The swelling may include the muscles located below [9]. The lesions seen in X-ray tests occur in one or many bones; the mandible is most commonly affected (95% of cases) but it affects also ribs, collarbone, scapulae, and diaphysis [7, 8]. There has been no case of phalanges and vertebrae being affected so far. X-ray scans show cortical bone thickening in the form of extensive periosteal thickening covering the affected diaphysis [9, 10]. The affected bones may have doubled or tripled width. The distribution of bone lesions may be symmetrical or asymmetrical. Radiographic lesions in flat bones can have a varied image; for example, the lesions within the scapula are usually one-sided and occur only within the first six months of life [1]. Radiographic lesions within the mandible have a form of bone loss and thinning, but in the case of collarbones the lesions are characterised by one- or two-sided periosteal thickening, and as for the ribs the lesions occur in lateral parts (in 70% of cases the lesions are accompanied by a pleural effusion).

Laboratory tests do not have any diagnostic value [1, 7]. Increased level of alkaline phosphatase, anaemia, thrombocytopaenia, and high erythrocyte sedimentation rate are most commonly observed [1, 11]. We do not observe any correlation between acute phase rate and the development of bone lesions in X-rays.

Infantile cortical hyperostosis is caused by a mutation in *COL1A1* gene on 17q21 chromosome (LOD score 6.78) [7, 8]. An arginine-to-cysteine substitution takes place in the α1 chain of collagen type I (Arg836Cys or R836C) [12]. The mutation results in creating type I collagen fibres that are of variable shape and size; however, the mechanism by which the mutation initiates a cascade of inflammatory events and bone lesions is still unknown [12]. Changes in molecular testing of the *COL1A1* gene cause also other collagen-related diseases, such as osteogenesis imperfecta type I–IV and VII, and Ehlers-Danlos syndrome type I [7, 8, 12].

In the past, the cause of ICH was associated with viral, bacterial infections, immunological, allergic, and vascular factors, but none of these hypotheses have ever been proven [9, 10].

Moreover, it has been shown that long-term use of prostaglandin E in order to retain the patent ductus arteriosus in patients with ductus-dependent cyanotic heart disease causes periostitis and bone cortex hyperplasia, which may play a certain role in Caffey disease ethology [10, 13]. Woo K. *et al.* proved that 62% of newborns receiving PGE1 infusion had radiographic lesions typical for ICH persisting for over 60 days [14]. However, the pathophysiological mechanism by which PGE1 is actually working remains unknown [12].

Two types of the nature of Caffey-Silverman heredity have been described: type I, so-called sporadic/prenatal, and type II classic/familial [1, 12]. A familial type is inherited in an autosomal dominant manner with incomplete penetration, which means that not all family members who inherit the mutation suffer from its symptoms [7]. However, the prenatal type is inherited in an autosomal recessive manner and it is very acute, often lethal [5, 8]. In prenatal type the dominant affected bone is the tibia, and the mandible is most commonly affected in the familial type [15].

Currently, there is no direct treatment of ICH. A good response to nonsteroidal anti-inflammatory drugs (NSAIDs), glucocorticosteroids, inhibitors of prostaglandins were described; however, these medications do not affect any bone lesions [7]. Therefore, we must treat the symptoms with analgesics, nonsteroidal anti-inflammatory drugs, and antipyretics. The disease is self-limited and, in most patients, leaves no undesirable effects [7]. However, the most severe cases confirm developmental delay with deformations and disproportionate growth of forearms and forelegs [1]. Furthermore, ICH in older children may be the cause of delayed and hampered eruption of the milk teeth, hence the dentist's care is very important. In order to prevent deformations within the musculo-skeletal system, the cooperation of many specialists, including physical therapists, orthopaedists, surgeons, and plastic surgeons, is recommended. We can observe remissions and relapses of the disease even after a few years [9, 13].

The clinical case presented below is a perfect confirmation of literature data on infantile cortical hyperostosis.

CASE REPORT

A two-month-old male infant admitted to a regional hospital due to gastroenteritis presented with painful swelling of both forelegs, primarily the left. Family history showed that one of his siblings and his mother's sisters were diagnosed with ICH. For the purpose of further diagnostics and assessment of calcium and phosphate metabolism the infant was transferred to the Department of Paediatric Propaedeutics and Metabolic Bone Diseases. The medical interview confirmed that the boy was born with CV, PIV, and a birth weight of 3650 g, with Apgar score 10, developing properly. The infant was administered with vitamin D_3 on a regular basis, according to the applicable rickets-prevention scheme. On admission to the Department, during clinical examination, the child presented with swelling of the left foreleg and limited mobility within the left hip joint, and no changes in skin colour and temperature around the limb. Face skin and the groin area was covered with papular lesions, no external wounds or bruising were found. During the examination an innocent systolic heart murmur was heard. The boy had no fever and was calm during the examination.

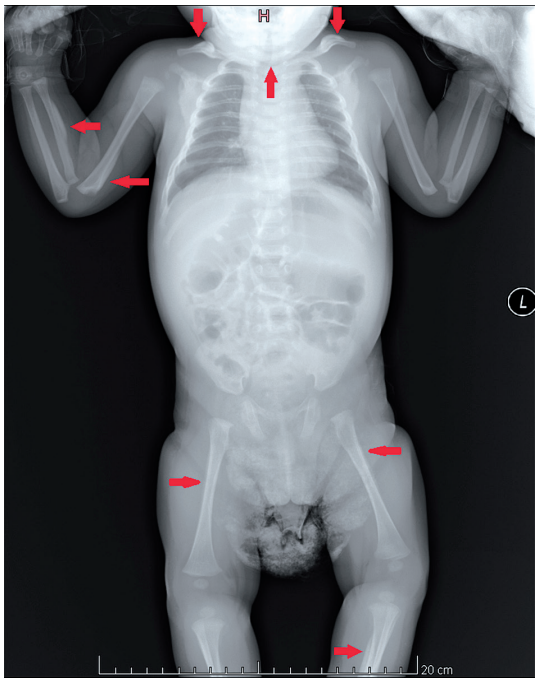

FIGURE 1. Babygram. In the X-ray, intensive periosteal layering along the mandible, both collarbones, and long limb bones was seen

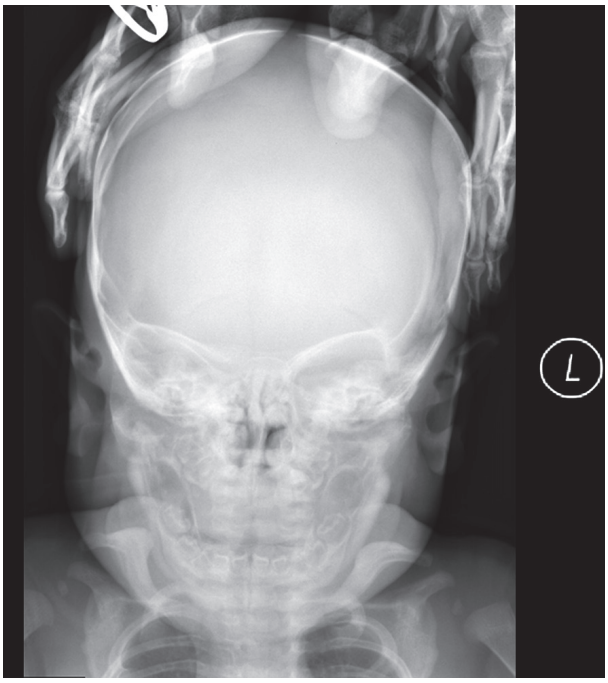

FIGURE 2. Babygram. Anteroposterior radiograph of the skull showed bones smoothly scratched

The results of performed laboratory tests confirmed increased level of osteocalcin (elevated bone turnover) in the form of elevated alkaline phosphatase (760 U/l, normally 82–283 U/l), elevated urinary excretion of pyrylinx D and the deficit of $D_3$25(OH) vitamin (24.6 mg/ml). Elevated bone turnover with prevalence of bone formation process is probably related to the active infection. In addition, CBC, acute-phase proteins, parathormone, ions such as: calcium, phosphorus, and magnesium remained within normal range.

Performed hip joint ultrasound scanning did not show any fluids within joints and confirmed an even bone outline. Diagnostics included also an X-ray babygram (Fig. 1, Fig. 2), which showed periosteal thickening along the bottom outline of the mandible, upper outline of both collarbones, posterior outline of the right humerus, anterior outline of the right radius, and paracentral outlines of both tibial bones. Furthermore, small periosteal thickening along the left humerus and both femoral bones and periosteal thickening along the lateral outlines of the shoulder blades were found. Also, the cranial plates were smoothly outlined (Fig. 2). Taking into consideration laboratory test results, imaging tests, and positive family history, biological material was collected from the boy for the purpose of molecular testing. The test was performed by Sanger DNA sequencing method with the use of a system of optimised reagents for testing the point mutations – on a Hitachi 3500 Genetic Analyser (after prior PCR reaction with the use of specific primers and electrophoretic assessment PCR reaction products). The analysis of the sequencing results was performed with the use of Sequencing Analysis Programme (LifeTech,

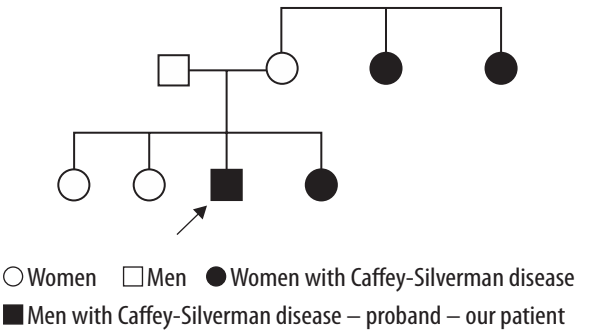

FIGURE 3. Family pedigree where involvement of the sister and two maternal aunts can be seen

USA) and Sequencher (GeneCode, USA). The presence of heterozygotic mutation c.3040C>T resulting in arginine-to-cysteine substitution in position 1014 of the polypeptide chain of type I collagen was confirmed, which in turn substantiated the clinical diagnosis of ICH (Fig. 3). The hospital treatment included NSAIDs and antihistamines (for papular lesions on the skin). After four days of hospitalisation the boy was discharged home in good condition with a recommendation to administer NSAIDs and vitamin D_3 (1770 IU/d) for 1.5 months.

After three months the boy was again admitted to the department for the purpose of general assessment of his calcium and phosphate metabolism. The clinical examination on admission showed mild swelling of both forelegs, and, as before, no changes in colour and temperature of the skin were found. Additionally, the nasal passages were filled with thick discharge, and the lung auscultation revealed single transmitted rhonchi. Laboratory tests

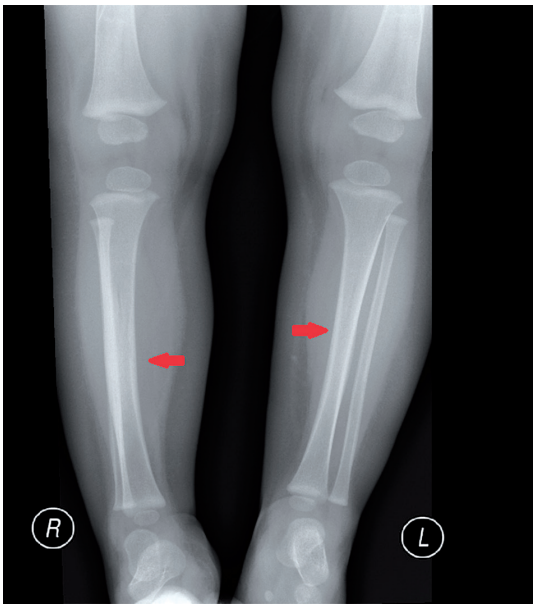

FIGURE 4. Anteroposterior view of bilateral lower limbs. In the X-ray, intensive periosteal layering along the tibia

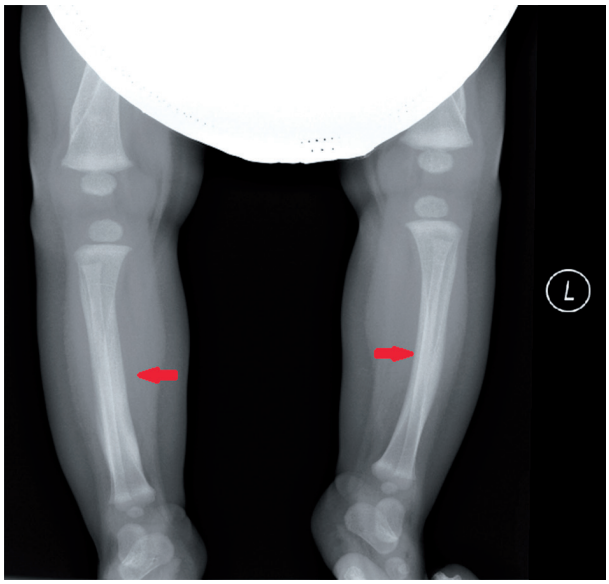

FIGURE 5. Anteroposterior view of bilateral lower limbs. Compared with the previous study, significantly smaller periosteal layers along both tibia bones

confirmed that the value of alkaline phosphatase was still elevated and value of pyrylinx D excreted with the urine was still high. Furthermore, increased phosphorus excretion was observed, while the ion concentration in the serum was normal and the osteocalcin level remained within the reference range. The follow-up X-ray of the foreleg bones (Fig. 4) showed a significant degree of periosteal thickening of both tibial bones; compared to the previous examination the reactions were more abundant. Very heavy periosteal reactions were also seen along the femoral epiphysis. The remaining parts of femoral bones were obscured. Due to the clinical condition, laboratory tests, and imaging tests it was decided to continue the treatment with NSAIDs for further 1.5 months. Furthermore, symptomatic therapy was given in order to treat upper respiratory tract infection.

At 12 months of age the boy was again admitted to the department for a general health assessment. Clinical examination did not show any significant abnormalities, and joint mobility was preserved. Biochemical test results still indicated elevated bone turnover in the form of elevated alkaline phosphatase – 362 U/l; however, compared to the tests performed previously the result could be considered an improvement. Elevated urinary excretion of phosphorus and normal concentration of ions in the serum were still observed.

The follow-up X-Ray of the foreleg bones (Fig. 5) indicated an improvement of periosteal lesions within both tibial bones. The right tibial bone was broader than the left and the periosteal thickening along both tibial bones was much smaller compared to the previous examination. The child was discharged home in general good condition.

DISCUSSION

This paper presents a case of a rare genetic disease: Caffey-Silverman syndrome (OMIM 114000). Despite the fact that the diagnosis is provided on the basis of a clinical picture and additional test results, recognising infantile cortical hyperostosis can be delayed because it imitates a wide range of other diseases, such as: osteomyelitis, chronic hypervitaminosis A, congenital syphilis, bony tumours (osteosarcoma, Ewing's sarcoma), hyperphosphataemia, scurvy, tuberculosis, and teething disturbances [1, 4, 8, 10]. The final diagnosis must be carefully considered because ICH can also imitate battered child syndrome, which is why any possible cases of child maltreatment by caregivers must be excluded [9]. In the case of our patient there was no sign of skin abrasions and no visible skin bruising that could suggest battered child syndrome.

It should be emphasised that the presented child did not receive PGE infusion that might induce ICH. The heart murmur heard during clinical examination of the boy was a functional (innocent) murmur.

The literature indicates that the first symptoms of subacute phase of ICH start during infancy. In the discussed case the observed symptoms appeared in the second month of life. The only symptoms observed in our patient was painful swelling and limited joint mobility. The described ailments and affected bones seen on X-ray proved to be consistent with the literature [4, 6–9]. This disease can be insidious, in 2017 Sachin Khanduri *et al.* presented for the first time the case of a boy in whom the mandible and collarbone were not affected, but the child was diagnosed with ICH [16].

The follow-up X-ray showed in our patient a substantial reduction of periosteal thickening, which confirms

that the disease gradually resolves and does not leave any undesirable consequences. However, further observation of our patient is required. It was proven that upright posture and walking in children with ICH is usually delayed. Pedro Carlos M. Sarmento Pinheiro *et al.*, during eight years of observing a patient, noted that the child diagnosed with ICH on the 17th day of life started walking only in the second year of life [11]. This serves as a confirmation that successful treatment of ICH, without consequences, is possible; however, complete recovery might be delayed [11].

Despite the fact that in our patient elevated bone turnover in the form of elevated alkaline phosphatase and elevated urinary excretion of pyrylinx D was confirmed, it should be emphasised that laboratory tests are not specific for the diagnosis of ICH [17]. Furthermore, increased phosphorus excretion was observed while the ion concentration in the serum was normal, probably due to the child's diet. However, the literature describes cases of hyperphosphataemia (high phosphorus level in the serum) accompanying ICH [18, 19]. Positive family history of the patient confirms that the disease is inherited. In our case the boy had healthy parents, one sick sibling, and two sick aunts – the mother's sisters, but Robert C. Gensure *et al.* presented the mutation *COL1A1* in twins, the parents and the brother of whom were clinically healthy [8]. The literature provides analyses of whole genomes in families, and a heterozygotic missense mutation in 41 exon (3040C – T, R836C) was recognised [8, 20, 21]. This confirms that ICH is caused by a single mutation in the *COL1A1* gene with incomplete penetration. In order to ensure genetic counselling for future generations, it is recommended that the genome of other members of our patient's family be analysed.

The authors observed that the individuals with the mutation of *COL1A1* gene have hyperelastic skin, inguinal hernias, and joint subluxations [8, 12]. The above symptoms did not occur in our patient and the performed ultrasound scanning of the joint was normal. The therapy of the boy included NSAIDs, which brought expected benefits. After administering Ibuprofen in the form of a syrup, we observed an improvement in his clinical condition. Narayanan Kutty *et al.* [17] and Sachin Khanduri *et al.* [16] also observed a good therapeutic effect of ibuprofen. However, the literature describes the case of one of the dizygotic twins, a two-month-old boy, suffering from ICH, whose treatment with ibuprofen was ineffective and only administration of glucocorticosteroids (prednisolone 1 mg/kg/24 h) brought about positive results [22]. Moreover, Thometz *et al.* presented a case of a girl suffering from recurring Caffey disease, whose symptoms fully resolved after treatment with naproxen [13]. Whereas other authors described a therapeutic role of indomethacin (3 mg/kg/24 h) – inhibition of prostaglandin synthesis – in reducing ICH symptoms [4, 13, 22, 23]. Currently, there are no guidelines concerning the treatment of ICH, implemented drug therapy aims at alleviating pain; however, it does not affect the bone lesions [7].

CONCLUSIONS

In summary, the presented case shows that despite the low incidence of ICH, we should not forget this rare medical condition. We should remember that recognising ICH is possible on the basis of properly taken family history, clinical symptoms, and bone X-ray, which are considered to be pathognomonic in diagnosing this disease.

DISCLOSURE

The authors declare no conflict of interest.

REFERENCES

1. Pytrus T, Zaleska-Dorobisz U, Piasecka A, et al. Caffey-Silverman Syndrome – case report. Adv Clin Exp Med 2005; 14: 843-848.
2. Szwed A, Kołban M, Romanowska H, et al. Familial Occurrence of Caffey-Silverman Syndrome. Ortop Traumatol Rehabil 2012; 14: 75-83.
3. Caffey J. Infantile cortical hyperostosis; a review of the clinical and radiographic features. J R Soc Med 1957; 50: 347-354.
4. Özdemir ÖMA, Tancer-Elçi H, Polat A, et al. Familial mutation in Caffey disease with reduced penetrance: a case report. Turk J Pediatr 2016; 58: 650-653.
5. Rodríguez M, Martínez LE, Cortés J, et al. Infantile cortical hyperostosis: case report. Rev Chil Pediatr 2016; 87: 401-405.
6. Nayak C, Samal BP. Infantile cortical hyperostosis, masquerading as osteomyelitis: a case report with three year follow up and review of the literature. Int J Contemp Pediatr 2015; 2: 249-253.
7. Prior AR, Moldovan O, Azevedo A, et al. Caffey disease in neonatal period: the importance of the family! BMJ Case Rep 2012; 10.1136/bcr-2012-006996.
8. Gensure RC, Mäkitie O, Barclay C, et al. A novel COL1A1 mutation in infantile cortical hyperostosis (Caffey disease) expands the spectrum of collagen-related disorders. J Clin Invest 2005; 115: 1250-1257.
9. Al Kaissi A, Petje G, De Brauwer V, et al. Professional awareness is needed to distinguish between child physical abuse from other disorders that can mimic signs of abuse (Skull base sclerosis in infant manifesting features of infantile cortical hyperostosis): a case report and review of the literature. Cases J 2009; 2: 133.
10. Agrawal A, Purandare N, Shah S, et al. A rare variant of Caffey's disease – X-rays, bone scan and FDG PET findings. Indian J Nucl Med 2011; 26: 112-114.
11. Sarmento Pinheiro PCM, Aymore IL, Amoedo AR, et al. Infantile Cortical Hyperostosis: Report of a Case with Observations on Clinical Manifestations, Radiology, and Pathology with a Late Follow-Up of Eight Years. Case Rep Pediatr 2016; 2016: 2073854.
12. Nistala H, Mäkitie O, Jüppner H. Caffey disease: new perspectives on old questions. Bone 2014; 60: 246-251.
13. Thometz JG, DiRaimondo CA. A case of recurrent Caffey's disease treated with naproxen. Clin Orthop 1996; 323: 304-309.
14. Woo K, Emery J, Peabody J. Cortical hyperostosis: a complication of prolonged prostaglandin infusion in infants awaiting cardiac transplantation. Pediatrics 1994; 93: 417-420.
15. Borochowitz Z, Gozal D, Misselevitch I, et al. Familial Caffey's disease and late recurrence in a child. Clin Genet 1991; 40: 329-335.

16. Khanduri S, Katyal G, Goyal A, et al. Disease Sans Mandibular and Clavicular Involvement: A Rare Case Report. Cureus 2017; 9: e1170.
17. Kutty N, Thomas D, George L, et al. Caffey Disease or Infantile Cortical Hyperostosis: A Case Report. Oman Med J 2010; 25: 134-136.
18. ALBagshi MH, ALZoayed HI. Infantile cortical hyperostosis – a report of Saudi family. Sudan J Paediatr 2015; 15: 61-64.
19. Talab YA, Mallouh A. Hyperostosis with hyperphosphatemia: a case report and review of the literature. J Pediatr Orthop 1988; 8: 338-341.
20. Cerruti-Mainardi P, Venturi G, Spunton M, et al. Infantile cortical hyperostosis and COL1A1 mutation in four generations. Eur J Pediatr 2011; 170: 1385-1390.
21. Suphapeetiporn K, Tongkobpetch S, Mahayosnond A, et al. Expanding the phenotypic spectrum of Caffey disease. Clin Genet 2007; 71: 280-284.
22. Dutta S, Jain N, Bhattacharya A, et al. Infantile cortical hyperostosis. Indian Pediatr 2005; 42: 64-66.
23. Heyman E, Laver J, Beer S. Prostaglandin synthetase inhibitor in Caffey disease. J Pediatr 1982; 101: 314.