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Forestier-Zhang, L.Y., Arundel, P., Gilbey-Cross, R. et al. (3 more authors) (2021) Short report: craniosynostosis, a late complication of nutritional rickets. Journal of Pediatric Endocrinology and Metabolism, 34 (8). pp. 1055-1060. ISSN 0334-018X

https://doi.org/10.1515/jpem-2020-0580

Title

Short Report: Craniosynostosis, a late complication of nutritional rickets

Authors

Lydia Y Forestier-Zhang, Paul Arundel, Robyn Gilbey-Cross, M Zulf Mughal, Amaka C Offiah, Moira S Cheung

Corresponding Author

Dr Moira S Cheung

Paediatric Endocrinology Consultant

Department of Paediatric Endocrinology

Evelina London Children's Hospital

3rd Floor Becket House

Westminster Bridge Road

London SE1 7EH

Moira.Cheung@gstt.nhs.uk

Word count in article: 1792

Word count in abstract and structured bullet points: 156

Number of tables and figures: 1 table, 4 figures

Supplemental Material: None

Abstract

Nutritional rickets may be a preventable cause of craniosynostosis. This potential association is under-recognised. A late diagnosis of craniosynostosis may result in reduced brain growth, raised intracranial pressure and long-term psychosocial problems. We present four cases of craniosynostosis secondary to nutritional rickets. Those who had delayed presentation underwent emergency craniotomy. Treatment of nutritional rickets and early identification of craniosynostosis can reduce morbidity in these children.

What is new?

- This case series demonstrates the association between craniosynostosis and nutritional rickets.
- A review of the literature suggests this association is under-recognised and poorly understood.

List of Abbreviations

NR	Nutritional rickets
VDD	Vitamin D deficiency
PTH	Parathyroid hormone
ALP	Alkaline phosphatase
CT	Computed tomography
FGFRs	Fibroblast growth factor receptors
ENT	Ears, nose and throat

Introduction

Craniosynostosis is the premature fusion of one or more cranial sutures. It is important to identify as complications include restriction of brain growth, raised intracranial pressure, deformity, dental anomalies and increased psychosocial difficulties(1).

Rickets is a disorder of defective chondrocyte differentiation, and failure of growth plates and osteoid mineralisation(2). When caused by isolated or combined nutritional deficiencies of vitamin D, calcium and phosphate it is termed nutritional rickets (NR). Although phosphate deficiency alone is rare, rickets caused by vitamin D and/or calcium deficiency in children is on the rise worldwide. NR is entirely preventable, however if untreated can lead to severe consequences including lifelong deformity, disability, impaired growth and pain(2). The association between craniosynostosis and NR was first described by Heschl in 1873(3). However, since the 1960s only five further cases have been reported in the literature(4, 5). The mechanism, clinical course and severity of this association remain poorly understood.

Although NR associated craniosynostosis appears to be rare, we have encountered cases in clinics across the UK. In this case series we present four cases of craniosynostosis associated with NR seen in three paediatric metabolic bone centres over a five-year period. An average total of 18 children are treated for NR across the three centres each year, and the estimated annual incidence of NR in children under 16 years in the UK is 0.48 cases per 100000(6). The aim of this article is to raise awareness of craniosynostosis as a possible late complication of NR so that early detection and neurosurgical referral can be made.

Case Series

Case 1

An African-Caribbean male first presented at 17 months of age with marked scoliosis, bilateral wrist and ankle swelling, and bowing at the ankles. He was exclusively breastfed as an infant and was a picky eater. He had radiological evidence of rickets including fraying of the distal radial and ulnar metaphyses. His vitamin D level was low with hypocalcemia, raised parathyroid hormone (PTH) and alkaline phosphatase (ALP), and normal phosphate levels (Table 1). He was diagnosed with severe vitamin D deficiency (VDD) rickets. He was treated with 6000 units of vitamin D supplements and 400ml of milk daily for six weeks.

At 22 months he developed a prominent sagittal suture with ridging and scaphocephaly. CT head showed multi-sutural craniosynostosis involving complete fusion of the lambdoid and sagittal sutures and partial fusion of the coronal sutures. At the time he did not have signs of raised intracranial pressure and was monitored. A genetic cause of craniosynostosis was not identified by genetic testing.

At age three years he developed the ‘volcano sign’, a raised collar of bone palpable around his anterior fontanelle, a sign of local raised intracranial pressure. Ophthalmology assessment found new bilateral papilloedema. He underwent urgent posterior cranial vault expansion.

Case 2

A 2-year-old male of Sri Lankan origin presented as small for age with swelling of his wrists and ankles bilaterally, as well as a prominent box shaped forehead. He was

exclusively breastfed and at presentation was inadequately weaned and a picky eater. At presentation his head circumference was 50cm (25-50th centile for age), weight was 8.6kg (<0.4th centile) and length was 72cm (<0.4th centile). He had clinical and radiological signs of florid rickets with severe osteopenia of all bones, and swelling of distal long bones. He had low serum corrected calcium, vitamin D, raised ALP and raised PTH (Table 1). CT showed sagittal craniosynostosis without signs of raised intracranial pressure. He was diagnosed with severe NR secondary to a combination of VDD and dietary calcium deficiency. He was treated with 6000 units of vitamin D and calcium supplements for six weeks. He was monitored by the neurosurgical team and did not require surgery.

Case 3

A 3-year-old female of mixed south Asian and African ethnicity presented with concerns regarding her head shape. She was initially breastfed. Then at five months diagnosed with a milk allergy and was then intermittently taking vitamin D and calcium supplements. Clinically she had scaphocephaly and sagittal suture ridging. Her head circumference was 53cm (>99th centile for age). Her lateral skull radiograph showed dolichocephaly with ill-defined major sutures (Figure 1). In addition, she had a rachitic rosary and radiographs showed signs of healing rickets (Figure 2). At presentation she had vitamin D insufficiency, low corrected calcium with normal phosphate and PTH (Table 1). CT head confirmed sagittal synostosis and raised intracranial pressure. Genetic causes of craniosynostosis were not identified. She underwent a two-stage biparietal cranial vault expansion.

Case 4

A male of Pakistani ethnic origin, born to consanguineous parents, presented at 16 months of age with scalp swelling following a fall from a table. The skull radiographs showed biparietal skull fractures and a 'copper-beaten' skull with multi-sutural craniosynostosis involving the sagittal and coronal sutures, confirmed on CT (Figure 3). Clinically he had a prominent sagittal ridge and proptosis. He underwent a full skeletal survey, which identified other features of healing rickets including mild osteopenia and bowing of long bones with mild metaphyseal cupping (Figure 4). He had vitamin D insufficiency, raised PTH with normal calcium, phosphate and ALP levels. His nutritional rickets had not been previously identified or treated. A genetic cause of craniosynostosis was not identified through genetic testing. A year later he underwent subtotal calvarial remodelling to relieve raised intracranial pressure. A skeletal survey at the age of 3 years confirmed a return to normal modelling of his long bones.

Discussion

In these cases, craniosynostosis was diagnosed between the age of 16 months and three years. There was a male predominance (3/4). All children had risk factors for vitamin D deficiency (VDD): African-Caribbean or Asian ethnic backgrounds with darker skin pigmentation (N=4); multiple food intolerances (N=1) prolonged breastfeeding with picky eating habits (N=2). All children had clinically evident scaphocephaly and radiological evidence of active or previous rickets. The patients can be divided into two groups based on their different presentations.

Group 1 (Cases 1 and 2) presented with clinical and radiological signs of severe rickets after a long period of untreated severe VDD. They were managed with treatment

doses of vitamin D and calcium supplementation where necessary. In Case 1, vitamin D treatment had been completed and clinical signs of rickets were resolved when the craniosynostosis was diagnosed up to a year later.

Group 2 (Cases 3 and 4) presented with clinical and radiological features of craniosynostosis, associated with healing rickets on radiographs. Clinically there were few other signs of NR and serum 25OH vitamin D concentrations were 33-44nmol/l with normal PTH and bone profiles. Their rickets had not been previously appropriately treated.

CTs of all cases showed fusion of the sagittal sutures. Three children had multiple sutural fusions. All in Group 1 were initially managed conservatively. One child (Case 1) developed signs of raised intracranial pressure one year from presentation and required surgery. Group 2 patients had raised intracranial pressure at presentation, and both underwent urgent cranial vault remodelling.

In these cases, craniosynostosis was identified at or after the diagnosis of NR. No other known causes of craniosynostosis were found. We hypothesise that craniosynostosis was associated with NR in these cases. However, the possibility that the two conditions co-existed remains.

Literature Review

Since the 1960s five cases of craniosynostosis associated with NR have been described. In 1964 Reilly et al reported four of 16 children who developed craniosynostosis after vitamin D deficiency rickets was treated. All presented before

nine years of age. Two had coronal, and two had multiple suture involvement. There was no sex difference. They found the likelihood of developing craniosynostosis increased with increased severity of rickets and early age of onset.(5) More recently Wang et al described coronal and metopic synostosis in an African American male who was born preterm and had NR at six months of age.(4) His craniosynostosis developed at two years of age following full resolution of rickets, requiring cranial vault reconstructive surgery.

Craniosynostosis is common, estimated to occur in 1 in 1600-4000 live births. In recent years the incidence has been rising, potentially due to increased awareness amongst healthcare professionals.(7) Aetiology may be primary or secondary to underlying conditions, including metabolic disorders, cerebral malformations and mucopolysaccharidosis.(8) The mechanism of craniosynostosis is complex and not fully understood. Many genes, particularly fibroblast growth factor receptors (FGFRs); cellular mechanisms and signalling pathways have been identified. How NR affects these mechanisms and pathways is not clear. In previous cases (4, 5), and in this series (Case 1), craniosynostosis developed following treatment and resolution of NR. Reilly et al observed evidence of accelerated maturation at the cranial bone margins as rickets healed with treatment. Under-mineralisation in rickets results in the accumulation of osteoid in all sites of new bone formation(9). Therefore, excess osteoid in the cranial sutures may predispose to fusion, though the mechanism is unknown.

Recommendations

It is important to monitor for craniosynostosis in patients with NR, particularly if rickets is clinically severe. Previous cases and this series suggest craniosynostosis can occur months to years after NR has been treated and resolved. We therefore recommend that parents are aware of this possible complication and that these children should be monitored either in clinic or primary health care.

Craniosynostosis often presents with an unusual head shape. Diagnosis involves a focused history, physical examination, plain radiography and computed tomography (CT). A history should include perinatal history, family history of unusual head shapes and functional consequences such as visual disturbance, airway and feeding difficulties. Examination involves assessing head shape from above, head circumference, palpating for suture ridging, a neurological examination and identifying signs of raised intracranial pressure.(10) CT with 3D reconstruction is the best imaging modality for diagnosis and preoperative planning. However due to radiation risk and potential anaesthesia requirement, its indication should be carefully considered. Though visualising cranial sutures on plain radiographs is less accurate, these are readily available and often used as an initial screening tool.

Craniosynostosis is an important condition to recognise and prompt referral of the child to a specialist craniofacial centre is advised, as delayed treatment may lead to restriction of cerebral growth, strabismus, malocclusions and significant raised intracranial pressure(8). At craniofacial centres, patients are managed by specialist multi-disciplinary teams of neurosurgeons, maxillofacial surgeons, plastic surgeons, ENT surgeons, neurologists, geneticists, ophthalmologists, dentists, psychologists, clinical nurse specialists and speech and language therapists. Cranial vault

remodelling is currently the standard corrective operation, though surgical techniques continue to evolve. Often patients with mild single suture craniosynostosis are monitored and may not undergo surgery unless there is evidence of raised intracranial pressure.

In conclusion, we report four children with NR who developed craniosynostosis. The association between craniosynostosis and NR remains inadequately understood. We acknowledge that the association between craniosynostosis and NR in this case series may be coincidental. However, craniosynostosis can cause significant morbidity and any potential relationship with NR warrants further study.

Learning points:

- Craniosynostosis may be an uncommon but potentially preventable complication of nutritional rickets.
- Craniosynostosis can occur months to years after NR has been treated and resolved.
- It is important to identify craniosynostosis and monitor for this possible complication in patient with NR, as delayed diagnosis results in significant morbidity.
- Further research is required to better understand the association between NR and craniosynostosis.

Author contributions: All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.

Research funding: None declared.

Employment or leadership: None declared.

Honorarium: None declared.

Competing interests: The funding organization(s) played no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the report for publication.

Ethical approval: The research related to human use has complied with all the relevant national regulations, institutional policies, conducted in accordance to the tenets of the Helsinki Declaration, and has been approved by the authors' institutional review board or equivalent committee.

Consent: Informed consent was obtained from parents/guardians of individuals included in this study.

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Keywords

Rickets complications

Craniosynostoses

Metabolic bone diseases

Paediatrics

Vitamin D deficiency

Tables

Table 1: Summary of case data

Case	Age at diagnosis	Sex	Sutures involved	Vitamin D nmol/L*	Corrected calcium mmol/L (2.1-2.6)	Phosphate mmol/L (1.0-1.8)	ALP IU/L+	PTH ng/L (6.4-88.6)	Outcome	Age at surgery
1	22m	M	Sagittal, lambdoid, coronal	<20	2.11	1.5	998 (60-370)	210	Cranial vault remodelling	3yrs
2	2yrs	M	Sagittal	34	2.00	1.01	1011 (60-300)	318	Conservative	-
3	3yrs	F	Sagittal	44	2.06	1.5	373 (60-320)	44	Cranial vault remodelling	3yrs
4	16m	M	Sagittal, coronal, lamboid	33.4	2.5	1.65	281 (60-270)	167	Cranial vault remodelling	3yrs

Reference ranges displayed in brackets

*Vitamin D reference range: sufficiency >50nmol/L, insufficency 30-50nmol/L, deficiency <30nmol/L(2)

+Age and sex specific reference ranges for ALP in brackets under results

Figures

Figure 1: Lateral skull radiograph of Case 3 (3-year-old female) showing dolichocephaly with ill-defined sutures and prominent convolutional markings of the skull. Note artefact (2 rounded densities) caused by hair clips

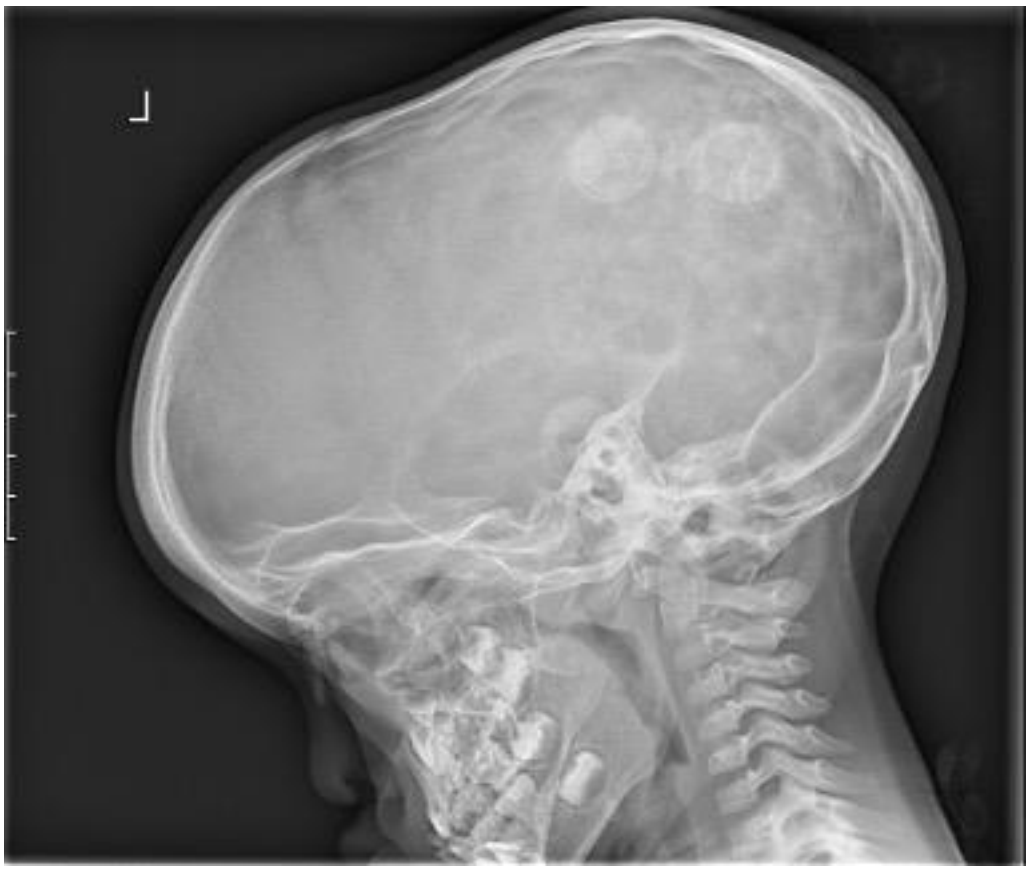


Figure 2: DP wrist radiograph of Case 3 (3-year-old female) showing mild cupping and sclerosis of right distal radial and ulnar metaphyses in keeping with healing rickets

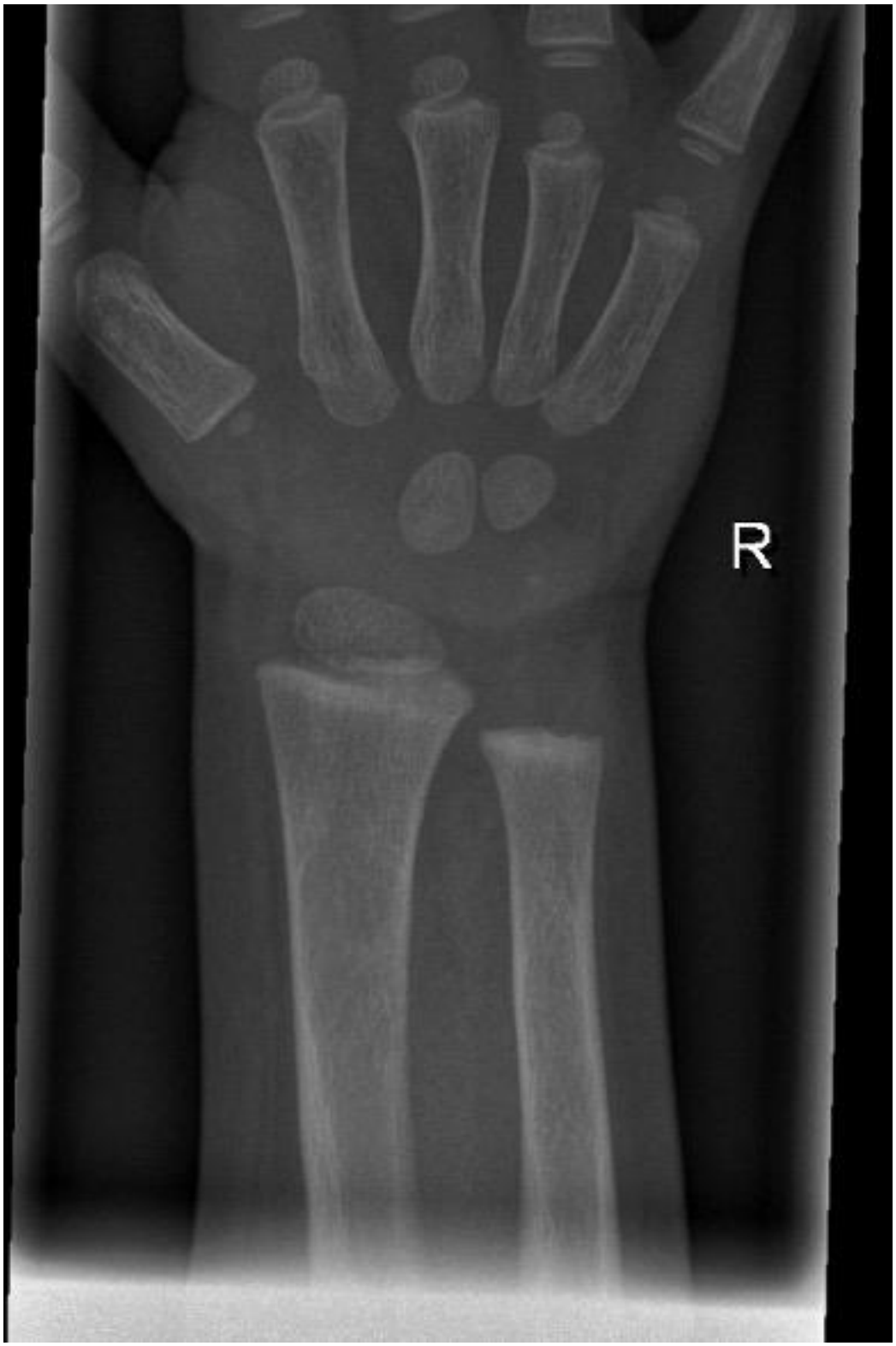
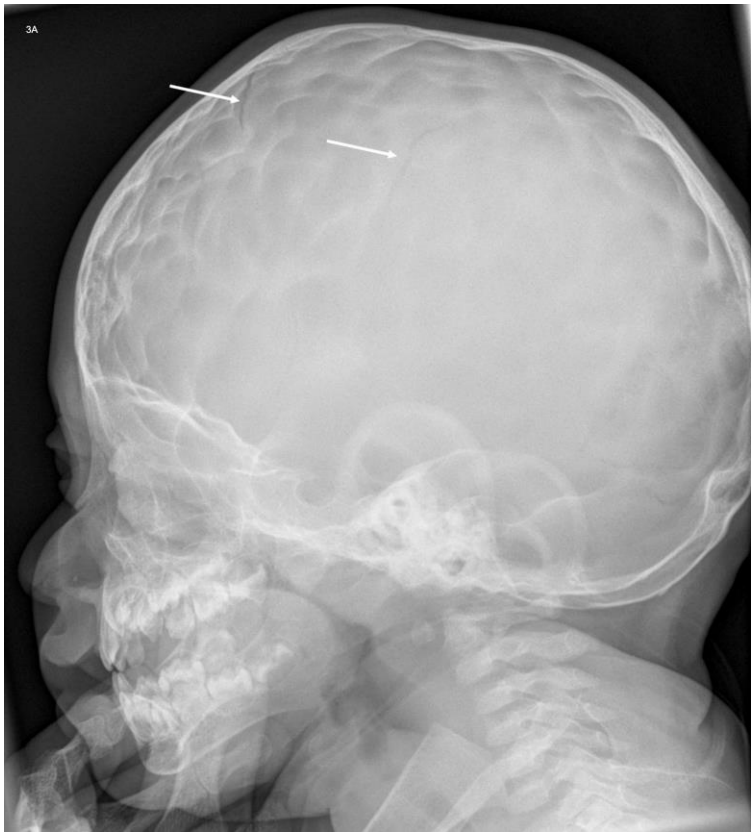
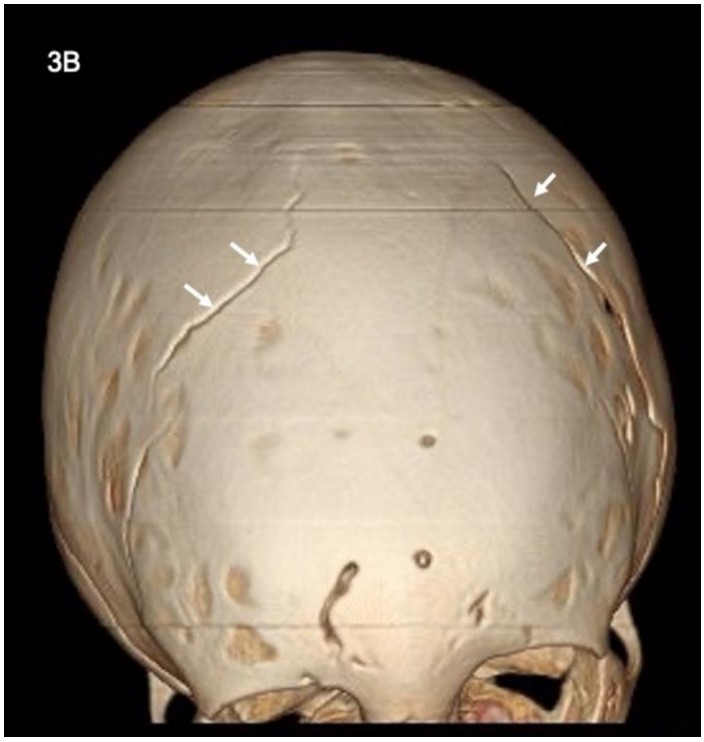


Figure 3: Lateral skull radiograph (A) and anterior (B) and posterior (C) views of the 3D reconstructed CT skull of Case 4 (16-month-old male) show a “copper-beaten” appearance of the skull (A), with fusion of sagittal and coronal sutures (B), but patent lambdoid sutures (C). Note also the biparietal skull fractures (arrows)




3B

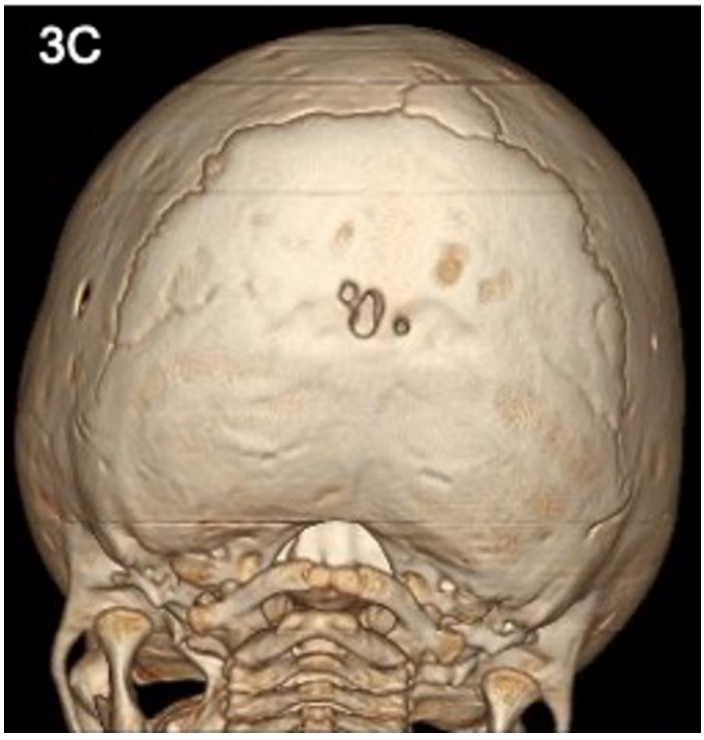

3C

Figure 4: AP radiographs of the left wrist (A) and right tibia/fibula (B) of Case 4 (16-month-old male), showing mild metaphyseal cupping and sclerosis and mild bowing of the distal tibia, consistent with healing rickets