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Craniosynostosis and metabolic bone disorder. A review

Craniosténoses et pathologies métaboliques osseuses

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Abstract

Introduction: Some metabolic bone disorders may result in the premature closure of one or more calvarial sutures during childhood, potentially leading to a cranioencephalic disproportion. The aim of this paper is to review the characteristics and consequences of craniosynostosis associated with metabolic disorder.

Material and methods: A review of the literature on metabolic forms of craniosynostosis was performed.

Results: The most common forms of craniosynostosis associated with metabolic bone disorder were isolated sagittal suture fusion with or without scaphocephaly, and sagittal suture fusion associated with coronal suture fusion (oxycephaly) or also with lambdoid suture fusion (pansynostosis). Synostosis may be well tolerated, but in some subjects results in neurodevelopmental and functional impairment that is sometimes severe.

Conclusion: The impact of metabolic synostosis is very variable, depending on the specific underlying metabolic disease, with a large spectrum of morphological and functional consequences. Diagnosis should be early and management should be carried out by a multidisciplinary team with expertise in both rare skeletal disorders and craniosynostosis. The impact of emergent medical therapies recently developed for some of these diseases will be assessed by systematic coherent follow-up of international registries.

Résumé

Introduction: Certaines pathologies du métabolisme minéral osseux peuvent entraîner dans leurs formes infantiles la fermeture prématurée d'une ou plusieurs sutures crâniennes entraînant une disproportion crano-encéphalique. L'objet de cette étude est de résumer les caractéristiques et conséquences des craniosténoses associées à des anomalies du métabolisme osseux.

Matériel et méthodes: Une révision de la littérature sur les formes métaboliques de craniosténoses a été menée.

Résultats: Les formes principales de craniosténose que l'on peut retrouver dans ces formes métaboliques sont la perte isolée de la suture sagittale avec ou sans scaphocéphalie, la perte de la suture sagittale associée à celle des sutures coronales (oxycéphalie) voire aussi à celles des sutures lambdoïdes entraînant une pansynostose. Ces craniosténoses peuvent être bien tolérées mais parfois elles peuvent s'accompagner de risques neurodéveloppementaux et fonctionnels potentiellement sévères

Conclusion: L'impact de ces craniosténoses est très variable selon le type de maladie métabolique sous-jacente avec de degrés très variables d'atteinte morphologique et fonctionnelle. Leur diagnostic doit être précoce et amener à une prise en charge en milieu spécialisé qui associe une expertise dans le métabolisme minéral osseux et dans les craniosynostoses. L'impact des nouvelles thérapeutiques médicaux visant certaines de ces conditions sera à évaluer par l'analyse systématique et cohérente des registres internationaux.

Keywords

Hypophosphatasia, hypophosphatemic rickets, PHEX, ALP, 1alpha hydroxylase deficiency, pseudohypoparathyroidism, mucopolysaccharidosis, mucopolipidosis, craniostenosis, syndromic synostosis, secondary craniosynostosis, osteopetrosis, skull

Introduction

Craniosynostosis is defined as the deformation of skull growth associated with premature closure of one or more skull vault sutures. Most craniosynostoses are isolated but they can also be part of a syndrome (7). Several genes responsible for skull growth and morphogenesis have been identified; those most often involved in craniosynostoses are *FGFR1*, *2* and *3*, *TWIST* and *TCF12*. In some children, craniosynostosis is secondary to genetic disorder, including syndromes with other associated anomalies, or associated with underlying metabolic disease affecting both intramembranous and endochondral ossification in the skull. In some cases, craniosynostosis may be the inaugural symptom leading to the discovery of the metabolic disorder; otherwise, it may be found during systematic follow-up of such rare genetic disorders.

The present report focuses on craniosynostosis secondary to rickets, mineral metabolism disorder and mucopolysaccharidosis.

Material and methods

A review of the literature was performed for secondary metabolic forms of craniosynostosis associated with rickets, mineral metabolism disorder or mucopolysaccharidosis, using the following search-terms: “metabolic craniosynostosis”; “craniosynostosis AND rickets”, “craniosynostosis AND mucopolysaccharidosis”. Only articles in English were considered, for the period 1950-2019.

Results

Craniosynostosis and rickets

The association of craniosynostosis and rickets has been known since the XIXth century, with the first reported description by Heschl in 1873 [1]. At that time, nutritional rickets was, by far, the major rickets etiology. In 1964, Reilly and Fraser evaluated the incidence of craniosynostosis in nutritional rickets as $\approx 1/4$ in a series of 16 patients [2]. Since then, the epidemiology of rickets has evolved. Nutritional rickets is less frequent and craniosynostosis due to nutritional rickets is thus nowadays exceptional, such as the cases described by Wang et al. (children with nutritional rickets) [3] or Shetty et al. (rickets secondary to prolonged exposure to anti-acid treatment) [4].

Currently the association between craniosynostosis and rickets concerns mainly familial forms of rickets or mineral disorders with an underlying genetic origin [5,6]. Craniosynostosis can, for example, be found in X-linked hypophosphatemia (XLH), in vitamin-D-resistant rickets (VDDR) due to 1 α hydroxylase deficiency, or in hypophosphatasia (HPP) [7].

X-linked hypophosphatemia and craniosynostosis

X-linked hypophosphatemia is a rare inherited disorder due to loss-of-function mutations in the *PHEX* gene. Impaired expression and function of *PHEX* in osteocytes, osteoblasts and odontoblasts leads to accumulation of mineralization inhibitors such as ASARM peptides and osteopontin (OPN) in calcified tissues, and increased production and secretion of FGF23. As a result, children present bone deformation at walking age, rickets, bone pain and growth retardation. Around 2/3 of patients with XLH show craniosynostosis [8]. Prevalence on MRI is even higher (personal data). Beyond the impaired mineralization responsible for rickets and short stature, cross-binding of FGF23 with FGFR2 and FGFR3 at the cranial sutures has also been suggested to contribute to cranial suture fusion [9]. Like for other causes of rickets and mineral disorders, diagnosis of craniosynostosis usually follows diagnosis of XLH. Many questions remain unanswered, such as the age of development of craniosynostosis, progression and the main determinants of suture fusion [8].

VDDR due to 1-alpha hydroxylase deficiency and craniosynostosis

Biallelic mutations in the 25-hydroxyvitamin D 1-alpha-hydroxylase gene (*CYP27B1*) cause vitamin-D-resistant rickets. Patients present typical hypocalcemic rickets in early childhood, resembling nutritional rickets that does not resolve despite vitamin D therapy [10]. Similarly to patients with nutritional rickets, these patients are at risk of developing craniosynostosis. Though the association between 1-alpha hydroxylase deficit and craniosynostosis is well known, its actual incidence is unknown because of the rarity of the condition.

Other anomalies in mineral metabolism may be associated with craniosynostosis, such as hypophosphatasia, pseudohypoparathyroidism and mucopolysaccharidosis.

Hypophosphatasia and craniosynostosis

Hypophosphatasia is a rare inborn error of metabolism characterized by defective bone mineralization, with highly variable clinical expression. It is due to mutations in the *ALPL* gene, causing deficiency in alkaline phosphatase enzyme activity. Depending on the severity of the enzymatic defect, patients present variable degrees of bone impairment or other tissue defects. The perinatal form is frequently lethal, usually associated with neonatal respiratory distress, convulsions, hypotrophy and hypotonia. Diagnosis is rapidly suggested by an association of typical radiological features, hypercalcemia/hyperphosphatemia and low alkaline phosphatase (ALP) activity. In the infantile form, clinical signs appear before 6 months of age, and include variable features such as stunting, hypotonia, frequent respiratory infections, hypercalcemia, pectus deformity, and progressive craniosynostosis. The radiological features are cupping and fraying of long-bone metaphyses, with widened and heightened growth plates and global hypomineralization. The disease may also be diagnosed in adults presenting with fracture, chondrocalcinosis or dental issues. Hypophosphatasia is a differential diagnosis of rickets, as patients have low levels of alkaline phosphatase, and may have high circulating levels of calcium and phosphate [11]. About 2/3 of patients with infantile hypophosphatasia present craniosynostosis [2,12,13], mainly associated with the most severe forms of hypophosphatasia. The pathophysiology of the cranial fusion in *ALPL* deficiency is still unknown. Biochemical analyses on bone samples of operated patients and analyses of the different types of *ALPL* mutation associated with hypophosphatasia have failed to identify which factors play a role in certain patients developing synostosis [12]. When diagnosis of hypophosphatasia is early, the

craniosynostosis, when present, is usually taken into consideration and recognized promptly, since synostosis is a classical feature of the infantile form of hypophosphatasia [6,14,15]. In some rare cases the diagnosis of synostosis will precede diagnosis of hypophosphatasia.

Pseudohypoparathyroidism and craniosynostosis

Pseudohypoparathyroidism has been recently reclassified as part of a larger group of disorders named 'inactivating PTH/PTHrp Signaling Disorders' (iPPSD). This disease group encompasses type 1A and 1B pseudohypoparathyroidism and acrodysostosis. These disorders share abnormal biochemical features such as PTH resistance and premature fusion of the growth plate, usually known as 'Albright hereditary osteodystrophy' [16]. Craniosynostosis has been reported repeatedly in these diseases, sometimes as severe synostosis affecting several sutures with raised intracranial pressure [17]. However, there are as yet no cohort studies analyzing the incidence of craniosynostosis in the various iPPSDs [18].

Mucopolysaccharidosis, mucopolipidosis and craniosynostosis

Mucopolysaccharidosis (MPS) and mucopolipidosis belong to the family of heritable disorders caused by a deficiency of the lysosomal enzymes required to degrade glycosaminoglycans and impairing lysosomal enzyme transport. These disorders are chronic and progressive, usually displaying a wide spectrum of clinical manifestations for a given enzyme deficiency. There is wide variability in severity. Patients with severe forms of the disease exhibit symptoms occurring early in childhood and simultaneously affecting diverse organ systems, with cognitive retardation. Conversely, individuals with attenuated disease have fewer and later symptoms, with mild or no cognitive impairment. On screening, suture abnormalities are commonly detected in severe forms of MPS, with ≥ 1 abnormalities in more than 75% of cases, although skull morphology is abnormal in only half. In some rare cases, it is skull deformation that leads to further examinations and finally to diagnosis of MPS [19].

Craniosynostosis in MPS usually develops within the first years of life, and is present in 40% of children under 6 years of age. Several sutures are affected: 2/3 of subjects have 2 or 3 sutures partially or completely fused while the remaining third develop pansynostosis [20]. Type II and III mucopolipidosis may also develop pansynostosis, often severe.

Osteopetrosis and craniosynostosis

Osteopetrosis is a heterogeneous group of ultra-rare skeletal disorders characterized by increased bone mass associated with a defect in osteoclast function. At least 10 genes have been identified, with various patterns of inheritance; the most severe types, often referred to as “malignant types” because of the rapid disease progression, are autosomal recessive. In these types, bone remodeling may alter skull growth; in some cases this can be associated with craniosynostosis, most commonly multisutural [21]. Because of the abnormal thickness of the skull vault, the risk of cranioencephalic disproportion and brain compression is extremely high in this condition, if untreated.

Discussion

Diagnosis of craniosynostosis is clinical, based on skull deformation associated with premature skull suture fusion.

However, in rare skeletal disorders, suture closure occurs secondarily, generally later than in isolated synostosis, at a developmental stage in which the vault is only mildly deformable; thus the change in morphology will be limited. This limited or absent deformation hinders clinical recognition of the synostosis. Radiological examination may be required to identify and confirm the associated skull synostosis.

It is noteworthy that, in some instances, even radiological diagnosis can be difficult, as a persistent sclerotic inactive ridge might be interpreted as a normal suture [22–25].

Two main forms of synostosis are associated with skeletal metabolic bone disorders: i) isolated fusion of the sagittal suture; ii) multisutural fusion with oxycephaly or pansynostosis (see Table).

In some metabolic bone disorders, the sagittal suture is predominantly affected. This is the case of most patients with XLH and vitamin-D-resistant rickets, though in some rare cases sagittal suture fusion can be associated with premature coronal suture fusion in XLH [8]. Cases of synostosis limited to the sagittal suture have also been reported in MPS [19]. However, in MPS, as in pseudohypoparathyroidism and osteopetrosis, radiological examination mostly finds oxycephaly or pansynostosis.

In hypophosphatasia, both scaphocephaly and pansynostosis can be found [26].

It is noteworthy that suture closure is a dynamic event and can be asynchronous. Thus at an early stage of the disease, some sutures might be still present, whereas on later examination they appear as fused [12].

The morphology of the skull depends on the type and number of affected sutures, but also on the age at which closure occurs and on the underlying skeletal disorder.

The typical scaphocephalic deformation of the skull, with increased anteroposterior growth, reduced transversal growth and protrusion of the forehead, develops in case of antenatal sagittal suture closure or of sagittal fusion occurring in the first months of life. This deformation is similar to that typical of isolated scaphocephaly and is easily recognizable clinically. Conversely, when sagittal closure

occurs at a later stage, there may be no deformation of the skull and "non-scapocephalic" closure of the sagittal suture is identified only on radiological examination. This is often the case in XLH patients [8]. In case of early fusion of the sagittal and coronal sutures, the skull may develop an oxycephalic aspect. A bregmatic bump can be palpated or even seen. There may be retrusion of the supraorbital bandeau. Pansynostosis may occur when the lambdoid sutures also close. However, it should be stressed that, even in case of closure of several sutures, the morphological impact may very limited in a large percentage of subjects and, in most cases of rare skeletal disorders, because of this limited or absent skull deformation, purely clinical diagnosis of synostosis may be missed.

Progression risks

The risks associated with metabolic synostosis are, like in isolated synostosis, functional and esthetic. However, because skull deformation is mild in most subjects with metabolic disorders, the esthetic consequences are often minimal. Conversely, the risk of functional complications is high in metabolic synostosis, depending on the underlying condition. It seems to be higher in hypophosphatasia with pansynostosis or in some cases of pseudohypoparathyroidism than in mucopolysaccharidosis. Probably, the changes in skull content (the brain itself, and CSF spaces) characteristic of mucopolysaccharidosis provide enough room to compensate for the effects of the craniosynostosis. Although sutural alteration is frequent, functional impact in MPS is extremely rare [20]. Nevertheless, some cases of children with MPS and documented intracranial hypertension needing decompressive surgery have been reported [19,20].

Like in isolated or complex craniosynostosis, the functional risk in craniosynostosis associated with metabolic bone disorder concerns cranioencephalic disproportion, leading to intracranial pressure elevation and caudal descent of the cerebellar tonsils into the upper cervical canal (Chiari type 1 malformation) due to the reduced intracranial volume. A role of impaired venous flow has also been postulated as contributing to these anomalies in case of metabolic craniosynostosis during fetal life or in the first weeks after birth.

Chronic headache is the typical clinical manifestation of cranioencephalic disproportion. However, cognitive and behavioral impairment is also sometimes seen in children with metabolic craniosynostosis in whom the cranio-encephalic disproportion is overlooked and not treated timely.

Rarely, and only in case of severe intracranial hypertension, visual function can be affected, with a risk of papilledema and optic atrophy.

Syringomyelia can occur in case of herniated cerebellar tonsils. The risk of acquired herniation of the cerebellar tonsils (Chiari type I malformation) is relatively high in XLH, pseudohypoparathyroidism and osteopetrosis, not only in subjects with pansynostosis but also in cases where only the sagittal suture is affected, independently of changes in skull shape. In other words, Chiari type 1 malformation can also be found in non-dolichocephalic patients [8].

The craniovertebral junction can also be affected in MPS, but without cerebellar tonsils herniation in the great majority of cases.

Investigations for craniosynostosis

Complementary investigations in addition to those required for diagnosis of the underlying bone metabolic disorder are warranted when associated synostosis is suspected.

Skull computed tomography (CT) with 2D and 3D reconstruction confirms the diagnosis of synostosis and analyzes the skull and its contents, screening for radiological signs of intracranial pressure (ICP) elevation (thumb-printing) and determining position of the cerebellar tonsils (Chiari malformation). Though highly reliable, the use of this examination in young children is limited because of the risks associated with irradiation. However, it can enable discovery of craniosynostosis in the majority of older children, especially in case of "non-dolichocephalic" sagittal synostosis and in subjects with relatively normal skull morphology.

Brain magnetic resonance imaging (MRI) provides precise brain study without X-ray exposure. However, the cranial vault remains difficult to assess on MRI, which further requires sedation in young children. Nevertheless, this examination is particularly useful in case of Chiari malformation, to screen for associated syringomyelia.

Fundoscopy or optical coherence tomography (OCT) should also be performed in all patients, to screen for papilledema.

Neuropsychological testing and school performance assessment can be useful in case of confirmed synostosis. However, the results of such investigations can be difficult to interpret in rare skeletal disorders because of the concomitant effects of the synostosis and of the underlying disease.

Management

The management of symptomatic craniosynostosis associated with rare skeletal disorders is surgical, pharmacological treatments showing limited results [27,28]. Nevertheless, some rare metabolic disease may respond to specific drugs or treatments, but impact on skull growth remains to be determined. This is the case, for example, of some types of osteopetrosis, which respond to bone-marrow transplantation but, in most cases, without any significant impact on the associated synostosis and raised ICP.

Similarly, some forms of skeletal disease which respond to new therapeutic drugs, such as asfotase alpha for severe hypophosphatasia, and had 1-year survival of less than 20% before the advent of enzymotherapy [29], still develop craniosynostosis.

The question of the impact of these emergent therapies developed in recent years will probably be answered by systematic and coherent follow-up of large cohorts of patients through registries.

Surgical treatment of craniosynostosis associated with rare skeletal disorder aims to treat (or prevent) the functional consequences and to improve the esthetic component.

Surgery should always be discussed by a multidisciplinary team with expertise in both craniofacial and also rare skeletal disorders. Surgical treatment is usually indicated if the patient is symptomatic, but the prognosis of the disease should always be taken into account (e.g., in type II mucopolidosis with pansynostosis). In other cases, prophylactic surgery may be discussed.

Surgery can be proposed in case of pansynostosis: for example, biparietal skull decompression to prevent the potential consequences of chronic ICP elevation, or occipito-cervical decompression without duraplasty to treat progressive or extensive cervical syringomyelia.

In asymptomatic children with well-tolerated synostosis, surgery is usually not mandatory. However, strict clinical and instrumental surveillance is required to detect any clinical or anatomical deterioration.

Conclusion

Because of the potentially severe consequences of craniosynostosis, it is essential to screen for sutural abnormalities in children with rare skeletal metabolic disorders known to be associated with craniosynostosis at the time of diagnosis of the underlying condition. Craniosynostosis should also be screened for in case of abnormal skull morphology, clinical manifestations of raised ICP, or symptoms and signs suggesting Chiari type 1 malformation or syringomyelia.

Conversely, metabolic bone disorders should be screened for during follow-up of patients operated on for craniosynostosis in the first months of life.

Referral to specialized centers with multidisciplinary teams, combining double expertise in the management of rare skeletal disorders and craniofacial malformations, is recommended.

References

- [1] Heschl M. Einige Bemerkungen über Föntale und prä-mature obliterationen des Schädelnähte. *Vjscher Prakt Heilk* 1873;120:135.
- [2] Reilly BJ, Leeming JM, Fraser D. Craniosynostosis in the Rachitic Spectrum. *J Pediatr* 1964;64:396–405. doi:10.1016/s0022-3476(64)80192-x.
- [3] Wang PI, Marcus JR, Fuchs HE, Mukundan S. Craniosynostosis Secondary to Rickets: Manifestations on Computed Tomography. *Radiol Case Rep* 2007;2:43. doi:10.2484/rcr.v2i3.43.
- [4] Shetty AK, Thomas T, Rao J, Vargas A. Rickets and secondary craniosynostosis associated with long-term antacid use in an infant. *Arch Pediatr Adolesc Med* 1998;152:1243–5.
- [5] Coleman EN, Foote JB. Craniostenosis with familial vitamin-D-resistant rickets. *Br Med J* 1954;1:561–2. doi:10.1136/bmj.1.4861.561.
- [6] Millán JL, Narisawa S, Lemire I, Loisel TP, Boileau G, Leonard P, et al. Enzyme replacement therapy for murine hypophosphatasia. *J Bone Miner Res Off J Am Soc Bone Miner Res* 2008;23:777–87. doi:10.1359/jbmr.071213.
- [7] Di Rocco F, Arnaud E, Renier D. Evolution in the frequency of nonsyndromic craniosynostosis. *J Neurosurg Pediatr* 2009;4:21–5. doi:10.3171/2009.3.PEDS08355.
- [8] Rothenbuhler A, Fadel N, Debza Y, Bacchetta J, Diallo MT, Adamsbaum C, et al. High incidence of cranial synostosis and Chiari I malformation in children with X-linked hypophosphatemic rickets (XLHR). *J Bone Miner Res Off J Am Soc Bone Miner Res* 2018. doi:10.1002/jbmr.3614.
- [9] Beck-Nielsen SS, Mughal Z, Haffner D, Nilsson O, Levchenko E, Ariceta G, et al. FGF23 and its role in X-linked hypophosphatemia-related morbidity. *Orphanet J Rare Dis* 2019;14:58. doi:10.1186/s13023-019-1014-8.
- [10] Kitanaka S, Takeyama K, Murayama A, Sato T, Okumura K, Nogami M, et al. Inactivating mutations in the 25-hydroxyvitamin D3 1alpha-hydroxylase gene in patients with pseudovitamin D-deficiency rickets. *N Engl J Med* 1998;338:653–61. doi:10.1056/NEJM199803053381004.
- [11] Linglart A, Biosse-Duplan M. Hypophosphatasia. *Curr Osteoporos Rep* 2016;14:95–105. doi:10.1007/s11914-016-0309-0.
- [12] Collmann H, Mornet E, Gattenlöhner S, Beck C, Girschick H. Neurosurgical aspects of childhood hypophosphatasia. *Childs Nerv Syst ChNS Off J Int Soc Pediatr Neurosurg* 2009;25:217–23. doi:10.1007/s00381-008-0708-3.
- [13] Fraser D. Hypophosphatasia. *Am J Med* 1957;22:730–46.
- [14] Taillandier A, Domingues C, Dufour A, Debiais F, Guggenbuhl P, Roux C, et al. Genetic analysis of adults heterozygous for ALPL mutations. *J Bone Miner Metab* 2018;36:723–33. doi:10.1007/s00774-017-0888-6.
- [15] Wenkert D, McAlister WH, Coburn SP, Zerega JA, Ryan LM, Ericson KL, et al. Hypophosphatasia: nonlethal disease despite skeletal presentation in utero (17 new cases and literature review). *J Bone Miner Res Off J Am Soc Bone Miner Res* 2011;26:2389–98. doi:10.1002/jbmr.454.
- [16] Thiele S, Mantovani G, Barlier A, Boldrin V, Bordogna P, De Sanctis L, et al. From pseudohypoparathyroidism to inactivating PTH/PTHrP signalling disorder (iPPSD), a novel classification proposed by the EuroPHP network. *Eur J Endocrinol* 2016;175:P1–17. doi:10.1530/EJE-16-0107.
- [17] Mamoei S, Cortnum S. Raised intracranial pressure as a result of pansynostosis in a child with Albright's hereditary osteodystrophy. *Childs Nerv Syst ChNS Off J Int Soc Pediatr Neurosurg* 2017;33:865–8. doi:10.1007/s00381-016-3330-9.
- [18] Linglart A, Fryssira H, Hiort O, Holterhus P-M, Perez de Nanclares G, Argente J, et al. PRKAR1A and PDE4D Mutations Cause Acrodysostosis but Two Distinct Syndromes with or without GPCR-Signaling Hormone Resistance. *J Clin Endocrinol Metab* 2012;97:E2328–38. doi:10.1210/jc.2012-2326.
- [19] Ziyadeh J, Le Merrer M, Robert M, Arnaud E, Valayannopoulos V, Di Rocco F. Mucopolysaccharidosis type I and craniosynostosis. *Acta Neurochir (Wien)* 2013;155:1973–6. doi:10.1007/s00701-013-1831-9.
- [20] Oussoren E, Mathijssen IMJ, Wagenmakers M, Verdijk RM, Bredero-Boelhouwer HH, van Veelen-Vincent M-LC, et al. Craniosynostosis affects the majority of mucopolysaccharidosis patients and can contribute to increased intracranial pressure. *J Inherit Metab Dis* 2018;41:1247–58. doi:10.1007/s10545-018-0212-1.
- [21] Stella I, Vinchon M, Guerreschi P, De Berranger E, Bouacha I. Case update on cranial osteopetrosis: which is the role of the neurosurgeon? *Childs Nerv Syst ChNS Off J Int Soc Pediatr Neurosurg* 2017;33:2181–6. doi:10.1007/s00381-017-3553-4.

- [22] Millán JL, Narisawa S, Lemire I, Loisel TP, Boileau G, Leonard P, et al. Enzyme replacement therapy for murine hypophosphatasia. *J Bone Miner Res Off J Am Soc Bone Miner Res* 2008;23:777–87. doi:10.1359/jbmr.071213.
- [23] Salles JP. Clinical Forms and Animal Models of Hypophosphatasia. *Subcell Biochem* 2015;76:3–24. doi:10.1007/978-94-017-7197-9_1.
- [24] Whyte MP. Physiological role of alkaline phosphatase explored in hypophosphatasia. *Ann N Y Acad Sci* 2010;1192:190–200. doi:10.1111/j.1749-6632.2010.05387.x.
- [25] Whyte MP, Wenkert D, Zhang F. Hypophosphatasia: Natural history study of 101 affected children investigated at one research center. *Bone* 2016;93:125–38. doi:10.1016/j.bone.2016.08.019.
- [26] Di Rocco F, Baujat G, Cormier-Daire V, Rothenbuhler A, Linglart A. Craniosynostosis and hypophosphatasia. *Arch Pediatr* 2017;24:5S89-85S92. doi:10.1016/S0929-693X(18)30022-8.
- [27] Gasque KCS, Foster BL, Kuss P, Yadav MC, Liu J, Kiffer-Moreira T, et al. Improvement of the skeletal and dental hypophosphatasia phenotype in *Alpl*^{-/-} mice by administration of soluble (non-targeted) chimeric alkaline phosphatase. *Bone* 2015;72:137–47. doi:10.1016/j.bone.2014.11.017.
- [28] Liu J, Campbell C, Nam HK, Caron A, Yadav MC, Millán JL, et al. Enzyme replacement for craniofacial skeletal defects and craniosynostosis in murine hypophosphatasia. *Bone* 2015;78:203–11. doi:10.1016/j.bone.2015.05.005.
- [29] Kosnik-Infinger L, Gendron C, Gordon CB, Pan BS, van Aalst JA, Vogel TW. Enzyme replacement therapy for congenital hypophosphatasia allows for surgical treatment of related complex craniosynostosis: a case series. *Neurosurg Focus* 2015;38:E10. doi:10.3171/2015.2.FOCUS14847.

Figure Legends

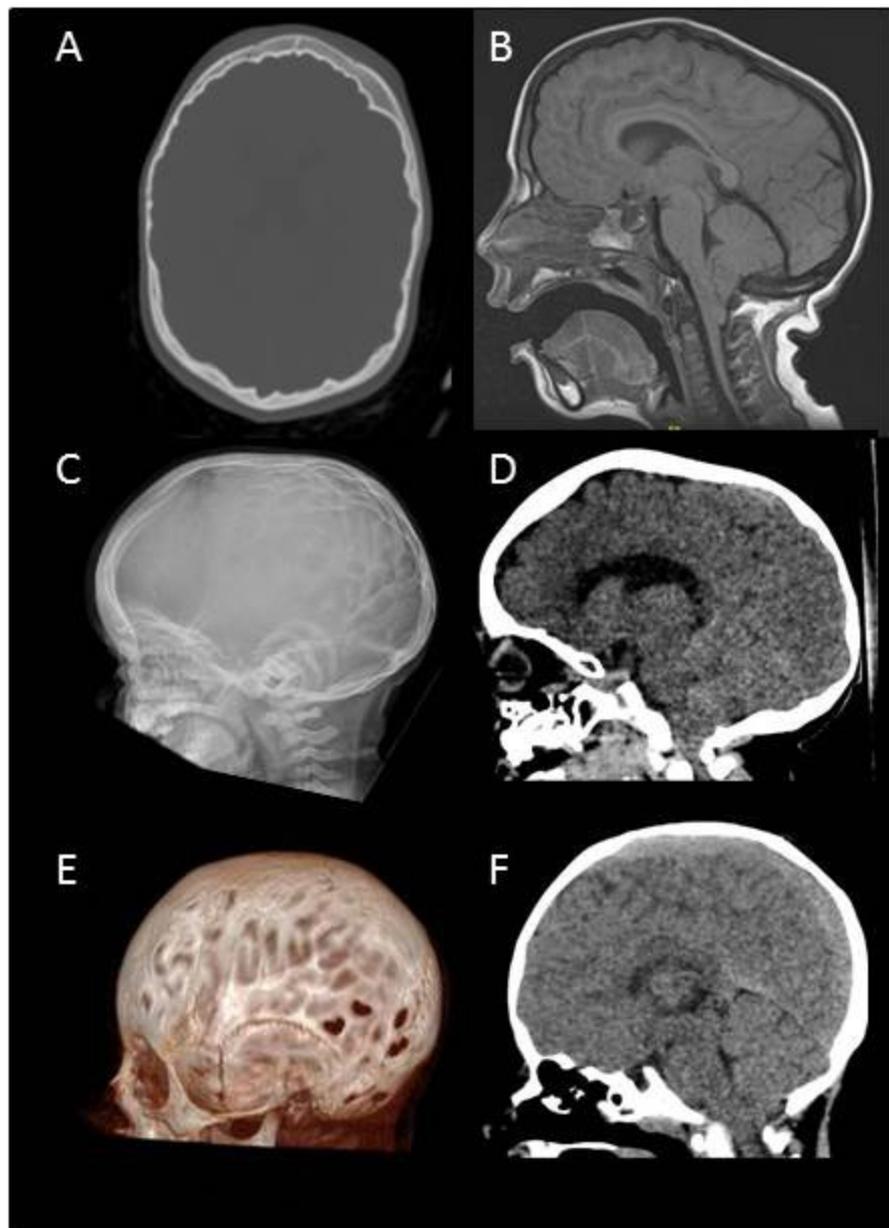
Figure 1.

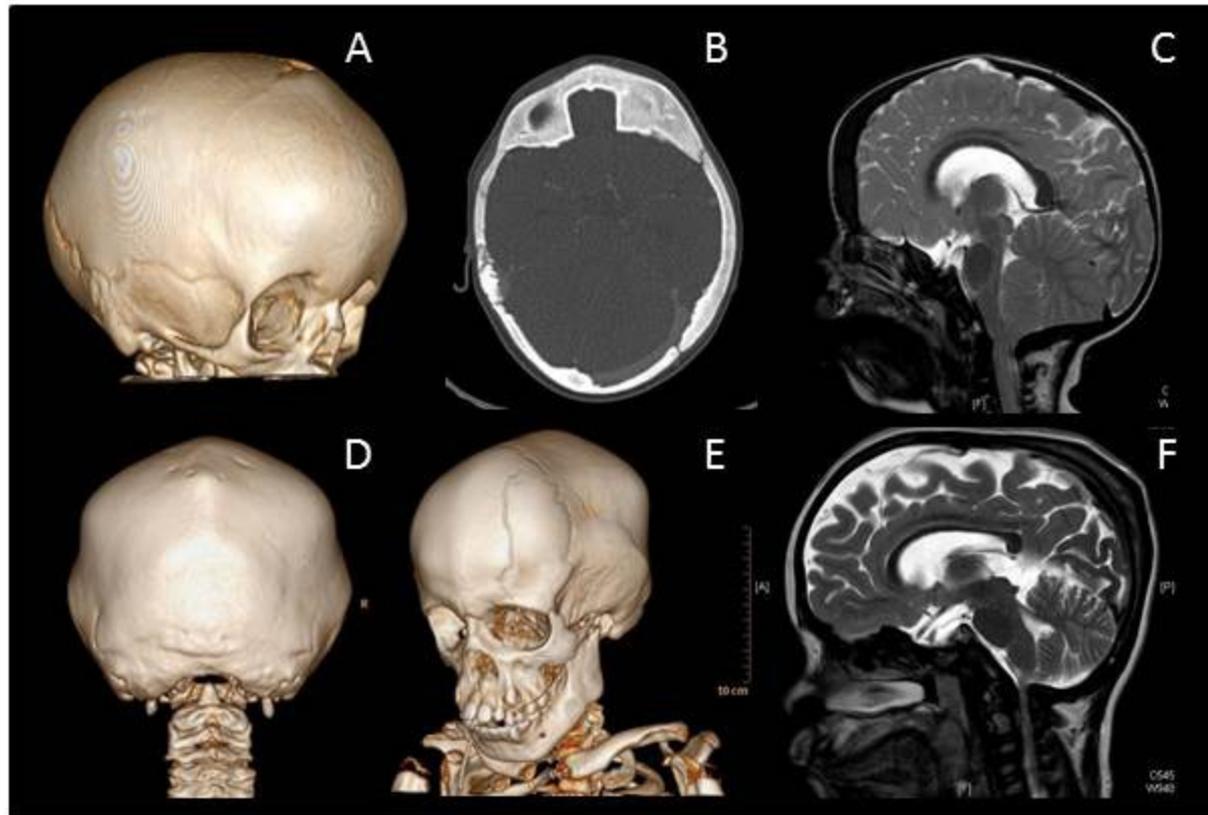
Axial Skull CT (A) and sagittal MRI (B) of a child with X-linked hypophosphatemia; Lateral view X-rays (C) and CT sagittal reconstruction (D) of the skull of a child with pseudohypoparathyroidism; 3D skull CT (E) and sagittal reconstruction (F) of a child with hypophosphatasia.

Note the thumb-printing and descent of cerebellar tonsils.

Figure 2.

Skull CT and MR imaging in a child with osteopetrosis (A, B , C) and in a child with MPS (D, E, F).





	Sagittal suture fusion	Pansynostosis/oxycephaly
X-linked hypophosphatemia	+	
VDDR due to 1-alpha deficiency	+	
Hypophosphatasia	+	+
Pseudohypoparathyroidism		+
Mucopolysaccharidosis	+/-	+
Mucopolipidosis type 2		+
Osteopetrosis		+