

Western University
Scholarship@Western

Paediatrics Publications

Paediatrics Department

3-1-2020

Bulging anterior fontanelle and dense bones in an infant.

Camilla Raya Halgren

Jenna Lakhani

Samantha Colaiacovo

Chitra Prasad

chitra.prasad@lhsc.on.ca

Follow this and additional works at: <https://ir.lib.uwo.ca/paedpub>



Part of the [Pediatrics Commons](#)

Citation of this paper:

Halgren, Camilla Raya; Lakhani, Jenna; Colaiacovo, Samantha; and Prasad, Chitra, "Bulging anterior fontanelle and dense bones in an infant." (2020). *Paediatrics Publications*. 507.

<https://ir.lib.uwo.ca/paedpub/507>

Clinician's Corner

Bulging anterior fontanelle and dense bones in an infant

Camilla Raya Halgren MD¹, Jenna Lakhani MD², Samantha Colaiacovo MS CGC³,
Chitra Prasad MD FRCPC FCCMG FACMG⁴

¹Department of Paediatrics, London Health Sciences Centre, Schulich School of Medicine and Dentistry, Western University, London, Ontario; ²Department of Paediatrics, London Health Sciences Centre, Schulich School of Medicine and Dentistry, Western University, London, Ontario; ³Department of Medical Genetics, London Health Sciences Centre, Schulich School of Medicine and Dentistry, Western University, London, Ontario; ⁴Department of Genetics, Metabolism and Department of Paediatrics, London Health Sciences Centre, Schulich School of Medicine and Dentistry, Western University, London, Ontario

Correspondence: Chitra Prasad, Department of Genetics, Metabolism and Department of Paediatrics, London Health Sciences Centre, Schulich School of Medicine and Dentistry, Western University, 800 Commissioners Rd E, London, Ontario, N6A 5W9. Telephone 519-685-8140, fax 519-685-8214, e-mail Chitra.prasad@lhsc.on.ca

CASE PRESENTATION

A 3-month-old term nonconsanguineous female infant was found to have a bulging anterior fontanelle at her 2-month visit. Two weeks later upon presenting to the emergency room with a viral illness, investigations showed hypophosphatemia 0.49 mmol/L (1.3 to 2.6 mmol/L), normocalcemia 2.65 mmol/L (2.24 to 2.74 mmol/L), and parathyroid hormone (PTH) <0.3 pmol/L (1.6 to 6.9 pmol/L). Workup for hypophosphatemia including head and renal ultrasounds was unremarkable. X-rays showed flaring of metaphyses in femurs, tibiae, and fibulae, and she was started on phosphate (3 mmol 4 times a day) and vitamin D (Calcitriol equivalent to 1,000 IU daily) for presumed congenital rickets. Two weeks into treatment, she was admitted to the Paediatric Critical Care Unit with status epilepticus secondary to hypocalcemia with an ionized calcium of 0.97 mmol/L (1.09 to 1.3 mmol/L). 1,25-Dihydroxy Vitamin D levels returned at >480 pmol/L (60 to 208 pmol/L) ruling out congenital rickets. She had significant anemia with hemoglobin 85 g/L (100 to 140 g/L), thrombocytopenia $131 \times 10^9/L$ (150 to $400 \times 10^9/L$), and blasts ($0.141 \times 10^9/L$) on peripheral smears. Clinical examination revealed nystagmus and no hepatosplenomegaly. Skeletal survey showed a new finding of diffuse bone sclerosis along with fraying of metaphyses diffusely (Figures 1 and 2). A head magnetic resonance imaging demonstrated enlarged lateral and third ventricles (Figure 3). A bone marrow biopsy sample was difficult to obtain. However, findings of hypophosphatemia, hypocalcemia, bicytopenia, and x-ray abnormalities prompted molecular studies, which confirmed the diagnosis.

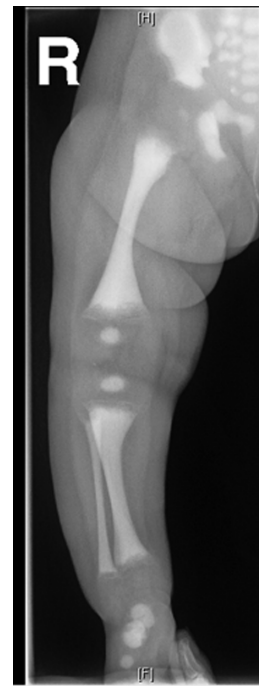


Figure 1. Extensive sclerosis of femurs and fraying of metaphyses

Received: January 9, 2018; Accepted: August 16, 2018

© The Author(s) 2019. Published by Oxford University Press on behalf of the Canadian Paediatric Society. All rights reserved. For permissions, please e-mail: journals.permissions@oup.com

DIAGNOSIS: MALIGNANT INFANTILE OSTEOPETROSIS

Next-generation sequencing identified a pathogenic mutation in the T-cell immune regulator 1 (*TCIRG1*) gene (c.1674-1G>A), which confirmed the suspicion of malignant infantile osteopetrosis (MIO). This gene is associated with an autosomal recessive form of MIO. As only one pathogenic mutation was found, deletion/duplication and whole-exome sequencing were undertaken to identify a second mutation, however, no relevant abnormalities were identified. It is possible a second *TCIRG1* mutation is present which current genetic testing technology cannot detect, as previous reports have described patients with a clinical phenotype of MIO with only one identified mutation (1). With the corresponding clinical phenotype, we proceeded with definitive management for MIO, which is bone marrow transplantation (BMT). The patient's brother was a favourable HLA match. In preparation for transplant, a CT head demonstrated obstructive hydrocephalus with transependymal edema and splaying of the skull fissures. The patient had a ventriculo-peritoneal shunt inserted with subsequent resolution of hydrocephalus. She underwent a successful allogeneic BMT and is currently in follow-up but unfortunately, has ongoing visual impairment.

Autosomal recessive MIO is the most severe form of osteopetrosis, with an estimated annual incidence of 1/100,000 to 500,000. It is a disorder of bone remodelling caused by failure of osteoclasts to resorb immature bone (2). This leads to abnormal bone marrow cavity formation and subsequent displacement of hematopoietic cells from the medullary cavity, resulting in extramedullary hematopoiesis and possible bone marrow failure (anemia, infection, and blasts on peripheral

smear). Impaired bone remodelling can cause narrowing of cranial nerve foramina resulting in optic nerve compression, visual impairment, or obstructed cerebrospinal fluid flow and hydrocephalus. Abnormal remodelling of primary bone to lamellar bone leads to bones that are prone to fracture. These abnormalities result in the classic features of the disease: bone marrow failure, visual impairment, and fractures.

Children often present within the first 3 months of life, frequently due to parental concern for the child's vision. Other common presentations include failure to thrive and recurrent infections (3). Less common presentations include hypocalcemic seizures, bruising, fractures, nasal congestion, and abnormal craniofacial appearance. A diagnosis of MIO relies strongly on clinical suspicion. Visual impairment, hypocalcemia, and anemia can suggest a diagnosis of MIO. Typical x-ray findings of sclerotic bony changes, as seen in our patient, can help support the diagnosis with confirmation of sclerosis through bone biopsy.

When assessing a neonate presenting with hypocalcemia, such as our patient, it is important to confirm that this is a true result using ionized calcium. Then, assess the status of other extended electrolytes including magnesium and phosphate, which if low, could indicate losses through either the GI or renal systems. A 24-hour urine sample could be considered to accurately assess potential losses. Concurrently, investigate for a potential endocrinologic cause by obtaining both PTH and 25-hydroxy vitamin D levels. An elevated PTH indicates a secondary

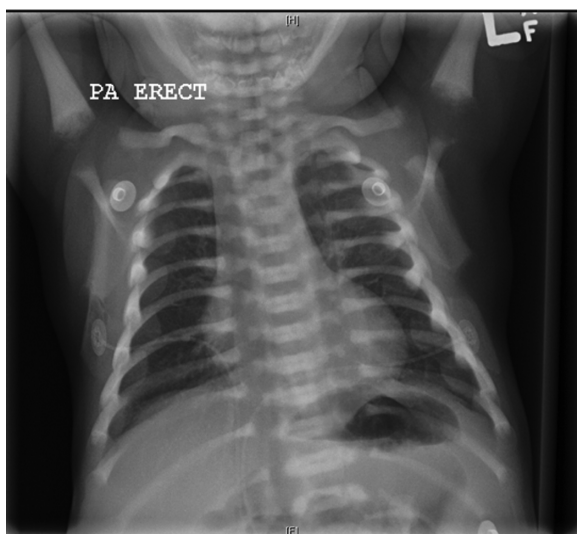


Figure 2. Frayed metaphyses of humeral heads and scapula, expansion of anterior ribs at costochondral junctions.

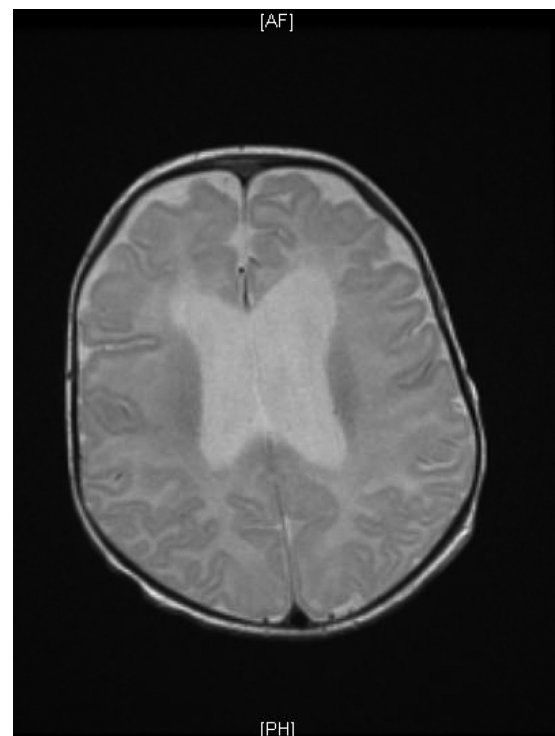


Figure 3. Enlarged lateral ventricles on magnetic resonance imaging.

hyperparathyroidism which has numerous causes including vitamin D-dependent rickets. In this case, vitamin D levels would be low. A low or inappropriately normal PTH along with a normal vitamin D level would indicate hypoparathyroidism, for which a separate workup would need to be initiated (2). If despite these investigations, a diagnosis is not clear, it is then worthwhile to consider rarer causes such as osteopetrosis.

Genetic investigation is needed to confirm the diagnosis. MIO is a heterogeneous disease with numerous possible associated genetic loci. A pathogenic heterozygous mutation in *TCIRG1*, as seen in our patient, has been associated with MIO. *TCIRG1* codes for vacuolar H⁺ ATPase which plays an essential role in osteoclast function. Autosomal dominant forms of osteopetrosis are more benign.

Management of MIO involves supportive treatment until curative BMT. Patients with MIO can have severe pancytopenia and may become transfusion dependent. Failure to thrive is another common complication, which requires a team of allied health professionals to optimize growth in preparation for transplantation. Medical therapies including steroids, calcitriol and interferon gamma-1B have been studied; however, BMT is the only treatment shown to alter the disease's course (4).

MIO has a high mortality rate in those with severe disease and bone marrow failure. A common cause of early death is overwhelming infection. A favourable prognosis is seen in patients who are not transfusion dependent and alive at age two (3). Timing of BMT can affect outcomes significantly, as delay can cause complications including visual loss and obstructive hydrocephalus. Although BMT will halt further disease progression, previous morbidity from bone remodelling cannot be reversed.

Hypophosphatemia is an unusual presenting symptom of MIO. The development of hypocalcemia in our patient eventually led to the diagnosis, as this along with her distinctive x-ray findings and signs of bone marrow failure are classic features of the disease.

CLINICAL PEARLS

1. Bony changes on plain films, including striking sclerosis, may be the first sign of MIO.
2. The combination of hypocalcemia, cytopenias, and bony abnormalities (on x-ray and clinical exam) may indicate early MIO.
3. Timely BMT can be life-saving in MIO and significantly decreases morbidity. Therefore, early recognition of this rare condition is essential and genetic counselling is important for the family.

ACKNOWLEDGEMENTS

We thank Dr. Serina Patel MD FRCPC Hematologist LHSC and Dr. Peter Kannu, MB ChB (Otago), PhD, DCH, FRACP Staff Physician, Division of Clinical and Metabolic Genetics for their help with the clinical care.

Informed Consent: We thank the family for allowing us to share their information.

Funding Information: There are no funders to report for this submission.

Potential Conflicts of Interest: All authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

Origin of Work: London Health Sciences Centre, London, Ontario, Canada.

References

1. Shamriz O, Shaag A, Yaacov B, et al. The use of whole exome sequencing for the diagnosis of autosomal recessive malignant infantile osteopetrosis. *Clin Genet* 2017;92(1):80–5.
2. Kliegman R, Stanton B, St. Geme JW, Schor NF, Behrman RE. *Nelson Textbook of Pediatrics*, 20th edn. Philadelphia, PA: Elsevier, 2016.
3. Wilson CJ, Vellodi A. Autosomal recessive osteopetrosis: Diagnosis, management, and outcome. *Arch Dis Child* 2000;83(5):449–52.
4. Wu CC, Econs MJ, DiMeglio LA, et al. Diagnosis and management of osteopetrosis: Consensus guidelines from the osteopetrosis working group. *J Clin Endocrinol Metab* 2017;102(9):3111–23.