

Late-onset Visual Loss in Osteopetrosis

*Abdul-Majid Wangai,¹ Sheila Waa,¹ Maryam Wangai,² Erastus Amayo,³ Oluoch Olunya⁴

فقدان البصر المتأخر في تصخر العظم

عبد المجيد وانجي، شيلا وا، مريم وانجي، ايراستوس أمايو، اولونيا اولوش

المخلص: حدوث فقدان البصر المتأخر هو من مضاعفات انفخاخ العصب وزيادة الضغط داخل الجمجمة. هذا وصف للحالة الأولى في شرق أفريقيا لمريضة عمرها 32 عاما جاءت تشكو من العمى المفاجئ، والصداع وضعف الجسم. وقالت أنها سبق لها أن عولجت من كسور عديدة بدون أسباب معينة. أوضح فحص العين عن انفخاخ العصب البصري الذي برر هذا العمى. هذه القضية تسلط الضوء على أهمية الاشتباه في حالات الكسور غير المبررة مع ظهور العمى المتأخر.

مفتاح الكلمات: تصخر العظم؛ العمى؛ وقت متأخر، تقرير حالة؛ شرق أفريقيا.

ABSTRACT: Late-onset visual loss is a complication of nerve entrapment and increased intracranial pressure. We hereby describe the first case in Eastern Africa. A 23 year-old lady presented with sudden blindness, headaches and body weakness. She had previously had treatment for multiple unexplained fractures. Findings of optic nerve entrapment explained this blindness. This case highlights the need to have a high index of suspicion in cases of unexplained fractures with late-onset blindness.

Keywords: Osteopetrosis; Blindness; Late onset; Case report; Eastern Africa

OSTEOPETROSIS IS A CONGENITAL clinical syndrome characterised by failure of osteoclasts resulting in impaired bone remodelling. The resultant bony defect leads to bone fragility (with a resultant propensity to fractures despite increased bone mass), haemopoietic insufficiency, nerve entrapment syndromes and growth impairment. Osteopetrosis was first described by a German radiologist, Albers-Schonberg in 1904.¹ It is a heterogeneous disorder describing a cluster of clinical entities sharing a common pathogenic nexus in the osteoclast.² This rare condition is often missed; it presents with multiple fractures and osteosclerotic bones of no known cause and without any prior traumatic events. Three forms of the disease are diagnosed in infancy, childhood and adulthood.³ We hereby describe the first case from Eastern Africa of the adolescent-onset form of osteopetrosis.

Case Report

A 23 year-old lady presented in Nairobi, Kenya

for admission with a 2-week history of headaches, general malaise and body weakness. Over the 3 days prior to admission, she had gone blind and had to drop out of her college work in order to visit the hospital for care. Six months prior to presentation she had been seen elsewhere for episodes of severe temporal headaches associated with some visual disturbance and nausea/vomiting. The diagnosis was optic neuritis and she was put on methylprednisolone for 6 months until her presentation with blindness. For the 4 months prior to admission, she noted increased weight; she also had a previous history of fractured tibia, fibula and humerus for which internal fixation had been done.

On examination, she was pyrexia and had obvious cushinoid features. Neurologically, she was fully awake with Glasgow Coma Scale (GCS) scale of 15/15. The only findings were those of quadriparesis (motor power 3, all limbs) and the optic fundii being oedematous with raised obscuring everted margins and bilateral optic atrophy. She had suprapubic tenderness and epigastric guarding with marked tenderness and hepatosplenomegaly.

¹Aga Khan University Hospital, Nairobi, Kenya; ²Management Sciences for Health, Nairobi, Kenya; ³Departments of ³Medicine and ⁴Surgery, School of Medicine, University of Nairobi, Kenya.

*Corresponding Author email: drmajidwangai@yahoo.co.uk

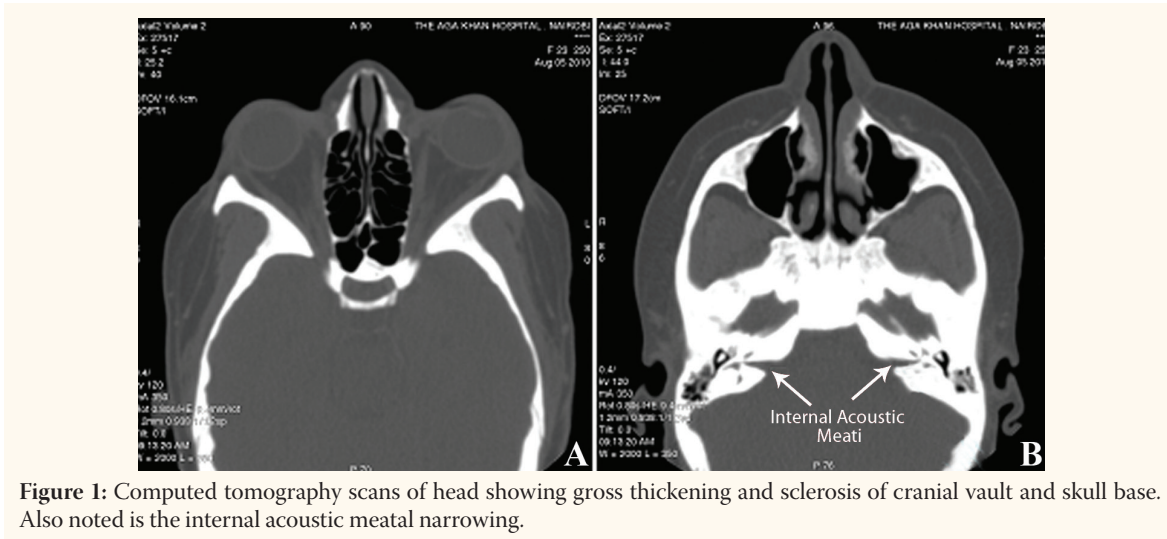


Figure 1: Computed tomography scans of head showing gross thickening and sclerosis of cranial vault and skull base. Also noted is the internal acoustic meatal narrowing.

She had frontal bossing and nystagmus. During the physical examination she had a grand mal seizure.

Only limited investigations could be done due to the financial limitations of the family. The pertinent ones were as follows. The urine culture sensitivity parameters showing increased pus cells and white blood cells (WBC) at 20–40 /hpf; 48 hours incubation yielded a growth of *Escherichia coli* organisms sensitive to all quinolones. A full haemogram showed haemoglobin of 9.5 gm and WBC count of 23 with a neutrophilic preponderance. The peripheral film showed a microcytic hypochromic picture. Liver function tests showed raised transaminases. Renal function tests, uric acid and thyroid function tests were all normal; however, the calcium levels were low at 1.8 Mmol/L. Serial blood sugars remained elevated and were controlled on a sliding scale of insulin therapy tailored to a glycaemic level of 4–7 Mmol/L. The

glycaemic excursions remained erratic throughout the admission period with sporadic high levels (26 Mmol/L), but mainly an average of 16 Mmol/L as the highest peak. Glycated haemoglobin was elevated at 12%. Both C reactive protein and D-Dimers were elevated (15 and 23 respectively), but there were unreactive serum HIV antigens. A previous antibody test had been inconclusive. The electroencephalogram (EEG) reading was unremarkable.

A lumbar puncture was done under aseptic condition at lumbar levels 3/4 regions with one pass. The cerebrospinal fluid (CSF) was under pressure (240 mm of water) and appeared clear on observation. The CSF sample was sent for cytology, biochemistry and microbiology testing. The only significant finding was an increased glucose level of 14 Mmol/L.

Blood lipids were markedly elevated (both

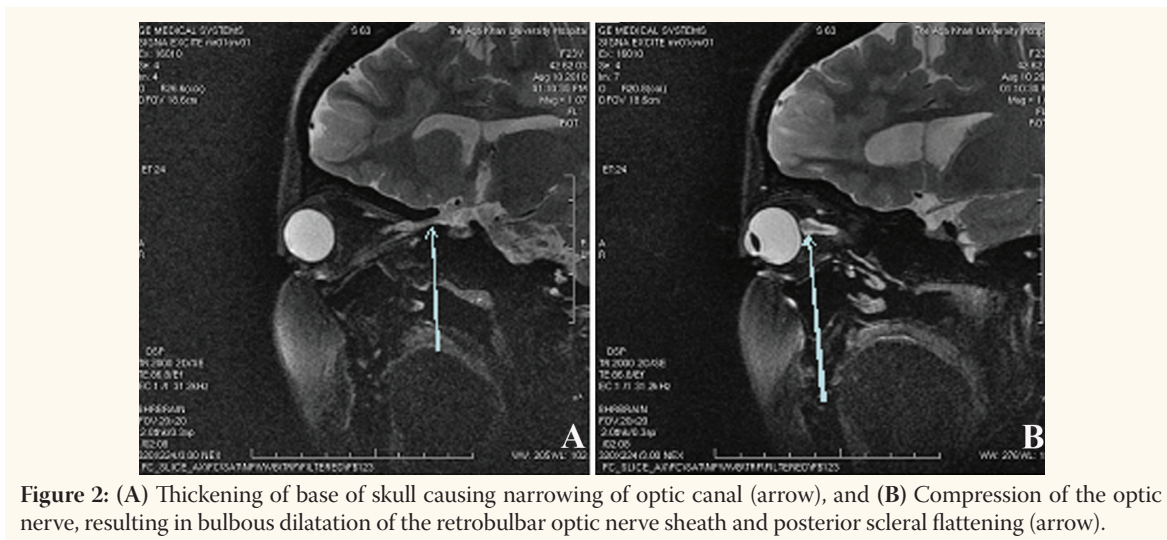


Figure 2: (A) Thickening of base of skull causing narrowing of optic canal (arrow), and (B) Compression of the optic nerve, resulting in bulbous dilatation of the retrobulbar optic nerve sheath and posterior scleral flattening (arrow).

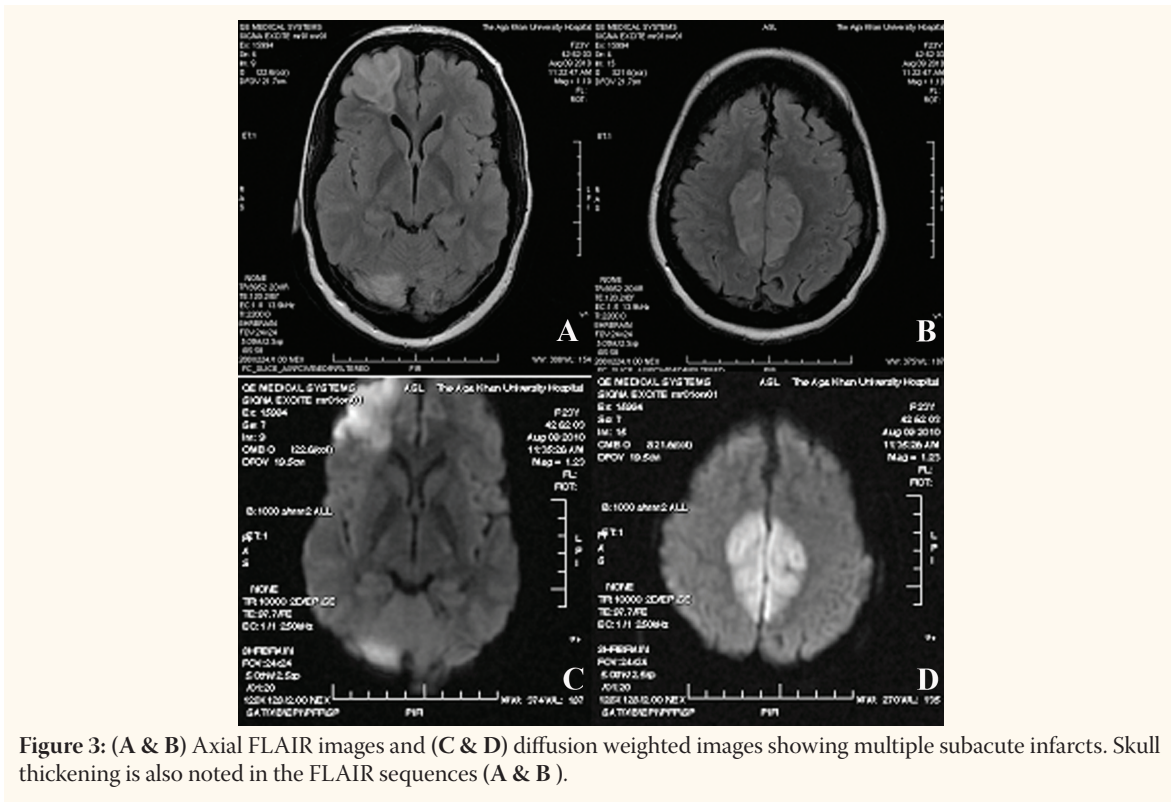


Figure 3: (A & B) Axial FLAIR images and (C & D) diffusion weighted images showing multiple subacute infarcts. Skull thickening is also noted in the FLAIR sequences (A & B).

total and low density lipoprotein cholesterol and triglyceride levels). Blood cultures were done as part of the septic screening and no growth was obtained. Anti-nuclear antibodies and factors, hepatitis A, B, C, and tuberculosis polymerase chain reaction tests were all negative.

The chest radiograph showed generalised osteoporosis with a visible humerus fracture and metallic implant in situ. Generalised bone osteosclerosis was noted. The abdominal ultrasound was normal with the exception of hepatosplenomegaly. No other abnormalities were seen. An enhanced computed tomography (CT) scan of the head showed gross hyperdensity of the cranial vault and the base of skull consistent with osteopetrosis [Figure 1]. Also visible was a narrowing of the optic canals and internal auditory meatus. A CT scan of the orbits showed bilateral dense sclerosis of the bones consistent with osteopetrosis with reduced optic canal circumference (4.4 mm x 3.7 mm right and 4.0 mm x 3.5 mm left) [Figure 2]. Magnetic resonance (MR) imaging showed multiple subacute infarcts with thickening of the orbital bones at the optic canal causing narrowing of the optic nerve [Figure 3]. The optic nerve was tortuous causing the flattening of sclera posteriorly as well as bilateral bulbous dilatation of the retrobulbar

optic nerve sheath. This had led to bilateral optic canal stenosis causing optic nerve atrophy. An MR angiography showed bilateral segmental narrowing of the distal vertebral arteries and proximal basilar artery and, to a milder extent, of both internal carotid arteries at the level of the siphon [Figure 4]. Focal narrowing of proximal right middle cerebral artery was also observed.

This was a clear case of late-onset osteopetrosis with the long term steroid use associated conditions of Cushing's disease, diabetes, dyslipidaemia, peptic ulcer syndrome and osteoporosis. The osteopetrosis had caused anaemia, internal carotid compression and narrowing of vertebral arteries, cerebral infarcts, multiple fractures, and bilateral optic canal stenosis causing bilateral optic atrophy.

The patient was treated with sodium valproate to prevent seizures, enteric-coated aspirin with clopidogrel, rosuvastatin, insulin, iron supplement, ciprofloxacin, sertraline, metformin, glimepiride, calcitriol supplement, oxybral, vitamin D, gamma interferon, erythropoietin, diclofenac and physiotherapy. Calcitriol use is controversial, but in this index case it was also given for the assumed short-term benefit. The patient made a moderate improvement and was able to be ambulated with minimal support and could feed herself as well as

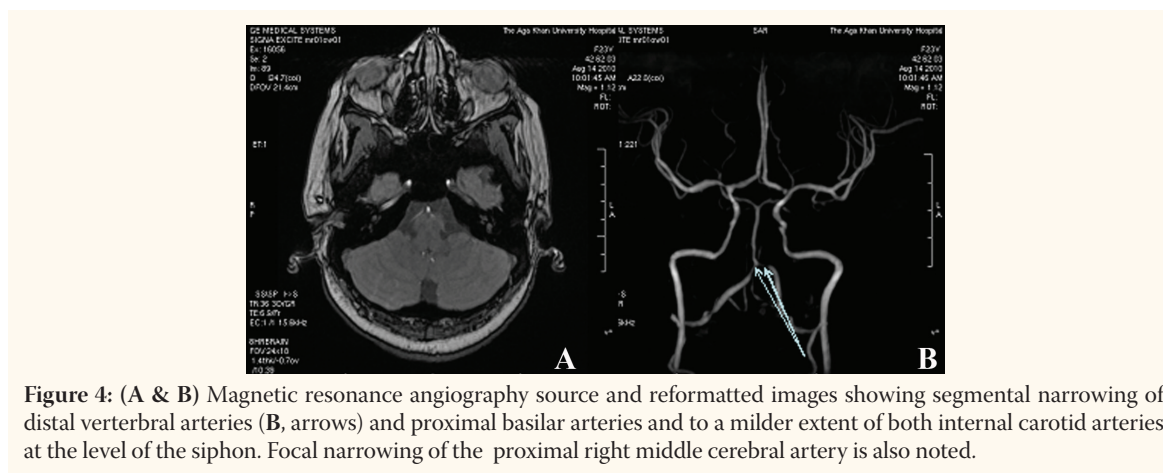


Figure 4: (A & B) Magnetic resonance angiography source and reformatted images showing segmental narrowing of distal vertebral arteries (B, arrows) and proximal basilar arteries and to a milder extent of both internal carotid arteries at the level of the siphon. Focal narrowing of the proximal right middle cerebral artery is also noted.

undertake basic living activities unaided.

An intraventricular catheter was placed showing an intracranial pressure of 32 mmHg. Via the same catheter, the cerebral spinal fluid was drained until the levels reached 8 mmHg. The catheter was left in situ as further surgical options were being discussed with the patient's family. The visual acuity remained poor (with only finger movements visible) and she thus became very depressed, as she had to discontinue college work and start learning Braille. On antidepressants and psychosocial counselling support this depressive component of her condition improved well.

Unfortunately, the patient's family was unable to pay for the much needed definitive optic canal decompression and cranial vault expansion surgery. The hospital did not have the ability at the time to offer complimentary care. Hence a referral to the public hospital system was the only option. A surgical widening of the optic canal and decompression of the vertebral arteries was considered to be too dangerous in a public hospital due to their lack of equipment and level of postoperative care. Consequently, the consensus was to abandon the option of surgical intervention and refer the patient to a public hospital for conservative and supportive management.

Discussion

In 1999, Baron reviewed what is known in cell biology of bone remodelling⁴ and the process of bone remodeling was further elucidated by Plow *et al.*⁵ Osteoblasts are of fibroblastic origin whose function is to synthesise bone matrix in new osteocytes. In contrast, osteoclasts are derived from macrophage/monocyte lineage and they function in solubilisation of bone mineral causing bone resorption.

Bone modelling is the process of changing bone shape and is prominent in childhood causing growth. Remodelling, on the other hand, is the degradation of bone tissue from existing bony structures and replacing these with newly synthesised bony cells. Osteopetrosis is the failure of modelling leading to improper growth and overgrowth of bony surfaces. This causes constriction of other structures, which leads to the myriad of conditions that constitute the disease process. The primary underlying defect in osteopetrosis is failure of the osteoclasts to reabsorb bone. The exact molecular or genetic defect and site of these mutations are largely unknown.

Osteopetrosis is thought to be autosomal dominant in adult-onset disease, but recessive in both infantile- and intermediate-onset. The condition is often diagnosed incidentally (usually before age 1 year) due to the effects on other tissues affected by the bone modeling limitations of the disease.

Overall, the global incidence is unknown because no epidemiological studies have been conducted; however, one estimate suggested 1 case in 100,000–500,000 in the population.⁶ Untreated, the infantile form results in death by the first

decade of life due to severe anaemia, resultant cardiac failure, bleeding and/or severe sepsis. In its adult form, osteopetrosis is usually a milder form of disease with good prognosis.

From the history, our patient had the childhood form with the consequences of bony defects: neuropathies due to nerve entrapment (in our case optic canal stenosis/atrophy/blindness), frontal bossing and paraparesis; haemopoetic consequences (anaemia, hepatosplenomegaly), and infections (in our case urinary tract infection and septicaemia).

Medical care with high dose calcitriol (vitamin D) helps by stimulating dormant osteoclasts and thus stimulating bone resorption.⁷ Although controversial, this treatment usually produces a dramatic result which unfortunately is not sustained after the therapy ceases. Gamma interferon produces long-term benefits especially in combination with calcitriol. Erythropoietin corrects anaemia, and corticosteroids have been used to correct the anaemia and stimulate bone resorption. In our index case, the patient was put on steroids for too long (6 months) prior to our seeing her and she had thus developed steroid therapy side effects.

Definitive treatment also involves novel approaches such as bone marrow transplants, although these are unavailable in the Eastern Africa region. In several case series where this has been possible, there has been proven success in altering the course of the disease; however, visual improvement rarely occurs.⁸

Conclusion

In osteopetrosis, surgical treatment is often necessary for the constellation of problems related to bony defects,⁹ usually to manage fractures. Prior to presentation, our patient had had four surgeries for internal fixation of fractures. There is a definite benefit from intracranial surgery to decompress soft tissue (vessels and nerve) entrapment syndromes. Such definitive optic canal decompression and

cranial vault expansion surgery would have assisted this case.

Unfortunately, a surgical widening of the optic canal and decompressing the vertebral arteries was considered to be too dangerous in a public hospital with resource constraints, yet the parents could not afford the care at the private facility where she was admitted. We were unwilling to refer the patient for surgery in a public hospital. Although the facilities are there, the surgical supplies, equipment and, more importantly, postsurgical care were wanting in a public facility. We thus had to defer surgery in the private hospital and refer her to a public health facility for conservative care.

References

1. Albers-Schonberg H. Roentgenbilder einer seltenen Knochenkrankung (X-rays of an unusual bone disease). *Munch Med Wochenschr* 1904; 51:365.
2. Stark Z, Savarirayan R. Osteopetrosis. *Orphanet J Rare Dis* 2009; 4:5.
3. Tolar J, Teitelbaum SL, Orchard PJ. Osteopetrosis. *N Engl J Med* 2004; 351:2839–49.
4. Baron R. Anatomy and Ultrastructure of Bone. In: Favus MJ, Ed. *Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism*. 4th ed. Philadelphia: Lippincott Williams & Wilkins, 1999. Pp. 3–10.
5. Plow EF, Qin J, Byzova T. Kindling the flame of integrin activation and function with kindlins. *Curr Opin Hematol* 2009; 16:323–8.
6. Beighton P, Hamersma H, Cremin BJ. Osteopetrosis in South Africa. The benign, lethal and intermediate forms. *S Afr Med J* 1979; 55:659–65.
7. Key L, Carnes D, Cole S. Treatment of congenital osteopetrosis with high dose calcitriol. *N Engl J Med* 1984; 310:409–15.
8. Kulkarni ML, Marakkanavar SN, Sushanth S, Pradeep N, Ashok C, Balaji MD, et al. Osteopetrosis with Arnold Chiari malformation Type I and brain stem compression. *Indian J Paediatr* 2007; 74:412–5.
9. Armstrong DG, Newfield JT, Gillespie R. Orthopaedic management of osteopetrosis: Results of a survey and review of the literature. *J Paed Orthop* 1999; 19:122–32.