IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 19, Issue 3 Ser.15 (March. 2020), PP 30-34
www.iosrjournals.org

Bilateral Optic Atrophy Associated With Central Retinal Atrophy in a Patient with Malignant Infantile Osteopetrosis: A Case Report and Review of the Literature

Dr M. Hassoune, Pr L. Elmaaloum, Dr A. Idrissi, Dr K. Hosni, Dr S. Belaaroussi, Pr B. Allali, Pr A. Elkettani
(Pediatric ophthalmology department, CHU Ibn Rochd, Casablanca, Morocco)
Corresponding Author: M. Hassoune

Abstract: *Osteopetrosis (marble bones, Albers-Schönberg disease, osteosclerosis fragilis generalisata) is a disease of abnormal bone development characterized by an increased thickness and density of cortical and spongy bone. If the base of the skull is involved in osteopetrosis, optic-nerve atrophy may be present as a result of narrowing of the optic foramina. Visual impairment from optic-nerve atrophy may be one of the presenting symptoms. (1) We report a 5-year-old male patient, diagnosed as malignant infantile osteopetrosis while investigating the cause of hepato-splenomegaly associated with severe anemia. Fundus examination revealed atrophy of the optic nerve with visible central retinal atrophy in both eyes. Our finding is similar to characteristics previously reported in the literature about patients with osteopetrosis. Optic canal decompression may be beneficial in some patients but not in others with chorioretinal degeneration*

Key words*: osteopetrosis, bone disease, optic-nerve atrophy, central retinal atrophy*

Date of Submission: 16-03-2020 Date of Acceptance: 01-04-2020

I. Introduction

Osteopetrosis (marble bones, Albers-Schönberg disease, osteosclerosis fragilis generalisata) is a rare hereditary bone disorder characterized by an increased thickness and density of cortical and spongy bone. There are three clinical groups: infantile malignant autosomal recessive; fatal within the first few years of life (in the absence of effective therapy), intermediate autosomal recessive; appears during the first decade of life but does not follow a malignant course, and autosomal dominant; with full-life expectancy but many orthopaedic problems. In all three forms, the main features are pathologic alteration of osteoclastic bone resorption and thickening of cortical and lamellar bones. They are generally described according to the amount of bony involvement and the variations of the clinical manifestations (2). In the former types, multiple symptoms are usually present in infancy or early childhood, whereas in the latter type, the cases are often diagnosed as a chance X-ray finding in adults. Osteopetrosis appears to affect each sex equally; Cases have been reported from fetal life to 75 years of age (1). Optic atrophy, secondary to narrowing of the optic foramina, is the chief ocular manifestation. In the severe forms of the disease, complete bilateral optic atrophy may be present in the first few months of life. Very few visual field studies have been made in individuals with partial optic atrophy, and those studies indicate that there is a generalized contraction of the peripheral fields. In addition to optic nerve atrophy, other ocular disorders may be present. Ophthalmoplegias, nystagmus, exophthalmia and dilated retinal vessels have also been reported. The reduction in haematopoietic cells can also cause haematological abnormalities including thrombocytopenia, anemia, susceptibility to infections and extramedullary haematopoiesis. In the infantile form of the disease, the anemia is usually quite severe, while, if present in the adult form of the disease, it is mild (4). We report a case of malignant infantile osteopetrosis with numerous complications including bilateral optic atrophy, severe anemia and bone fractures.

II. Case Report

A 5-year-old male child, diagnosed as having osteopetrosis autosomal recessive variant since the age of six months, was presented at the department of pediatric ophthalmology of Casablanca with gradual onset loss of vision over a period of 2 years, with neurological abnormalities, such as hearing disorders, mental retardation. He was born full-term of a consanguineous marriage and his birth weight was 3200g. There was no history of similar ocular visual problems in the family. However, there was history of frequent fractures in the past with minimal trauma. An ophthalmologic examination reported loss of visual fixation and pursuit, exophthalmia, strabismus, and paralysis of ocular muscles causing uncoordinated ocular movements. Fundoscopic examination showed bilateral optic atrophy with degenerative maculopathy (image1). The examination of the visual evoked

potentials (VEPs) shows a significant bilateral decrease in the functional activity of the optical pathways. Electroretinogram revealed disorders of retinal electrogenesis concerning photoreceptors mainly cones. On general physical examination, the patient was short statured (his length and weight were both < 3rd percentile), with increased head circumference and frontal bossing (image 2). Patient was pale and was not icteric. Abdomen was distended with hepatomegaly with the liver noted to be 4cm and splenomegaly with the spleen noted to be 7 cm. intraoral examinations showed delayed tooth eruption. A characteristic feature observed in the patient, a marked, uniform and symmetrical increase in bone density, with a loss of distinction between the cortex and the spinal cord, which is typical of osteopetrosis (image 3). Laboratory examination yielded the following: Microcytic hypochromic anemia; thrombocytopenia. Computed tomographyscan of the brain and orbit showed stenosis of both optic canals along with optic nerve sheath dilatation (image 4).

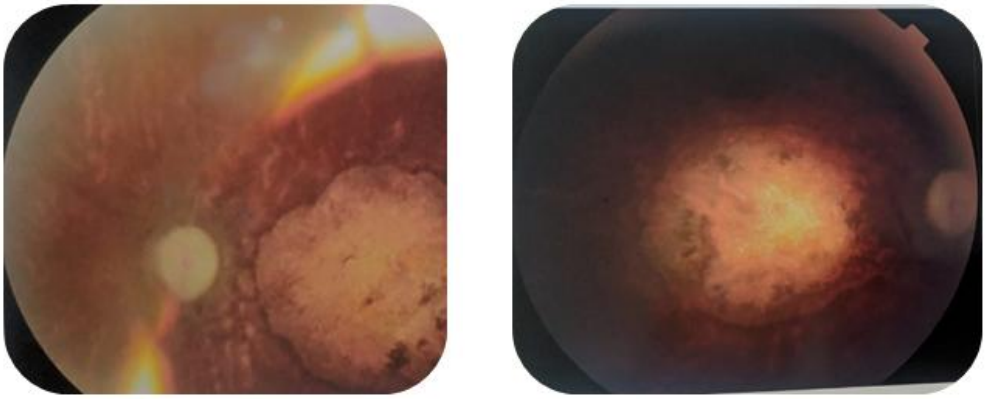

Fig. 1 *Fundoscopic examination showing bilateral optic atrophy with degenerative maculopathy*

Fig. 2 *Patient with osteopetrosis showing strabismus with increased frontal bossing*

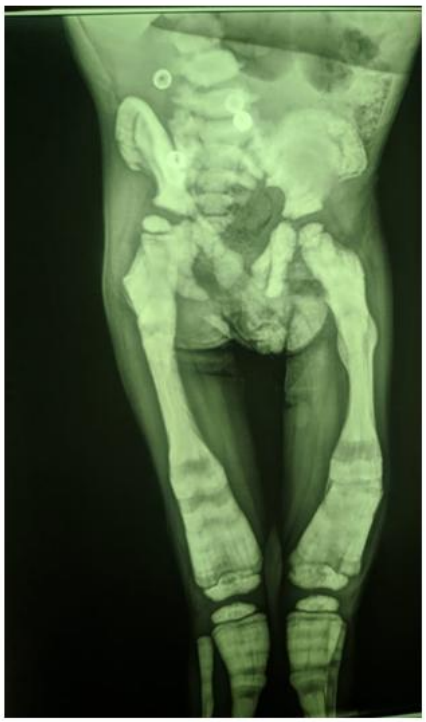

Fig. 3 *Pelvis and femurs. a generalized increase in bone density, the clubbing of the ends of the long bones, and the alternating lines of increased and decreased density parallel to the epiphysis*

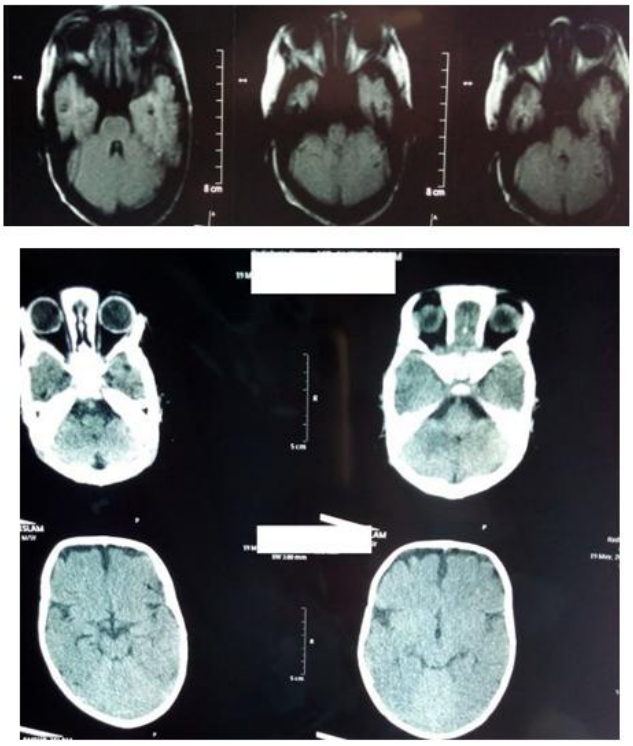

Fig. 4 *Computed tomographyscan of the brain and orbit showed stenosis of both optic canals along with optic nerve sheath dilatation*

III. Discussion

In 1904 the German radiologist, Albers-Schönberg, described a 26-year-old man with generalized skeletal sclerosis and multiple fractures. He introduced the term "marble bone disease." In 1926 Karshner coined the term "osteopetrosis''. It is clinically a highly heterogeneous group of conditions that share the hallmark of increased bone density on radiographs due to abnormalities in osteoclast differentiation or function. Three clinical variants that have been described are: (5) MIOP, an autosomal recessive disorder; (6) the autosomal dominant type that presents during adolescence and are a more benign form; and (7) osteopetrosis combined with renal tubular acidosis due to carbonic anhydrase II deficiency. The incidence of MIOP is 1/250,000 in the

general population. It is more frequent in certain ethnic groups including inhabitants of Costa-Rica in whom its incidence is much higher than elsewhere (3.4/100,000) (8). Malignant infantile osteopetrosis (MIOP) generally begins in utero(9). it presents at birth (10-11), or within the first year of life and is associated with increased severity compared to the autosomal dominant form (12). The diagnosis of osteoepetrosis was reported in our patient at the age of one year. Mutations in the gene ATP6i (TCIRG1) coding for an osteoclast specific a3 subunit V-ATPase vacuolar pump have been found in an approximately 50% of affected children (13-14). Recently mutations in the ClC7 (Clcn7) chloride channel have been found to also cause infantile recessive osteopetrosis (15). Abnormal bone formation and fibrous tissue replace the bone marrow space and finally hematopoesis is decreased. Extramedullar hematopoesis occurs resulting in leukoerythro-blastic anemia and thrombocytopenia. Liver and spleen enlarge progressively. Hemolysis resulting from hypersplenism worsens the anemia and thrombocytopenia (16-17). The diagnosis of osteopetrosis was revealed in our case by hepato-splenomegaly associated with severe anemia. Optic atrophy, secondary to narrowing of the optic foramina, is the chief ocular manifestation of osteopetrosis with the degree of involvement. Other ophthalmic manifestations in osteopetrosis include chorioretinal degeneration, nystagmus, strabismus, proptosis, ptosis (18). Sporadic ocular association of cataract has been reported. Severe visual loss is present in ~ 80% of cases of the infantile form of the disease and is due primarily to optic atrophy. The optic disc is chalky white with well defined margins without any gliosis with vessels being normal and physiological cup being present, pointing towards primary optic atrophy. Chorioretinal degeneration may also be a significant cause of visual loss in patients with infantile malignant osteopetrosis, and this may explain lack of response to decompression surgery (18). As is reported in our case presenting optic atrophy associated with degenerative maculopathy, the visual evoked potentials (VEPs) are the most useful way of monitoring optic nerve involvement, while an electroretinogram (ERG) may help rule out associated neurological disease (18). The visual loss is progressive and almost always occurs within the first year of life. Severely affected children may show absent or severely attenuated VEPs within the first three months, and in some this is apparent at birth. Because the rate of visual deterioration tends to plateau after 18 months to two years, some children, despite poor early neurophysiological findings, maintain a degree of visual acuity into later childhood. The pathology of the deafness is probably secondary to a combination of bony compression of the nerve, sclerosis of the middle ear ossicles, and/or chronic middle ear effusion. Early insertion of ventilatory "grommet" tubes should be considered (15). Radiographically, the involved bones have a dense, structureless sclerotic appearance. Differentiation between the bone components cortex, epiphyseal plates, spongios and medullary cavity may be lost (3). Usually cases are diagnosed on X-rays; sometimes bone marrow biopsy may be required. Molecular diagnosis is also possible. Human leucocyte antigen-matched allogeneic haematopoietic stem-cell transplantation (to provide the diseased bone with normal osteoclasts) is the only treatment known to significantly alter the course of the disease (16-20). Optic canal decompression may be beneficial in some patients but not in others with chorioretinal degeneration. Optic nerve decompression is a hazardous procedure and reports suggest success only in mildly affected older children. Calcitriol (1,25-hydroxyvitamin D3) and Interferon-1b (1.5 µg/kg, three times per week) (macrophage-activating cytokine) have also been used with some benefit. (21) Glucocorticoids may help to stabilize hematopoietic function (6). Symptomatic care such as dental care, transfusions for anemia, and antibiotic treatment of infections, is important for patients who survive infancy (22). Genetic counseling: all cases of infantile osteopetrosis are likely to be inherited in an autosomal recessive fashion. Thus there is a 1 in 4 (25 %) risk of having another affected child with each subsequent pregnancy. Molecular analysis is available. Antenatal diagnosis: A radiological diagnosis is possible in the third trimester. Molecular diagnosis is possible much early (CVS 11-13 weeks). Synthesis of the growth factor for cells of the mononuclear phagocytic system, colony-stimulating factor 1 (CSF-1), is disrupted in the osteopetrotic mouse as a result of a mutation in the CSF1 gene. This leads to an almost complete lack of osteoclast development, and reduced bone resorption. These findings indicate that CSF-1 is essential for the development of osteoclasts (23-24). Other mouse models have demonstrated that two proto-oncogenes, c-src and c-fos, are also important in osteoclast differentiation and function (24). It is hoped that the information gained from these animal models will translate into improved treatment for patients with osteopetrosis.

IV. Conclusion

Although diagnosis of Malignant Infantile Osteopetrosis is easy and depends mainly on radiographic examination, it's often delayed due to rarity of the disease and lack of clinical suspicion. It should be kept in mind as a rare cause of hepato-splenomegaly and the patient should be referred for stem cell transplantation before neurologic or visual impairment develops. Optic canal decompression may be beneficial in some patients but not in others with chorioretinal degeneration as is reported in our case.

References

[1]. Albers-Schönberg, H: Röntgenbilder einer seltenen Knochenerkrankung. Münch. med. Wehr, 51: 365, 1904
[2]. Karshner, R. G.: Osteopetrosis. Am. J. Roent. & Rad. Ther., 16:405, 1926
[3]. Caffey, J. P.: Pédiatrie X-ray diagnosis. Chicago, Year Book Publications, Inc., 1956.
[4]. Montgomery, R. D., and Standard, K. L.: Albers-Sch.nberg disease: A changing concept. T. Bone & Joint Surg., 42-B : 303, 1960
[5]. Usta M, Gulec SG, Karaman S, Erdem E, Emral H, Urganci N. A case report of malignant infantile osteopetrosis. Iran J Pediatr 2012;22:421-4)
[6]. Gerritsen EJ, Vossen JM, van Loo IH, Hermans J, Helfrich MH, Griscelli C, et al. Autosomal recessive osteopetrosis: Variability of findings at diagnosis and during the natural course. Pediatrics 1994;93:247-53
[7]. Kapelushnik J, Shalev C, Yaniv I, Aker M, Carmi R, Cohen Z, et al. Osteopetrosis: A single centre experience of stem cell tranisplantation and prenatal diagnosis. Bone Marrow Transplant 2001;27:129-32
[8]. Subramaniam A, Singh A, Chavan M, Kunte S. Autosomal recessive osteopetrosis: Case report of two siblings. Oral Radiol 2008;24:80-4
[9]. Managutti Sunita, Anil Managutti, Michael Pragasm. Infantile Osteomyelitis Secondary to Malignant Osteopetrosis. Journal of maxillofacial and oral surgery. 2012;11(1):109–114
[10]. Engiz Ozlem, Kara Semra, Bagrul Denizhan, et al. Infantile malignant osteopetrosis: a rare cause of neonatal hypocalcemia. J Pediatr Endocrinol Metab. 2012;25(11-12):1205–1207
[11]. Kurtoglu S, Hatipoglu N, Mehmet Canpolat, et al. Malignant infantile osteopetrosis presenting with neonatalypocalcemia. Erciyes Medical Journal. 2009;31(1):70–73
[12]. Tolar Jakub, Steven LT, Paul JO. Osteopetrosis. New England Journal of Medicine. 2004;351(27):2839–2849
[13]. Frattini A, Orchard PJ, Sobacchi C, et al. Defects in TCIRG1 subunit of the vacuolar proton pump are responsible for a subset of human autosomal recessive osteopetrosis. Nat Genet 2000;25:343-346Kornak
[14]. Kornak U, Kasper D, Bösl MR, Kaiser E, Schwalzer M, Schulz A, Friedrich W, Delling G, Jentsch TJ: Loss of the ClC-7 chloride channel leads to osteopetrosis in mice and man. Cell 2001, 104:205-215
[15]. Wilson CJ; Autosomal recessive osteopetrosis. Orphanet encyclopedia, March 2003
[16]. Gerritsen EJA, Vossen JM, Van Loo IHG, et al. Autosomal recessive osteopetrosis: variability of findings at diagnosis and during the natural course. Pediatrics. 1994;93(2):247–53
[17]. Ozsoylu S. Malignant osteopetrosis and juvenile chronic myeloid leukemia. Pediatr Hematol Oncol. 1994; 11(3):337–8
[18]. Albert DM, Miller JW, Azar DT, Blodi BA. Volume four, Chapter 330 Osseous and Musculoskeletal Disorders. Albert & Jakobiec's Principles & Practice of Ophthalmology, 3rd Edition, Philadelphia, PA, USA: Saunders, Elsevier; 2008. p. 4507-8
[19]. Thompson DA, Kriss A, Taylor D, et al. Early VEP and ERG evidence of visual dysfunction in autosomal recessive osteopetrosis. Neuropediatrics 1998; 29:137–44
[20]. Solh H, Da Cunha AM, Giri N, et al. Bone marrow transplantation for infantile malignant osteopetrosis. J Pediatr Hematol Oncol 1995; 17:350–5
[21]. Key LL, Ries WL, Rodriguiz RM, Hatcher HC. Recombinant human interferon gamma therapy for osteopetrosis. J Pediatr 1992; 121:119–24.
[22]. Kliegman RM, Behrman RE, Jenson HB, Stanton BF. Part XXXXII,Section 3,Chapter 690. Disorders Involving Defective Bone Resorption. Nelson Textbook of Pediatrics, 19th Edition, Philadelphia, PA, USA: Saunders, Elsevier; 2011. p. 2432-2433
[23]. Cecchini MG, Hofstetter W, Halasy J, et al. Role of CSF-1 in bone and bone marrow development. Mol Reprod Dev 1997; 46:75-83
[24]. Wada T, Nakashima T, Oliveira-dos- Santos AJ, et al. The molecular scaffold Gab2 is a crucial component of RANK signaling and osteoclastogenesis. Nat Med 2005; 11:394–99

M. Hassoune,etal. "Bilateral Optic Atrophy Associated With Central Retinal Atrophy In A Patient With Malignant Infantile Osteopetrosis: A Case Report And Review Of The Literature." *IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)*, 19(3), 2020, pp. 30-34.