Disabling Osteopetrosis in an Young Lady

Gouranga Santra¹, Shinjan Patra², Partha Pratim Chakraborty³

Abstract

Osteopetrosis is a rare disorder of osteoclastic bone resorption leading to hyperostosis. Albers-Schonberg disease, an autosomal dominant variant of osteopetrosis occurs in young adults and has a benign course. A 17 year old female presented with generalized weakness and pallor for last two months. She had insidious onset and gradually progressive loss of vision and hearing for last two years. Plain x-ray of skull revealed increased radio-opacity of skull bones specially in the base, severe under-pneumatization of frontal and sphenoidal sinuses. Maxillary and ethmoid sinuses were also opaque and under-pneumatised. Bone scintigraphy with technetium-99m methylene diphosphonate showed diffusely increased uptake in whole skull. Bone marrow biopsy revealed a reactive marrow with areas of fibrosis without any evidence of granuloma or malignancy. The case had cranial entrapment neuropathies and severe anaemia due to osteopetrosis. High level of awareness is needed to diagnose the case properly and to help the patient to cope with the disabling features of the disease.

Introduction

Osteopetrosis is a rare genetic disorder that results from severe impairment of osteoclast-mediated bone resorption leading to hyperostosis. The spectrum of disease ranges from mild medical illness to severe, lethal conditions. Autosomal recessive infantile form is very severe. Autosomal dominant type II is known as Albers-Schonberg disease. It is benign and compatible with life and it occurs in young adults. An intermediate recessive type is seen occasionally in children younger than ten years old.¹ The clinical presentation and radiological picture vary as per severity of the disease. Here we report a case of osteopetrosis in a young lady who presented with some disabling clinical features.

Case Report

A 17 year old female presented with generalized weakness and pallor since last two months. She had no history suggestive of any bleeding tendencies. She had no nutritional deficiency. Menstrual history was normal. She had normal physical and mental development in childhood. She had reduced hearing and decreased vision since last two years. Her hearing loss was gradual without any abnormal sound perception, tinnitus, heaviness in ears or recurrent ear infections in childhood. There was no history of ear-discharge in childhood and any operations in neck region. Her visual loss was also insidious in onset and gradually progressive. She had studied up to class seven without any aid or difficulty. But during her visit to us she was unable to see anything. No history of recurrent fracture was present. Her siblings were completely normal.

On general examination patient had severe pallor without oedema, cyanosis, icterus or clubbing. She was irritable and apprehensive. Her vital parameters were within normal limit. There was no lymphadenopathy or organomegaly. Sternal-tenderness was absent. Respiratory and cardiovascular system examinations were normal. On neurological examination, apart from defects in cranial nerves II and VIII, no other abnormality was detected. On ophthalmoscopy, anterior chambers and optic discs looked normal. The light reflex and near reflex were within normal limits. On visual acuity testing, only perception of light was positive with accurate projection of rays. On otic examination, external appearance was normal. Tympnic membranes were intact. No discharge or foul smelling pus was found. Simple tuning-fork test revealed sensory-neural type of deafness.

Laboratory investigations showed haemoglobin level of 5.4 g/dl, total leucocyte count 6460/cmm (differential count: neutrophil 63%, lymphocytes 31%, monocytes 5%, eosinophils 1%), and platelets count 2,15,000/cmm. Her red blood cell (RBC) indices were P.C.V.-7.6%, MCV-86.4 fl, MCH-27.3 pg, MCHC-31.6 g/dl, RDW 18.3%. ESR was 120 mm/hour. Reticulocyte count was 0.2 %. Peripheral blood smear showed normocytic normochromic RBCs. Direct Coombs test was negative. Her serum hormonal and electrolytes assays

¹Associate Professor, ²Post-graduate Trainee, ³Assistant Professor, Dept. of Medicine, Midnapore Medical College, Midnapore, West Bengal

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revealed serum cortisol level 9.99 mcg/dl, sodium 138 meq/L, potassium 4.8 meq/L, 25-hydroxy cholecalciferol 14.02 ng/ml, parathyroid hormone 60.6 pg/ml, calcium 9 mg/dl and phosphorus 3.9 mg/dl. Serum alkaline phosphatase level was 102 U/L. Serum creatinine was 0.41 mg/dl. Serum iron profile suggested anaemia of chronic disease. Anti-nuclear antibody test was negative (Hep-2 method). Her serology profiles (HIV I and II, HBsAg, anti-HCV) were non-reactive. Her cerebrospinal fluid (CSF) examination was within normal limit. However, oligoconal band was present at gamma globulin region. Anti-aquaporin 4 antibody (Ig G) was negative both in serum and CSF. Her 24 hours urine (total 2090 ml) examination revealed total excretion of calcium 88 mg, phosphate 194 mg and creatinine 338 mg. Urine pH was 5.86. No evidence of excretion of methylmalonic acid, malonic acid, malic acid and glutaric acid in urine was present. Her thyroid function tests, FSH and LH assays were within normal limit.

To detect the cause of decreased hearing and vision, we did a plain x-ray of skull which showed symmetrically increased radio-opacity of skull bones specially in the base, severe under-pneumatization of frontal and sphenoid sinuses. Maxillary and ethmoid sinuses were also opaque and under-pneumatised (Figures 1 and 2). Bone scintigraphy following IV administration of technetium-99m methylene diphosphonate showed diffusely increased uptake in whole skull. No abnormality was detected in other bones of the body.

MRI of brain was normal except for thickening of clivus. Her visual evoked potential study revealed retinooptic nerve pathway dysfunction. Her brainstem evoked response audiometry studies suggested bilateral sensorineural hearing Loss. Nerve conduction velocity and electromyography of all four limbs was normal. Echocardiography revealed no abnormality. Ultrasonography of abdomen revealed mild hepatosplenomegaly. To detect the cause of severe anaemia we went for bone marrow aspiration study and trephine biopsy. Bone marrow aspiration came as dry-tap. Trephine biopsy revealed reactive marrow with areas of fibrosis without any evidence of granuloma or malignancy.

The case was finally diagnosed as cranial entrapment neuropathies and severe anaemia due to osteopetrosis.

**Discussion**

Osteopetrosis is associated with a defect in the mechanism of bone remodeling. Malfunction of osteoclastic activity results in excessive formation of immature bone, thickening of cortical bones and narrowing or obliteration of medullary cavities. Defects in different genes lead to different phenotypes of osteopetrosis. These defects include mutations in the gene encoding carbonic anhydrase II, proton pump gene and chloride channel gene. Albers-Schonberg disease (autosomal dominant osteopetrosis type-II) is associated with mutation in CICN7 chloride channel gene. Recently, immune response has been implicated in pathogenesis of osteopetrosis. Both cytotoxic T lymphocyte-associated antigen 4 and programmed death-1, a newly identified immunoregulatory receptor, have been shown to negatively regulate immune responses and to affect osteoclastogenesis and bone remodelling.2 As thickened and dense bones fail to remodel, they lead to narrowing of the various neural-foramina. Failure of skeletal remodelling also results in inadequate marrow spaces leading to severe anaemia and sometimes pancytopenia even. Hypocalcaemia due to lack of osteoclastic bone resorption may occur in infants and young children.

Osteopetrosis has no racial or sexual predisposition. Clinical manifestations vary in severity and time of onset. The malignant form presents with devastating symptoms early in childhood and rapid worsening of the condition resulting in a short lifespan, whereas the benign form (Albers-Schonberg disease) may be diagnosed late in childhood with a variety of prominent clinical features, such as frontal bossing, leonine facies, malocclusion of teeth and hepatosplenomegaly.3 Cranial imaging of autosomal dominant osteopetrosis shows small optic canals, orbits and nasoethmoid complex. The paranasal sinuses are almost always poorly pneumatized or show bud formation.4 Areas of condylar cartilage calcification may be seen.5 Stenosis and compression of the cranial foramina result in palsies of optic, olfactory, trigeminal, facial and cochlear nerves. In our patient under-pneumatization of paranasal sinuses and cranial foramina compression features were very well documented. Our case showed the potential severity of osteopetrosis. Despite normal childhood physical and mental development, cranial nerve palsies including deafness and loss of vision disabled her quality of life.

Other disorders associated with increased bone-density are pyknodysostosis, dysosteosclerosis, hyperostosis corticalis generalisata

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**Fig. 1:** Skull x-ray occipito-mental view showing symmetric hyperostosis of skull bones predominantly at the base with under-pneumatization of paranasal sinuses

**Fig. 2:** Skull x-ray lateral view showing hyperostosis of skull bones predominantly at the base
Anaemia was a chief presenting complaint of our patient. In autosomal dominant type II osteopetrosis (Albers-Schonberg disease) bone marrow function is usually not compromised. However, occasionally it may present with a refractory anaemia without other systemic symptoms. Osteopetrosis leads to increased bone mass along with a decreased haematopoietic tissue that can lead to normocytic anaemia. A leukoerythroblastic picture can be seen in peripheral smear. In osteopetrosis some amount of bone marrow fibrosis is always expected. During bone marrow aspiration dry tap is common. Bone marrow biopsy can reveal disorganization of bony trabeculae and effacement of haemopoietic space by fibrous tissue. In our patient we got exactly the same kind of reports. Unexplained anaemia without much information in bone marrow studies should always raise suspicion of osteosclerotic diseases.

From above discussion we can diagnose our case as mild form of osteopetrosis i.e. Albers Schonberg disease. Though we couldn’t find any siblings affected by similar conditions, we can diagnose the case with confidence from characteristics clinical features and radiological corroboration. Genetic mutation may be first time in the case and penetrance is not universal.

Treatment is mainly supportive. Steroids may be used to decrease the bone density, but it has serious adverse effects. Vision and hearing problems unfortunately do not have any definite solutions. Surgical decompression can be done but efficacy is doubtful. Anaemia needs periodical haemoglobin measurements and blood transfusions. Associated depression needs psychiatric evaluation and management. Bone marrow transplantation has been shown to restore the osteoclastic activity and to alleviate symptoms. We managed our patient conservatively with blood transfusion and psychiatric support.

Conclusion

Being one of the rarest diseases of the world, we have reported this case to highlight the disabling features of the disease. High level of awareness is needed to diagnose the case properly.

References

5. Sreekala Sreehari, Divya Rani Naik, Malini Eapen. Osteopetrosis: A rare cause of anaemia. Hematol Rep 2011; 3(1); e1