Early Diagnosis of Osteopetrosis Type 3 with Neonatal onset with Life-Threatening Complications: A case Report with Review of the Literature

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Abstract. Osteopetrosis Type 3 with Renal Tubular Acidosis (OPTB3) is a rare inherited autosomal recessive disorder. It is manifested clinically with osteopetrosis, renal tubular acidosis (RTA), cerebral calcification, and growth retardation. Neonatal onset with life-threatening complications warrants a thorough clinical evaluation with an assessment of specialized tests such as x-ray. Here, we discuss a rare case of carbonic anhydrase II deficiency syndrome, presenting with poor feeding and thrombocytopenia, in which the diagnosis was initially missed in the first hospitalization. Upon second admission, re-exanimation of the CXR was suggestive of marble bone disease. Further tests confirmed OPTB3. Following conservative management and family counseling, the patient was discharged in a good general condition. In conclusion, this highlight the need of early identification of the disease, as early appropriate treatment is necessary to improve the patient outcome and prevent complications.

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Keywords: OPTB3; Autosomal recessive osteopetrosis type 3; Marble Bone disease.

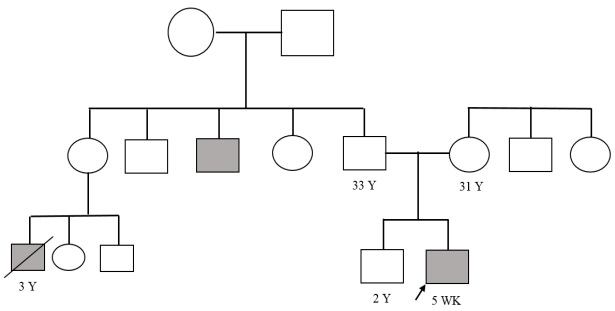
1. Introduction:

Autosomal recessive type of osteopetrosis is a rare inherited disorder of bone resorption characterized by increased bone density due to the failure of osteoclasts to resorb bone (Sly, Hewett-Emmett, Whyte, Yu, & Tashian, 1983). It is more common in highly consanguinity cultures such as Saudi Arabia (Suliman, Khedr, & Al Ruthae, 2010). The classical features of osteopetrosis, in general, is bone marrow failure, fractures, visual impairment or neurological abnormality (Suliman et al., 2010). Because of the infrequency of this type of osteopetrosis, we report a case of a male neonate who presented with recurrent life-threatening episodes of poor feeding and thrombocytopenia at the age of 5 weeks old.

2. Case Report:

A Five weeks-old male infant was presented to Pediatric Emergency Department of King Khalid University Hospital (KKUH) because of poor feeding and thrombocytopenia. Past medical history of the patient revealed that he was hospitalized in the first day of life in the neonatal intensive care unit for two weeks for the same issues. Full septic workup was done. He received empirical therapy of ampicillin and gentamycin.

He was born after an uncomplicated full-term pregnancy and spontaneous vaginal delivery in Al-Qassim. Birth weight was 3200 grams. Apgar score was 8 at 1 minute and 9 at 5 minutes. He was born to non-consanguineous couple. The family history was significant for global developmental delay and easy fractures in one of his paternal uncles. Additionally, he had paternal cousin with metabolic acidosis who passed away at 3 years old due to unknown etiology.



The patient was admitted to our Pediatric Intensive Care Unit for close observation and further workup of severe metabolic acidosis. Systemic examination revealed a weight 4.3 kg (on the 10th percentile), a height of 52 cm (on the 10th percentile) and head circumference of 37 cm (on the 25th percentile). He had a pale appearance with large open, flat anterior fontanel, and normal funduscopic examination, no hepatomegaly or splenomegaly was appreciated. other examinations unremarkable.

His arterial blood gas analysis revealed (hyperchloraemic) acidosis with normal anion gap (PH= 7.17, Pco2= 41, Hco3=14). Other workup showed a Hemoglobin 11.6 g/dl; white blood cell counts 23,100 cells/mm3 and platelet count 117,000/mm3. Biochemical analysis was normal except for Ammonia of 55 µmol/L, Chloride 109 mmol/L, GGT 107 unit/L and Osmolality 281 mOsm/kg. Serology for RSV A/B, Influ A/B, Para Influ 1.2.3.4, Adeno, H1N1, Corona MERS, HBoV, MPV, Rhinovirus, and Enterovirus were negative. Plasma amino acid and urine organic acid analyses were also normal. CSF, blood and, urine cultures all were negative.

On renal ultrasonography both kidneys were of average size with normal shape and location and maintained corticomedullary differentiation. No stones, calcification or hydronephrosis were seen. Right kidney measures 4.8 cm and left kidney measured 4.9 cm in longitudinal diameter. The urinary bladder was grossly unremarkable with volume of 7.4 ml.

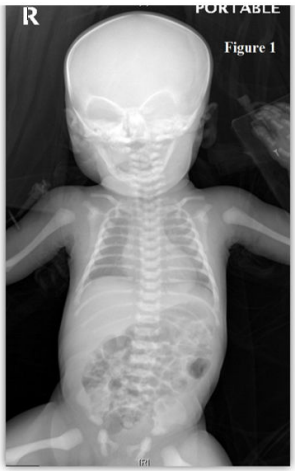


Figure 1. Plain films of the patient skull show generalized increased in density and thickening of the skull base and calvarium. His chest film shows generalized increased density of the bones and squaring off of the anterior rib margins

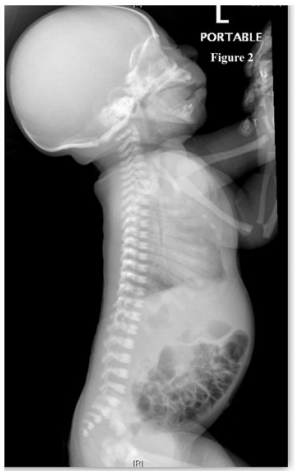


Figure 2. Lateral view of his lumbosacral spine shows the generalized increased density of the spine.

Our initial diagnosis was osteopetrosis type III with secondary RTA, due to carbonic anhydrase II deficiency syndrome, supported by the presence of metabolic acidosis with an alkaline urine pH and the bone changes. Genetic testing was ordered for the known Arab pathogenic CA2 variant, c.232+1G>A. The patient was discharged on oral sodium bicarbonate supplement and follow up with nephrology and genetics clinics. Genetics testing came back, and the patient was found to have the CA2 variant, c.232+1G>A in homozygous state confirming the diagnosis.

3. Discussion:

Carbonic Anhydrase II (CA II) is a metalloenzyme, located in the cytoplasm. There are 14 known isoforms in humans (Alvarez, Fanjul, Carter, & Hollande, 2001; Sly et al., 1983). These enzymes responsible for reversible hydration reaction of carbon dioxide (CO2). CA II has a major role in the creation of gastric acidity, pancreatic enzymes, aqueous humor and cerebrospinal fluid. It also plays a role in gluconeogenesis, lipogenesis, urogenesis, bone resorption and renal reabsorption of bicarbonate (Pushkin et al., 2004).

Patients with carbonic anhydrase type II deficiency have various manifestations; neuropathy in the form of reduced vision decreased hearing and seizures. Other features include short stature, multiple skeletal fractures, developmental delay and pancytopenia (Bosley et al., 2011). These have all been described more frequently in Arab patients where consanguinity is very common (Abdel-Al et al., 1994). The metabolic disorder may be partially treated with bicarbonate supplement, bone marrow transplantation (Orchard et al., 2015) or possibly gene therapy (Lai, Chan, Erickson, Hsu, & Lien, 1998).

4. Conclusion:

This highlights the need of early identification of the disease, as early appropriate treatment is necessary to improve the patient outcome and prevent complications.

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