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Case Report: Four Siblings with Osteopetrosis and Pyloric Stenosis and Three Cousins with Osteopetrosis

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Abstract

Osteopetrosis incidence is less than 1:200,000 births in most populations. It's more common in consanguineous people as it's unusual for two members of the same family. The incidence of Hypertrophic pyloric stenosis is 1 in 300 - 900 newborns. Hypertrophic pyloric stenosis is due to hypertrophy of the smooth muscle of the pyloric sphincter. The classic age of occurrence is the first few months of life, and the classic presentation is non-bilious projectile vomiting after feeding. We report a rare association of osteopetrosis and pyloric stenosis in four siblings and osteopetrosis in three cousins. All four patients were operated on and followed by nephrology and metabolic departments for osteopetrosis and metabolic acidosis.

Keywords

Osteopetrosis, Pyloric Stenosis, Siblings

1. Introduction

Osteopetrosis incidence is less than 1:200,000 births in most populations [1]. It's more common in consanguineous people as it's unusual in two members of the same family [2]. Osteopewasosis is derived from the Greek "osteo", meaning bone and "petros", stone. Osteopetrosis was described in 1904 by a German radiologist, also known as "marble bone disease" and "Albers-Schönberg disease". [3].

There are four types of osteopetrosis:

1) Autosomalrecessive infantile "malignant" osteopetrosis, 2) autosomalrecessive "mild" osteopetrosis, 3) autosomal dominant osteopetrosis and 4) osteopetrosis due to carbonic anhydrase deficiency [4].

Osteopetrosis results from the impaired function of osteoclasts [5]. The osteoclast function disorder results in clinical variants for the disease in humans: infantile, intermediate, and adult [6].

The defined treatment for osteopetrosis is Hematopoietic stem cell transplantation (HSCT). With a five-year disease-free survival rate of 73% in donors [7].

Interferon-gamma1b (IFNg1b) treatment was used in those who didn't respond to HSCT; IFNg1b leads to improved immune function, increased bone resorption, and increased bone marrow space [8]. Medication advised to be used in osteopetrosis includes Vitamin-D supplements and corticosteroids-sti- mulate bone resorption. While some may be asymptomatic, many of these patients require orthopaedic surgery for fractures at some point in their lives [9].

The incidence of hypertrophic pyloric stenosis is 1 in 300 - 900 newborns. Hypertrophic pyloric stenosis is due to hypertrophy of the smooth muscle of the pyloric sphincter. The classic age of occurrence is the first few months of life, and the classic presentation is non-bilious projectile vomiting after feeding [10].

The theory behind pyloric stenosis is the pyloric sphincter swelling from hypertrophy, and the growth-enhancing effect of high gastrin levels aids in repeated sphincter contraction. There is no evidence that pyloric stenosis results from an abnormal collection of growth factors within the sphincter or any genetic connection other than the association with Blood group O [11].

The diagnosis of hypertrophic pyloric stenosis (PS) in infants mainly depends on the clinical picture as the patient is the first-born male child with a family history of pyloric stenosis, and presenting with projectile vomiting at four weeks of age, with the pathognomonic finding a palpable "olive" mass in the upper abdomen. An upper-gastrointestinal series radiological studies or ultrasounds images if the diagnosis is unclear [12].

We are presenting a rare association of osteopetrosis and pyloric stenosis in siblings and cousins of one family.

2. Case Presentation

A two-month-old Saudi boy known case of osteopetrosis (The carrier status of the CA2 variant is confirmed by genetic study), born full-term and delivered vaginally, with no neonatal intensive care admission. His birth weight was 2.5 kg, and his current weight is 2.5 kg.

Presented to the emergency department with a history of abdominal distention and frequent progressive vomiting, projectile and non-projectile, milk content non-bilious for the last three weeks.

His bowel habit is constipation, but he started to have a one-day history of diarrhoea.

Passing urine and history of fever.

2.1. Family History

- History of pyloric stenosis in three of his elder brother, operated on in their first month of life; both were diagnosed with osteopetrosis with a genetic study on follow-up.
- Consanguineous parents.
- Variant of osteopetrosis initially identified in sister.
- Three of his cousin had an osteopetrosis diagnosis confirmed by a generic study.
- Patient sisters were medically free.

2.2. On Examination

No dysmorphic features, Looks fare dehydrated.

Normal vital signs.

Abdomen: Mild Distended, soft, lax, no tenderness, no hepatosplenomegaly or masses.

Cauterization marks in the abdominal wall.

Systemic examination was normal.

Investigations **(Table 1):**

ABDOMINAL X-RAY in Figure 1: Marked distended stomach with air.

US ABDOMEN-WALL: In Figure 2(a) & Figure 2(b).

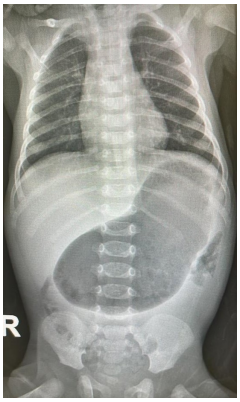
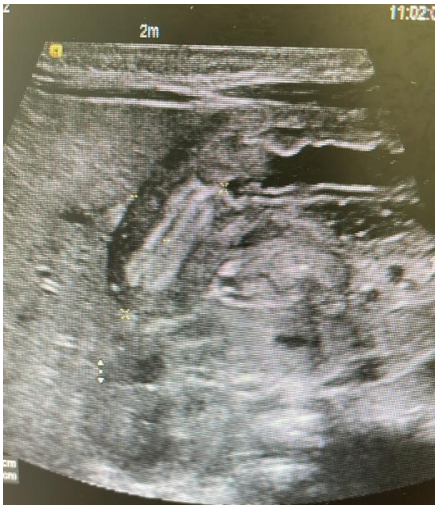


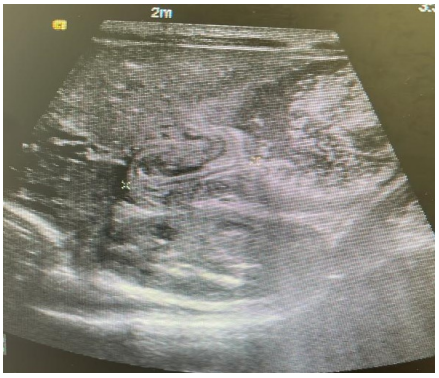
Figure 1. Abdominal X-ray.

Table 1. Laboratory investigations.

Investigation	Result
Complete Blood Count	Normal
C-Reactive Protein	1.3 mg/dl
Renal Function	Normal
Liver Function	Normal
HCO_3	29.4
PH	7.640
PCO_2	41



(a)



(b)

Figure 2. (a) Ultra sound abdomen; (b) Ultra sound abdomen.

2.3. Findings

The pylorus demonstrates a thickened wall measuring approximately 0.7 cm, with an elongated channel measuring approximately 2.5 cm. Features suggestive of pyloric stenosis.

Innumerable tiny diffusely scattered echogenic foci are seen at the periphery of the liver and within the portal vein. Findings are suggestive of portal vein gas. The portal and hepatic veins are patents.

No intrahepatic biliary dilatation.

The Common Bile Duct is not dilated, measuring 0.1 cm.

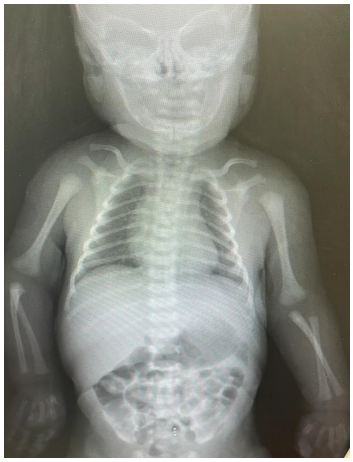
The spleen measures approximately 4.8 cm, with no focal lesions.

2.4. Impression

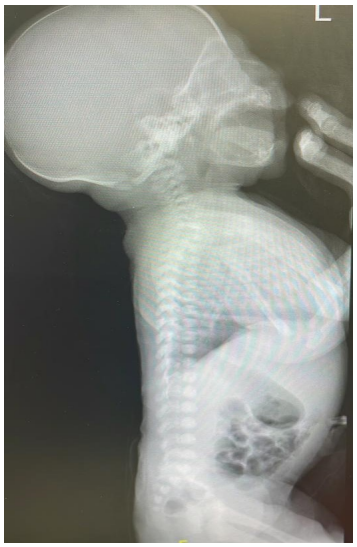
1) Findings are in keeping with hypertrophic pyloric stenosis.

2) Scattered echogenic foci seen in the periphery of the liver and within the portal vein; concerning portal venous gas, follow-up with an abdominal radiograph and surgical consultation is recommended.

Bone scan in Figure 3(a) & Figure 3(b): Normal



(a)



(b)

Figure 3. (a) Bone scan; (b) Bone scan.

Genetic study: The CA2 variant c.232 + 1G > A is predicted to disrupt the highly conserved donor splice site; this variant has previously been described as a disease-causing Carbonic anhydrase deficiency. It is classified as pathogenic (class 1) for osteopetrosis.

Progress of patient: Surgery for pyloric stenosis was done successfully, tolerated orally, and follow-up with nephrology and the metabolic unit was given.

3. Discussion

Our patient came with classic symptoms and signs of pyloric stenosis; a genetic study showed osteopetrosis.

In 1972, an association between osteopetrosis and renal tubular acidosis (RTA) was first described, called Guibaud-Vainsel syndrome or marble brain disease [13] [14].

Ohlsson, *et al.* reported three Saudi Arabian families with cases of osteopetro-

sis, RTA (Renal Tubular Acidosis), and cerebral calcification, all of whom had first-cousin marriages. These cases were collectively referred to as "marble brain disease" [15]. In 1988, Al Rajeh, *et al.* reported that two sisters in Saudi Arabia who had a marble brain disease [16]. Marble brain disease was reported in Turkey in 2001 in a family [17].

In 1943, it was suggested that a single recessive gene, with penetrance dependent on sex and birth order, was responsible for pyloric stenosis [18]. Later many authors [19] [20] concluded that no single gene was found, and the gene expressed required some environmental component for their expression [21].

Other than the male sex, the most commonly reported risk factors for pyloric stenosis are a family history of pyloric stenosis and the firstborn child [22] [23] [24] [25] [26].

Many studies [27] believed multifactorial factors are the leading causes of pyloric stenosis. Some studies have reported that other risk factors for pyloric stenosis include prematurity, caesarean delivery, and maternal smoking [28]. Additionally, a hereditary factor contributing to the prevalence of pyloric stenosis has been documented [29].

In Denmark, between 1977-2008, they reported maternal smoking, male sex, premature birth, small for gestational age (SGA) newborns, caesarean delivery, and firstborn children were the main risk factors for pyloric stenosis [30]. The same study in Denmark supported the presence of decisive genetic factors in the pathophysiology of pyloric stenosis, with a high incidence rate in monozygotic (200-fold higher rate) and dizygotic twins (20-fold) [29].

The possible increased risk of pyloric stenosis among cousins of pyloric stenosis cases has been conflicting [31] [32] with a statistically significant 3-fold increased risk in cousins of both sexes. Krogh's study found a 60% increased risk in half-cousins; although this increase was not significant, it suggests aggregation in even distant relatives [29].

4. Conclusion

Osteopetrosis had variable Clinical manifestations, ranging from asymptomatic to fatal course. To our knowledge, the association of osteopetrosis with pyloric stenosis was not reported; our four siblings were diagnosed with osteopetrosis with a genetic study, and all were operated on for pyloric stenosis. A familial cascade carrier testing and Genetic counselling is recommended for the extended family.

Consent

Consent from the hospital was taken.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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