Case Report

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The Essential on the Alagille Syndrome and the Associated Oral Manifestations

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ABSTRACT

The Alagille Syndrome (SAG), known as syndromic ductular paucity, is a multisystemic hereditary disorder of autosomal dominant transmission with a prevalence of 1/70000 live births. SAG is caused by a mutation in the Jagged1 gene (JAG1), a ligand encoding a Notch receptor that plays an important role in determining the fate of the developing cell. SAG is characterized by the association of chronic cholestasis with cardiac, ocular, skeletal and facial features. Other signs described as minor may include renal, pancreatic, and oral manifestations. The objective of our article is to provide an update on this rare syndrome and the associated oral manifestations.

Keywords

Alagille syndrome, Cholestasis, Oral manifestations.

Introduction

Alagille's syndrome (SAG) or syndromic ductular paucity [1], is an inherited multisystemic disorder of autosomal dominant transmission, characterized by chronic cholestasis related to intrahepatic bile duct paucity, stenosis of the peripheral pulmonary arteries, vertebral anomalies, characteristic facies, posterior embryotoxon/anterior segment abnormalities, retinopathy, pancratic involvement and oral manifestations.

Epidemiology

Its prevalence is about 1/70,000 live births [1,2].

Etiology

Most commonly, SAG is due to mutations in the JAG1 (20p12) gene (SAG1) coding for a ligand of the Notch signalling pathway. SAG2 is due to mutations in NOTCH2 (1p12).

Clinical Description

- **Major Signs**

The disease can manifest itself in the newborn by prolonged jaundice due to conjugated hyperbilirubinemia and/or cardiac manifestations. Cardiac abnormalities include pulmonary atresia or stenosis, ventricular and/or atrial septal defect, tetralogy of Fallot and ductus arteriosus persistence [3,4]. Cholestasis is manifested by conjugated hyperbilirubinemia, hepatosplenomegaly, hypercholesterolemia, hypertriglyceridemia and coagulopathy. Pruritus and xanthomas may occur. Minor skeletal abnormalities include "butterfly wing" vertebrae (approximately 50% of cases) and shortening of the radii, ulna and phalanges. If present, facial dysmorphia usually appears in childhood and includes a prominent forehead, deep-set eyes in the sockets, palpebral slits pointing up and out, hypertelorism, a flat nose root and a pointed chin (Figure 1). Ophthalmic abnormalities include a posterior embryotoxin (75% of cases), Axenfeld's anomaly (see this term), retinitis pigmentosa, papillary or optic disc abnormalities (Figure 2). Growth retardation, fat malabsorption (rickets may occur) and sometimes developmental delay are present. Patients may have

small dysplastic kidneys (common in SAG2) and hypothyroidism [5].

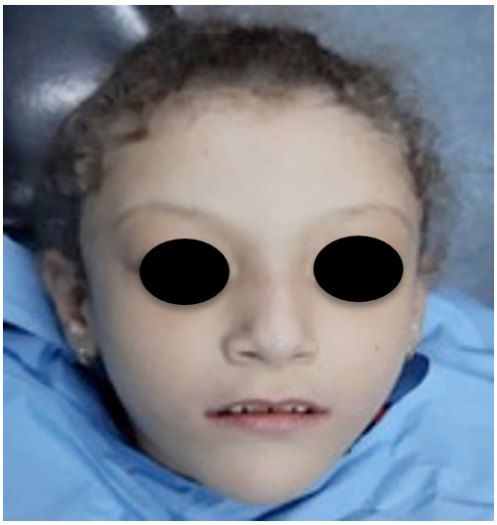

Figure 1: Characteristic facies of Alagille syndrome.

Figure 2: Jaundice at eye level (yellow sclera).

- **Oral Manifestations**

Depending on the state of the hepatic disorders, SAG can also damage the teeth, salivary glands, periodontium and mucous membranes. Dental manifestations are not a main characteristic of the syndrome, but they inevitably occur as a complication of long-term cholestasis and are related to hyperbilirubinemia. As a consequence of cholestasis during odontogenesis, enamel opacities, hypomineralization and hypoplasia of the dental enamel may occur. In children with serum bilirubin levels above 30 mg/dl, bilirubin accumulates in dental tissue, causing variable greenish-brown dyschromia of the teeth (Figure 3). Oral manifestations may involve both temporary and permanent dentition [6]. Other authors have reported cases that present macrodontia of the maxillary incisors associated with tauraodontism [7].

Etiology

Most commonly, SAG is due to mutations in the JAG1 (20p12) gene (SAG1) coding for a ligand of the Notch signalling pathway. SAG2 is due to mutations in NOTCH2 (1p12).

Diagnostic methods

Diagnosis is based on the clinical picture and liver biopsy revealing chronic cholestasis and paucity of interlobular bile ducts. Imaging (abdominal ultrasound, cholangiography) allows the identification of the biliary anatomy. Ophthalmic, skeletal, vascular and thyroid abnormalities should be investigated. DNA sequencing allows confirmation of the diagnosis [8].

Differential Diagnosis

The differential diagnosis includes biliary atresia, congenital hepatic fibrosis, cystic fibrosis, neonatal jaundice, polycystic kidney disease, familial progressive intrahepatic cholestasis and tyrosinemia.

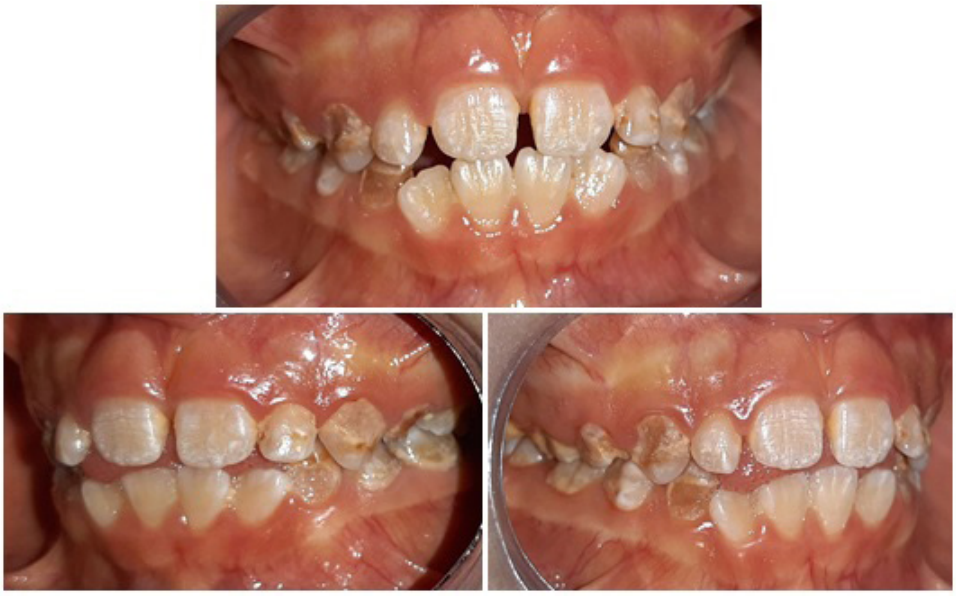

Figure 3: Generalized enamel hypoplasia on primary and permanent teeth.

Prenatal Diagnosis

If the pathogenic mutation has been identified, prenatal diagnosis is possible based on molecular analysis of amniocytes or chorionic villi. Cardiac and/or renal abnormalities, if present, can be identified by fetal ultrasound [9].

Genetic Counselling

Transmission is autosomal dominant, but low penetrance (over 50% of cases) and somatic mosaicism (~8%) are common.

Management and Treatments

The treatment is non-specific, it includes a diet rich in carbohydrates and medium-chain triglycerides and a vitamin supplement. Pruritus is reduced by cholestyramine or rifampin. A liver transplant may be necessary in case of refractory disease. Cardiac or vascular procedures are considered for significant lesions [10].

All dental treatments must be performed in collaboration with the physician, who will prescribe proper drug selection, and use of antibiotics as a prophylaxis or in a case of bleeding after extraction control of hemostasis. After liver transplantation surgery, all patients require regular dental control visits because of permanent and continuous immunosuppressive treatment. The prolonged immunosuppression after transplantation can give rise to the suppression of bone narrow, which may result in leucopenia, thrombocytopenia, or anemia. It can predispose patients to excessive bleedings, opportunistic infections like mycosis, herpes superinfection, and development of leucoplakia. Cyclosporine intake is associated with drug-induced gingival hypertrophy, which may lead to gingivitis and periodontal tissue damage. Regular dental care and prophylaxis, appropriate hygiene monitoring, and the cyclosporine replacement in consultation with the physician, can prevent the development of these symptoms. In AGS patients with less severe general manifestations, it is possible to perform orthodontic treatment combined with esthetic restorative procedures or surgery, but only with careful control. Monitoring of oral hygiene and caries control is mandatory [11].

Prognosis

In general, the prognosis is favorable, but cirrhosis, varicose vein rupture, refractory ascites and spontaneous bacterial peritonitis are possible complications. The disease often stabilizes between 4 and 10 years. Liver failure and/or heart damage increase the risk of mortality.

Conclusion

Contrary to healthy children, patients with Alagille syndrome have many problems, depending on factors such as the severity of cholestasis and scarring in the liver, heart or lung problems, presence of infections, or other problems related to poor nutrition. But in general, AGS children have better outcome than others with different liver disorders at the same age. Many adults with Alagille syndrome are leading normal lives and have few problems during dental treatment. Nevertheless, everyday problems may affect psychological and emotional well-being. Dental disorders are not the main problems of people with AGS, but dental surgeons may come across patients with AGS in their practice. The most important points are careful observation, accurate diagnosis, and planned management of such patients, especially during the patient's formative years, to prevent complications. Aggressive preventive oral care and consultations with medical specialists before any invasive procedure are obligatory. All this can improve quality of life in patients with Alagille syndrome.

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