ALAGILLE SYNDROME: A REVIEW

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Abstract

Alagille Syndrome (AGS) is a genetically determined multisystem disorder affecting liver, hearth, eyes, skeleton and facies, less commonly kidney and CNS. The prognosis depends on the severity of the associated anomalies. The liver pathology plays a central role in that most clinical complications are due to long standing cholestasis as a consequence of lack of bile excretion secondary to paucity/absence of interlobular bile ducts. That results in hyperbilirubinemia, hypercholesterolemia, hypertriglyceridemia, fat and liposoluble vitamin malabsorption, pruritus and cutaneous xanthoma.

Liver transplantation represents the only curative therapy for the liver pathology. Most hepatic symptoms reverse after liver transplantation. Therapeutical education for oro-dental hygiene is required before and after liver transplantation. The green pigmentation of teeth requires dental rehabilitation.

This paper reviews the clinical manifestations of AGS with special regard to the cephalic district, and highlights the necessity for a multidisciplinary approach in order to minimize complications and to ameliorate the quality of life in AGS patients.

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Introduction

Alagille syndrome (AGS) (synonyms: paucity of interlobular bile ducts, artriohepatic dysplasia, 20p11.2 deletion syndrome COD ICD 10: Q44.7) was first described in 1969 and further refined in 1975 by Danielle.

Alagille as hepatic ductular hypoplasia associated with a characteristic facies, vertebral malformations, cardiac murmur, retarded physical, mental and sexual development.[1]

The disease presents at birth with neonatal cholestasis. Paucity of interlobular bile ducts is the hallmark of the liver pathology.

The prognosis is extremely variable due to the severity of the associated extrahepatic abnormalities. Mortality accounts for 10-17%. The main causes of death are liver and cardiovascular pathologies, including endocranic hemorrhage.[2, 3, 4] The life expectancy is about 20 years in75% of patients, 60% of whom are cured by liver transplantation.[4, 5]

Liver transplantation has dramatically changed the outcome of Alagille syndrome and so far represents the only curative treatment.

In this paper we review the main features

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of the syndrome with special regard to cephalic district manifestations and complications.

Etiology Genetics and Diagnosis

AGS is transmitted in an autosomal dominant way with 94% penetrance and variable expressivity, in the same family a few members being asymptomatic.[5, 6] The prevalence of AGS is estimated betwen 1/70.000 and 1/100.000 live births.[2, 3, 5, 7]

Recently, the cause of the disease has been elucidated, but the pathogenesis remains unclear: AGS appears to be caused by the alteration of the gene JAG1 (AGS type I) REFERENZA DI JAG1), at chromosomal location 20p12, that encodes a ligand for the Notch receptor, a transmembrane protein of which four types have been identified: Notch 1,2,3,4.

A minority of AGS (type II) is due to a mutation of the gene Notch2 at chromosomal location 1p12.[8]

The diagnosis of AGS has evolved over the years. Nowadays it is based upon clinical criteria and genetic test[2, 3, 4, 6, 8] that are summarized in Tab.1

Clinical Diagnosis	3 of 5 criteria	1) chronic cholestasis 2) cardiac abnormalities 3) skeletal abnormalities 4) eye anomalies 5) characteristic facies
	A positive family history	
	Liver biopsy	Paucity of interlobular bile ducts. Paucity means the absence of bile ducts in more than 50% of portal tracts, when at least 10 of them were examined.
Genetic test	mutation of JAG1 (94% of cases)	Deletion of Jagged1 of chromosome 20 (Notch ligand receptor)
	mutations of NOTCH2 (1% of cases)	

Tab. 1. Alagille syndrome: criteria for diagnosis

Clinical Manifestations

AGS is a multisystem disorder affecting the liver, heart, eyes, face, skeleton. Kidney, vascular, neurologic abnormalities and growth disorders are part of the syndrome.[2, 3, 6, 9] Major clinical manifestations of AGS are congenital heart disease, characteristic facial phenotype, chronic cholestasis, posterior embryotoxon in the eye, and butterfy vertebrae.[10] Cardiovascular abnormalities include pulmonary vein atresia or stenosis , interatrial or interventriculat defects, tetralogy of Fallot.[11] Skeletalabnormalities comprise butterfly vertebrae, reduced length of radium, ulna or falanges.[12] Ophtalmic abnormalities include posterior embryotoxon (opacity of corneal margins, Axenfeld anomaly, pigmentary retinopathy, papilla and optic disc abnormalities.[13] Mental retardation and delayed sexual represent further features of AGS. Extrahepatic complications are due to long standing cholestasisand manifest as jaundice, pruritus, xanthoma and high serum levels of bilirubin, cholesterol, tryglycerids. Kidney pathology is mainly represented by tubular acidosis; anatomic abnormalities have also been reported.[9]

The main systemic manifestations are summarized in Tab.2.

Manifestations of the Cephalic Disrict

Facial features are considered characteristic for the syndrome. They include: a prominent forehead, deep-set eyes with moderate hypertelorism, a pointed chin and a saddle or straight nose with a bulbous tip. The combination of these features gives the face a triangular inverted appearance. [2, 3, 4, 6, 11]

The facial characteristics may be present early in infancy but in general they become more dramatic with increasing age: the eyes remain deep-set, whilst prognathism develops leading to a more pronounced inferior part of the facies and mandible.[2, 3] Macrocephaly and craniosinostosis are rarely found.[4]

Dental manifestations are not a primary feature of the syndrome. However they invariably occur as a complication of the long-standing cholestasis and are linked to hyperbilirubinemia.

Indeed, due to the paucity/absence of interlobular bile ducts, only a minor (if any) part of bile is exported into the small intestine. As a consequence of the defective flow, the bile is retained within the liver (intrahepatic intralobular cholestasis), thus the absorption of bile-dependent liposoluble vitamins as well as the enterohepatic bile recirculation do not take place. The conjugated biliribin regurgitates into the blood and produces hyperbilirubinemia and jaundice. There is also serum elevation and skin deposition of bile acids causing pruritus.

SYSTEMIC EXPRESSION	prevalence	CONSEQUENCES CLICHE
Liver diseases		
chronic cholestasis	96%	increase in serum concentrations of: • Serum bile acid • alkaline phosphatase • cholesterol • GGT • triglycerides • amino transferase
paucity of intrahepatic bile ducts	85%	
conjugated hyperbilirubinemia in the newborn period		
intractable pruritus	frequent	
Hepatic cirrhosis	frequent	15% require transplantation
hepatocellular carcinoma.	rare	
Cardiovascular diseases		
• stenosis and hypoplasia of the pulmonary arteries (67%) • tetralogy of Fallot (7-10%), Interventricular septal defects • and, • stenosis and aortic coarctation	90%	severity and symptoms vary widely
Congenital anomalies of the intracranial vasculature		risk of intracranial hemorrhage
intracranial hemorrhage	15%	30-50% of these cases are fatal
Ocular abnormalities		
Embryotoxon posterior	89-95%	moderate decrease in visual acuity, potential cause of glaucoma
anomalies: • retinal • corneal • iris • hypopigmentation of the ocular fundus	 45% 57%	
ocular abnormalities, not specific		secondary deficiency vitamins A and E.
Skeletal abnormalities		
"butterfly vertebrae"	51%	asymptomatic
anomalies: -at the costal level - In the spine - in the upper limbs ←		eg spina bifida eg shortening of the ulna and distal phalanges in the hands
significant osteopenia with mild symptoms (due to reduced absorption of calcium and vitamin D)		risk of pathological fractures
Malnutrition and impaired growth		

SYSTEMIC EXPRESSION	prevalence	CONSEQUENCES CLICHE
☒ • linked to genetic mutation Jag 1 • caused by poor solubilization and absorption of lipids, essential fatty acids and fat-soluble vitamins.		• coagulopathy (vitamin K deficiency) • rickets (vitamin D deficiency) • retinopathy, peripheral neuropathy and myopathy (deficiency vitamins A and E)
growth deficiency and newborn small for date	50-90%	
Delayed peak of growth	frequent	
Anomalies of central nervous system		
mental retardation (IQ between 60 and 80)	30%	can be prevented by treatment with vitamin E
syndromes of hyperactivity or attention deficit disorders		
dystonia and tremors		may resolve after liver transplantation
Other Systemic Manifestations:		
Renal anomalies	40%	• anatomical abnormalities • renal tubular acidosis • renal failure.
skin manifestations	28%	xanthomas, spider veins, often associated with intractable pruritus

Tab. 2. Alagille syndrome: systemic manifestations

Further metabolic derangements involve the lipids. Hypercholesterolemia is a constant feature and is responsible for vascular complication and xanthoma formation.

In children with serum bilirubin level > 30 mg/dl, bilirubin accumulates in the dental germ during odontogenesis causing a green dyschromy. Both the decidual and the permanent teeth developing before the (eventual) resolution of jaundice are heavily affected.[14-17]

Teeth present with green striations of variable degree (Figure 1). The pigmentation can be modified by the hemel translucency that transmits the dentinal coloration.[14, 16] Decidual teeth may display in a few cases a taurodontic appearance with a widened pulpar cavity. Extensive decalcification of predentin and interglobular dentin occurs invariably.

Cephalometric evaluation shows a shorter mandibular branch and a wide gonion.

Nutritional deficiencies, continuous intake of edulcorated or high glucose content food result in an increased risk for caries formation.

A poor hygiene predisposes to the development of paradontopathies.

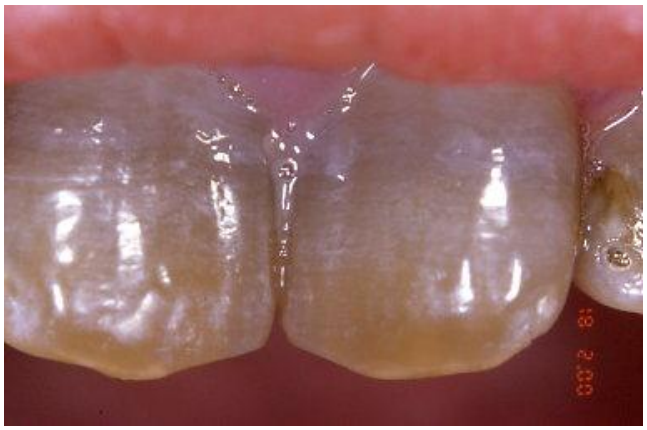

Fig. 1. Alagille syndrome patient. Pigmentation and discoloration of the permanent dentition.

A number of oro-dental changes occur after liver transplantation owing to immunosuppression.

With cyclosporine, gingival hypertrophy was in the past a most prominent adverse effect. The cyclosporine replacement with tacrolimus has led to a marked decrease of this complication.[15, 17, 18]

The prolonged immunosuppression treatment after transplantation can give rise to leucoplakia, mycosis, herpes superinfection.[17]

Treatment

AGS patients are affected by various alterations and pathologies, for which a multidisciplinary approach is required.

The main aim of the treatment is to keep under control the main complications due to cholestasis, i.e. pruritus, hypercholesterolemia, Vit A, D, E, K deficiency.

The therapeutic education of parents is essential to prevent sequelae due to nutritional deficiency and poor oral hygiene.[14, 15]

UDCA is the treatment of choice and has largely replaced cholestiramin/rifampicin.[4, 5, 19] Surgical biliary diversion represents an alternative when medical treatment is uneffective.[19]

Dental dyschromy requires esthetic remedy especially to prevent psychological discomfort in the social life.

Substances and procedures to restitute whitness to the teeth are crowns, backet clay facette, decolourizing agents.

Urinary colture and kidney US are useful means to monitor potential evolution of renal pathology.[9, 19] Fifteen to thirthy per cent AGS require liver transplantation in early infancy, that represents 2% of all pediatric liver transplantation. Liver cirrhosis and malabsorption resistant to parenteral nutrition are the main indications for liver transplantation. Post-operative mortality is influenced by cardiovascular pathologies.[5, 19]

Before liver transplantation, it is mandatory to treat caries and to sterilize the decidual teeth, whilst with the mixed dentition, restauration with a less conservative approach may be necessary as compared to healthy patients.

After transplantation an appropriate hygiene monitoring is recommended.

Two additional recommendations refer to the dental management of AGS patients: 1) vit K administration in case of dental extraction or surgical intervention, 2) antibiotics prophylaxis according to the guidelines for bacterial endocarditis on the occasion of dental treatment at risk of bacteremia.

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