

# Alagille Syndrome Nowadays: “One, no-One and One Hundred Thousand”

M. Arrabito<sup>1,\*</sup>, S. D’Amico<sup>1</sup>, C. Gulizia<sup>1</sup>, L. Marino<sup>1</sup>, G.F. Parisi<sup>2</sup>, M. Papale<sup>2</sup>, S. Manti<sup>3</sup> and S. Leonardi<sup>2</sup>

<sup>1</sup>*Department of Clinical and Experimental Medicine, Section of Pediatrics, University of Catania, Catania, Italy*

<sup>2</sup>*Unit of Pediatric Broncho-Pneumo-Allergology, University of Catania, Catania, Italy*

<sup>3</sup>*Department of Human and Pediatric Pathology “Gaetano Barresi” University of Messina*

**Abstract:** Alagille syndrome [ALGS] is an autosomal dominant, complex multisystem disorder that includes a wide range of clinical aspects, most commonly manifest in infancy or early childhood. It is mostly caused by mutations of genes involved in the Notch signaling pathway. The major of clinic manifestations occur in liver, but also other organs, like heart, eye and skeleton can be impaired. Herein we report the story of a family in which four members were diagnosed with ALGS, leading the same gene mutation. The peculiarity of our case lies in the fact that they manifested the disease in different time of their life and with many different symptoms, highlighting the impressive clinical variability of the ALGS and the importance of considering it in the differential diagnosis of liver impairment disease.

**Keywords:** Multisystem disorder, Different phenotypic expression, Liver impairment.

## INTRODUCTION

Alagille syndrome [ALGS] is an autosomal dominant, complex multisystem disorder that includes a wide range of clinical aspects, most commonly manifest in infancy or early childhood. This syndrome is caused by a mutation in the JAG1 gene on chromosome 20p12 in 94% of cases [1], and in the remaining cases, by mutations in NOTCH2 on chromosome 1p13 [2]. Both genes are involved in the Notch signaling pathway which cooperates with other developmentally significant cellular signaling pathways [3]. In a study of 1977, the ALGS incidence was estimated of roughly 1 in 70,000 live births [4]. In contrast, in 2014, this estimation was reviewed to 1 in 30,000 to 50,000 live births thanks to the introduction of molecular testing, which permitted the identification of mildly affected individuals [1]. “Classic Criteria” of AGS were settled basing on five main systems: liver, heart, eye, facial features and skeleton. The most involved organ is liver: in many cases, ALGS is manifested in infancy with cholestasis [conjugated hyperbilirubinemia with high GGT, elevated serum bile acids, and increased cholesterol and triglycerides], and patients show jaundice, intense pruritus, xanthomas [fatty deposits on the extensor surfaces], and infertility due to fat malabsorption [5]. The necessity of liver transplantation because of unceasing cholestasis and

progressive liver disease, occurs in ~15% of individuals with ALGS [6]. Pulmonic stenosis [peripheral and branch] is the most common cardiac anomaly [67%], but it could also possible finding tetralogy of Fallot, which is seen in 7%–16% of patients [6]. The most common ocular feature in ALGS is posterior embryotoxon that is a central thickening and displacement of the Schwalbe line. Other usual findings encompass iris hypoplasia, anomalous optic discs, abnormalities of the retinal vessels, and pigmentary retinopathy [7]. The pattern of facial features comprises a high forehead with frontal bossing, sunken eyes with modest hypertelorism, pointed chin, and flattened nose root with a bulbous tip [8]. The most common skeleton radiographic aspect is butterfly shaped thoracic vertebrae, due to clefting abnormality of the vertebral bodies, which it can be found from 33% to 93% of cases [9]. The short-term effects of ALGS lies on the heart impairment that sometimes could cause a fast and sudden death, instead the long-term ones are most related to liver impairment, indeed this disease could lead to portal hypertension and liver failure that need liver transplantation. Another chronic consequence in the pediatric field is the poor growth because of the malabsorption derived from the liver injury, thus it should be considered this diagnosis when there is a child with poor height and weight and malabsorption. Due to these aspecific symptoms, during past years the ALGS incidence was subestimated and it was often difficult to think about it when there was a child with liver impairment of poor growth. Recently, thanks also to the introduction of genetic tests, the ALGS is always considered as differential diagnosis when these type of

\*Address correspondence to this author at the Department of Clinical and Experimental Medicine, Section of Pediatrics, University of Catania, Catania, Italy;  
E-mail: marta-arrabito@hotmail.it

symptoms occurs. Nevertheless, the diagnosis of ALGS is difficult because of its highly variable clinical manifestations including life-threatening conditions and mild features; and this broad variability of phenotypic expression can be even found in the same family members who share the same mutation, as the family case herein reported. We describe a family in which four members suffer from ALGS caused by AG 1 mutation, but with variable phenotypic expressions and disease severity.

## CASE REPORT

### Case 1 (Proband)

Third-born of parents not related to each other belonging to Caucasian race and born at term with normal weight, from spontaneous birth after normal pregnancy. At the age of about 18 months, globular abdomen, loss of appetite and poor growth occurred. Blood tests were performed and increasing in cholestasis indices, like direct bilirubin, alkaline phosphatase, gamma gt and transaminases, was detected. An enlarged liver with inhomogeneous parenchyma was revealed at the abdominal ultrasound. Eye examination showed posterior embryotoxon. During the cardiological visit pulmonary stenosis was found. Finally, thinking to a syndromic pathology, a column x-ray was performed which showed butterfly vertebrae at the level of D6, D8 and D11. In the suspicion of Alagille syndrome, a liver biopsy was proposed but refused by the family, therefore a genetic examination (through blood sampling) was performed. ALGS with mutation 2757-2757 + 1 of the AG in the 'exon 18 of the JAGGED1 gene was diagnosed. The patient is now 22 years old and is on list for liver transplantation because of a severe liver disease in progression.

### Case 2 (Father of Proband)

Consequently to the discovery of the disease in the proband, a genetic test to his parents and sister was performed and the same mutation in the father who was 33 years old at the time, was detected. Up to that moment his story was unremarkable, but carrying out specific examinations, posterior embryotoxon and pulmonary stenosis [even if not clinically significant] were highlighted. He also presented peculiar facies just like the son. However, unlike his son, he never presented liver disease and cholestasis indexes were always within the norm. Therefore, this could be considered a form of ALGS diagnosed by chance in an asymptomatic patient, because of a diagnosis made in the proband.

### Case 3 (Brother of Proband)

In this patient, the youngest member of the family, the diagnosis was made at birth following family history for ALGS. The same mutation of his father and the other brother was revealed. The infant, now 10 years old, is in quite good conditions and presents peculiar facies; mild pulmonary artery stenosis; no posterior embryotoxon but papilla with blurred edges and dystrophy of the retinal pigment epithelium; liver with finely inhomogeneous echostructure; pyelic ectasia on the left [ 6mm] and butterfly vertebrae. This can be considered a case with a mild presentation of the pathology.

### Case 4 (Sister of Proband)

This is the second child, full term-born after spontaneous childbirth but died at only one month of life from complications related to Tetralogy of Fallot. Having been born before the proband, no genetic examination has ever been done for ALGS but in retrospect, considering that there are forms of this

	Case 1	Case 2	Case 3	Case 4
Relationship	Third born	Father	Fourth born	Second born
Age	22 years old	55 years old	10 years old	Dead at one month old
Sex	male	male	male	female
Liver involvement	yes	no	yes	unknown
Eye involvement	yes	yes	yes	unknown
Heart involvement	yes	no	yes	yes
Bone malformations	yes	no	yes	unknown
Facial dysmorphism	no	yes	yes	unknown

syndrome that can occur even with only heart involvement, it could be possible that this baby has inherited the same mutation of her relatives but because of the disease was manifested only with the Tetralogy of Fallot and immediately led to death, it did not allow the other ALGS features to give a sign of themselves.

## DISCUSSION

Alagille syndrome is a multisystem disease which involves many organs with variable expressivity. It is caused by a defect of the Notch signaling pathway, occurring in the majority of cases dominant mutations in the Notch ligand JAG1 or the NOTCH2 receptor. This signaling pathway was first observed and described during the early 1900's in *Drosophila melanogaster* by Otto L. Mohr. He identified flies with small notches on their wings, crossed them with wild-type flies and found that the notched phenotype segregated in offspring. This observation proved that the wing shape was genetically controlled and the locus responsible for this wing phenotype was called the "Notch" locus [10].

This pathway is implicated in the development of many tissues and organs, as ALGS manifest with various clinical presentations. Emerick *et al.* describe cases of ALGS patients who manifested with neurological symptoms like a 3-year-old male with ALGS who presented loss of use of his right arm and incapacity to speak due to a restriction of the distal left internal carotid [ICA] artery [11]. Shrivastava *et al.* present a case of a patient with Alagille syndrome manifested with hypertension and renal failure [12]. Kamath *et al.* describe family members with ALGS who have isolated cardiac defects [including Tetralogy of Fallot and pulmonic stenosis] and who have been found to share the same familial JAG1 mutation as the proband with whole syndromic peculiarities [13]. González Pastor *et al.* present a clinical case of special interest due to the association of ALGS with intestinal atresia in the neonatal period. They described a full-term newborn, with pulmonary branch stenosis and difficult feeding, vomiting, and abdominal distension from the first hours of life, who underwent abdominal X-ray that showed intestinal atresia. Subsequently he manifested jaundice and unremitting cholestasis, thus liver biopsy was performed and revealed paucity of bile ducts which, associated with cholestasis, heart disease and peculiar facial features, suggested the diagnosis of ALGS [14]. Bales *et al.* report cases of children with ALGS started with pathologic fractures, involving mainly the lower extremity long bones [15]. Hannoush

*et al.* present a unique case of a patient diagnosed with ALGS who presented xanthomatosis and high levels of hypercholesterolemia [16]. Moreover, even if this syndrome is usually found in childhood, it can be diagnosed, for the first time, also in adult patient. Zhang *et al.* report a case of ALGS associated with a new JAG1 mutation that was diagnosed in adulthood who manifested intrahepatic cholestasis, without a well-specified familial history [17]. Like this one, Kim *et al.* present a 31-year-old male patient who showed elevated serum alkaline phosphatase and gamma-glutamyl transpeptidase and was diagnosed with ALGS associated with the JAG1 mutation configuring that, though ALGS is inherited in an autosomal dominant way, a considerable portion of ALGS is sporadic [18].

We described a family with four members suffered from ALGS through two successive generations. We focused on these family members because the mother was negative for the mutation and the other son didn't inherit this one due to the fact that, being the ALGS an autosomal dominant disease, there is the 25% possibility to not bring the specific mutation. Despite sharing the same mutation in the JAG 1 gene, these patients manifested different clinical presentation and only one of them had clinically significant hepatic disease. A similar condition was reported by Kamath *et al.* They studied 53 mutation positive relatives of 34 ALGS probands and reported that seventeen of the 53 [32%] relatives had mild features of ALGS, revealed only after targeted evaluation following the diagnosis of a proband in their family. They also noticed that the frequency of cardiac and liver disease was notably lower in the relatives than in the probands, characterizing the milder end of the phenotypic spectrum [13].

In our autochthon experience we had already found this heterogeneity: Leonardi *et al.* described two brothers affected by ALGS with variable expressivity in symptoms. The first diagnosis was made in the 15 days-old patient who presented with jaundice, cholestasis and pulmonic stenosis, and subsequently the ALGS was diagnosed to his 11 years-old sister that had milder hepatic symptoms than her brother [19].

This enormous variability of the clinical expression of ALGS can be explained by the implication of NOTCH receptor and its ligand in many important cellular signaling pathways. There is growing evidence that confirm the Notch pathway involvement in vascular development; in particular, studies in human embryos show strong expression of JAG1 in all major arteries [20]. Moreover, there are evidence that highlight the

pivotal role of vasculogenic endothelial cells in the early development of the liver. Consequently, if Notch signaling is disrupted in ALGS and results in abnormal vascular development, this might explain the mechanism for the resulting bile duct paucity seen in ALGS [21]. Therefore, the vascular anomalies seen in AGS (cardiac, cerebral and renal defects) could be a direct consequence of the disruption of this pathway. The intestinal atresia associated with ALGS could also be linked to alteration in vascularisation during the embryonic development of the digestive tract.

Recent evidence suggests that Notch signaling plays a critical role in establishing normal skeletal microstructure at various stages of development. It has shown that mice with targeted mutations in Notch pathway components develop significant reductions in trabecular bone mass [22], so it could also explain the bones implications of the syndrome. Moreover, JAG1 is overexpressed in many cancer types playing an important role in several aspects of tumor biology and pan-Notch inhibitors and therapeutic antibodies targeting one or more of the Notch receptors, have been investigated for cancer therapy [23].

Taken together, these data show that ALGS is a disorder with a wide spectrum of phenotypic manifestations, even between individuals from the same family sharing the same mutation. For this reason, the diagnosis may be difficult and it should be usually considered in differential diagnosis in patient (children or adults) with intrahepatic cholestasis, jaundice and pulmonic stenosis. JAG1 expression correlates well with the clinical heterogeneity described in these patients, but there is a weak correlation between the type and location of the JAG1 mutation and the severity of the disease, suggesting that other genomic modifiers beyond the known JAG1 mutation may be the cause of this variable expressivity. Further studies are needed to analyze the regulation of JAG1. It could be helpful to make a specific genetic panel to study the expression of other genes related to the JAG1 and the proteins produced by these genes to check if the production of different proteins might be linked to the severity of the disorder. This can pave the way for better understanding the ALGS physiopathology and symptoms that can be manifested in number of: "one, no-one and one hundred thousand", meaning that within the same disease it could be possible to find in different patients no one symptom, just one or many of them, because of its different phenotypic expressivity.

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