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REVIEW ARTICLE

Neuroradiological findings in Alagille syndrome

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ABSTRACT

Alagille syndrome (ALGS) is a multisystemic disease caused by mutations in genes of *Notch* pathway, which regulates embryonic cell differentiation and angiogenesis. Clinically, ALGS is characterized by cholestasis, cardiac defects, characteristic facial features, skeletal and ophthalmologic abnormalities. The aim of this review is to illustrate neuroradiological findings in ALGS, which are less well-known and prevalent, including cerebrovascular anomalies (such as aneurysms, dolichoectasia, Moyamoya syndrome and venous peculiarities), Chiari 1 malformation, craniosynostosis, intracranial hypertension, and vertebral anomalies (namely butterfly vertebra, hemivertebra, and craniocervical junction anomalies). Rarer cerebral midline malformations and temporal bone anomalies have also been described.

INTRODUCTION

Alagille syndrome (ALGS, OMIM 118450), also known as arteriohepatic dysplasia, is a multisystem autosomal dominant disorder with heterogenous clinical manifestations. The organs mainly affected are liver, heart, skeleton, eyes and kidneys, though endocrine and central nervous system may also be involved. Furthermore, patients usually have characteristic facial features. ALGS has an estimated prevalence of 1:30,000–1:50,000 live births, probably underestimated due to its wide phenotypical variability.[1,2] Most cases (97%) are caused by heterozygous mutations in *Jaged1 (Jag1)* gene, a cell surface protein that functions as ligand for *Notch* receptors, which plays a crucial role in embryonic cell differentiation and angiogenesis (Figure 1).[3]

ALGS clinical spectrum is wide. The most characteristic pathological and clinical manifestations are cholestasis due to bile duct paucity (interlobular bile ducts are particularly involved), cardiovascular defects, ophthalmologic, skeletal (especially vertebral), and facial abnormalities.

ALGS should be suspected in individuals with at least three of the following five major clinical features: cholestasis, cardiac defects (most commonly stenosis of the peripheral pulmonary artery and its branches), skeletal abnormalities (most commonly butterfly vertebrae), ophthalmologic abnormalities (most commonly posterior embryotoxon), and characteristic facial features (triangular-shaped face with a broad forehead and a pointed chin, bulbous tip of the nose, deeply set eyes, and hypertelorism). Furthermore, bile duct paucity on liver biopsy should be present. To confirm the diagnosis, genetic tests may be required.[4]

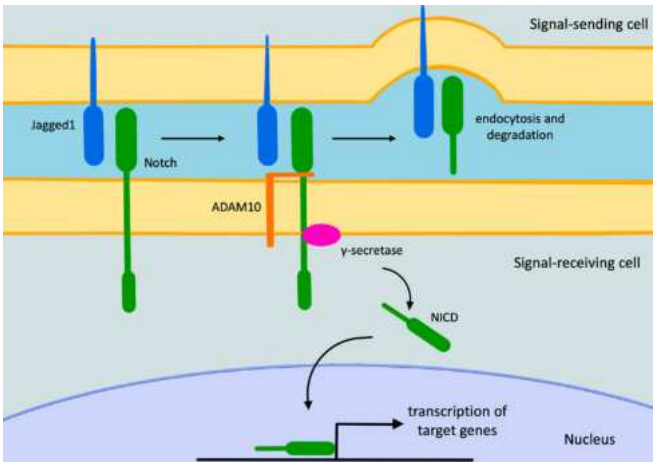
Various cerebrovascular anomalies have been associated with ALGS (Table 1). Their knowledge could be useful for the diagnostic work-up of the syndrome even though they are not part of the major diagnostic criteria and are less frequently described in the scientific literature. In this review, we aim to depict all the neuroradiological anomalies reported in ALGS so far.

Cerebrovascular anomalies

Intracranial arterial and venous anomalies represent a well-recognized feature of ALGS, with an estimated total prevalence of 30–40%.[5] In particular, arterial abnormalities may cause increased morbidity and mortality, with strokes and intracranial hemorrhage occurring in almost 14% and 14–16% of ALGS patients, respectively.[6,7]

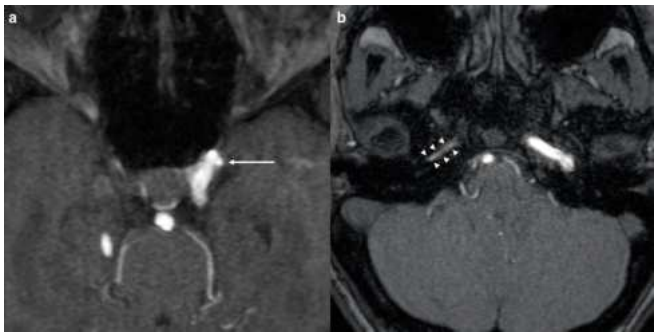
Notch plays an important role in angiogenesis as it is expressed by vascular endothelium during embryogenesis.[8] This could explain the predisposition to develop

Figure 1. The *Notch* signaling pathway. The pathway starts with *Notch/Jagged1* interaction, causing the *Adam10* metalloprotease activation. This last cleaves *Notch* allowing the *Notch-Jagged1* complex to be endocytosed by the ligand-expressing cell. Subsequently, the γ-secretase enzyme cleaves the remaining part of *Notch* releasing its intracellular domain that moves to the nucleus, where it regulates gene expression. NICD, intracellular domain of the *Notch* protein.



vascular abnormalities in ALGS. Intracranial aneurysms have been reported in patients with ALGS in the scientific literature (Figure 2).[7] This association should always be taken into account due to the risk of aneurysmal rupture and cerebral bleeding.[9] For instance, Doberentz et al[7] reported a case of massive and fatal subarachnoid hemorrhage due to the rupture of a large aneurysm of the basilar artery. In addition, cerebral arteries in ALGS have been reported to be more frequently enlarged and elongated or tortuous than in general population. This condition is referred to as dolichoectasia and it has also been reported to occur more

Figure 2. Cerebrovascular anomalies in a 9-year-old girl affected by ALGS. Axial 3D-time of flight MRA of the circle of Willis (a, b) depicts a small aneurysm of the cavernous segment of the left internal carotid artery (*arrow* in a) and narrowing of the petrous segment of the right internal carotid artery (*arrowheads* in b). ALGS, alagille syndrome; MRA, MR angiography.



frequently in other genetic conditions such as connective tissue disorders (*e.g.* Marfan syndrome, Ehlers-Danlos syndrome) and PHACE syndrome.[10,11] On the other hand, arterial stenosis (Figure 3) and Moyamoya syndrome (MMS) have been described in ALGS by different authors.[12–15] MMS is an intracranial arteriopathy causing progressive narrowing and occlusion of the distal part of the internal carotid arteries and their main branches. The compensatory dilation of smaller branches at the base of the brain and in basal ganglia is responsible of the characteristic angiographic appearance called "hazy puff of smoke", which gives the name to this syndrome.[16] MMS may cause ischemic stroke in children and hemorrhage in adults.[17] Another very rare condition described in ALGS is internal carotid agenesis.[18,19] Kamath et al[20] evaluated systemic vascular anomalies in 268 ALGS patients. Regarding the cerebrovascular system, they

Table 1. Summary table listing facial and craniospinal abnormalities found in patients with ALGS sort by system

System	Abnormalities
Cerebrovascular	• Arteries: aneurysms, dolichoectasia, stenosis, Moyamoya syndrome, agenesis of internal carotid artery. • Veins: persistent falcine sinus, cerebral veins tortuosity.
Skull	• Craniosynostosis • Clivus hypoplasia • Foveola pharyngica • Temporal bone malformations (agenesia/hypoplasia of the posterior semicircular canals, cochlear hypoplasia)
Face	• Prominent forehead • Deep-set eyes • Hypertelorism • Straight nose with a flattened tip • Large ears • Midface hypoplasia • Prominent and pointed chin • Micrognathia • Cleft palate
Brain	• Chiari 1 malformation • Idiopathic intracranial hypertension • Midline malformations (corpus callosum thinning, hypoplasia of the splenium and the isthmus of the corpus callosum, isolated agenesis of the septum pellucidum, bilateral incomplete hippocampal inversion)
Spine	• Vertebral anomalies (*e.g.* butterfly vertebra, hemivertebra, segmentation abnormalities) • Craniocervical junction abnormalities

ALGS, alagille syndrome.

Figure 3. Cerebral arterial anomalies in a 2-year-old boy with ALGS. Coronal 3D-time of flight MRA of the circle of Willis shows stenotic narrowing of the carotid siphons (*arrows*). ALGS, alagille syndrome; MRA, MR angiography.

discovered two aneurysms of the basilar artery, one aneurysm of the left middle cerebral artery, one MMS and seven anomalies of the internal carotid arteries (four stenosis, two agenesis and one dolichoectasia). Intracranial bleeds were seen in 14% of patients and accounted for 25% of mortality in their cohort.

Carpenter et al[5] evaluated 19 out of 52 patients with ALGS using different cerebrovascular imaging techniques (MR angiography (MRA), computed tomographic angiography, and digital subtraction angiography) and identified both arterial and venous anomalies. They reported four patients with single or multiple arterial dolichoectasia, three of which also had asymptomatic saccular aneurysms. MMS was discovered in two patients, with one suffering from multiple strokes and the other one from recurrent episodes of bilateral paresthesia and vision blackouts. Regarding venous anomalies, they reported one patient with isolated developmental venous anomaly and three with persistent falcine sinus (the latter with an estimated prevalence of 5.8% compared to 1–2.1% in the general pediatric and adult population). Persistent falcine sinus consists of a normal fetal vein which arises from the

Figure 4. Cerebral venous anomalies in a 15-year-old boy with ALGS. Coronal 3D-phase contrast MRA shows diffuse tortuosity of cerebral veins compared to a child of comparable age without ALGS (b). ALGS, alagille syndrome; MRA, MR angiography.

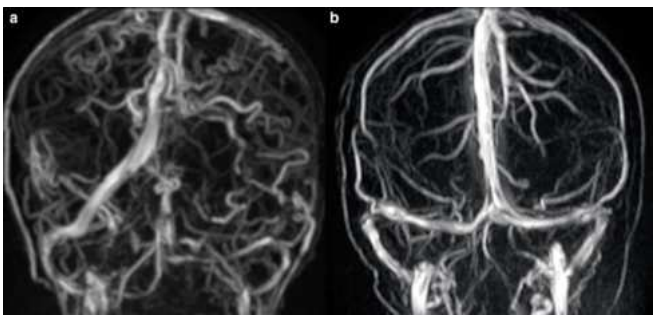
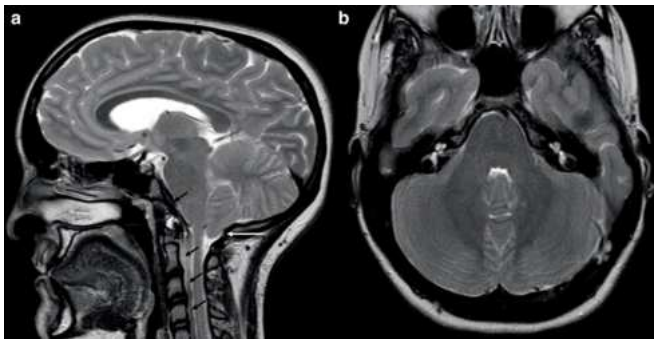


Figure 5. Chiari 1 in a 17-year-old boy with ALGS. Sagittal (a) and axial (b) turbo spin echo T_2 weighted images depicting low lying cerebellar tonsils (white *arrow* in A) and reduced volume of the posterior fossa (b). Clivus and cervical vertebral bodies are hypoplastic (black *arrows* in A). Note also scaphocephaly and frontal bossing. ALGS, alagille syndrome



straight sinus and drains into the superior sagittal sinus. It may persist in adult age, possibly influencing neurosurgery, in particular in case of transtentorial approach. We report an anomalous case of tortuosity of multiple cerebral veins in a patient affected by ALGS (Figure 4).

Given the genetic predisposition of ALGS patients to cerebrovascular abnormalities, an accurate clinical and neuroradiological screening with brain MRI and MRA of the circle of Willis is recommended as some of these conditions (such as arterial stenoses and aneurysms) are associated with high morbidity and mortality also in absence of prodromal symptoms.[20]

Skull, facial, and brain anomalies and malformations

Skull malformations represent the second most common bone anomaly in ALGS.[21] Their prevalence is 0.9%, compared to that of 0.03% occurring in the general population.[22] Premature fusion of cranial sutures is defined as craniosynostosis and can be simple or complex (if one or more sutures are affected, respectively). Craniosynostosis in ALGS has been reported more frequently as simple, with premature coronal closure being the most common.[23] A molecular explanation of craniosynostosis in ALGS has been given by Yen et al who demonstrated that *Jag1* plays a key role in skull suture development and fusion.[24]

Chiari 1 has been frequently reported in patients with ALGS, with an estimated prevalence of 33% (Figure 5).[25–27] This malformation is defined by cerebellar tonsil caudal tip descent of more than 5 mm past the foramen magnum,[28] whose pathophysiology is still unknown, though it might be partially related to underdevelopment of the bony components of posterior fossa.[29,30]

Idiopathic intracranial hypertension (IIH) has also been reported in ALGS (Figure 6).[31] Narula et al evaluated 55 ALGS patients, three of which had IIH.[32,33] Pathogenesis of IIH in ALGS is still not defined but it can be related to craniosynostosis. Furthermore, *Jag1* may play a role in IIH as well, as it may also influence cerebrospinal fluid production due to its involvement in angiogenesis.[34]

Figure 6. IIH in a 17-year-old boy with ALGS suffering from chronic headache. Axial turbo spin echo T_2 weighted image (a) and coronal 3D-phase contrast MRA (b) depict dilation of the optic nerve sheaths (black *arrows* in A) and a signal gap in the right transverse sinus (white *arrows* in b) due to stenosis, respectively. Also note flattening of the posterior globes contour (a). ALGS, alagille syndrome; IIH, idiopathic intracranial hypertension; MRA, MR angiography.

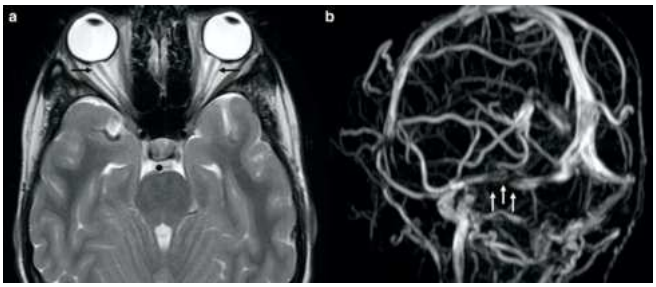
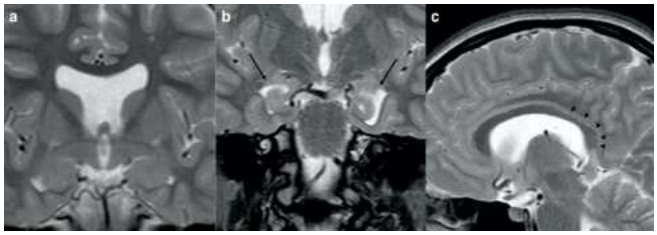


Figure 8. Cerebral midline anomalies in a 15-year-old-girl with ALGS. Coronal turbo spin echo T_2 weighted image shows isolated agenesis of the septum pellucidum (a). Cerebral midline and hippocampal anomalies in a 14-year-old girl with ALGS. Coronal (b) and sagittal (c) turbo spin echo T_2 weighted images demonstrate bilateral incomplete hippocampal inversion (black *arrows* in b) and mild hypoplasia of the splenium and the isthmus of the corpus callosum (black *arrowheads* in c). ALGS, alagille syndrome



Temporal bone malformations have also been reported. Okuno et al[35] performed a histopathological evaluation of six temporal bones from four pediatric patients with ALGS. All had partial or total absence of the posterior semicircular canals, whereas three had partial absence of the superior ones. The lateral semicircular canals were not affected. In one subject, cochlea was bilaterally shortened. Koch et al[36] also reported the absence of posterior semicircular canals and hypoplasia of anterior semicircular canals in a patient with ALGS. Although isolated absence of the posterior semicircular canals is overall extremely rare, it could still be a feature of the syndrome. Various genetic syndromes have been frequently associated with semicircular canals anomalies (such as Goldenhaar and CHARGE), whereas posterior semicircular canals aplasia is reported as a characteristic finding of Waardenburg syndrome.[37–39] Furthermore, Kierman et al[40] reported that mice with missense mutation of *Jag1* have dysplastic posterior semicircular canals without involvement of the lateral ones.

Regarding skull bone anomalies, here we report one patient with clivus hypoplasia and foveola pharyngica (Figure 7), the latter consisting of persistence of notochordal remnants. It is a rare finding, thought to be a variant of the residual canalis basilaris medianus, which is a round recess in the basiocciput.[41]

Facial abnormalities in ALGS are characteristic and consist of prominent forehead, deep-set eyes, hypertelorism, straight nose with a flattened tip, large ears, midface hypoplasia and prominent and pointed chin.[42,43] These findings give the overall appearance of the face as an inverted triangle and are often associated with decreased mandibular ramus length and a wide gonion.[44] Other frequent characteristics are micrognathia and cleft palate.[45]

Finally, midline cerebral malformations could also be associated with ALGS. Corpus callosum thinning has been reported in rare cases.[27] A possible genetic explanation is given by the role of *Notch* in corpus callosum development.[46] We found two cases of midline brain abnormalities, one with isolated agenesis of the septum pellucidum, and one with mild hypoplasia of the splenium and the isthmus of the corpus callosum and concomitant bilateral incomplete hippocampal inversion (Figure 8).

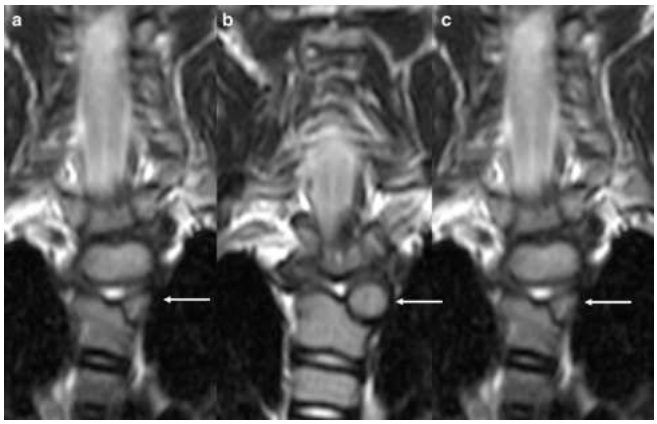
Figure 7. Basicranium anomalies in a 14-year-old girl with ALGS. Sagittal (a) and axial (b) turbo spin echo T_2 weighted images show foveola pharyngica recess (*white arrows* in A and B) and clival hypoplasia (*black arrow* in a). ALGS, alagille syndrome

Figure 9. Spine malformations in a 35-year-old male with ALGS. Coronal turbo spin echo T_2 weighted image depicts severe vertebral dysmorphism, consisting of C5 and C6 fusion (segmentation anomaly) and typical median split of the vertebral body (butterfly vertebra) (white *arrows*). ALGS, alagille syndrome

Spine malformations

Vertebral anomalies are the most frequent skeletal malformation in ALGS (prevalence of 51–66%), being multiple in 48% of patients.[47,48] A possible explanation is given by the role played by *Notch* signaling during somitogenesis and craniovertebral junction development.[48–51] The most frequent vertebral malformations reported in ALGS patients are butterfly vertebra and hemivertebra. Butterfly vertebra is characterized by the presence of a central sagittal cleft in the vertebral body, caused by failed fusion of lateral chondrification centers during spinal embryogenesis due to aberrant persistence of notochordal tissue (Figure 9).[21,52] It can be complete or partial, depending on presence of a bone bridge across the defect. This malformation is frequently asymptomatic and most commonly affects thoracolumbar spine.[47,48] Spina bifida occulta has been described only in three patients with ALGS so far.[6,53,54]

Figure 10. Spine malformation in a 10-year-old boy with ALGS. Coronal turbo spin echo T_2 weighted images (a–c) depict a left thoracic hemivertebra (*arrows* in a–c). ALGS, alagille syndrome



Hemivertebra represents agenesis of half of the vertebral body (Figure 10).[55] It is thought to be caused by lack of development of one of the paired chondrification centers during embryogenesis. Again, thoracic and lumbar spine are more frequently affected, causing kyphosis and/or scoliosis.[56]

Other types of vertebral malformations (such as segmentation anomalies, including block vertebra) have been reported in ALGS as well as anomalies of the craniocervical junction (including partial atlantooccipital joint assimilation).[48,57]

CONCLUSIONS

Craniospinal manifestations of ALGS are extremely wide and neuroradiologists should be familiar with them, especially as some may significantly influence prognosis. In particular, acute complications of vascular stenosis and rupture of aneurysms can cause ischemic strokes and hemorrages, respectively. Therefore, arterial screening with unenhanced brain MRA is suggested in patients with ALGS.

On the other hand, knowledge of the aforementioned neuroradiological findings can further corroborate clinical suspicion of ALGS, thus improving diagnostic work-up.

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