

Vascular Anomalies in Alagille Syndrome

A Significant Cause of Morbidity and Mortality

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Background—Alagille syndrome (AGS) is a dominantly inherited multisystem disorder involving the liver, heart, eyes, face, and skeleton, caused by mutations in *Jagged1*. Intracranial bleeding is a recognized complication and cause of mortality in AGS. There are multiple case reports of intracranial vessel abnormalities and other vascular anomalies in AGS. The objective of this study was to characterize the nature and spectrum of vascular anomalies in AGS.

Methods and Results—Retrospective chart review of 268 individuals with AGS was performed. Twenty-five patients (9%) had noncardiac vascular anomalies or events. Sixteen patients had documented structural vascular abnormalities. Two had basilar artery aneurysms, 7 had internal carotid artery anomalies, and another had a middle cerebral artery aneurysm. Moyamoya disease was described in 1 patient. Three of the 16 patients had aortic aneurysms, and 2 had aortic coarctations. One of the patients with a basilar artery aneurysm also had coarctation of the aorta. One of the individuals with an internal carotid artery anomaly also had renal artery stenosis. Nine more patients had intracranial events without documented vessel abnormalities. Vascular accidents accounted for 34% of the mortality in this cohort.

Conclusions—The vascular anomalies described in our cohort of AGS individuals identify an underrecognized and potentially devastating complication of this disorder. It is a major cause of morbidity and mortality in this population, accounting for 34% of the mortality. We have also reviewed the body of evidence supporting a role for *Jagged1* and the Notch signaling pathway in vascular development. (*Circulation*. 2004;109:1354-1358.)

Key Words: aneurysm ■ angiogenesis ■ cerebrovascular disorders ■ vasculature

Alagille syndrome (AGS) is a dominantly inherited multisystem disorder involving the liver, heart, eyes, face, skeleton, and other systems. *Jagged1* (*JAG1*), a ligand in the developmentally important Notch signaling pathway, has been identified as the AGS disease gene.¹ Currently, *JAG1* mutations have been identified in approximately 60% to 70% of individuals with clinically diagnosed AGS.² There is no evidence suggesting a second locus for the disorder at this time, and the inability to identify a mutation in the remaining 30% is thought to be because of technical limitations in testing this fairly large gene. The main clinical manifestations of AGS have been well characterized (cholestasis caused by intrahepatic bile duct paucity, congenital heart defects involving primarily the pulmonary arteries, butterfly vertebrae, anterior chamber defects of the eye, typically posterior embryotoxon, and facial dysmorphism) and are the basis for the clinical diagnosis. Several other consistent clinical findings have been reported, although not with as high a frequency as the main manifestations, including renal abnormalities, retinal pigmentary changes, and pancreatic insufficiency.³ One finding that has been reported with greater frequency over

the past several years and is of particular concern because of its significant contribution to morbidity and mortality is intracranial bleeding.³

Vascular anomalies have been noted in AGS from some of the earliest descriptions of this syndrome.^{4,5} Indeed, even the alternative name for the condition, arteriohepatic dysplasia, recognizes the vascular contribution. Pulmonary artery involvement is a hallmark feature of the condition and one of the most common manifestations.³ However, the literature documents multiple case reports of intracranial vessel abnormalities and other vascular anomalies in AGS. The latter include involvement of the aorta, renal, celiac, superior mesenteric, and subclavian arteries (Figure).⁶⁻¹³

Unexplained intracranial bleeding is a recognized complication and cause of mortality in AGS. Intracranial bleeds were seen in 14% of our patients and accounted for 25% of the mortality in our cohort.³ Intracranial bleeds have been seen in up to 16% of patients in other series.¹⁴ There does not seem to be any pattern to the location and/or severity of the intracranial bleeding, which ranges from massive fatal events

Received October 7, 2003; revision received December 10, 2003; accepted January 5, 2004.

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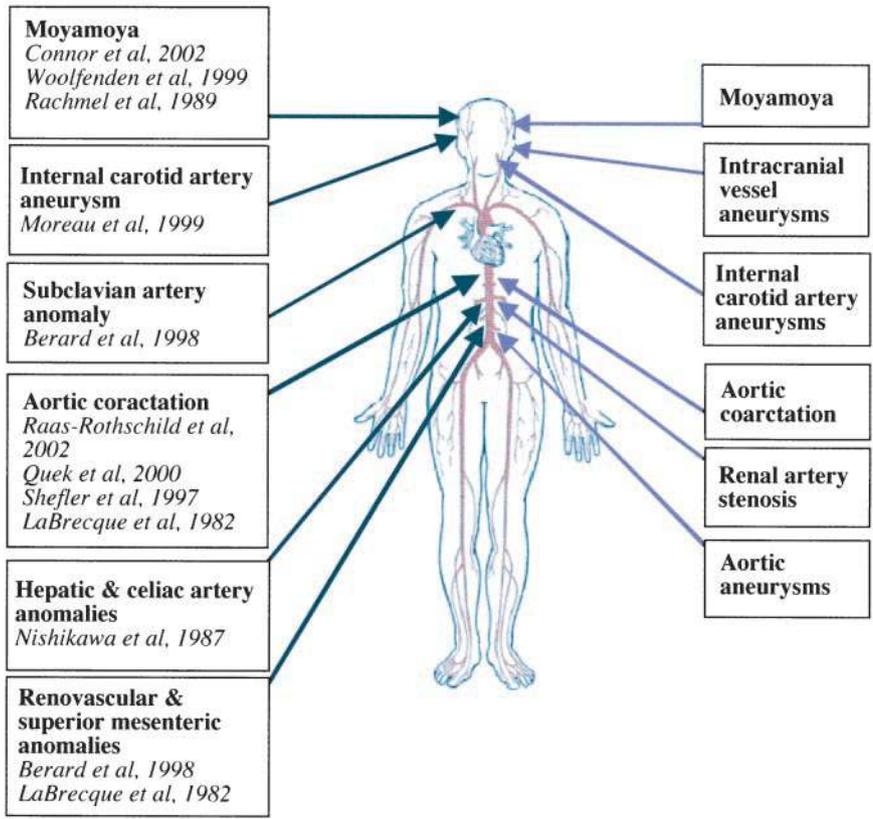
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Circulation is available at <http://www.circulationaha.org>

DOI: 10.1161/01.CIR.0000121361.01862.A4

REPORTS FROM THE LITERATURE

THIS REPORT



Spectrum and localization of vascular anomalies in our cohort of AGS patients and in previous reports.^{6-13,28}

to asymptomatic cerebral infarcts. Underlying central nervous system vascular abnormalities have been described in some AGS individuals, which could explain the intracranial events.^{8,14}

The aim of this study was to determine the prevalence of noncardiac vascular anomalies and events in a cohort of individuals with AGS. In addition, the impact of these findings on patient mortality was assessed. There is a growing body of evidence that implicates the Notch signaling pathway in vascular development and indicates that the vascular anomalies seen in AGS are a direct consequence of the disruption in this pathway. We outline the evidence that demonstrates a role for *JAG1* and the Notch signaling pathway in vascular development and suggest that defects of vasculogenesis may be the primary underlying abnormality in AGS.

Methods

From 1992 to 2002, 268 probands and family members with AGS have been enrolled in our database at The Children’s Hospital of Philadelphia. These individuals had been referred to us for clinical evaluation and/or mutational analysis. All individuals have been enrolled under an institutional review board–approved protocol of informed consent. Those individuals included in the database either met clinical criteria for AGS, carried a mutation in or a deletion of *JAG1*, or were obligate carriers of a mutation. Mutational analysis was performed by single-strand conformational polymorphism, as previously described.¹

Clinical information was obtained by direct examination of medical records, physician questionnaire, and family interviews. Families and/or referring physicians were asked about any history of vascular problems. Whenever possible, individuals were ascertained at The Children’s

Hospital of Philadelphia. When patients were not seen at our institution, the records of relevant evaluations and studies were reviewed.

Results

Retrospective review of the records of 268 individuals in our database determined that 9% have documented vessel abnormalities or a history of a vascular event. We report 25 individuals who had vascular complications (Table 1). Fourteen of these had mutations in *JAG1*, and 2 have had mutations identified in the family but the individuals themselves were not tested (these individuals were obligate carriers). Four patients did not have a mutation in *JAG1* but met clinical criteria for AGS. Samples were not available for mutational analysis in another 4 patients; however, they also met clinical criteria for AGS. In 1 case, mutational analysis and further clinical evaluation were not possible, but the individual had typical AGS facies and a daughter with mutation-proven AGS. The age range of affected individuals in this study was 4 months to 44 years.

Of the 25 individuals reported, 16 had documented structural abnormalities of the vascular system. These included intracranial vessel, aortic, and renal artery anomalies (Table 1; Figure). Of note, we report the first mutation-proven case of moyamoya in AGS. In 12 individuals, the results of a cardiac evaluation were known, and in these, 10 of 12 (83%) had stenosis at some level in the pulmonary tree.

The remaining 9 individuals (8 children, 1 adult) had significant intracranial vascular events with no documented vessel abnormality. Two children had complicated courses in

TABLE 1. Clinical Features of AGS and Specific Vascular Event/Anomaly Present in Our Cohort of 25 Patients

Case	Mutation (Exon/Type)	Cholestatic Liver Disease	Cardiac Defect	Anterior Chamber Defect	Vertebral Anomaly	Facies	Vascular	Clinical Correlate
Structural anomaly								
1	24, Splice	—	+	—	UNK	+	Moyamoya	Presented with right-sided weakness
2	17, Frameshift	+	+	+	UNK	+	Basilar artery aneurysm	Presented with headaches
3	4A, Frameshift	+	+	+	UNK	+	Basilar artery aneurysm Coarctation of the aorta	Presented with acute headache Coarctation identified during evaluation for renal failure
4	18, Nonsense	+	+	—	+	UNK	Basal ganglia infarct Internal carotid anomaly	Presented with acute unilateral paralysis
5	—	+	+	—	UNK	—	Aneurysm of L middle cerebral artery	Died in sleep—aneurysm identified at autopsy
6	UNK	+	+	+	+	+	Attenuated L internal carotid artery—CVA Renal artery stenosis	Presented with acute unilateral paralysis and numbness Evaluated for hypertension
7	2A, Nonsense†	UNK	UNK	UNK	UNK	+	Aortic aneurysm	Catastrophic outcome—autopsy
8	17, Missense*	UNK	UNK	UNK	UNK	+	Aortic aneurysm	Catastrophic outcome—autopsy
9	18, Nonsense*	UNK	UNK	UNK	UNK	+	Sinus of Valsalva aneurysm	Catastrophic outcome—autopsy
10	—	+	+	UNK	+	+	Coarctation of the aorta	Routine cardiological evaluation
11	UNK	+	UNK	UNK	+	+	Coarctation of the aorta	Evaluation for hypertension
12	5, Nonsense	+	+	+	—	+	Narrow L internal carotid artery	MRA screening
13	5, Nonsense	+	+	+	—	+	Narrow R internal carotid artery	MRA screening
14	—	+	+	—	—	+	Absence of L internal carotid artery with collaterals	MRA screening
15	11, Splice site	UNK	+	+	UNK	+	Nonvisualization of L internal carotid artery	Presented with headaches
16	25, Frameshift	+	+	+	+	+	Dolichoectasia of R internal carotid artery	MRA screening
Bleed/infarct								
17	4, Missense	+	+	—	+	+	Cerebral and adrenal hemorrhage	Ischemic event while ventilated for respiratory failure—CT
18	24, Frameshift	+	+	+	UNK	+	Subdural hematoma	Presented with seizures—CT & MRI
19	13, Nonsense	+	+	—	—	+	Intracranial bleed	Complications post liver tx—CT
20	4, Splice site	+	+	+	UNK	+	Cerebral infarcts	Complications post cardiac catheterization—autopsy
21	23, Frameshift	+	+	UNK	—	+	CVA	Clinical symptoms—CT
22	UNK	+	—	+	—	+	CVA	Complications post liver tx—CT
23	—	+	+	UNK	UNK	+	SAH & SDH	Ischemic event awaiting lung tx—autopsy
24	UNK	+	+	UNK	+	+	Epidural hematoma	Preceding trauma—autopsy
25	3, Frameshift	+	+	+	—	—	Intracranial bleed	Complications post liver tx—CT

CVA indicates cerebrovascular accident; SAH, subarachnoid hemorrhage; SDH, subdural hemorrhage; L, left; R, right; +, feature present; —, feature absent; ?, feature not screened for or result of study unknown; and tx, transplant.

*Obligate mutation carrier.

†Presumed affected parent of adult with known mutation.

CT/MRI/autopsy, when noted, indicates method by which vascular abnormality or event was identified.

the post-liver transplant period and intracranial bleeding episodes during this time. Two individuals had a clear history of trauma preceding the bleeding event. Another infant developed seizures, was found to have a left subdural hema-

toma, and died during attempted evacuation. One child suffered multiple areas of infarcts in the right parietal and left frontal lobes after cardiac catheterization, although no vessel anomalies were seen. Finally, 1 mutation-positive infant

TABLE 2. Causes of Mortality in AGS Cohort of 268 Individuals

Cause of Mortality	No.
Liver disease	3/29 (10)
Cardiac disease	6/29 (21)
Noncardiac vascular complications	10/29 (34)
Structural anomalies	4/10
Functional event	6/10
Sepsis	2/29 (7)
Unknown	8/29 (28)

Values are n/N (%).

developed respiratory failure and suffered an ischemic event while intubated and ventilated.

Further analysis of the data revealed that 29 individuals from the original cohort have died. Ten of these 29 died of complications of noncardiac vascular disease, thereby accounting for 34% of the mortality in this population. These results are summarized in Table 2.

Discussion

This review of a large cohort of AGS probands and relatives demonstrates the extent and frequency of vascular anomalies and events seen in this population. This is the first retrospective study highlighting the documented and suspected vascular anomalies in a large cohort of AGS patients. In this database, 9% of individuals with AGS have had a vascular event or documented structural abnormality. This study substantiates the multiple case reports in the literature describing vascular anomalies in AGS (Figure). In comparison, the incidence of cerebrovascular disease in children has been reported as 2.5 cases per 100 000 per year.¹⁵ Although the incidence of peripheral vascular anomalies in children has not been documented, they are generally considered to be rare. In addition, we have demonstrated that noncardiac anomalies contribute substantially (34%) to the mortality in this AGS cohort.

Typical pulmonary artery anomalies are seen in 67% individuals with AGS.³ In our cohort, the group of individuals with documented structural vessel abnormalities had a frequency of 83% of pulmonary tree stenosis. It is possible that stenosis in the pulmonary tree may even be a predictor of another vascular anomaly in AGS.

In addition to classic pulmonary artery abnormalities, we have described intracranial and extracranial anomalies and vascular events in AGS. Intracranial hemorrhages and stroke have been well documented in up to 16% of AGS patients and contribute significantly to morbidity and mortality.¹⁴ Underlying vessel abnormalities in the central nervous system that could explain the occurrence of bleeding and stroke in AGS have been described in some of these patients.^{8,14} In our database, 2 cases had basilar artery aneurysms, 1 had an aneurysm of the left middle cerebral artery, and 2 had internal carotid artery anomalies accounting for the intracranial events. Another 5 patients had internal carotid artery anomalies that were detected on MR/MRA imaging. Moyamoya disease (progressive intracranial arterial occlusive disease) has also been described in 4 other children with AGS,^{6,11,13} although the child reported here is the first *JAG1* mutation-proven case of moyamoya.

This study also documents the existence of systemic vascular abnormalities in AGS. In our population, 3 patients had aortic aneurysms and 3 had aortic coarctations. Case reports of individuals with AGS and aortic involvement have been described.^{7,10,12} Renovascular anomalies have been described in a series of 5 patients with AGS.¹⁶ Angiography demonstrated unilateral or bilateral renal artery stenosis in all of these patients who presented with hypertension. In addition, these 5 patients also all had other abnormalities of their large arteries, namely the aorta, celiac artery, superior mesenteric artery, and subclavian artery.

Nine patients in our database had vascular events without structural abnormalities. Two of these events were clearly associated with trauma, and it is not clear whether there were underlying anomalies that predisposed to the bleeding. In 5 cases, the individuals were critically unwell or had a comorbid condition such as hypertension at the time of the event and therefore may have bled as a result of their illness rather than a structural vessel abnormality.

Seventeen of 25 (68%) of the individuals described in this report with vascular events or anomalies had a mutation in *JAG1* identified in themselves or a first-degree relative. This is consistent with the mutation detection rate for AGS, as previously reported.² The alterations seen in *JAG1* are spread throughout the gene and consist of protein-truncating, missense, and splice site mutations. There is no apparent clustering of specific mutations with a particular vascular anomaly/event (ie, no genotype-phenotype correlation was observed).

Characteristic pulmonary vessel anomalies, together with the increasing awareness of other arterial involvement in AGS, as documented and reviewed in this report, suggest that the Notch signaling pathway plays an important role in vascular development. We further suggest that vasculopathy may explain the multisystemic phenotype of AGS. Evidence supporting this hypothesis comes from clinical case reports as well as developmental and molecular studies implicating *JAG1* and the Notch signaling pathway in vascular development. That a vasculopathy exists in AGS has been suggested elsewhere^{17,18}; however, we propose that the vasculopathy is the primary abnormality in AGS. The Notch signaling pathway is an evolutionarily conserved intercellular signaling mechanism. Currently, 4 Notch family receptors and 5 ligands (including *JAG1*) have been described in mammals. Because both the ligands and receptors are transmembrane receptors, the Notch pathway is limited to regulating interactions between physically adjacent cells. Evidence supporting a role for *JAG1* and Notch in vascular development beyond that demonstrated in pulmonary arteries includes the expression of Notch ligands and receptors in vascular endothelium or supporting cells.^{19–21} In particular, studies in human embryos show strong expression of *JAG1* in all major arteries.²²

Further evidence of the role of *JAG1* and Notch in vascular development is provided by the phenotype of targeted Notch pathway mutants. Mice homozygous for a mutation in *Jag1* die of hemorrhage during early embryogenesis because of defects in angiogenic vascular remodeling in the yolk sac and embryo.²³ Both Notch1 mutant and Notch1/Notch4 double-mutant mouse embryos also display severe defects in angiogenic vascular remodeling.²⁴ In fact, even activated expression of Notch4 protein leads to similar abnormal vessel structure and patterning and embryonic lethality,

demonstrating that appropriate levels and regulation of Notch signaling are critical for proper vascular development.²⁵

A human model also exists to support a role for the Notch pathway in vascular homeostasis. In adults, CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy), a degenerative disorder characterized by late-onset strokes and dementia, is caused by mutations in the Notch3 receptor that results in alterations of vascular smooth muscle cells.²⁶

If vasculopathy is the primary abnormality in AGS, it would be expected that the clinical features of the syndrome might be explained by abnormal vascular development. The cardiac anomalies in AGS, involving predominantly the pulmonary arteries, are easily explained by disordered vasculogenesis. Recent evidence implicates the importance of vasculogenic endothelial cells in the early development of the liver. There is evidence that the development of intrahepatic bile ducts is dependent on intrahepatic arterial branch formation.²⁷ The formation of mature tubular bile ducts is always preceded by the development of intrahepatic arterial branches. If Notch signaling is disrupted in AGS, resulting in abnormal vascular development and signaling, this may suggest the mechanism for the resulting bile duct paucity seen in AGS. Similarly, a lack of vascular support specifically dependent on *JAG1* signaling may account for the development of the other structural anomalies seen in AGS, although there is no evidence to support this at the present time.

It is possible that the frequency of noncardiac structural vascular anomalies in individuals with AGS is actually greater than the 9% reported here. It was clearly not possible to fully evaluate all patients in the cohort with radiological studies. The data do, however, support a need for further systematic studies to identify structural vessel abnormalities in this population (eg, using total body MRA).

The findings in our cohort of AGS probands and family members identify a concerning and potentially devastating complication of this disorder. Vascular anomalies and events have resulted in significant morbidity and mortality in AGS, with vascular accidents accounting for 34% of the mortality in this population. These defects are dynamic and may manifest at any age. Further studies are needed to identify the true prevalence of vascular abnormalities in this population and to determine whether presymptomatic screening is possible and/or warranted. Given the data presented in this report and previous case reports, it would seem to be prudent to aggressively evaluate individuals with AGS for vascular involvement if concerning symptoms are present (ie, neurological deficits, persistent headaches, hypertension, etc). We have also reviewed the body of evidence supporting a role for *JAG1* and the Notch signaling pathway in vascular development and suggest that vasculopathy is the primary abnormality in AGS and may explain the multisystemic phenotype.

Acknowledgments

This study was supported by the National Institute of Diabetes and Digestive and Kidney Diseases (1 K08-DR-02641-01, 1-RO1-DK-53104); the National Center for Research Resources (M01-RR-08084); and the Fred and Suzanne Biesecker Center for Pediatric Liver Disease at the Children's Hospital of Philadelphia.

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