The Turkish Journal of Pediatrics 2026; 68: 680-688
https://doi.org/10.24953/turkjpediatr.2026.7715

Case Report

Phenotypic characteristics and clinical management of Alagille syndrome with multiple intracranial aneurysms: a case report and literature review

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ABSTRACT

Background. Alagille syndrome (ALGS) is an autosomal dominant multisystem developmental disorder associated with *JAG1* and *NOTCH2* mutations. Although vascular involvement is recognized, life-threatening intracranial hemorrhage as the initial presentation is extremely rare.

Case Presentation. A 5-year-old male presented with a severe headache and was diagnosed with intracerebral and subarachnoid hemorrhage caused by multiple ruptured intracranial aneurysms. Genetic testing confirmed a pathogenic *JAG1* mutation, establishing the diagnosis of ALGS. The patient, who had known aortic stenosis, developed infective endocarditis—raising the possibility that infection was driving the aneurysms. After two microsurgical craniotomies, he ultimately died of multi-organ failure.

Conclusions. This case highlights a rare presentation of ALGS involving acute rupture of multiple intracranial aneurysms, complicated by cardiac malformation and infective endocarditis, with newly formed aneurysms highly suspected to be infection-driven. ALGS should be considered in young children presenting with early intracranial hemorrhage, particularly when cardiac anomalies coexist. Early multidisciplinary intervention may prevent the catastrophic sequelae of ALGS-associated intracranial aneurysms.

Key words: Alagille syndrome, multiple intracranial aneurysms, intracranial hemorrhage, infective endocarditis, infectious intracranial aneurysms.

Alagille syndrome (ALGS) is a rare autosomal dominant, multisystem developmental disorder linked to mutations in *JAG1* and *NOTCH2*.[1] Classic features include sparse or hypoplastic intrahepatic bile ducts, congenital heart defects, spinal deformities, characteristic facial features, ocular manifestations, and vascular anomalies.[1] The incidence is reported to ranger from 1:30,000 to 1:100,000, with mortality rates of 10–20 %.[2,3] In addition to severe hepatic and cardiac disease, intracranial hemorrhage is a major cause of death. Isolated reports have associated ALGS with multiple intracranial aneurysms. We describe the diagnostic and therapeutic course of a 5-year-old patient with ALGS and multiple intracranial aneurysms and discuss the genetic profile, possible pathogenesis, and management strategies for this rare comorbidity.

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Received 21st Dec 2025, revised 17th Jan 2026, 22nd Mar 2026, 7th Apr 2026, accepted 23rd Apr 2026.

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Case Presentation

A 5-year-old right-handed boy presented with coma (Glasgow Coma Scale score of 9). The computed tomography angiography (CTA) showed a right frontoparietal hematoma of >35 mL and a right middle cerebral artery (MCA) aneurysm (Fig. 1a and Fig. 1b); clot evacuation and clipping were performed within 4 hours, and he was discharged 1 month later.

Two weeks later, his headache recurred and progressed to deep coma with herniation. A left hematoma of >25 mL and a left MCA aneurysm (Fig. 1c and Fig. 1d) prompted emergency craniectomy with clipping. Given the recurrent intracranial multi-aneurysmal hemorrhage in a child accompanied by cardiac pathology (aortic stenosis) and aortic valve vegetations (Fig. 1e and Fig. 1f), a multisystem disorder was suspected. The foremost

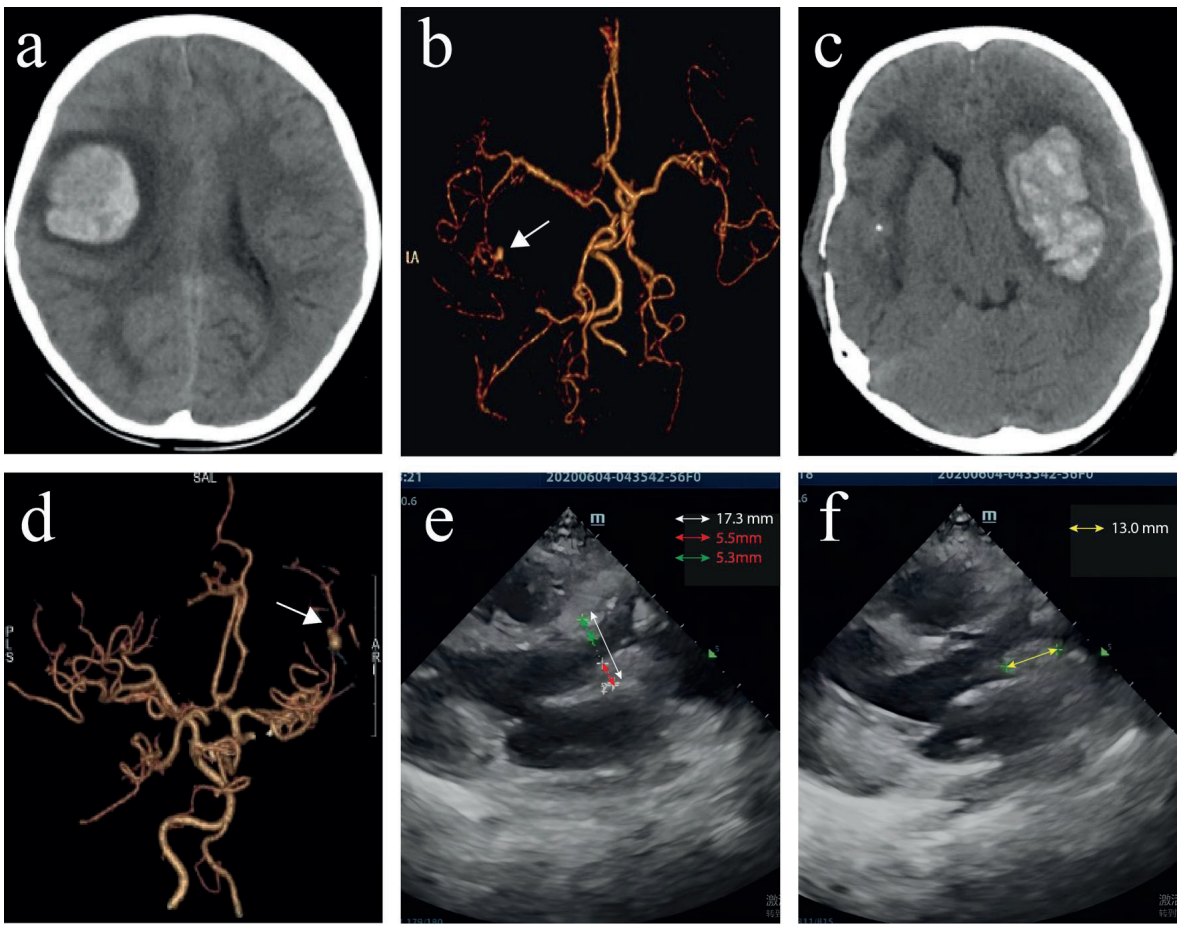

Fig. 1. a) Computed tomography (CT) showing the hematoma in the right frontoparietal lobe. **b)** CT angiography showing a right MCA aneurysm (arrow). **c)** CT showing the hematoma in the left frontoparietal lobe. **d)** CTA showing a left MCA aneurysm (arrow). **e, f)** Echocardiography images demonstrating that the right coronary cusp and non-coronary cusp of the aortic valve are both thickened, with vegetations present on the aortic valve, resulting in significantly restricted valve opening. The white double arrow (e) indicates the anteroposterior diameter of the aortic root (17.3 mm). The red double arrow (e) marks the distance from the non-coronary cusp to the posterior aortic wall (5.5 mm), i.e., the vegetation thickness. The green double arrow (e) indicates the distance from the right coronary cusp to the anterior aortic wall (5.3 mm). The yellow double arrow (f) indicates the vegetation length (13.0 mm). The aortic valve opening diameter is 6.5 mm (calculated as 17.3 mm - 5.5 mm - 5.3 mm).

consideration was infective endocarditis (IE) superimposed on congenital heart disease, most likely a dysplastic aortic valve or coarctation, while connective-tissue disorders and vasculitides remained in the differential. Inflammatory markers and the autoimmune antibody screen were unremarkable, shifting suspicion toward a heritable connective tissue disorder. However, the combination of aortic stenosis (a cardiac lesion less typical of classic connective tissue disorders such as Marfan or Ehlers-Danlos syndromes) and recurrent aneurysmal hemorrhage in a child raised the possibility of other genetic syndromes. Among these, Alagille syndrome (ALGS), caused by pathogenic variants in *JAG1* or *NOTCH2*, was considered, as it can present with congenital heart defects (including aortic stenosis and peripheral pulmonic stenosis), intracranial aneurysms, and multisystem involvement. Although the patient lacked overt cholestasis or characteristic facial features, the absence of inflammatory and autoimmune markers, together with the specific cardiac and vascular findings, prompted targeted *JAG1* sequencing. Peripheral blood DNA samples were obtained from the patient and both parents for Sanger sequencing analysis. The results revealed that the patient harbored a heterozygous frameshift variant NM_000214.2:c.3218dupT (p.(Ser1074Glufs*35)) in *JAG1*, which was absent in both parents, indicating that this was a pathogenic variant of the gene (Fig. 2). Post-operative fever and blood cultures positive for *Streptococcus viridans*, together with valvular vegetations on echocardiography (Fig. 1e and Fig. 1f), confirmed infective endocarditis. The *JAG1* mutation and the cardiac findings satisfied the diagnostic criteria for ALGS. After antibiotics and rehabilitation, right-sided strength recovered, and the child could walk.

Three weeks after the second discharge, a third hemorrhage was managed conservatively with external ventricular drainage. A fourth hemorrhage followed, leaving the patient in deep coma with high fever and rigid limbs; cerebrospinal fluid culture grew *Acinetobacter baumannii*, and multi-organ failure ensued, leading to death.

The study was approved by the appropriate ethics review board (approval number: KYLL-2025-2608). Informed consent for publication was obtained from the patient's legal guardian.

Discussion

The *JAG1* gene encodes Jagged1, a critical ligand in the Notch signaling pathway, whose dysfunction leads to multisystem developmental disorders such as ALGS.[4] Located at 20p12.2, this gene regulates cell fate determination and organogenesis during embryonic development by binding to Notch receptors (primarily Notch2).[5] Approximately 94% of patients with ALGS carry pathogenic *JAG1* variants, with haploinsufficiency representing the core pathogenic mechanism.[4]

JAG1 pathogenic variants are diverse, with about 70% being truncating variants (nonsense, frameshift, splice-site) that reduce functional protein by 50% through nonsense-mediated mRNA decay.[6,7] The present c.3218dupT (p.(Ser1074Glufs*35)) frameshift variant falls into this category. Missense variants account for approximately 30%, mainly affecting protein folding and stability.[7] No mutational hotspots exist, but pathogenic variants cluster in functional domains such as the Delta-Serrate-LAG-2 (DSL) domain and epidermal growth factor (EGF)-like repeats.[7]

Clinical phenotypes of *JAG1* pathogenic variants demonstrate highly variable expressivity and incomplete penetrance. Classic ALGS involves five systems: the liver (cholestasis), heart (pulmonary stenosis), skeleton (butterfly vertebrae), eyes (posterior embryotoxon), and characteristic facial features.[8] Family members carrying identical variants may exhibit markedly divergent severity, including asymptomatic carriers, which may be attributable to genetic background modifiers and environmental factors.[4] Beyond classic ALGS, *JAG1* variants can cause non-syndromic

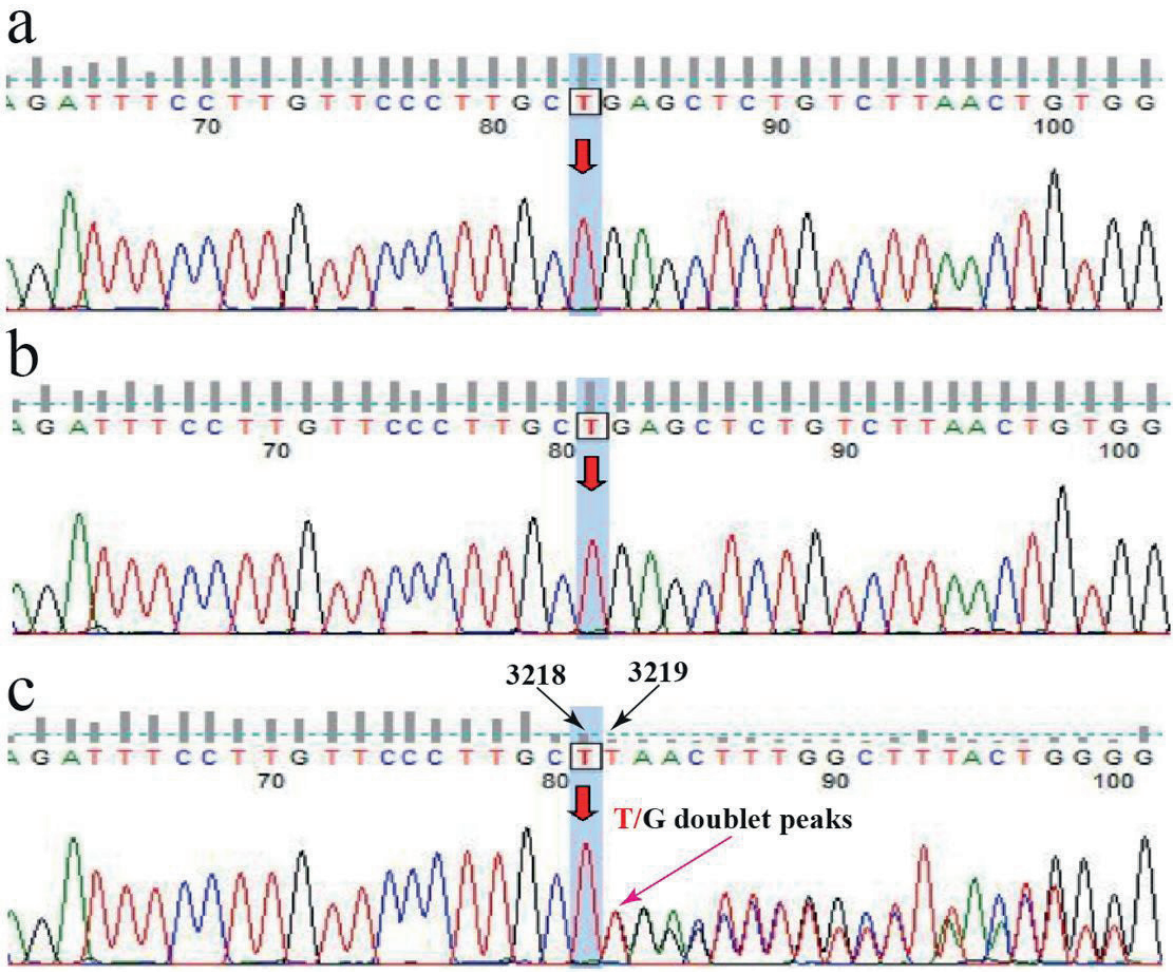

Fig. 2. Sanger sequencing chromatograms of the *JAG1* gene.

(a, b) Parents: wild-type sequence. At position c.3218, a single T peak is present; at position c.3219, a homozygous G peak is observed. No c.3218dupT mutation is detected.

(c) Proband: heterozygous frameshift mutation c.3218dupT (p.(Ser1074Glufs*35)). Due to the T duplication at c.3218 (marked "3218"), the expected homozygous G at c.3219 is replaced by a T/G doublet peak (labeled "T/G doublet peaks" and marked "3219"), indicating a reading frame shift from this point onward.

presentations including isolated bile duct paucity and specific congenital heart defects, though cerebrovascular involvement remains rarely reported.[9]

A loss of *JAG1* expression in endothelial cells may inhibit Notch signaling and disrupt angiogenesis.[10] Homozygous *JAG1*-knockout mice exhibit embryonic lethality and severe cardiovascular malformations, highlighting the critical role of *JAG1* in vascular development.[11,12] Under normal physiological conditions, endothelial *JAG1* drives the recruitment of vascular smooth muscle cells and pericytes.[13] Its absence results in flawed vessel wall architecture and irregular luminal surfaces, predisposing patients to aneurysm formation, although the detailed molecular mechanisms remain to be fully elucidated. Previous reports[14-16] indicate that 1.1% of individuals with ALGS develop intracranial aneurysms, compared with 0.8% to 5% in the general pediatric population, where aneurysms are typically large or giant saccular lesions—the leading cause of aneurysmal subarachnoid hemorrhage in children. This combination significantly increases the risk of hemorrhagic events in ALGS patients, with

Table I. 17 patients with Alagille syndrome and intracranial aneurysms.

Authors, years	Sex	Age (years)	Location of Intracranial Aneurysms	Other comorbidities	Hunt-Hess Grade	Treatment Modality	Outcome
Moreau et al., 1999[28]	M	17	Right C4	CD	0	Endovascular therapy	Survived
Kamath et al., 2004[14]	NA	NA	BA	CD, Jaundice, FD	0	NA	Survived
	NA	NA	BA	CD, Jaundice, FD, AS	0	NA	Survived
	NA	NA	Left MCA	CD, Jaundice	5	NA	Died
Schlosser et al., 2004[26]	F	30	Right C4, C5, Left C5, C6, BA	family history, Dysplasia of the bile duct, FD, AS, aneurysms of the right renal artery	5	Craniotomy clipping	Survived
Cowan et al., 2004[27]	M	23	BA, Left C7	Aortic dissection, AS	2	Craniotomy clipping	Survived
Emerick et al., 2005[25]	F	20	Left MCA	PS, IDDM, Chronic renal insufficiency, Cholestasis, FD, CD	5	NA	Died
	F	11	BA	Cholestasis, CD, FD	0	NA	Survived
	F	1.7	Right C5×2	CD, FD, MMD (Bilateral ICA and MCA stenosis)	0	NA	Survived
Tumialán et al., 2006[24]	F	21	BA	Ascending aortic aneurysm, Jaundice, CD, FD	0	Endovascular therapy	Died
Gaba et al., 2008[23]	F	28	Right Vertebrobasilar Junction	Jaundice, CD, FD, MMD (CAS)	2	Endovascular therapy	Survived
O'Connell et al., 2012[22]	F	17	Right ICA, Left SCA	Cholestasis, PS, FD	2	Endovascular therapy	Survived
Doberentz et al., 2015[18]	F	25	BA	Liver transplantations, FD, PS, Vertebral anomalies	5	NA	Died
Pavanello et al., 2015[21]	F	10	BA	Dysplasia of the bile duct, FD, retinitis pigmentosa, MMD (CAS), PS	0	Endovascular therapy	Survived
Fiorda-Diaz et al., 2017[20]	F	17	Left PCoA	Tetralogy of Fallot, PS	2	Endovascular therapy	Survived
Wali et al., 2021[19]	M	11	Left MCA	Pancytopenia, peripheral pulmonary stenosis	0	Craniotomy clipping	Survived
Present case	M	5	Left MCA, Right MCA	AS	4	Craniotomy clipping	Died

Hunt-Hess Grade: Grade 0: Unruptured aneurysm; Grade 1: Asymptomatic or mild headache only, without meningeal irritation signs and neurological deficits; Grade 2: Moderate to severe headache, with meningeal irritation signs and cranial nerve palsies; Grade 3: Consciousness disorder, with focal neurological signs; Grade 4: Coma, with severe hemiplegia, and early decerebrate rigidity or autonomic dysfunction; Grade 5: Deep coma, decerebrate rigidity, moribund state.
ACA, anterior cerebral artery; ACoA, anterior communicating artery; AS, aortic stenosis; CAS, carotid artery stenosis; CD, cardiac disease; FD, facial dysplasia; F, female; ICA, internal carotid artery; IDDM, insulin dependent diabetes mellitus; M, male; MCA, middle cerebral artery; MMD, moyamoya disease; NA, not available; PCoA, posterior communicating artery; PS, pulmonary stenosis.

bleeding rates ranging from 9% to 16% and mortality rates reaching as high as 25% to 67%.[2,14,17,18]

As of 2025, we reviewed 12 published studies on ALGS complicated by intracranial aneurysms.[14,18-28] Including the present case, a total of 17 patients were analyzed in this literature summary (Table I). Among the 14 cases with available data on sex and age, the male-to-female ratio was 4:10, with a mean age of 16.91 ± 8.38 years (ranging from 1.7 to 30 years); notably, 57.14% were minors. Out of the 17 cases, 5 patients (29.41%) presented with multiple intracranial aneurysms. In total, 25 aneurysms were identified: 10 in the internal carotid artery (including 1 posterior communicating artery aneurysm), 5 in the middle cerebral artery, and 10 in the basilar artery (including 1 vertebrobasilar junction and 1 superior cerebellar artery aneurysm). Nine patients (52.94%) experienced aneurysmal rupture, including 1 case that occurred postoperatively, and 5 patients (29.41%) died. Previous reports[14] indicate that 34% of patients with ALGS succumb to vascular complications. All 17 patients had associated cardio- or cerebrovascular pathology: 3 (17.65%) had moyamoya disease, and 10 (58.82%) had arterial stenosis. Furthermore, most children with ALGS have congenital heart disease—most commonly pulmonary stenosis, coarctation of the aorta, and Tetralogy of Fallot. Aortic coarctation has been established as a risk factor for cerebral aneurysm formation, observed in 0.19% to 1.9% of adults with unruptured aneurysms and 4.8% in those with ruptured aneurysms.[27,29]

The primary surgical approaches for intracranial aneurysms include endovascular therapy, microsurgical clipping, and combined procedures.[30,31] The selection of treatment is influenced by several factors, including the aneurysm's type, location, size, morphology, rupture status, the presence and volume of associated intracranial hematoma, the patient's overall systemic condition, and the available local technical expertise.[30,32,33]

These same criteria apply to aneurysms related to ALGS. Among the 9 cases of ALGS reported in previous studies[19-24,26-28], 66.7% (6 cases) were treated with endovascular methods, while 33.3% (3 cases) underwent clipping. The endovascular group demonstrated a survival rate of 83.33% (5 out of 6), with a mortality rate of 16.67% (1 out of 6). In contrast, the clipping group achieved a 100% survival rate (3 out of 3). In our case, both episodes of aneurysm rupture were accompanied by large intracerebral hematomas, providing a clear indication for open surgery. Additionally, both aneurysms originated from the middle cerebral artery, which led us to opt for microsurgical clipping. Regrettably, the child ultimately succumbed to the combined effects of recurrent hemorrhage and sepsis.

ALGS is a multisystem disorder that necessitates a thorough systemic evaluation when managing intracranial aneurysms in affected patients. This should include assessments of cardiac, hepatic, renal, and ocular function, as well as a spinal radiography and an evaluation of nutritional status and developmental levels. Ursodeoxycholic acid is recommended for the treatment of jaundice, and liver transplantation should be considered for patients with end-stage liver disease.[2,34] Most vertebral anomalies and ocular manifestations do not require surgical intervention.[34] Given that biliary stasis-related vitamin K malabsorption or decompensated liver disease can trigger coagulopathy, coagulation tests are essential.

In this case, intracranial aneurysms and cerebral hemorrhage were accompanied by aortic stenosis and IE. A fusiform aneurysm developed within days, likely due to emboli from IE vegetation (Ando et al.[35] reported rupture within 35 days). In patients with congenital heart disease complicated by infective endocarditis (IE), 2%–9% develop infectious intracranial aneurysms (IIAs), and once these rupture, mortality exceeds 80%.[36,37] IE is a bacterial infection of the endocardium—usually the valves—and one of its most feared complications is the formation of septic emboli.[38] These emboli

can dislodge and disseminate throughout the systemic circulation; when they reach cerebral vessels, they directly invade the wall and incite a local inflammatory response that degrades the vascular matrix, weakening the wall and producing a focal, pathological dilatation—an infectious cerebral aneurysm.[39,40] Such aneurysms are exquisitely fragile and prone to catastrophic intracranial hemorrhage. Although uncommon in the pediatric population, IIAs represent a severe cerebrovascular complication of IE, accounting for roughly 0.5–6.5% of all intracranial aneurysms in children.[39] In this context, the vegetations on the aortic valve are the hallmark of IE, and the infection can also distort valvular anatomy, leading to aortic stenosis or insufficiency.[41,42] When surgery is required to eradicate the infected valve, the presence of a concurrent intracranial aneurysm makes the timing and approach extremely challenging. Treatment for IE should combine antibiotics with surgery when necessary, with the goals of eradicating pathogens, preserving valve function, and preventing sudden death.

The limitations of this study include the fact that the marked phenotypic variability of ALGS precludes determining the association between this variant and the severity of the cerebrovascular phenotype from a single case. The coexistence of infective endocarditis in the patient makes it difficult to disentangle the relative contributions of *JAG1*-related vasculopathy and infectious factors to aneurysm formation.

In summary, ALGS should be considered in children who present with intracranial hemorrhage or aneurysms, especially when congenital cardiac anomalies coexist. If IE is present, vigilance for the occurrence of IIAs is warranted. Immediate antimicrobial therapy should be initiated, and surgical intervention performed when necessary, to reduce rupture risk and improve survival.

Ethical approval

The study was approved by Ethics Committee of Ningxia Medical University General Hospital (date: November 21, 2025, number: KYLL-2025-2608). Before the commencement of the study, informed consent was obtained from the patient's legal guardian, who also consented to the release of the patient's identifiable information.

Author contribution

The authors confirm contribution to the paper as follows: : Study conception and design: YW, YS; data collection: YW, YS, JC; analysis and interpretation of results: DH, ZY, DW; draft manuscript preparation: YW, YS. All authors reviewed the results and approved the final version of the manuscript.

Source of funding

The authors declare that the study is supported by the Key Research and Development Program of Ningxia Hui Autonomous Region, grant number: 2023BEG03018.

Conflict of interest

The authors declare that there is no conflict of interest.

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