Long-term Outcomes of Cerebral Aneurysms in Children

Aymeric Amelot, MD, PhD,[a,b] Guillaume Saliou, MD, PhD,[c,d] Sandro Benichi, MD,[b] Quentin Alias, MD,[c] Grégoire Boulouis, MD,[e,f] Michel Zerah, MD, PhD,[b] Nozar Aghakhani, MD, PhD,[g] Augustin Ozanne, MD, PhD,[c] Thomas Blauwblomme, MD, PhD,[b] Olivier Naggara, MD, PhD[e,f]

abstract

BACKGROUND: Our aim was to report the long-term clinical and imaging outcomes of ≤15-year-old children treated for ruptured or symptomatic cerebral aneurysms and to identify prognostic factors for clinical outcome, recurrence, and rebleeding.

METHODS: We retrospectively identified all pediatric cases of cerebral aneurysm from 2000 to 2015 and then prospectively evaluated long-term occlusion using brain MRI and clinical outcome measures: outcome was considered favorable if King's Outcome Scale for Childhood Head Injury score was ≥5. We performed univariate analysis and logistic binary regression to identify variables associated with clinical and imaging outcomes.

RESULTS: Fifty-one children (aged 8.5 ± 1.1 years [mean ± SD], with 37 ruptured and 14 symptomatic aneurysms) were included, and endovascular treatments (84%) or microsurgical procedures (16%) were performed. Despite a 19.6% death rate, at a mean follow-up of 8.3 years, 35 children (68.6%) had a favorable outcome. Annual bleeding and aneurysm recurrence rates were 1.4% ± 1.1% and 2.6% ± 1.8%, respectively. Cerebral ischemia, whether initial or delayed within the first month, was predictive of poor clinical outcome in multivariate analysis (odds ratio: 25; 95% confidence interval: 0.43–143; $P < .0001$), whereas aneurysm size >5 mm was the only factor associated with recurrence (odds ratio: 14.6; 95% confidence interval: 2.4–86.1; $P = .003$).

CONCLUSIONS: Two-thirds of studied ≤15-year-old children suffering from ruptured or symptomatic cerebral aneurysms had long-term favorable outcome. Annual bleeding and aneurysm recurrence rates have shown to be low after endovascular or surgical treatment. Long-term imaging follow-up helps to depict aneurysm recurrence or de novo aneurysm formation and to prevent rebleeding.

[a]*Department of Neurosurgery, La Pitié-Salpétrière Hospital, Université Paris Sorbonne, Paris, France;* [b]*Departments of Pediatric Neurosurgery and* [e]*Pediatric Radiology, Necker Hospital for Sick Children, Université Paris Descartes, Paris, France; Departments of* [c]*Neuroradiology and* [g]*Neurosurgery, Kremlin-Bicêtre Hospital, Le Kremlin-Bicêtre, France;* [d]*Department of Neuroradiology, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland; and* [f]*Department of Neuroradiology, Sainte-Anne Hospital and Université Paris Descartes, INSERM UMR S894, Paris, France*

Drs Amelot, Blauwblomme, Naggara, and Saliou conceptualized and designed the study, conducted the initial analyses, and drafted the initial manuscript; Drs Alias, Boulouis, Ozanne, Benichi, Zerah, and Aghakhani drafted and reviewed the manuscript; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Address correspondence to Aymeric Amelot, MD, PhD, Department of Neurosurgery, Groupe Hospitalier Universitaire de la Pitié-Salpêtrière, 47-83, Boulevard de l'Hôpital, 75013 Paris, France. E-mail: aymmed@hotmail.fr

WHAT'S KNOWN ON THIS SUBJECT: Cerebral arterial aneurysms are extremely rare in children in comparison with adults. Long-term clinical and imaging follow-up studies on pediatric cerebral aneurysms are scarce, especially in young patients under 15 years old that are managed endovascularly.

WHAT THIS STUDY ADDS: We demonstrated that two-thirds of children suffering from a ruptured or symptomatic cerebral aneurysm had a long-term favorable outcome. Annual bleeding and aneurysm recurrence rates are low after treatment. Long-term imaging follow-up is mandatory to detect aneurysm recurrence and de novo aneurysm.

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Cerebral arterial aneurysms are extremely rare in children compared with adults, accounting for <4% of all intracranial aneurysms.[1–3] Endovascular treatment (EVT) and surgical clipping are treatment options; the transarterial embolization with coiling procedure has increased in recent years. Long-term clinical and imaging follow-up studies on pediatric cerebral aneurysms are scarce, especially in young patients under 15 years old or in current endovascular cohorts.[4,5]

Our aim here was to report the long-term clinical and imaging outcomes of ≤15-year-old children taken in charge from the year 2000 to 2015 and treated for ruptured or symptomatic cerebral aneurysms as well as to identify prognostic factors for clinical outcome, recurrence, and rebleeding.

METHODS

Study Design and Participants

We performed this study according to the strengthening the reporting of observational studies in epidemiology (STROBE) statement[6] and French legislation, and because the study implied retrospective analysis of anonymized data collected as part of routine clinical care, it did not require formal approval by an ethics committee nor patient written informed consent. We informed each patient of his or her participation in the study. The study was a multicenter retrospective pediatric study (Bicêtre Hospital, Necker Hospital, Saint-Anne Hospital, Paris, France) that included all consecutive children treated between 2000 and 2015. Inclusion criteria were (1) intracranial arterial aneurysm (IAA) and (2) age <18 years. We excluded patients with (1) arteriovenous malformation–related aneurysms, (2) vein of Galen aneurysmal malformation, and (3) mycotic pseudoaneurysm, because they correspond to different diseases.

Clinical and Imaging Parameters

We extracted clinical and demographic data from patient charts. We registered the World Federation of Neurological Surgeons (WFNS) grade for aneurysmal subarachnoid hemorrhage (SAH) and the Fisher's score at onset.[7,8] We defined aneurysm size and location at onset on magnetic resonance angiography, computed tomography–angiography, or digital subtraction angiography (DSA) obtained at admission. They were then classified as saccular or acute dissecting and/or fusiform aneurysms.[9,10] Two neuroradiologists came to a common agreement concerning posttreatment as well as classifying long-term aneurysm occlusion using magnetic resonance angiography or DSA, according to the 3-grade Raymond classification: grade 1, no contrast filling; grade 2, neck remnant; and grade 3, opacification of the aneurysmal sac.[11]

Treatment Strategy

Except in cases requiring emergency intracranial hemorrhage evacuation (Glasgow Coma Scale score <8, posterior fossa intracranial hemorrhage [ICH], or with mass effect), the treatment modality was decided at a multidisciplinary consensus meeting including pediatric neurosurgeons and

TABLE 1 Baseline Patient and Aneurysm Characteristics

Symptomatic Patient Characteristics	*n* (%) or Mean ± SD
Patients	51
Male sex	35 (68.6)
Age, y	8.5 ± 1.1
Vascular disease	5 (9.8)
Sickle cell disease	4 (7.3)
Genetic dysmorphic syndrome	3 (5.8)
Familial history of aneurysm	2 (4)
Clinical presentation	
SAH	37 (72.5)
Initial coma (GCS score <8)	7 (13.7)
WFNS score 3–5	18 (35.3)
Fisher's score 4–5	26 (50.9)
Headaches	9 (17.6)
Epilepsy	1 (1.9)
Cranial nerve palsy	2 (3.9)
Ischemic stroke	2 (3.9)
Baseline treated aneurysm characteristics	51
Aneurysm type	
Saccular	31 (60.7)
Fusiform or dissecting	20 (29.3)
Ruptured	37 (72.5)
Patients with multiple aneurysms	8 (15.6)
Fundus size, mm	9.9 (7.5)
<10	30 (58.8)
10–25	18 (34.6)
>25	3 (5.8)
Anterior circulation location	36 (70.5)
Middle cerebral artery	11 (21.5)
Anterior complex[a]	4 (7.3)
Internal carotid artery[b]	21 (41.2)
Posterior circulation location	15 (29.5)
Posterior communicating artery	3 (5.4)
Posterior cerebral artery	6 (10.9)
Vertebral-basilar artery	4 (7.3)
Superior cerebellar artery	2 (3.6)

GCS, Glasgow Coma Scale.

[a] Included anterior communicating artery and A1-A2 junction aneurysms.

[b] Included ophthalmic artery region, supraclinoid, superior hypophyseal artery, and internal carotid artery bifurcation.

pediatric interventional neuroradiologists. For children in good clinical condition in which surgical ICH evacuation was not indicated, EVT was considered as first-line therapy. In cases of EVT failure, surgical clipping was performed.

Follow-up

We collected clinical and imaging follow-up data during hospitalization and follow-up DSA during an external consultation or by telephone interviews. We contacted all patients to undergo a physical examination and brain magnetic resonance angiography. We made repeated telephone calls to contact missing patients and their families (family, relatives, and general physician). When appropriate, we collected causes of death. The total number of months of clinical and imaging follow-up for each patient was recorded. Clinical outcome was defined according to the King's Outcome Scale for Childhood Head Injury (KOSCHI).[12] Favorable clinical outcome was defined as a KOSCHI score ≥5.

Statistics

Associations between variables were analyzed by Fisher's exact test or χ^2 test. The distribution of categorical variables was described by frequencies and percentages, continuous and normally distributed variables by means and SDs, and continuous and non-normally distributed variables by medians and interquartile range. Predictive factors for unfavorable outcome, aneurysm recurrence, or rebleeding were tested by univariate statistics by using analysis of variance and χ^2 or Fisher's exact tests, as appropriate. According to the number of pairwise comparisons of interest, type 1 error was adjusted by using the Bonferroni multiple comparison adjustment. For example, α level of .05 divided by 17 comparisons yielded an adjusted α of .003; thus, the statistical significance level was set at $P = .003$. All variables with a significant association in the univariate analyses after adjustment were entered into a multiple logistic regression model by using backward elimination procedures to analyze potential predictors of unfavorable outcome. Statistical analyses were performed using Stata version 11 (Stata Corp, College Station, TX).

RESULTS

Clinical Presentation

We present child and aneurysm baseline characteristics in the supplemental Table 1. Over the study period, 51 children (73 aneurysms; mean age ± SD: 8.5 ± 1.1 years; interquartile range: 5.1–11.1 years) met our inclusion criteria.

Thirty-seven children (72.5%) presented with SAH from a ruptured aneurysm. We show WFNS grade and Fisher's scores in Table 1.

Fourteen patients (27.5%) had a symptomatic unruptured aneurysm (9 thunderclap headaches without SAH, 1 epilepsy or seizure, 2 partial third nerve deficits, and 2 related to ischemic stroke).

Five children (9.8%) had a vascular disease, 3 (5.8%) had a genetic dysmorphic syndrome (dwarfism or unlabeled), and 4 (7.8%) had a sickle cell disease. Two children (4%) had at least 1 first-degree family relative with IAA.

Initial Treatment

Aneurysm characteristics are presented in Table 1. All symptomatic children ($n = 51$) were treated (Fig 1) with EVT ($n = 43$) or clipping ($n = 8$). We encountered failure in 2 EVTs (3.9%) and 1 surgical clipping (12.5%), but they were all then successfully treated using the alternative technique.

Clinical Outcome

Mean clinical follow-up was 8.3 years (range: 12 months–19.5 years, 423.3 patient years), with favorable outcome encountered in 35 out of 51

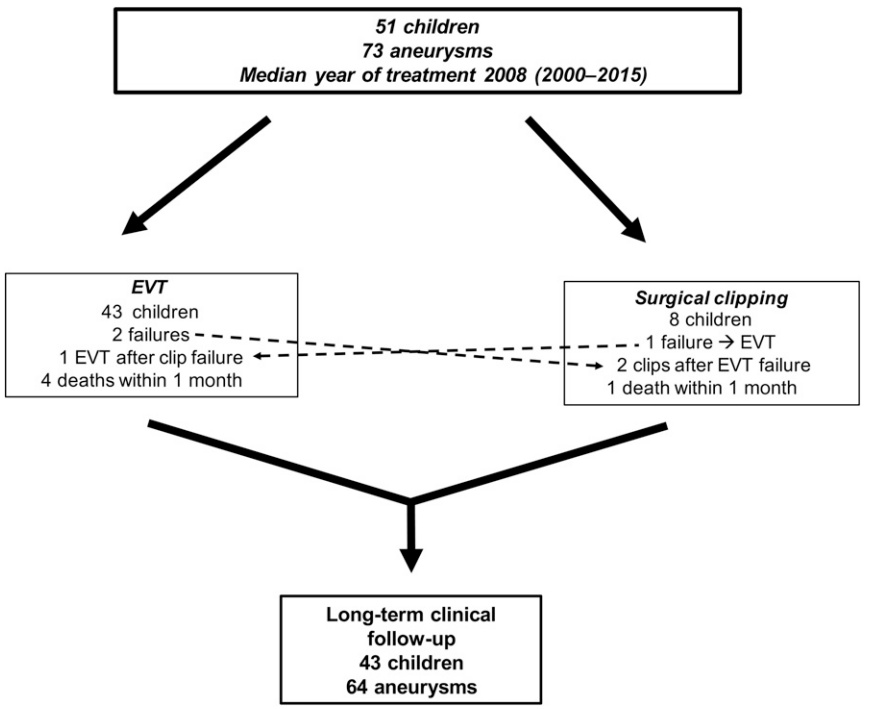

FIGURE 1
Flowchart diagram.

TABLE 2 Clinical and Aneurysmal Predictive Factors for Death, Unfavorable Outcome, Rebleeding, and Recurrent Aneurysm (*P* Values Were Calculated by the Log-Rank Test)

Baseline Clinical and Aneurysm Characteristics	Univariate Analysis, *P*				Multivariate Analysis, OR (95% CI) *P*			
	Death	Unfavorable Outcome	Aneurysm Rebleeding	Aneurysm Recurrence	Death	Unfavorable Outcome	Aneurysm Rebleeding	Aneurysm Recurrence
Sex	.58	.99	.60	.23	—	—	—	—
Age, y								
<2	.353	.118	.202	.328	—	—	—	—
<5	.113	.099	.908	.169	—	—	—	—
<8	.486	.126	.640	.236	—	—	—	—
<12	.714	.527	.706	.925	—	—	—	—
SAH	.08	.13	.40	.18	—	—	—	—
Coma	.004[a]	.005[a]	.738	.670	16.7 (2.3–115.1) .004[a]	4.4 (0.6–27.0) .137	—	—
Multiple aneurysms	.11	.70	.30	.13	—	—	—	—
Posterior circulation aneurysm	.11	.39	.15	.34	—	—	—	—
Aneurysm size >5 mm	.03[a]	.04[a]	.30	.002[a]	1.0 (0.1–2.7) .99	0.17 (0.1–2.21) .179	—	14.6 (2.4–86.0) .003[a]
Aneurysm form								
Saccular	.46	.15	.41	.23	—	—	—	—
Fusiform or dissecting	.63	.66	.57	.73	—	—	—	—
Complications								
Hydrocephalus	.67	.68	.86	.73	—	—	—	—
Stroke	.018[a]	.0001[a]	.70	.29	8.6 (1.4–53.1) .003[a]	24.7 (4.3–142.1) <.0001[a]	—	—
Vasospasm	.46	.99	.79	.05	—	—	—	—
Rebleeding	.016[a]	.06	—	.52	9.2 (3.7–38.1) .02[a]	—	—	—

—, not applicable.
[a] Statistically significant.

(68.6%) children (31 and 4 had KOSCHI 5B and KOSCHI 5A, respectively). Unfavorable outcome included 1 child with moderate disability (KOSCHI 4), 1 with severe disability (KOSCHI 3), 4 who presented a vegetative state (KOSCHI 2), and 10 who died (KOSCHI 1).

Among 37 SAH patients, 23 children had a favorable outcome. Among the 14 unfavorable outcomes, 10 children died within the first month of SAH onset (n = 9; mean onset-to-death delay: 12 days) or from the bleeding of an untreated additional aneurysm (n = 1; annual case fatality rate from rebleeding: 0.2% ± 0.1%). Rebleeding occurred in 6 patients (annual bleeding rate: 1.4% ± 1.1%; median delay: 26 months; range: 1.2–36 months), 4 from aneurysm recurrence, 1 from a de novo aneurysm, and 1 from an additional aneurysm. We did not identify risk factors for rebleeding in the univariate survival analysis (data not shown).

In univariate analysis (Table 2), unfavorable outcome was associated with aneurysm size of >5 mm (P = .04), ischemic stroke (P = .0001), and initial coma (P = .005). Ischemic stroke was the only factor independently associated with unfavorable outcome (odds ratio [OR]: 24.7; 95% confidence interval [CI]: 4.3–142.1; P < .0001). Acute ischemic strokes recorded in our series were due to dissecting aneurysms and occurred via perforating branches from the dissection or in the vascular territory downstream. Ischemic stroke (OR: 8.6; 95% CI: 1.4–53.1; P = .003), coma at onset (OR: 16.7; 95% CI: 2.3–115.1; P = .004), and rebleeding (OR: 9.2; 95% CI: 3.7–38.1; P = .02) were independent risk factors of death.

Imaging Outcome

Forty children were prospectively managed on imaging (DSA, n = 9; 1.5 Tesla, n = 17; 3.0 Tesla, n = 14) for a mean follow-up period of 7.1 years (range: 6 months–19.5 years; 312.4 patient years).

Eight aneurysm recurrences occurred in 8 patients (EVT, n = 7 [19%]; surgery, n = 1 [14%]; mean delay: 1.7 ± 1.4 years; annual aneurysmal recurrence rate: 2.6% ± 1.8%). No significant association was found between recurrence and aneurysm type (Table 2). The annual re-treatment rate was 1.2% ± 1.00% (5 re-treatments; EVT, n = 3; surgery, n = 2), and the annual de novo aneurysm rate was 0.7% ± 0.4% (2 IAAs in 2 patients). Aneurysm size >5 mm was independently associated with aneurysm recurrence (OR: 14.6; 95% CI: 2.4–86.0; P = .003).

TABLE 3 Detailed Characteristics of Previous Studies With Follow-up ≥3 Years

Authors	Study	Setting, Enrollment	Median Year of Treatment	No. patients, No. aneurysms	Mean Age, y	Ruptured, Symptomatic, Incidental	Type of EVT: Elective, Nonelective[a]	Type of Surgery: Clipping, Other[b]	Fusiform, Saccular	Mean Clinical FU, y	Mean Imaging FU	Annual Recurrence Rate, %	Annual De Novo or Enlarging Rate of Untreated Aneurysm, %
Sanai et al[13]	Observational, United States	Single center, retrospective	1997–2003	32, 43	11.7	7, 13, 12	12, 14	8, 9	21, 22, unknown, unknown	5.7	5.7	1.8[c]	2.4[c]
Hetts et al[2,14]	Observational, United States	Single center, retrospective	1981–2010	77, 103	12.0	25, 29, 6	20, 11	19, 10	31, 47, 12, 15	Unknown	3.0[c]	Unknown	3.7[c]
Kakarla et al[3]	Observational, United States	Single center, retrospective	1989–2005	48, 72	12.3	11, 35, 26	0	48, 24	28, 32, 5, 7	4.9	4.5	2.6	7.8
Koroknay-Pál et al[4,5]	Observational, Finland	Single center, retrospective	1937–2009	114, 130	14.5	89, 18, 7	3, 0	60, 20	Unknown	Unknown	34.0[d]	0.6	1.3
Saraf et al[15]	Observational, Finland	Single center, retrospective	1998–2010	23, 28	13.0	14, unknown, unknown	10, 10	0	17, 6, 5, unknown	3.0	3.0	1.4	Unknown
Present study	Observational, France	Multicenter, prospective	2000–2015	51, 73	8.5	37, 14, 0	43	8	31, 20, 0, 0	8.3	7.1	2.6	0.7

FU, follow-up

[a] Includes parent vessel occlusion with coils or glue and flow reversal.

[b] Includes trapping, wrapping, ligation, bypass, or high-flow bypass.

[c] Recalculated from published data.

[d] Follow-up of the subgroup of 1-y survivors (n = 88).

DISCUSSION

In this study of ≤15-year-old children treated for ruptured or symptomatic IAA, a favorable outcome occurred in two-thirds of cases. The annual bleeding rate after treatment, re-treatment rate, and aneurysmal recurrence rate were, respectively, 1.4%, 1.2%, and 2.6%. Annual de novo aneurysm rate, mainly based on 3 Tesla MRI examinations, was 0.7%.

The current study focused on patients treated after the year 2000 and therefore concerned recent management strategy. Indeed, a majority of pediatric IAA studies in the literature include few patients, treated often over several decades. The current study significantly differs from the previous studies, and we provide additional information on outcomes after symptomatic cerebral aneurysms in children (summarized in Table 3). First, we focused on a young population, for >25% of our population was <5 years old. Our study showed favorable outcome for over two-thirds of cases. Concerning the risk of annual recurrence, in our series it was 2.6%, a rate similar to one observed in the adult series of aneurysms.[2,3] In contrast, the Finnish cohort reported a lower annual rate of aneurysm recurrence of 0.6% in the pediatric patients.[4] In this largest long-term cohort study (1939–2010), Koroknay-Pál et al[4] described 114 older children (mean age >14 years) that could, in part, explain the difference in results (Table 3).

Secondly, as our study concerns children treated recently, 84% of treatments were endovascular, a rate similar to the ones seen in the recent adult cohorts.[2,4,14,16] Conversely, in the study performed by Koroknay-Pál et al[4] on older children, 98% underwent surgical clipping, which may also explain our different results (Table 3).

With aneurysm formation being extremely rare in children, an underlying vascular disease is often

suspected or identified, for instance, sickle cell disease in the present series or in the literature.[17] However, in our series and as previously reported, no connective tissue disorders were diagnosed.[4]

The annual de novo aneurysm rate, mainly based on 3 Tesla MRI examinations, was low, estimated at 0.7%, whereas the annual rebleeding rate was 1.4%. In addition, these rates seem to compare favorably with adult cohorts.[18,19]

Furthermore, the good neurologic outcome rate reported here is higher than previously described.[2,4,16] This may be explained by a higher rate of treatment of ruptured aneurysms than before and by the major advances in neurointensive care because outcome was not significantly worsened by initial coma.[16] However, the long-term rate of aneurysm-related death was not as high as reported in the Koroknay-Pál et al[5] series, who described 26% aneurysm-related death.

A 10% to 19% excess of mortality 20 years after diagnosis in 1-year survivors of pediatric SAH was described.[4] Because this mortality is mainly aneurysm related (76%) after rebleeding from a recurrent or bleeding from a de novo aneurysm, long-term imaging follow-up is mandatory in children. We showed effectiveness of EVT with annual bleeding and aneurysm recurrence rates similar to those previously described for pediatric microsurgery or in adult endovascular series.[3,4,14] We identified a significantly higher recurrence rate in cases of larger aneurysms, a well-known association in adults,[20] not previously described in children. Interestingly, the 40% rate of fusiform or dissecting aneurysms did not influence this higher recurrence rate. We found a low de novo aneurysm rate, a finding that may be due to the short follow-up compared with the Finnish cohort.[5]

Even if safe and efficacious, the long-term durability of endovascular embolization remains a concern, especially in ruptured aneurysms, where stent-assisted coiling or a flow diverter is rarely used. Indeed, in unruptured aneurysms, this recurrence rate ranges from 7% to 27% and increases to 17% to 52% in ruptured aneurysms.[11,21–26] However, among our 7 patients treated surgically, 1 had a recurrence and subsequently bled and died. It was an acute dissecting aneurysm, initially misdiagnosed as a saccular carotid aneurysm: no mural hematoma, double lumen, or intimal flap were identified on angio-imaging (computed tomography–angiography and DSA) performed before surgery. The diagnosis was made during surgery, and although wrapping was successful to reconstruct the artery, it failed to prevent an early recurrence and fatal rebleeding. Because no guidelines for the treatment of ruptured dissecting aneurysms are available, at least early posttreatment follow-up imaging is mandatory to rule out fresh recurrence, which would indicate re-treatment to prevent new bleeding.

One limitation of this study is its retrospective design, although all our patients were prospectively registered in dedicated neurovascular databases. IAA remains rare, and randomized pediatric studies are probably unrealistic. We were unable to perform analysis on the basis of the treatment modality because only 8 children were in the surgical group. In addition, surgery was mainly performed in cases requiring emergency intracranial hemorrhage evacuation, precluding any outcome comparison with EVT. Researchers conducting further studies should help to provide more reliable data as well as a better understanding of this rare but sometimes devastating disease.

CONCLUSIONS

In this series, ruptured intracranial aneurysms are still associated with a high mortality rate in the acute phase in pediatric patients; however, a favorable long-term outcome is seen in two-thirds of cases. Despite a low annual rebleeding or aneurysm recurrence rate, lifelong clinical and imaging follow-up is mandatory to detect aneurysm recurrence and de novo aneurysm formation.

ABBREVIATIONS

DSA: digital subtraction angiography
EVT: endovascular treatment
IAA: intracranial arterial aneurysm
KOSCHI: King's Outcome Scale for Childhood Head Injury
SAH: subarachnoid hemorrhage
WFNS: World Federation of Neurological Surgeons

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Aymeric Amelot, Guillaume Saliou, Sandro Benichi, Quentin Alias, Grégoire Boulouis, Michel Zerah, Nozar Aghakhani, Augustin Ozanne, Thomas Blauwblomme and Olivier Naggara

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