Basilar artery stroke in childhood

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ABBREVIATIONS

BAO	Basilar artery occlusion
BAS	Basilar artery stroke
mRS	Modified Rankin Scale
NIHSS	National Institutes of Health Stroke Scale
PedAIS	Paediatric arterial ischaemic stroke
PedNIHSS	Pediatric National Institutes of Health Stroke Scale
SNPSR	Swiss Neuropaediatric Stroke Registry

AIM Little is known about basilar artery stroke (BAS) in children. The objective of this study was to calculate the incidence of BAS in children and to analyse the clinical presentation, risk factors, radiological findings, therapeutic approaches, and outcome of BAS in childhood.
METHOD A prospective, population-based study including children with arterial ischaemic stroke and a systematic review of the literature was undertaken.
RESULTS Seven children with BAS were registered at the Swiss Neuropaediatric Stroke Registry between January 2000 and June 2011 (incidence 0.037 per 100 000 children per year, 95% confidence interval [CI] 0.013–0.080). A further 90 cases were identified through the literature search. The majority of patients were male (73 males, 24 females) and the median age was 9 years (interquartile range [IQR]=6–13y). The median Pediatric National Institutes of Health Stroke Scale (PedNIHSS) score was 15 (IQR=4–27). Presenting signs and symptoms comprised impaired consciousness (*n*=64), quadri- or hemiparesis (*n*=58), bulbar dysfunction (*n*=46), vomiting, nausea (*n*=43), and headache (*n*=41). Prodromes occurred in 43% of cases. Aetiology was largely vasculopathic (*n*=38), but often unknown (*n*=40). Time to diagnosis varied from hours days; six patients received antithrombotic, thrombolytic, or mechanical endovascular treatment 12 hours or less after symptom onset. Outcome was good (modified Rankin Scale 0–2) in 45 patients; eight died. PedNIHSS score of up to 17 was a prognostic factor for good outcome.
INTERPRETATION BAS is rare in children. Compared with adults, outcome is more favourable despite a considerable delay in diagnosis and treatment. Outcome was better in children with a PedNIHSS score of 17 or less.

Only 10 to 30% of paediatric arterial ischaemic strokes (pedAIS) occur in the posterior circulation.[1,2] Arteriopathies are the most frequent cause of posterior circulation stroke in children. Recurrence (20–52%) is more frequent than in anterior circulation stroke, but the outcome is better, with a good outcome in 50% of children.[3,4] Paediatric basilar artery stroke (BAS) has been described only in case reports and case series. In a review of 13 published cases of paediatric BAS treated endovascularly, 10 children had a good outcome, two had a poor outcome, and one child died.[5]

In adults, BAS has a fatality rate of more than 85% if left untreated, and outcome is poor in two-thirds of patients despite treatment.[6,7] Clinical presentation varies from dizziness, headache, and focal neurological deficit to locked-in syndrome, coma, and death. Prodromes occur in 60% of patients.[7]

In the context of a national prospective registry we analysed the characteristics of BAS and performed a systematic review of the literature with the aim of improving our understanding of, and therapeutic strategies for, BAS in childhood.

METHOD

Participants

We analysed data from the Swiss Neuropaediatric Stroke Registry (SNPSR), a prospective nationwide multicentre registry that was introduced in Switzerland in January 2000, including all cases registered until June 2011. The methods of the SNPSR have been previously described.[8] The SNPSR is approved by the ethics committee of the Canton of Bern and the Swiss Federal Ministry of Health. The database was searched for BAS, defined as a clinical syndrome attributable to ischaemic brain injury in the territory of the basilar artery due to thrombotic occlusion of the basilar artery (BAO). Cases were included even if the occlusion itself was not apparent. All children from 1 month to 16 years with clinical and

radiological evidence of BAS were included. The patients' charts were searched for additional data, such as a detailed description of presenting signs, in order to calculate the Pediatric National Institutes of Health Stroke Scale (PedNIHSS) score. The PedNIHSS is an adaptation of the National Institutes of Health Stroke Scale (NIHSS) for adults, a measure used to quantify neurological deficit caused by a stroke, for use in children aged 2 to 18 years. As in the adult NIHSS, the PedNIHSS has 11 neurological domains and 15 scored items, with a total score ranging from 0 (least severe) to 42 (most severe). The PedNIHSS can be retrospectively scored from medical records with a high degree of reliability and validity.[9] Neuroimaging was reviewed by a neuroradiologist (ME-K), who was blinded to the clinical findings. Localization of BAO was categorized according to Archer and Horenstein:[10] distal (distal to the superior cerebellar artery), mid-basilar (superior cerebellar to anterior inferior cerebellar artery), and proximal (anterior inferior cerebellar artery to confluence of the vertebral arteries). BAO was defined as 'short' if one-third of the basilar artery was occluded, and 'long' if two-thirds or the whole length of the basilar artery was occluded.

Outcome was expressed by the modified Rankin Scale (mRS), a global outcome measure focusing on symptoms and disability in adults after stroke that has been used in studies on childhood stroke, even though it is not validated for children.[11,12] Scores range from 0 (no symptoms at all) to 6 (dead). The incidence rate and its exact 95% confidence interval (CI) for the Swiss population aged 0 to 16 years, based on the data provided by the Swiss Federal Office for Statistics by the end of 2011, were calculated as Poisson rates using StatXact 9.0.0 software (Cytel Inc., Cambridge, MA, USA).

Systematic review of the literature

We performed a literature search using PubMed, EMBASE, Web of Science, and the Cochrane Library with the search terms 'basilar artery obstruction', 'basilar artery occlusion', 'basilar artery thrombus', and 'basilar artery stroke', limited to humans and children, as well as the combination of 'paediatric stroke' and 'basilar artery'. Publications from 1 January 1960 to 30 June 2011 in English, French, German, Italian, and Spanish were considered. References found in the articles were also assessed. Inclusion criteria were in accordance with the inclusion criteria of the SNPSR: reports of children (1mo–16y) with BAS confirmed by imaging (computed tomography, magnetic resonance, catheter angiography) or by autopsy.

Clinical data were analysed. PedNIHSS scores were calculated from the data on acute phase signs if information on at least motor function and level of consciousness were available. If grading of a neurological deficit, for example facial palsy, was lacking, one point was added as a suspected minimal clinical finding. Zero points were given for PedNIHSS items not reported. Outcome was expressed by the mRS and if not indicated it was estimated based on the data provided. Good outcome was defined as an mRS of 0 to 2, poor outcome as an mRS of 3 to 6.

What this paper adds

- Basilar artery stroke (BAS) is rare in children.
- A Pediatric National Institutes of Health Stroke Scale score of up to 17 is a prognostic factor for good outcome.
- Almost half of children with BAS have a good outcome despite a considerable delay in diagnosis and treatment.

Statistical analyses

Statistical analyses were performed by BGS and BR using GraphPad Prism 4.01 (GraphPad Software, San Diego, CA, USA) and SPSS Statistics 17 (IBM Corporation, Armonk, NY, USA). The Kolmogorov–Smirnov test was used to check for normal distribution. Data are expressed in median and interquartile ranges (IQRs). Correlations among variables were assessed by using the Spearman's *rho* test.

Forward stepwise multivariate linear regression analysis was performed to identify the significant independent factors influencing outcome. A p-value of <0.05 was considered significant. A receiver operator curve was performed to set a cut-off value for the PedNIHSS as related to outcome. Sensitivity, specificity, and odds ratio were calculated with a Fisher's exact test.

RESULTS

SNPSR cases and incidence of basilar artery stroke in children

Out of the 172 children with pedAIS who were registered in the SNPSR from January 2000 until June 2011, 43 had a posterior circulation stroke, and seven of these had BAS. One of the seven patients diagnosed and treated in Switzerland was a foreign citizen living in proximity to the Swiss border; thus, he was excluded from the population-based calculation of the incidence. The incidence of BAS in children in Switzerland is 0.037 per 100 000 children per year (exact 95% CI 0.013–0.080). BAS accounts for 3.5% of pedAIS. All patients were Caucasian. Clinical and radiological findings, therapy, and outcome are summarized in Table SI (supporting information published online).

Results of the systematic literature review

The systematic search revealed 558 publications. Excluding duplicates, 354 articles remained for screening. In 77 records, the title or abstract contained the search terms and the information that at least some patients were children, and a further eight publications were also identified from the reference lists. From these 85 publications, 68 publications matched the inclusion criteria, providing data on 90 childhood BAS cases.[4,5,s1–s66] Sixty-six publications were case reports or case series[5, s1–s52, s54–s66] and two were prospective case studies (registries) .[4,s53]

Clinical features, management, and outcome of all basilar artery stroke cases

In total, 97 children with BAS (seven SNPSR cases, 90 reported cases) were included in this study. There was a male predominance (73 males, 24 females), particularly in the 5- to 10-year age group. Median age was 9 years (IQR 6–13y). Ethnicity was indicated in 16 cases (eight Caucasian, four African, and four Asian). Presenting signs and symptoms are listed in

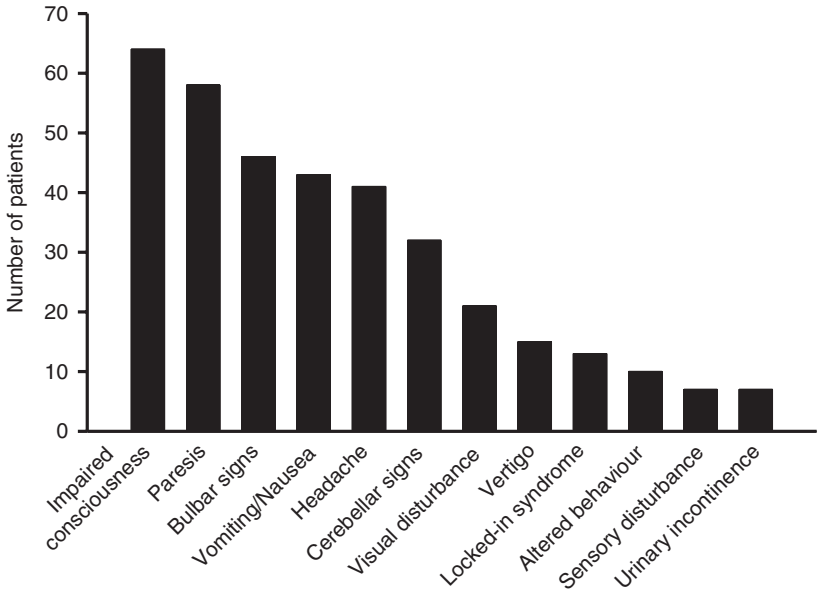

Figure 1: Presenting signs and symptoms of paediatric basilar artery stroke.

Figure 1, with impaired consciousness and hemi- or quadriparesis being the most frequent mode of presentation.

The NIHSS was provided in four cases and information to calculate the PedNIHSS score was available in a further 86 patients. The median PedNIHSS score at diagnosis was 15 (IQR 4–27).

Prodromes (Fig. 2), defined as transient signs and symptoms occurring at least 24 hours before the onset of stroke, were reported in 42 patients (43%) with a median time of 22 days before onset of stroke symptoms (range 1–120d; IQR 11–37.5d).

Time from onset of BAS symptoms to diagnosis was up to 88 days. In the 17 children in whom the delay was indicated in hours, the median was 19 hours (range 2–96h), with only six children being diagnosed within 12 hours.

Diagnosis was established by magnetic resonance imaging/magnetic resonance angiograpy in 43 children, catheter angiography in 37, computed tomography in 14, and autopsy in three cases.

BAO localization was indicated in 89 patients, being short in 37 (23 in the distal third, 12 mid-basilar, two proximal) and

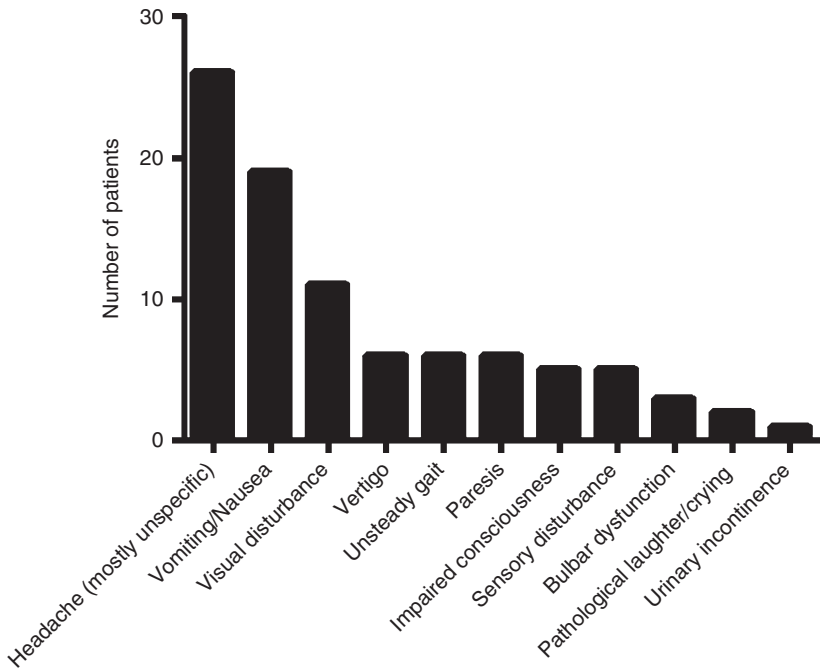

Figure 2: Prodromal signs and symptoms of basilar artery stroke in children.

long in 52 patients (28 whole length of the basilar artery, 22 middle and distal thirds, two proximal and middle thirds).

Aetiology was mostly vasculopathic (*n*=38: dissection [*n*=26], vasculitis [*n*=6], steno-occlusive cerebral arteriopathy [*n*=2], and other [*n*=4], such as fibromuscular dysplasia), followed by haematological (*n*=9), and cardioembolic (*n*=4). Aetiology was unknown in 40 patients and not stated in six. The cases with known aetiology were published more recently (p=0.016) and more likely to have been investigated with magnetic resonance angiography (p=0.028) than cases with unknown aetiology.

Contributing risk factors were reported in 53 patients and multiple risk factors in nine patients. Risk factors included trauma (*n*=28), infection (*n*=10), cardiac disease (*n*=8), haematological disorders (*n*=8), elevated risk of arteriopathy (*n*=3, e.g. post irradiation), positive family history of thromboembolic events (*n*=4), dehydration (*n*=1), migraine (*n*=1), or other entities (*n*=3).

Blood pressure at diagnosis was only stated in 37 out of 97 children (38%), being above the 95th centile for age in eight patients, low in one, and normal in 28.

Antithrombotic or thrombolytic acute-phase treatment was administered to 47 patients, consisting of acetylsalicylic acid (*n*=16), heparin (*n*=20), intra-arterial thrombolysis (*n*=12), and systemic (intravenous) thrombolysis (*n*=5), with five children receiving more than one agent (in combination or consecutively). Endovascular mechanical thrombectomy was combined with acetylsalicylic acid in one patient and balloon angioplasty in another. Time from onset of symptoms to antithrombotic treatment was up to 7 days, with a median of 20 hours (range 4–168h), in the 16 children in whom the delay was measured in hours. Six patients were treated within 12 hours.

PedNIHSS score, delay to treatment, and outcome were not significantly different in children who received endovascular therapy. Haemorrhagic transformation was described as minimal in one child. All children undergoing thrombolysis had a complete BAO.

Forty-five patients received long-term antithrombotic treatment (18 acetylsalicylic acid, 15 oral anticoagulants, 12 heparin).

Outcome was indicated in 90 patients, being good in 45 and poor in 45 (eight patients died; Fig. S1, supporting information online). When dichotomizing outcome according to the Basilar Artery International Cooperation Study (BASICS) on BAS in adults,[7] defining poor outcome as an mRS score of 4 or more, 31 (35%) children fell into this category, compared with 58 (65%) children with a good to moderate outcome (mRS score 0–3). Nine of the 13 patients presenting with a locked-in syndrome had a poor outcome (mRS >2). Median follow-up lasted 6 months (IQR=3–24mo). Eight patients (8%) had a recurrent stroke, with good outcome in three, poor in two, and no information in three patients. Stroke recurrence was located in the basilar artery in six cases whereas localization was not specified in two cases. Three of these eight children received antithrombotic treatment (one acetylsalicylic acid, one heparin, one oral anticoagulant), one had no antithrombotic treatment, and no information on secondary prevention was provided in four cases.

Follow-up imaging with information on recanalization of the basilar artery was provided in 50 cases, with no recanalization in 16, partial in 18, and complete in 16 patients.

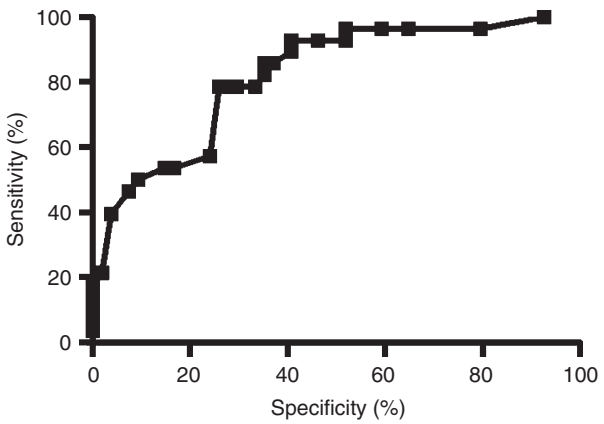

Figure 3: Receiver operator curve for the Pediatric National Institutes of Health Stroke Scale as a predictor of good outcome (modified Rankin scale [mRS] 0–2; n=45) versus poor outcome (mRS 3–6; n=45). Area under the curve=0.8201 (95% confidence interval 0.72600.9142).

In a univariate analysis, outcome was significantly worse with a high PedNIHSS score (r=0.47; 95% CI 0.29–0.63; p<0.001), coma (r=0.39; 95% CI 0.19–0.56; p<0.001), or quadriplegia (r=0.34; 95% CI 0.13–0.51; p=0.001) as presenting signs, as well as with a long BAO (r=0.24; 95% CI 0.02–0.44; p=0.03); and significantly better after an acute antithrombotic, thrombolytic, or mechanical endovascular treatment (r=−0.24; 95% CI −0.46–0.003; p=0.047). In a multivariate analysis including PedNIHSS score, length of BAO, BAO recanalization, antithrombotic, thrombolytic and mechanical endovascular treatment, quadriplegia, and coma, only PedNIHSS score was significantly associated with outcome (β=0.06; 95% CI 0.009–0.11; r^2=0.131; p=0.02). A PedNIHSS score of up to 17 was the cut-off value set by the receiver operator curve, distinguishing (p=0.001) the good- (mRS 0–2, *n*=45) from the poor-outcome group (mRS 3–6, *n*=45) with an odds ratio of 5.0, a sensitivity of 71%, and a specificity of 67% (Fig. 3).

DISCUSSION

The incidence of paediatric BAS of 0.037 per 100 000 children per year in the Swiss population is, to our knowledge, the only published incidence rate of paediatric BAS. The most striking finding of this study is the survival rate of 92%, with a good outcome in 50% of children with BAS, compared with 45 to 80% survival rate and 20 to 30% good outcome in adults,[6] despite a significant delay in diagnosis (children 19h vs mostly <6h in adults[7]). Information on paediatric BAS is largely based on case reports; thus, a bias in favour of good outcomes is probable. However, good outcome also predominated in the cases of the prospective population-based registry SNPSR, which are similar to the literature cases. Better collateral supply and less comorbidity are possible explanations for a better outcome in children. However, when comparing only young adults with children after arterial ischaemic stroke in general, children do not have a better outcome.[13]

Considering that half of children still have a poor outcome after BAS, management needs to be improved. Children with

antithrombotic, thrombolytic, or mechanical endovascular acute-phase treatment had a better outcome, even though recanalization of BAO did not reach statistical significance. There is not enough evidence to determine which of these treatment modalities is best. In view of the severity of the disorder, the few complications reported with thrombolysis or mechanical endovascular treatment in this review and with thrombolysis on pedAIS in general,[14] and the evidence on BAO treatment in adults, thrombolysis or mechanical endovascular treatment may be preferred over antithrombotic treatment in the absence of data from randomized controlled trials in children.

Good outcome factors in adults with BAS are recanalization of BAO, younger age, low NIHSS score at presentation, short time to treatment, short BAO, and good collateral state.[6,15,16] The clinical presentation of BAS in children does not substantially differ from that found in the adult population. The signs may be less severe (median PedNIHSS score 15) than in adults (NIHSS score of 18–20),[7,15] but taking into account the fact that the PedNIHSS score was retrospectively calculated in most cases in this review, assuming a minimal severity of signs where not otherwise specified, the severity of presenting signs is likely to be underestimated. As in adults, a low NIHSS score had a significant association with a good outcome, with a similar cut-off value, being 17 in this review compared with 20 in adult patients.[15] The long time to diagnosis is in keeping with the findings of a study on diagnostic delay in childhood stroke, revealing that pedAIS diagnosis was particularly delayed if occurring in the posterior circulation.[17]

Stroke recurrence in children was found to be as equally frequent as in adults after BAS, in whom the prevalence ranges from 4 to 13%.[18,19] The recurrence rate in pedAIS in general is 11 to 19%,[2,20] and is estimated to be higher in the posterior circulation (up to 52%).[3,4] Since none of the publications on posterior circulation pedAIS specifically addressed the recurrence rate after BAS, the recurrence rate after occlusion of other posterior circulation vessels, such as the vertebral arteries, might be higher than after BAS. Another possible explanation for the fact that this review shows fewer recurrent strokes after BAS than previous data on posterior circulation pedAIS is the longer follow-up in the studies mentioned (2–4y).

Vasculopathy was the most common aetiology for BAS in children, as in adults. In contrast to the atherosclerotic vasculopathy predominating in adults, the most common vasculopathy reported in children was arterial dissection (27% vs 10% in adults).[7] Moreover, children have other types of vasculopathies, such as para-/infectious arteriopathies.

In 42% of childhood BAS, aetiology remained unknown, which might be partly explained by the fact that imaging studies are often less readily performed because of the need for general anaesthesia and in order to avoid radiation exposure. Thus, diagnoses such as vasculitis or arterial dissection might have been missed.

Ganesan et al.[3] reported that children with a posterior circulation stroke were previously healthy, whereas 50% of those with an anterior circulation stroke had a pre-existing medical condition. In this review on BAS, 44 children (45%) had no pedAIS risk factor. In the remaining 53 children, previous trauma was the most common risk factor (29%) and was reported in 12 of the 26 patients with arterial dissection.

Arterial hypertension is one of the most important risk factors for vertebrobasilar stroke in adults.[21] Ganesan et al.[3] observed a high rate of hypertension (n=9/22 patients) in children with posterior circulation stroke. In this study, blood pressure was stated in a minority of patients only, indicating that blood pressure is still too infrequently measured in children. However, among those in whom blood pressure was measured, the majority of values were normal.

The majority of cases of paediatric BAS occur in males. A male preponderance is observed in all pedAIS subtypes, even when corrected for trauma due to presumed sex differences in risk-taking behaviour, and remains unexplained.[22] Although trauma was more frequent in males than in females in this review, dissection was equally distributed. Elevated testosterone levels, independent of pubertal stage, have been discussed as a pedAIS risk factor. Thus, even though half of the males were prepubertal (<9y of age), testosterone might play a role in BAS.[22,23]

Limitations of the study

Comparison of stroke cases in childhood is hampered by patchy recording of baseline characteristics, the use of different functional scales, and treatment approaches such as heterogeneity in the timing of outcome assessments. Data collection in a registry is not as accurate as in a randomized treatment trial. As an outcome measure, the mRS was applied retrospectively and simplified into two categories. Finally, as already mentioned, a publication bias is likely.

In conclusion, BAS is rare in children, mainly occurring at school age, with a marked male preponderance. Children seem to have a higher chance of a good outcome than adults, despite a considerably longer delay from onset of symptoms to diagnosis and treatment. The index of suspicion of BAS in children needs to be raised in order to offer these children a timely diagnosis. Impaired consciousness, paresis, vomiting, nausea, and headache with bulbar or cerebellar signs, especially if occurring within days after prodromes such as headache, visual disturbances, or vertigo, should raise the suspicion of BAS and prompt urgent neuroimaging, particularly searching for dissection. Antithrombotic, thrombolytic, and mechanical endovascular treatment have a beneficial effect, but optimal treatment modalities are still unknown.

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SUPPORTING INFORMATION

The following additional material (including references from the systematic review of the literature) may be found online.

Table SI: Swiss Neuropaediatric Stroke Registry patients' clinical and radiological characteristics.

Figure S1: Modified Rankin Scale (mRS) scores.

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