Clinical Management Issues

Basilar Artery Occlusion:
Clinical Management and Therapy

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Abstract
Basilar artery occlusion is a potentially life-threatening subset of the larger category of posterior circulation strokes, carrying >80% fatality rate without treatment. This condition accounts for about 1% to 4% of all ischemic strokes and is generally related to local atherothrombosis or cardioembolism. Diagnosis can be challenging because presenting symptoms are often non focal, such as headache, dizziness, and vertigo. The onset of the symptomatology can be abrupt without preceding events, abrupt with prodromal symptoms, or progressive and stuttering. Finally, the severity of clinical presentation may range from isolated cranial nerve palsies to tetraplegia, locked-in state, or coma. If basilar artery occlusion is readily recognized and confirmed with the aid of neuroimaging, intravenous thrombolysis or endovascular treatment can be undertaken immediately in order to recanalize the occluded artery and thus reduce mortality and improve outcome.

Keywords: Stroke; Basilar Artery Occlusion; Headache Disorders; Magnetic Resonance Image; Thrombolysis

INTRODUCTION
The vertebrobasilar arterial system receives only 20% of cerebral blood flow and supplies the posterior portion of the brain including the brainstem, the thalami, the cerebellum, and parts of the occipital and temporal lobes [1,2]. Posterior circulation ischemia (PCI) is a clinicopathological condition associated with an infarction within the vertebrobasilar arterial system and is characterized by a complex symptomatology, course, and outcome [1,2]. PCI accounts for about 20–25% of all ischemic strokes and has an adjusted incidence of 18 per 100,000 person-years (95% confidence interval—CI: 10/100,000 to 26/100,000) [1,2]. Basilar artery occlusion (BAO) is a potentially life-threatening subset of PCI, carrying >80% fatality rate without treatment and accounts for about 1% to 4% of all ischemic strokes [3]. BAO still represents one of the most challenging conditions to diagnose and manage. Despite better imaging techniques, in fact, the diagnosis of this condition is often delayed, especially because in many cases presenting symptoms are non-focal, such as headache, dizziness, and vertigo [1-3]. The aim of this article is to provide clinicians with an easy and reliable tool for promptly recognizing and treating BAO.

ETIOLOGY
The most frequent causes of BAO are local thrombosis and artery-to-artery thromboembolism originating from arteriosclerotic lesions [3]. Other important etiologies are cardiac emboli and vertebral artery dissec-

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caused by irritation of trigeminovascular afferents located in brainstem [12]. In a study by Ferbert et al. of 85 patients with BAO, headache was reported in 25.8% of cases on admission [8]. The headache occurred during the 2 weeks before the stroke and had a predominantly occipital localization. The onset was both sudden and the main complaint, so that initially it was considered subarachnoid hemorrhage [8].

the onset of symptomatology is quite variable

Based on the symptoms onset, three major clinical types of BAO presentation have been described [3,13]:

- **Abrupt without preceding events.** This form is characterized by sudden onset of severe motor and bulbar symptoms (i.e. quadriplegia, ophthalmoplegia, and anarthria) combined with reduced consciousness.
- **Abrupt with prodromal symptoms.** Transient prodromal symptoms, such as double vision, dysarthria, vertigo, paraesthesiae, etc., precede the monophasic BAO symptoms by several days or even months.
- **Progressive and stuttering.** This form is characterized by gradual or stuttering course of posterior circulation symptoms such as blurred vision, balance disturbance, dysarthria, bilateral paresthesiae, or motor weakness, which finally are associated with a reduced consciousness [3,13].

The clinical picture varies depending on the site and type of the BA obstruction

Owing to different degrees of the brainstem involvement, the severity of the clinical presentation may range from isolated cranial nerve palsies to tetraplegia, locked-in state, or coma [3].

- **Oclusions of the proximal or middle segments of the BA usually cause large pontine strokes with quadriplegia, reduced consciousness, dysarthria and dysphagia, horizontal gaze paresis, and other cranial nerve palsies [3].**
- **Oclusions in the distal segment of the BA result in strokes bilaterally in the mesencephalon and thalamus with decreased consciousness, quadriaparesis, and nuclear or supranuclear oculomotor and pupillo-motor dysfunctions [3].**

CLINICAL FEATURES

Several aspects, described hereafter, contribute to make BAO one of the most challenging conditions to diagnose and manage:

Presenting symptoms are often non-focal

Most common premonitory symptoms of BAO are dizziness and vertigo, followed by headache and neck pain [3,8,9].

Dizziness and vertigo are two terms used interchangeably by patients to indicate non-specific symptoms accounting for about 4 million emergency department visits annually in the United States [9]. Dizziness is usually described as a feeling of light-headedness or lack of mental clarity [10]. Vertigo more specifically describes a sensation of spinning and usually indicates dysfunction of the peripheral vestibular or central vestibule–cerebellar system [6]. Vertigo and/or dizziness caused by BAO are usually associated to other brainstem or cerebellar symptoms [6]. However, when vertigo is the only symptom and the neurologic examination is normal it is not easy to establish the central or peripheral origin of the symptomatology. In these cases the head-impulse-nystagmus-test of skew (HINTS) can be a useful bedside test to distinguish between vertigo caused by peripheral or central lesions [11].

In patients with PCI headache is a common presenting symptom that seems to be caused by irritation of trigeminovascular afferents located in brainstem [12]. In a study by Ferbert et al. of 85 patients with BAO, headache was reported in 25.8% of cases on admission [8]. The headache occurred during the 2 weeks before the stroke and had a predominantly occipital localization. The onset was both sudden and the main complaint, so that initially it was considered subarachnoid hemorrhage [8].
This rare type of primary headache disorder, previously referred to as basilar migraine, is characterized by attacks preceded and/or accompanied by transitory focal neurologic symptoms pointing to dysfunction in the region supplied by the BA and its branches [18]. The diagnosis is based on the finding of at least two migraine attacks accompanied by at least two of the following fully reversible symptoms: dysarthria, vertigo, tinnitus, impaired hearing, double vision, ataxia, and decreased level of consciousness [18,19].

**INVESTIGATION**

Computed tomography (CT), contrast-enhanced CT angiography (CTA), MRI, magnetic resonance angiography (MRA), and Doppler sonography can be used in the acute setting to evaluate patients with suspected BAO. If a patient is a candidate for thrombolytic therapy, neuroimaging should be performed as soon as possible to reduce the door to needle time.

Non-contrast CT (NCCT) is essential to quickly rule out hemorrhagic stroke and other intracranial space occupying lesions. The pc-Alberta stroke program early CT score (pc-ASPECTS) measuring early ischemic changes in 8 different brain regions has been recently proposed as a grading system to evaluate stroke extension and predict outcome in PCI [20]. Unfortunately, in PCI beam hardening due to the skull base, reduces CT sensitivity, and stroke could be identified in the acute phase only in around 20-40% of patients [21]. A dense basilar artery sign is visible in only about two-thirds of patients, but, when present, it is highly specific for BAO [3]. Contrast-enhanced CT angiography (CTA) has great value to detect vascular occlusions and is increasingly used in comprehensive stroke centers to select candidates for endovascular treatment. Currently, great attention is given to the prognostic value of collateral blood flow in the hyperacute phase of stroke. Recently, two semiquantitative CTA-based grading systems have been proposed to quantify the potential collateral flow in patients with acute BAO: the posterior circulation collateral score (PC-CS) and the basilar artery on Computed Tomography angiography (BATMAN) score [22,23]. Both of these...
scores proved to be strong predictors of functional outcome as well as mortality in BAO and can help to select patients for endovascular treatment [22,23]. CT whole brain volume perfusion (PCT) measures changes in Hounsfield unit values per pixel over time after contrast injection, providing information about capillary-level hemodynamics of brain parenchyma. PCT allows to measure parameters such as mean transit time (MTT), time to peak (TTP), cerebral blood flow (CBF), and cerebral blood volume (CBV) [24]. A mismatch between a hypoperfused area (reduced CBF and increased MTT and TTP) and the ischemic core (reduced CBV) may entail the presence of the so-called ischemic penumbra—hypoperfused still viable parenchyma. Therefore, PCT has been used to select patients with strokes with salvageable tissue, eligible for endovascular treatment also outside common time windows [25–27]. Using multimodal CT, encompassing NCCT, CTA and PCT, vertebrobasilar strokes were diagnosed in the acute phase in up to 76% of patients. Sensitivity for pons/midbrain lesion was around 60% [28,29].

- MRI is more sensitive than CT in the assessment of PC infarcts, particularly in the brainstem, and can detect early evidence of infarction with diffusion-weighted imaging (DWI) sequences [1,2,30]. MRI-DWI is considered the gold standard to evaluate infarct core [31]. MRI-perfusion weighted imaging (PWI), likewise PCT, can define the hypoperfused brain area during ischemic stroke. MRI diffusion-perfusion mismatch may be helpful to select patients for acute recanalization therapies [31]. MRA allows, even without contrast injection, to identify the type and location of BA occlusion or stenosis.

- Angiography is still the gold standard for collateral evaluation in BAO and is used in the hyperacute phase only for therapeutic purposes [1,3,9].

- Transcranial echo-color-Doppler can show intracranial vascular occlusions [2,30]. However, ultrasound investigation is more operator-dependent and less sensitive in the diagnosis of posterior circulation disease than MRA or CTA, and can be rarely used as the sole or primary investigation for the assessment of PC strokes [1,30].

## ACUTE TREATMENT

Acute BAO treatment aims to restore the cerebral blood flow in the occluded vessel and salvage brain tissue. It has been shown that BA recanalization can substantially enhance a patient’s chances of survival and of good functional recovery [3]. A meta-analysis of 45 studies (n = 2056) on acute BAO, in particular, has shown that recanalization of BA results in a two-fold reduction in mortality and 1.5-fold reduction in death or dependency [32].

Furthermore, the existence of a relationship between the time from symptom onset to arterial recanalization and clinical outcome has been widely demonstrated. As evidenced in the BASICS registry, a significantly increased risk of poor outcome seems to occur when recanalization therapy is started > 6 hours after the estimated time of BAO [33]. In this regard, it is necessary to clarify the concept of “time to recanalization therapy”, i.e. the interval between estimated time of BAO and start of recanalization therapy. Since BAO is preceded by prodromal symptoms in > 60% of cases [3,34,35], most of these patients are likely to be excluded from any acute therapeutic option if it is considered as an inclusion criterion the time of onset of any symptom to treatment. Therefore, as suggested in the BASICS registry, the estimated time of BAO is defined as “time of onset of acute symptoms leading to clinical diagnosis of BAO or, if not known, last time the patient was seen normal before onset of these symptoms” [33].

Acute treatment options for BAO include intravenous fibrinolysis (IVT), intra-arterial thrombolysis (IAT), and/or endovascular mechanical treatment [1-3,23].

- **IVT.** It is the first therapeutic strategy introduced for the management of acute ischemic stroke. This treatment was first evaluated in several randomized controlled trials (RCTs) with recombinant tissue plasminogen activator (rt-PA), such as NINDS, ECASS, ECASS II, and ATLANTIS [36–39]. In particular, the NINDS study found a benefit of IVT when treatment was started within three hours of the onset of symptoms and demonstrated that patients treated with rt-PA were at least 30% more likely to have a good functional outcome than patients treated with placebo [36]. The safety and efficacy of IVT were then evaluated in three multicenter studies, that are the
Different types of devices. Currently, the so-called “stent retrievers” are the most commonly used ones. These new devices can be deployed within the clot, quickly removing the clot and restoring the blood flow once retrieved. Compared to previous treatments, MT methods reach higher recanalization rates and have lower risk of hemorrhages and wider time window [45,47]. Recently, an observational, multicenter study, including 148 consecutive patients with BAO treated with endovascular procedures, the ENDOSTROKE study, reported a good outcome (mRS 0-2) in up to 34% of treated patients, irrespective of stroke severity, and complete recanalization in 79% of cases [48]. More recently, Gory and colleagues analyzed 22 consecutive patients with basilar stroke treated at their hospital with Solitaire™ stent-retrievers and performed a systematic review of published data (15 studies involving a total of 312 subjects). The recanalization rate reached 81% (95% CI: 73% to 87%), good outcome was found in 42% (95% CI: 36% to 48%), and symptomatic intracranial hemorrhage was observed in 4% (95% CI: 2% to 8%) of cases [49].

Over the past decade, treatment for acute ischemic stroke has evolved to include both IVT and endovascular procedures. Phan et al. analyzed six randomized controlled trials involving 1943 patients to assess the functional outcomes and complications of IVT with and without endovascular treatment. In this study, patients who received IVT with endovascular treatment had significantly higher rates of excellent functional outcomes (mRS 0-1) (95% CI: 1.29-2.39; RR: 1.75) in comparison with those who received IVT alone. Endovascular treatment increased the RR of a good functional outcome by at least 30% compared to IVT alone [50].

Perfect timing for endovascular treatment in BAO is not well established. Recently, published American guidelines suggest to perform MT in PCI only within 6 hours from stroke onset [51]. However, most centers, considering the poor prognosis associated with BAO, apply recanalization therapies for this pathology up to 12-24 hours after symptom onset [52].

An analysis of 19 published cohorts of patients with BAO showed that higher recanalization rates, such as those obtained with endovascular mechanical treatments, decrease mortality but do not necessarily trans-

"SITS-MOST, the ECAS III, and the IST-3, with a therapeutic window of 3, 4.5, and 6 hours, respectively [40-42]. However, the vast majority of data from these studies concern patients with anterior circulation infarcts (ACI). Indeed, data regarding PC strokes in the SITS-MOST and ECASS III studies are lacking and only 8.1% of patients included in the IST-3 trial had PCI [42]. In the last years, several trials performed with angiographic assessment have reported a progressive improvement of the recanalization rate and functional outcome in patients with BAO treated with IV rtPA. In a Finnish single-center consecutive IVT series the rate of recanalization was 65% and 30 of 116 patients (26%) had good outcome (modified Rankin Scale (mRS) 0-2) by 3 months [43]. A study by Strbian et al. on 184 patients with angiography-proven BAO treated with IVT showed that recanalization of BAO produced good outcomes in 50% of patients without extensive baseline ischemia (pc-ASPECT ≥ 8) [44].

• IAT. Findings from uncontrolled and controlled studies with IAT have shown a high recanalization rate, ranging on average from 63% to 65% [13,45]. The results of an analysis of 420 non-randomized patients with BAO treated with IAT (82%) or with IVT (18%) showed not significant differences between the two groups of patients in death, dependency, and favorable outcomes, although the recanalization rate was higher in patients treated with IAT (65% vs. 53%) [13]. The Basilar Artery International Cooperation Study (BASICS), a prospective, observational study of patients with BAO, compared efficacy of antithrombotic treatment, IVT and IAT [46]. In patients with mild-to-moderate basilar stroke, a good outcome (mRS 0-2) was achieved in higher proportion in the IV thrombolysis group compared to intra-arterial treatment group (respectively 53% vs. 30%). Outcome did not differ significantly when considering patients with severe stroke (mRS ≤ 2 in 20% vs. 11%). Recanalization occurred in 72% of patients treated with endovascular procedures compared to 63% of patients treated with IV thrombolysis and was associated with increased independency [46].

• Endovascular mechanical treatment. In the last years, mechanical thrombectomy (MT) has been performed using many different types of devices. Currently, the so-called “stent retrievers” are the most commonly used ones. These new devices can be deployed within the clot, quickly removing the clot and restoring the blood flow once retrieved. Compared to previous treatments, MT methods reach higher recanalization rates and have lower risk of hemorrhages and wider time window [45,47]. Recently, an observational, multicenter study, including 148 consecutive patients with BAO treated with endovascular procedures, the ENDOSTROKE study, reported a good outcome (mRS 0-2) in up to 34% of treated patients, irrespective of stroke severity, and complete recanalization in 79% of cases [48]. More recently, Gory and colleagues analyzed 22 consecutive patients with basilar stroke treated at their hospital with Solitaire™ stent-retrievers and performed a systematic review of published data (15 studies involving a total of 312 subjects). The recanalization rate reached 81% (95% CI: 73% to 87%), good outcome was found in 42% (95% CI: 36% to 48%), and symptomatic intracranial hemorrhage was observed in 4% (95% CI: 2% to 8%) of cases [49].

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Patients should be placed on continuous cardiac monitoring to detect cardiac arrhythmias (i.e. atrial fibrillation, etc.) and to check the blood pressure. Patients with BAO may be particularly sensitive to changes in blood pressure [9]. However, so far the balance of risk and benefit in lowering blood pressure in these cases is not yet clear. In a study that analyzed the association between blood pressure and stroke in patients undergoing endarterectomy for symptomatic carotid stenosis it was found higher risk of stroke at lower blood pressure, especially if systolic blood pressure < 140 mmHg [54]. There are no similar studies in patients with BAO, but the same possibility of hemodynamic insufficiency at lower blood pressures exists. Therefore, caution is advised in lowering the pressure aggressively in these patients, particularly if they have limited or absent posterior communicating arteries as well as other collateral flow abnormalities [1].

The choice of the appropriate medical therapy for secondary prevention of BAO should be based on the causative stroke mechanism (i.e. cardioembolic, atherosclerotic, etc.) as well as on the risk stratification for recurrence [1-3,30]. Therefore, possible medical treatments include antiplatelet agents or anticoagulants, as well as lipid-lowering drugs. Recommended treatment is detailed in recent guidelines [51,55]. In patients with indications for anticoagulation (i.e. atrial fibrillation), treatment should be started generally within two weeks after an acute ischemic stroke, to avoid the risk of hemorrhagic transformation of the infarct.

Key points

- BAO is a potentially life-threatening neurologic emergency that requires high suspicion index
- Patients presenting with sudden onset of headache or vertigo need an accurate neurologic and neuroradiological evaluation
- Multimodal CT (if available) or MRI must be promptly used in the acute setting to confirm the diagnosis of BAO
- As soon as BAO is confirmed with neuroimaging, intravenous thrombolysis or endovascular treatment can be undertaken
- Shortening the time from the symptoms onset to start of the treatment can give patients better chance to survive and avoid severe complications
- Identification causes of BAO is essential for choosing the most appropriate secondary medical therapy
- Screening of uncommon causes of BAO is mandatory
- MRI is a gold standard for follow up of BAO
PROPOSED ALGORITHM FOR ACUTE BAO MANAGEMENT

BAO = basilar artery occlusion; CT = computed tomography; CTA = computed tomography angiography; MRA = magnetic resonance angiography; MRI = magnetic resonance imaging

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