



Posterior circulation ischemic stroke—a review part II: imaging and acute treatment

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Abstract

Posterior circulation strokes affect the vertebrobasilar arterial system, account for about 20–25% of all ischemic strokes, and are a significant cause of patient disability and mortality. Diagnosis can be challenging; clinical presentation and common pitfalls facing posterior circulation stroke have been discussed elsewhere. In the first part of the review, we focus on the imaging, discussing the information that can be gathered through a correct selection and interpretation of different possible studies helping to achieve an early diagnosis and to select the best medical treatment. In the second part of the review, we will discuss the best therapeutic treatments available at the moment for posterior circulation ischemia.

Keywords Posterior cerebral ischemia · Imaging · Endovascular therapy

Introduction

Posterior circulation ischemia (PCI) accounts for about 20–25% of all ischemic strokes with an annual incidence of 18 per 100,000 person-years and is an important cause of disability and mortality [1, 2]. Due to the broad area of brain tissue supplied by the vertebrobasilar arterial system and the rich collateral support, PCI can present a wide spectrum of clinical presentations ranging from isolated cranial nerve palsies to tetraplegia, locked-in state, and coma [3–6]. Even if there is a substantial overlap with symptoms and signs of anterior circulation ischemia (ACI) [4, 6] at admission, patients with PCI more often show decreased consciousness, visual field defects, and vestibulo-cerebellar signs and less commonly hemisymphromes, dysarthria, and cognitive symptoms [7].

Some posterior circulation (PC) strokes present with non-focal symptoms (i.e., non-rotatory dizziness, vertigo, dysarthria, and headache) or as “stroke chameleons,” mimicking other conditions, in such a way as to make challenging the diagnosis on purely clinical grounds and to partially justify the low number of patients with PCI so far enrolled in several randomized controlled trials (RCTs) on iv thrombolysis [8–11]. However, presenting symptoms of PCI and suggestions to improve bedside clinical evaluation have been extensively discussed in the first part of this review.

To date, imaging remains a cornerstone in the diagnosis of stroke. In the last years, many advances have been made increasing the different imaging techniques available to study PCI and there are now many possible investigations that—if properly used—may give important diagnostic and prognostic information in the acute setting of stroke workup. Thereafter, a correct imaging study will help to choose the best therapy. Here, we would like to focus on the neuroradiological and neurosonological investigations and the different therapeutic options available at the moment, with a glimpse to future prospective.

Investigation

Computed tomography (CT), magnetic resonance imaging (MRI), and Doppler sonography can be used in the acute setting to evaluate patients with stroke.

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CT is essential in the diagnostic workup of stroke. Non-contrast CT (NCCT) is the most widely available imaging technique, essential to quickly rule out hemorrhagic stroke and other intra-cranial space-occupying lesions. Brain ischemia is visualized as hypodensity and loss of gray-white matter differentiation on CT. The posterior circulation—Alberta Stroke Program Early CT Score (pc-ASPECT)—measuring early ischemic changes in 8 different regions (pons, midbrain, right or left thalamus, right or left cerebellum, and right or left posterior cerebral artery territory) has been proposed as a grading system to evaluate stroke extension and predict outcome in PCI [12] (Fig. 1). 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 [13–15], with lower sensitivity for pons/midbrain lesions. A basilar artery (BA) or posterior cerebral artery (PCA) hyperdensity, indicating acute thrombosis, may add sensitivity if these vessels are involved [16]. *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. *CTA-source images* (CTA-SI) evaluate diminished parenchymal contrast enhancement (hypoattenuated areas) to pinpoint acute brain infarction. It may increase sensitivity up to 65% for early ischemic changes [12]. Posterior circulation ASPECT calculated with CTA-SI has been associated with functional independency and death at 1 and 3 months [12, 17]. Recently, attention has been drawn to the prognostic value of collateral blood flow in the hyperacute phase of stroke. The gold standard for collateral evaluation is angiography, used in the hyperacute phase for therapeutic purpose only. Many studies proved a positive relationship between good collateralization and functional independency in anterior circulation stroke using multiphase CTA, a time-resolved technique acquiring images after mean contrast administration in the arterial and

in the venous phase [18]. PCI's collateralization can be assessed using CTA, evaluating the presence and caliber of posterior communicating arteries [19]. Furthermore, the patency of posterior inferior cerebellar artery, anterior inferior cerebellar artery, and superior cerebellar artery, evaluated with CTA, in some case may point to the presence of collateralization through anastomoses between close vessels (i.e., anastomoses between branches of superior cerebellar artery and of posterior inferior cerebellar artery in case of mid-basilar occlusion) [20]. Recently, two studies associated good collateralization—evaluated using different scoring systems—with a better outcome in PCI [19, 20] whereas another study did not confirm such results [21]. *CT whole-brain volume perfusion* (PCT) measures changes in Hounsfield unit values per pixel over time after contrast injection providing different parameters such as cerebral blood flow (CBF), mean transit time (MTT), and time to peak (TTP), which are abnormal in hypoperfused brain area due to vessel occlusion. A reduced cerebral blood volume (CBV), on the other hand, represents an irreversibly damaged ischemic core [22]. Multimodal CT, encompassing NCCT, CTA, and PCT increases the sensitivity for vertebrobasilar strokes and pons/midbrain lesions up to 76% and 60%, respectively [14, 15]. Finally, a mismatch between a hypoperfused area and the ischemic core may entail the presence of the so-called ischemic penumbra—hypoperfused still viable parenchyma. PCT has been used to select patients with anterior circulation strokes with salvageable tissue, eligible for endovascular treatment [23, 24] also outside the common time windows [25, 26]. To the best of our knowledge, the feasibility of PCT-guided treatment of PCI has not been investigated yet and is still a matter of debate whether PCT maps may provide an exact representation of ischemic penumbra (Fig. 2).

MRI is considered the gold standard for diagnosis of stroke and is particularly sensitive for PCI. However, it is time-

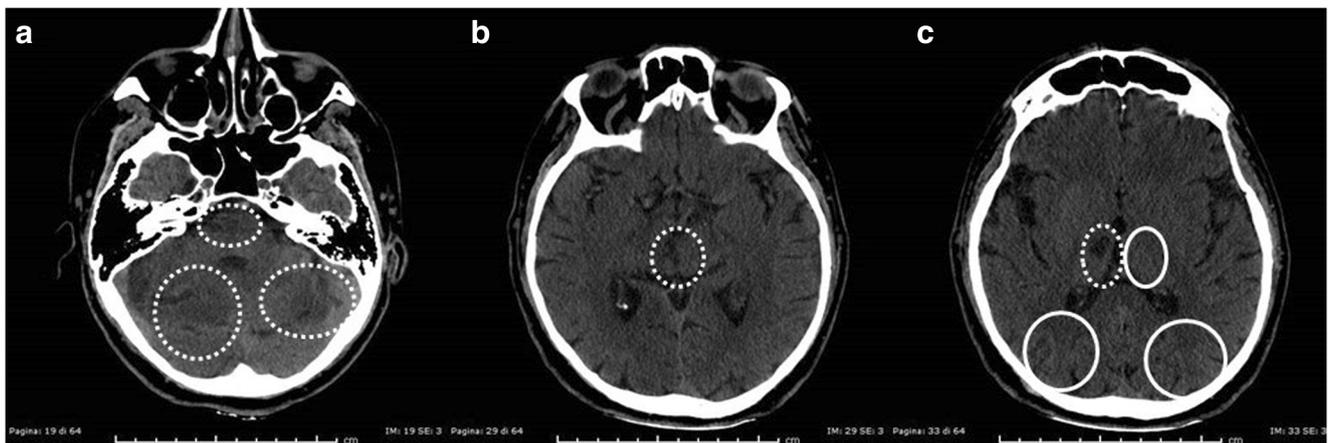
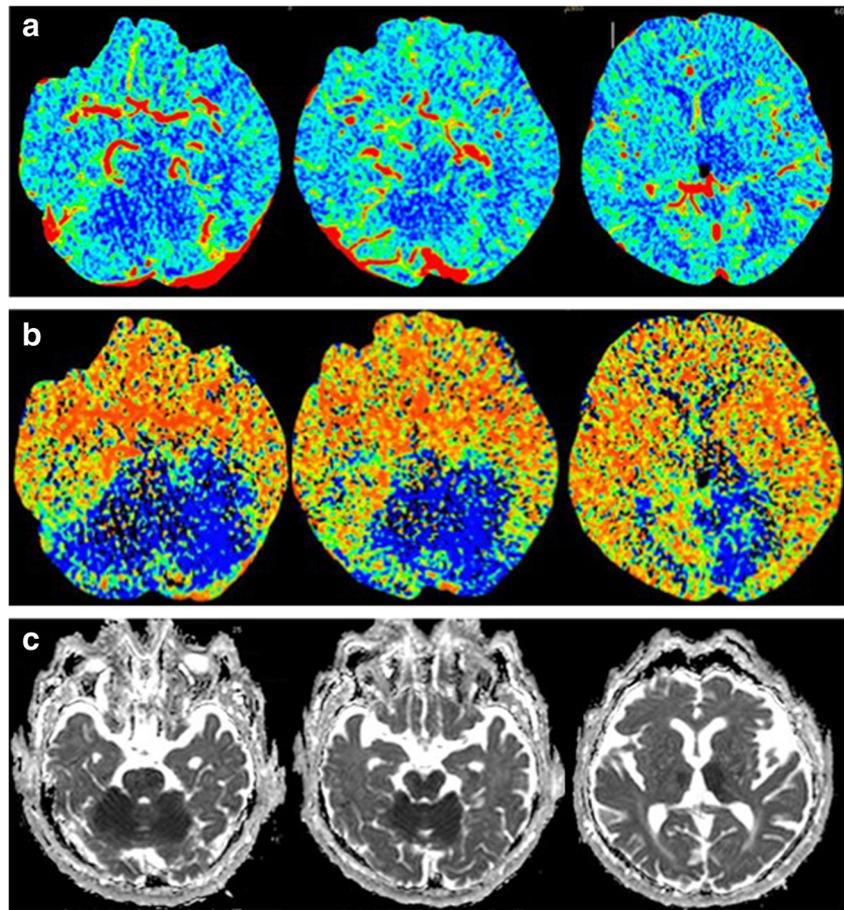


Fig. 1 Posterior circulation ASPECT (pc-ASPECT) in patients admitted to our emergency room in a coma. Posterior circulation ASPECT is calculated starting from 10 and subtracting 2 points if ischemia is found in the pons or midbrain, 1 point for the cerebellum, posterior cerebral

artery territory, and each thalamus. In our example, dotted circles show the affected areas and continuous circles the unaffected ones; pc-ASPECT, in this case, was 3. *Reproduced with the courtesy of Dr. S. Vallone (Modena, Italy)*

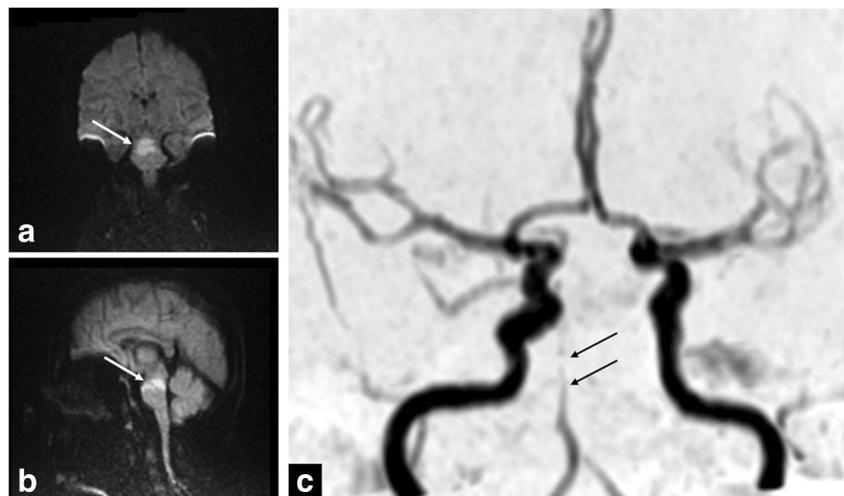
Fig. 2 Patient admitted to our emergency room in a coma, with a basilar occlusion. CTP showed reduced cerebral blood volume (CBV) in the medulla oblongata, cerebellum, midbrain, and left thalamus (**a**)—ischemic core—and increased mean transit time (MTT) (**b**)—hypoperfused area—in the same regions with a small mismatch. MRI apparent diffusion coefficient (ADC) (**c**) showed irreversible ischemia perfectly overlapping with the CBV map. Based on these findings, acute recanalization therapy was not attempted. *Reproduced with the courtesy of Dr. S. Vallone (Modena, Italy)*



consuming, expensive, and not commonly available in the emergency setting. It 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 [27] (Fig. 3). It must be noted that 6% to 10% of all strokes are initially DWI-negative with more false-negative MRIs occurring in cases of PC stroke [28–31].

Oppenheim and his colleagues [29] found that false-negative DWI rate for PC strokes was almost 10 times higher than that of the AC (19 vs. 2%). The sensitivity of MRI seems to increase with time from symptom onset to imaging. In their study, DWI imaging was false-negative in 5.8% of all patients with stroke symptoms lasting > 24 h, when imaging was obtained within 48 h of onset [29]. Up to a third of patients

Fig. 3 Basilar artery occlusion on MRI. Hyperacute ischemic changes in the upper portion of the pons on diffusion-weighted imaging (DWI) (**a** and **b**, arrow). MR angiography shows occlusion of the mid-basilar artery (**c**, arrow)



presenting with vertebrobasilar ischemic symptoms had a false-negative DWI study during the first 24 h and a positive MRI imaging on the follow-up [29]. Therefore, in the presence of an early negative MRI, a PC stroke should not be ruled out. Aforementioned pc-ASPECTS has been applied also to MRI-DWI to predict the functional outcome of PC stroke [32]: a pc-ASPECT score ≥ 8 on MRI is an independent predictor of favorable outcomes, whereas a pc-ASPECTS < 8 may identify patients with BA occlusion unlikely to have favorable outcomes despite recanalization [12, 32]. MRI-DWI is considered the gold standard to evaluate infarct core, although cases of reversible hyperacute DWI lesions have been reported [33]. 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 [34]. The correct etiological diagnosis of stroke is essential to choose the best treatment for secondary prevention. Many studies have shown that different types and different locations of ischemic lesions, most keenly evaluated with MRI-DWI, may be associated with different etiologies [35, 36]. Of note, cardioembolic stroke has been more commonly reported in ACI than in PCI [37]. MRI angiography is commonly used to detect the site of occlusion in PCI with good sensitivity and specificity [38].

Ultrasound sonography includes several techniques that allow to study the extra- and intra-cranial PC arteries. In the acute setting, cervical duplex and Doppler ultrasound can be used to demonstrate obstruction or dissections in the vertebral arteries (VAs). However, this investigation has limited ability to visualize the V1 segment and V2 segment within the transverse foramina [5]. In the same conditions, transcranial color Doppler (TCD) can show intra-cranial vascular occlusive lesions affecting the V4 segment of the VAs, the BA, or the PCA. However, both these investigations are operator-dependent and less sensitive in the diagnosis of PC disease than MRA or CTA and are rarely used as the sole or primary investigations for the assessment of PC strokes. Nevertheless, they may still be useful in cases of contraindications to contrast agents (i.e., advanced kidney failure and allergy to iodine-based contrast agents) and in peripheral hospitals that do not have advanced imaging facilities to select patients to be addressed to comprehensive stroke centers.

Ultrasound sonography is widely used in the subacute and chronic phase of the stroke for the follow-up of the patients and for finding less common risk factors such as the patent foramen ovale (PFO). For this purpose is commonly used the contrast TCD that has shown a relatively good sensitivity and specificity [39]. Recently, He et al. showed that a higher amount of right-to-left shunt in patients with cryptogenetic stroke was correlated with a higher percentage of small cerebral cortical lesions in both DWI and T2 MRI sequences and a more likely involvement of the PC [40].

Finally, although considered the gold standard for large vessel occlusion detection, *conventional angiography* is rarely used as the first diagnostic imaging technique, because it is an invasive and expensive procedure, and is most commonly performed for therapeutic purposes in previously selected patients. Most recently, in order to optimize the in-hospital workflow in severe strokes, it has been proposed to transfer patients directly to the angiosuite, where they will receive a CT scan and, if negative for hemorrhage, primary angiography. A pilot study showed that direct angiosuite access, compared with selection using multimodal CT, significantly reduced the door-to-groin-puncture time; however, around 17% of patients in the direct transfer to angiosuite group did not receive any treatment because no large vessel occlusion was detected [41].

Management of acute PC stroke

As outlined in the recent guidelines, acute treatment options for ACI and PCI are very similar including IV recombinant tissue plasminogen activator (IV rtPA) and endovascular treatment [42].

IV thrombolysis

The safety and efficacy profile of IV rtPA has been evaluated first in several randomized controlled trials (RCTs), such as NINDS, ECASS, ECASS II, and ATLANTIS [43–46], then in three multicenter studies, the SITS-MOST, the ECASIII, and the IST 3, with a therapeutic window, respectively, of 3, 4.5, and 6 h [47–49]. However, data on PCI IV thrombolysis are less abundant than those available on ACI, probably because specialist assessment and IV administration of rtPA are often hampered by a delayed or missed diagnosis. Case series, in fact, have shown a door-to-needle time longer in patients with PCI than in those with AC strokes [50]. The observations made in some studies that PCI patients generally arrive later at hospital and have a lower mean National Institute of Health Stroke Scale (NIHSS) score and a higher mean Glasgow Coma Scale (GCS) score on admission can further explain why somehow these patients have fewer chances to receive IV thrombolysis than ACI patients [7, 37].

Only 5% of patients included in the NINDS trial had PCI [43]. Data regarding PCI in the SITS-MOST and ECASIII studies are lacking. The IST 3 trial randomized 3035 ischemic stroke patients to rtPA or control within 6 h of the onset of symptoms, regardless of age or severity [49]. However, only 246 of 3035 (8.1%) randomized patients had PC stroke [49, 51].

Among PC infarcts, BA occlusion (BAO) is a neurological emergency burdened by $> 80\%$ fatality rate without treatment [34, 52]. 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 IV thrombolysis series, the rate of recanalization was 65%, and 30 of 116 patients (26%) had a good outcome (mRS 0–2) by 3 months [53]. A study by Strbian et al. on 184 patients with angiography-proven BAO treated with IV thrombolysis followed by full-dose heparin showed that recanalization of BAO produced good outcomes in 50% of patients without extensive baseline ischemia (pc-ASPECT ≥ 8) [54]. The same group in another study found a strong independent association between thrombus length and success of BAO recanalization [55]. However, they found that the probability of BAO recanalization was 30 to 50% even for patients with thrombus length between 20 and 30 mm [55].

Finally, high recanalization rate (78%) and good outcome (44% of patients independent at 3 months) have been shown also in patients with BAO treated with low-dose IV rtPA (0.6 mg/kg) [56].

Acute endovascular therapy

In the last years, the efficacy of endovascular therapy in ACI has been documented by many randomized controlled trials [57]. There are not many studies, however, proving the efficacy of this treatment in PC stroke and most of such studies focus on BAO. As well as for ACI, many endovascular procedures have been used to treat large vessel occlusion in PC strokes [58–60]. At the beginning, *intra-arterial (IA) thrombolysis* was attempted and it was associated with high recanalization rate in PCI ranging on average from 63 to 65% [52, 61]. Findings from uncontrolled and controlled studies have shown a correlation between angiographic evidence of BAO recanalization and favorable outcome, including improved survival [16, 62, 63]. However, the higher BAO recanalization rate obtained with IA thrombolysis compared with that achieved with IV thrombolysis does not seem associated with better functional outcome. The results of an analysis of 420 non-randomized patients with BAO treated with IA thrombolysis (82%) or with IV thrombolysis (18%) showed no significant differences between the two groups of patients in death, dependency, and favorable outcomes, although the recanalization rate was higher in patients treated with IA thrombolysis (65 vs 53%) [61]. *Mechanical thrombectomy* has been proven to achieve high recanalization rate for all target vessels [34]. In the last years, the so-called stent retrievers have been released. These new devices can be deployed within the clot, quickly removing the clot and restoring the blood flow once retrieved. They have been proven to be more effective than older devices and are nowadays most commonly used.

Between 2014 and 2015, 6 randomized controlled trials have been published showing superiority of systemic

fibrinolysis plus mechanical thrombectomy compared with systemic fibrinolysis alone in AC strokes [23, 24, 64–67]. In three pilot studies [59, 60, 68], a total of 29 patients with BAO were treated with endovascular procedures and a high recanalization rate was achieved (68–82%). However, clinical outcomes for BAO were reported adequately in only one trial [59]: seven of 16 patients (44%) had good outcomes (mRS 0–2) after 3 months and four (25%) died. In the same study, ten patients (62%) were treated with full-dose IV thrombolysis followed by rescue mechanical endovascular treatment. Jung et al. [16] compared the outcomes of 49 patients with BAO treated with IA thrombolysis from 1992 to 2003 with those of 57 individuals treated with mechanical thrombectomy, with or without intra-arterial urokinase, from 2004 to 2010. Better outcomes (respectively 52% vs 35%) and lower mortality (respectively 39% vs 43%) were recorded in patients treated from 2004 to 2010.

A prospective, observational study of patients with BAO—the BASICS (Basilar Artery International Cooperation Study) registry study [69]—compared the efficacy of antithrombotic treatment, systemic fibrinolysis, and intra-arterial therapies. 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 with the 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 with 63% of patients treated with IV thrombolysis and was associated with increased independency. Of note, almost 50% of recruited patients received intra-arterial therapies but only about a third of them received mechanical thrombectomy. Stent retrievers were not available during the recruitment period and were not used [69]. An ongoing randomized controlled trial, the BASICS trial, is trying to validate endovascular treatment for PCI [70]. The recruitment, however, is hampered by the reluctance of many clinicians, already convinced of endovascular treatment superiority, to randomize patients with BAO to receive IV thrombolysis only. More recently, two prospective studies of patients treated with endovascular procedures, the ENDOSTROKE study [71] and a single-center case series [20], reported good outcome (mRS 0–2) in up to 37% of treated patients, irrespective of stroke severity, and good recanalization in 79–89%. Functional independency (mRS 0–3) was achieved in up to 50% of patients. Gory and colleagues [72] analyzed patients with basilar stroke treated at their hospital with stent retrievers and performed a systematic review of published data. Good outcome occurred in 42% of cases and good recanalization in 81%. It is a matter of debate whether direct aspiration first-pass technique (ADAPT), performed with a large catheter, followed by mechanical thrombectomy in case of unsuccessful recanalization is superior to direct thrombectomy alone. The recently published

ASTER trial [73] showed that ADAPT in ACI was faster than mechanical thrombectomy but it was associated neither with increased reperfusion rate nor with a better outcome. A retrospective study [74] comparing the two approaches in patients with BAO showed a trend toward better recanalization with ADAPT compared with stent retriever with an unadjusted OR of 2.56, with lower groin-puncture-to-reperfusion time. The outcome in the two groups, however, was similar.

Finally, perfect timing for endovascular treatment in PCI is not well established. The recently published American Guidelines [42] suggest to perform mechanical thrombectomy in PCI only within 6 h from stroke onset. However, it looks reasonable, considering the poor prognosis associated with PCI, to extend such window, especially after advanced neuroimaging with CT or MRI [32]. As already mentioned, CT perfusion is not validated for such purpose, yet.

In-hospital management

Since it is widely demonstrated that stroke unit care is effective in reducing death and dependency in patients with acute stroke [75], it is not trivial to stress the need for patients with PCI to have fast access to such facility. Patients should be clinically monitored for signs of increased intra-cranial pressure such as headache, vomiting, lethargy, disorientation, or neurologic deterioration, as well as for evidence of irregular respiratory patterns. Cerebellar infarctions, in fact, can cause edema that generally peaks 3 to 5 days after infarction and may cause compression of the fourth ventricle, obstructive hydrocephalus, and/or herniation [76].

Patients should be placed on continuous cardiac monitoring to detect cardiac arrhythmias (i.e., atrial fibrillation) and tight blood pressure control. Patients with BAO may be particularly sensitive to changes in blood pressure [76].

Conclusion

PCI is a potentially life-threatening neurological emergency that requires high suspicion index.

Multimodal CT and MRI are useful tools in the acute setting to confirm the diagnosis of PCI and to improve the selection of candidates for intravenous thrombolysis or endovascular treatment. Straightforward evidences about superiority of mechanical thrombectomy over systemic fibrinolysis in PCI are still missing. Currently available literature data suggest that the use of new devices for endovascular therapy of basilar stroke ensures an increased recanalization rate associated with a good outcome and reduced mortality.

Author contributions Dr. Sparaco: study design, manuscript drafting/revising, and study supervision

Dr. Ciolli and Dr. Zini: manuscript drafting/revising

Compliance with ethical standards We performed a review of the literature about the state of art of vertebrobasilar stroke; therefore, our work involves neither human participants nor experiments on animals.

Conflict of interest Marco Sparaco reports no disclosures.

Ludovico Ciolli reports no disclosures.

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