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REVIEW

What drives progressive motor deficits in patients with acute pontine infarction?

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Abstract

Progressive motor deficits are relatively common in acute pontine infarction and frequently associated with increased functional disability. However, the factors that affect the progression of clinical motor weakness are largely unknown. Previous studies have suggested that pontine infarctions are caused mainly by basilar artery stenosis and penetrating artery disease. Recently, lower pons lesions in patients with acute pontine infarctions have been reported to be related to progressive motor deficits, and ensuing that damage to the corticospinal tracts may be responsible for the worsening of neurological symptoms. Here, we review studies on motor weakness progression in pontine infarction and discuss the mechanisms that may underlie the neurologic worsening.

***Key Words:** nerve regeneration; pontine infarction; progressive motor deficits; basilar artery; penetrating artery; corticospinal tract; Wallerian degeneration; review; neural regeneration*

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Introduction

The brainstem plays an essential role in controlling balance, coordinated movement, hearing, speech, eye movement and swallowing, and patients who have sustained brainstem infarction suffer from not only ataxia and dysphagia, but also paralysis, diplopia and dysarthria (Maeshima et al., 2012). Pontine infarctions are often part of a larger ischemic event involving the brainstem, either in isolation or as part of multilevel ischemia (Moncayo, 2012). Pontine infarctions constitute approximately 7% of all ischemic infarctions and 15% of acute vertebrobasilar ischemic strokes (Silverstein, 1964; Saia and Pantoni, 2009). Unilateral pontine infarctions usually manifest with lacunar syndromes, including pure motor stroke, ataxic hemiparesis or dysarthria clumsy hand (Kim et al., 1995, 2009; Bassetti et al., 1996; Oh et al., 2012). Progressive pure motor hemiparesis is a common feature in acute pontine infarction cases and is frequently associated with increased functional disability (Kunz et al., 2003; Oh et al., 2012). Numerous studies have examined the pathogenesis and etiology of the uniform clinical features; however, the pathological mechanisms underlying the clinical progression of motor deficits in pontine infarctions remain unclear. In this paper, we provide an overview of the current state of knowledge on the mechanisms underlying the development of progressive motor deficits in pontine infarction. Furthermore, we analyze the available data to provide insight into the pathogenesis of the common features and suggest therapeutic targets for combinatorial therapy.

Basilar artery and penetrating artery disease

Patients with unilateral pontine infarctions typically present a pure motor hemiparesis that generally progresses within 72 hours of onset and is accompanied by dysarthria and homolateral ataxia (Kunz et al., 2003). Basilar artery and related branch disease are the most common causes in patients with isolated pontine infarctions and are often correlated with a progressive condition (Fisher and Caplan, 1971; Kaps et al., 1997; Schmahmann et al., 2004; Yamamoto et al., 2011) and a relative frequency of about 40% (Ohara et al., 2010; Yamamoto et al., 2010). Furthermore, these patients have a worse prognosis than patients with lacunar pontine infarctions (Erro et al., 2005; Oh et al., 2012). A large retrospective study showed that basilar artery branch disease is the most common cause of stroke in patients with pontine infarction, and patients with basilar artery branch disease were found to have a worse short-term outcome (Kumral et al., 2002; Vemmos et al., 2005). Basilar artery stenosis was reported to be related to an increase in lesion volume in pontine infarctions (Karepov et al., 2006). High-resolution magnetic resonance imaging (MRI) in patients with pontine infarction identified atherosclerotic plaques in the basilar artery in more than 70% of cases. The relationships among the occurrence of basilar artery atherosclerotic disease, the increase in pontine lesion volume and clinical outcome have been analyzed by a number of researchers (Kim et al., 2009; Saia and Pantoni, 2009), which revealed that the occurrence of basilar artery atherosclerotic disease is significantly related to an increase in lesion volume in the subacute phase of stroke (Saia and Pantoni, 2009). Pontine infarcts extending to the surface of the pontine base associated with atheromatous plaque occlusions at the penetrating branch of the basilar artery have been described, and ensuing studies have shown that basilar artery branch disease is strongly correlated with atheromatosis of the

basilar arteries and a progressive course (Fisher and Caplan, 1971; Kaps et al., 1997; Kumral et al., 2002; Schmahmann et al., 2004; Kwon et al., 2009; Yamamoto et al., 2011; Ju et al., 2013). Yamamoto et al. (2011) showed that basilar artery atherosclerotic disease is strongly associated with progressive motor deficits and worse functional outcome in both the lenticulostriate artery and anterior pontine artery territories. The presence of basilar artery disease has an impact on lesion size, lesion volume and functional outcome in pontine base infarction patients (Kim et al., 2009). Progressive motor deficits are common in penetrating artery infarctions during the acute stage and sometimes lead to severe disability. Anterior pontine arteries are delicate vessels that branch acutely from the basilar artery and angle in a slightly caudal direction (Yamamoto et al., 2010). A study investigating progressive motor deficits in penetrating artery infarctions suggested that patients with infarctions topographically located within the territories of the anterior pontine arteries constitute about 29.0% of cases of progressive motor deficits (Yamamoto et al., 2010). Basilar artery branch atheromatous disease likely contributes to progressive motor deficits in patients with penetrating artery infarction.

Topographic location of pontine infarctions

In ischemic stroke, there is a gradual progression in neurological impairment leading to increased mortality and functional disability. Clinical deterioration was found to be more frequent in large vessel disease and in the vertebrobasilar arterial territory in a large retrospective analysis. These studies also suggest that the mechanisms involved in the development of ischemic damage are very complex, and that different mechanisms could be responsible for clinical deterioration in different etiologic subtypes and lesion locations (Yamamoto et al., 1998; Saia and Pantoni, 2009). However, only a few studies have focused on the topography of lesions in brainstem infarctions. In a study on isolated pontine infarction, neurologic worsening seemed to be more prevalent in patients with lesions extending to the basal surface of the pons, compared with patients with deep pontine lesions. Moreover, in the same study, clinical deterioration was positively correlated with large vessel disease and branch atheromatous disease (Watson and Colebatch, 2002; Saia and Pantoni, 2009). Oh et al. (2012) examined factors impacting the progression of motor weakness in pontine infarction cases during the acute phase, such as the presence of basilar artery stenosis and the location of the infarction. The authors found that lower pons lesions may contribute to progressive motor deficits in patients with acute pontine infarction. The infarct in the lower pons may affect the extent of ischemic degeneration in the corticospinal tract, leading to progressive motor deficits. Infarct topography is, therefore, a potential prognostic factor for progressive motor deficits. The location of the infarction was found to be a predictor of motor progression in subcortical infarct patients (Konishi et al., 2005; Kim et al., 2008; Oh et al., 2012). Subcortical infarctions are known to have similar causes as pontine infarctions. In the present study, our analysis revealed that lower pontine infarctions were significantly associated with progressive motor deficits in patients with acute pontine infarctions. In pure motor pontine infarcts, the topography of the infarct lesion has been reported to be related to prognosis; lesions causing severe hemiparesis are generally large and involve the ventral surface of the paramedian caudal or middle pons (Kim et al., 1995; Kataoka et al., 1997; Oh et al., 2012).

Corticospinal tract and Wallerian degeneration in the basis pontis

The classical mechanisms underlying pontine infarction cannot explain the majority of neurologic worsening (Saia and Pantoni, 2009). A previous study reported that basilar artery stenosis is only related to the subacute increase in lesion volume in pontine infarctions and not to neurological progression. Progression of motor deficits is unlikely to be caused by hemodynamic compromise related to basilar artery stenosis (Kim et al., 2009; Oh et al., 2012). The corticospinal tract is located in the center of the pontine basis, which is surrounded by transpontine fibers (Jang, 2011). The corticospinal tracts are situated in the dorsolateral part of the pontine base at the level of the upper pons (Kim and Pope, 2005; Ino et al., 2007; Yu et al., 2009; Jang, 2011). Therefore, infarcts in the lower pontine region may cause more damage to the corticospinal tracts than upper pontine region infarcts because of proximity (Oh et al., 2012).

Degeneration of distal axons and their myelin sheaths after proximal axonal or cell body injury is referred to as Wallerian degeneration, which occurs in both the peripheral and central nervous systems (Qin et al., 2012). In the early stage, axonal swelling and fragmentation with disruption of the myelin sheaths occur, followed by degradation of the myelin sheath and infiltration by macrophages and microglia. Wallerian degeneration of the fiber tract in the middle cerebellar peduncle after pontine infarction has been studied (Grassel et al., 2010; Qin et al., 2012). These studies suggest that Wallerian degeneration in the middle cerebellar peduncle may hinder neurological recovery following a focal pontine infarct. The degeneration of axons and their myelin sheaths after proximal axonal or cell body injury in fiber tracts distal to a focal cerebral infarct has been demonstrated in animal experiments and in postmortem studies, as well as by MRI and diffusion tensor imaging (Kobayashi et al., 2005; Gresle et al., 2006; Matsusue et al., 2007; Sylaja et al., 2007; Liang et al., 2009). In a Japanese-language study on autopsy of pontine lesions in the elderly, necrosis of the basis pontis, characterized by loss of myelin and axons, without reactive astrocytes or inflammatory cells, was found (Inagaki et al., 1996). Wallerian degeneration of the corticospinal and pyramidal tracts after motor pathway ischemic stroke can be characterized by diffusion tensor imaging. A prospective study on Wallerian degeneration of the corticospinal tract after paramedian pons infarction showed that Wallerian degeneration can be detected after the onset of symptoms (Forster et al., 2010; Grassel et al., 2010).

The basis pontis is anatomically unusual in both gray and

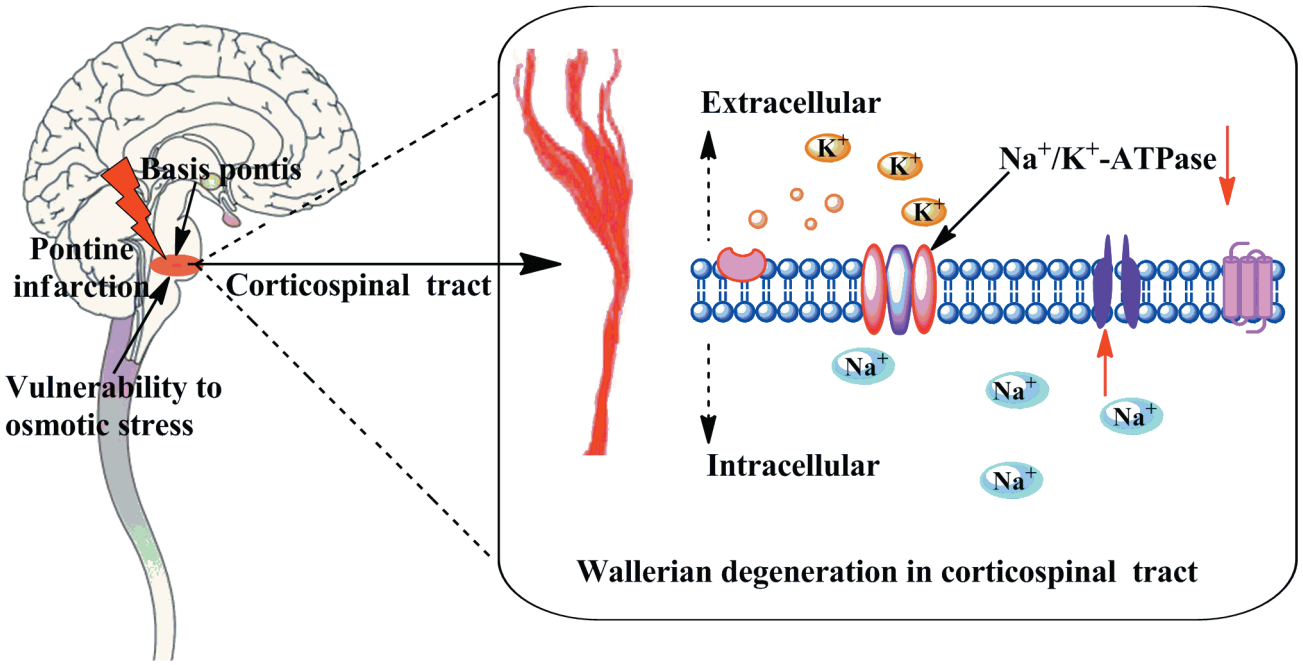

Figure 1 Schematic: The basis pontis may have a relatively higher vulnerability to osmotic stress, which can result in Wallerian degeneration of the corticospinal tract.

During the acute stage of pontine infarction, the reduction in cerebral blood flow and glucose and oxygen deprivation lead to the inhibition of the Na^+/K^+-ATPase and the perturbation of osmotic homeostasis. As a result of osmotic stress in the basis pontis, secondary degeneration of axons and demyelination occur. This may contribute to the progressive motor deficits observed in patients with pontine infarctions.

white matter, and this feature is presumed to account for the vulnerability of this area to perturbations in ionic and osmotic homeostasis (Park and Jung, 2010; Hurley et al., 2011). The reduction of cerebral blood after ischemia initially causes oxygen and glucose deprivation and acute cell death, eventually leading to an infarct core.

Central myelinated axons are critically dependent on a continuous supply of oxygen and glucose (Dirnagl et al., 1999; Stys, 2004; Nanetti et al., 2008). Na^+/K^+-ATPase is an integral membrane protein that plays a key role in cellular osmotic regulation through the maintenance of the transmembrane Na^+ and K^+ gradients, and is responsible for the maintenance of ionic homeostasis in both astrocytes and neurons. (D'Ambrosio et al., 2002). Accumulating evidence supports a key role of energy deficiency and dysfunction of the Na^+/K^+-ATPase in ischemia-induced cell volume changes and cell death. In a focal cerebral infarct, degeneration of associated fiber tracts and neuronal damage have been shown to be related to a disruption in ionic homeostasis resulting from reduced energy metabolism (Fuller et al., 2003).

Conclusions and perspective

During the acute phase of pontine infarction, cerebral blood flow is reduced, resulting in oxygen and glucose deprivation, which leads to neuronal necrosis. We hypothesize that the inhibition of the Na^+/K^+-ATPase leads to intracellular Na^+ overload and the perturbation of osmotic homeostasis. As a result of osmotic stress in the basis pontis, Wallerian degeneration of the corticospinal tract occurs after the onset of symptoms. This may underlie the progressive motor deficits in pontine infarctions. The hypothesis is summarized schematically in **Figure 1**.

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Conflicts of interest: *None declared.*

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