Case report

Recurrent thrombolysis of a stuttering lacunar infarction captured on serial MRIs

Imama Naqvi, Alexis N. Simpkins, Kaylie Cullison, Emily Elliott, Dennys Reyes, Richard Leigh, John K. Lynch

ARTICLE INFO

Keywords:
Thrombolysis
Ischemic stroke
Lacunar infarct
MRI
Small vessel disease
Rapidly improving stroke symptoms
Ischemic tolerance

ABSTRACT

Lacunar strokes account for about a fourth of all ischemic strokes. Pontine infarcts often present with stuttering symptoms, referred to as pontine warning syndrome (PWS). Patients presenting with fluctuating symptoms can appear to have rapidly improving symptoms and thus often go untreated despite the risk of recurrent deficits. MRI carries a higher sensitivity in detecting posterior circulation strokes compared to computed topagraphy, but does not always indicate irreversible injury. Here we present the first description of a stuttering lacune, captured radiographically on serial magnetic resonance imaging (MRI), that was initially averted with the administration of intravenous (IV) tissue plasminogen activator (tPA), only to return a month later and progress on imaging despite re-administration of tPA. During the first admission, our patient had spontaneous resolution of symptoms with complete reversal on restricted diffusion soon after IV tPA administration. On the second admission, the stuttering symptoms returned as did the same pontine lesion. Although his stuttering lesions lasted for several days, and the pontine lesion did ultimately progress to partial infarction on MRI, he was discharged home without neurologic deficits. Our case suggests that tPA may be of benefit in patients with lacunar pontine strokes even if symptoms rapidly improve or resolve.

1. Introduction

A 77-year-old man with a history of hypertension, hyperlipidemia, coronary artery disease, and a recent coronary artery bypass graft (CABG) presented with acute onset left side weakness, slurred speech, and dizziness (NIHSS = 8) 66 min after last seen normal. Consideration for thrombolysis with brain magnetic resonance imaging (MRI) showed restricted diffusion and decreased perfusion in the right medial pons (Figs. 1 and 2A). Intravenous (IV) tissue plasminogen activator (tPA) was administered 110 min after symptom onset. Within 30 min of initiating thrombolysis, his NIHSS decreased to 2. MRI obtained shortly after IV tPA infusion revealed resolution of the re-appearance of the previously seen right pontine diffusion and perfusion lesions (Fig. 2C and D). During the hospital stay, the patient had 3 episodes of clinical worsening lasting between 30 min to several hours. His blood pressure during both the initial and second admission ranged from a systolic of 130–160’s and a diastolic of 80–100’s. There was no correlation between the re-occurrence of symptoms and the patient’s blood pressure. However, he did seem to respond to intravenous fluid bolus with normal saline.

The patient was discharged home without neurologic deficits. An MRI at discharge showed hyperintensity on diffusion imaging with a...
corresponding FLAIR lesion and persistent perfusion deficit. A week after discharge, the patient reported no further re-occurrence of his symptoms.

2. Background

Lacunar strokes account for about a fourth of all ischemic strokes. Fisher first demonstrated that lacunar infarcts can be the result of a single perforating artery occlusion [1]. Compared to non-lacunar strokes, lacunar strokes occur in younger patients with lower National Institutes of Health Stroke Scale (NIHSS) resulting in lower 90-day modified Rankin scale (mRS) and mortality rates [2–4]. Incidence of lacunar pontine lacunar infarcts is unknown, but approximately 15% of acute vertebrobasilar infarcts are pontine, commonly caused by lipohyalinosis of the paramedian basilar arteries [5].

Pontine infarcts often present with stuttering symptoms that resolve approximately 1 h after thrombolysis was given, but the perfusion deficit persisted (D). By the time of discharge, the patient was still clinically asymptomatic despite having a persistent perfusion deficit for 4 days and a diffusion lesion evident on the FLAIR.
and return over time, referred to as pontine warning syndrome (PWS) [5–7]. The clinical presentation of pontine lacunar syndromes can be variable despite corresponding to the same anatomical location [7]. MRI carries a higher sensitivity in detecting posterior circulation strokes compared to CT, but the presence of hyperintensity on diffusion weighted imaging (DWI) or hypointensity on apparent diffusion coefficient (ADC) does not always indicate irreversible injury [7,8]. In our case, reversibility of the restricted diffusion occurred with resolution of the perfusion deficit.

Patients presenting with fluctuating symptoms can appear to have rapidly improving symptoms and thus often go untreated despite the risk of recurrent deficits. There is limited literature on benefits of treating pontine infarcts, but one large cohort study found IV tPA to be beneficial for lower discharge mRS in lacunar stroke [9]. Moreover, another study found that in patients deemed “too good to treat,” those who went untreated, were more likely to have poor outcome than those that were treated with IV tPA [10].

Repeated treatment with IV tPA for recurrent stroke is rare. However, a small study of 19 patients with repeated IV tPA administration for recurrent stroke within 3 months did not report any symptomatic intracranial hemorrhages [11].

3. Discussion

Here we present the first description of a stuttering lacunar, captured on MRI, that was initially averted with the administration of IV tPA, only to return a month later and progress on imaging despite re-administration of tPA. The early time course of this case is very similar to a previous case we reported [5]; for both patients, there was complete reversal of the clinical and radiographic appearance of a lacunar stroke within hours. However, the previous patient (first case) was not treated during either admission while the current patient (second case) received IV tPA at both time points. Although both patients had a return of the diffusion lesion, the first case recurred within days while the second case’s recurrence was avoided for a month. With MR imaging, it was possible to capture the stuttering nature of lacunar strokes along its natural history, and contrast this with the clinical symptoms in the presence of acute IV tPA administration. This draws attention to the underlying pathophysiology of lacunar stroke.

Lacunar syndromes result from small vessel disease. Basilar artery branch disease represents a common mechanism of isolated pontine stroke. The underlying pathophysiology of this type of pontine lacunar infarction can occur secondary to micro-embolization from an atheromatous plaque in the ostium of a pontine penetrator, direct disease of the occluded vessel due to lipohyalinosis, a non-thrombotic occlusive disease, or from thrombosis of the vessel [1,12]. It is also possible that some combination of these pathologies was present in our patient. Despite a thorough investigation, we did not find evidence of significant vertebrobasilar disease, so we believe the pathology of the stroke is likely small vessel disease or a combination of lipohyalinosis and micro-embolization.

As described previously, pontine warning syndrome occurs when a patient has recurrent stereotyped episodes of posterior circulation associated neurological symptoms such as motor or sensory dysfunction, dysarthria or ophthalmoplegia that herald basilar artery branch stroke causing permanent deficits [13]. This also resembles capsular warning syndrome described in the anterior circulation where angioPATHY of a single penetrating vessel such as lenticulostriate branches are implicated [14].

Another intriguing aspect of this case is the lack of deficits on hospital discharge, despite fluctuating clinical symptoms during his second admission and imaging evidence of infarction in the pons. During the first admission, our patient had spontaneous resolution of symptoms with complete reversal on restricted diffusion soon after IV tPA administration. He did not present again till a month later with recurrent symptoms. The second time he had a stuttering course but ultimately complete neurological recovery despite sustaining partial infarction in the pons on diffusion imaging with corresponding FLAIR and persistent perfusion deficit, as noted on post treatment images. One possible mechanism for his clinical outcome is ischemic tolerance [15].

Ischemic preconditioning has been shown to protect against cerebral ischemia in animal models and has gained interest as a possible neuroprotective mechanism in humans. Furthermore, tPA has been shown to have neuroregenerative effects such as protection of cerebral cortical neurons from oxygen and glucose deprivation induced cell death, which may have contributed to our patient’s complete clinical recovery [16].

Multiple studies have shown a beneficial effect of treating lacunar stroke with tPA [17,18]. However, the benefit of thrombolysis in mild stroke and lacunar stroke is debated. A large registry reported that 61% of tPA eligible patients were not offered tPA due to mild or rapidly improving symptoms, but these patients had worse clinical outcomes than patients given tPA on case-matched analysis [10]. In a large Canadian case-cohort study, lacunar stroke patients that received thrombolysis were more likely to be discharged home and independent [9]. A recent study that closed early to not meeting the enrollment target was the Study of the Efficacy and Safety of Alteplase in Participants with Mild Stroke (PRISMS) [19]. No difference was found between aspirin and thrombolysis in the PRISMS clinical trial, but unlike our case, MRI was not required for patient selection.

4. Concluding remarks

This case, captured on serial MRI, highlights a dynamic clinical outcome of a stuttering pontine stroke in the setting of repeated treatment with IV thrombolysis. It suggests that tPAs should be considered in patients with lacunar pontine strokes even if they are rapidly improving or clinically resolved.

Author contributions

IAN and ANS collected data, drafted, edited and equally contributed to the manuscript. KC contributed to draft and editing of the manuscript. EE contributed to draft of the manuscript. DR contributed to the editing of manuscript. JKL and RL critically revised the manuscript. All authors made contributions to conception and interpretation of the case presentation.

Sources of funding/research study

I.A. Naqvi, A.N. Simpkins, K. Cullison, D. Reyes, R. Leigh and J.K. Lynch are supported by the Intramural Program of NIH, NINDS. The patient was consented and enrolled in the NINDS Intramural Study (01-N-0007).

Disclosures

The authors report no disclosures.

References

[1] C.M. Fisher, The arterial lesions underlying lacunes, Acta Neuropathol. 12 (1) (1968) 1–15.
[2] Y. Yang, A. Wang, X. Zhao, et al., The Oxfordshire Community Stroke Project classification system predicts clinical outcomes following intravenous thrombolysis: a prospective cohort study, Ther. Clin. Risk Manag. 12 (2016) 1049–1056.
[3] S. Sacco, C. Marini, R. Totaro, et al., A population-based study of the incidence and prognosis of lacunar stroke, Neurology 66 (9) (2006) 1335–1338.
[4] I. Miedema, G.J. Luijckx, R. Brouns, et al., Admission hyperglycemia and outcome after intravenous thrombolysis: is there a difference among the stroke-subtypes? BMC Neurol. 16 (2016) 104.
[5] A. Enríquez-Murulanda, P. Amaya-González, J.L. Orozco, Pontine warning syndrome: a chameleone of ischemic stroke, Neurologist 21 (6) (2016) 93–96.
[6] J. Oliveira-Filho, H. Ay, W.J. Kornshetz, et al., Localization of clinical syndromes using DWI: two examples of the ‘capsular’ warning syndrome, J. Neuroimaging 11 (1) (2001) 44–47.
[7] J. Benito-Leon, J. Alvarez-Linera, J. Porta-Etessam, Detection of acute pontine infarction by diffusion-weighted MRI in capsular warning syndrome, Cerebrovasc. Dis. 11 (4) (2001) 350–351.

[8] P. Tahsili-Fahadan, A.N. Simpkins, R. Leigh, et al., Stuttering lacunar infarction captured on serial MRIs, Neurol. Clin. Pract. 6 (5) (2016) e37–e39.

[9] N. Shohda, J. Fang, M.D. Hill, Do lacunar strokes benefit from thrombolysis? Evidence from the registry of the Canadian Stroke Network, Int. J. Stroke 8 (2013) 45–49 Suppl A100.

[10] S.F. Ali, K. Siddiqui, H. Ay, et al., Baseline predictors of poor outcome in patients too good to treat with intravenous thrombolysis, Stroke 47 (12) (2016) 2986–2992.

[11] T. Kahles, M.L. Mono, M.R. Heldner, et al., Repeated intravenous thrombolysis for early recurrent stroke: challenging the exclusion criterion, Stroke 47 (8) (2016) 2133–2135.

[12] J.M. Wardlaw, What causes lacunar stroke? J. Neurol. Neurosurg. Psychiatry 76 (5) (2005) 617–619.

[13] G. Saposnik, L. Noel de Tilly, L.R. Caplan, Pontine warning syndrome, Arch. Neurol. 65 (10) (2008) 1375–1377.

[14] G.A. Donnan, H.M. O’Malley, L. Quang, et al., The capsular warning syndrome: pathogenesis and clinical features, Neurology 43 (5) (1993) 957–962.

[15] J.D. Bernstock, L. Peruzzotti-Jametti, D. Ye, et al., Neural stem cell transplantation in ischemic stroke: a role for preconditioning and cellular engineering, J. Cereb. Blood Flow Metab. 37 (7) (2017 Jul) 2314–2319.

[16] M. Yepes, Tissue-type plasminogen activator is a neuroprotectant in the central nervous system, Front. Cell. Neurosci. 9 (2015) 304.

[17] National Institute of Neurological Disorders Stroke rt PASSG, Recombinant tissue plasminogen activator for minor strokes: the National Institute of Neurological Disorders and Stroke rt-PA Stroke Study experience, Ann. Emerg. Med. 46 (3) (2005) 243–252.

[18] S. Lahoti, S. Gokhule, L. Caplan, et al., Thrombolysis in ischemic stroke without arterial occlusion at presentation, Stroke 45 (9) (2014) 2722–2727.

[19] P. Khatri, D.O. Kleindorfer, T. Devlin, et al., Effect of alteplase vs aspirin on functional outcome for patients with acute ischemic stroke and minor nondisabling neurologic deficits: the prisms randomized clinical trial, JAMA 320 (2) (2018) 156–166.