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Can we stop the stuttering in stroke? Interventions in 40 patients with acute lacunes

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ABSTRACT

Background: Whether any treatment can stop fluctuations of stuttering lacunar syndromes (SLS) is unclear. Case reports have variably suggested effectiveness of intravenous thrombolysis, dual antiplatelet treatment, blood pressure augmentation and anticoagulation. We aim to describe our experience with different treatments used in in patients presenting with SLS and their effect on clinical fluctuations and functional outcome.
Methods: We collected demographic and clinical data of consecutive adult patients with SLS. Descriptive summaries were reported as median and inter-quartile range (IQR) for continuous variables and as frequencies and percentages for categorical variables.
Results: Forty patients (72 ± 10 years, 36% female) were included. Pure motor syndrome (57%) was the most frequent clinical presentation. Clinical fluctuations stopped and the improvement was temporally related to aspirin-clopidogrel in 11/17 cases, intravenous thrombolysis in 4/6 cases, blood pressure augmentation in 1/3 cases and aspirin in 1/7 cases. Two patients continued fluctuating after IVT and later responded to blood pressure augmentation (n = 1) or aspirin-clopidogrel (n = 1).
Conclusions: Aspirin plus clopidogrel may be followed by clinical improvement when intravenous thrombolysis is not an option. Blood pressure augmentation may beneficial as ad-on treatment in patients with labile blood pressure.

1. Introduction

Lacunar strokes (LS) are small subcortical infarcts caused by occlusion of a single penetrating branch of a larger cerebral artery [1] and account for 15–26% of all ischemic strokes. [2,3] Microatheroma of small penetrating arteries is the main pathologic mechanism of LS with a possible contribution of microembolism, endothelial dysfunction and hypoperfusion. [1,4,5] In a minority of patients, LS symptoms fluctuate, a condition known as capsular warning or stuttering lacunar syndrome (SLS). [6] SLS represent only 1.5% of transient ischemic attack presentations but have a poor prognosis, with a 7-day stroke risk of 60%. [7]

The pathophysiology underlying a SLS presentation is unknown. Whether any treatment can stop stuttering episodes is also unclear. Given the rarity of this condition, available data are limited to case reports and small case series proposing different therapeutic approaches, including intravenous thrombolysis (IVT) [8–10], dual antiplatelet treatment [11–13], blood pressure augmentation [14,15] and anticoagulation [16].

The aim of this study is to describe the different treatments used in our experience with patients presenting with SLS and their effect on clinical fluctuations and overall outcome.

2. Materials and methods

2.1. Definitions

Pure motor syndrome, pure sensory syndrome, sensory-motor syndrome, dysarthria and clumsy hand or ataxic-hemiparesis were considered lacunar syndromes. Brainstem or subcortical hemispheric infarcts with a maximal diameter of < 1.5 cm were considered lacunar strokes. SLS was defined as a neurologic deficit that developed and had periods of improvement and worsening (with or without full resolution between episodes) with a maximum interval between discrete periods

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of worsening shorter than 24 h. We considered that a treatment was possibly effective when 1) fluctuations stopped and the severity of the residual deficits was milder than the severity the deficits upon the worst fluctuation, 2) the improvement was chronologically related to the intervention and 3) the treating physician unequivocally documented the improvement.

2.2. Patient selection

Adult patients (≥ 18 years of age) with acute ischemic stroke receiving care on an inpatient neurology service between 2007 and 2016 in whom physician notes included the terms lacune, lacunar, stutter, stuttering, rapidly-resolving or capsular were identified from Saint Mary's Hospital electronic data base. Resultant medical records were manually screened, and patients with SLS included in the study. Pure sensory syndromes were excluded due to the difficulty of objectively assess clinical response of subjective symptoms. Demographic data, including age, gender, vascular risk factors, number of stuttering episodes, outpatient medications, imaging findings, inpatient treatment provided, response to treatment, and National Institute of Health Stroke Scale (NIHSS) on admission and discharge were assessed. This study was approved by the institutional review board at Mayo Clinic.

2.3. Statistical analysis

Descriptive summaries were reported as median and inter-quartile range (IQR) for continuous variables and as frequencies and percentages for categorical variables.

3. Results

Our initial search yielded 575 unique patient records, which were then manually reviewed for evidence of a SLS presentation. Half of patients with stuttering presentations had non-lacunar strokes. (Fig. 1) The manual review resulted in the identification of 44 patients with SLS presentation. Four patients were subsequently excluded because the presentation was a pure sensory syndrome ($n = 2$) or because brain imaging demonstrated larger infarctions (subcortical infarcts > 1.5 cm). Hence, 40 patients were included in the study.

The mean age was 72 ± 10 years. Fourteen patients (36%) were female. The most frequent pre-existing vascular risk factors were hypertension (77%) and dyslipidemia (58%). At the time of the ictus 19 patients were on antithrombotic drugs and 12 were on statins. Most patients presented with pure motor syndrome (57%) or sensory motor syndrome (30%). Median NIHSS at presentation was 3 [IQR 1–6]. Twenty-eight patients (70%) had three or more clinical fluctuations (Table 1).

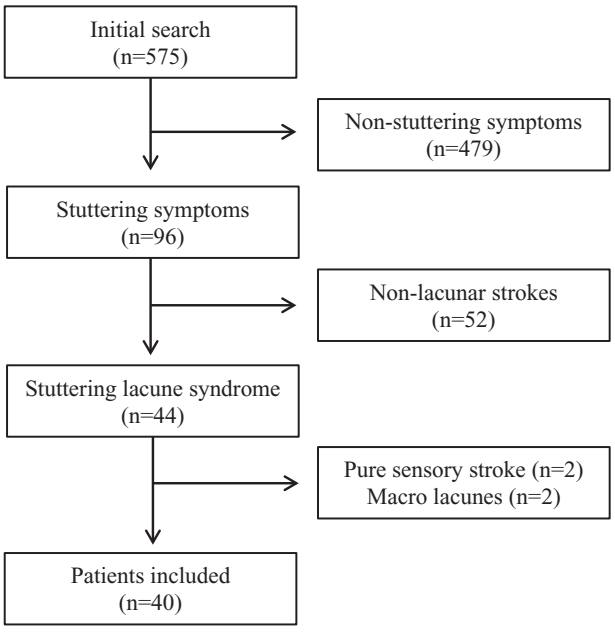

Fig. 1. Patients' flowchart.

Table 1
Demographics and clinical characteristics.

Demographics	
Gender, female (%)	14 (35)
Age, median (SD)	70 (10)
Vascular risk factors	N, (%)
Hypertension	31 (77)
Diabetes	10 (25)
Dyslipidemia	22 (55)
Coronary artery disease	5 (13)
Atrial fibrillation	2 (5)
Tobacco Use	9 (23)
Obstructive sleep apnea	3 (8)
Metabolic syndrome	2 (5)
Alcoholism	3 (8)
History of stroke/TIA	9 (23)
Obesity	2 (5)
Pre-Admission Medications	N, (%)
Aspirin	17 (44)
Aspirin-clopidogrel	1 (2.5)
Clopidogrel	0
Warfarin	1 (2.5)
Apixaban	1 (2.5)
Statins	8 (20)
Lacunar syndrome	N (%)
Pure motor	23 (57)
Motor sensory	12 (30)
Ataxia hemiparesis	4 (10)
Dysarthria clumsy hand	1 (3)
Initial NIHSS, median (range)	3 (0 − 12)
Discharge NIHSS, median (range)	1 (0 − 10)
Number of fluctuations	N, (%)
2	12 (30)
3	12 (30)
≥ 4	16 (40)

Half of patients ($n = 20$) received dual antiplatelet treatment, followed by single antiplatelet treatment ($n = 9$) and intravenous thrombolysis ($n = 6$). (Table 2) Dual antiplatelet treatment consisted on aspirin plus clopidrogrel in most cases ($n = 17$). A loading dose of 300 mg of clopidogrel was administered along with aspirin in all cases. Except for one patient who had a gastrointestinal bleeding requiring transfusion of blood products, all patients who received aspirin plus

Table 2
Initial treatment and clinical response.

Initial treatment (N, %)	Improvement related to treatment*
Dual antiplatelet (20, 50%)	
Aspirin + clopidogrel (17, 42%)	11
Aspirin + dipyridamole (3, 8%)	0
Single Antiplatelet (11, 28%)	
Aspirin (7, 64%)	1
Dipyridamole (2, 18%)	0
Clopidogrel (1, 9%)	0
Aspirin + BP augmentation (1, 9%)	1
Aspirin and heparin (3, 8%)	0
Thrombolysis (6, 15%)	
tPA alone (4, 66%)	4
tPA + BP augmentation (1, 17%)	1
tPA + dual antiplatelet (1,17%)	1

BP: blood pressure; tPA: tissue plasminogen activator.
* Refer to Methods for the definition of clinical improvement.

clopidogrel were discharged on this treatment. The patient who experienced the gastrointestinal bleeding was kept on aspirin alone. All patients who received IVT ($n = 6$) had experienced two clinical fluctuations and the symptoms were considered disabling at the time of treatment. Most patients who did not receive IVT had experienced 3 ($n = 11$) or ≥ 4 ($n = 15$) clinical fluctuations. Initial NIHSS was similar in patients who received IVT and those who did not (median 3, IQR 1–5).

The severity of the stroke deficits upon stabilization was milder than the severity at the time of worst fluctuation in 28 patients (70%). In 19 of them, clinical fluctuations stopped and the improvement was temporally related to a single therapeutic intervention: aspirin-clopidogrel ($n = 11$), IVT ($n = 4$), blood pressure augmentation (n = 1) and aspirin (n = 1). Two patients continued fluctuating after IVT and later responded to blood pressure augmentation (n = 1) or aspirin-clopidogrel (n = 1). (Table 2) Both patients who had clinical response to blood pressure augmentation had labile blood pressure along with symptom fluctuation.

A follow-up CT scan of the head was performed in 38 patients. It showed the culprit lesion in a minority of cases located in the pons ($n = 2$) and internal capsule ($n = 2$). Brain MRI was performed in 36 patients and revealed LS in the pons ($n = 4$), corona radiata ($n = 2$), and thalamus or internal capsule ($n = 26$). MRI was normal in 4 patients, all of whom had experienced 3 clinical fluctuations before their symptoms resolved shortly after the administration of aspirin plus clopidogrel.. The median NIHSS of the entire cohort at hospital discharge was 1 (range 0–10). Seven patient had a NIHSS > 4 at discharge. They were treated with aspirin ($n = 3$), dipyridamole ($n = 1$), clopidogrel (n = 1) and a combination of aspirin and blood pressure augmentation (n = 1).

4. Discussion

Patients with suspected SLS should be carefully evaluated since stuttering lacunes can be mimicked by non-lacunar strokes, including large vessel disease [17] (Fig. 1). The treatment of stuttering lacunes is challenging and data to guide it are scant. Small case series and case reports have proposed different therapeutic approaches including IVT [8–10], dual antiplatelet treatment with aspirin and clopidogrel [11–13], intravenous heparin [16], clopidogrel alone [18], and blood pressure augmentation. [14,15] This therapeutic heterogeneity may reflect the low frequency of SLS, their particular clinical characteristics (i.e. rapidly improving and fluctuating symptoms, low NIHSS at presentation and mild deficits followed by new worsening that occurs beyond the 4.5-h window) and complex pathophysiology which includes lipohyalinosis or atheromatosis of small penetrating arteries (with or without superimposed thrombosis) and hemodynamic factors such hypoperfusion and hemorheologic changes [17].

To our knowledge, this is the largest series of patients with SLS and the first study addressing whether any therapeutic approach can stop stuttering episodes in these patients. We found that two interventions were possibly effective in 65% of recipients each: IVT and the combination of aspirin and clopidogrel. Blood pressure augmentation was effective as ad-on treatment only in a minority of patients with labile blood pressure along with the fluctuating symptoms. Intravenous heparin, single antiplatelet treatment and the combination of aspirin and dipyridamole appeared to be less effective options. Comparable to a prior series, our patients had a low NIHSS at discharge. [19] Remarkably, none of the patients with higher NIHSS at discharge (> 4) had received IVT or aspirin plus clopidogrel. These results are novel and clinically relevant because 1) they suggest that, besides IVT, a load with aspirin and clopidogrel may have a role in the treatment of acute lacunar stroke, and 2) provide clinical guidance to help treat individual patients who present with a SLS.

Intravenous thrombolysis is the mainstay for acute stroke treatment within 4.5 h of symptom onset [7]. Subgroup analyses of clinical trials have demonstrated benefit of IVT in patients with strokes caused by small vessel disease [20]. Our study adds to prior reports on the effectiveness of IVT to stop stuttering in patients with SLS [8–10,17], which might be explained by recanalization of occluded penetrating arteries. In this setting, IVT should be the therapeutic choice when patients with SLS present within the therapeutic time window with disabling symptoms.

Dual antiplatelet therapy and blood pressure augmentation appear as reasonable options for those patients who are not suitable candidates for IVT or keep stuttering despite IVT. These options could be particularly effective when systemic hemorheologic changes or hypoperfusion underlie the stuttering presentation.

The combination of aspirin and clopidogrel blocks platelet aggregation through the P2Y12-receptor, prostaglandin and thromboxane A2 pathways. This dual therapy has been more effective than aspirin alone as secondary prevention strategy in acute coronary syndromes [21] and minor ischemic stroke or high-risk TIA. [22] In our experience, this approach appeared effective for the acute treatment of SLS, as it was chronologically associated with resolution of the clinical fluctuations in most of the recipients. Remarkably, the only four patients who did not have an acute radiographic infarction on the follow-up MRI received the combination of aspirin and clopidogrel. While this approach is reasonable for patients who are not candidates for IVT, its administration within 24 h of IVT is controversial due to a potential increase in the risk of bleeding. Current guidelines recommend the initiation of antiplatelet therapy 24 h after IVT, but the timing should be individualized, balancing the risks of ongoing ischemia and the potential for severe bleeding versus the potential benefit of early treatment [23]. In our study, aspirin and clopidogrel were administered within 24 h of IVT in one patient with good results and no complications. Data on the safety of antiplatelet therapy in the first 24 h of IVT are scant with only one single center study, limited by its observational and retrospective nature, reporting no increased risk of hemorrhage with early antiplatelet therapy or anticoagulation [24]. Additionally, there is one other report of a patient with stuttering symptoms who was treated with IVT and dual antiplatelet agents without complications. [25]

Blood pressure augmentation was used as add-on treatment in only two patients who had stuttering episodes accompanied by fluctuations of their blood pressure. Blood pressure fluctuation has been uniformly present in all prior reports of benefit from blood pressure augmentation for SLS. [14,15] Therefore, a trial of blood pressure augmentation may be considered when patients are hypotensive or have documented hemodynamic fluctuation in relation with the stuttering neurological deficits.

Our study has limitations. Our retrospective design and the small size of our cohort only allow us to present a descriptive analysis of clinical observations. Treatment effectiveness was defined as a binary outcome based on the timing of clinical improvement and the clear documentation of such improvement by the treating physician. We acknowledge that this definition may be imprecise but we were unable to use a more specific definition because of the low NIHSS scores in most cases (i,e. using the standard change of 2 points in the NIHSS would have classified several patients as having no improvement despite the occurrence of frank clinical improvement according to the treating physician). There is no way to know if the resolution of the fluctuations with deficits milder than those at nadir was actually related to the treatment administered rather than the natural history of the syndrome due to the small sample and the lack of control arm. Thus, we cannot make any conclusive claims of therapeutic effectiveness.

5. Conclusions

SLS are infrequent and their clinical characteristics may defy a uniform therapeutic approach. IVT should be the mainstay of treatment within 4.5 h of symptom onset. In patients who are not candidates for

IVT, our experience suggests that the acute administration of with aspirin and clopidogrel may be followed by clinical improvement. Blood pressure augmentation may benefit a subgroup of patients with SLS and labile blood pressure. In the absence of clinical trial data particularly applicable to patients with SLS, our findings may help guide individualized treatment for these patients.

Conflict of interest statement

The authors have nothing to disclose.

References

[1] C.M. Fisher, Lacunar strokes and infarcts: a review, Neurology 32 (8) (1982) 871–876.
[2] A. Chamorro, R.L. Sacco, J.P. Mohr, M.A. Foulkes, C.S. Kase, T.K. Tatemichi, et al., Clinical-computed tomographic correlations of lacunar infarction in the stroke data Bank, Stroke 22 (2) (1991) 175–181.
[3] S. Sacco, C. Marini, R. Totaro, T. Russo, D. Cerone, A. Carolei, A population-based study of the incidence and prognosis of lacunar stroke, Neurology 66 (9) (2006) 1335–1338.
[4] L.R. Caplan, Intracranial branch atheromatous disease: a neglected, understudied, and underused concept, Neurology 39 (9) (1989) 1246–1250.
[5] J.M. Wardlaw, C. Smith, M. Dichgans, Mechanisms of sporadic cerebral small vessel disease: insights from neuroimaging, The Lancet Neurology 12 (5) (2013) 483–497.
[6] G.A. Donnan, H.M. O'Malley, L. Quang, S. Hurley, P.F. Bladin, The capsular warning syndrome: pathogenesis and clinical features, Neurology 43 (5) (1993) 957–962.
[7] N.L. Paul, M. Simoni, A. Chandratheva, P.M. Rothwell, Population-based study of capsular warning syndrome and prognosis after early recurrent TIA, Neurology 79 (13) (2012) 1356–1362.
[8] R.M. Vivanco-Hidalgo, A. Rodriguez-Campello, A. Ois, G. Cucurella, C. Pont-Sunyer, M. Gomis, et al., Thrombolysis in capsular warning syndrome, Cerebrovascular diseases (Basel, Switzerland) 25 (5) (2008) 508–510.
[9] R. Tassi, A. Cerase, M. Acampa, P. D'Andrea, F. Guideri, G. Lo Giudice, et al., Stroke warning syndrome: 18 new cases, J. Neurol. Sci. 331 (1) (2013) 168–171.
[10] A. Gonzalez Hernandez, O. Fabre Pi, J.C. Lopez Fernandez, S. Diaz Nicolas, Thrombolysis in capsular warning syndrome, Medicina clinica 134 (13) (2010) 612–613.
[11] T. Asil, N. Ir, F. Karaduman, B. Cagli, S. Tuncel, Combined antithrombotic treatment with aspirin and clopidogrel for patients with capsular warning syndrome: a case report, Neurologist 18 (2) (2012) 68–69.
[12] C.D. Fahey, M.J. Alberts, R.A. Bernstein, Oral clopidogrel load in aspirin-resistant capsular warning syndrome, Neurocrit. Care. 2 (2) (2005) 183–184.
[13] H. Kawano, M. Nakajima, Y. Inatomi, T. Yonehara, Y. Ando, Loading dose of clopidogrel in combination with other antithrombotic therapy for capsular warning syndrome, J. Stroke Cerebrovasc. Dis. 23 (5) (2014) 1265–1266.
[14] P.H. Lalive, I. Mayor, R. Sztajzel, The role of blood pressure in lacunar strokes preceded by TIAs, Cerebrovasc. Dis. 16 (1) (2003) 88–90.
[15] F. Ladeira, R. Barbosa, S. Calado, M. Viana-Baptista, Capsular warning syndrome: the role of blood pressure, J. Neurol. Sci. 381 (2017) 20–21.
[16] B.H. Dobkin, Heparin for lacunar stroke in progression, Stroke 14 (3) (1983) 421–423.
[17] O. Ozdemir, V. Beletsky, R. Chan, V. Hachinski, Thrombolysis in patients with marked clinical fluctuations in neurologic status due to cerebral ischemia, Arch. Neurol. 65 (8) (2008) 1041–1043.
[18] E.B. Marsh, R.H. Llinas, Stuttering Lacunes: An Acute Role for Clopidogrel, Journal of neurology & translational neuroscience 2 (1) (2014).
[19] P. Camps-Renom, R. Delgado-Mederos, A. Martinez-Domeno, L. Prats-Sanchez, E. Cortes-Vicente, M. Simon-Talero, et al., Clinical characteristics and outcome of the capsular warning syndrome: a multicenter study, Int. J. Stroke 10 (4) (2015) 571–575.
[20] Group TNt-PSS, Generalized efficacy of t-PA for acute stroke. Subgroup analysis of the NINDS t-PA stroke trial, Stroke 28 (11) (1997) 2119–2125.
[21] A.D. Bowry, M.A. Brookhart, N.K. Choudhry, Meta-analysis of the efficacy and safety of clopidogrel plus aspirin as compared to antiplatelet monotherapy for the prevention of vascular events, Am. J. Cardiol. 101 (7) (2008) 960–966.
[22] S.C. Johnston, J.D. Easton, M. Farrant, W. Barsan, R.A. Conwit, J.J. Elm, et al., Clopidogrel and aspirin in acute ischemic stroke and high-risk TIA, N. Engl. J. Med. 379 (3) (2018) 215–225.
[23] W.J. Powers, A.A. Rabinstein, T. Ackerson, O.M. Adeoye, N.C. Bambakidis, K. Becker, et al., Guidelines for the early Management of Patients with Acute Ischemic Stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association, Stroke 49 (3) (2018) (e46-e110).
[24] H.G. Jeong, B.J. Kim, M.H. Yang, M.K. Han, H.J. Bae, S.H. Lee, Stroke outcomes with use of antithrombotics within 24 hours after recanalization treatment, Neurology 87 (10) (2016) 996–1002.
[25] Y. Fuseya, M. Kawamura, E. Matsuda, K. Takada, K. Watanabe, J. Fujitake, rt-PA with antithrombotic therapies in a case with capsular warning syndrome, Internal medicine (Tokyo, Japan) 56 (4) (2017) 441–444.