Stroke warning syndromes

Abstract

It is important for physicians to be aware of stroke warning syndromes because, although rare, there is a high associated risk of subsequent ischaemic infarction. Stroke warning syndromes present as stereotypical, recurrent transient episodes of focal neurological deficit, in the absence of cortical signs, occurring within a short period of time. They are broadly divided into two main subtypes, based on vascular territory: capsular warning syndrome and pontine warning syndrome. The exact underlying pathophysiology related to stroke warning syndromes is incompletely established, but proposed pathophysiological hypotheses for cerebral hypoperfusion include micro-atherosclerosis (cerebral small vessel disease) and haemodynamic instability (e.g. hypotension). Atherosclerotic disease involving small perforating arteries in the anterior circulation (e.g. lenticulostriatal arteries) gives rise to capsular warning syndrome and subsequent risk of capsular infarcts. Conversely, involvement of the posterior circulation pontine perforator arteries gives rise to pontine warning syndrome, which can result in paramedian pontine infarcts. Although the evidence is limited, recommended treatment modalities include permissive hypertension, intravenous recombinant tissue plasminogen activator, dual antiplatelet therapy and statins.

Key words: Capsular warning syndrome; Pontine warning syndrome; Stroke warning syndromes

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Arup Sen[1]

Jonathan Birns[1]

Ajay Bhalla[1]

Author details can be found at the end of this article

Correspondence to:
Arup Sen; arupsen86@doctors.net.uk

Introduction

Transient ischaemic attacks are brief episodes of neurological dysfunction caused by focal brain ischaemia, usually lasting less than 1 hour and without evidence of acute infarction (Albers et al, 2002). Transient ischaemic attacks may sometimes occur recurrently in 'bursts' over a short period of time, commonly referred to as 'crescendo transient ischaemic attacks' (Rothrock et al, 1988). Donnan et al (1993) first described a clinical subset of crescendo transient ischaemic attacks involving the internal capsule as the capsular warning syndrome. They defined the capsular warning syndrome as three or more transient episodes of focal sensory or motor neurological deficit affecting the face, arm and leg, in the absence of any cortical signs, occurring within a 24-hour period. However, more recent literature extends this period to 72 hours (Camps-Renom et al, 2015).

Although initial cases of capsular warning syndrome described by Donnan et al (1993) were, as the name would suggest, clinically localised to the internal capsule, it subsequently became apparent that a similar syndrome may also affect the pons. Indeed, with the advent of magnetic resonance imaging and the associated increased sensitivity of detecting posterior circulation infarcts, more cases of pontine ischaemia are now being detected (Farrar and Donnan, 1993). The term pontine warning syndrome came in to use in 2008 (Saposnik et al, 2008) and collectively capsular warning syndrome and pontine warning syndrome have been termed the stroke warning syndromes.

While only approximately 2% of acute ischaemic strokes occur in the context of a stroke warning syndrome (Tassi et al, 2013), it is a very important clinical syndrome for physicians to be aware of given the associated high risk of subsequent completed infarction. Indeed, the prevalence of acute ischaemic stroke in patients with capsular warning syndrome has been reported to be as high as 71% (Camps-Renom et al, 2015).

Pathophysiology

The precise pathophysiology underlying stroke warning syndromes remains unclear. Numerous hypotheses for cerebral hypoperfusion have been proposed such as arterial vasospasm or artery-to-artery microembolism; however, the most widely accepted aetiologies

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include intrinsic cerebral small vessel disease and haemodynamic instability (Asil et al, 2012; Enriquez-Marulanda et al, 2016; Fuseya et al, 2017).

With regard to cerebral small vessel disease, it is suggested that the main associated pathological process is micro-atherosclerosis (as opposed to lipohyalinosis) at the origin of a deep perforating artery, leading to stenosis or occlusion and subsequent distal focal hypoperfusion of the associated vascular territory. Patients with a single dominant lenticulostriate artery (in contrast to the typical 4–15 lenticulostriate arteries) arising from the middle cerebral artery are considered to be at increased risk of capsular warning syndrome because of poor collateralisation of the lenticulostriate territory (Lee et al, 2010). Reductions in cerebral blood flow because of hypotension or ipsilateral large vessel stenosis further increase the risk of stroke warning syndromes in such patients.

Clinical features

As with all strokes or transient ischaemic attacks, stroke warning syndromes present clinically with negative symptoms and a focal neurological deficit, directly related to the associated hypoperfused vascular territory, which is both sudden and maximal at onset. Atherosclerotic disease involving small perforating arteries in the anterior circulation (e.g. lenticulostriatal arteries) gives rise to capsular warning syndrome and subsequent risk of capsular infarcts (Case study 1). Typically, capsular warning syndrome presents clinically with unilateral sensory and/or motor deficits involving two or more of the face, arm or leg. Dysarthria may also be present. However, capsular warning syndrome most commonly presents clinically as a pure motor hemiparesis (Donnan et al, 1993; Camps-Renom et al, 2015).

Conversely, involvement of the posterior circulation pontine perforator arteries gives rise to pontine warning syndrome, which can result in paramedian pontine infarcts (Case study 2). Similarly to capsular warning syndrome, pontine warning syndrome can also present with unilateral sensory and/or motor deficits and/or dysarthria. However, individuals with pontine warning syndrome may also present with ophthalmoplegia (Saposnik et al, 2008). Cortical signs are not present in either capsular or pontine warning syndrome.

Pharmacological management

Antiplatelet therapy

Antiplatelet monotherapy is both effective and safe in the treatment of acute ischaemic stroke, as reported in a systematic review including eight randomised trials (over 40 000 patients) published in 2014 (Sandercock et al, 2014). Two trials published in 1997 (IST and CAST), testing aspirin 160–300 mg once daily, started within 48 hours of stroke onset, contributed 98% of the data evaluated in this systematic review. The authors concluded that antiplatelet therapy, as described, reduced the risk of early recurrent ischaemic stroke and improved long-term outcomes, with no associated major risk of early haemorrhagic complications.

Case study 1: Capsular warning syndrome

A 72-year-old man presented to the emergency department with a 5-hour history of sudden onset right-sided weakness. On further questioning, he had suffered two identical self-limiting episodes – one the night before and one earlier the same day. These two initial episodes were transient and, as such, he did not feel the need to seek urgent medical attention at the time. On initial assessment, he was hypertensive at 231/117 mmHg and had a right hemiparesis (power 4/5 arm and leg). The hypertension was treated with intravenous labetalol. Electrocardiogram showed sinus rhythm and brain imaging demonstrated an acute left capsular infarct in the middle cerebral artery lenticulostriate perforator territory on a background of small vessel disease. Carotid Doppler imaging reported minor disease in both internal carotid arteries.

He was treated with standard antiplatelet monotherapy (aspirin 300 mg daily for 14 days, followed by clopidogrel 75 mg daily lifelong for stroke secondary prevention) and atorvastatin 40 mg daily. He had no further ischaemic episodes during his admission and was discharged after a short period of inpatient rehabilitation with a mild residual right hemiparesis.

Case study 2: Pontine warning syndrome

A 64-year-old man, with a background of hypertension and hypercholesterolaemia, developed sudden onset left-sided weakness and slurred speech. He presented to the emergency department within the thrombolysis time window and had a left hemiplegia and dysarthria (National Institutes of Health Stroke Scale (NIHSS) of 7). Urgent computed tomography of the brain was normal and he required intravenous labetalol to manage severe hypertension (blood pressure 200/110 mmHg). He was subsequently thrombolysed with intravenous recombinant tissue plasminogen activator and made a full neurological recovery soon after.

He suffered an identical episode the following afternoon; repeat computed tomography of the brain was normal and he received a further dose of intravenous recombinant tissue plasminogen activator (29 hours post initial thrombolysis), again making a full neurological recovery within 1 hour. He also received aspirin 300 mg. Unfortunately, despite these medical interventions, he had a third episode of left-sided hemiparesis and dysarthria a few hours later (NIHSS 10). Computed tomography of the brain was again normal. He immediately received clopidogrel 300 mg and was started on dual antiplatelet therapy (aspirin 75 mg and clopidogrel 75 mg) and atorvastatin 40 mg daily. He did not suffer any further episodes.

On day three, brain magnetic resonance imaging demonstrated an acute right paramedian pontine infarct in the basilar artery perforator territory on a background of mild chronic small vessel disease. Magnetic resonance angiography did not reveal any abnormalities of the large vessels. There were no cardio-embolic sources identified on echocardiography or 24-hour Holter monitoring. He was discharged on dual antiplatelet therapy for a total duration of 1 month, followed by lifelong clopidogrel 75 mg daily. On discharge, he had a persistent left hemiparesis with 4/5 power in the left arm proximally and 1/5 power distally.

In addition to standard aspirin antiplatelet therapy, there have been reports of clopidogrel being used as an adjunct in patients with capsular warning syndrome. Asil et al (2012) described two cases of capsular warning syndrome who received combined antithrombotic treatment with aspirin 300 mg and clopidogrel 300 mg acutely. Despite confirmed capsular infarcts on magnetic resonance imaging brain diffusion-weighted sequences, both cases made a full neurological recovery and were discharged shortly after. The most recent case report by Kawano et al (2014) describes a patient with capsular warning syndrome who initially failed to respond to conventional aspirin monotherapy, but did not suffer any further transient ischaemic attacks following a loading dose of clopidogrel 300 mg.

Nonetheless, the existing evidence for the use of clopidogrel in addition to aspirin, in the management of stroke warning syndromes specifically, remains anecdotal and insufficient. Notably, however, Wang et al (2019) have recently published new recommendations advocating the use of dual antiplatelet therapy in the acute management of minor stroke and high risk transient ischaemic attack, based on evidence from clinical trials (e.g. CHANCE and POINT) showing that it is both safe and effective.

Anticoagulation and thrombolysis

Anticoagulation with intravenous heparin infusion has been instigated as an acute therapy for capsular warning syndrome but there is no conclusive evidence to support it as a proven efficacious treatment (Donnan et al, 1993; Farrar and Donnan, 1993).

A review showed intravenous thrombolysis in stroke warning syndromes (González Hernández et al, 2014) to be effective and safe, and a case report (Fuseya et al, 2017) reported a good clinical course following use of recombinant tissue plasminogen activator, with no complications. In a retrospective multicentre study looking at characteristics and outcomes of capsular warning syndrome, 12 patients received intravenous thrombolysis, with a favourable outcome in 75% (modified Rankin scale 0–2 at 3 months) (Camps-Renom et al, 2015). However, these studies were limited by their retrospective nature and small study population.

While the literature suggests that intravenous thrombolysis is safe in the acute management of stroke warning syndromes, with no reported bleeding complications (Camps-Renom et al, 2015), its efficacy may be limited by its mechanism of action. Thrombolytic agents such as alteplase orchestrate the breakdown of blood clots through fibrinolysis, thus restoring blood flow following thromboembolic stroke (Gravanis and Tsirka, 2008). However, in

terms of proposed pathophysiological mechanisms for stroke warning syndromes, brain tissue hypoperfusion is secondary to vasospasm, haemodynamic instability or stenosis of perforator vessels.

Lipid-lowering therapy

Given the proposed role of atherosclerosis in the pathophysiology of stroke warning syndromes, one might reason that statin therapy would be beneficial in its management. Statins have been proven to stabilise, and even regress, atherosclerotic plaques via their inhibition of 3-hydroxy-3-methylglutaryl coenzyme A reductase (Toth and Banach, 2019). However, evidence is scarce regarding the efficacy of statins in stroke warning syndrome specifically.

Zhou et al (2014) described two cases of capsular warning syndrome, reporting perceived benefit of statin therapy (in combination with dual antiplatelet therapy) in preventing recurrent ischaemic events. In both cases, following treatment with dual antiplatelets (aspirin 200 mg and clopidogrel 75 mg) and statin (atorvastatin 20 mg), there were no further reported ischaemic events. This evidence is limited by its anecdotal nature and given that multiple medications were given simultaneously it would be difficult to comment on the role of atorvastatin specifically with regards to the reported positive clinical outcomes post-treatment.

Optimising cerebral perfusion

Maintenance of high blood pressure (‘permissive hypertension’) has previously been recommended in the literature as a treatment modality to avert haemodynamic instability and hypoperfusion of small perforating vessels (Lalive et al, 2003). Donnan et al (1993) postulated that atherosclerotic disease of small penetrating arteries makes them susceptible to fluctuations in blood pressure leading to transient ‘flow failure’, thereby causing the stereotypical transient ischaemic attacks associated with stroke warning syndromes. However, case studies of capsular warning syndrome (Springer and Labovitz, 2013) have subsequently described patients with fluctuating focal neurological deficits independent of blood pressure. In patients with ipsilateral large vessel arterial stenosis and/or stenosis of the ostium of a dominant perforator vessel, interventional approaches have been successful. Lee et al (2010) described a case of capsular warning syndrome with reduced flow in a dominant lenticulostriate artery where symptoms resolved following intracranial angioplasty.

Conclusions

In view of the relatively rare nature of stroke warning syndromes, current evidence for their management is limited and their optimal treatment is yet to be established. Further larger scale, multicentre research studies are warranted, given the emergent nature of the syndromes and associated high risk of stroke. Given that the recent evidence (Wang et al, 2019) suggests that dual antiplatelet therapy is both effective and safe in the management of high risk transient ischaemic attacks, one could reasonably extrapolate this to include management of stroke warning syndromes. Furthermore, given the likely pivotal role of atherosclerosis in the pathophysiology of stroke warning syndromes, treatment with statins ought to be considered in combination with dual antiplatelet therapy.

Author details

[1]Department of Ageing and Health, Guy’s and St Thomas’ NHS Foundation Trust, London, UK

Conflicts of interest

The authors declare no conflicts of interest..

References

Albers GW, Caplan LR, Easton JD et al. Transient ischemic attack: proposal for a new definition. N Engl J Med. 2002;347(21):1713–1716. https://doi.org/10.10.1056/NEJMsb020987

Asil T, Ir N, Karaduman F, Cagli B, Tuncel S. Combined antithrombotic treatment with aspirin and clopidogrel for patients with capsular warning syndrome: a case report. Neurologist. 2012;18(2):68–69. https://doi.org/10.1097/NRL.0b013e318247b9a5

Key points

- Stroke warning syndromes present as stereotypical, recurrent transient episodes of focal neurological deficit, in the absence of cortical signs, occurring in a short period of time.
- There are two main subtypes, based on vascular territory: capsular warning syndrome and pontine warning syndrome.
- Although rare, these are clinically important syndromes for physicians to be aware of because of the high risk of subsequent ischaemic infarction.
- The exact disease mechanism is incompletely established, but proposed hypotheses for cerebral hypoperfusion include micro-atherosclerosis and haemodynamic instability.
- Although the evidence is limited, recommended treatment modalities include permissive hypertension, intravenous recombinant tissue plasminogen activator, dual antiplatelet therapy and statins.

Camps-Renom P, Delgado-Mederos R, Martínez-Domeño A et al. Clinical characteristics and outcome of the capsular warning syndrome: a multicenter study. Int J Stroke. 2015;10(4):571–575. https://doi.org/10.1111/ijs.12432

Donnan GA, O'Malley HM, Quang L, Hurley S, Bladin PF. The capsular warning syndrome: pathogenesis and clinical features. Neurology. 1993;43(5):957–962. https://doi.org/10.1212/WNL.43.5.957

Enriquez-Marulanda A, Amaya-Gonzalez P, Orozco JL. Pontine warning syndrome: a chameleon of ischemic stroke. Neurologist. 2016;21(6):93–96. https://doi.org/10.1097/NRL.0000000000000092

Farrar J, Donnan GA. Capsular warning syndrome preceding pontine infarction. Stroke. 1993;24(5):762. https://doi.org/10.1161/01.STR.24.5.762

Fuseya Y, Kawamura M, Matsuda E et al. rt-PA with antithrombotic therapies in a case with capsular warning syndrome. Intern Med. 2017;56(4):441–444. https://doi.org/10.2169/internalmedicine.56.7522

Gravanis I, Tsirka SE. Tissue-type plasminogen activator as a therapeutic target in stroke. Expert Opin Ther Targets. 2008;12(2):159–170. https://doi.org/10.1517/14728222.12.2.159

González Hernández A, Fabre Pi O, Cabrera Naranjo F, López Veloso AC. Intravenous thrombolysis with recombinant tissue plasminogen activator in vascular warning syndromes. Neurologia. 2014;29(6):334–338. https://doi.org/10.1016/j.nrl.2013.07.005

Kawano H, Nakajima M, Inatomi Y, Yonehara T, Ando Y. Loading dose of clopidogrel in combination with other antithrombotic therapy for capsular warning syndrome. J Stroke Cerebrovasc Dis. 2014;23(5):1265–1266. https://doi.org/10.1016/j.jstrokecerebrovasdis.2013.09.020

Lalive PH, Mayor I, Sztajzel R. The role of blood pressure in lacunar strokes preceded by TIAs. Cerebrovasc Dis. 2003;16(1):88–90. https://doi.org/10.1159/000070121

Lee J, Albers GW, Marks MP, Lansberg MG. Capsular warning syndrome caused by middle cerebral artery stenosis. J Neurol Sci. 2010;296(1–2):115–120. https://doi.org/10.1016/j.jns.2010.06.003

Rothrock JF, Lyden PD, Yee J, Wiederholt WC. 'Crescendo' transient ischemic attacks: clinical and angiographic correlations. Neurology. 1988;38(2):198–201. https://doi.org/10.1212/WNL.38.2.198

Sandercock PA, Counsell C, Tseng MC, Cecconi E. Oral antiplatelet therapy for acute ischaemic stroke. Cochrane Database Syst Rev. 2014;(3):CD000029. https://doi.org/10.1002/14651858.CD000029

Saposnik G, Noel de Tilly L, Caplan LR. Pontine warning syndrome. Arch Neurol. 2008;65(10):1375–1377. https://doi.org/10.1001/archneur.65.10.1375

Springer MV, Labovitz DL. The capsular warning syndrome reconsidered. Cerebrovasc Dis. 2013;36(2):152. https://doi.org/10.1159/000352045

Tassi R, Cerase A, Acampa M et al. Stroke warning syndrome: 18 new cases. J Neurol Sci. 2013;331(1–2):168–171. https://doi.org/10.1016/j.jns.2013.05.027

Toth PP, Banach M. Statins: then and now. Methodist Debakey Cardiovasc J. 2019;15(1):23–31. https://doi.org/10.14797/mdcj-15-1-23

Wang Y, Johnston SC, Bath PM et al. Acute dual antiplatelet therapy for minor ischaemic stroke or transient ischaemic attack. BMJ. 2019;364:l895. https://doi.org/10.1136/bmj.l895

Zhou L, Ni J, Xu W et al. High-resolution MRI findings in patients with capsular warning syndrome. BMC Neurol. 2014;14:16. https://doi.org/10.1186/1471-2377-14-16