Sultan Qaboos University Med J, May 2018, Vol. 18, Iss. 2, pp. e202–207, Epub. 9 Sep 18
Submitted 18 Dec 17
Revision Req. 1 Feb 18; Revision Recd. 12 Mar 18
Accepted 5 Apr 18
doi: 10.18295/squmj.2018.18.02.013

CONTINUING MEDICAL EDUCATION

"Different Strokes"
A management dilemma

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"السكتات الدماغية المختلفة"
معضلات التشخيص وخطة العلاج

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ABSTRACT: Stroke is a common medical emergency resulting from numerous pathophysiological mechanisms and with varied clinical manifestations; as such, the diagnosis of stroke requires diligent clinical assessment. When different stroke syndromes occur in the same patient, it may cause a dilemma in terms of diagnosis and management. This continuing medical education article describes an interesting patient with recurrent neurological events, highlighting the complex pathophysiological processes associated with cerebrovascular syndromes. It offers readers the opportunity to apply their own basic neuroscience knowledge and clinical skills to solve the challenges encountered during the course of diagnosing and treating this patient. Specifically, the article aims to familiarise readers with an approach to diagnosing brainstem strokes and the diverse manifestations of a common stroke syndrome.

Keywords: Stroke; Lacunar Stroke; Cerebral Hemorrhage; Cerebral Small Vessel Disease; Continuing Medical Education.

الملخص: السكتات الدماغية هي حالات طوارئ طبية شائعة تنتج عن عوامل مختلفة ولها أعراض سريرية مختلفة؛ وعلى هذا النحو، يتطلب تشخيص السكتة الدماغية التقييم السريري الدؤوب. عندما تحدث متلازمات السكتة الدماغية المختلفة في نفس المريض، فإنه قد يتسبب في معضلة من حيث التشخيص والعلاج. تصف هذه المقالة التعليمية الطبية مريضًا حدثت له أعراض عصبية متكررة أثرت على الجهاز العصبي، وهي تبين مدى صعوبة وتداخلات العمليات الفيزيولوجية المرضية المصاحبة للمتلازمات الدماغية الوعائية. تتيح هذه المقاله للقراء الفرصة لتطبيق معلوماتهم الأساسية في علم المخ والأعصاب ومهاراتهم السريرية من أجل حل التحديات التي تواجههم أثناء تشخيص وعلاج هذا المريض على وجه التحديد. تهدف المقالة إلى تعريف القراء بالنهج الصحيح لتشخيص السكتات الدماغية والأعراض المتنوعة الناتجة عن متلازمة السكتات الدماغية الشائعة التي تصيب ساق المخ.

مفتاح الكلمات: السكتة الدماغية؛ السكتة الدماغية الجوبية؛ نزف فى المخ؛ أمراض الأوعية الدموية الدماغية؛ التعليم الطبي المستمر.

Stroke is a fairly common medical emergency which can potentially cause long-term disability or even death; furthermore, the incidence of stroke has been increasing in developing countries in recent years.[1] There are several different types of stroke according to their specific pathophysiological mechanisms. Large artery atherothrombosis, cardioembolism and lacunar infarction are examples of ischaemic stroke, while an intra-cerebral or subarachnoid haemorrhage are examples of haemorrhagic stroke.[1] The effective management of stroke requires diligent evaluation of the patient with a detailed medical history as well as a systemic and neurological examination.

Overall, the clinical examination and diagnostic work-up of a patient with suspected stroke has multiple objectives, including localising the site of the stroke in the neuraxis, understanding its pathophysiology and cause and determining the most effective form of treatment. Moreover, stroke recurrence is a major concern for all patients following the initial stroke event; therefore, choosing appropriate measures to prevent recurrence is a mandatory component of management.[1] However, challenges may arise when more than one variety of stroke occurs in the same patient.

This continuing medical education article presents an interesting case, wherein a female patient had recurrent stroke, in order to highlight the complex pathophysiology behind cerebrovascular syndromes. Readers are encouraged to apply their basic neuroscience knowledge and clinical skills to solve the various diagnostic and management-related dilemmas encountered in this case.

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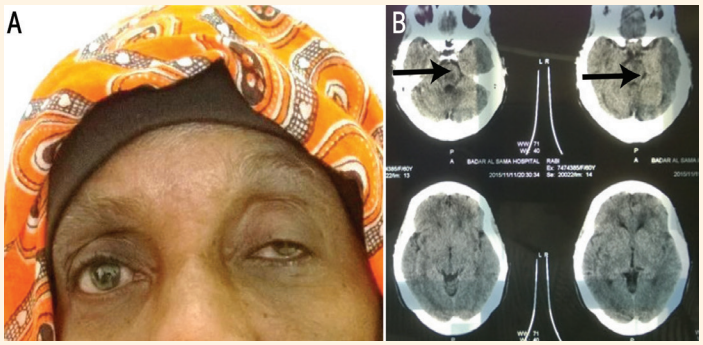

Figure 1: A: Photograph of a 55-year-old hypertensive woman with left *ptosis* and a divergent squint. **B:** Computed tomography scan of the brain showing brainstem and periventricular hypodensities (arrows).

Case Study

A 55-year-old African woman initially presented to a secondary hospital in Muscat, Oman, in 2015 with drooping of the left eyelid which had begun a few hours previously. The patient reported a history of double vision. She was being treated for hypertension with amlodipine, which she had taken for the past 20 years, although with poor compliance. Upon examination, she was observed to have an elevated blood pressure of 180/120 mmHg. A neurological examination revealed left *ptosis* with a dilated pupil which reacted sluggishly to light and limited movements of the left eye, except for abduction [Figure 1A]. Her blood glucose and haemoglobin levels, cell counts and erythrocyte sedimentation rate (ESR) were all normal. A computed tomography (CT) scan of the brain showed hypodensities in the brainstem and periventricular regions [Figure 1B]. She was prescribed amlodipine, telmisartan, atenolol, aspirin and atorvastatin before being discharged, with advice to take her medication regularly.

Question 1: ***Based on the patient's symptoms and signs, which cranial nerve was affected? What was the likely cause of the cranial nerve palsy?***

Overall, the clinical signs are suggestive of left third cranial nerve palsy. Isolated palsy of this variety may occur due to involvement anywhere along the course of the affected nerve.[2] *As the patient had no headaches or signs indicating the involvement of any other cranial nerves, it is likely that the involvement of the left third cranial nerve is localised along the skull base or in the cavernous sinus region. Diabetic cranial neuropathy is unlikely as it usually causes pupil-sparing nerve palsy.*[2] *Furthermore, the absence of long tract signs at this stage may argue against a sizeable brainstem lesion. The computed tomography brain scan shows midbrain hypodensity—likely a lacunar infarct—with no evidence of another lesion along the course of the third cranial nerve. Hence, the possible causes of third nerve palsy are either lacunar stroke in the ventral midbrain or ischaemic neuropathy.*[2] *Meningitis, malignancy or autoimmune disorders are unlikely in the context of the patient's clinical picture and the findings of various investigations. However, an aneurysm, for instance in the posterior communicating artery, may also be possible.*[2]

Subsequently, 10 days later, the patient was admitted to the Emergency Department of the Sultan Qaboos University Hospital, a tertiary hospital in Muscat. According to her relatives, she had been speaking on the phone at home before suddenly dropping the phone from her right hand and slumping over. She had remained conscious, but was noted to have right-sided weakness and slurred speech. At presentation, her blood pressure was 165/110 mmHg. She was alert, oriented and appeared able to comprehend and answer questions, although her speech continued to be slurred. The *ptosis* and ophthalmoparesis in the left eye persisted, while the movement, pupil and visual fields of the right eye were normal. New neurological signs were evident, including right upper motor neuron facial *paresis*, dense right-sided hemiparesis with a power of 0–1/5 on the Medical Research Council muscle power scale in both the right upper and lower limbs [Figure 2], reduced touch and pinprick sensations over the right side of the body and face and right extensor *plantar* responses. Her tendon reflexes on the right side were brisk over the course of the next couple of days.

Question 2: ***What are the likely locations of the patient's stroke, considering the new neurological signs of dense right-sided hemiparesis and hemihypoesthesia?***

The patient had dense right-sided hemiparesis with right hemihypoesthesia; however, her language functions remained unaffected. This supports the possibility of left subcortical stroke, potentially located at the corona radiata, internal capsule or, less commonly, the ventral midbrain or pons.[2]

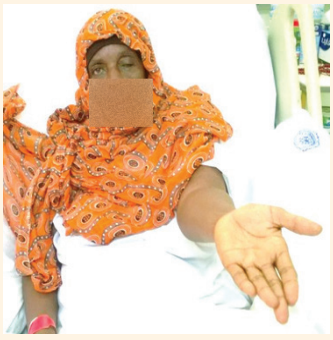

Figure 2: Photograph of a 55-year-old hypertensive woman with left eye-lid *ptosis* and right-sided hemiparesis.

Question 3: ***The combination of left ptosis, ophthalmoparesis and right-sided hemiparesis in this case suggests which specific location of neuraxial involvement? What eponym is used to describe this?***

The combination of left oculomotor nerve involvement with right-sided hemiparesis indicates a crossed brainstem syndrome, particularly a lesion in the left half of the midbrain at the level of the third nerve nucleus.[3] This is known as Weber's syndrome, named after Sir Hermann David Weber who first described this condition in 1863.[4] However, the occurrence of two temporally and spatially separated stroke episodes—a lacune and a haematoma—should perhaps instead be labelled pseudo-Weber's syndrome.

The patient's complete blood count, ESR, levels of blood glucose and serum lipids, liver and renal function, coagulation profile and echocardiogram were normal. An electrocardiogram revealed signs of left ventricular hypertrophy. At this stage, a CT scan of the brain showed a hyperdensity in the left thalamocapsular region, suggestive of haemorrhage [Figure 3A]. Two days later, magnetic resonance imaging (MRI) of the brain revealed left thalamocapsular intracerebral haemorrhage as well as scattered hyperintensities in the periventricular white matter and the brainstem [Figures 3B–E]. A susceptibility-weighted MRI sequence, which is sensitive to haemorrhages, displayed hypointensities scattered in the deep ganglionic and periventricular regions and the brainstem [Figure 4A], in addition to a large haematoma. Magnetic resonance angiography confirmed that the cervical carotid and vertebral arteries were normal, with some irregularities in the intracranial arteries, suggestive of atherosclerosis [Figure 4B]. However, no aneurysms or vascular malformations were observed.

Question 4: ***What is the likely cause of the sequential ischaemic episodes seen in this case, subsequently followed a few days later by intracerebral haemorrhage?***

The likely cause is cerebral small vessel disease, presumably due to chronic poorly-controlled hypertension. This diagnosis is supported by the serial occurrence of lacunar infarct in the midbrain followed by hypertensive thalamocapsular haemorrhage, with multiple periventricular hyperintensities seen upon magnetic resonance imaging, microhaemorrhages scattered in the deep ganglionic structures and brainstem as well as the recent haematoma.[3,5] While cerebral amyloid angiopathy, central nervous system angiitis, systemic vasculitis and, rarely, a central nervous system lymphoma may be considered in the differential diagnosis, the investigations performed in this case excluded most of these conditions.

Question 5: ***In the context of both ischaemic and haemorrhagic stroke, and considering the background of chronic hypertension, which intervention might be beneficial in preventing stroke recurrence in this patient?***

Hypertension control is currently the only intervention recognised to be of some value for patients with cerebral small vessel disease. Lacunar infarction due to small vessel disease, as opposed to large artery disease, may not be significantly influenced by antiplatelet therapy.[3,6,7]

Following these findings, aspirin and atorvastatin were discontinued and the patient received intravenous labetalol for emergent control of her hypertension; later, other oral antihypertensive agents were prescribed and physiotherapy was initiated. A week after the onset of the right-sided hemiparesis, the patient reported diffuse aching pain over the right side of her body, including the face. The pain was present throughout the day and disturbed her sleep. Fortunately, it improved gradually following the administration of oral pregabalin.

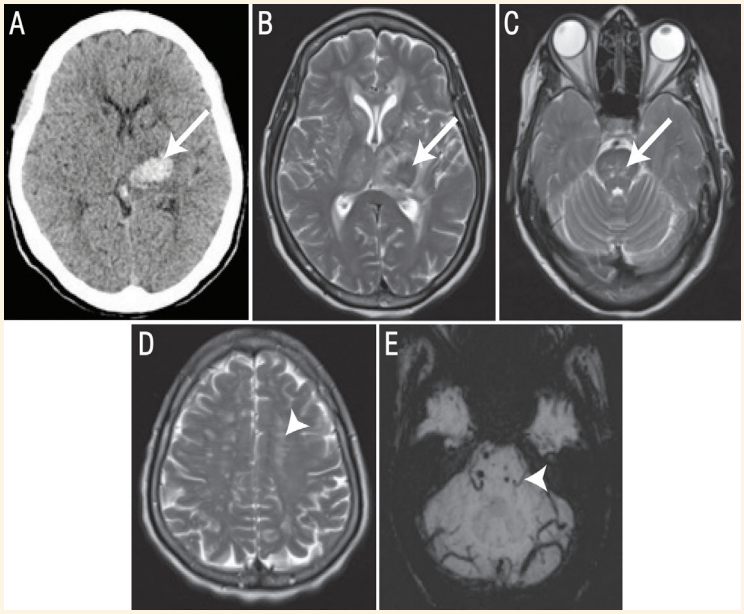

Figure 3: A: Computed tomography scan of the brain of a 55-year-old hypertensive woman three hours after the onset of right-sided hemiparesis showing left thalamocapsular haemorrhage (arrow). **B–E:** Magnetic resonance images of the brain two days later showing (**B and C**) left thalamocapsular intracerebral haemorrhage (arrows), as well as scattered hyperintensities (arrowheads) in the (**D**) periventricular white matter and (**E**) brainstem.

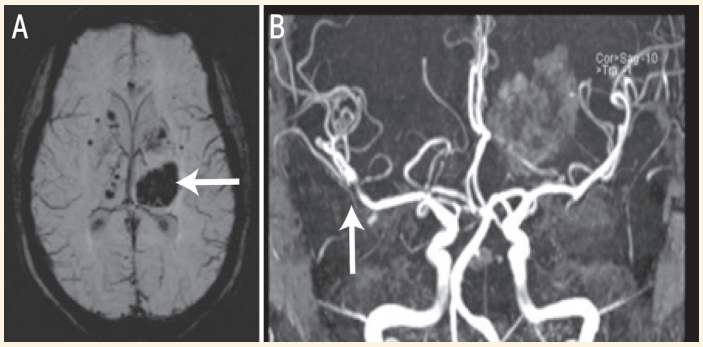

Figure 4: A: Susceptibility-weighted magnetic resonance image of the brain of a 55-year-old hypertensive woman two days after the onset of right-sided hemiparesis showing additional hypointensities scattered in the deep ganglionic and periventricular regions and the brainstem (arrow). **B:** Magnetic resonance angiography showing irregularities of the intracranial arteries, suggestive of atherosclerosis (arrow).

Question 6: ***What is the likely cause of the patient's right-sided pain?***

Aching pain involving the right side of the body following dense right-sided hemiparesis and hemihypoesthesia, with evidence of left thalamocapsular haemorrhage upon computed tomography, strongly suggests the possibility of thalamic pain syndrome or central pain syndrome.[8] This is reported in 4–9.5% of stroke patients and may occur either a few days, months or even years after the insult. The pain may be due to the spontaneous irritability of surviving neurons or ephaptic transmission.[8] Pregabalin, gabapentin and carbamazepine are known to be effective in the initial management of thalamic pain.[3,6,7]

The patient was discharged two weeks after admission with persistent right-sided weakness and sensory impairment. At a follow-up appointment one year later, the ophthalmoparesis and lower limb weakness had improved significantly, although she continued to experience weakness in the right arm.

Discussion

The aforementioned case describes a middle-aged woman with a long history of poorly-controlled hypertension who experienced two varieties of stroke sequentially within a few days—ischaemic stroke followed by intracerebral haemorrhage—leading to crossed hemiparesis syndrome causing *ptosis* and ophthalmoparesis on the left side, followed by hemiparesis and hemihypoesthesia on the right side with preserved speech function. This patient was unique in several aspects. Over the course of 10 days, she had sequential neurological deficits which initially seemed consistent with Weber's syndrome, but which were in fact due to a combination of two different stroke mechanisms, with third nerve palsy likely due to a midbrain *lacune* and contralateral hemiparesis due to a left thalamocapsular haematoma. This unusual sequence of events resulted in a picture of pseudo-Weber's syndrome, as the responsible events were distinct and separated by time as well as location. The patient also developed thalamic pain syndrome shortly after an episode of deep ganglionic haemorrhage.

Cerebral small vessel disease (CSVD) is a fairly common vascular syndrome in which hypertension is the main risk factor, with others being age and the presence of diabetes mellitus.[3,5,9] While the disease can remain 'silent' for long periods of time, it commonly manifests as white matter and periventricular MRI hyperintensities, lacunar infarcts, microhaemorrhages and hypertensive intracerebral haemorrhage, as demonstrated in the current case.[5,9] Such changes are typically clustered deep in the brain in the territory supplied by the penetrating end arteries arising from the circle of Willis. In addition, CSVD may be associated with progressive cognitive, gait, mood and bladder function changes.[3]

Overall, CSVD is the cause of approximately one-fifth of all stroke cases and up to 45% of dementias.[3] Lacunar stroke constitutes 15–25% of all stroke cases, while intracerebral haemorrhage accounts for 10–15%.[1] Cerebral amyloid angiopathy is the main differential diagnosis and may have similar manifestations.[3,5] Non-hypertensive lobar haemorrhages are often recurrent and typical of amyloid angiopathy, along with MRI evidence of white matter hyperintensities and micro-haemorrhages which are more prominent in the peripheral subcortical regions of the hemispheres. Superficial siderosis on the cortical surface is also a feature of amyloid angiopathy, sometimes leading to focal seizures.[3,5] Together with hyperintensities, the deposition of amyloid in the brain is known to occur in several degenerative disorders of the brain, the most prominent of which is Alzheimer's disease, with no specific treatment known to date. Inherited small vessel disease includes cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy and Fabry disease; autoimmune

vasculitis and irradiation may also cause small vessel disease.[3,5] A family history of similar or related manifestations, onset in young non-hypertensive individuals, prominent headaches, imaging evidence of vasculopathy and cerebrospinal fluid abnormalities may assist in the diagnosis. Other than for a few specific conditions (i.e. Fabry disease or cerebral angiitis), the treatment and prevention of the progression of many of these conditions is still poorly understood.[3,5]

Few studies to date have addressed the management of CSVD as a whole. Effective long-term hypertension control is considered the main method of preventing CSVD progression.[7] Several therapeutic trials addressing stroke or dementia have included individual components of CSVD, thereby providing some evidence for the efficacy of certain interventions.[3,7] Thrombolysis is known to be of benefit for patients with acute lacunar stroke, although CSVD may be associated with a higher risk of intracerebral haemorrhage.[10] The efficacy of antiplatelet agents among patients with CSVD is unclear.[3,6,7] In the double-blind Secondary Prevention of Small Subcortical Strokes trial, no difference in stroke prevention was observed among patients undergoing dual antiplatelet therapy (aspirin with clopidogrel) compared to those taking aspirin and a placebo; in fact, there was a greater risk of haemorrhage and death with dual antiplatelet therapy.[6] Another study demonstrated a significant reduction in recurrent stroke among patients, most of whom had lacunar stroke, treated with cilostazol rather than a placebo (relative risk: 41.7%; P <0.015).[11] Thus, it is possible that antiplatelet agents may be of benefit among patients with CSVD who present with lacunar stroke.

Patients with intracerebral haemorrhage due to CSVD are treated similarly to those due to other primary causes of intracerebral hemorrhage.[11] How-ever, no studies or guidelines have addressed the management of patients with CSVD who present with sequential ischaemic and haemorrhagic stroke, as in the current case. In the context of intracerebral haemorrhage, antiplatelet agents are conventionally withheld for a period of between a few weeks to three months. Later, the reintroduction of antiplatelet agents may often be indicated by a coexisting risk of ischaemic stroke, ischaemic heart disease or peripheral arterial disease.[12] While lacunar stroke is recognised as a risk factor for stroke recurrence and may require antiplatelet therapy, no studies address the issue of whether and when to reintroduce this therapy in cases of sequential ischaemic and haemorrhagic stroke.[6,7] Therefore, in the absence of other risk factors for ischaemic events and due to the presence of significant cerebral microhaemorrhages as well as a haematoma, management of the patient in the current case consisted solely of hypertension control. No stroke recurrence was observed over the following year.

Conclusion

This article describes a patient with crossed hemiparesis syndrome—left third nerve palsy with right-sided hemiparesis—due to two distinct episodes of ischaemic and haemorrhagic stroke. The underlying causes were a lacunar infarct and thalamocapsular haemorrhage due to CSVD, which is a fairly common syndrome with diverse manifestations. For patients with recurrent stroke or multiple stroke syndromes, diligent clinical assessment is important in order to understand the location of each event as well as the underlying pathophysiological mechanism.

ACKNOWLEDGEMENTS

The authors wish to acknowledge the cooperation of the patient and her family. The patient consented to the use of all clinical photographs and radiological images included in this article.

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