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Letter to the Editors

Recurrent transient global amnesia associated with internal jugular vein thrombosis

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Dear Editor,

Transient global amnesia (TGA), defined as sudden anterograde and retrograde amnesia lasting for up to 24 h [1], has an annual recurrence rate of 5.8% [2]. The underlying mechanism by which TGA develops remains uncertain. No case of recurrent TGA associated with internal jugular vein thrombosis has been reported. We present a patient with recurrent TGA that might have been caused by thrombosis of the internal jugular vein.

A 58-year-old woman with history of dyslipidaemia with no history of migraines or pulmonary disease and no family history of TGA presented with her first episode of TGA in 2014. After a severe episode of coughing for a few minutes, she questioned anxiously about where she was and why she was there. Her inability to retain new information persisted until she was admitted to our hospital after 2 h. She was found to have antegrade and retrograde amnesia, without any other neurological deficits. MRI of the brain was obtained the day after the onset of amnesia using a 3.0 T MR imaging unit. Diffusion-weighted imaging (DWI) revealed two small hyperintense spots: one each in the right hippocampus and the right cingulate gyrus (Fig. 1A and B). Time-of-flight magnetic resonance angiography (TOF MRA) and carotid ultrasonography excluded arterial stenosis. However, intracranial retrograde venous flow was evident (Fig. 1C). Ultrasonography showed a thrombus in the left internal jugular vein and venous reflux distal to the thrombus (Fig. 1D). Electrocardiogram and 24-hour Holter electrocardiogram monitoring excluded atrial fibrillation. Transthoracic echocardiography was normal. Transoesophageal echocardiography using saline contrast with Valsalva manoeuvre excluded intrapulmonary and intracardiac right-to-left shunts. She did not have antiphospholipid antibody syndrome or inherited coagulation disorders. She completely recovered from the amnestic state after 19 h. However, memory loss for this time period remained. She was prescribed 5 mg per day of apixaban, a direct oral anticoagulant. Two months later, ultrasonography showed lysis of the thrombus. Although she had no recurrence of TGA for one year, apixaban was stopped because of the bleeding tendency associated with it. After three months, she was diagnosed with recurrent thrombosis of the jugular vein by ultrasonography and was started on 15 mg per day of edoxaban, another direct oral anticoagulant. However, the thrombus remained.

In September 2016, she had a second attack of TGA after a severe episode of coughing. The amnestic attack lasted for 11 h following which she recovered completely. DWI done on that day showed no abnormalities, whereas MRA and ultrasonography showed congestion in the left jugular vein. Following this, her therapy was switched back from edoxaban to apixaban. After three months, the thrombus and congestion had resolved. In May 2018, two years after her second TGA attack, apixaban was stopped since she developed subcutaneous bleeding. Five days later, she developed a third attack of TGA after a severe episode of coughing. The amnestic state lasted for about 20 h, similar to the other attacks. Five milligrams per day of apixaban was restarted immediately. MRI of the brain, acquired on the day of the attack, was normal. However, four days later, DWI showed abnormal punctate hyperintensities in bilateral hippocampi (Fig. 1E and F). Ultrasonography showed congestion in the left jugular vein with retrograde flow. The hippocampal lesions disappeared in DWI and fluid attenuated inversion recovery (FLAIR) within three weeks (Fig. 1G and H).

Our patient fulfilled the diagnostic criteria for TGA [3]. Her MRI findings corresponded with characteristics of TGA. Kim et al. reported that the hippocampal lesions on DWI are located in the hippocampal body as well as in the hippocampal tail and head, and that extrahippocampal lesions are also detected in the cingulate gyrus, central portion of the tegmentum, centrum semiovale, and external capsule [4].

We learnt two important clinical issues from this case. Firstly, TGA might be associated with jugular vein thrombosis and reflux. The aetiology of TGA remains obscure. Several pathophysiological mechanisms including arterial ischaemia, abnormalities of venous flow, epilepsy, mechanisms related to migraines, and psychological mechanisms have been suggested to be associated with TGA, and Valsalva-associated manoeuvres are frequently reported to be precipitating events [1,5]. During Valsalva-associated manoeuvres, retrograde flow in the internal jugular vein occurs. The venous pressure increases leading to congestion in the hippocampal veins. Subsequent ischaemia develops since the CA1 neurons are vulnerable to ischaemia [5]. The prevalence of an

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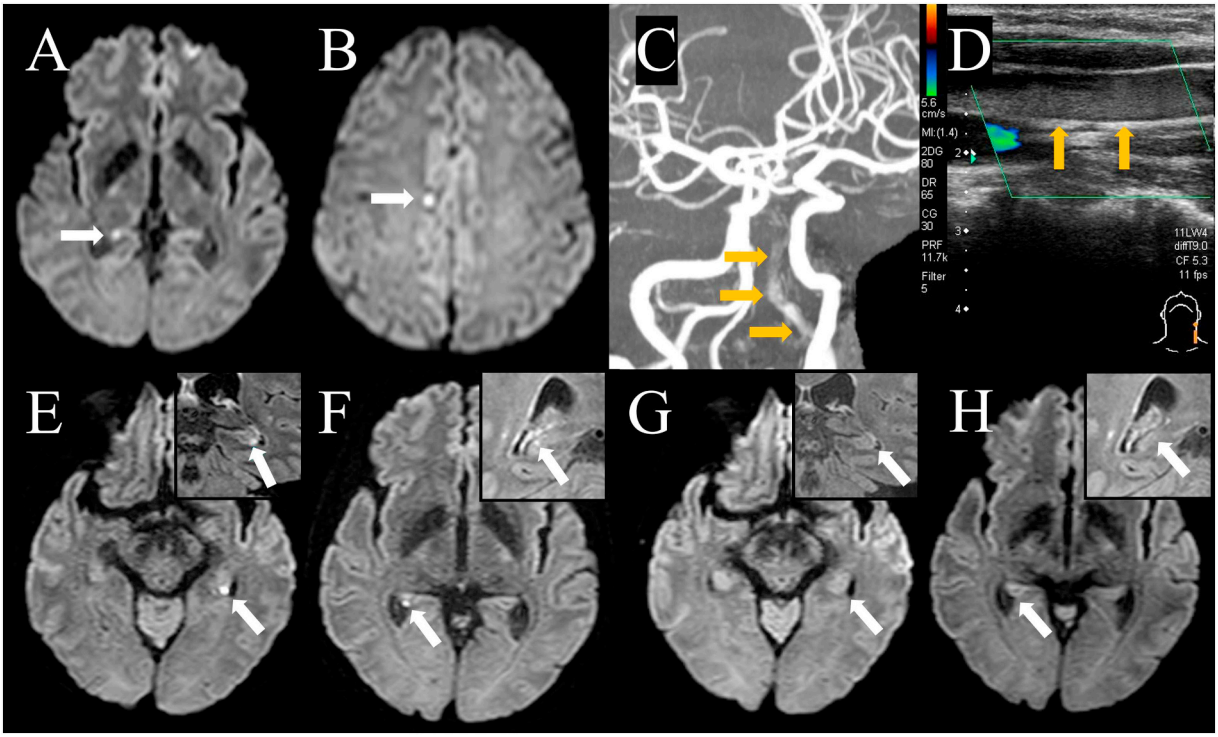

Fig. 1. Brain MRI and carotid ultrasonography findings.
Diffusion weighted imaging (DWI) performed one day after the first attack of TGA in 2014 shows abnormal punctate hyperintensities in the right hippocampal tail and the right cingulate gyrus (A and B, arrow). Time-of-flight magnetic resonance angiography shows an abnormal venous signal from the left internal jugular vein to the left inferior petrosal sinus, indicating an intracranial jugular vein reflux (C, arrow). Ultrasonography shows thrombosis of the left internal jugular vein (D, arrow). DWI performed four days after the third attack of TGA in 2018 shows hyperintense spots in the right hippocampal tail and the left hippocampal body (E and F, arrow). Small insets in E and F show coronal views of the fluid attenuated inversion recovery (FLAIR) images. At the one-month follow-up, the DWI and FLAIR images show that these lesions have completely resolved (G and H, arrow).

insufficient jugular venous valve with retrograde flow in the jugular vein on ultrasonography is higher among patients with TGA than among healthy, matched controls [6,7]. Chung et al. report that intracranial retrograde venous flow was found on the TOF MRA of five out of ten patients with TGA and in none of the controls [8]. However, recent studies report ambiguous associations between jugular venous flow and TGA, and argue against this hypothesis [9,10].

A PubMed search revealed only two case reports of TGA related to cerebral venous thrombosis [11,12]. They describe thrombi in venous sinuses that elevate the pressure in the cerebral venous system leading to venous ischaemia of the hippocampus. No case of recurrent TGA associated with thrombosis of the internal jugular vein has been reported. We suggest that in our case, the jugular vein reflux and thrombosis resulted in hippocampal venous congestion and subsequent ischaemia, leading to the development of TGA. Cough, being a Valsalva-like activity, elevated the intrathoracic pressure, resulting in the retrograde transmission of pressure to the intracerebral venous vasculature.

Secondly, anticoagulants could be useful in preventing recurrent TGA associated with venous thrombosis. No established treatment is indicated for TGA since it is a self-limiting condition that resolves without intervention and its recurrence is rare. Since our case had no further attacks of TGA after anti-coagulation therapy with apixaban, we suggest that apixaban might be effectively prophylactic against TGA with thrombosis of the jugular vein.

In conclusion, in this case, recurrent TGA might have been associated with jugular venous thrombosis and reflux. Hence, it is necessary to examine the jugular vein and cerebral venous system in cases of recurrent TGA. Anti-coagulation could be useful in preventing recurrence of TGA caused by venous thrombosis.

Declarations of interest

None.

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Authors' contributions

Ai Ogawa Ito, Asako Tamura, Atsushi Niwa and Hidekazu Tomimoto were responsible for the study concept and the interpretation of data. Ai Ogawa Ito, Asako Tamura, Atsushi Niwa, Yuichi Nakayama and Yamato Nishiguchi acquired the clinical and the laboratory data. Ai Ogawa Ito wrote the manuscript. The manuscript was edited by Asako Tamura, Atsushi Niwa, Akihiro Shindo and Hidekazu Tomimoto. All authors have read and approved the manuscript.

Ethical standards

Consent to publish was obtained from the patient using our institutional consent form. The patient also consented to the publication of all individual details and images. The study was performed in accordance with the guideline of the ethics committee of Mie University Hospital.

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