Bilateral, vertical supranuclear gaze palsy following unilateral midbrain infarct

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SUMMARY
A 60-year-old man recently admitted for bipedal oedema, endocarditis and a persistently positive COVID-19 swab with a history of anticoagulation on rivaroxaban for atrial fibrillation, transitional cell carcinoma, cerebral amyloid angiopathy, diabetes and hypertension presented with sudden onset diplopia and vertical gaze palsy. Vestibulo-ocular reflex was preserved. Simultaneously, he developed a scotoma and sudden visual loss, and was found to have a right branch retinal artery occlusion. MRI head demonstrated a unilateral midbrain infarct. This case demonstrates a rare unilateral cause of bilateral supranuclear palsy which spares the posterior commissure. The case also raises a question about the contribution of COVID-19 to the procoagulant status of the patient which already includes atrial fibrillation and endocarditis, and presents a complex treatment dilemma regarding anticoagulation.

BACKGROUND
Cerebrovascular accidents (CVA) comprise the second leading cause of death worldwide and the third leading cause of disability, with approximately 80% of all stroke being ischaemic in origin, 10% due to haemorrhage, 5% due to subarachnoid haemorrhage and the remainder due to other causes of stroke.1 It can manifest in a variety of presentations depending on location of the defect. Vertical gaze palsy describes a conjugate bilateral limitation of upgaze and/or downgaze. It primarily affects the saccadic eye movement pathway but can also affect smooth pursuit or optokinetic movements, and can be considered as a supranuclear, nuclear or infranuclear problem of origin. Three key anatomical centres are most important in the vertical gaze centre: (1) the rostral interstitial nucleus of the medial longitudinal fasciculus (riMLF) in the midbrain for control of vertical and torsional saccades, (2) the interstitial nucleus of Cajal (INC), the neural integrator of vertical and torsional gaze and (3) and the posterior commissure (PC) in the dorsal aspect of the superior end of the cerebral aqueduct. Vertical gaze palsies are recognised in a variety of syndromes not limited to Parkinsonism-plus syndromes (progressive supranuclear palsy and corticobasal syndrome), storage disorders (Niemann-Pick Type C) or Parinaud’s syndrome, but should also be recognised as a result of autoimmune, malignant, drug-induced and traumatic causes. Vascular causes of supranuclear gaze palsy typically localise to the midbrain or the thalamus. This case combines an interesting unilateral lesion causing bilateral symptoms, an awareness of the multifactorial aetiology of strokes and a lesson in managing the risk–benefit of anticoagulation in the context of both ischaemic and haemorrhagic risk factors.

CASE PRESENTATION
A 60-year-old man with a background of hypertension, diabetes, chronic obstructive pulmonary disease and atrial fibrillation, for which he was taking rivaroxaban, and a diagnosis of transitional cell carcinoma of the bladder 5 years prior (undergoing chemotherapy and cysto-prostatectomy), presented with rapidly-progressive bilateral ankle oedema (progressing to upper legs in 2 days), back pain, reduced appetite and intermittent fever. X-ray of the lungs were clear, but an echocardiogram detected mitral vegetations and subsequent blood cultures grew Streptococcus sanguinis, a common oral commensal bacterial. He had no history of dental work. Roughly 10 days after admission, he developed a new dry cough and tested positive for SARS-CoV2 RNA, improving with oxygen support. One week later, he developed a non-ST elevated myocardial infarction.

During the last phase of isolation for COVID-19, he developed sudden onset of vertical diplopia, lightheadedness, vertigo and unsteady gait. On examination, there was restricted bilateral upward gaze movements with mild limitation for abduction in the right eye and inability for bilateral downgaze on either side (video 1). The vertical vestibulo-ocular reflex (VOR) was preserved (video 2). Pupils were equal and reactive to light directly and indirectly. Diffusion-weighted MRI (figure 1) showed an acute, small left-sided paramedian midbrain infarct without thalamic involvement, and T2* (echo gradient) imaging showed a couple of small, chronic microhaemorrhages in the parietal and temporal lobes, secondary to long-standing asymptomatic amyloid angiopathy. He had no history of transient neurological attacks, seizures, dysesthesia, hemi-ataxia, diplopia or hemiparesis. Almost simultaneously, he also developed a sudden onset of black patch obstructing his central and superior field of view and could only manage to see hand movement from the right eye, which was suggestive of a branch/hemi-retinal artery occlusion and later confirmed using optical coherence tomography. Also, single embolus in the inferior branch of the retinal artery was clearly visible (figure 2), confirming the occlusion of branch or hemi-retinal artery. The patient never complained of either headache, temperature changes or recent history of weight loss.

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reactive protein and erythrocyte sedimentation rate were mildly elevated; however, there was no evidence of temporal arteritis. Autoantibody testing, in the form of anti-nuclear antibodies, antineutrophil cytoplasmic antibodies, membrane P3 and C4/D3 were all negative and thus incompatible with an autoimmune cause. It was felt that these inflammatory reactants were more likely linked to active COVID-19 infection and bacterial endocarditis. Coagulation, full blood count and lipid profile were all in normal range. D-dimer was 348.

He was diagnosed with bilateral supranuclear gaze palsy secondary to a left paramedian midbrain infarct and a right branch retinal artery occlusion. Treatment with high-dose aspirin (300 mg/day) was given for 1 week, followed by apixaban for long-term secondary prevention of strokes. He also continued antibiotic treatment for endocarditis, with gradual improvement.

A repeat SARS-CoV2 RNA test was positive after 2 weeks of the initial result; however, the patient was asymptomatic at the time.

INVESTIGATIONS
► CT and MRI of the brain.
Case report

Echocardiogram.
● Blood investigations including antibody testing for SARS-CoV2.
● CT carotid arteries.
● A 24-hour tape was not requested as the patient was already known to have atrial fibrillation.

DIFFERENTIAL DIAGNOSIS
The acute onset of vertical diplopia was suggestive of an ischaemic event; however, the cause for the acute onset of bilateral vertical gaze palsy was not obvious. A normal VOR confirmed the supranuclear nature of the condition. Ischaemic events have been reported to cause bilateral supranuclear vertical gaze palsy, but they are not common. Other differential diagnoses considered were metastasis or a primary brain tumour, causing downward compression of the midbrain (and on the upward gaze centres). An MRI confirmed a midbrain infarction.

We considered various causes for infarction, as for the embolic branch retinal artery occlusion, including atrial fibrillation, bacterial endocarditis, previous neoplastic disorder and a persistently positive SARS-CoV2, which appears to have a pro-coagulant effect.

TREATMENT
The patient was treated with aspirin 300 mg initially, then changed to apixaban for secondary prevention of cardioembolic events. He was also treated with antibiotics for bacterial endocarditis.

OUTCOME AND FOLLOW-UP
The patient has continued to make a good recovery in the ward, with gradual improvement of eye movements and is due for follow-up by the stroke team 6 weeks after initial presentation, by neurology 2 months later and cardiology in 6 weeks following discharge. He has continued to make good functional recovery.

DISCUSSION
Premotor control of vertical gaze depends on the integrity of the PC, INC and the riMLF. Neurons for upward saccades innervate both ipsilateral and contralateral oculomotor and trochlear nerve nuclei whereas those that mediate downward saccades innervate the oculomotor and trochlear nerve nuclei ipsilaterally only. The riMLF and INC are thought to work together to generate ipsilateral torsional eye movements and the PC is involved in vertical gaze as well as pupillary reflexes. Supranuclear pathways for vertical saccades travel from both frontal eye fields to innervate the riMLF on each side. Vertical saccades require simultaneous activation of both frontal eye fields.

From both a clinical and radiological point of view, the patient had involvement of the riMLF and INC, but neither of the PC nor of the nucleus of Edinger-Westphal. The supranuclear nature of the palsy was confirmed by a preserved vertical VOR. There was no evidence of pupillary dysfunction (no fixed and dilated pupil due to parasympathetic damage), ruling out involvement of the Edinger-Westphal nucleus. The left, unilateral paramedian ischaemic lesion damaged the pathways involved in vertical gaze before they decussate (figure 3), resulting in a bilateral supranuclear gaze palsy. As seen in figures 1 and 3, the infarction does not involve the PC.

In most cases, isolated dysfunction of vertical eye movements localises to a midbrain lesion affecting the riMLF, INC, PC or periaqueductal grey matter. Unilateral infarction precipitating bilateral vertical gaze palsy are rare and earliest case reports focused on thalamic involvement, with the earliest case described as that of a patient with midbrain and thalamic involvement. Further cases reported paramedian thalamic infarction without midbrain involvement, usually secondary to an artery Percheron (a variant branch of posterior cerebral artery trunk providing bilateral input to the paramedian thalami and rostral midbrain) infarct resulting in bilateral paramedian thalami infarct, those that presented with a coexisting midbrain lesion.

Buttner-Ennever et al reported a case of vertical gaze palsy secondary to riMLF involvement. Bogousslavsky et al described a histologically confirmed case of vertical gaze palsy due to selective unilateral infarction of riMLF. Vertical gaze palsies without PC involvement are even rarer. A unilateral riMLF and INC lesion but sparing PC tract causing complete upward
but partial downward vertical gaze palsy was first reported in 1988. Further reports have been reported in Japan, Turkey, and Belgium, and iatrogenically secondary to cerebral digital subtraction angiography, in all the cases, there was INC and riMLF involvement with sparing of the PC, with no evidence of pupillary dysfunction. Only in the Belgian iatrogenic case was there both upward and downward gaze palsy, but VOR was also impaired unlike in our case.

Evidence for vertical one-and-a-half syndrome was sought, but no evidence was found. This phenomenon was first described in 1983 following a thalamomesencephalic infarction and again in 2012. The patient had vertical gaze disorder associated with ipsilateral downward gaze palsy and only contralateral upward gaze palsy. This is an important differential diagnosis to consider in any patient with an acute onset of bilateral upward gaze palsy. In such cases, apart from the upward gaze palsy, there is also ipsilateral downward gaze palsy. As seen in video 1, the patient did not have downward gaze palsy.

The aetiology and long-term management of the ischaemic stroke in this case also warrants further discussion. The patient not only had a history of small vessel disease in the context of cerebral amyloid angiopathy (CAA) but also had a history of atrial fibrillation controlled with rivaroxaban as well as S. sanguinis endocarditis.

Acute ischaemic stroke is the most common neurological manifestation of infective endocarditis, reported in up to 40% of cases and classically affecting the middle cerebral artery and the vegetation affecting mitral valve. Cerebral microbleeds are also a common complication of infective endocarditis and there is no evidence to support the use of anticoagulants or antiplatelet drugs in acute stroke due to infective endocarditis. This patient also had CAA, which is one of two cerebral small vessel diseases that cause the majority of non-traumatic haemorrhagic stroke, the risk–benefit analysis of anticoagulation is more complicated. CAA results from an age-related deposition of beta-amyloid protein in the leptomeningeal and cortical cerebral vessels. A major prospective cohort study of 1490 participants, the Clinical Relevance of Microbleeds In Stroke trial (CROMIS-2), compared the rate of symptomatic intracranial haemorrhage in patients with electrocardiogram-confirmed non-valvular atrial fibrillation who presented with transient ischaemic attack or ischaemic stroke and who were candidates for direct oral anticoagulants (DOAC). The main findings were that those who had a symptomatic intracranial haemorrhage had a higher prevalence of diabetes, vitamin K antagonist use (as opposed to DOAC) or cerebral microvascular bleeding (which confirmed a three times higher hazard ratio). Therefore, had the patient solely had CAA, anticoagulation would be avoided due to the risk of intracranial bleeding.

However, acutely, the patient also presented with COVID-19. COVID-19 is caused by the SARS-CoV-2, the seventh known variant of coronavirus that affects humans. Cellular entry is primarily through ACE-2 receptors. The exact mechanism of central nervous system entry has not been elucidated but both haematogenous spread from systemic to cerebral circulation and dissemination through cribriform plate and olfactory bulb are considered. A recent systematic review reported a prevalence of 34.6% of neurological symptoms across 214 patients, with those with more severe systemic presentations more likely to have neurological symptoms. Several case reports in the literature have also reported an association of COVID-19 and stroke but the overall prevalence reported is rare. The earliest description was in a single centre retrospective analysis in China which reported a stroke prevalence of 5% among those hospitalised at a median of 12 days from initial COVID-19 diagnosis and a mean age of 71.6 years and classically with multiple cardiovascular risk factors. A much higher prevalence was found among cohort of 725 patients from Italy, with a reported prevalence of 31% of ischaemic stroke. The link with systemic risk factors was reinforced in a case series involving COVID-19 patients with large vessel stroke under the age of 50 years, with three of them having vascular risk factors (diabetes, dyslipidaemia and hypertension). ‘Sepsis-driven coagulopathy’, and the hypercoagulability and vascular endothelial dysfunction it confers is thought to be the main mechanism driving ischaemic stroke. However, other factors include the presence of lupus anticoagulant and the high D-dimers during the course of the disease. Cases of ischaemic strokes have occurred even with previous long-term anticoagulation and thromboprophylaxis is advised in all patients with COVID-19.

Ischaemic stroke management in the long term usually involves the use of long-term anticoagulation. In this patient, who has atrial fibrillation, anticoagulation also becomes more important given the fivefold increased risk in these patients for ischaemic stroke, contributing to 30% of ischaemic strokes. This patient had strong cardiac risk factors (atrial fibrillation and established infective endocarditis) but could potentially have a long-standing procoagulant disposition following his persistently positive COVID-19 status. Such complex situations warrant multidisciplinary input from neurologists, cardiologists and neuroradiologists in assessing risk–benefit, as although direct oral anticoagulants have been reported to carry a lower risk of intracranial haemorrhage, other options, such as left atrial appendage, may avoid long-term anticoagulation. For this situation, a switch to apixaban after initial treatment with aspirin 300 mg was preferred because it presents the least risk for secondary bleeding in a patient with chronic CAA microhaemorrhages, while reducing the risk of cardioembolism due to atrial fibrillation.

Learning points

- Acute onset of supranuclear gaze palsy may likely be a presenting sign of a midbrain infarction. In such cases, an MRI is required, as a CT will not suffice to detect a lesion.
- Posterior commissure involvement, as described in Parinaud’s syndrome, is not always necessary to cause vertical gaze palsy.
- Unilateral midbrain infarction can lead to bilateral supranuclear palsy, vertical one-and-a-half syndrome or half-and-a-half syndrome.
- The apparent pro-coagulant effect of COVID-19 is not negligible and must be considered a vascular risk factor.

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**REFERENCES**

1. Truelsen T, Begg S, Mathers C. The global burden of cerebrovascular disease.
2. Yanoff M, Duker J. Ophthalmology, 4th edition, (in print and online) Yanoff M, Duker JS. (2013) ISBN 978-1455-7398-44, Elsevier. Graefes Arch Clin Exp Ophthalmol 2017.
3. Castaigne P, Lhermitte F, Buge A, et al. Paramedian thalamic and midbrain infarct: clinical and neuropathological study. *Ann Neurol* 1981; 105:127–48.
4. Bhattacharjee S, Ng KL. Vertical gaze palsy due to acute bilateral thalamic infarct. *Brain*: 1982;105:125–49.
5. Bogousslavsky J, Mikhail J, Regli F, et al. Vertical gaze palsy and selective unilateral infarction of the rostral interstitial nucleus of the medial longitudinal fasciculus (riMLF). *J Neurol Neurosurg Psychiatry* 1990;53:67–71.
6. Ranalli PJ, Sharpe JA, Fletcher WA. Palsy of upward and downward saccadic, pursuit, and vestibular movements with a unilateral midbrain lesion: pathophysiological correlations. *Neurology* 1988;38:114–22.
7. Yokose M, Furuya K, Suzuki M, et al. Vertical gaze palsy caused by selective unilateral rostral midbrain infarction. *Neuropathology* 2018;42:309–11.
8. Alemdar M, Kamaci S, Budak F. Unilateral midbrain infarction causing upward and downward gaze palsy. *J Neurol Neurosurg Psychiatry* 2006;77:173–6.
9. Prothall D, Gille M. Conjugate downward and upward vertical gaze palsy due to unilateral rostral midbrain infarction. *J Neurol* 2012;259:779–82.
10. Kim H, Kim WJ. Bilateral vertical gaze palsy after cerebral digital subtraction angiography due to unilateral midbrain infarction. *Korean J Ophthalmol* 2018;32:154.
11. Bogousslavsky J, Regli F, Ugozzi palsy and monocular paresis of downward gaze from ipsilateral thalamo-mesencephalic infarction: a vertical “one-and-a-half” syndrome. *J Neurol* 1984;231:43–5.
12. Ahmad R, Riachi N. Vertical ‘half-and-a-half’ syndrome: Figure 1. *J Neurol Neurosurg Psychiatry* 2012;83:834–5.
13. Bettencourt S, Ferro JM. Acute ischemic stroke treatment in infective endocarditis: systematic review. *J Stroke Cerebrovasc Dis* 2020;29:104598.
14. Jad I, Gill SK, Krutikov M, et al. When the heart rules the head: ischaemic stroke and intracerebral haemorrhage complicating infective endocarditis. *Pract Neurol* 2017;17:28–34.
15. Yamada M. Cerebral amyloid angiopathy: emerging concepts. *J Stroke Cerebrovasc Dis* 2015;17:17–30.
16. Wilson D, Ambler G, Shakeshaft C, et al. Cerebral microbleeds and intracranial haemorrhage risk in patients anticoagulated for atrial fibrillation after acute ischaemic stroke or transient ischaemic attack (CROMIS-2): a multicentre observational cohort study. *Lancet Neurol* 2018;17:539–47.
17. Mao L, Jin H, Wang M, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. *JAMA Neurol* 2020;77:683.
18. Li Y, Li M, Wang M, Zhou Y, et al. Acute cerebrovascular disease following COVID-19: a single center, retrospective, observational study. *Stroke Vasc Neurol* 2020;5:279–284.
19. Mahammedi A, Saba L, Vagali A, et al. Imaging in neurological disease of hospitalized COVID-19 patients: an Italian multicenter retrospective observational study. *Radiology* 2020;201933:201933.
20. Oxley TJ, Mocco J, Majidi S, et al. Large-Vessel stroke as a presenting feature of Covid-19 in the young. *N Engl J Med* 2020;382:e60.
21. Zhang Y, Xiao M, Zhang S, et al. Coagulopathy and antiphospholipid antibodies in patients with covid-19. *N Engl J Med* 2020;382:e38.
22. Helms J, Tacquard C, Severac F, et al. High risk of thrombosis in patients with severe SARS-CoV-2 infection: a multicenter prospective cohort study. *Intensive Care Med* 2020;46:1.
23. Dumitrascu OM, Veldh Q, Bose S, et al. Acute ophthalmic artery occlusion in a COVID-19 patient on apixaban. *J Stroke Cerebrovasc Dis* 2020;29:2–4.
24. DeSimone CV, Graff-Radford J, El-Harasis MA, et al. Cerebral amyloid angiopathy: diagnosis, clinical implications, and management strategies in atrial fibrillation. *J Am Coll Cardiol* 2017;70:1173–82.
25. Cunnistano RJ, Meschia JF. The clinical dilemma of anticoagulation use in patients with cerebral amyloid angiopathy and atrial fibrillation. *Curr Cardiol Rep* 2018;20:1–9.
26. Vinozadova Y, Coupland C, Hill T, et al. Risks and benefits of direct oral anticoagulants versus warfarin in a real world setting: cohort study in primary care. *BMJ* 2018;362:k2505.
27. Llobrera-Fernandez J, Baksh S, Nemec E. Elderly bleeding risk of direct oral anticoagulants in nonvalvular atrial fibrillation: a systematic review and meta-analysis of cohort studies. *Drugs R D* 2019;19:235–45.

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