A healthy 19-year-old man with no risk factors presented with focal neurological symptoms (dysphasia and right hemiparesis) in the setting of an acute febrile illness and severe cough. Initial CTs showed pan-sinusitis and pulmonary infiltrates. The cerebrospinal fluid was normal. Human coronavirus OC43 was identified in nasal swabs. Repeat CTA/MRA revealed multiple infarcts in the territory of the left middle cerebral artery (MCA) and proximal intra-luminal left internal carotid artery filling defects due to thrombi were demonstrated. No thrombophilia was found and there are no reports of sinusitis-associated carotid thrombosis in the literature. Recent infection, in particular respiratory infection is a confirmed risk factor of ischemic stroke (IS) in both adults and intrinsically, also in young patients. Myriad mechanisms have been demonstrated or postulated in the very young and our report suggests adding carotid thrombi. Previously described cough-induced carotid dissection could not be demonstrated, but similarly, cough-induced intimal injury of the carotid artery remains the most likely culprit, precipitating local thrombus formation and embolization.

**KEYWORDS**

Ischemic stroke (IS) is strongly age-dependent showing a steady increase in incidence with advancing age for both genders. The same pattern was identified among young adult patients who experience IS before 45 years (1). However, these patients differ from older IS patients in their risk factors and etiology: a minority have cervical artery atherosclerosis or small vessel occlusion, while cardioembolism represents a major cause, together with arterial dissections, autoimmune diseases, vasocostriction and hypercoagulable states (2-4). Even in series of young IS patients, events occurring before the age of 20 are few and far between. For example, in the Helsinki young stroke registry, the age-specific occurrence rate of stroke at 15-19 years was only 1.2 per 100,000 (95% CI 0.5-1.8) vs. 9.4, 15.4 and 32.9 among 35-39, 40-44 and 45-49 year-old patients, respectively (1). We report a healthy 19-year-old patient who presented with a serious focal neurological deficit due to cerebral emboli from carotid artery thrombi in the context of a febrile illness with prominent cough, and suggest a novel potential mechanism.

**REPORT OF A CASE**

A 19-year-old soldier was admitted after sounding confused, unable to find words and speaking gibberish instead. His mother reported a preceding cough over 3 weeks in February which became severe and associated with fever (39.1°C) in the last 5 days and headache for 2 days. He had been previously healthy, never smoked or abused alcohol or drugs, had no history of migraine, and his family history was unremarkable.

Physical examination showed fever, sinus tachycardia, nasal mucosa edema and inflammation and clear lungs. The neurological examination revealed dysphasia (nominal, fluent) with normal comprehension/orientation and mild right hemiparesis with extensor plantar response. Meningeal irritation signs were not found. Hb was 12.1 gr/dL (later, 10.2 gr/dL), WBC 15X10^3/L, platelets 300 X10^3/L, CRP 173 mg/dL, ESR 65 mm/hr, normal urine analysis and biochemistry tests. Chest X-ray and CT showed bilateral small pulmonary infiltrates (Fig. 1). Head CT demonstrated acute pansinusitis (Fig. 2). Cerebrospinal fluid was normal, including an extensive screen for viruses by PCR. Serology and PCR for HIV, HBV, HCV, herpes viruses, WNV, rabies virus, rickettsia and coxiella were negative. Cultures, serology and molecular testing for multiple infectious agents (BioFire FilmArray) were negative, as were all blood and urine cultures. HCoV43 was repeatedly (4/4 tests) discovered in nasopharyngeal swabs by PCR (FilmArray Respiratory Panel, BioFire; National Virus Laboratory). All other viruses and infectious agents tested negative.

Repeat neuroimaging demonstrated several acute brain infarctions in the territory of the left middle cerebral artery (MCA) (Fig. 3). CT and MR angiography (CTA, MRA) detected small thrombi in the proximal left internal carotid artery (ICA) (Figure 4). Notably, the cervical and cerebral vasculature was otherwise normal.

On admission he was treated empirically with intravenous ceftriaxone and acyclovir and oral doxycycline. Then, aspirin 100mg/day and full dose LMWH were given. He improved rapidly and at 3 days showed no motor deficits but mild language deficits persisted. A repeat CTA at one month demonstrated completely normal arteries and infarcts in evolution.

**DISCUSSION**

On the patient’s presentation, acute meningoencephalitis/encephalitis was the first concern. However, the normal CSF and subsequent demonstration of cerebral infarcts changed our diagnostic approach, especially as the patient’s acute febrile illness could be accounted for by the demonstration of human coronavirus OC43 infection.

The differential diagnosis of an acute arterial occlusive event is quite large (Table 1) (5). However, the patient’s young age and concurrent febrile illness considerably narrow the differential of IS. It is especially important to rule out infective endocarditis; APS or systemic vasculitis; and possibly pulmonary arteriovenous malformation. An acute sinusitis had been associated with IS in rare reports (6, 7), which incidentally also found ICA narrowing suggesting vascular spasm. Adjacent cerebral venous thrombosis may also occur in sinusitis (7), however, our case is different because of the multiple IS - all in the territory of the left MCA, and thrombi discovered at the proximal left ICA (Figure 4), far from the infected sinuses. The absence of any other vascular pathology narrows the diagnosis down to cerebral emboli (Table 1, I). Cardiac or aortic sources were definitely ruled out (including paradoxical emboli) leaving carotid emboli (Table 1, Ib).
Our patient was a very young, healthy and active man with no discernible traditional or novel cardiovascular risk factors (8). He developed dysphasia and right hemiparesis in the setting of an acute febrile illness. This sequence was well-suited to violent cough, sinusitis and pulmonary infiltrates typical of severe human coronavirus OC43 infection (9), the only infectious organism discovered. Coronaviruses predominantly infect the upper (mild illness) and lower (potentially severe disease) respiratory tract, consistent with the patient’s presentation. Although human coronaviruses have strong CNS tropism (10, 11), and may cause encephalitis in mice (12), no direct involvement of this virus in human CNS disease had been reported. The patient’s neurological symptoms were caused by multiple brain infarcts in the territory of the left MCA, consistent with the patient’s dysphasia. These were very likely due to embolization of a thrombus detected at the left ICA (Figure 4). What could be the cause of this very unusual major artery thrombus in a healthy 19-year-old and how was it related to his acute respiratory infection? Several etiologies need to be considered.

First, some infectious agents proliferate in endothelial cells and may cause vasculitis/perivasculitis, with thrombosis of a major artery. This was reported in VZV or rickettsial infection for example (13), but despite sparse in-vitro and in-vivo data, endothelial cell invasion and vasculitis is not a property of coronaviruses. Second, a group reported an association of a HCoV-NH with acute Kawasaki disease, which can involve coronary, and rarely, also carotid arteries and present late in young adulthood (14). However, the association had been refuted (15), and carotid thrombus was not reported.

Third, acute infections are associated with an increased risk of subsequent coronary and cerebral vascular events (16-18). An increased incidence of IS associated with respiratory infections is well documented, but patients at risk are mostly elderly, with pre-existing atherosclerosis. Carotid thrombi were not reported. In young adults or children, minor respiratory infections in the preceding week, have also been strongly associated with IS (OR 6.3 to 12.1) while vaccinations reduce the risk (19, 20). However, these were case-control studies with no angiography data and mechanisms cannot be inferred.

Fourth, “when you have eliminated the impossible, whatever remains, however improbable, must be the truth” advises Dr Conan Doyle in the words of Sherlock Holmes (21). In our case, cough-induced carotid artery intimal injury and secondary mural thrombi remain the most likely mechanism accounting for all facets of the case in the best tradition of Occam (22). Acute coronavirus infection causing violent coughing, mediated vessel wall injury and precipitated ICA thrombus formation which embolized in part to the ipsilateral MCA and led to his neurological symptoms. Cough is a protective reflex, but can become violent, vigorous and repetitive, sometimes associated with myriad harm including rib fractures, hemarthrosis, and cerebral artery dissections leading to cerebral ischemia or infarction in 67% (23, 24). These dissections tend to occur in the autumn/winter, are often preceded by an infection (23, 25) and are rarely seen in patients with an inherited connective tissue disorder (26). In addition, the sensitivity of CTA/MRA for the detection of cerebral artery dissection is excellent, but imperfect (50%-100%) (27) so that a fraction of dissections may be missed.

In conclusion, our young patient's embolic stroke was due to the ICA thrombus that was likely secondary to intimal injury associated with his violent cough caused by the acute human coronavirus infection. The potential of cough-induced carotid pathology needs to be better recognized and suppression of violent cough should be considered individually for each patient. Moreover, the infection/IS association discussed above could arguably be mediated by cough-induced damage to the ICA in some of the cases, either similar to our patient or carotid artery dissections. This may explain why most infections reported in the context of IS are minor respiratory infections (20) and requires further study.

Table1. Main mechanisms and differential diagnosis of an acute arterial occlusive event*

I. Embolic sources

| A. Cardiac embolism |
|--------------------|
| Mural thrombi (mostly associated with atrial fibrillation)|
| Aortic arch plaques; Carotid artery plaques or other arterial sites; Cervical artery dissection (=minor trauma); Cholesterol-crystal embolism syndrome; infected [myotic] aneurysm.**|

** Cardiac embolism: mural thrombus, most often associated with atrial fibrillation. Aortic arch plaques or other arterial sites; cervical artery dissection = minor trauma; cholesterol-crystal embolism syndrome; infected myotic aneurysm.

II. In-situ thrombosis

| A. Malignancy-associated |
|-------------------------|
| Adenocarcinoma, primarily lung and pancreas (pro-coagulant tissue factor by tumor cells); Myeloproliferative disorders (mostly polycythemia vera, essential thrombocytosis); Waldenstrom macroglobulinemia (hyperviscosity or thrombocytosis). Also, secondary DIC. |

C. Hyperhomocysteinemia

| Genetic (MTHFR variant) | or acquired (mostly folate or vitamin B6, B12 deficiencies) – accelerating atherosclerosis. |

D. Vessel wall disease

| Atherosclerosis; Lipohyalinosis; Amyloid deposition; Dissection – often minor trauma, fibromuscular dysplasia or other connective tissue disease; Vasculitis **; Vascular infection **; Moyamoya; Thrombangiitis obliterans; Trauma; Radiation; DIC; Adjacent mass pressure. |

E. Vasoospastic states

| Migraine or migraine variants; cocaine abuse; methamphetamine; ergotamine; other drugs. |

F. Hypoperfusion states

| Low cardiac output / hypotension due to any cause. May be exacerbated by vasoactive drugs and atherosclerosis. |

G. Sickle cell disease

| Stroke (predominantly). |

H. Prothrombotic medications

| Oral contraceptives, cocaine abuse (see under e.). |

I. Cryptogenic

* In adults, excluding the pulmonary circulation. A combination of two or more mechanisms can occur (e.g. hypoperoxidation and embolism).

** Including patent foramen ovale (PFO) – possible paradoxical emboli originating in the systemic venous circulation; atrial septal defect (ASD), and atrial septal aneurysm (ASA). Controversial role, according to sources.

*** Arterial to arterial embolization of thrombus or plaque can occur spontaneously or after interventions such as arterial catheterization.

# Takayasu arteritis, Giant cell arteritis, Polyrarteritis nodosa, Kawasaki disease, primary CNS angiitis, Behcet's disease, other vasculitides.

### May originate from bacterial endocarditis (myotic aneurysm) or other antecedent infection causing aortitis or infected aneurysm (e.g. salmonella species, staphylococcus aureus, treponema pallidum, HIV and aspergillus - among other potential pathogens). Acute CMV infection and varicella Zoster virus had also been associated with thrombosis.
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