A 24-year-old man with cerebral infarction

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Presentation of case

Dr Ko*: Today's clinicopathological conference is about a 24-year-old man who presented to the Accident and Emergency Department at the Prince of Wales Hospital with a cerebral infarction. The patient was a bank teller who had good past health except for allergic rhinitis. He was a non-smoker and a non-drinker, and had no history of drug abuse. He was brought into hospital by ambulance, following his sudden collapse in the street during his lunch hour. Passers-by had noticed that his right arm had a twitching movement. The patient himself was unable to give a history because he was unconscious.

In the resuscitation room, the patient was semiconscious and had a score of 11 on the Glasgow coma scale. He could open his eyes spontaneously, utter a few incomprehensible sounds, and had localised pain on the left side of his body. His blood pressure was normal, at 110/67 mm Hg, and his pulse was 65 beats per minute and regular; he did not have a fever. The neck was soft, and pupils were equal and reactive to light. Fundal examination showed neither papilloedema nor haemorrhage. Neurological examination showed a flaccid paralysis on the right side. Reflexes were depressed on that side and the plantar was up-going. Cardiovascular and abdominal examinations were normal. The neurosurgeons were called and a plain computed tomography (CT) scan was immediately taken.

Dr Lau†: Before the CT scan, X-rays were taken of the patient's chest, lateral neck, and skull; they were unremarkable. The plain CT scan showed neither a mass lesion nor hydrocephalus. Although there was a suspicion of a loss of grey-white matter junction at the left parietal lobe, this was not clear-cut. If I were the radiologist reporting this CT scan, I would probably have reported it as being normal. Three hours later, a contrast CT scan was performed (Fig 1). There was a loss of grey-white matter junction in the territory of

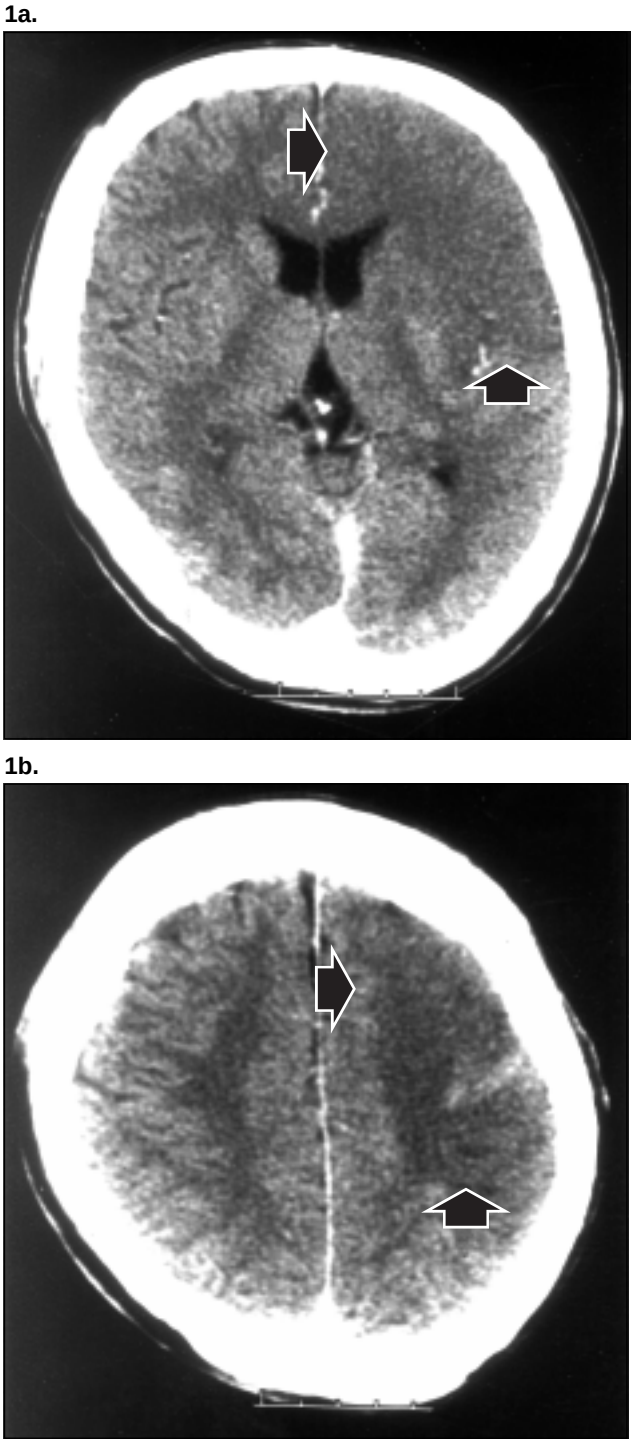

Fig 1. Contrast computed tomography scans performed 3 hours after admission
Scans show loss of grey-white matter differentiation (arrows; 1a & 1b) in the left fronto-parietal region, with effacement of the adjacent cerebral sulci

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the left-middle cerebral artery when compared with other parts of the cerebral hemisphere. There was, however, no substantial mass effect. The appearance was consistent with acute infarction. The vertex of the left cerebral hemisphere, corresponding to the distribution of the callosomarginal artery, was spared. The posterior division of the left-middle cerebral artery was also spared; the whole left-middle cerebral artery was thus not involved. A follow-up chest X-ray was taken 2 days later and was essentially normal.

Dr Ko: The patient was admitted to the medical ward with a diagnosis of cerebral infarction. He developed profuse vomiting which subsided. Results of blood investigations were as follows: haemoglobin level 164 g/L (normal range, 140-180 g/L); white cell count $13.2x10^9$/L (normal range, $4.0\text{-}10.8x10^9$/L); and platelet count normal. The erythrocyte sedimentation rate was 5 mm/hr, and the clotting profiles, renal function, and liver function were normal, as were blood gases and levels of blood glucose, cholesterol, and triglyceride. The electrocardiogram was also normal. A cardiologist in our team performed an echocardiogram. There was good left ventricular function and the left atrium was not enlarged. We specifically looked for a patent foramen ovale, but it was absent. It is worth noting that a transthoracic echocardiogram but not a trans-oesphageal echocardiogram was performed. The VDRL test, and urine and blood cultures were negative. Autoimmune factors such as antinuclear factor, and anti-DNA and anti-cardiolipin antibodies were absent; complement levels were low.

The patient subsequently had a fever (temperature, 40°C), but sepsis work-up was negative. Intravenous cefuroxime was given, and glycerol was administered to reduce cerebral oedema. Fraxiparine (Sanofi, Surrey, UK), a low molecular weight heparin, was given to treat the cerebral infarction. The patient remained stable over the next 2 days with a score of 10-11 on the Glasgow coma scale. However, he developed a sudden deterioration 2 days after admission. The left pupil became fixed and dilated, and the patient exhibited an extended posture of the right side of the body. A CT scan was repeated. The neurosurgeons reassessed the patient and decided not to use active intervention. The patient died shortly afterwards on the same day.

Dr Lau: This is the plain CT that was taken 3 days after the patient's admission to hospital (Fig 2). There is a hypodense area on the left cerebral hemisphere and mass effect is compressing the ventricles and midline shift of the anterior division of the left-middle cerebral artery and left anterior cerebral artery. All the

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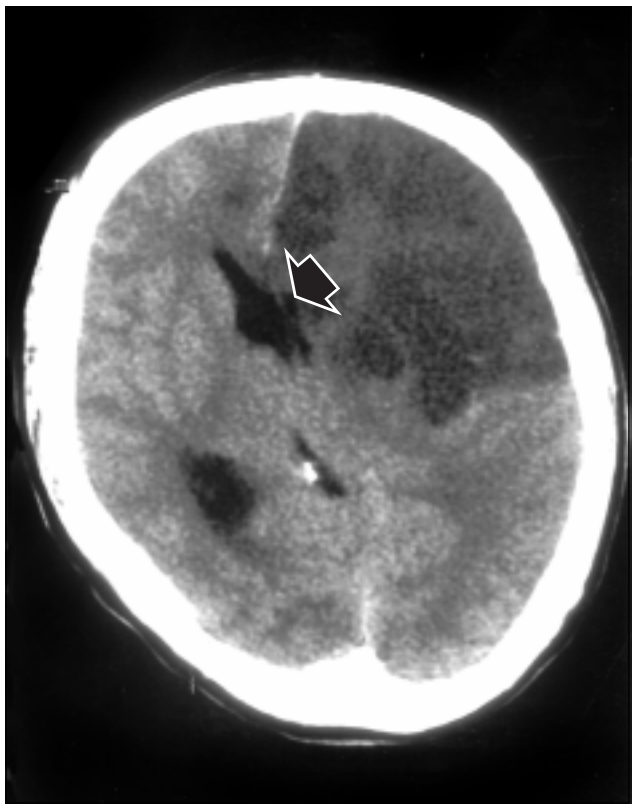

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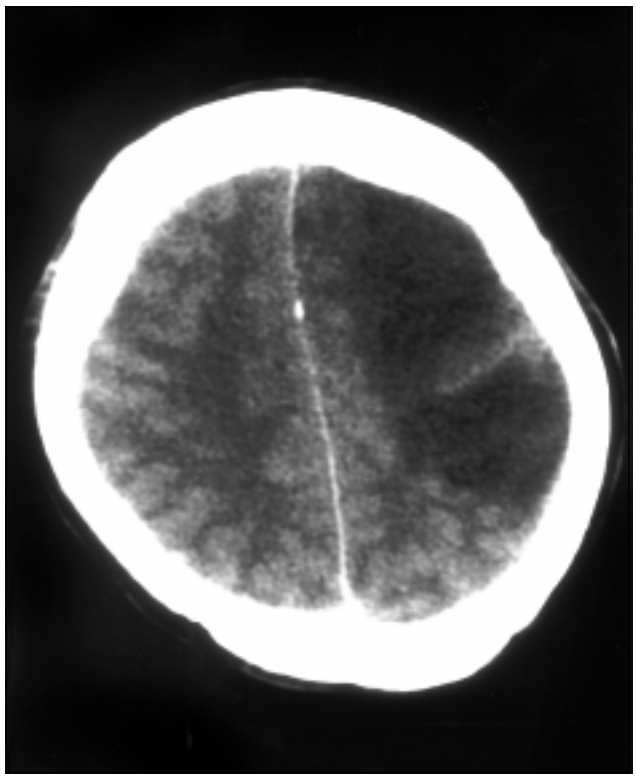

Fig 2. Non-contrast computed tomography scans performed 3 days after admission
(2a & 2b) subacute infarction in the left fronto-parietal region is obvious and corresponds to the anterior division of the left middle cerebral artery and left anterior cerebral artery distribution; the callosomarginal artery was spared; note the extensive positive mass effect, with compression on the frontal horns, and marked left to right midline shift (arrow)

Table 1. Causes of ischaemic stroke in adults younger than 30 years*

Causes	Patients, n=41 No. (%)
1 Mitral valve prolapse	12 (29.3)
2 Arterial dissection	9 (22.0)
3 Migraine	6 (14.6)
4 'Intracranial segmental angiopathy'	2 (4.9)
5 Intracranial arteritis	2 (4.9)
6 Sagittal sinus thrombosis	2 (4.9)
7 Probable atherosclerosis	1 (2.4)
8 Possible atherosclerosis	1 (2.4)
9 Intraluminal thrombosis	1 (2.4)
10 Mitochondrial cytopathy	1 (2.4)
11 Unknown	4 (9.8)

*Table modified from reference 2; study included 26 females and 15 males; 3 patients died and 81% of survivors returned to work

vital structures have been displaced to the right. Compared with the first CT scan, the infarct has become much more obvious but the same area is affected. I am not convinced that there is any haemorrhage into the infarcted area.

Differential diagnoses

Prof Lee[‡]: We will ask Dr Richard Kay to give us the differential diagnoses.

Dr Kay[§]: Dr Ko gave a very good history which was unfortunately not very helpful, because it does not contain any diagnostic clue. I understand that the patient did not have a carotid bruit. The only diagnostic clue is the patient's age. The incidence of strokes in patients under the age of 45 years accounts for about 5% of all strokes.[1] When death occurs, as in this case, it is thus tragic and for that reason, I think we ought to approach young patients with strokes with particular care.

As we do not have enough experience ourselves to make an immediate diagnosis, the only intelligent option is to refer to the literature. There are two properly conducted studies of strokes in young patients. The first one was published by Bogousslavsky and Regli in Lausanne, Switzerland, in 1987; the study was probably conducted in the early 1980s.[2] Diagnostic techniques have since changed and these researchers were able to do angiography but not magnetic resonance imaging (MRI) studies. According to Table 1, the commonest condition is mitral valve prolapse. It was very popular to look for this diagnosis 10 years ago and it can be easily diagnosed using a 2-dimensional echocardiogram. I think it had been excluded for this particular patient. The second most common condition on the list is arterial dissection. We will come back to this later, as this is probably the diagnosis. The third condition on this list is migraine. We have not encountered many infarctions due to migraine in this hospital because migraine in the Chinese population is relatively uncommon compared with the population in Switzerland. The fourth cause of infarction is 'intracranial segmental angiopathy'. I use inverted commas because it is really just an angiographic description with no pathological diagnosis implied. Not all of the lesions are related to atherosclerosis, which is the assumed cause for most cases of segmental arteriopathy; I have also been told by some neurologists in China that some cases could be due to parasitic infection. Intracranial arteritis is probably not the cause in this case because the complement level is normal.

Sagittal sinus thrombosis is a cause of strokes in young people. There is usually a predisposing cause; a major cause is dehydration. Sagittal sinus thrombosis in pregnant women has recently been described.[1] An important radiological sign of this type of thrombosis is haemorrhagic transformation, but as Dr Lau said earlier, there were no convincing signs of haemorrhage in this case. The parasagittal distribution of infarcts in sagittal sinus thrombosis was also not seen in this case in which the infarct was clearly arterial in distribution.

Causes 7 and 8 in Table 1 refer to probable and possible atherosclerosis. In a 24-year-old Chinese man, this diagnosis would be unlikely. The ninth cause, intraluminal thrombosis, refers to patients with a hypercoagulable state, the most important of which is the anti-cardiolipin or anti-phospholipid antibody syndrome. Most of these patients, however, present with venous thromboembolism rather than a sudden stroke.

There is a condition termed mitochondrial cytopathy. It is an interesting cause of stroke in children,

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Table 2. Causes of death in young adults with ischaemic stroke*

Causes	No. of deaths (%)
1 Large vessel atherosclerosis	19 (31.1)
2 Cardioembolism	18 (29.5)
3 Other	
systemic lupus erythematosus	3
vasculitis	3
dissection	2
hypovolaemia	2
moyamoya disease	1
cocaine abuse	1
neck cancer	1
trauma	1
Subtotal	14 (23.0)
4 Small vessel disease	5 (8.2)
5 Haematological	4 (6.6)
6 Unknown	1 (1.6)
Total	61

*Table modified from reference 4; subjects were aged between 15 and 45 years

but not so much in young adults. It is commonly referred to as MELAS—mitochondrial encephalopathy with lactic acidosis and stroke-like syndrome. On a CT scan, multiple infarcts can be detected. Finally, there are a few cases of infarction with unknown causes, which would be expected in a properly conducted survey. I understand that these cases included young women taking contraceptive pills, who were smokers. Three patients (7.3%) in the Swiss series died and 81% of the survivors returned to work.

Dr Ng[‖]: Would you like to comment on moyamoya disease?

Dr Kay: Moyamoya disease is included in the second study (Table 2). It was described by a Japanese group,[3] and 'moyamoya' literally means 'puff of smoke'. On an angiogram, the intracranial vessels look like a puff of smoke as the contrast medium stops at the carotid siphon. The collaterals are outlined as a puff of smoke, implying that there is severe intracranial occlusion. The American study from lowa (Table 2)[4] examined patients who died, unlike the previous series from Lausanne. The young adults were also defined as being between 15 and 45 years. Thirty-one percent of deaths were due to large vessel disease. Cardioembolism accounted for another 30% of deaths. Small vessel disease constituted 8% of deaths, which is unusual, as lacunar infarcts generally do not cause mortality. Other causes of death include systemic lupus erythematosus, vasculitis, and dissection. You will remember that dissection was the second commonest cause in the previous study (Table 1)—patients with this do not always die.

Combining the information from these two series, I think that we have not yet excluded dissection. It seems to be common and can occur in previously healthy people who may be just walking in the street. Although trauma is supposed to be a cause of dissection, the trauma required to induce dissection is usually not big. Turning one's head to reverse a car can be sufficient. The aetiology of dissection also includes diseases like Marfan's syndrome, Ehlers-Danlos syndrome, and cystic medial necrosis. The latter is essentially a histological diagnosis. The site of dissection is usually at the internal carotid artery, which is compatible with an infarct in the anterior and middle cerebral artery territories. Secondly, I think we have not adequately excluded a patent foramen ovale. You would need a transoesophageal echocardiogram to exclude it properly; only a transthoracic one was performed in this case. Preferably, the patient should also be doing a Valsalva manoeuvre. Patent foramen ovale gives paradoxical emboli; venous thrombi from the venous circulation can pass through the foramen and produce arterial emboli. The incidence of patent foramen ovale has been reported to be 25%.[5] Other diseases include left atrial appendage and atrial septal aneurysm; these are diagnoses following echocardiography. However, I understand that the patient in this case was dying, and transoesophageal echocardiography might not have been possible.

Finally, what other tests could we have done? The patient probably needed MRI. Although the infarct was clearly visible in the CT scan, one might be able to diagnose dissection from the MRI. The lower cuts of the neck on the MRI would show blood inside the carotid artery; blood clot collection inside the carotid artery is a good sign of dissection. In addition, MRI would be much less invasive than conventional angiography. What about treatment? With the patient having such a massive infarct, the clinicians probably had done all that they could. In other parts of the world, a hemispherectomy may have been performed, as the infarction involved the non-dominant hemisphere. His life might have been saved, but he would have been left with severe neurological deficits.

Student: What about the patient's fever? Was a blood culture taken?

Dr Ko: Blood and urine culture results came back only after the patient died, and they were negative.

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Student: Was the cardiologist asked to exclude a cardiac myxoma? Is it easy to miss it in an echocardiogram?

Dr Kay: A cardiac myxoma would be very obvious in an echocardiogram.

Pathology

Prof Lee: Could the dissection have come from the aorta?

Dr Kay: Perhaps the pathologist can answer that question. Aortic dissection would occlude all three major branches of the aorta and would produce a whole brain infarct.

Dr Ng: We have seen cases where dissection aneurysm of the ascending aorta have resulted in a stroke and even transient ischaemic attacks. In these cases, the ascending aorta usually produces extensive haemorrhage and is rapidly fatal. Occasionally, blood dissects back into the lumen; the patient does not die but presents instead with a cerebral infarction.

As regards this patient, an autopsy was performed and apart from the brain, there was nothing else found to be abnormal. The mitral valve was normal and there was no patent foramen ovale. Figure 3 shows a large left cerebral infarct in the brain. There was a mid-line shift to the right, with compression of the ventricle. The students will recall that early acute infarction produces only cerebral swelling. Cystic liquefactive necrosis occurs at a later stage. You can see loss of grey-white matter junction. Histological examination detected cerebral oedema, pallor, and loosening of the neuropils. Many shrunken ischaemic neurons were also visible. There was little cellular reaction yet the infarction was very acute. The carotid arteries at the neck were normal.

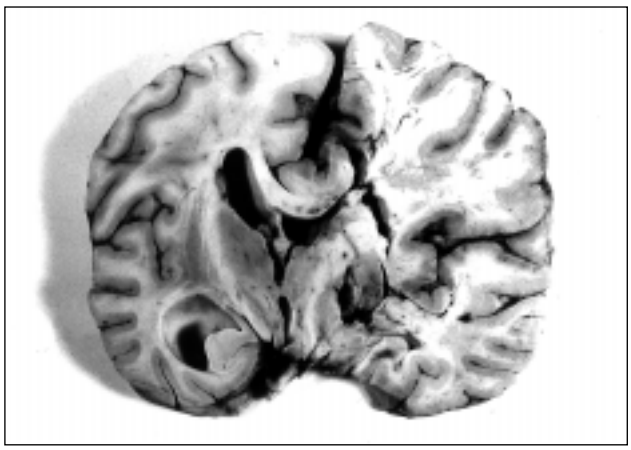

Fig 3. Photograph of post-mortem brain showing severe swelling of the left cerebral hemisphere with infarction

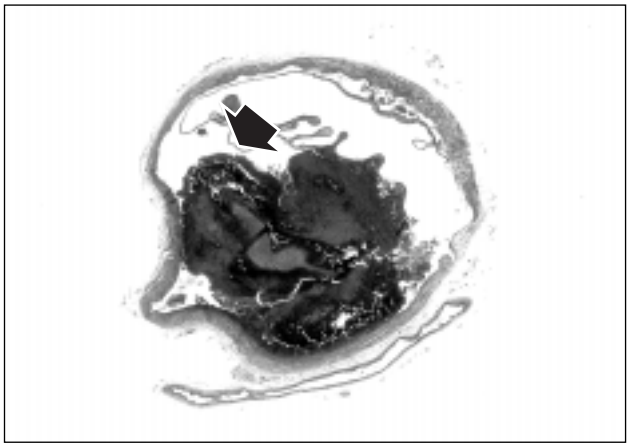

Fig 4. Histological section of the left internal carotid artery showing extensive subintimal dissection and haematoma formation
Arrow shows the internal elastic lamina (H & E, x 15)

At brain cutting, however, I could see a fresh blood clot at the left internal carotid artery. At first, I thought it was an artefact because the clot was so fresh, but the histological section of this artery (Fig 4) surprised me, as it showed seepage of blood into the intima of the vessel, which produced an occlusion of the vessel, that is, a dissection had occurred. You can see the internal elastic lamina, outlined in this slide by an elastic stain, which has been lifted up into the lumen by the subintimal blood clot. The cause of spontaneous dissection of the intracranial artery is usually trauma although, as Dr Kay has said, the trauma may be minor; the subintimal dissection is typical in such instances.[1,5-7] Dissection may also be totally spontaneous, as in this particular case.[8-9]

Pathological discussion

Dr Ng: For the purpose of comparison, I will show you a case of dissection of the vertebral artery that we saw about 15 months ago. A 75-year-old man had extensive athero-

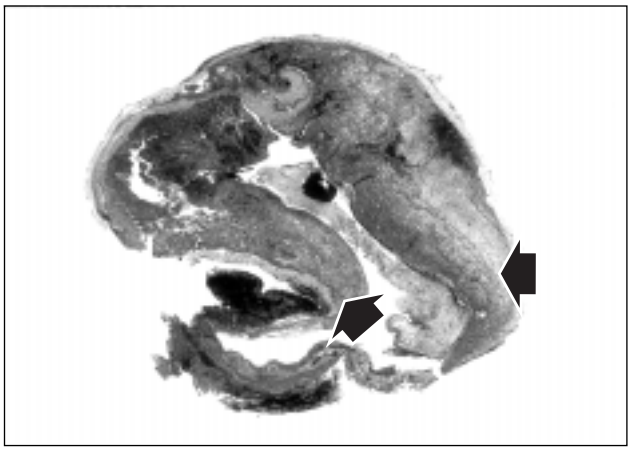

Fig 5. Vertebral artery from a 75-year-old man who presented with subarachnoid haemorrhage
Autopsy showed intramural dissection of an atherosclerotic vertebral artery. Arrows indicate site of dissection (H & E, x 15)

sclerotic disease and dissection occurred in an atherosclerotic vertebral artery (Fig 5). In such cases, the dissection is often intramural,[10] unlike the subintimal blood clot in trauma-induced dissection that you saw in the previous picture. You can see the atherosclerotic vessel wall and a disrupted internal elastic lamina (Fig 5). The same is true for dissection in an atherosclerotic aorta.[11] In the case of the 75-year-old man, there was profuse subarachnoid haemorrhage and blood had collected around the foramen magnum; this contrasts with the situation during a subarachnoid haemorrhage due to ruptured berry aneurysm, where blood appears in the basal cisterns. The neurosurgeons were actually able to make a correct diagnosis before the patient died.

To supplement what Dr Kay has already said, dissection of cervical vessels is not uncommon in criminal assaults that are encountered in forensic medicine. The classic scenario is that someone falls to the ground and gets kicked at the side of the neck by someone wearing heavy boots. The vertebral artery may rupture and produce fatal subarachnoid haemorrhage. In road traffic accidents, neck injuries due to sudden hyperextension or whiplash can produce dissection. Even an apparently minor trauma (eg chiropractic, yoga, gymnastics, windsurfing) can potentially produce dissection.[6] Rarely, you can get it in extensive atherosclerosis, as I have shown you, and in rare diseases such as Marfan's syndrome and Ehlers-Danlos syndrome. In these conditions, there is a malformation of collagen and the vessel is poorly supported.

Presentation of carotid artery dissection is as a stroke or ischaemic attack; the former most commonly occurs at the middle cerebral artery territory. It is possible to diagnose carotid dissection by angiography, MRI, or even Doppler ultrasonography.[12,13] If the patient survives, the rate of recurrence is not high.[14] Some patients have been treated successfully with aspirin or anticoagulants; canalisation of a previously thrombosed carotid artery due to dissection has also been documented.[13,14]

Pathological diagnosis

Cerebral infarction due to carotid artery dissection

Addendum

During the reviewing process, it was questioned why a contrast CT scan was performed in the first instance, as intravascular contrast agents may be harmful in cases of cerebral infarction. One must take into account the desperate clinical situation of a comatose young man, and contrast CT might have, for example, revealed a brain stem tumour.

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