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A history of research on the clinical and pathological features of transient ischaemic attack

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ABSTRACT

We examine the history of research on transient ischaemic attack, from its initial conception as a group of reversible neurological deficits to the establishment of the modern clinical-pathological concept. We analysed classic treatises and publications addressing the clinical and pathological features of transient neurological deficits. These episodes were attributed to numerous mechanisms, including vasospasm, blood pressure changes, and cardiac dysfunction. Likewise, we compare descriptions of different proposed aetiologies appearing up to the second half of the 20th century and underscore the importance of clinical observation and drug trials in the establishment of a new clinical form of altered cerebral circulation.

KEYWORDS
Transient ischaemic attack, cerebrovascular disease, pathogenesis, aetiology, embolism, history

The introduction of such new techniques as angiography, CT, MRI, and Doppler ultrasound during the second half of the 20th century helped define new conditions with different manifestations. Transient ischaemic attack (TIA) was one such new entity to be added to the list of cerebrovascular diseases.

TIA refers to a transient episode of focal neurological deficits which resolve in less than 24 hours. Symptoms are attributed to interrupted blood supply in an area of the brain that consequently displays functional loss.

Diagnosing TIA is extremely important because of the associated risk of a cerebrovascular accident able to elicit permanent and more or less immediate sequelae.

Clinical observations of transient cerebral deficit appear among the writings of Hippocrates of Kos (c. 460 BCE - 370 BCE). This author regarded symptoms of TIA as heralding imminent apoplexy: "unaccustomed attacks of anaesthesia and numbness are impending signs of apoplexy".[1(p862)]

Clinical observations of transient neurological deficits do not provide insights on the aetiology. In line with this idea, Soranus of Ephesus (98 CE - 138 CE) stated that apoplexy may be preceded by a prodromal syndrome, although these manifestations are non-specific and may also precede epileptic seizures or attacks of mania.[2]

In 1783, Jean-Paul Grandjean de Fouchy provided the first self-reported case of TIA. He experienced motor aphasia lasting nearly one minute; during this time, he was fully aware of his symptoms.[1(p864)]

In 1862, Maurice Raynaud concluded that some cases of transient vision loss and other temporary neurological deficits were caused by a spasm in a cerebral artery, similar to the one causing the syndrome he had described in the extremities.[3]

In 1909, William Russell put forth the hypothesis that transient cerebral deficits were caused by arterial vasospasm. He presented the case of a 50-year old man who had experienced three episodes of paraesthesia in his right cheek and arm associated with marked difficulty articulating speech. Some time later, this patient experienced right homonymous hemianopsia. Based on findings from the anamnesis and examination, Russell ruled

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out embolism and thrombosis in favour of vasospasm, as Raynaud had suggested.[3]

In 1911, renowned internist William Osler published an article on transient attacks of aphasia and paralysis in patients with hypertension and arteriosclerosis. Osler too attributed these transient deficits to vasospasm.[3]

In an article published in 1914, Hunt described the symptoms associated with internal carotid artery occlusion. When considering compensatory circulatory mechanisms in the circle of Willis, he described a syndrome which he called 'cerebral intermittent claudication'. He compared symptoms of this condition to those of intermittent claudication affecting the lower limbs and resulting from arteriosclerosis of the iliac or femoral arteries.[4]

In 1948, Pickering cast doubt on the hypothesis that arterial vasospasm caused transient cerebral deficits. This author stated that cerebral arteries were the least reactive in the body and that when spasms did occur, it was very difficult to determine their causative agent.[5]

Pickering observed macroscopic lesions in neuropathology studies of patients with hemiplegia. In contrast, these lesions were much less noticeable in patients who had exhibited transient neurological deficits. Transient cerebral deficits were once included within the uraemia symptom complex, known today as pseudouraemia.

Pickering summarised Volhard's findings of observed papilloedema in the eye fundus of patients with acute cerebral hypertension and acute nephritis or pregnancy toxaemia. Based on these observations, Volhard had concluded that cerebral deficits that resolved after hypertension had normalised were due to acute oedema of the brain. Volhard theorised that anoxia of brain capillaries would allow fluid and proteins into the intercellular space, thus causing neurological deficits.

Pickering opposed this hypothesis based on having recorded no increase in CSF protein levels either during or after attacks of hypertension in 3 different patients.[5]

In 1953, Corday, Rosenberg, and Putnam published an article on cerebrovascular disease and established the clinical-pathological concept of cerebrovascular insufficiency.[1]

Their article was criticised 7 years later by Denny-Brown, who stated that this concept had multiple and non-specific clinical applications and maintained that this 'insufficiency' could not be detected in neuropathology studies.[6] According to Denny-Brown, the causes of insufficiency, unlike its consequences, could not be verified, and compared insufficiency to migraine and chest pain, two clinical phenomena with no associated organic lesions.

This author classified cerebrovascular insufficiency attacks in two groups by aetiology: 1) those caused by haemodynamic disorders secondary to a sudden drop in arterial blood pressure, frequently occurring in association with stenosis of carotid or vertebrobasilar arteries; and 2) those of embolic origin, that is, caused by an embolus of non-cardiac origin and formed by platelet aggregation.

The emboligenic mechanism as a cause of recurrent neurological deficits was studied experimentally by Denny-Brown, Meyer, and Leiderman.[7] By performing arterial ligations in monkeys, these researchers observed that emboli moved along arteries before eventually breaking and disappearing through the terminal branches. Emboli were soft and friable, which suggested that they were formed by platelets and fibrin and devoid of red blood cells. Embolus formation was attributed to endothelial lesions in the area where the artery had been ligated.

The results from these experimental observations made by Denny-Brown in 1960 resembled those from a case that had been published by Miller Fisher one year before.[8] This author described the case of a patient with recurrent attacks of amaurosis in the left eye; one episode was accompanied by mild right hemiparesis and dysarthria. During one of the episodes, Miller Fisher examined the eye fundus and found an embolus consisting of a white material that was slowly moving along one of the retinal arteries. He ruled out a cardiac origin of the embolus and suggested that it was formed by fibrin. An angiography study revealed narrowing of the left carotid artery at the level of the carotid sinus and no abnormalities in the right carotid artery. The patient was treated with dicoumarol and experienced no additional episodes of amaurosis. Miller Fisher concluded that this drug prevented the aggregation of fibrin and platelet masses on the atheromatous plaque located in the carotid sinus.

In his study published in 1960, Denny-Brown concluded that a lesion to an artery or arteriole may result in the aggregation of fibrin and platelets to form friable emboli,

which in turn may cause transient ischaemia in areas irrigated by that vessel. No arterial spasm was detected and emboli were found to disintegrate spontaneously. The author cited the observations made by several ophthalmologists who had reported cases of retinal emboli breaking down as they passed through the retinal arteries. Klippel-Feil observed platelet microemboli secondary to trauma to the supra-aortic vessels arising from congenital abnormalities or osteoarthritis in the cervical vertebrae.[6]

Hutchinson and Yates made significant contributions to our understanding of vascular pathology and cervical osteoarthritis.[9] These authors studied lesions in the vertebrobasilar system, especially at the level of the vertebral artery as it passes through the cervical vertebrae. According to Hutchinson and Yates, these lesions had received little attention, perhaps due to the difficulty of conducting a pathology study of the cervical column. They developed a new technique consisting of studying the cervical portion of the vertebral column as a whole, from the atlas to the seventh cervical vertebra. They decalcified the vertebrae in nitric acid to facilitate dissection and permit a thorough study of vertebral arteries. According to these authors, stenosis of the supra-aortic vessels was frequent in elderly patients. The endothelium may form platelet microemboli over these lesions.

Lesions to the carotid artery at the level of the cervical column were determined to cause stroke thanks to studies published by Denny-Brown[6] and Miller Fisher.[8] Likewise, the study by Hutchinson and Yates demonstrated that lesions to vertebrobasilar arteries, with similar clinical manifestations, may also cause stroke.

It became more and more evident that transient focal brain deficits were caused by emboli arriving in the large vessels carrying blood to the brain. Two cases studied by Ross Russell confirmed the emboligenic hypothesis[10]; both patients experienced transient episodes of amaurosis in one eye and motor deficits on the contralateral side. Eye fundus examination revealed papillary pallor and low blood flow rate, and the inside wall of the artery displayed alternating light and dark segments. Subsequent eye fundus examinations revealed no abnormalities in retinal blood vessels. However, the first patient displayed retinal oedema; he was diagnosed with internal carotid artery thrombosis and treated surgically. During the procedure, a thrombus was identified in the proximal segment of the internal carotid artery. The patient died in the postoperative period and the autopsy revealed thrombi in the internal and external carotid arteries. There was an infarcted area in the territory of the middle cerebral artery, mostly affecting the parietal lobe and to a lesser extent, the frontal and temporal lobes.

The second patient experienced several episodes of amaurosis in the right eye. Eye fundus examination revealed white, friable emboli on several occasions. Recurrent episodes of amaurosis over several days led to irreversible amaurosis. Coinciding with the last episodes of amaurosis, the patient experienced paraesthesia and sensory alterations in his contralateral limbs.

Ross Russell concluded that in the absence of anomalies in arterial blood pressure and heart rate, transient episodes of brain ischaemia were caused by microemboli travelling from atheromatous plaques in the arteries supplying the brain (Figure 1).

In 1963, McBrien, Bradley, and Ashton[11] reported the case of a patient with amaurosis in the right eye who subsequently experienced left hemiparesis. Arteriography revealed stenosis caused by atheromatous plaque in the right carotid artery. The patient underwent thromboendarterectomy but died during the postoperative period. An autopsy revealed oedema and an embolus within the lumen of a nasal artery. The embolus consisted of platelets, some leukocytes, small amounts of lipids, and no fibrin or red blood cells.

The study by McBrien, Bradley, and Ashton, and the others mentioned previously all support the results of experimental studies by Florey (1929) and Zucker (1947), who found that platelet deposition is the first step in thrombus formation.[11]

Describing the natural history of TIA was decisive for establishing the conceptual basis of that entity. The study

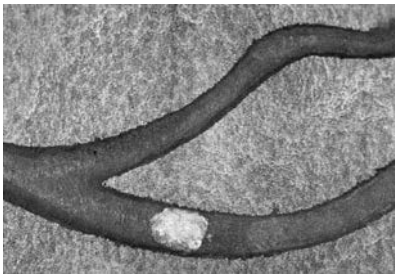

Figure 1. Platelet microembolus. SEN Historical Archive

by Acheson and Hutchinson described the clinical progression of this condition.[12]

These authors reiterated the idea that patients experiencing TIAs were at risk for experiencing a stroke, which would leave permanent sequelae. They also observed that the risk of stroke was similar in patients whether or not they were treated with anticoagulants. In light of this paradox, they decided to monitor these patients for extended periods of time (a mean of 3 years and 2 months). Inclusion criteria were as follows: 1) episodes lasting a maximum of one hour, 2) complete recovery between episodes, and 3) for patients with vertigo, at least two other symptoms of hindbrain ischaemia. Patients with heart rate or blood pressure anomalies were excluded.

These authors studied and followed up on 82 patients with a history of TIA: 42 of these patients went on to present infarcts and the remaining 40 displayed no permanent deficits.

According to their results, TIAs were more frequent in the vertebrobasilar system, whereas infarcts were more common among patients whose TIA involved the carotid arteries. A higher frequency of TIA was not associated with a greater risk of experiencing stroke. The percentage of patients with TIAs who developed stroke was similar in patients with carotid system or vertebrobasilar system involvement.

Acheson and Hutchinson concluded that TIAs may be caused by two different mechanisms: 1) cerebral circulatory insufficiency secondary to systemic blood pressure changes or cardiac output anomalies in patients with previously damaged arteries; and 2) thromboembolism, due to embolus fragmentation, which allows small embolic pieces to enter the cerebral arteries without causing organic damage to the brain.

These two mechanisms have been confirmed in numerous observations of transient amaurosis with visible microemboli. This hypothesis was put forth by Millikan[1] and may be extrapolated from the retinal level to the entire cerebral circulation.

In 1975, Toole et al.[13] conducted a prospective study of 160 patients with TIAs. All patients underwent angiography (supra-aortic and intracranial vessels); results were normal in only six patients. Patients were monitored during a mean of 3.8 years. Cerebrovascular disease was associated with other conditions in 86%, whereas the remaining 14% had no associated disorders. Within the first group, some 64% had high blood pressure and 47% had heart disease.

Of the patient total, 77 patients were treated with warfarin and 82 underwent surgery. Toole et al. concluded the following:

1) Anticoagulants reduced the incidence of TIA but did not protect against stroke.

2) Surgical treatment protected against TIA and stroke, whether for unilateral or for bilateral lesions to the carotid artery.

3) In patients with multiple vascular lesions, surgery did not improve prognosis in terms of life expectancy.

4) Patients with lesions to the subclavian artery had a lower risk of experiencing a stroke than those with lesions to the carotid.

5) By the 4-year follow-up visit, 23% of the patients who had TIA died: only 9% due to stroke and the remainder due to acute myocardial infarction.

6) Mortality rates were 4 times higher among patients with heart disease.

7) Surgical treatment did not change survival rates in patients with TIA who also had heart disease.

Since TIAs were first identified as a warning sign for stroke leaving irreversible sequelae, several authors have tested different prophylactic treatments against platelet emboli to prevent TIAs and progression to cerebral infarct.[1]

In 1978, Barnett et al.[14] published the results of a Canadian study investigating whether aspirin, sulfinpyrazone, or a combination of the two would improve prognosis, in terms of infarct and mortality rates, in patients with TIAs.

This double-blind, randomised, factorial study included 585 patients who were monitored for 26 months. All participants had to have experienced multiple episodes of brain or retinal TIA at least 3 months before the study began.

Patients were allocated to four different treatment groups: sulfinpyrazone, aspirin, sulfinpyrazone plus aspirin, and placebo.

The study found aspirin to effectively prevent TIA recurrence and cerebral infarcts causing permanent sequelae or even death. Similar results were obtained with aspirin plus sulfinpyrazone as combination treatment.

Sulfinpyrazone alone failed to decrease incidence of TIA and progression to stroke; however, it was found to prevent myocardial infarction. The authors could not explain the differences between the effects of these two drugs.

After reviewing the literature, we can conclude that thorough clinical observation is extremely valuable for establishing new clinical forms of cerebrovascular diseases, as occurred with TIA. The data provided by neuroimaging techniques, especially angiography of the cerebral arteries and supra-aortic trunks, was essential for demonstrating the pathogenic mechanism underlying TIA.

Conflicts of interest

The author has no conflicts of interest to declare.

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