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The definition of stroke

Alexander P Coupland[1], Ankur Thapar[1], Mahim I Qureshi[1], Harri Jenkins[2] and Alun H Davies[1]
[1]Section of Vascular Surgery, Imperial College London, Charing Cross Hospital, London, W6 8RF, UK
[2]Department of Neurology, Imperial College Healthcare NHS Trust, Charing Cross Hospital, London W6 8RF, UK
Corresponding author: Alun H Davies. Email: a.h.davies@imperial.ac.uk

It is impossible to cure a severe attack of apoplexy, and difficult to cure a mild one

– Hippocratic Aphorism[1]

Introduction

Hippocrates could never have imagined the progress made in stroke care since this statement, yet the world is still unable to agree on a universal definition. This review charts the evolution of the definition of stroke and highlights current problems.

Apoplexy

The first recorded use of 'stroke' as a lay term was in 1599, attributing the sudden onset of symptoms to a 'stroke of God's hande'.[2,3] It was not adopted into the medical lexicon of the time and physicians used the term 'apoplexy', a diagnosis that had been in existence since the Hippocratic writings.[1]

The word 'stroke' is related to the Greek word 'apoplexia' which implies being struck with a deadly blow,[4] but it would be incorrect to draw direct parallels between our modern concept of stroke and what has been classically referred to as apoplexy.

Apoplexy was an umbrella term, describing a condition in which the patient had a 'sudden abolition of all activities of the mind with the preservation . . . of the pulse and respiration'.[5] Hippocrates describes a patient experiencing sudden pain, losing speech, with a rattle in his throat, urinating without awareness and being unresponsive.[1] These events describe a dramatic pathology and some cases of apoplexy were likely strokes, but the presentation encompassed conditions we now consider 'stroke mimics' such as epilepsy, migraine and sudden cardiac death.[6]

To strengthen the correlation between apoplexy and our modern concept of stroke, the condition has long been associated with paralysis. In the Hippocratic writings, the word used to describe such findings was 'paraplexy' and, though now obsolete, is understood to be synonymous with what we now term 'paraplegia'.[1] In the 19th century, Dr James Copland recognised the intimacy between apoplexy and 'palsy' (paralysis) stating that they are 'so intimately connected . . . it [is] most difficult, if not altogether impossible, to treat . . . one apart from the other'.[7]

From humours to autopsies

Hippocrates hypothesised that the pathogenesis of 'apoplexy' was linked to humoural theory. He believed that blood (one of the four humours alongside yellow bile, black bile and phlegm) held our spirit or 'vitality'. Consequently, any interference with the flow of vitality to the brain would result in apoplexy.

His hypothesis was supported by his proponent, Galen (born AD 131)[2] who also believed that the causes of apoplexy were due to humoural aberrations such as the accumulation of phlegm or black bile in the cerebral ventricles.[5] It was not until the 17th century and the rise of physician-anatomists that this position was challenged.

Among the most important advances in the understanding of stroke were those made by the Swiss physician Johan Jakob Wepfer (1620–1695). Wepfer is credited with being the first to observe that apoplexy was associated with cerebral haemorrhage.[4] He published the results of four autopsies in his *Historiae apoplecticorum* (published 1658)[8] and with a lack of black bile or phlegm in the cerebral ventricles, Galen's hypothesis began to be doubted and the pathogenesis of apoplexy recast in pathological terms.

Over time, the number of autopsies being performed increased and the most significant work published in the 17th century was Theophile Bonet's *Sepulchretum sive Anatomia Practica* (published in

1679), of which Section II of Book I is dedicated to apoplexy. At this time, varying causes of apoplexy had begun to be recognised, and though Bonet did not formally categorise aetiologies, the autopsy findings did point to a number of possibilities. It was recognised that apoplexy could be caused by intracranial haemorrhage, tumours and even cerebral abscesses. In Bonet's autopsies, excess fluid, or serum, was also found in the head. Unlike the other causes of apoplexy, the mechanism of this fluid causing disease was more difficult to explain, particularly since it was recognised that hydrocephalics could live for many years with large amounts of cerebral fluid, without becoming apoplectic.[5] The main hypothesis was that it blocked pores in the brain, and hence the passage of 'spirits'.[4]

Bonet's *Sepulchretum* was highly regarded, but was eventually superseded by the publication of Giovoanni Morgagni's (1682–1771) *De Sedibus et Causis Morborum Per Anatomen Indagatis* in 1761. Morgagni, considered to be the founder of pathology,[5] built on Bonet's work but with fundamental differences: he did not recognise head trauma as a cause of apoplexy (though he acknowledged it could cause an 'apoplectic condition') and he divided the causes of apoplexy into two principle groups: 'sanguineous' and 'serous'.[5]

The move towards dichotomous causes (sanguineous and serous) was a significant step. The 'sanguineous' form represented intracranial haemorrhage and the excess fluid referred to in the 'serous' form (also found by Bonet) has been postulated as being normal cerebrospinal fluid. The corresponding cerebral infarcts may have been missed, though he did point to abnormalities in the corpus striatum in some cases that may have represented infarcted tissue.[5]

With such observations, apoplexy began to be understood as a predominantly vascular disease, a position strengthened by the discoveries of John Abercrombie (early 19th century) and Rudolf Virchow (early 20th century), the former recognising a link between arterial occlusive disease and areas of cerebral softening (caused by infarctions), and the latter reclassifying the causes of apoplexy as *sanguinea* (haemorrhagic) and *ischaemica* (Virchow's term).[9] Figure 1 depicts an historical timeline.

Differentiating stroke and transient ischaemic attacks

In the 1960s, transient ischaemic attacks were considered to be sudden, focal neurological deficits of vascular origin lasting less than 24 h (an arbitrarily assigned endpoint). A stroke was considered to have occurred if a neurological deficit remained for more than seven days. Those neurological events that lasted between 24 h and the seven-day stroke threshold were classified as a *reversible ischaemic neurological deficit* – a term now rendered obsolete. Its removal from the clinical lexicon arose when it was proven that most events lasting 24 h to seven days were associated with cerebral infarction[10] and thus should carry the diagnosis of stroke. This led to a divergence in the North American and World Health Organization's view of stroke, one emphasising the evidence of infarction and the other clinical symptoms.

The World Health Organization's definition

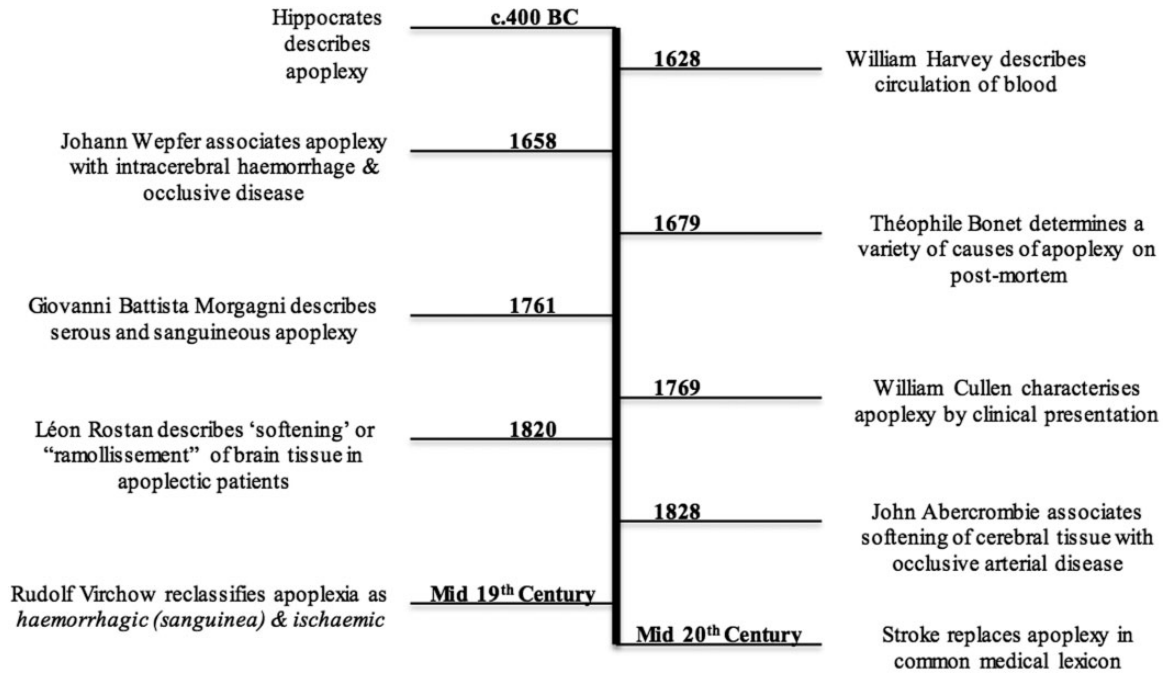
In 1970, the World Health Organization defined stroke as 'rapidly developed clinical signs of focal (or global) disturbance of cerebral function, lasting more than 24 hours or leading to death, with no apparent cause other than of vascular origin'.[11] Although still widely used, the World Health Organization definition relies heavily on clinical symptoms and is now considered outdated by the American Heart Association and American Stroke Association due to significant advances in the 'nature, timing, clinical recognition of stroke and its mimics, and imaging findings that require an updated definition'.[12]

New definition of transient ischaemic attack

There has been a stepwise progression to the endorsement of a new definition of stroke in the United States that began with reclassifying transient ischaemia. Transient ischaemic attacks were previously defined as '*a sudden, focal neurologic deficit that lasts for less than 24 hours, is presumed to be of vascular origin, and is confined to an area of the brain or eye perfused by a specific artery*'.[13] Due to mounting evidence that the arbitrary 24-h time period for diagnosing a transient ischaemic attack was inaccurate, with up to 50% showing brain injury on diffusion-weighted magnetic resonance imaging,[10] in 2002, Albers et al.[13] proposed a new definition of transient ischaemic attack. It stepped away from the assumption that transient neurological deficits could not be accompanied by cerebral infarction.

Subsequently, the Stroke Council of the American Heart Association/American Stroke Association removed time as a definitional factor and in 2009 endorsed their current definition of transient ischaemic attack: *'a transient episode of neurological dysfunction caused by focal brain, spinal cord or retinal ischaemia, without acute infarction'*.[10] The transition

Figure 1. Historical timeline formulated from descriptive prose.[9]



to a new definition of transient ischaemic attack that includes radiological exclusion of brain infarction had inherent consequences for the definition of stroke.

The American definition of stroke

In 2013, the American Heart Association/American Stroke Association updated their endorsed definition of stroke to one that includes silent infarctions (inclusive of cerebral, spinal and retinal) and silent haemorrhages.[12] The 'traditional' clinical definition of stroke is still included by the American Heart Association/American Stroke Association, but the inclusion of 'silent' pathology is a significant addition. The rationale behind such a change was to move towards a radiological demonstration (tissue-based definition) of infarction or haemorrhage.

Implications

The new American definition is at odds with the definition endorsed by the World Health Organization, European Stroke Organisation and the World Stroke Organisation, none of which consider silent pathology to be equivalent to stroke. The implications of not arriving at a universal definition of stroke are far-reaching.

First, when published in 2018, the International Classification of Diseases 11th Revision (ICD-11) will include definitions for the first time and continue to be used as a classification system for reporting morbidity and mortality data. It is likely that the ICD-11 definitions will differ from those endorsed by American Heart Association/American Stroke Association and therefore survival data, incidence and prevalence rates for stroke in the United States may differ dramatically to other countries worldwide. This is especially important in ageing societies as prevalence rates for silent brain infarctions approach 20% in those older than 70 years.[14]

Second, the impact of being diagnosed with a silent stroke on individual health and life insurance premiums will need to be considered in the United States. Silent brain infarctions confer an increased risk of future stroke[15] (World Health Organization definition), but the cumulative risk is perhaps less than the risk of stroke recurrence following the first presentation of stroke (World Health Organization definition),[16] raising the question of whether silent and symptomatic infarctions can be considered the same clinical entity.

Third, surgeon outcome data will also differ across the Atlantic. Silent cerebral infarctions following carotid intervention would be reported as iatrogenic strokes. The synthesis of American trials such as

CREST-2 with European trials will be more difficult as these silent strokes would have to be removed for parity.

Conclusion

The definition of stroke now endorsed by the American Heart Association/American Stroke Association follows in the footsteps of history and places faith in tissue findings reminiscent of the scientific advances made by Wepfer, Bonet and Morgagni. What separates this definition from historical precedent is the inclusion of 'silent' brain, retinal and spinal infarcts and silent cerebral haemorrhages, thereby removing an association with clearly defined clinical symptoms.

The inclusion of silent pathology within stroke epidemiology has the potential to dramatically alter incidence and prevalence rates in the United States and will have an impact on mortality and morbidity data. It will be important in the coming years for international bodies to arrive at a consensus in order to standardise data reporting and research endpoints.

Declarations

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