Chapter

The History of Neurosurgical Management of Ischemic Stroke

Lydia Kaoutzani and Scott Y. Rahimi

Abstract

Stroke remains a major public health issue and the second leading cause of death worldwide. The Hippocratic Corpus used the word apoplexy to describe a person collapsing while retaining pulse and respiration. This is believed to be the first written description of stroke. The theories of what caused stroke evolved over the years. When autopsies were performed stroke was attributed to emboli and thrombi formation. Carotid endarterectomies (CEA) were then performed for the treatment of stroke. Originally CEA were seen with skepticism but the North American Symptomatic Carotid Endarterectomy trial (NASCET) and the European Carotid Surgery trial (ECS) helped restore their efficacy in the management of ischemic stroke. A milestone in the management of ischemic stroke was the use of intravenous tissue plasminogen activator (tPA). Secondary to the limitations of the use of tPA other avenues were sought which included intraarterial recombinant prourokinase and mechanical thrombectomy. The field of mechanical thrombectomy continues to be rapidly changing and evolving. Various randomized controlled trials and meta-analysis have been conducted in order to evaluate who will benefit from mechanical thrombectomies, the timing, the best device to use and the role of combining this intervention with the administration of intravenous tPA.

Keywords: Ischemic stroke, history of stroke, carotid endarterectomy, intravenous tissue plasminogen activator, endovascular mechanical thrombectomy

1. Introduction

The World Health Organization in 1980 defined stroke as "the rapidly developed clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting 24 hours or longer or leading to death, with no apparent cause other than of vascular origin" [1]. In 2013, the American Stroke Association for the 21st century came up with a new broader definition of stroke [2]. The new definition of stroke includes "brain, spinal cord, or retinal cell death attributable to ischemia, based on 1. pathological, imaging, or other objective evidence of cerebral, spinal cord, or retinal focal ischemic injury in a defined vascular distribution; or 2. clinical evidence of cerebral, spinal cord, or retinal focal ischemic injury based on symptoms persisting ≥24 hours or until death, and other etiologies excluded" [2]. Stroke is a major cause of morbidity and it remains the second leading cause of death worldwide after ischemic heart disease [3, 4]. Stroke is also the third most common cause of disability with significant increase in stroke burden in the world and especially in developing countries [5]. On average in the United States (U.S.) someone has a stroke every 40 seconds [6].

Stroke is divided into ischemic and hemorrhagic stroke. Hemorrhagic stroke is further divided into intracerebral and subarachnoid hemorrhage. Approximately 85% of all strokes are ischemic with the remaining 15% being hemorrhagic [7]. We have currently moved away from using terms such as "cerebrovascular accident" and "reversible ischemic neurologic deficit" [7].

Transient ischemic attacks (TIA) also known as "warning strokes" are defined by the American Heart Association and American Stroke association as "brief episodes of neurological dysfunction resulting from focal cerebral ischemia not associated with permanent cerebral infarction" [8]. Although it is difficult to count the exact numbers of patients suffering from TIAs, in the U.S. this number has been estimated to be 200,000–500,000 per year [8].

Ischemic stroke is the result of a blockade of the arteries that supply the brain. The most common criteria used for classifying the causes of ischemic stroke are the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) criteria [9]. The TOAST criteria group the causes for ischemic stroke into five main groups which include: 1) large-artery atherosclerosis, 2) cardioembolic, 3) small-vessel occlusion, 4) stroke of other determined etiology and 5) stroke of undetermined etiology [9].

Hemorrhagic stroke results from the rupture of a blood vessel resulting in blood outside the vessel in the brain parenchyma. Intracerebral hemorrhage has an annual incidence of 10–30 per 100,000 population and there has been an 18% increase in intracerebral hemorrhage in the last ten years [10]. Subarachnoid hemorrhage is the presence of blood in the subarachnoid space, the space between the arachnoid mater and the pia mater. Common causes of subarachnoid hemorrhage include trauma, rupture of an intracranial aneurysm and perimesencephalic hemorrhage [11]. The overall global incidence of aneurysmal subarachnoid hemorrhage is 7.9 per 100,000 people per year [12]. Rupture of a cerebral aneurysm resulting in subarachnoid hemorrhage remains a neurosurgical emergency. The mortality rate for patients hospitalized with non-traumatic subarachnoid hemorrhage can be higher than 25% [13].

Risk factors of stroke have been well established some of which are hypertension, hyperlipidemia, diabetes and smoking [14]. Prevention of stroke can be achieved by managing the above risk factors. Prevention of stroke is key as survivors of stroke often face poor functional outcome as well as cognitive and physiological impairment [15].

The National Institutes of Health Stroke Scale (NIHSS) is a scale used by medical personnel to determine the severity of the neurological deficit following a stroke [16]. The scale ranges from 0 to 42 with higher scores reflecting a worse neurological impairment [16]. The NIHSS can also be used after treatment to assess any improvement in clinical symptoms. The NIHSS is probably the most widely used stroke scale. However due to some limitations efforts are made to improve and modify it [17]. Another widely used scale to predict functional outcome following a stroke is the modified Ranking Scale (mRS) [18]. The mRS is a categorical scale ranging from 0 to 6 with score 0 referring to a fully independent patient and score 6 referring to someone being dead [18].

The key in managing a patient who is experiencing a stroke is early recognition of symptoms. Any patient who is suspected of having a stroke should undergo emergent computed tomography of the brain in order to determine whether the stroke is ischemic or hemorrhagic in nature. If hemorrhagic stroke is excluded, ischemic stroke is suspected and if there are no contraindications intravenous tissue plasminogen (tPA) activator should be administered. Computed tomography perfusion (CTP) is necessary to identify the salvageable brain region. Computed cerebral angiography (CTA) should also be performed to look for any large vessel occlusion. If a proximal large vessel occlusion in the anterior circulation is identified patients who meet the criteria can undergo endovascular mechanical thrombectomy to relieve the obstruction.

Following mechanical thrombectomy the modified Thrombolysis in Cerebral Infarction (mTICI) grade is used to determine the percent of arterial revascularization. Over the years the scale has been modified. The original scale had scores ranging from 0 to 4 [19]. The scores on the most recent scale range from 0 to 3 with score 2 being divided into a, b and c [20]. mTICI 0 refers to no perfusion or antegrade flow beyond the site of occlusion [20]. mTICI 1 refers to penetration but no perfusion [20]. mTICI 2a refers to some perfusion with distal branch filling of less than 50% of territory visualized [20]. mTICI 2b refers to substantial perfusion with distal branch filling of more than equal to 50% of territory visualized [20]. mTICI 2c refers to near complete perfusion except for slow flow in a few distal cortical vessels, or presence of small distal cortical emboli [20]. mTICI 3 refers to complete perfusion with normal filling of distal branches [20].

Stroke is a health condition that neurosurgeons deal with on an everyday basis. Over the years the management of ischemic stroke is a field that has been rapidly evolving and advancing. The focus of this book chapter will be to discuss the history that has led to the current techniques used by neurosurgeons for treating ischemic stroke.

2. Early understanding of stroke

The word "apoplexy" was first documented in the Hippocratic Corpus and refers to a person collapsing while retaining pulse and respiration [21]. In Greek language the word αποπληξία (apoplixia) means to be struck with violence. The following extract from the Hippocratic writings gives a description of apoplexy: "The healthy subject is taken with a sudden pain; he immediately loses his speech and rattles in his throat. His mouth gapes and if one calls him or stirs him he only groans but understands nothing. He urinates copiously without being aware of it. If fever does not supervene, he succumbs in seven days, but if it does he usually recovers." [22]. In the Greco-Roman period apoplexy was a term used to describe strokes, epilepsy and migraines [21, 23]. The four humours (blood, phlegm, yellow bile and black bile) were first mentioned in the Hippocratic treatise called *The Nature of Man*, and it was actually the work of Polybus, Hippocrates' student [24]. According to Hippocrates, apoplexy was secondary to heating of the head blood vessels that brought phlegm or caused the flow of black bile to the head [22]. Aretaeus was the first to document the concept that apoplexy to one side of the brain results to the contralateral paralysis of the body [25]. Galen claimed that stroke was the result of humors imbalance resulting in blocking the transmission of the animal spirit [26]. Specifically, Galen believed that blood accumulated in the brain whereas phlegm and black bile accumulated in the cerebral ventricles [26].

During the Medieval era the concepts around apoplexy remained grossly unchanged [21]. The ideas of apoplexy in the Medieval era remained influenced by ideas from Greco-Roman works [21].

More information into the cause of apoplexy was obtained during the Renaissance era, between the 14th and 17th century [21]. During the Renaissance era autopsies were permitted and the ancient works were translated in this way expanding the knowledge of apoplexy [21]. In 1599, the Oxford English Dictionary gave a synonym for the "stroke of the palsy" as the "stroke of God's hands" [27].

From the 17th century and onwards the various conditions that made up the term apoplexy started to be individually explored [21]. In 1658, Johan Jakob Wepfer published "*Historiae apoplecticorum*" which was the first time that apoplexy was related to intracerebral hemorrhage [28]. Wepfer performed an autopsy on a patient who suffered from "apoplexy" and found that the brain and the ventricles

were filled with blood and no signs of external trauma were evident [28]. In 1689, William Cole was the first to use the term stroke to refer to apoplexy [21]. Others such as Morgagni (1761), Biumi (1765), Blackall (1814), Rochoux (1814) and Rostan (1819) shed light into diseases ranging from unruptured to ruptured aneurysms, as well as the difference between ischemic and hemorrhagic stroke [21].

3. The development of carotid endarterectomy

In 1852, Rudloph Virchow played an important role in shaping our understanding of stroke as he was the first to identify that stroke was the result of an embolism and/or thrombus [21, 29]. In fact Virchow was the first to use the term "thrombosis" and "embolus" that can lead to decrease blood flow in distal vessels and can result in stroke [30].

Approximately 8% of all ischemic strokes are due to extracranial internal carotid artery stenosis [31]. Chiari in 1906 and Hunt in 1914 performed autopsies in patients who had suffered from cerebral infarction and noted that lesions in the cervical carotid artery could be the culprit for the stroke [32]. Fisher in 1951, published case reports that showed that the cause of cerebral infarction was secondary to occlusion of internal carotid artery [32]. The introduction of cerebral angiography in 1927 by Moniz played a crucial role in the understanding of carotid artery disease and the subsequent development of carotid endarterectomy (CEA) [33]. The first carotid artery reconstruction was completed in 1951 in Buenos Aires and it was the result of the combined work of Fisher, Murphy, Carrea and Mollins [34]. In 1953, Debakey successfully completed the first CEA surgery for a patient with cerebrovascular insufficiency [35]. However, Debakey did not publish this case report until 1975 [36]. In the meanwhile, in 1956 Cooley was the first to publish a case report on a patient undergoing a successful CEA [37]. This was also the first report of the application of a temporary shunt during a CEA [37].

In 1969, the Joint Study of Extracranial Arterial Occlusion was published that showed that in 2,400 operations performed between 1961 and 1968 there was a 4.5% surgical mortality [38]. The indications for CEA remained unclear and given the surgical risk associated with the surgery, it took years before it became the standard of care [39]. In 1991, The North American Symptomatic Carotid Endarterectomy trial (NASCET) and the European Carotid Surgery (ECS) trial proved that patients with symptomatic carotid stenosis of 70–99% who underwent CEA had better outcomes when compared to patients who were treated medically [40, 41]. Specifically, the NASCET study showed that there was an absolute risk reduction of 17 ± 3.5 percent ($P < 0.001$) of having any ipsilateral stroke at two years and an absolute risk reduction of 10.6 ± 2.6 percent ($P < 0.001$) for a major or fatal ipsilateral stoke when comparing patients who underwent CEA versus those who underwent medical management [42]. The ECS trial showed that patients with carotid artery stenosis of 70–99% ($P < 0.0001$) had a six fold reduction in their risk of experiencing stroke during the next three years if they underwent surgical treatment versus medical management [43].

In addition, in 1995 the Asymptomatic Carotid Artery Stenosis (ACAS) trial showed that patient with asymptomatic carotid artery stenosis of 60% or greater benefited from CEA [44]. In this study there was a 53% risk reduction of having a stroke in patients treated surgically versus those treated medically [44].

Subsequently there was also interest as to whether carotid artery stenting (CAS) could replace CEAs. In 2010, a randomized controlled trial showed that CAS was associated with a significant higher periprocedural risk of stroke, whereas CEA was associated with a higher risk of myocardial infarction [45]. This study also showed

that in the four year follow up there was no significant difference of further strokes between the two groups [45].

4. Intravenous tissue plasminogen activator

A milestone in the management of ischemic stroke occurred in 1995 when the National Institute of Neurological Disorders and stroke rt-PA Stroke Study (NINDS) showed that administering intravenous recombinant tissue plasminogen activator (tPA) within 3 hours of symptoms onset had favorable outcomes in stroke management [46]. Intravenous tPA is a thrombolytic agent used to break down a clot [47]. In particular, it converts the inactive plasminogen into plasmin a proteolytic enzyme that breaks down fibrin [47]. The NINDS study was a randomized, double-blind trial with patients either randomized to receiving intravenous tPA or placebo, within 3 hours of the onset of symptoms [46]. The results of the study showed that neurological improvement was similar between the two groups 24 hours after treatment and better in the group that received intravenous tPA at three months [46]. The major adverse effect in the treatment group was symptomatic intracerebral hemorrhage within 36 hours after treatment that occurred in 6.4% of the treatment group versus 0.6% of the placebo group ($P < 0.001$) [46].

The European Cooperative Acute Stroke Study (ECASS) I published in 1995 was a randomized controlled study that divided subjects into two groups those receiving 1.1 mg per kg of body weight of intravenous tPA or placebo [48]. Patients were included in the study if they presented within 6 hours from onset of symptoms and had moderate to severe neurological deficit [48]. Patients receiving intravenous tPA had better mRS at 90 days and better neurological recovery in comparison to the placebo group [48]. The incidence of intracerebral hemorrhage and mortality rate was similar between the groups [48]. However, the group receiving intravenous tPA had a higher incidence of large intracerebral hemorrhage [48].

Other randomized controlled studies including the ECASS II in 1998 and the Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke (ATLANTIS) B in 1999 urged against the use of intravenous tPA beyond 3 hours in management of ischemic stroke [49, 50]. This conclusion was based on the high incidence of intracerebral hemorrhage that was observed in those who received intravenous tPA [49, 50].

In 2008, ECASS III study, a randomized controlled study, showed that administration of intravenous tPA to patients with ischemic stroke up to 4.5 hours after the onset of stroke symptoms was beneficial [51]. Patients were randomly assigned to either receive intravenous tPA or placebo and the median time for administration of the medication was 3 hours and 59 minutes [51]. The study showed that the group that received tPA had better outcomes than the placebo group (52.4% vs. 45.2%, confidence interval (CI), 1.02 to 1.76; $P = 0.04$) [51]. Both incidences of any intracerebral hemorrhage and symptomatic intracerebral hemorrhage were higher in the treatment group versus the placebo group with results being 27% vs. 17.6%, $P = 0.001$ and 2.4% vs. 0.2%, $P = 0.008$ respectively [51]. Mortality and other serious adverse events were similar between the groups [51].

Intracerebral hemorrhage following intravenous tPA remains a concern that can lead to devastating results. To decrease the risk of intracerebral hemorrhage following intravenous tPA, the American Heart Association and American Stroke Association issued guidelines with strict criteria for which patients are eligible for receiving intravenous tPA [52]. Other limitations to consider is that larger and more proximally located thrombi might not respond to intravenous tPA [53]. It has been

reported that restoration of blood flow in large vessel occlusion after intravenous tPA ranges between 10 and 30% depending on the large vessel that is occluded [53].

Given the limitations of intravenous tPA other avenues for management of ischemic stroke were needed. The Prourokinase (Prolyse) in Acute Cerebral Thromboembolism (PROACT II) study, a randomized controlled study aimed to determine the effects of administrating intraarterial recombinant prourokinase (r-proUK) compared to heparin within 6 hours of onset of symptoms [54]. The PROACT II study showed an increase in recanalization rate and improvement in modified Rankin score in patients treated with r-proUK versus those who were treated with heparin alone [54]. The major limitation of r-proUK was an increase in intracerebral hemorrhage 24 hours after administration that was associated with neurological deterioration (10% in treatment group versus 2% in control group, $P < 0.06$) [54].

Another medication that has been considered for the management of acute ischemic stroke is tirofiban [55]. Tirofiban is a glycoprotein IIb/IIIa platelet receptor antagonist [55]. The Safety of Tirofiban in acute Ischemic Stroke (SaTIS) trial aimed to determine whether tirofiban could be used for the treatment of acute ischemic stroke [55]. SaTIS was a prospective, open-labeled treatment, blinded outcome reading multicenter trial [55]. Patients that were included in the study had an NIHSS between 4 and 18 and received either intravenous tirofiban or placebo up to 48 hours from onset of symptoms [55]. There was no difference between the two groups in terms of intracerebral hemorrhage or neurological outcome up to five months of treatment [55]. Five months following intervention mortality was lower in the treatment group [55].

5. Endovascular Mechanical Thrombectomy

In 2005, the Mechanical Embolus Removal in Cerebral Ischemia (MERCI) trial revolutionized the way ischemic strokes are managed [56]. This was the first study that showed how endovascular embolectomy using a first generation device can improve outcomes of ischemic stroke [56]. The MERCI trial used the embolectomy device (Merci Retriever) for patients who presented within 8 hours of onset of stroke and were otherwise ineligible for intravenous tPA administration [56]. The study showed that recanalization was achieved in 48% of patients who underwent embolectomy and the risk of intracranial hemorrhage was significantly lower, only 7.8%, in comparison to 10% in the PROACT II study [56]. In 2008, after the development of the Merci Retriever the Penumbra System was developed. The Penumbra device is a second generation thrombectomy device that is inserted all the way through the clot followed by application of mechanical aspiration with the use of a suction pump [39]. By using the Penumbra System partial to normal reperfusion was achieved in 81.6% of patients, a percentage higher than that achieved by using the Merci Retriever [56, 57]. Intracranial hemorrhage was observed in 28% of patients on post procedural 24 hour CT scan however only 11.2% were symptomatic [57]. Despite the increase in intracranial hemorrhage observed with the Penumbra device in comparison to the Merci Retriever the 90-day mRS of less than or equal 2 was similar between the two groups, with 25% for the Penumbra system and 27.7% for the Merci Retriever [56, 57]. Shortly thereafter stent retrievers were developed for the use as thrombectomy devices.

In 2012, a third generation mechanical thrombectomy device was introduced. The Solitaire Flow Restoration device versus the Merci Retriever in patients with acute ischemic stroke was studied [58]. The SWIFT study was a randomized, parallel-group, non-inferiority trial that showed that Solitaire Flow Restoration

device is significantly better than the Merci retriever device [58]. In particular, patients treated with the Solitaire Flow Restoration device had a rate of recanalization of 61% in comparison to 24% in those treated with the Merci Retriever device [58]. With the use of the Solitaire flow restoration device the rate of symptomatic intracranial hemorrhage was decreased and the overall neurological outcomes were better [58].

Another area of interest was whether devices that combined direct aspiration with thrombectomy would be beneficial in the management of ischemic stroke. The MAX reperfusion catheters as well as a direct aspiration first pass technique (ADAPT) enabled direct aspiration with thrombectomy [53]. In 2018, a randomized controlled study aimed to determine whether there was a difference in ischemic stroke outcomes when the novel 3-dimensional (3-D) stent retriever was used in conjugation with an aspiration-based mechanical thrombectomy device (Penumbra System; Penumbra) versus the aspiration-based thrombectomy alone [59]. The results of the study showed that 87.2% in the 3-D stent retriever with aspiration group versus 82.3% in the aspiration based thrombectomy alone group had a mTICI of 2–3 [59]. The 90-day mRS score of 0 to 2, device-related serious adverse events and procedure-related serious adverse events were similar between the two groups [59].

The next step in the management of acute ischemic stroke was to determine whether endovascular thrombectomy was superior to standard medical care alone [60]. There were five key randomized control studies that aimed to answer this question: MR CLEAN, ESCAPE, REVASCAT, SWIFT PRIME, and EXTEND IA [61–65].

The MR CLEAN trial aimed to determine whether patients who presented within 6 hours after onset of ischemic symptoms and proximal intracranial occlusion of the anterior circulation would benefit from mechanical thrombectomy [61]. In particular, all patients in the study received intravenous tPA and were subsequently randomized to receive either intraarterial treatment or not [61]. The study showed that there was improvement in functional independence in the treatment group but no changes in mortality or the occurrence of symptomatic intracerebral hemorrhage between the two groups [61].

The ESCAPE study assessed whether patients who presented within 12 hours of onset of symptoms would benefit from mechanical thrombectomy [62]. The patients included in the study had a proximal vessel occlusion in the anterior circulation and they all received intravenous tPA [62]. The experimental group also received mechanical thrombectomy [62]. The results of the study showed that patients who received mechanical thrombectomy had substantial increase of functional independence (53% in the treatment group versus 29.3% in the control group; $P < 0.001$), decreased mortality in the intervention group and similar intracerebral hemorrhage rates [62].

The REVASCAT study examined whether there is a difference in outcome in patients when treated with a combination therapy of both intravenous tPA (if eligible) and mechanical thrombectomy than those treated with medical therapy alone [63]. The patients who were included in the study had to present within 8 hours of onset of symptoms and had to have a proximal anterior circulation occlusion [63]. Solitaire stent retriever was the device used for the thrombectomy group [63]. The results of the study showed that functional independence was increased in the experimental group, with 43.7% having functional independence (mRS score of 0–2) in 90 days versus 28.2% in the control group [63]. The rates of intracerebral hemorrhage remained the same in both groups [63].

The SWIFT PRIME study aimed to determine whether patients treated with both intravenous tPA and Solitaire Revascularization Device within 6 hours of

symptoms onset had better outcome than those who were treated with intravenous tPA alone [64]. The results of the study showed that there was a greater proportion of patients in the experimental group that were functional independent at 90 days in comparison to the control group [64]. Secondary outcomes such as functional independence at 90 days, improvement in NIHSS score and successful reperfusion at 27 hours were better in the treatment group versus the control group [64]. There was no significant difference in complications between the two groups [64].

The EXTEND IA study aimed to determine whether patients treated with both intravenous tPA and Solitaire Revascularization Device within 4.5 hours of symptom onset had better outcome than those who were treated with intravenous tPA alone [65]. The results of the study showed that reperfusion at 24 hours was better in the experimental group versus the control group (median, 100% vs. 37%, $P < 0.001$) [65]. The neurological improvement at 3 days and the functional outcome was better in the experimental group versus the control group [65]. With regards to adverse consequences such as death and intracerebral hemorrhage the results were similar between the two groups [65].

Subsequently, a meta-analysis published in 2016 looked at the results from the above five randomized controlled trials [60]. There were 1287 patients that were included in the study and who had an acute proximal anterior circulation stroke [60]. Prior to randomization to the two groups patients received intravenous tPA if they met the inclusion criteria [60]. The major results of this meta-analysis were: 1) endovascular thrombectomy led to reduced disability at 90 days, 2) the risk of intracerebral hemorrhage and symptomatic hemorrhage did not differ between the groups and 3) the mortality rate was similar between groups [60].

In 2018, two major randomized controlled studies the DAWN and the DEFUSE 3 were published [66, 67]. The data collected from these studies showed that mechanical thrombectomy can be extended to 24 hours from onset of stroke symptoms [66, 67]. The DAWN study randomized patients to receive either intravenous tPA alone (control group) or thrombectomy plus intravenous tPA (experimental group) [66]. The patients had an intracranial internal carotid artery or proximal middle cerebral artery occlusion and were last known well 6–24 hours prior [66]. The patients included in the study had disproportionately worse neurological exam in comparison to the infarct volume that was observed on imaging [66]. The study showed that at 90 days the thrombectomy group had a better mRS score and improved functional independence [66]. Adverse effects such as intracerebral hemorrhage and death were similar between the two groups [66].

The DEFUSE 3 study was a multicenter, randomized, open-label trial, in which the control group received intravenous tPA and the experimental group received endovascular therapy plus intravenous tPA [67]. Patients who were included in the study had onset of symptoms 6–16 hours prior to presentation, were found to have proximal middle cerebral artery or internal carotid artery occlusion with initial infarct size less than 70 ml and a ratio of the volume of ischemic tissue on perfusion imaging to infarct volume of 1.8 [67]. The study showed that patients who underwent mechanical thrombectomy had an increase chance of being functionally independent (45% vs. 17%, $P < 0.001$) and the 90-day mortality rate was 14% in the experimental group versus 26% in the control group [67]. Symptomatic intracerebral hemorrhage and adverse effects were similar between the groups [67].

It is worth mentioning that acute ischemic stroke can be managed by artery stenting. The Stent-Assisted Recanalization in Acute Ischemic Stroke (SARIS) trial was a prospective trial the goal of which was to determine whether cerebral arterial stenting would be beneficial in the management of acute ischemic stroke [68]. In a series of twenty patients the mRS score of 3 was achieved in 60% and that of 1 was achieved in 45% [68]. Symptomatic intracerebral hemorrhage was present in 5% of the patients

and asymptomatic intracerebral hemorrhage was present in 10% [68]. There is, however, no consensus on whether the benefits of arterial stenting in acute stroke outweigh the risks primarily due to the lack of randomized controlled trials [69].

6. Decompressive hemicraniectomy for malignant middle cerebral artery territory infarct

Patients who suffer from middle cerebral artery infarction can have a mortality rate secondary to elevated intracranial pressure. Neurosurgeons often perform decompressive craniectomies when such situations arise. Multiple studies were conducted over the years to determine the efficacy of this practice. There were three randomized controlled landmark studies and a meta-analysis of these studies that aimed to address this issue.

The first trial was the "Decompressive Surgery for the Treatment of Malignant Infarction of the Middle Cerebral Artery (DESTINY)" that was published in 2007 [70]. The second trial was the "Sequential-Design, Multicenter, Randomized, Controlled Trial of Early Decompressive Craniectomy in Malignant Middle Cerebral Artery Infarction (DECIMAL Trial)" that was published in 2007 [71]. The third trial was the "Hemicraniectomy after middle cerebral artery infarction with life-threatening Edema trial (HAMLET)" published in 2009 [72].

In 2007 a meta-analysis of the above three randomized controlled studies was conducted while the above studies were ongoing [73]. The aim of the study was to determine whether performing decompressive hemicraniectomy in patients who had suffered malignant middle cerebral artery territory infarct had good long-term outcomes [73]. The study showed that more patients in the hemicraniectomy group had an mRS of less than equal to 4 in comparison to the control group [73]. The study also showed that survival rate in the hemicraniectomy group was higher than in the control group [73]. This meta-analysis favored decompressive hemicraniectomy in patients with malignant middle cerebral artery infarction who underwent surgery within 48 hours of stroke onset in order to reduce mortality and improve mRS score in survivors [73].

7. Conclusion

Stroke is a medical entity that was known in ancient Greece as apoplexy. Hippocrates was the first to describe a patient with stroke like symptoms followed by Areteus and Galen. Ischemic stroke was once a disease process of which we had a scarce understanding. Efficient treatments were, however, made possible with more insight into the anatomical and pathophysiological changes that are associated with ischemic stroke. These developments were attributed to Wepfer, Virchow, Murphy, Cooley and others. The advancement in technology, such as the development of cerebral angiography, CTA and CTP, were also crucial in the advancements made in treating ischemic stroke.

Neurosurgeons are able to perform a wide range of procedures to manage ischemic stroke and thus their role in this disease remains pivotal. For prevention of stroke, CEAs are performed; for reperfusion of salvageable brain tissue, mechanical thrombectomies improve outcomes; and for management of brain herniation hemicraniectomies are carried out. Additionally, endovascular mechanical thrombectomies have undoubtedly revolutionized the way ischemic stroke is managed. But, more progress remains to be made, with several previous and on-going randomized controlled studies attempting to find the gold standard for treating ischemic stroke.

Ischemic stroke remains a major public health concern that can undoubtedly cause severe disability. Even with increase efforts for public education and primary prevention, neurosurgeons still need to be able to manage ischemic strokes efficiently.

Conflict of interest

The authors declare no conflict of interest.

Author details

Lydia Kaoutzani* and Scott Y. Rahimi
Department of Neurosurgery, Augusta University Medical Center, Augusta, Georgia, USA

*Address all correspondence to: lkaoutzani@augusta.edu

References

[1] K. Aho, P. Harmsen, S. Hatano, J. Marquardsen, V. E. Smirnov, and T. Strasser, "Cerebrovascular disease in the community: results of a WHO collaborative study," Bull. World Health Organ., 1980.

[2] R. L. Sacco *et al.*, "An Updated Definition of Stroke for the 21st Century," Stroke, 2013, doi: 10.1161/str.0b013e318296aeca.

[3] P. B. Gorelick, "The global burden of stroke: persistent and disabling," The Lancet Neurology. 2019, doi: 10.1016/S1474-4422(19)30030-4.

[4] M. A. Khan *et al.*, "Global Epidemiology of Ischemic Heart Disease: Results from the Global Burden of Disease Study," Cureus, 2020, doi: 10.7759/cureus.9349.

[5] V. L. Feigin, B. Norrving, and G. A. Mensah, "Global Burden of Stroke," Circ. Res., 2017, doi: 10.1161/CIRCRESAHA.116.308413.

[6] S. S. Virani *et al.*, "Heart disease and stroke statistics—2020 update: A report from the American Heart Association," *Circulation*. 2020, doi: 10.1161/CIR.0000000000000757.

[7] T. D. Musuka, S. B. Wilton, M. Traboulsi, and M. D. Hill, "Diagnosis and management of acute ischemic stroke: Speed is critical," CMAJ. 2015, doi: 10.1503/cmaj.140355.

[8] J. D. Easton *et al.*, "Definition and Evaluation of Transient Ischemic Attack," Stroke, 2009, doi: 10.1161/strokeaha.108.192218.

[9] H. . Adams *et al.*, "Classification of Subtype of Acute Ischemic Stroke," *Stroke*, 1993.

[10] A. I. Qureshi, A. D. Mendelow, and D. F. Hanley, "Intracerebral haemorrhage," The Lancet. 2009, doi: 10.1016/S0140-6736(09)60371-8.

[11] C. P. Marder, V. Narla, J. R. Fink, and K. R. Tozer Fink, "Subarachnoid hemorrhage: Beyond aneurysms," American Journal of Roentgenology. 2014, doi: 10.2214/AJR.12.9749.

[12] N. Etminan *et al.*, "Worldwide Incidence of Aneurysmal Subarachnoid Hemorrhage According to Region, Time Period, Blood Pressure, and Smoking Prevalence in the Population: A Systematic Review and Meta-analysis," JAMA Neurol., 2019, doi: 10.1001/jamaneurol.2019.0006.

[13] A. M. Shea, S. D. Reed, L. H. Curtis, M. J. Alexander, J. J. Villani, and K. A. Schulman, "Characteristics of nontraumatic subarachnoid hemorrhage in the United States in 2003," Neurosurgery, 2007, doi: 10.1227/01.neu.0000306090.30517.ae.

[14] A. K. Boehme, C. Esenwa, and M. S. V. Elkind, "Stroke Risk Factors, Genetics, and Prevention," Circulation Research. 2017, doi: 10.1161/CIRCRESAHA.116.308398.

[15] S. L. Crichton, B. D. Bray, C. McKevitt, A. G. Rudd, and C. D. A. Wolfe, "Patient outcomes up to 15 years after stroke: Survival, disability, quality of life, cognition and mental health," J. Neurol. Neurosurg. Psychiatry, 2016, doi: 10.1136/jnnp-2016-313361.

[16] P. Lyden, "Using the National Institutes of Health Stroke Scale," Stroke. 2017, doi: 10.1161/STROKEAHA.116.015434.

[17] P. D. Lyden, M. Lu, S. R. Levine, T. G. Brott, and J. Broderick, "A modified national institutes of health stroke scale for use in stroke clinical trials preliminary reliability and validity," Stroke, 2001, doi: 10.1161/01.str.32.6.1310.

[18] J. L. Banks and C. A. Marotta, "Outcomes validity and reliability of the modified rankin scale: Implications for stroke clinical trials - A literature review and synthesis," Stroke. 2007, doi: 10.1161/01.STR.0000258355.23810.c6.

[19] R. T. Higashida *et al.*, "Trial design and reporting standards for intra-arterial cerebral thrombolysis for acute ischemic stroke.," Stroke, 2003, doi: 10.1161/01.str.0000082721.62796.09.

[20] M. Goyal *et al.*, "2C or not 2C: Defining an improved revascularization grading scale and the need for standardization of angiography outcomes in stroke trials," Journal of NeuroInterventional Surgery. 2014, doi: 10.1136/neurintsurg-2013-010665.

[21] E. Engelhardt, "Apoplexy, cerebrovascular disease, and stroke: Historical evolution of terms and definitions," Dement. Neuropsychol., 2017, doi: 10.1590/1980-57642016dn11-040016.

[22] E. CLARKE, "APOPLEXY IN THE HIPPOCRATIC WRITINGS.," Bull. Hist. Med., 1963.

[23] A. P. Coupland, A. Thapar, M. I. Qureshi, H. Jenkins, and A. H. Davies, "The definition of stroke," J. R. Soc. Med., 2017, doi: 10.1177/0141076816680121.

[24] J. Jouanna, "The Legacy of the Hippocratic Treatise The Nature of Man: The Theory of the Four Humours," in *Greek Medicine from Hippocrates to Galen*, 2012.

[25] J. M. S. Pearce, "The Neurology of Aretaeus: Radix Pedis Neurologia," Eur. Neurol., 2013, doi: 10.1159/000352031.

[26] A. Karenberg, "Blood, Phlegm and Spirits: Galen on Stroke," Istor. meditsiny, 2015, doi: 10.17720/2409-5583.t2.2.2015.15k.

[27] F. Schiller, "Concepts of stroke before and after Virchow," Med. Hist., 1970, doi: 10.1017/S0025727300015325.

[28] J. M. Pearce, "Johann Jakob Wepfer (1620-95) and cerebral haemorrhage.," J. Neurol. Neurosurg. Psychiatry, 1997, doi: 10.1136/jnnp.62.4.387.

[29] S. Safavi-Abbasi et al., "Rudolf Ludwig Karl Virchow: pathologist, physician, anthropologist, and politician. Implications of his work for the understanding of cerebrovascular pathology and stroke.," Neurosurg. Focus, 2006, doi: 10.3171/foc.2006.20.6.1.

[30] J. M. Pearce, "Rudolf Ludwig Karl Virchow (1821-1902).," J. Neurol., 2002, doi: 10.1007/s004150200049.

[31] M. L. Flaherty *et al.*, "Carotid artery stenosis as a cause of stroke," Neuroepidemiology, 2012, doi: 10.1159/000341410.

[32] S. P. Saha, S. Saha, and K. S. Vyas, "Carotid endarterectomy: Current concepts and practice patterns," Int. J. Angiol., 2014, doi: 10.1055/s-0035-1558645.

[33] M. Artico *et al.*, "Egas Moniz: 90 years (1927-2017) from cerebral angiography," Front. Neuroanat., 2017, doi: 10.3389/fnana.2017.00081.

[34] C. J. Estol, "Dr C. Miller Fisher and the history of carotid artery disease," Stroke, 1996, doi: 10.1161/01.STR.27.3.559.

[35] M. E. Debakey, "Successful Carotid Endarterectomy For Cerebrovascular Insufficiency: Nineteen-Year Follow-up," JAMA J. Am. Med. Assoc., 1975, doi: 10.1001/jama.1975.03260100053020.

[36] S. G. Friedman and N. M. Rich, "The first carotid endarterectomy," J. Vasc. Surg., 2014, doi: 10.1016/j.jvs.2014.08.059.

[37] F. Robicsek, T. S. Roush, J. W. Cook, and M. K. Reames, "From Hippocrates to Palmaz-Schatz, The History of Carotid Surgery," Eur. J. Vasc. Endovasc. Surg., 2004, doi: 10.1016/j.ejvs.2004.01.004.

[38] W. F. Blaisdell, R. H. Clauss, J. G. Galbraith, A. M. Imparato, and E. J. Wylie, "Joint Study of Extracranial Arterial Occlusion: IV. A Review of Surgical Considerations," JAMA J. Am. Med. Assoc., 1969, doi: 10.1001/jama.1969.03160250045010.

[39] J. Withrow, N. Todnem, and S. Rahimi, "The Evolution of the Neurosurgical Treatment of Ischemic Stroke," J. Cerebrovasc. Endovasc. Neurosurg., 2018, doi: 10.7461/jcen.2018.20.1.53.

[40] G. G. Ferguson *et al.*, "The North American Symptomatic Carotid Endarterectomy Trial: Surgical results in 1415 patients," Stroke, 1999, doi: 10.1161/01.STR.30.9.1751.

[41] C. Warlow, B. Farrell, A. Fraser, P. Sandercock, and J. Slattery, "Randomised trial of endarterectomy for recently symptomatic carotid stenosis: Final results of the MRC European Carotid Surgery Trial (ECST)," Lancet, 1998, doi: 10.1016/S0140-6736(97)09292-1.

[42] NASCET, "Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. North American Symptomatic Carotid Endarterectomy Trial Collaborators," *N. Engl. J. Med.*, 1991.

[43] C. Warlow, "MRC European Carotid Surgery Trial: interim results for symptomatic patients with severe (70-99%) or with mild (0-29%) carotid stenosis," Lancet, 1991, doi: 10.1016/0140-6736(91)92916-P.

[44] "Endarterectomy for asymptomatic carotid artery stenosis. Executive Committee for the Asymptomatic Carotid Atherosclerosis Study," *JAMA J. Am. Med. Assoc.*, 1995, doi: 10.1001/jama.273.18.1421.

[45] T. G. Brott *et al.*, "Stenting versus endarterectomy for treatment of carotid-artery stenosis," N. Engl. J. Med., 2010, doi: 10.1056/NEJMoa0912321.

[46] "Tissue plasminogen activator for acute ischemic stroke," *N. Engl. J. Med.*, 1995, doi: 10.1056/NEJM199512143332401.

[47] S. Bhaskar, P. Stanwell, D. Cordato, J. Attia, and C. Levi, "Reperfusion therapy in acute ischemic stroke: Dawn of a new era?," BMC Neurology. 2018, doi: 10.1186/s12883-017-1007-y.

[48] W. Hacke et al., "Intravenous Thrombolysis With Recombinant Tissue Plasminogen Activator for Acute Hemispheric Stroke: The European Cooperative Acute Stroke Study (ECASS)," JAMA J. Am. Med. Assoc., 1995, doi: 10.1001/jama.1995.03530130023023.

[49] W. Hacke *et al.*, "Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II)," Lancet, 1998, doi: 10.1016/S0140-6736(98)08020-9.

[50] W. M. Clark, S. Wissman, G. W. Albers, J. H. Jhamandas, K. P. Madden, and S. Hamilton, "Recombinant tissue-type plasminogen activator (Alteplase) for ischemic stroke 3 to 5 hours after symptom onset the ATLANTIS study: A randomized controlled trial," J. Am. Med. Assoc., 1999, doi: 10.1001/jama.282.21.2019.

[51] W. Hacke *et al.*, "Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke," N. Engl. J. Med., 2008, doi: 10.1056/NEJMoa0804656.

[52] W. J. Powers *et al.*, "Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke a guideline for healthcare professionals from the American Heart Association/ American Stroke A," *Stroke*. 2019, doi: 10.1161/STR.0000000000000211.

[53] C. J. Przybylowski, "Evolution of endovascular mechanical thrombectomy for acute ischemic stroke," World J. Clin. Cases, 2014, doi: 10.12998/wjcc.v2.i11.614.

[54] A. Furlan *et al.*, "Intra-arterial prourokinase for acute ischemic stroke. The PROACT II study: A randomized controlled trial," J. Am. Med. Assoc., 1999, doi: 10.1001/jama.282.21.2003.

[55] S. M. et al., "Safety of tirofiban in acute ischemic stroke: The SaTIS trial," Stroke, 2011.

[56] W. S. Smith *et al.*, "Safety and efficacy of mechanical embolectomy in acute ischemic stroke: Results of the MERCI trial," Stroke, 2005, doi: 10.1161/01.STR.0000171066.25248.1d.

[57] S. Po Sit, "The penumbra pivotal stroke trial: Safety and effectiveness of a new generation of mechanical devices for clot removal in intracranial large vessel occlusive disease," Stroke, 2009, doi: 10.1161/STROKEAHA.108.544957.

[58] J. L. Saver *et al.*, "Solitaire flow restoration device versus the Merci Retriever in patients with acute ischaemic stroke (SWIFT): A randomised, parallel-group, non-inferiority trial," Lancet, 2012, doi: 10.1016/S0140-6736(12)61384-1.

[59] R. G. Nogueira *et al.*, "Safety and efficacy of a 3-dimensional stent retriever with aspiration-based thrombectomy vs aspiration-based thrombectomy alone in acute ischemic stroke intervention a randomized clinical trial," JAMA Neurol., 2018, doi: 10.1001/jamaneurol.2017.3967.

[60] M. Goyal *et al.*, "Endovascular thrombectomy after large-vessel ischaemic stroke: A meta-analysis of individual patient data from five randomised trials," Lancet, 2016, doi: 10.1016/S0140-6736(16)00163-X.

[61] O. A. Berkhemer *et al.*, "A Randomized Trial of Intraarterial Treatment for Acute Ischemic Stroke," N. Engl. J. Med., 2015, doi: 10.1056/nejmoa1411587.

[62] M. Goyal *et al.*, "Randomized Assessment of Rapid Endovascular Treatment of Ischemic Stroke," N. Engl. J. Med., 2015, doi: 10.1056/nejmoa1414905.

[63] T. G. Jovin *et al.*, "Thrombectomy within 8 Hours after Symptom Onset in Ischemic Stroke," N. Engl. J. Med., 2015, doi: 10.1056/nejmoa1503780.

[64] J. L. Saver *et al.*, "Stent-Retriever Thrombectomy after Intravenous t-PA vs. t-PA Alone in Stroke," N. Engl. J. Med., 2015, doi: 10.1056/nejmoa1415061.

[65] B. C. V. Campbell *et al.*, "Endovascular Therapy for Ischemic Stroke with Perfusion-Imaging Selection," N. Engl. J. Med., 2015, doi: 10.1056/nejmoa1414792.

[66] R. G. Nogueira *et al.*, "Thrombectomy 6 to 24 hours after stroke with a mismatch between deficit and infarct," N. Engl. J. Med., 2018, doi: 10.1056/NEJMoa1706442.

[67] G. W. Albers *et al.*, "Thrombectomy for Stroke at 6 to 16 Hours with Selection by Perfusion Imaging," N. Engl. J. Med., 2018, doi: 10.1056/nejmoa1713973.

[68] E. I. Levy *et al.*, "First food and drug administration-approved prospective

trial of primary intracranial stenting for acute stroke: SARIS (Stent-Assisted Recanalization in Acute Ischemic Stroke)," Stroke, 2009, doi: 10.1161/STROKEAHA.109.561274.

[69] J. Gralla, C. Brekenfeld, P. Mordasini, and G. Schroth, "Mechanical thrombolysis and stenting in acute ischemic stroke," Stroke. 2012, doi: 10.1161/STROKEAHA.111.626903.

[70] E. Jüttler *et al.*, "Decompressive surgery for the treatment of malignant infarction of the middle cerebral artery (DESTINY): A randomized, controlled trial," Stroke, 2007, doi: 10.1161/STROKEAHA.107.485649.

[71] K. Vahedi *et al.*, "Sequential-design, multicenter, randomized, controlled trial of early decompressive craniectomy in malignant middle cerebral artery infarction (DECIMAL Trial)," Stroke, 2007, doi: 10.1161/STROKEAHA.107.485235.

[72] J. Hofmeijer, L. J. Kappelle, A. Algra, G. J. Amelink, J. van Gijn, and H. B. van der Worp, "Surgical decompression for space-occupying cerebral infarction (the Hemicraniectomy After Middle Cerebral Artery infarction with Life-threatening Edema Trial [HAMLET]): a multicentre, open, randomised trial," Lancet Neurol., 2009, doi: 10.1016/S1474-4422(09)70047-X.

[73] K. Vahedi *et al.*, "Early decompressive surgery in malignant infarction of the middle cerebral artery: a pooled analysis of three randomised controlled trials," Lancet Neurol., 2007, doi: 10.1016/S1474-4422(07)70036-4.