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Gail Pyne-Geithman · Norberto Andaluz
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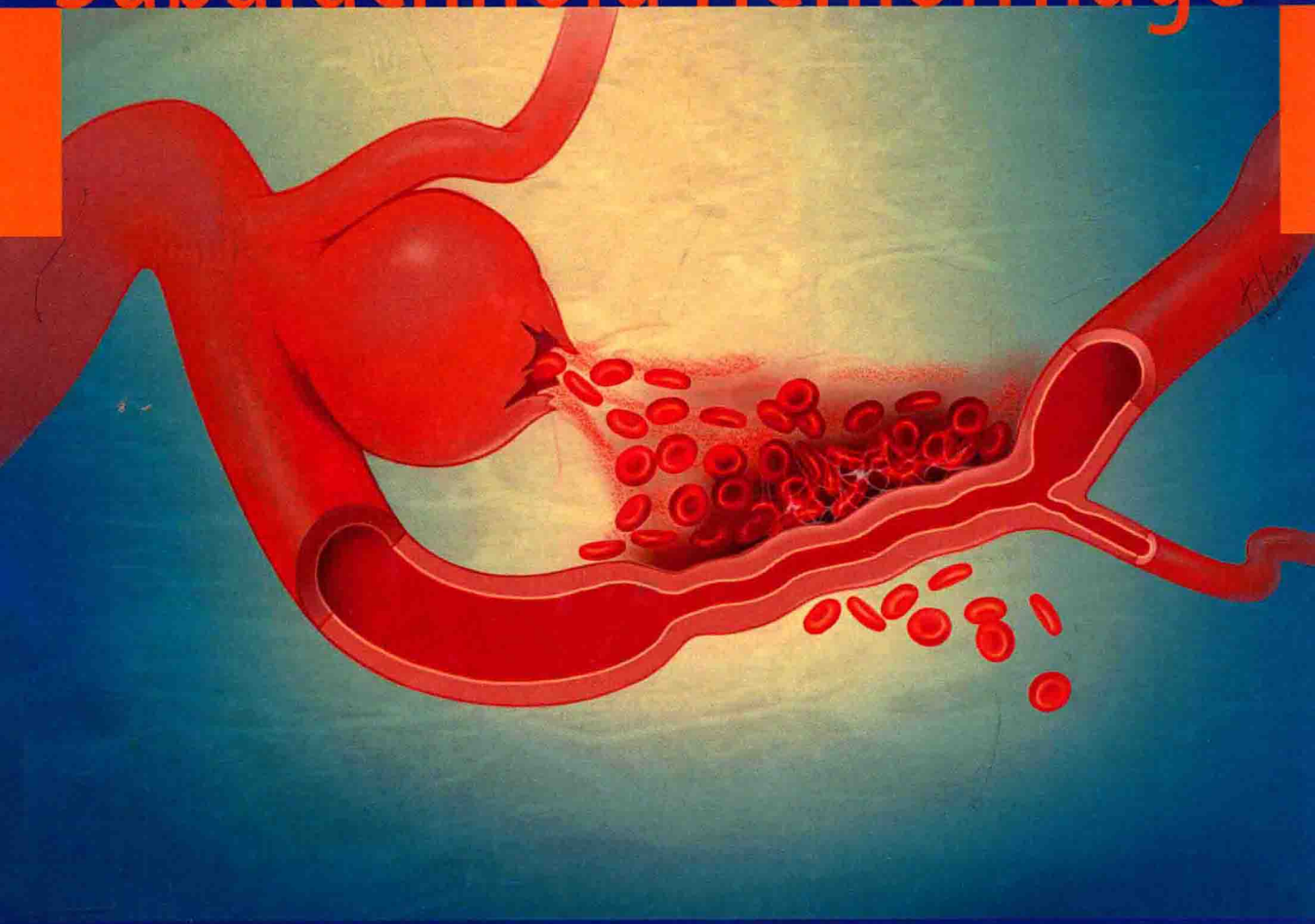
Neurovascular Events After Subarachnoid Hemorrhage



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Cerebral Vasospasm: Neurovascular Events After Subarachnoid Hemorrhage

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Preface

This book contains the proceedings of the *11th International Conference on Cerebral Vasospasm: Neurovascular Events after Subarachnoid Hemorrhage*. The conference was held in Cincinnati, Ohio, USA, from July 21–23, 2011, with the recurrent goal to share the latest knowledge on the pathophysiologic phenomena that take place after aneurysmal subarachnoid hemorrhage. This collection of papers represents a cross section of the enormous progress that has been made toward a thorough understanding and effective treatment of neurovascular events following aneurysmal subarachnoid hemorrhage, including cerebral vasospasm. The editors would like to extend their gratitude to the many participants of this most recent conference and thank previous participants for setting the stage for continued progress in this field. We also want to acknowledge the authors of the chapters of this book. We are indebted to these contributors for providing such excellent material. Finally, we would like to express our deepest gratitude to all those who made a flawless meeting possible: our sponsors, the scientific committee, and the members of the organizing committee, especially Ms. Christa McAlpin and Ms. Joanie Pope. This book will be of interest to basic scientists wishing to expand their understanding of cerebrovascular and neural pathophysiology related to subarachnoid hemorrhage and to clinicians who wish to apply state-of-the-art knowledge to their management of this devastating condition.

Cincinnati, USA

Mario Zuccarello
Joseph F. Clark

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Contents

Frank H. Mayfield, MD, FACS, FAANS (1909–1991): 75th Anniversary Tribute

John M. Tew Jr.

In this special issue, coinciding with Mayfield Clinic's 75th anniversary, we recognize the vision and practical wisdom of Dr. Frank H. Mayfield, who inspired solutions to the devastating problems of cerebral vasospasm after subarachnoid hemorrhage (SAH). This conference proceedings, *Vasospasm 2011: 11th International Conference on Neurovascular Events after SAH*, is dedicated to Dr. Mayfield, a University of Cincinnati professor and pioneer in neurosurgery who directed the graduate neurosurgical training programs at The Christ Hospital and Good Samaritan Hospital from 1946 to 1977. His lasting, distinguished contributions in aneurysm surgery formed, in part, some of the foundational science for this conference's nearly 200 cerebrovascular experts from 20 nations who are taking important steps toward developing the first optimal clinical management strategy for vasospasm.

Being curious and fascinated by possibilities of the future, Dr. Mayfield would have valued the opportunity to have attended this conference with you—the dedicated scientists, surgeons, neurologists, nurses, students, and practitioners. Your commitment to research in vasospasm and clinical care as well as cortical spreading depolarizations and to your fellow colleagues is exemplified throughout this special supplement. In recognition of Dr. Mayfield's contributions to the advancement of our profession, this dedication highlights specific areas: service to his patients, commitment to education, integrity in science, collaboration, and dedication to improving medicine. He noted, "Throughout all ages and all fields of endeavor, man has sought to overcome the unpredictability of nature by reformulating existing knowledge in search of new principles." He understood that in a slow, orderly process, science inspires and disseminates new concepts. This conference's proceedings represent your creative work as basic scientists and clinicians whose research offers hope in determining the practical applications to human disease, in this case disorders associated with SAH and vasospasm.

Known as a creative thinker, Dr. Mayfield looked at all events constructively and, when faced with a problem, changed them to opportunity. He was well acquainted with the devastation associated with SAH and uniquely aware of the importance of preventing recurrent hemorrhage and the deadly consequences of vasospasm.

Dr. Mayfield's vision and practical wisdom fueled his drive for solutions to the problems of recurrent hemorrhage or during occlusion of parent vessel surgery for saccular aneurysms. With strong focus, he sought resolution to the disaster that often ensued when a surgeon clipped an aneurysm with permanent ligatures of malleable metallic clips. That is, the surgeon could not determine the clip's optimal location, retain its closing force, or safely remove or replace it after positioning. Neurosurgeon and creative thinker Frank Mayfield collaborated with other physicians and scientists to develop a definitive aneurysm clip; his resulting designs forever changed aneurysm and brain surgery [1].

Nearly 60 years ago, Dr. Mayfield and medical artist George Kees, Jr., began working on the clip and forceps, later known as the Mayfield clip [2]. This small, cross-legged clip and its applicator with tweezers-like dexterity enabled the trial-and-error placement needed during aneurysm surgery. The clip's malleability allowed it to be twisted into shape but retain its springy recoil. These first Mayfield clips of 6–15 mm were stainless steel. Testing, first in laboratory animals and later in patients, ensured that there was no evidence of corrosion and only minimal signs of foreign body reaction and verified that the clips remained positioned, even against pulsatile forces of 400 mm mercury. With these encouraging results, Dr. Mayfield and his colleagues applied these clips to saccular aneurysms in patients. Work continued diligently to improve this design as the clip then underwent modifications and additional testing in the United States, Great Britain, and Sweden by a number of noted neurosurgeons (e.g., James Poppen, James Gardner, Eben Alexander, Lawrence Pool, Charles Drake). George Kees developed patents and produced and marketed the Mayfield clips and appliers.

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Modifications to the Mayfield clip followed: The Heifetz modification provided firmer fixation in the applicator; the McFadden design had a round jaw and blunt tips made of 301 stainless steel; and Drs. Sundt and Nofzinger modified the clip for the treatment of intracranial aneurysms. A call from Dr. Drake, who was having difficulty operating on a basilar aneurysm, prompted Dr. Mayfield and Mr. Kees to devote a late night working in the laboratory. By the next morning, the clip was redesigned and shipped to Dr. Drake; such a practical invention was then possible before the Food and Drug Administration oversight and clinical trials. It was eventually called the Drake fenestrated clip.

Today's neurosurgeons and their patients continue to benefit from the innovative work of Dr. Mayfield and those he later inspired. His commitment and compassion led to other far-reaching improvements for patients with spinal disorders and neurological diseases—a collaboration toward the invention of the seat belt and development of professional neurosurgical organizations. Described as the "conscience of neurosurgery" by Eben Alexander, Dr. Mayfield's legacy calls for each to develop one's own creativity for advancing the field of medicine. Dr. Mayfield would be excited to greet all of you today and salute this international commitment to curing vasospasm through collaboration in science and practice.

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History and Definition of Delayed Cerebral Ischemia

R. Loch Macdonald

Abstract A list of the vasospasm meetings is provided. The early descriptions of angiographic vasospasm and delayed cerebral ischemia are presented. Selected advances in knowledge in the field and some controversies are described. A proposal for definitions of neurological deterioration due to delayed cerebral ischemia, of cerebral infarction, and of vasospasm is reviewed.

Keywords Vasospasm • History • Delayed cerebral ischemia Subarachnoid hemorrhage

Introduction

Martin Luther King, Jr., said: "We are not makers of history. We are made by history," meaning that our thinking about the present is influenced by understanding and interpretation of history. But, in medicine it also is important in that history provides the basis for advancing knowledge. As George Santayama said, "Those who cannot remember the past are condemned to repeat it."

The Vasospasm Meetings

Robert R. Smith organized and chaired the first meeting of what would later become the series of meetings focused on cerebral vasospasm. There were 18 participants at the conference in Jackson, Mississippi, in 1972. The attendees were or would become authorities in the field; they included Francis Echlin, John Kapp, James T. Robertson, Frederick A. Simeone, Robert R. Smith, Thoralf M. Sundt, Bryce Weir, Richard White, Robert H. Wilkins, and Nicholas T. Zervas. A series of conferences followed, with titles that have evolved over time because of changes in theories of brain injury after subarachnoid hemorrhage (SAH; Table 1).

Early Descriptions

Perhaps the earliest description of a patient with delayed cerebral ischemia (DCI) was by Gull in 1859 [12]. He wrote of a 30-year-old female, "While walking, she suddenly called out, "Oh my head," and put up her left hand. She vomited and, as her friend thought, fainted. After a brief interval she partially recovered, and was able to walk back to her residence with the support of two men. When admitted to the hospital at noon the following day, only a slight impression could be made by any attempt to rouse her. The right arm was quite paralyzed, the muscles flaccid; the right leg in the same condition." She improved, and by 3 days after the ictus was able to eat. On the 4th day, she spoke some words, but on the 5th day, she worsened; her pupils became fixed and dilated, and she died. At autopsy, there was SAH in the left Sylvian fissure with massive softening of the left hemisphere and two aneurysms on the middle cerebral artery, one of which had ruptured.

Robertson described findings in 27 cases of death from aneurysm rupture in 1949 [17]. He found infarctions in brain irrigated by patent arteries and wrote: "Hence, it seems possible that the ischaemic changes were due to temporary spasm of the supplying vessels."

Ecker and Reimenschneider reported angiographic vasospasm in six patients with known ruptured aneurysms and noted that it was not observed on angiograms done 26 or more days after SAH [7].

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Table 1 Meetings focusing on angiographic vasospasm and delayed cerebral ischemia

Meeting title	Location, organizer(s)	Resulting book
Subarachnoid Hemorrhage and Cerebrovascular Spasm. The First International Workshop	Jackson, Mississippi, USA, 1972, Robert R. Smith, 18 attendees	Smith, R.R., Robertson, J.T., eds. *Subarachnoid Hemorrhage and Cerebrovascular Spasm. The First 'International' Workshop*. Springfield: Charles C. Thomas Publisher, 1975.
Second International Workshop on Cerebral Arterial Spasm	Amsterdam, the Netherlands, 1979, A.J.M. van der Werf, 200 participants	Wilkins, R.H., ed. *Cerebral Arterial Spasm. Proceedings of the Second International Workshop*. Amsterdam, the Netherlands/Baltimore: Williams & Wilkins, 1980.
3rd International Symposium on Cerebral Vasospasm	Charlottesville, Virginia, USA, 1987, Neal Kassell, 197 contributors	Wilkins, R.H., ed. *Cerebral Vasospasm. Proceedings of the III International Symposium in Charlottesville*. New York: Raven Press, 1988.
4th International Conference on Cerebral Vasospasm	Tokyo, Japan, 1990, Keiji Sano, K. Takakura, Tomio Sasaki	Sano, K., Takakura, K., Kassell, N.F., Sasaki, T., eds. *Cerebral Vasospasm. Proceedings of the International Conference on Cerebral Vasospasm*. Tokyo: University of Tokyo Press, 1990.
5th International Conference on Cerebral Vasospasm	Edmonton and Jasper, Alberta, Canada, 1993, Bryce Weir	Findlay, J.M., ed. Cerebral Vasospasm. *Proceedings of the V International Conference on Cerebral Vasospasm, Edmonton*. Amsterdam, the Netherlands: Elsevier Publishing Company, 1993.
6th International Conference on Cerebral Vasospasm	Sydney, Australia, 1997, Nicholas Dorsch	Dorsch, N.W.C., ed. *Cerebral Vasospasm VI. Proceedings of the VIth International Conference on Cerebral Vasospasm*. Oslington, Leichhardt, Australia, 1999.
7th International Conference on Cerebral Vasospasm	Interlaken, Switzerland, 2000, Rolf Seiler, 75 participants	Seiler, R.W., Steiger, H.-J., eds. *Cerebral Vasospasm. Acta Neurochirurgica*, Suppl. 77. Wien, New York: Springer, 2001.
8th International Conference on Cerebral Vasospasm	Chicago, Illinois, USA, R. Loch Macdonald, 90 participants	Macdonald, R.L., ed. *Cerebral Vasospasm. Advances in Research and Treatment*. New York: Thieme Medical Publishers, 2005.
9th International Conference on Cerebral Vasospasm	Istanbul, Turkey, Talat Kiris	Kiris, T., Zhang, J.H., eds. *Cerebral Vasospasm. New Strategies in Research and Treatment. Acta Neurochir* Suppl. Wein: Springer-Verlag, 2008.
10th International Conference on	Chongqing, China, Hua Feng, 90 participants	Feng, H., Mao, Y., Zhang, J.H., eds. *Early Brain Injury or Cerebral Vasospasm*. Volume 1: *Pathophysiology. Acta Neurochir* Suppl 110/1. New York: Springer, 2011.
		Feng, H., Mao, Y., Zhang, J.H. eds. *Early Brain Injury or Cerebral Vasospasm*. Volume 2: *Clinical Management. Acta Neurochir* Suppl 110/2. New York: Springer, 2011.
11th International Conference on Neurovascular Events After Subarachnoid Hemorrhage	Cincinnati, Ohio, USA, Mario Zuccarello, Joseph F. Clark	To be published in *Acta Neurochir Suppl.*

Advances

In the past, neurosurgeons wrote about pre- and postoperative vasospasm as if surgery had some impact on the timing of angiographic vasospasm. It is known now that while the severity might be affected by surgery, the time course is related to the time of SAH and has nothing to do with the time of surgery. DCI varies with time of surgery, however, probably due to effects of surgery on the brain, which is already injured by SAH and made even more vulnerable by reduction in cerebral blood flow (CBF) from angiographic vasospasm.

Fisher described clinical characteristics of DCI in 1975 [8]. The onset of DCI was described as is now known 3–13 days after a single SAH and in about one third of patients. Only severe vasospasm tended to be associated with symptoms. Weir and colleagues defined the time course of angiographic vasospasm by measuring the diameters of cerebral arteries on 627 angiograms from 293 patients with ruptured aneurysms [23]. Angiographic vasospasm had its onset at 3 days, was maximal at 6–8 days, and resolved by 12 days after SAH. The invention of computed tomography (CT) was critical to neurosurgery. Within 4 years, Katada et al. discovered there was a

relationship between the volume of SAH on CT and development of angiographic vasospasm [14]. Takemae and colleagues expanded on this concept, showing in a series of 73 patients with SAH studied by CT that high-density areas (blood) in the basal cisterns within 4 days of SAH were associated with the location of where angiographic vasospasm would develop and whether it would [19]. Fisher et al. later described a similar idea but classified the subarachnoid blood into four grades, which could be used to predict whether angiographic vasospasm would develop and how severe it would be [9]. Aaslid and colleagues described transcranial Doppler ultrasound, a now widely used method for determining CBF velocities and other parameters in patients with SAH [1].

Knowledge of the time course of angiographic vasospasm and improved diagnostic tools, principally angiography, CT, and medical tests, made it possible to associate vasospasm and delayed neurological deterioration. The clinical picture was called by various terms, including delayed ischemic deficit [10], DCI, delayed ischemic neurologic deficit, and symptomatic vasospasm.

The incidence of angiographic vasospasm was 67% (1,842 of 2,738 patients) in 38 studies until 1993 as reviewed by Dorsch et al. when angiography was done 7–14 days after SAH [5]. It was 49% (2,077 of 4,238 patients) in 31 references published from 1993 to 2009 [4]. Whether the incidence has declined or detection is lower now that patients do not all have angiograms in 7–14 days after SAH is not known. The incidence of DCI, variously defined, has not been rigorously reviewed, but according to Dorsch et al. the incidence was 32% (10,445 of 32,188 patients) in 297 references published until 1993 and 29% (6,775 of 23,806 patients) in papers published from 1993 to 2009 [4, 5].

Controversies

The existence of angiographic vasospasm and its significance were questioned initially. Millikan wrote in 1975 that he could not find any data to indicate that angiographic vasospasm had any specific clinical presentation, or that it contributed to complications of SAH [15]. He noted many investigations showing no correlation between CBF and angiographic vasospasm, which is not unexpected since only severe vasospasm reduces CBF, and linear correlations will not be obvious. That angiographic vasospasm, even severe in some cases, occurs without symptoms also was evident in some cases. Whether this is due to adequate collateral flow or lack of other secondary processes that must be added to angiographic vasospasm to cause DCI continues to be unknown. This controversy continues in a modified form today (Fig. 1).

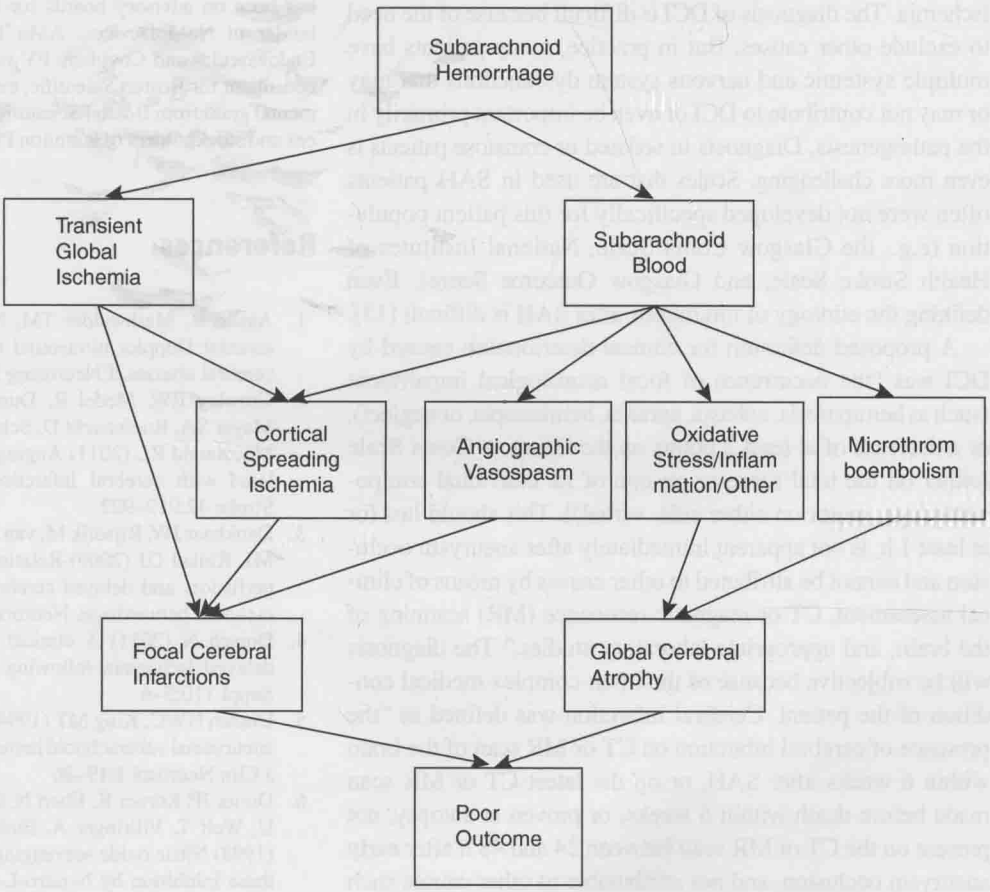

Fig. 1 A simplified scheme of possible processes and pathways leading to focal and global brain injury and ultimately poor outcome after SAH

There is no question about the association of angiographic vasospasm with reduction in CBF and development of DCI and frank infarction [2, 3, 11]. Numerous studies, beginning in the 1960s, reported correlations between reduced CBF and angiographic vasospasm [22]. The correlations are imperfect, which is not surprising considering the multiple contributing factors, technical and imaging issues, and complexities of human disease [20]. What may be more important is if and how multiple pathophysiological processes may contribute to DCI. The existence of these processes in humans is only beginning to be documented, such as cortical spreading ischemia and microthromboemboli [6, 18]. It is not known now how they, along with early brain injury and other delayed effects of the SAH like delayed apoptosis, contribute to DCI.

Definitions

Vergouwen and colleagues proposed definitions of angiographic vasospasm and DCI [21]. Since patients can have angiographic vasospasm without DCI and there may be a few patients with DCI and no angiographic vasospasm, it was recommended to separate the definitions. The pathogenesis of the conditions is not completely defined, so terms implying pathogenesis were avoided, although DCI attributes the deficits to ischemia. The diagnosis of DCI is difficult because of the need to exclude other causes. But in practice, many patients have multiple systemic and nervous system dysfunctions that may or may not contribute to DCI or even be important primarily in the pathogenesis. Diagnosis in sedated or comatose patients is even more challenging. Scales that are used in SAH patients often were not developed specifically for this patient population (e.g., the Glasgow Coma Scale, National Institutes of Health Stroke Scale, and Glasgow Outcome Score). Even defining the etiology of infarctions after SAH is difficult [13].

A proposed definition for clinical deterioration caused by DCI was "the occurrence of focal neurological impairment (such as hemiparesis, aphasia, apraxia, hemianopia, or neglect), or a decrease of at least 2 points on the Glasgow Coma Scale (either on the total score or on one of its individual components (eye, motor on either side, verbal)). This should last for at least 1 h, is not apparent immediately after aneurysm occlusion and cannot be attributed to other causes by means of clinical assessment, CT or magnetic resonance (MR) scanning of the brain, and appropriate laboratory studies." The diagnosis will be subjective because of the often-complex medical condition of the patient. Cerebral infarction was defined as "the presence of cerebral infarction on CT or MR scan of the brain within 6 weeks after SAH, or on the latest CT or MR scan made before death within 6 weeks, or proven at autopsy, not present on the CT or MR scan between 24 and 48 h after early aneurysm occlusion, and not attributable to other causes such as surgical clipping or endovascular treatment. Hypodensities on CT imaging resulting from ventricular catheter or intraparenchymal hematoma should not be regarded as cerebral infarctions from DCI." It was recommended that terms like vasospasm or arterial narrowing be applied to descriptions of what the arteries look like on a radiological test (computed tomographic, magnetic resonance or digital subtraction angiography). These terms would not to apply to clinical manifestations of DCI. Transcranial Doppler ultrasound was not included in the diagnostic testing since it has lower sensitivity and specificity to diagnose angiographic arterial narrowing.

Conclusion

In conclusion, the history of angiographic vasospasm and DCI has been briefly summarized. The reader is encouraged to delve deeper into the rich heritage of the field. Indeed, many of the cited papers are among the 100 most cited papers in neurosurgery [1, 9, 16].

Conflicts of Interest RLM receives grant support from the Physicians Services Incorporated Foundation and is a stockholder of Edge Therapeutics. RLM, RTH, EK, SAM, AMo, AR, PV, IW, and NK are consultants for Actelion Pharmaceuticals. SAM is a consultant for Edge Theraputics. RLM is Chief Scientific Officer of Edge Theraputics. EK has been on advisory boards for Roche Diagnostics, and is a stockholder in NeMoDevices. AMo has been a consultant for Micrus Endovascular and Covidien. PV is a consultant for Aesculap. IW is a consultant for Boston Scientific, ev3, and BALT, and receives a departmental grant from Boston Scientific. DB, AF, AMa, and SR are employees and stockholders of Actelion Pharmaceuticals.

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