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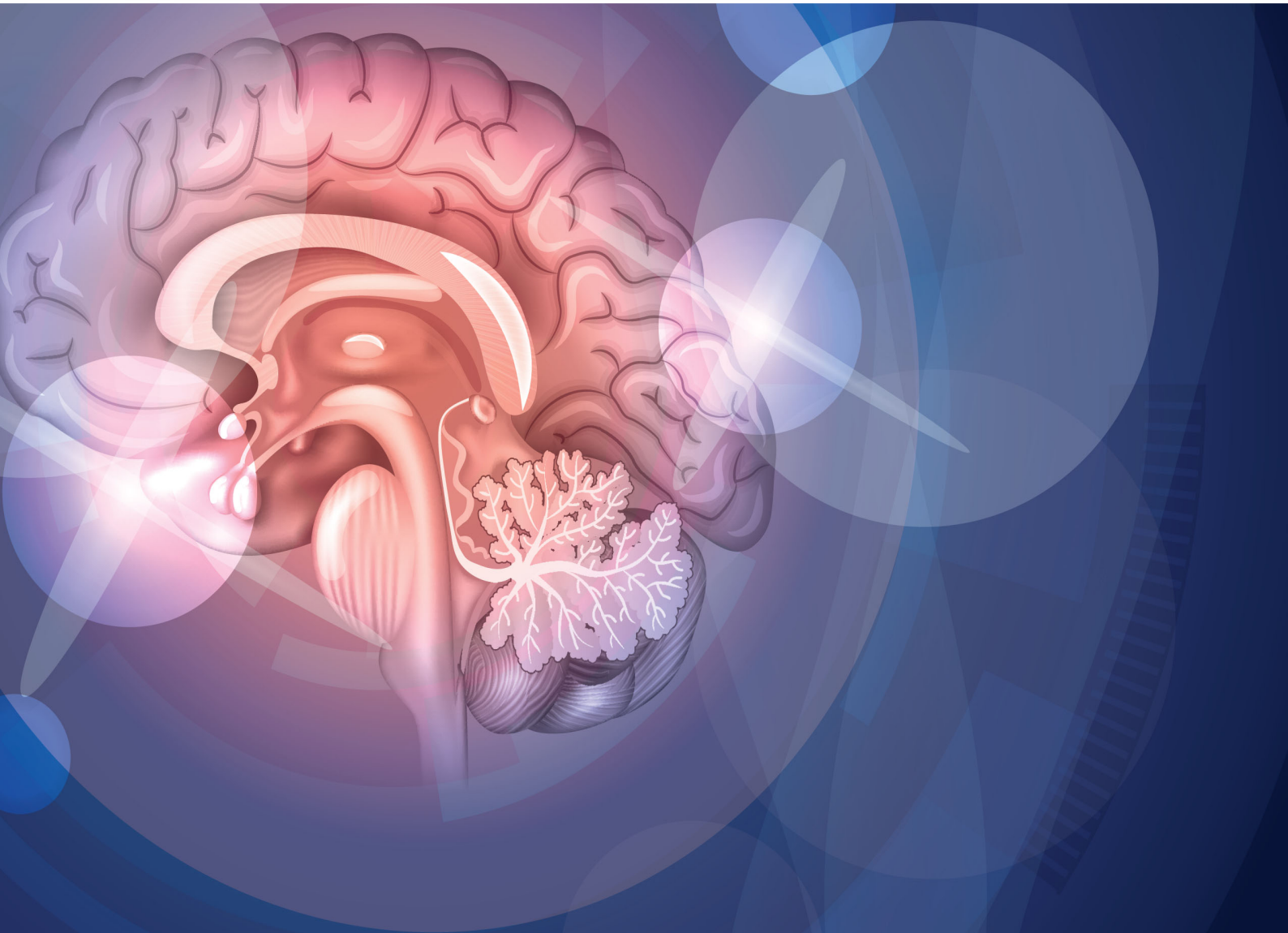
BRAIN ISCHEMIC STROKE - FROM DIAGNOSIS TO TREATMENT

VOLUME 3



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Simone Peschillo

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Frontiers in Neurosurgery

Volume 3

Brain Ischemic Stroke - From Diagnosis to Treatment

Edited by

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CONTENTS

FOREWORD

I read with a lot of interest the book by Simone Peschillo and his collaborators. This book presents the current knowledge on cerebral ischaemia and its treatment. It will be for sure very useful for all those who are interested on this topic.

It starts by the very concerning epidemiological and economic aspect of the disease and then it presents all the main themes of the subject. It will be a reference book that aims to be complete and it does not only present the therapeutic endo vascular techniques but also, and it is fundamental, all the medical environment and intensive care techniques which are essential.

We can only admire the progresses made, even in the diagnosctic plan. I personnally began to practise neuroradiology 45 years ago … It was the time when the diagnosis of an intracerebral hemorrhage could only be made if this bleeding was voluminous enough to displace the adjacent arteries angiography ...

I had the privilege in 1971 of attending the first french private presentation on CT by Ambrose who showed unrefined images made of black and white spots. It was a revolution : we were able to see directly, for the first time, the image of intracerebral blood. Nowadays, despite of MRI, CT remains a fundamental tool of decision in the field of cerebral ischaemia because it is fast and easily accessible.

In the 70s, there were few interventional neuroradiologists and they were more interested in angiomas and tumors than in cerebral ischaemia. I was personnally rapidly interested in this topic and the 80s were very important for me. In 1980 I began using angioplasty to treat major supra aortic arteries, then in 1983, after Mathias [1] I started simple angioplasty in carotid arteries [2]. I described in 1984 the concept of cerebral protection [3]. After Zeumer [4], I also in 1985 performed our first cases of intra arterial thrombolysis [5]. In 1990 I dared to put in place the first carotid stent [6] and then developed this technique [7, 8]. It activated some turbulences in the vascular surgery environment…

I am now delighted that this tool has become a classic in the treatment of carotid stenoses. Nevertheless let me summarize what I keep thinking on this matter:

At the opposite of the other arteries, post stenting restenoses are quite rare in carotid artery because of its high flow. Long closed stents remain for us the best choice because they treat the whole pathological area and correct partially the artery tortuosity.

The only real difficulty that remains is its approach on atheromatous patients. This is why we described the radial approach [9].

I keep thinking that a cerebral protection is mandatory and that the only real protection is the temporary occlusion of the distal internal catotid artery [10]. Filters offer a protection only for big emboli and are themselves reponsible of emboli. The temporary occlusion of the common carotid artery with simultaneous occlusion of the external carotid artery, that we also have described and later abandoned, seems to be reserved for the treatment of complete occlusions of the internal carotid.

Post revascularisation hemorrhage occurs in most cases on brains with previous silent infarctions. Its occurence is clearly limited by the control of blood pressure. Actually it can also be a delayed embolic hemorrhagic complication.

The book presents a very detailed chapter on non atheromatous arterial lesions. It is a very interesting topic that covers several diseases. We have been early interested in the disease of Takayasu when we worked in Canada [11] and we performed endovascular treatments on similar cases. More studies will be necessary in the future to adopt a common therapeutic strategy because the reaction to endovascular techniques can be quite different from one disease to the other.

In acute brain ischaemia I have to say my enthusiasm by seeing strengthening in the idea that a cerebrovascular accident is not any more a fate and that it exist therapeutic tools to treat it. After intravenous and intra arterial thrombolysis, mecanichal revascularisation technics are now available and are more and more sofisticated and effective. This book presents the various current possibilities. The time will tell us which ones are the best for each case. What is sure is that the number of necessary intervetionists will grow dramatically in the future. I am delighted at it for the whole world population.

However I would like to add about this topic some personal ideas that have meant a lot to me for years: we know that it is necessary to save time and CT remains the basic emergency investigation which allows make the diagnosis of intracerebral bleeding. We dreamt of CTs in a light truck and we spoke of it for many years. It does exist presently. If we deal with an ischemic case it will allow start immediately the intravenous thrombolysis. Many lives will be saved and many brains will be less damaged.

Arrived at the hospital, unless a complete clearance of the symptoms has be obtained, the patient will have an angiography. The good therapeutic decision will only be taken if the exact state of the cerebral vascularization is known. The cerebral parenchymography [12] remains for me the simplest and most adapted investigation. One single injection of contrast in the aortic arch is sufficient for confirming the arterial occlusion, its site and the exact devascularisation downstream to the occlusion. Anatomical variations are infinite and so are the individual possibilities of revascularisation. Vascularization of the cerebral parenchyma is

the only true key point to be known

In the decision of treating, occlusion of lenticulostriate arteries is for me a fundamental point. These arteries are terminal and their wall is very sensitive to ischaemia. It has been shown by Kamyjio on cat that their revasculaization after the 6er hour resulted in high purcentage of bleeding [13]. We have confirmed it [14] in showing that it was possible to eliminate post revascularization hemorrhage : intra arterial thrombolysis should not be performed on a patient after the 6th hour when the lenticulostriate arteries are occluded . On the other hand the therapeutic window can be widened if these arteries are not interested. This way of reasoning is obviously applicable also for the mechanical revascularisation.

Not using these information made that the possible therapeutic window was reduced in order to limitate the hemorrhagic complications. We are convinced that these simple rules should be used by all, day and at night, and that they could save numerous lives and handicaps.

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PREFACE

Someone suffers a stroke every 40 seconds in the USA; every year over 15 million people throughout the world suffer a stroke and 5 million are left significantly disabled. Stroke is thought to be the second biggest killer worldwide, and is responsible for over 5 million deaths per year.

The total economic burden of stroke is of the order of £7bilion per annum in England and Wales.

Even though many efforts to treat as much as possible stroke patients have been made, many of it are still left undertreated, mainly due to the short time window and other contraindications for intravenous (i.v.) rtPA. Furthermore, much more evidence demonstrates that endovascular treatment, in selected patients, is much more resolutive.

Various strategies have been developed to increase the number of treated patients: regarding the diagnosis, new neuroimaging tools allows neurologists and neurointerventionists to evaluate either the ischemic core and the vessel pattern and collateral status; regarding medical treatment, new molecules are being tested in RCTs (randomized clinical trials) with extended time windows.

In this context, endovascular treatment is a new technique that allows neurointerventionists to treat patients in whom intravenous rtPA has failed and those in extended time windows, in particular in large-vessels occlusion.

Regarding this novel approach, a new era has emerged with new devices (*i.e.* stent-retrievers and aspiration techniques), which have demonstrated in recently published RCTs higher rates of recanalization and clear superiority compared to previous devices.

Several ongoing RCTs are now investigating whether bridging therapy is more effective than i.v. treatment alone, whether mechanical thrombectomy is more successful than the best medical treatment in patients ineligible for i.v. thrombolysis and which kind of endovascular treatment is much effective.

The purpose of this eBook is to take stock of the latest news on the ischemic stroke treatment.

In 2020, mortality will be doubled due to this serious disease; everyone, health care assistants, social assistants and politicians as well, should be first in line to fight this battle.

This eBook is addressed not only to specialists in the treatment of patients with ischemic

stroke, but also nurses, physiotherapists and finally non-medical personnel whose task is to decide on health care.

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CHAPTER 1

Epidemiology and Social Costs

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Abstract: Stroke is a pathology that has a heavy socio-economic impact, considering that the annual incidence is 15 million new cases and only one-third of these has a positive clinical outcome. Stroke is the cause of 4% of all disabilities and it does, therefore, have very high indirect social costs. The purpose of this chapter is to analyse the societal costs of stroke and compare the various treatments in order to determine which gives the best results for a contained cost.

Clinical outcome was analysed using the modified Rankin Scale (mRS), in which patients are allocated a score that depends on the presence of neurological symptoms and an impaired capacity to perform daily-life activities. The indirect costs related to reduced productivity were calculated through the analysis of various indices: disability-adjusted life years (DAYLs), years of life lost (YLL) and years lived with disability (YLD).

We calculated that a mRS score <2 obtained in 13.5% more of cases by using endovascular treatment in patients with occlusion of large vessels rather than venous fibrinolysis would lead to a saving of about 56 billion euros. Using data on the lifetime cost of a stroke, we calculated that a saving of about 11,400 billion euros could be achieved with endovascular treatment.

Clearly the savings are related to positive results that avoid indirect costs, in an ideal situation in which all patients are treated with endovascular methods. In any case, the

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analysis is a mathematical demonstration of the notable potential of this therapeutic technique.

Keywords: Epidemiology, Healthcare, Incidence, Mortality, Prevalence, Prevention, Risk factors, Social costs, Stroke.

INTRODUCTION

Every year about 15 million people in the world suffer a stroke. Of these, 5 million die and another 5 million become severely disabled, creating an enormous financial and healthcare burden for the society and families of the patients.

In recent years improvements in diagnostic and therapeutic strategies have led to a reduction in deaths in the acute phase; however, there has been a notable increase in the incidence of ischemic strokes, particularly in developing countries, because of the more sedentary lifestyle and changes in dietary habits.

DEFINITION

An ictus, also known as a cerebrovascular accident (CVA) or brain attack, is a cerebrovascular disease, usually called a "stroke", from the original term "apoplectic stroke", although it does not refer only to a haemorrhagic condition. This term was introduced in 1689 by William Cole and was coined from the need to classify non-traumatic cerebrovascular accidents, which had previously all been called "apoplexy", from the time of Hippocrates in 400 B.C.

In fact, strokes include two nosological entities, ischemic accidents and haemorrhagic ones, which are extremely different with regards to aetiology, evolution and treatment. In the former case the condition is caused by a reduction or block in cerebral blood flow, which leads to cell death, whereas in the latter case, there is bleeding in the brain, with changes to the blood-brain barrier.

The currently used definition by the World Health Organization (WHO) is: *"rapidly developing 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 that of vascular origin."*

Subsequently, within the ischemic accidents a further distinction was made into

strokes, which by definition are irreversible, and transient ischemic attacks (TIA), which are focal, transient events.

Interest in TIAs continues to increase and in the 1970s they were defined as *"episodes of temporary and focal dysfunction of vascular origin, which are variable in duration, commonly lasting from 2 to 15 minutes, but occasionally lasting as long as a day (24 hours). They leave no persistent neurological deficit"*. However, progresses in the field of neurology made it important to have precise definitions, rather than the arbitrary temporal limit of 24 hours, which led the American Heart Association to define a TIA as *"a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia without acute infarction"* (Fig. **1**) [1].

Brief notes:

CENTRAL NERVOUS SYSTEM (CNS) INFARCTION: infarction of brain tissue, spinal cord or retina caused by ischemia, with symptoms that last more than 24h and have the anatomo-pathological and radiological correlates of an infarction.

STROKE: episode of loss of consciousness or focal motor and/or sensory neurological deficit caused by an ischemic or haemorrhagic infarction of central nervous system tissue.

HEMORRHAGIC STROKE: caused by blood leaking into the intracerebral or subarachnoid space.

TRANSIENT ISCHEMIC ATTACK (TIA): episode of loss of consciousness or focal motor and/or sensory deficit caused by ischemia, with symptoms that disappear within 24h and which do not have anatomo-pathological and radiological correlates of infarction.

EPIDEMIOLOGY

Worldwide, stroke is the second cause of death and the leading cause of permanent disability, making this a problem requiring particular attention, especially considering the substantial costs to the society. These include

CHAPTER 2

Brain Ischemia and Stroke: Mechanisms and Opportunities

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Abstract: Brain function and viability strictly depend on blood flow. In case of arrest of the cerebral circulation the brain cells would survive for only a few minutes. In the perinecrotic area, where a residual blood flow is present, the brain tissue may survive for a few hours or probably days to eventually die or regain function. Both innate and adaptive immune responses, together with oxidative stress and excitotoxicity activate a damage maturation process. The interplay of the events within the neurovascular unit includes both deleterious and protective mechanisms. The complexity of the post-ischemic damage offers a number of potential therapeutic opportunities. The same complexity, however, makes it likely that each individual, potentially therapeutic, approach embraces antithetical effects, by affecting both the deleterious and protective mechanisms that drive the maturation process. The perinecrotic area seems therefore to express a heterogeneous scenario, where a patchy pattern reflects different pathologic states, depending on the intensity of the ischemic insult and on both local and systemic variables.

Keywords: Cerebral blood flow, Hypothermia, Metabolism, Necrosis, Neurovascular unit, Post ischemic inflammation, Programmed cell death.

ABSOLUTE DEPENDENCE ON BLOOD FLOW

In spite of the relatively small size and weight (about 2% of the body weight) the brain takes as much as approximately ¼ of the whole body oxygen and glucose consumption. Such a metabolic demand must be fulfilled by a supply of metabolic

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Simone Peschillo (Ed.)

substrates from the blood. The supply must be continuous as the brain is without energy deposits. The average whole cerebral brain blood flow (CBF), is about 57 ml/100gr/min, in the healthy adult individual, which is about 800 ml/min, or approximately 15% of the total basal cardiac output. These data were obtained in the late 40s by means of the nitrous oxide method [1], which measures the average rates of energy metabolism and blood flow for the whole brain. The method is based on the Fick principle, which states that blood flow can be measured by assessing the concentrations of a substance within the blood as it enters and leaves the organ being supplied. The principle is an equivalent of the law of conservation of matter (Box 1).

The brain uses energy mostly for signaling-related processes. In primates, most of the energy (74%) is supposed to be consumed at postsynaptic level, for restoring the ion gradient across cell membrane. Glia may account for 5-6% of the total energy consumption [2]. Inhibitory signaling needs energy as well [3], as it depends on trans-membrane electrical potentials, which are maintained or restored by energy-dependent ion transport. The energy is obtained, under normal conditions, almost uniquely by glucose oxidation. Since the amount of oxygen stored in brain is small, the brain requires continuous supply of oxygen from systemic circulation. Glucose extraction by the brain from the blood is 10%, while oxygen extraction is 50-70%. Thus there is low extraction reserve for the oxygen. In addition there is no intracellular storage (in contrast to the muscle tissue) and an increase in blood flow is mandatory whenever there is increased energy demand. During brain activation, venous oxygen content immediately falls and blood flow must increase in order to maintain the energy supply.

However, there is no direct evidence that the hemodynamic response is consistently, or always, associated with the energy demand. Local CBF may increase as a consequence of increased signaling (mostly glutamate-, amine- or Ach-mediated). For instance, in the cerebellum activation of some pathways leads to an increase in CBF without consensual increase in metabolism [4]. Furthermore, the effects of energy consumption and neurotransmitter-related signaling may not be spatially restricted to the site of the cell firing, but the effects might be more widespread and cause an increase of CBF extended to distant areas. Such findings might be of relevance in the interpretation of the blood-

oxygen-level dependent (BOLD) contrast imaging, used in functional magnetic resonance (fMRI).

HETEROGENEOUS ORGAN

The development of quantitative autoradiography technique allowed measurements of local tissue concentrations of chemically inert, diffusible, radioactive tracer in all the structural brain areas visible in autoradiographs of serial sections of the animal brain [5]. The autoradiography technique was applied for measuring a number of functional parameters, including local rates of CBF following infusion of tracers such as [^{14}C] antypirine [6] and local rates of cerebral metabolism by using the [^{14}C] labeled analog of the glucose, the 2-deoxy-D- [^{14}C] glucose [7] (Box 1).

The exploitation of these methods in a variety of physiological conditions has definitely shown that rates of blood flow and energy metabolism are heterogeneously distributed within the brain. CBF and energy metabolism vary not only from area to area but they also vary with time, according to the dynamic changes of brain function. Under normal conditions changes in CBF and energy metabolism are concordant, and reflect local changes of functional brain activity. There are mechanisms to adjust CBF to changes in cerebral metabolic demand; there are also numerous physiological mechanisms to sustain adequate levels of blood even when arterial pressure falls (*autoregulation*). Any local increase in functional activity, under physiological conditions, is associated with local increase in CBF in order to meet the energy demand (*functional hyperemia*).

ISCHEMIC CORE

In case of arrest of the cerebral circulation the brain cells would survive for only a few minutes. Clinicians experience the dramatic result of sudden, whole brain ischemia during a cardiac arrest. A fall in CBF to half its normal rate is sufficient to cause loss of consciousness in normal, healthy, young men. Within seconds of an ischemic insult normal brain activity ceases. Within minutes after ischemia loss of ATP results in decreased function of the ion pumps. Under a Pasteur shift of glucose metabolism caused by oxygen deprivation the pH of the ischemic tissue drops and lactic acid accumulates. Extracellular K^+ increases because of massive

CHAPTER 3

New Imaging Techniques

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Abstract: Stroke represents an important cause of death and permanent disability in the industrialized world. Diagnostic imaging plays a key role in the clinical process, distinguishing, early in the acute phase, ischaemic stroke from primary haemorrhagic stroke. Nowadays, new imaging techniques, such as Computed Tomography Angiography (CTA), Magnetic Resonance Angiography (MRA) and perfusion imaging represents important tools in the definition of the severity of ischaemic stroke. The aim of advanced imaging techniques is to identify cerebral ischaemia within the first few hours and distinguish normal cerebral tissue from that at risk. This chapter focuses on imaging characteristics of stroke, with their anatomic-radiologic correlations, emphasizing the role of new imaging techniques, with their strengths and weaknesses.

Keywords: Brain infarct, Computed Tomography, Computed Tomography Angiography (CTA), CT perfusion (CTP), Ischaemic penumbra, Magnetic Resonance Angiography (MRA), Magnetic Rensonance Imaging, Stroke.

INTRODUCTION

Stroke is the third leading cause of death in industrialized countries, after ischemic heart disease and cancer, being responsible for about 10% of all deaths each year. From 15 to 30% of patients with ischemic stroke die within 30 days. Mortality within 30 days is even higher in patients with hemorrhagic stroke. Ischemic cerebrovascular disease is also a leading cause of disability, with social and economic consequences. The incidence of cerebrovascular disease increases with age, and is therefore an emerging problem, considering the aging of the

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general population; in industrialized countries stroke deaths are expected to double within 2030. [1, 2].

Stroke is defined as the sudden appearance of brain function alteration (neurological deficit), lasting more than 24 hours or resulting in death, due to an acute occlusion of an artery responsible for cerebral blood flow. Stroke diagnosis is therefore, exquisitely clinic. Anyway, diagnostic imaging plays a major role in the initial management of stroke, in the first instance being able to identify the real ischemic and non-hemorrhagic origin of the acute neurological deficit; imaging is also able to easily exclude the presence of extraparenchymal hemorrhages, tumors, abscesses and other conditions that may simulate a stroke and require different therapeutic management [3, 4].

Strokes are classified according to the triggering cause of the acute reduction of cerebral blood flow. The most common cause of ischemic stroke is an embolic vascular occlusion.

In most cases, clots originate from atherosclerotic plaques in the aortic arch or in the carotid artery (bifurcation, proximal segment or carotid siphon). Less commonly embolic occlusion can be of cardiac origin. In this case emboli originating from thrombotic material lay in the atrium, in the ventricle or in the aortic or mitral valve [4 - 6].

Less common causes of stroke, especially in Caucasians, are:

- atherosclerosis of a main intracranial vessel (most often the middle cerebral artery);

- occlusion of small intracranial arteries, often in charge of small infarcts (lacunar stroke);

- dissection of the internal carotid or vertebral artery (most common cause of stroke in younger patients);

- hemodynamic causes;

- hematologic disorders;

- vasculitis and vascular congenital anomalies [4 - 7].

PATHOPHYSIOLOGY

Infarction occurs when an acute vascular occlusion cause a critical reduction of the cerebral blood flow (CBF), and cerebral perfusion is unable to meet the metabolic demands of the tissue it is supplying [8].

In normal brain tissue, a stable CBF is the most important factor for cell survival, and its value is normally of 60 mL/100g /min for the gray matter and slightly lower for white matter. Cerebral autoregulation maintains a constant CBF within a broad spectrum of systemic pressure values [8, 9]. After vascular occlusion, CBF is maintained by capillary vasodilatation of the distal microcirculation with a resultant increase in cerebral blood volume (CBV) and prolongation of the arterial transit time (MTT) [8 - 11].

Unrecoverable neuronal damage occurs when CBF falls below the critical threshold of 20 mL/100 g/min (<20% of normal), activating a sequence of pathophisiological cellular events that cause cellular energy depletion and alteration of ionic transcellular gradients.

The deregulated activation of calcium and glutamate channels causes Cytotoxic neuronal damage, peri-infarction depolarizations, cell swelling and eventually neuronal death [12 - 14].

In the affected tissue, CBF reduction is variable, depending on compensation mechanisms that are strictly related on the type of occlusion and on collateral circulation.

The central zone is defined infarction core (CBF values <20ml/100g/min), where failure of the ion pump and depolarization of the cell membrane result in shift of water from extracellular to intracellular compartments (cytotoxic edema) and inevitable cell death.

A so called “penumbral zone” (CBF between 50 and 20 ml/100g/min) of electrically inactive but viable neurons surrounds the core. Tissue within this zone may remain viable up to 48 hours after (“therapeutic window”) [10, 11, 15, 16].

CHAPTER 4

Medical Acute Stroke Treatment

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Abstract: Despite the stroke burden has globally increased, particularly due to high rates of mortality and dependency in developing countries [1], advances are being made. In the last two decades, we witnessed important successes in the management of acute stroke patients, the principal of them being the development of stroke units, aspirin for the early secondary prevention, thrombolysis for the reperfusion of ischemic areas and decompressive craniectomy for malignant strokes.

This chapter will focus on the medical management of acute stroke, in particular on the thrombolytic treatment.

Keywords: Acute stroke, Evidence, Intra-venous thrombolysis, Ischemic stroke, Medical therapy, Neurovascular unit, Stroke unit, Systematic review, Treatment.

INTRODUCTION

Undoubtedly, in terms of patho-physiology, the thrombolytic therapy is the most suitable treatment for acute ischemic stroke, as it targets the ischemic penumbra [2], a "functionally impaired yet still viable tissue which is characterized by the potential for recovery without morphological damage, provided that local blood flow can be re-established at a sufficient level and within a certain time window", as it was originally defined by Astrup. In human patients, more recent imaging studies showed that the volume of irreversibly injured tissue in acute cerebral ischemia expands rapidly and relentlessly, consuming 2 million additional

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neurons per minute unless adequate reperfusion is restored [3].

GENERAL SUPPORTIVE CARE

The acute phase of stroke is crucial for long-term outcome as the majority of complications arise mainly within 24 hours from onset and rarely after four days [4]. The different types of complications can be neurological (6%), infective (21%), pressure sores (21%), deep venous thrombosis (1%), pulmonary embolism (2%), pain (22%) and psychological (11%) [5]. These complications, along with cardiac complications and mortality, may be related to the quality of care provided. Intensive monitoring of vital functions such as blood pressure, pulse rate, oxygen saturation, temperature, and heart rhythm assessed by electro-cardiogram (ECG), should be useful because acute medical interventions targeted at maintaining these essential physiological variables within a narrow physiological range should improve the outcome [6].

An ischemic stroke is caused by the failure of focal tissue oxygenation and energy supply, due to an arterial blood clot. Thus, it is paramount to avoid and correct those conditions which may potentially exacerbate the depletion of oxygen and glucose, such as systemic hypoxemia, hypoglycemia and hypotension, in order to limit further cellular damage.

The American Heart Association/American Stroke Association guidelines on the management of acute stroke [7] recommend “airway support and ventilatory assistance for the treatment of patients with acute stroke who have decreased consciousness or who have bulbar dysfunction that causes compromise of the airway” (Class I; Level of Evidence C). Moreover, supplemental oxygen should be provided to maintain oxygen saturation >94% (Class I; Level of Evidence C). The recent SO2S trial [8] was conducted to determine whether routine low-dose oxygen supplementation for 72 hours in patients with acute stroke and saturation levels <93% improves outcome and, further, to establish whether nocturnal oxygen supplementation is more effective than continuous oxygen supplementation. The trial failed to show any significant difference in terms of mortality or clinical outcome.

Cardiac arrhythmias that might reduce cardiac output should be corrected and

intravenous normal saline is indicated to correct hypovolemia (Class I; Level of Evidence C), at a dose of approximately 30 mL per kilogram of body weight. However, precaution is needed in patients affected by renal or heart failure, who are particularly vulnerable to intravascular volume overload.

Continuous cardiac monitoring is indicated for at least 24 hours after stroke onset in order to identify atrial fibrillation or other serious arrhythmias (Class I; Level of Evidence B).

In the acute phase of ischemic stroke, hyperthermia is associated with poor neurological outcome, as it may increase metabolic demands, enhance release of neurotransmitters, and increase free radical production. In the PAIS trial [9], treatment with high-dose paracetamol was showed to improve clinical outcome, above all in patients with a baseline body temperature of more than 36.5 °C. These findings are to be confirmed in the ongoing PAIS-2 trial. Therefore, it is recommended to identify and correct any possible source of hyperthermia (Class I; Level of Evidence C). Nevertheless, preventive antibiotic treatments only reduce the amount of infections in acute stroke patients, but do not alter the global outcome at three months, as shown by the PASS trial [10] presented at the 2014 World Stroke Conference. Whether therapeutic hypothermia is effective in acute stroke patients is being tested in the Euro-Hyp Trial.

Although stroke-related hyperglycemia is associated with greater brain injury, poorer functional outcomes, and increased mortality, intensive therapy to lower blood glucose levels does not appear to improve functional outcomes or mortality rates, as showed by a Cochrane Review [11]. It is however recommended to prevent hypoglycemia as it may cause autonomic and neurological disturbances, including stroke mimics and seizures (Class I; Level of Evidence C).

Arterial hypertension is common during an acute ischemic stroke. Both extremely high and extremely low arterial blood pressure levels are clearly detrimental, because the former carries the risk for encephalopathy, brain edema and hemorrhagic transformation, as well as cardiac and renal complications, while the latter exacerbates the ischemic damage by decreasing perfusion. Theoretically, moderate arterial hypertension during an acute ischemic stroke may improve

CHAPTER 5

Endovascular Stroke Therapy: Devices and Different Approaches

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Abstract: Acute ischemic stroke (AIS) is a significant medical disease with relevant mortality and morbidity associated, that, especially in recent years, has undergone a major development of drugs and devices used for its treatment. A poor number of patients respects the criteria for treatment with intravenous drug (IVT) with recombinant tissue plasminogen activator, and the efficacy of this treatment in large vessel occlusion is percentually low. Recently, incresead percentage number of patients with AIS are treated with mechanical embolectomy if IVT is ineffective or controindicated. An important technological upgrading of devices used for the endovascular treatment of AIS, has allowed a significant increase in rates of recanalization and neurological improvement of patients treated, completely replacing the old device. Furthermore the use of these new devices has not caused an increase in intracerebral hemorragic (ICH). This chapter highlights the devices used in current practice for endovascular treatment of AIS, the different endovascular approaches and a brief review about the recent randomized trials, which have evaluated the efficacy of these new devices.

Keywords: Acute Ischemic Stroke, Endovascular treatment, Large Vessel Occlusion, Mechanical Thrombectomy, Stentriviers, Tromboaspiration.

INTRODUCTION

Acute ischemic stroke (AIS) is a significant medical disease with relevant

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mortality and morbidity associated,that, especially in recent years, has undergone a major development of drugs and devices used for treatment. Poor number of patients respects the criteria for treatment with intravenous drug (IVT) with recombinant tissue plasminogen activator, and the efficacy of this treatment in large vessel occlusion is percentually low. Recently, incresead percentage of patients with AIS are treated with mechanical embolectomy if IVT is ineffective or controindicated. An important technological upgrading of devices used for the endovascular treatment of AIS, has allowed a significant increase in rates of recanalization and neurological of the patients treated, almost completely replacing the old device.

The new devices in endovascular stroke treatment is safe, with not increase in ICH. Ischemic strokes, caused by occlusion in arterial tree of the brain, regard as for 87% of all strokes and are a leading cause of death and disability. About 7500000 people present ischemic strokes each year. The 30-day mortality in this population is 8% to 12%. In the remaining patients, the morbidity is variable, with 50% present degree of hemiparesis, 30% unable to ambulate, 19% aphasic, 35% depressed, and 26% residing in a nursing home. Only 25% of patients who survive an ischemic stroke recover fully, while the majority become disabled and a substantial proportion of these their disability is so severe that they are no longer self sufficient and need to be managed in a chronic care setting [1]. The target of treatment for AIS is to reach quickly vascular recanalization and cerebral reperfusion cerebral reperfusion before onset brain damage becomes irreversible. The relationship between early vessel recanalization and favorable modified Rankin score is known [2], although clinical factors such as age, comorbidity and stroke severity are also likely to have significant impact on clinical outcome [3]. Previously, the only FDA-approved treatment with level 1 evidence for AIS is IVT with recombinant tissue plasminogen activator (alteplase) within three hours of symptom onset [4]. Recent studies showed that expanding time window to 4.5 h a greater number of selected patients can clinical benefit [5]. Nevertheless, few patients (< 10%) meet eligibility criteria for this therapy [6].

Furthemore, the clots located into the proximal-large vessel are often resistant to IVT [7]. Early and optimal recanalization of large vessel occlusion (LVO) with IVT alone is infrequent, in approximately 10%of cases with regard to the

occlusion of internal carotid artery and 30% occlusion of the middle cerebral, and IVT is associated with increasing risk of ICH [8]. In recent years, the endovascular mechanical recanalization was developed as a safe and effective treatment. The notable technology progression of devices for mechanical thrombectomy permitted to treat an increasing number of patients with AIS when IVT is ineffective or contraindicated [9].

SELECTION PATIENTS FOR ENDOVASCULAR TREATMENT

In management of acute ischemic stroke, the aim is to early identify clinical signs and thrombo-embolic occlusion of arterial tree and promptly recanalize the occluided arterial branch. Patients with hemispherical neurological stroke signs will have an occlusion of the internal carotid artery (ICA) or proximal middle cerebral artery (M1) segment in approximately 3/4 cases and will be eligible potentially for endovascular mechanical recanalization [10]. The National Institute of Health Stroke Scale Score (NIHSSS) is the most important clinical tool to evaluate patients with AIS, and his high score is predictive for LVO in those patients who may be poor responders to IVT and thus better candidates for endovascular treatment.

Recent clinical trials comparing clinical outcome and revascularization rates between endovascular revascularization therapy (ERT) and intravenous thrombolysis for anterior LVO, have yielded neutral results, [11] but more clinical series reported that patients with NIHSS score ≥14 and/or proximal LVO may benefit from ERT [12]. In addition to site of arterial occlusion and NIHSS at presentation, other clinical, technical and neuroimganig factors (successful recanalization, Alberta Stroke Program Early CT Score [ASPECTS], influence stroke outcome and need to be considered during patient selection for ERT [13] To attempt a better selection of patient, several prediction tools have been developed in clinical practice [14], but a standardized approach to patient selection for ERT is lacking across institutions [15].

Recently, some authors have established the Pittsburgh Response to Endovascular therapy score (PREs) that incorporates age, NIHSS at presentation and ASPECTS on initial head CT scan and definited this score in two large endovascular groups

CHAPTER 6

Mechanical Thrombectomy for Acute Ischemic Stroke: Review of the Evidence

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Abstract: Acute ischemic stroke secondary to large vessel occlusion (LVO) is a devastating condition resulting in death and disability in a high proportion of patients. Over the last 2 decades, we have witnessed a tremendous progress in the treatment of this disease. In fact, from an observational and mostly supportive care we are now in the era of acute endovascular intervention.

The first step in the right direction was the NIH/NINDS intravenous (IV) tissue plasminogen activator (tPA) trial. The trial introduced the concept of time-sensitive intervention in acute ischemic stroke. Subsequently, the endovascular approach was pioneered as treatment for this condition. However, 3 clinical randomized trials SYNTHESIS Expansion, IMS III and MR RESCUE failed to demonstrate superiority of the endovascular approach over standard IV tPA therapy. There were several drawbacks in these trials including i) not always demonstration of a LVO ii) long time to intervention and iii) most importantly, use of first generation thrombectomy devices. In fact, while these trials were ongoing, retrievable stents in SWIFT and TREVO 1 and 2 showed to be superior to first generation thrombectomy devices.

Using latest generation technology, MR CLEAN, ESCAPE, EXTEND IA, SWIFT-PRIME and REVASCAT, 5 multicenter, controlled, randomized, clinical trials showed overwhelming superiority of the endovascular approach over medical management for acute LVO.

Keywords: Ischemic stroke, Randomized clinical trials, SOLITAIRE stent retriever, Thrombectomy.

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INTRODUCTION

There has been a tremendous progress in the treatment of ischemic stroke secondary to large vessel occlusion (LVO). Recently, level 1A evidence was generated by multicenter, controlled, randomized clinical trials. These clinical trials showed that we now a treatment that can result in a life without disability for acute ischemic stroke patients.

The purpose of this chapter is review the development of endovascular stroke therapy though the analysis of the evidence presented in randomized clinical trials.

The first step in treating acute ischemic stroke successfully is the notion that early reperfusion of a large vessel occlusion (LVO) can produce dramatic improvement in the patient's symptoms [1]. Exactly 20 years ago, the National Institute of Neurological Disorders and Stroke (NINDS) investigators showed superiority of recombinant IV tissue plasminogen activator (r-tPA) *versus* placebo in acute ischemic stroke [1]. The data came on the shoulder of three well-performed but negative trials [2 - 4]. Undoubtedly, the NINDS IV tPA trial established once and for all the concept of acute, time-dependent reperfusion therapy in cerebral ischemia. At that time, it was an historical step forward. In fact, until then the approach to patients with acute ischemic stroke consisted of supportive care, rehabilitation, and secondary stroke prevention.

As IV tPA was being used world-wide, it was reported that it may result in low rates complete recanalization in LVO. This was particularly true for proximal occlusions [5]. Endovascular recanalization therapy was then the most logical development on the road to treat LVO successfully.

The initial attempt to endovascular therapy of acute ischemic stroke was based on intra-arterial thrombolysis and then first generation mechanical thrombectomy devices (*i.e*. Concentric Thrombus Retriever and Penumbra device) [6, 7]. The clinical utility of this approach was tested in 3 randomized clinical trials: 1) SYNTHESIS-Expansion 2) IMS III and 3) MR RESCUE. The trials were presented and concurrently published in *The New England Journal of Medicine* in 2013 [8 - 10].

SYNTHESIS-EXPANSION

Ciccone *et al.* deserve credit for being able to design and execute a multicenter randomized clinical trial of endovascular therapy that reflected the standard of care at that time [8]. In particular, the investigators selected and randomized 362 patients with acute ischemic stroke treated within 4.5 hours after symptom onset. The patients were randomized to IA thrombolysis with rtPA, mechanical thrombectomy (*i.e.* wire manipulation or Concentric Thrombus Retriever) or a combination of all. The trial did not mandate a diagnosis of LVO or time constrains for treatment. According to the trial design patients were treated "as soon as possible after randomization".

As primary outcome, SYNTHESIS-Expansion decided to use free of disability survival as assessed by a modified Rankin score (mRS) of 0 or 1 at 3 months.

In the trial, 181 patients were randomized to endovascular therapy while 181 were treated with 0.9 mg/Kg of IV rtPA. There was a significant delay in the time from stroke onset to treatment between endovascular therapy (3.75 hours) and IV rTPA (2.75 hours) ($P<0.001$). The trial missed the primary outcome for endovascular therapy. In fact only 55 patients (30.4%) had a mRS ≤ 1 in the endovascular arm *versus* 63 (34.8%) in IV rt-PA group. The difference was not statistically significant.

With regards to safety also there was no difference between the two treatments. In fact, symptomatic intracranial hemorrhage was present in 6% of the patients in each group. The investigator concluded that endovascular therapy as performed in the trial, was not superior to standard medical management with 0.9 mg/Kg of IV rtPA.

Interventional Management of Stroke (IMS III)

The Interventional Management of Stroke (IMS III) trial was a National Institute of Health (NIH) sponsored, multicenter, randomized clinical trial to evaluate if endovascular stroke therapy was superior to IV rTPA in patients eligible for IV tPA [9]. In particular, eligible subjects for the trials were patients who received IV tPA within 3 hours after symptom onset and were randomized to endovascular

CHAPTER 7

Neurosurgery in Brain Ischemic Stroke

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Abstract: Ischemic strokes caused by the complete occlusion of an intracranial artery are associated with poor outcomes overall, and high mortality rates. To improve the survival and the outcome otherwise not afforded by the available medical and interventional therapies a neurosurgical approach must be considered. In selected patients a microsurgical embolectomy and a decompressive craniectomy are effective therapies with which to treat occlusions of the middle cerebral artery or other territories when thrombolysis or an interventional endovascular embolectomy does not restore the vascular flow. A bypass procedure that employs a superficial temporal artery-to-middle cerebral artery (STA-to-MCA) surgical anastomosis can be performed to improve the blood flow in a deficient artery chronic angiopathic disorder.

Keywords: Bypass, Decompressive craniectomy, Encephalo-myo-synangiosis, Ischemia, Intracranial pressure, Microsurgical embolectomy, Middle cerebral artery, Neurosurgery, Stroke.

INTRODUCTION

Strokes are predominantly ischemic (up to 90%) rather than hemorrhagic events [1, 2]. In a 20-year comparative study, mortality from hemorrhagic stroke appeared to decrease significantly (nearly 50%), while the mortality rate associated with ischemic stroke in young adults decreased by only 15% [3]. When untreated, strokes caused by the occlusion of anterior circulation in the proximal intracranial artery are associated with poor outcomes overall, with mortality for

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ischemic stroke averaging 50% [4, 5]. A dismal prognosis is expected in when occlusion of the middle cerebral artery territory is complete, because space-occupying edema and concurrent brain herniation develop during the initial 5 days after presentation [6]. When more than 50% of the middle cerebral artery territory is involved, fatal brain swelling occurs [7, 8]. In the neurosurgical management of selected patients with ischemic stroke, there is an expanding role to improve the survival and the outcome otherwise not afforded by the available medical and interventional therapies.

Microsurgical Embolectomy

Patients with complete occlusion of the middle cerebral artery territory from an embolic specimen are eligible for thrombolytics within 4.5 hours of the onset of symptoms [9]. In those patients in which thrombolysis does not restore the vascular flow, an interventional endovascular embolectomy with a retriever device may be considered within 8 hours of symptom onset [10, 11]. When neither of these procedures is appropriate or neither resolves the occlusion, the possibility of an emergency microsurgical embolectomy (ME) should be evaluated in selected patients [12 - 17]. The first attempt to surgically remove embolic tissue from the middle cerebral artery dates back to 1956, when Keasley Welch (1920-1996) performed the procedure in two young adult patients [18]. ME data from magnetic resonance angiography (MRA)/diffusion-weighted imaging (DWI) mismatch indicate that a short median recanalization time (the interval between symptom onset and emergent surgery) appears to produce a high rate of complete recanalization and a low complication rate [15, 16]. The initial reports and series that described patients undergoing ME were in young adult patients [19 - 23]. More recently, single reports or case series of patients show that the majority are older (mean age 77-80 years), probably the effect of ME being employed as a second-tier treatment in these patients after other treatments have failed [12, 15, 16, 24, 25].

The microsurgical technique requires experienced hands [14]. The first step is the choice of a surgical approach that provides very fast access to the thrombosed artery during the short window in which ischemic stroke can be managed. For this reason, each neurosurgeon performs the surgery in accordance with their personal

skill and the location of the occluded vessel: pterional, frontotemporal, laterally extended superciliary, and anterior temporal approaches have been reported [13, 14, 26, 27, 28].

In case of middle cerebral artery occlusion, the arachnoid of the Sylvian fissure must be opened using the usual microsurgical technique. The small perforating branches that frequently originate from the insular segment of the middle cerebral artery (M2) are detected and carefully protected to avoid any injury from either traction or pressure. The distal portion of the occluded artery is exposed. A temporary vascular clip is placed proximal to the presumed vascular occlusion; a distal vascular clip may also be advisable in some cases to avoid the embolization of small fragments from a brittle clot in the distal patent artery. A longitudinal or transverse microarteriotomy (3 mm length) allows opening of the wall of the occluded vessel and removal of the clot through suction or gentle squeezing of the artery. Transient opening of the proximal vascular clip enables the blood flow to clean all residual clot fragments from the occluded branch and assures complete restoration of blood flow. In some cases, multiple arteriotomies may be required to remove a long embolus [27]. Intermittent sutures, vascular closure staples, or microclips are applied, and recanalization is confirmed by micro-Doppler ultrasound or indocyanine green angiography [26, 28, 29, 30].

Complications from the surgical procedure are those common to any intracranial neurosurgical approach, and are relatively rare. In 4% to 8% of patients treated with ME, on average, restoration of blood flow has reportedly changed an infarct into a hemorrhagic lesion (reperfusion injury) [15, 24, 26]. Treating the patient within a short interval appears to avoid such events, probably because the ischemic stroke is not complete or because the involved brain tissue is still viable [14, 16, 17, 27]. Indeed, collateral flow, which varies widely among individuals, is considered the best predictor of outcome [31 - 35]. The results of surgical embolectomy exhibit a high rate of complete recanalization, with 70% to 100% improvement of the National Institutes of Health Stroke Scale (NIHSS) score at 1 month after the event [15, 16]. Future series must better define the role of surgical embolectomy as an effective therapy with which to treat occlusions of the middle cerebral artery or other territories, to be considered at least in selected patients independent of other therapies.

CHAPTER 8

Clinical, Pharmacological and Endovascular Management of Cerebral Venous Thrombosis

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Abstract: Cerebral venous thrombosis is a quite infrequent condition (3-4 per million) that affects predominantely young patients. It is typically characterized by a variable clinical spectrum and prognosis is influenced by several factors. Diagnosis is sometimes difficult since symptomatology is often non-specific. Imaging work-up by CT and MRI plays an important role in patient triage and diagnosis. Modern modalities allow an excellent visualizaion of the venous system and a precise identification of the intra-luminal thrombus. Imaging may also add an interesting prognostic value. Medical management mainly consists in anticoagulation, reduction of intracranial hypertension and treatment of underlying triggering conditions. In recent years, endovascular techniques have emerged as a new interesting option in patients poorly responding to medical therapy, with promising results. In this chapter, we sought to review the current knowledge on the clinical management, imaging diagnosis, medical and endovascular treatment of this pathology.

Keywords: Anticoagulation, Cerebral venous thrombosis, Complications, CT, Diagnosis, Dural sinus, Endvascular treatment, Imaging, MRI, Symptoms, Thrombectomy, Thromboaspitation.

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INTRODUCTION

Cerebral venuos thrombosis (CVT) remains an often underdiagnosed pathology, being a relatively uncommon disease characterized by a wide spectrum of etiologies, clinical presentation, and variable prognosis. The purpose of this work is to review current knowledge about CVT concerning its clinical manifestations, diagnosis, and treatment, with particular focus on imaging modalities and endovascular treatment approaches.

Clinical Presentation

Onset of symptoms may be acute, subacute or even chronic. Even if clinical presentation of cerebral venous thrombosis can be highly variable, there are four described major clinical patterns which may appear either isolated or in different combinations:

- Isolated intracranial hypertension: headache is the most frequent symptom, present in nearly 90% of patients. It can be accompanied by papilledema, with or without visual loss. Sixth nerve palsy can also be observed. When those symptoms are isolated (up to 25% of patients), the diagnosis of CVT can be particulary difficult, the more so as the value of D-dimer is normal in 25% of the cases [1, 2].
- Focal deficit, including hemiparesis, hemiparesthesia or aphasia, are noted in 44% of patients [3] and are most often related to the presence of venous infarction.
- Focal or generalised seizures are presents in 30% to 40% of patients, mostly in case of thrombosis of the sagittal sinus or cortical veins [3].
- Encephalopathy can be observed in thrombosis of the straight sinus or in case of extensive thrombosis with severe cerebral edema [2].

The ISCVT cohort [4] illustrates the variability of symptoms onset: acute (<48h) in 37% of patients, subacute (>48h to 30 days) in 56% of patients, or even chronic (> 30days) in 7% of patients.

Risk Factors and Clinical Work-up

Causes of CVT are multiple and cause-effect relationship is sometimes difficult to

establish, except for severe admitted thrombophilia. General systematic work-up up must be completed for each patient.

The largest study, the ISCVT, is a multicenter, prospective observational study with 624 patients [4]. In this study, thirty-four percent of these patients were harboring a prothrombotic condition. However, no cause of CST was found in about 15 % of cases, although an underlying disease fmay be detected in these patients may detect up to several months later [4]. It is recommended in these cases to perform again the assessment of thrombophilia at the end of the anticoagulation treatment.

Table 1. Summarizes the different risk factors and the subsequent patient work-up.

(Table 1) contd.....

Risk Factors		**Work-up**
Thrombophilia	Antithrombin III, protein C and S deficiencies Antiphospholipid and anticardiolipin antibodies Factor V Leiden gene mutation and Resistance to activated protein C Prothrombin G20210 mutation (factor II) Hyperhomocysteinemia and MTHFR gene mutation	Standard blood cells and platelet count, BT, PT, APTT, fibrinogen Blood level of antithrombin III, protein C and S, homocysteinemia Genetic analysis of Factor V gene, prothrombin gene and MTHFR gene. Measure of the resistance of activated protein C
Women risk factor	Pregnancy and puerperium Oral contraceptives	Anamnesis
Local and systemic infections	Sinus, teeth, ear Meningitis	CT of sinuses, dental panoramic X-Ray Lumbar puncture

CHAPTER 9

Intracranial Stenosis: Medical and Endovascular Management

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Abstract: Intra-Cranial Arterial Stenosis (ICAS) represents a source of risk to develop stroke. There is some genetic and ethnic determinant in having a major risk. Non invasive diagnosis rely on Trans-Cranial Doppler (TCD) and Magnetic Resonance Angiography, while Computed Tomography has the best accuracy to be compared to the more invasive Digital Subtraction Angiography. The endovascular and medical therapy options are compared, passing through WASID and SAMMPRIS trials.

Keywords: Angiography, Arterial, ASA, CT, Measurement, MRA, Risk factors, Stenosis, Stroke.

INTRODUCTION

Intracranial atherosclerotic stenosis (ICAS) is one of the most frequent causes of stroke in the world [1][1].

NEUROIMAGING OF ICAS

Imaging characteristics affect both the risk of recurrent events and the clinical outcome of a patient with ICAS, undergoing to a stroke event [16]. The degree of the stenosis and the collateral circulation status [27 - 28] are two main factors

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influencing the cerebral hemodynamic and the clinical outcome of a ICAS . About the degree of the stenosis, stenosis > 70% of the vessel, affect differently the outcome than stenosis ranging 50-69% [29], while robust antegrade flow and good collaterals are protective factors toward stroke also in presence of a ICAS (Fig. **1**).

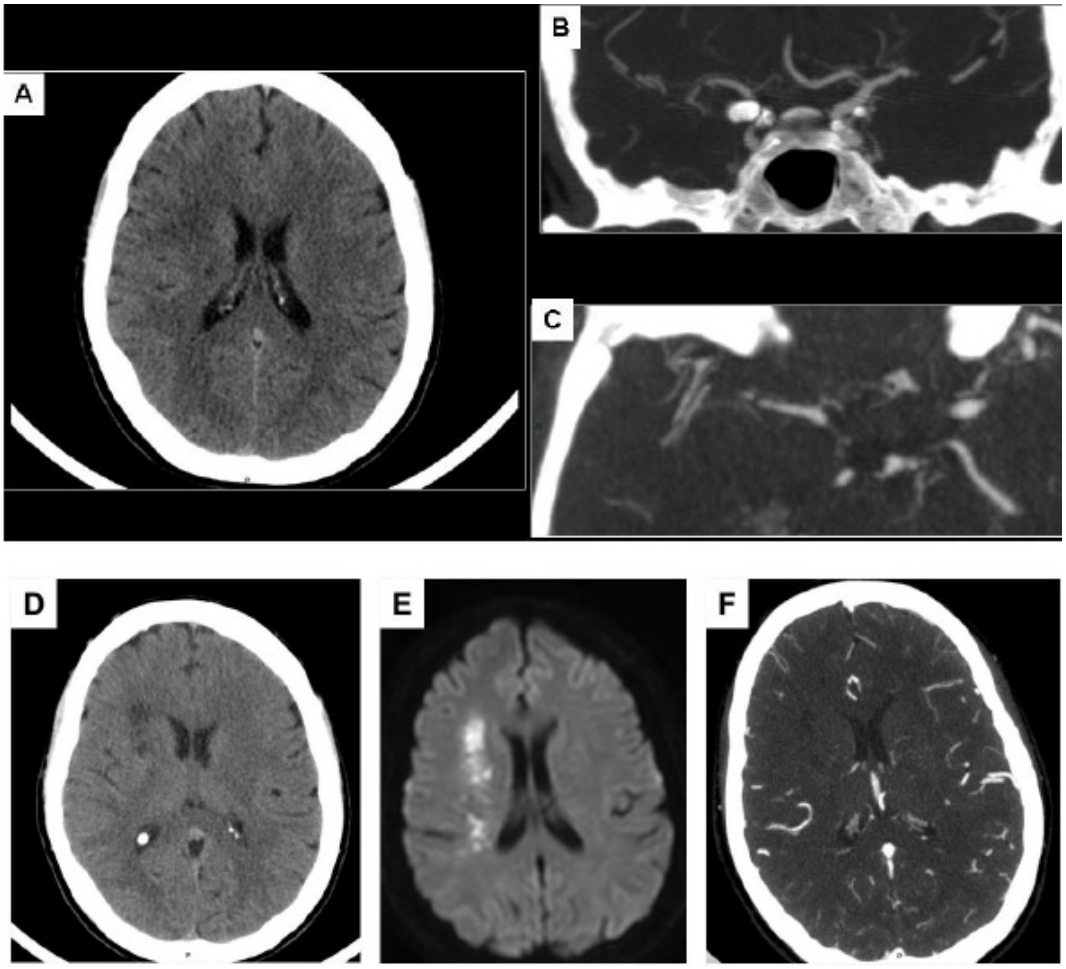

Fig. (1). A-F: Left Acute Hemiparesis in 50yrs smoker female. **A) mild subcortical right frontal hypodense area at not-enhanced CT (NECT); B**-C) CT Angiography elaborated with MIP algorithms at 5 mm of thickness, in coronal oblique and axial planes, showing the severe steno-occlusion of the right Middle Cerebral Artery; D) 48 hrs follow-up NECT showing evidence of the ischemic area; E) Diffusion Weighted Imaging (DWI) showing the white matter ischemica along the right corona radiata, less then expected in presence of a severe MCA steno-occlusion; F) the first CTA reformatted with large MIP sections to see the quality of collaterals, shows a pattern of good collaterals.

The pattern of ischemic lesions in Magnetic Resonance with Diffusion Weighted Imaging (DWI) can predict the recurrency of ischemic lesions in symptomatic patients with ICAS; subcortical or multiple lesions indicate a more severe stenosis and predict a recurrent stroke [30].

The trial callsed SONIA (Stroke Outcomes and Neuroimaging of Intracranial Atheroclerosis) trial assessed the accuracy of Trans Cranial Doppler (TCD) and Magnetic Resonance Aangiography (MRA) compared with catheter cerebral angiography [31] TCD and MRA yielded high negative predictive values (NPV) (86–91%) but low positive predictive values (36–59%). In this study, in TCD examinations, the middle cerebral artery and basilar/vertebral Mean Flow Velocity (MFV) were recorded placing cursors on peak systolic and end diastolic velocity values: for the first artery the cut off for identification of stenosis ≥ 50% was a MFV of ≥ 100 cm/s, for the basilar/vertebral was of 80 cm/s.

A high NPV allow to consider a test as screening for exclusion of intracranial arterial stenosis, while the low PPV isn't enough to considered it for correct diagnosis and accurate estimation of the severity of stenosis.

The detection of stenosis of intracranial vessels as Middle Cerebral Artery (MCA), is best accomplished by not-invasive diagnostic methods as TCD, for screening, and/or MRA both for screening or confirmation.

CTA is more accurate and with more sensitivity and specificity than MRA for the diagnosis and characterization in 50% or higher ICAS [32, 33].

CTA radiation exposure burden, make actually acceptable to firstly perform a MRA with 3D Time of Flight Technique, unless in an emergency condition.

MRA, better if in high resolution (3 Tesla) settings, and subject to further technological improvement, can allow a sensitivity of 78% - 85% and specificity of 95% in detecting a >50% stenosis, and 100% and 99% for the detection of complete occlusion [34]. This method is affected by flow void artifacts due to dephasing of the blood spins in very narrow vessels lumina, and by post-processing artifacts [35]. For this reason a congenital narrower lumen or an asymmetrical presentation between the two sides, can falsely be interpreted as an

CHAPTER 10

Uncommon Cause of Stroke: Diagnosis and Treatment (Part I)

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Abstract: This chapter contains detailed, up-to-date information about the nature, diagnosis, and treatment of those relatively uncommon types of cerebrovascular disease that cause strokes. Although many of the conditions discussed are rare, the chapter covers the causes of up to 10% to 15% of all strokes and of up to 40% of strokes in young adults. This chapter may be an essential resource to help physicians diagnose and treat stroke patients who do not fit well into the usual clinical categories.

Discussed within are the dissection of carotid and vertebral arteries, the more relevant cause of stroke in the young. The collagen vascular disorders causing stroke as a consequence of dissection , occlusion and, more rarely, rupture of extracranial and intracranial arteries are reported in detail. Various forms of cerebral angiitis, with focus on the primary central system vasculitis and reversible cerebral vasoconstriction syndrome are discussed.

Keywords: Cerebral infarction, Cerebral small vessel diseases, Cerebral vasculitis, Collagen vascular disorders, Genetic disorder, Metabolic disorders, Stroke.

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COLLAGEN VASCULAR DISORDERS AND OTHER NON INFLAMMATORY VASCULOPATHIES

Numerous non inflammatory vascular pathologies may cause stroke either ischemic or hemorrhagic. These include fibromuscular dysplasia, some genetically defined collagen vascular disorders (Marfan syndrome, Ehler- Danlos syndrome, osteo-genesis imperfecta, neurofibromatosis, pseudoxantoma elasticum and polycystic kidney disease) and other uncommon disorders such as Sneddon syndrome and Moya-moya syndrome.

FIBROMUSCULAR DYSPLASIA

Fibromuscular dysplasia (FMD) is nonatherosclerotic, noninflammatory arterial disorder that may result in arterial stenosis, occlusion, aneurysm, or dissection [1 - 4]. FMD has been reported in various arterial bed but most frequently affects the renal (causing hypertension) and extracranial carotid and vertebral arteries [5]. The natural history of cerebrovascular FMD is generally benign and the mean age of patients with cerebrovascular FMD is approximately 50 years [4].

Genetic studies have the potential to advance our understanding of FMD but no etiologic genes for FMD have been identified nowadays. Various classification of FMD have been proposed [5,6] the most recent being the AHA classification (Table **1**).

According with Harrison and McCormack [6] the classification system categorized FMD in relation to the arterial layer involved, namely intimal, medial, and adventitial disease (Table **1**). Angiographic correlations have been derived largely from the work of Kincaid and colleagues [7]. The medial FMD account of the majority of the cases and include three subtypes: the medial fibroplasia (60%–70%), the perimedial fibroplasia (15%–25%) and the medial hyperplasia (5%–15%. The most common features were multiple areas of stenosis and dilatation (string of beads) or focal and tubular stenosis (Figs. **1 - 3**).

The 2012 French and Belgian consensus statement [2] supported a radiographic classification, with multifocal, unifocal (<1 cm stenosis), and tubular (≥1 cm) subtype (Table **1**). It was further proposed by American Heart Association

classification [5] that the unifocal and tubular be combined into 1 definition of unifocal.

According to the Harrison's hypothesis [6] multifocal FMD is the subtype with string of beads appearance mostly due to medial fibroplasia. Focal FMD regardless of lesion length, is usually caused by intimal fibroplasia, but may also be caused by medial hyperplasia or adventitial FMD. Indeed, focal and multifocal FMD are not the same disease.

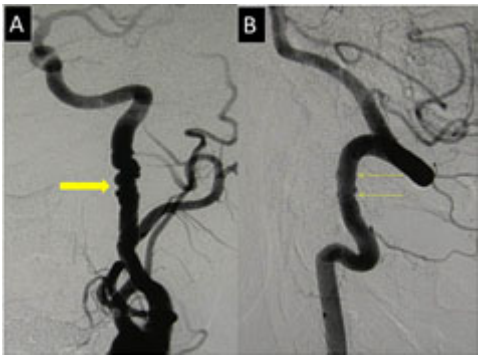

Fig. (1). Images of a patients with fibromuscular dysplasia. Cerebral angiography shows a "string of beads pattern" (arrow) at the level of extracranial internal carotid artery (**A**), as well as at the level of the V3 segment of vertebral artery (**B**, thin arrows).

Table 1. Classification of fibromuscular dysplasia.

Histological		**Angiographic**	
Harrison and McCormack (1971)		*French/Belgian Consensus (2012)*	*American Heart Association (2014)*
• Medial		• Multifocal	• Multifocal
	Medial fibroplasia (60-70%)		
	Perimedial fibroplasia (15-25%)		
	Medial hyperplasia (5-15%)		
• Intimal fibroplasia (1-2%)		• Unifocal (<1cm)	• Focal*
• Adventitial (<1%)		• Tubular (>1cm)	

*There may be multiple areas of focal disease (*e.g.* Renal artery and carotid artery in the same patient). Focal and multifocal disease can occur in the same patient.

CHAPTER 11

Uncommon Cause of Stroke: Diagnosis and Treatment (Part II)

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Abstract: This chapter contains detailed, up-to-date information about the nature, diagnosis, and treatment of those relatively uncommon types of cerebrovascular disease that cause strokes. Although many of the conditions discussed are rare, the chapter covers the causes of up to 10% to 15% of all strokes and of up to 40% of strokes in young adults. This chapter may be an essential resource to help physicians diagnose and treat stroke patients who do not fit well into the usual clinical categories.

Discussed in this chapter are the various form of inherited small vessel disease such as CADASIL but even the less known Col 4A1/2 related syndromes, CARASIL, TREX1-gene mutations disorders and the cerebroretinal microangiopathy with calcifications and cysts. Three form of metabolic disorders causing stroke such as Fabry disease, Homocystinuria and MELAS as well as the most relevant form of hematological disorders (antifospholipid syndrome and sickle cell disease) are discussed. Finally intriguing disorders such as migrainous infarction and drugs related stroke disorders are detailed as well as some other rare disease such as Kohlmeier–Degos disease and acute posterior multifocal placoid pigment epiteliopathy.

Keywords: Antifospholipid syndrome, Cerebral infarction, Cerebral small vessel diseases, Drugs, Genetic disorder, Metabolic disorders, Sickle cell disease, Stroke.

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HEREDITARY CEREBRAL SMALL VESSELS DISEASES

The existence of familial small vessel disease was supposed since the description of Van Bogaert in 1955, of two sisters affected by a rapidly evolving Biswanger disease. It is however only in 1993 that the first genetic small vessel disorder (CADASIL) was mapped on chromosome 19.

Since then several other monogenic disorders involving cerebral small vessels have been clinically and genetically characterized, the common features of which being represented by early onset of subcortical or lacunar strokes, leukoencephalopathy and involvement of small penetrating arterioles [1].

This chapter will focus on cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), Collagen 4A1 and 4A2 (COL4A1/A2) related disorders and the rarer cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL) and TREX1 related diseases.

Small vessel involvement is also present in hereditary cerebral amyloid angiopathies and it is described, in association with large vessel pathology, in several other monogenic diseases such as Fabry disease, pseudoxanthoma elasticum and homocystinuria. These disorders are detailed elsewhere.

Moreover several families are reported with a CADASIL like MRI phenotype, in which the genetic defects is currently unknown: it is the case of the hereditary multi infarction dementia of the Swedish type [2], the pontine autosomal dominant microangiopathy and leukoencephalopathy (PADMAL) [3]. Finally cerebral microangiopathy is a feature of Coats plus syndrome (actually renamed as cerebroretinal microangiopathy with calcifications and cysts – CRMCC).

CADASIL

CADASIL is the first hereditary small vessel disesase to be genetically defined [4]. The disease was identified more than 30 years ago, but the term CADASIL emerged in 1993 when the disease causing gene was first mapped on chromosome 19p13.1 and then identified as NOTCH3, three years later.

Since then CADASIL has been reported worldwide and although its prevalence is not known, it has been estimated approximately 5/100.000, based on studies from United Kingdom [5] CADASIL represents a non-arteriosclerotic, non-amyloid arteriopathy affecting the small perforating cerebral arteries whose pathological hallmarks are the accumulation of granular, osmiophilic material within the tunica media, the degeneration of vascular smooth muscle cell and the intimal thickening. These processes result in stenosis of the distal segment of medullary arteries and in loss of the autoregulation mechanisms of the cerebral vessels

PATHOGENESIS

The disease is caused by mutations in NOTCH3 gene that encodes a transmembrane receptor protein with 3 functional domains: an extracellular domain that is formed by 34 epidermal growth factors repeats (EGFR) and 3 Notch/lin repeats; a transmembrane domain and an intracellular domain. Notch3 receptor exists at the plasma membrane as a heterodimer and is predominantly expressed in vascular smooth muscle cells of small arteries and pericytes of brain capillaries.

In response to ligand binding, the receptor undergoes sequential proteolytic cleavages that release the Notch intracellular domain, which in turn translocates to the nucleus, binds to specific transcription factors and promote the transcription of genes.

CADASIL mutations occur in exon 2-24 and are usually missense mutations: in frame deletions and splice site mutations are rarer.

The vast majority of the mutations affect the EGFR extracellular domain and results in the gain or loss of a cysteine residue leaving an unpaired sulphidril group that can promote multimerization and aggregation of mutant Notch 3 receptor. There are increasing reports of cysteine sparing mutations and their role is still controversial, representing either rare single-nucleotide polymorphisms or CADASIL or other than CADASIL small vessel disease causing mutations. At least for several of these mutations, the ability to form Notch3 aggregates has been demonstrated [6].

CHAPTER 12

Endovascular Management of Atherosclerotic and Dissected Carotids

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Abstract: Treatment of lesions of the extracranial internal carotid artery plays an important role in the management of ischemic stroke, particularly in the secondary prevention of further events, but sometimes also in the acute phase. The endovascular management of atherosclerotic stenosis is not just an alternative to endarterectomy but frequently is the treatment of choice. Moreover, treatment of dissections of the carotid arteries, when not exclusively medical, is in almost all cases endovascular. Experience in the neurointerventional field is necessary to correctly deal with both types of lesions of the extracranial internal carotid artery.

Keywords: Carotid stenting, Carotid dissection, Carotid atherosclerosis, Atherosclerotic plaque, Carotid stenosis, Endovascular treatment.

INTRODUCTION

Atherosclerotic stenosis of the extracranial internal carotid artery (ICA) is a frequent cause of stroke [1, 2]. Discovered usually only after the patient has already suffered an ischaemic event, it is nowadays clear that symptomatic carotid stenosis requires treatment. The first evidence towards this came in 1998 from two large randomized trials, the North American Symptomatic Carotid Endarterectomy Trial (NASCET) [3] and the European Carotid Surgery Trial (ECST) [4]. These studies compared endarterectomy for symptomatic stenosis to conservative management (antiplatelets), both demonstrating the superiority of

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surgery in preventing new ischaemic events and death. Notably, later trials have also provided evidence in favour of surgically treating severe carotid stenosis even in asymptomatic patients, the benefit though is, in these cases, less pronounced [5, 6].

During the past couple of decades, minimally invasive therapies have been continuously gaining ground in the field of vascular diseases. In this context, carotid stenting was originally introduced as an alternative to endarterectomy for the elderly and high surgical risk patients. Although good results have been reported by several case series published in the literature [7 - 10], it has not been till recently that randomized trials were put into place to address the issue. Notably, most of these trials have failed to demonstrate any significant difference both in efficacy and safety between the two techniques [11, 12]. Studies that showed stenting associated with a higher risk profile have been largely disregarded as their results have been attributed to the limited experience of the centres involved rather than the technique itself [13, 14]. Furthermore, surgical complications such as cranial neuropathies, wound haematoma and infection have been underrated in most published studies and this is something that one should keep in mind when doing any comparisons.

Despite considerable debate in the past, current guidelines advocate that best medical treatment should be generally preferred over surgery/stenting in asymptomatic patients (there are selected cases though that non-conservative treatment may still be useful) [15].

The endovascular technique of carotid stenting is, in itself, relatively easy but it requires experience in patient selection, correct choice of devices and, mainly, appropriate management of possible adverse events.

The current chapter will focus on endovascular techniques applicable to carotid disease, either atherosclerotic stenosis or dissection. Carotid stenting, although rather straightforward in concept, requires careful choice of devices and appropriate perioperative management. Adverse events, even if rare, can prove devastating for the patient and should be thus readily recognized and treated.

INDICATIONS OF CAROTID STENTING

As previously stated, the NASCET and ECST trials showed, back in 1998, that symptomatic severe carotid stenosis benefits from surgical treatment [3, 4]. Most of the succeeding trials comparing standard endarterectomy to endovascular stenting found the former to be non-significantly better both in terms of safety (periprocedural stroke and death in the 30 days succeeding the treatment) and efficacy (the rate of stroke and death between 31 days and 6 months after the procedure) [11, 12]. However, further analysis revealed that there is still a place for stenting in specific patient sub-groups [11].

An in-depth analysis of all the randomized trials that have compared surgical and endovascular treatment of carotid disease is probably out of context here. Several authors have extensively reviewed the subject [11, 12, 15, 16] and identified critical factors that should be taken into consideration when choosing between surgical or endovascular treatment of carotid stenosis:

Patient Related Factors

- Age
- Surgical risk
- Comorbidities

Anatomy Related Factors

- Location of the carotid bifurcation
- Aortic arch conformation
- Tortuosity of the vessels
- Stability of the plaque

Contra intuitively, and despite previous beliefs, clinical trials have shown by now that elderly patients do not benefit from stenting [11], probably because of the higher atherosclerotic burden on their vessels and especially in the aortic arch. Navigation through such vessels (like in ultra-octogenarian) increases the risk of embolic complications due to plaque fragmentation. Of note is that in the CREST study, the crossover between endarterectomy and stenting occurred at approximately 70 year [17, 18].

CHAPTER 13

Intensive Care Management

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Abstract: Acute ischemic stroke represents a leading cause of mortality and morbidity worldwide. An increasing number of patients with massive stroke require admission to ICU for neurological monitoring and management of acute complications. Medical treatment in ICU consists of sedation, analgesia, ventilator support, hemodynamic monitoring, neuromonitoring, fluid management, thromboprophylaxis and treatment of complications. Principal complications are: cerebral edema, hemorrhage, seizures, myocardial complications, hyperglycemia and fever. Severe cerebral edema after stroke represents an important complication. In this case, decompressive craniectomy successfully decreases mortality and morbidity in patients with severe cerebral edema. Therapy with mannitol is the standard treatment for intracranial hypertension. Therapeutic hypothermia may also be considered for its neuroprotective effect but its role is not demonstrated in stroke. These aspects of critical care are considered in this chapter.

Keywords: Acute ischemic stroke, Cerebral edema, Intensive care management, Intracranial hypertension, Neurocritical care, Neuromonitoring, Reperfusion therapy, Stroke units.

INTRODUCTION

Acute ischemic stroke (AIS) is an important cause of morbidity and mortality in the world. Despite around 15-20 % of stroke patient being admitted to the intensive care units (ICU), the evidence base guiding the intensivist managing

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stroke is relatively poor [1]. The purpose of this chapter is to provide our recommendations about ICU management of AIS.

GENERAL SUPPORTIVE CARE AND TREATMENT OF ACUTE COMPLICATIONS

Currently 4 interventions in AIS supported by class I evidence: reperfusion therapy with the use of intravenous rt-PA within 4-5 h of symptom onset, the use of aspirin within 48 h of stroke onset, decompressive craniotomy for supratentorial hemispheric cerebral infarction and admission to a stroke unit [2]. Around 15-20% of patients require admission to an ICU to allow cares and interventions that cannot be provide on a stroke unit. There are not specific guidelines for ICU admission, but certainly the decreased conscious level , the need for mechanical ventilation and the intensive hemodynamic management, represents universal indications for admission to intensive care [3]. In the end, patients with massive stroke are admitted to ICU to facilitate organ donation in those who have expressed a wish to donate (Table **1**).

Table 1. Criteria for ICU admission: our recommendations.

Need for intubation and/or mechanical ventilation
Severe Stroke (National Institutes of Health Stroke Score > 17)
Management complications of reperfusion therapy
Persistent elevated blood pressure [systolic > 220 mmHg (not undergoing thrombolysis) or > 185 mmHg (undergoing thrombolysis)] or low blood pressure < 90 mmHg
Management of organ support
Postoperatively following decompressive craniectomy
To facilitate organ donation in patients who have expressed a wish to donate

Ventilation and Supplement Oxygen

Hypoxia is common after stroke. Hypoxia is determined by partial airway obstruction, aspiration, low ventilation, atelectasis and pneumonia. For these reasons, it is recommended continuous monitoring of oxygenation with pulse oximetry (SpO2) for all patients in the ICU. Although routine oxygen supplementation may seem intuitive, in literature is little know and more research is needed. In hypoxemic patients with AIS, recent AHA guidelines recommend

O2 supplementation to rice SpO2 > 94% [4]. The choice to keep normoxia include nasal cannula, Venturi mask, non-rebreathe mask, BIPAP, CPAP and, only as last choiche, orotracheal intubation. The orotracheal intubation is indicated in patients with altered consciousness or with severe bulbar damage that causes airway compromise and the loss of protective reflexes. Others criteria are reported in the Table **2**. Tracheostomy should be accomplished after 1 week of mechanical ventilation [5]. The mortality rate of intubated AIS patients was found to be between 40 and 80% and only a small percentage of patients improves after intubation [6] At last, the use of hyperventilation to decrease PaCO2 is a rapid way to reduce intracranial pressure (ICP) and may be tolerated for days in patients with severe brain edema. Indeed, hyperventilation (PaCO2 to 30-35 mmHg) cause vasoconstriction and reduce cerebral blood volume and, thus, ICP. However, in patients with brain injury, prolonged hyperventilation could cause cerebral ischemia. In conclusion, the use of extreme hyperventilation is reserved for a short time to reduce ICP and the its routine application is generally considered detrimental. In effect, hypocapnia is associated with poor prognosis. There are not evidence about use of hypercapnia to increase cerebral perfusion and to improve AIS outcomes [7].

Table 2. Criteria for mechanical ventilation: our recommendations

Glasgow Coma Score ≤ 8
Critical airway compromise
To prevent aspiration pneumonia
Therapy for intracranial hypertension
Acute respiratory failure
Generalized tonic-clonic seizures or status epilepticus
Apneic episodes

Sedation and Analgesia

Sedation and analgesia are often necessary in patients with brain edema after stroke to manage ICP, to improve endotracheal tube tolerance and patient-ventilator synchrony, to reduce cerebral metabolic rate of oxygen (CMRO2), to prevent delirium [8]. In the neurological ICU, sedation and analgesia are maintained by infusion of ipnotic agents, suchs as propofol, midazolam or

CHAPTER 14

The Trials and Tribulations of Ischemic Stroke Therapy

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Abstract: In this chapter, we focus on the recently published randomized controlled trials examining combined endovascular therapy with IV tPA *versus* IV tPA alone. In October 2014, the first evidence was presented from a randomized clinical trial conducted in the Netherlands showing the benefit of endovascular therapy in acute ischemic stroke secondary to emergent large vessel occlusion in the anterior circulation. Four randomized controlled trials later confirmed these results. The advances in techniques and devices which enabled these positive findings for intra-arterial therapy, including aspiration thrombectomy, stent retrievers, and combination strategies will be discussed herein. We will also consider where opportunities remain to maximize favorable outcomes while minimizing costs as these recent trial results are translated into clinical practice.

Keywords: Acute ischemic stroke, Endovascular therapy, Intra-arterial therapy, Mechanical thrombectomy, Randomized clinical trial, Reperfusion catheter, Stent retriever.

OVERVIEW

Excellent reviews of historical acute ischemic stroke trials have been published, for example see Nogueira *et al.* [1], which also cover the introduction of intravenous fibrinolytic agents and intra-arterial therapy. In early 2014, a review article accurately described the evolution of intra-arterial approaches and tools for acute stroke therapy [2]. Thus, we will dwell in this chapter upon the more recent

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studies, in particular those randomized clinical trials (RCT) comparing combined intra-arterial therapy (IAT) with IV tPA to standard medical management alone [3 - 9]. Endovascular approaches to stroke treatment have been available as a promising option for patients ineligible or refractory to IV thrombolytic therapy since 2004. Finally in late 2014, a watershed event in the acute ischemic stroke field was achieved when a large randomized controlled trial definitively demonstrated the benefit of IAT in acute stroke patients with evidence of proximal artery occlusion in the anterior cerebral circulation [3]. These findings were subsequently confirmed by four published randomized controlled trials, which were halted early due to lack of equipoise [4 - 7]. Two additional positive RCTs have been presented publicly as of this writing [8, 9].

DEVICES AND CLINICAL TRIALS IN ACUTE ISCHEMIC STROKE

The Beginning of Mechanical Thrombectomy

Acute stroke thrombectomy is ushering in the future of neurointervention. Around 87% of stroke is ischemic due to in-situ thrombosis, extracranial embolus, or other origins. Only 3-5% of stroke is a result of hemorrhage in the subarachnoid space due to aneurysm rupture. Although current neurointerventional treatment of stroke is restricted to large clot burdens, located within the proximal vessels of the Circle of Willis, and treated within eight hours of symptom onset, this subgroup still represents at least a ten-fold larger group than the whole of the treated aneurysm population. Ischemic stroke thrombectomy remains by far the largest opportunity for expansion in neuroendovascular research and development, as well as for positive impact on patients' survival and quality of life.

Mechanical thrombectomy of occlusions causing an acute ischemic event has been an accepted procedure since catheters were first placed in the neurovasculature. Catheter-based suction thrombectomy was first described by Gerhard Schroth as early as the late 1980's. Direct aspiration would remain central to neurointerventional thrombectomy from that time forward. By 2004, the first FDA-approved product specifically intended for thrombectomy in acute stroke patients was launched, called the Merci Retriever (Concentric Medical/Stryker Neurovascular). The first generation 'X' devices resembled a

wire with the shape of a corkscrew, which was placed inside the clot in an effort to engage it and retrieve out of the body. A balloon-tipped guide catheter would be delivered in the proximal internal carotid and inflated prior to fully withdrawing the Merci under "flow arrest" conditions. Aspiration was then applied on the balloon guide to capture residual emboli and thrombus not collected by the Merci. Later generations, including the "L" and "K-mini" devices, modified the configuration of the grabber wire, some adding suture strands to assist in retaining the thrombus. The Merci device was only moderately successful in the clinic because of challenges in realizing consistent success. Complete or mostly complete intracranial vessel reperfusion (TICI 2A-3 or TIMI 2/3) was achieved only 48% of the time in a major study [10].

Aspiration Thrombectomy Comes of Age

Four years later, in December 2007, the Penumbra System (Penumbra, Inc.) gained approval in the United States for use in revascularization of acute stroke patients. The Penumbra System used aspiration as its primary method of action. A flexible, large bore microcatheter was deployed to the site of occlusion and aspiration applied directly on the lesion itself. However, the early Penumbra System catheters, the largest of which was 0.041 in internal diameter, were not quite wide enough to avoid becoming obstructed by the thrombus and so another component, a Separator, was introduced to clear the catheter lumen and to continually break up the thrombus ingested under aspiration. Without a Separator, the early microcatheters could clog, at times necessitating removal and re-access, prolonging procedural times. Thus by using a Separator, direct aspiration and clot capture were combined to facilitate continuous thrombectomy. The Penumbra System increased the rate of successful reperfusion to 82% in the Pivotal trial for FDA approval [11], and improving further to 87% in the real-world POST study [12]. A stent-like three-dimensional (3D) binary nitinol device known as the Separator 3D was launched in Europe in January 2012 as an additional component of this system. The Separator 3D was designed to engage a thrombus in a third radial dimension, as the open body of the 3D is compressed and then retrieved into a Reperfusion Catheter positioned at the proximal margin of the primary occlusion [13, 14].

CHAPTER 15

Evolution of Devices for Endovascular Thrombectomy in Acute Ischemic Stroke: From the Beginning to the Adapt Technique

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Abstract: Acute ischemic stroke is a major cause of mortality and morbidity and its treatment has attracted great interest in the last decades. Innovative instruments such as stent-retrievers, intermediate catheters, and large-bore catheters have recently been introduced to perform endovascular thrombectomy. In cases of large vessel occlusion, this technique produces better results than intravenous pharmacological treatment.

In this chapter, we discuss the history of devices developed for thrombectomy, concluding with the state-of-the-art devices in each category.

Keywords: ADAPT technique, Aspiration, Mechanical thrombectomy, Stent.

INTRODUCTION

The treatment of ischemic stroke has evolved radically in recent years. The introduction of drugs that act directly on the thrombus has profoundly modified the therapeutic paradigms. However, despite the significant results achieved, some patients, particularly those with occlusion of large vessels, have not had clear improvements. For this reason, research has led to the development of devices that

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can be used in such cases; starting in the new millennium, with the introduction of the Merci system, until the direct aspiration technique (ADAPT), we have witnessed considerable technical advances, all to the benefit of patients. Furthermore, recent trials have demonstrated the clear superiority of mechanical thrombectomy in cases of large vessel occlusion. In this chapter we retrace the entire history of the devices used in mechanical thrombectomy, up to ADAPT, which has been another step towards perfecting the technique.

It was calculated that nearly 75% of patients with an acute stroke and score >10 on the National Institutes of Health Stroke Scale (NIHSS) treated with intravenous tissue-type plasminogen activator (tPA) do not achieve complete revascularization, and only 8% have significant clinical improvement [4, 5]. Treatment with mechanical thrombectomy devices leads to higher rates of revascularization [6 - 8].

In the last few years endovascular neurosurgeons and interventional neuroradiologists, with the support of medical device companies, have developed new techniques to remove cerebral blood clots directly. In selected cases, stent-retrievers, aspiration devices and other tools ensure complete thrombus removal in a shorter time. As mentioned in other chapters, time is the critical issue.

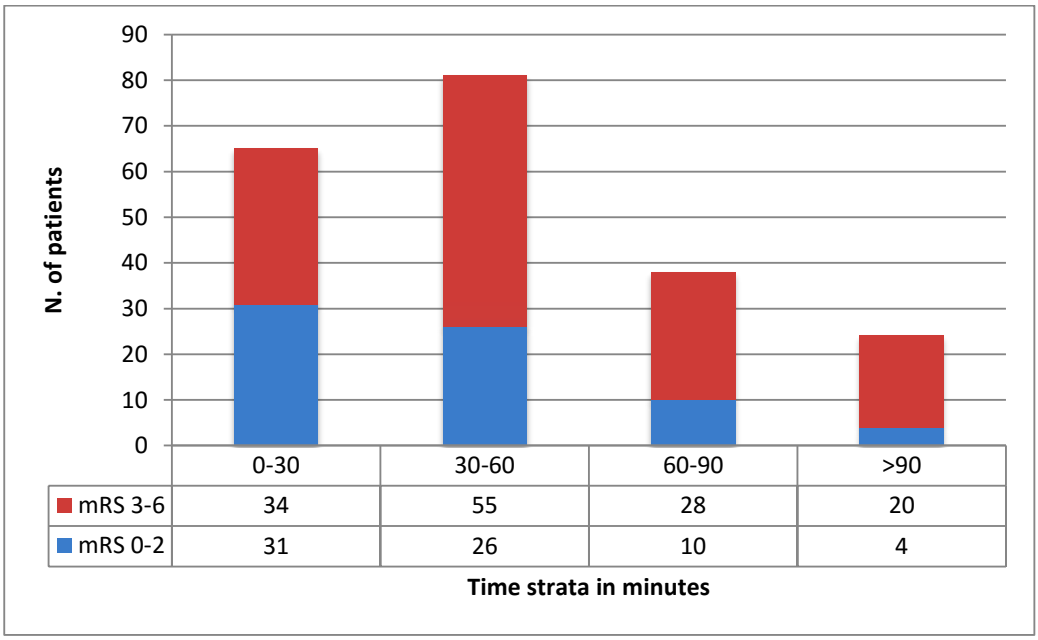
Current guidelines concentrate on the “time to microcatheter”, not to delay of recanalization after microcatheter placement (procedure time). “Door to treatment” in ≤180 minutes is considered the standard of care (golden hour) for obtaining clinical success [1]. Past studies focused on recanalization as a measure of treatment success [2], but the concept of futile recanalization shifted attention to the creation of treatment time-efficient protocols. Time to recanalization depends on the type, dimension, and consistency of the thrombosis as well as comorbidities associated with the thrombosis, so the time to microcatheter could be considered a metric to monitor, not a threshold for acceptable performance.

A recent study tried to determine the relationship between procedure time and clinical outcomes [3], showing that procedure time is indeed a critical determinant of outcomes following endovascular treatment (Table **1**).

Since the beginning of this century, different systems and devices have been used

to eliminate thrombi from the cerebral circulation (Table **2**). First of all pharmacological intra-arterial thrombolysis, then retrievers in the form of metal baskets that could catch blood clots. These were followed by a new generation of clot-disruptors and then stents used as clot retrievers. Most recently, a new aspiration technique has been introduced, acting directly on the thrombus through a large-bore catheter.

Table 1. The relationship between endovascular procedure time and clinical outcome (modified Rankin score, mRS) at discharge.



Considering the mechanism of action, we can summarize thrombectomy strategies into six different classes:

- Pharmacological intra-arterial thrombolysis
- Clot-disruptors
- Clot-catchers
- Stent retrievers
- SRLA (Stent Retriever with Local Aspiration)
- ADAPT (A Direct Aspiration first Pass Technique)

SUBJECT INDEX

A

B

C

D

E

I

K

L

M

T

U

V

W

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Born in Rome on December 20, 1978.

In the academic year 2003/2004 he graduated in Medicine and Surgery with 110/110 cum laude from the University of Rome "La Sapienza", with a thesis entitled: *The role of lumbar cerebrospinal fluid drainage in subarachnoid hemorrhage in patients with intracranial aneurysm underwent coil embolization* (Supervisor Prof. Roberto Delfini).

In 2005, he obtained authorization to practice medicine, and since then he was regularly admitted to the Rome Medical Association.

In the academic year 2008/2009 he obtained, the Certification in Neurosurgery at the University of Rome "La Sapienza", vote 70/70 *cum laude, with a thesis entitled: Endovascular treatment of cerebral aneurysms by using stents so-called "Flow diverter"* (Supervisor Prof. Giulio Guidetti).

In June 2013 he completed the PhD Course in Neurosurgery, Maxillofacial Surgery and Neuropathology of University of Rome "La Sapienza", with a thesis entitled: *Carotid-cavernous fistula: endovascular embolization through surgical access on the superior ophthalmic vein* (Tutor Prof. Giulio Guidetti).

Since January 2010 he has been working, in the Endovascular Neurosurgery/ Interventional Neuroradiology Department at University Hospital Umberto I° in Rome.

From 2008, he attended the Department of Interventional Neuroradiology Faculty of Medicine, Université de Nantes (France) directed by Prof. Axel de Kersaint-Gilly, the Department of Neuroradiology and Section of Interventional Neuroradiology Ospedale Niguarda - Ca 'Granda Milan (Italy) directed by Dr. Edoardo Boccardi and the Interventional Neuroradiology Department at University Hospital Umberto I° in Rome.

He participated as invited speaker to many conferences and congresses; furthermore he is the coordinator of many educational courses regarding Endovascular Neurosurgery.

Member since 2010 of the European Society of Minimally Invasive Neurological Therapy - ESMINT.

He is author of many articles published in international journals with high impact factors and Editor and co-author of various books.

He is also an ad hoc reviewer for several peer-reviewed journals.