Management and Therapeutics of Spontaneous Intracerebral Hemorrhage

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Edited by

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Module III: Therapeutics and Monitoring

PREFACE

This volume is dedicated exclusively to spontaneous or primary intracerebral haemorrhage, a clinical entity characterised by the extravasation of blood into the cerebral parenchyma. It manifests as a subtype of cerebrovascular accident, with an estimated incidence of 20% within the spectrum of stroke, underscoring its high clinical relevance.

The therapeutic approach to intracerebral haemorrhage necessitates a multidisciplinary collaboration involving emergency physicians, internists, neurologists, intensivists, neurosurgeons, and rehabilitation specialists. Comprehensive patient management requires the application of advanced medical strategies, specialised nursing support, neuro functional rehabilitation techniques, and contributions from multiple disciplines that enhance the overall care of this condition.

Over the past decade, numerous studies have provided significant advancements in the understanding of pathophysiology, neuroimaging-based diagnosis, and therapeutic interventions aimed at optimising clinical outcomes. The characterisation of secondary inflammatory processes, neuroprotection, and pharmacological strategies has facilitated targeted interventions, thereby minimising associated neuronal damage.

However, despite these advancements, critical gaps remain in the early identification and stratification of patients, the integration of precision medicine into haemorrhagic stroke therapy, and the refinement of neurocritical care protocols. This book aims to bridge these gaps by offering a synthesis of the most up-to-date research, not only providing evidence-based recommendations but also serving as a catalyst for future investigations.

Medical education is evolving towards evidence-based, integrative, and multidisciplinary models. This volume serves as a vital resource for clinicians in training, neurologists, intensivists, and researchers seeking structured yet profound insights into intracerebral haemorrhage. By combining theoretical foundations with practical applications, it enhances the capacity of academic institutions and training programmes to refine their curricula, ensuring the next generation of physicians is equipped with cutting-edge knowledge.

The work is directed at professionals involved in the treatment of intracerebral haemorrhage and is distinguished by its integration of complex concepts within a single volume—an attribute that constitutes its principal strength. To further its impact, this publication features contributions from internationally recognised authors—experts in neuroscience, emergency medicine, and critical care—who provide diverse perspectives and high-level analysis, making it a reference text beyond regional boundaries.

Each module rigorously examines the diverse clinical aspects of intracerebral haemorrhage, employing a methodical and critical analysis of the most recent scientific literature. Furthermore, special emphasis is placed on future research avenues, making this book not only an educational tool but also a foundation for innovation in cerebrovascular disease management.

It's important to thank those who gave us their time to dedicate to this project. Our families did so. And also those who educated us, but also left us with the specific interest in training us to ask better questions and attempt some answers. This book should express that.

MODULE I

BASIC CONCEPTS

CHAPTER 1

BASIC ANATOMY OF THE CEREBRAL CIRCULATION

RODOLFO J. RECALDE
AND EZEQUIEL YASUDA

Introduction

The brain is one of the organs with the most metabolic activity, receiving around 14% of the cardiac output. Also, it needs a continuous supply of oxygen and glucose, requiring 50-100 ml of every 100 gr of cerebral tissue. If the blood flow descends below that level, the neuronal activity is jeopardized, and if that deficit continues, the neuronal damage is irreversible.

The blood supply of the brain depends on the internal carotid artery (ICA) and the vertebral artery (VA). The ICA and their branches form the anterior circulation, also known as carotid circulation, and give blood supply to 80% of the cerebral hemispheres and most of the diencephalon. The VA and their branches, also known as the vertebral-basilar system or posterior circulation, gives the blood supply to the remaining 20% of cerebral hemispheres, part of the diencephalon and all the brain stem and cerebellum.

Carotid System

The ICA arises in the carotid bifurcation at the level of the superior margin of the thyroid cartilage and ends below the anterior perforated substance, where it gives rise to their two terminal branches, the middle cerebral artery (MCA) and the anterior cerebral artery (ACA).

The ICA has 4 segments: Cervical segment (C1) extends from its beginning up to the skull base where it enters through the carotid foramen.

Petrous segment (C2) runs inside the carotid canal inside the petrous bone and ends at the entrance of the cavernous sinus. Cavernous segment (C3) runs within the cavernous sinus and ends as it exits the cavernous sinus through the roof of it. Supra clinoid segment (C4) it begins when the

artery access into the subarachnoid space after leaving the cavernous sinus and ends by giving the two terminal branches. Both the cavernous and supraclinoid segments form the carotid siphon with an "S" shape, with an inferior turn given by the C3 segment anteriorly convex and a superior turn form by the C4 segment with a posterior convexity.

The ICA has 3 collateral branches that name the different segments of C4 before it gives rise to the terminal branches. Ophthalmic Segment: is the longest. Give rise to the ophthalmic artery. It is inmate related to the optic nerve, and both structures direct to the orbit. Posterior Communicating Segment: gives rise to the posterior communicating artery (PComA), which connects the carotid system with the vertebra-basilar. It is related to the III cranial nerve, and in some cases, it could give rise to the posterior cerebral artery (fetal configuration) (Fig1). Choroidal Segment: It gives rise to the anterior choroidal artery (AChoA); it has a posterior trajectory related to the optic tracts through the basal cisterns reaching the inferior choroidal point behind the temporal uncus where it enters the lateral ventricle through the choroidal fissure (a cleft between the fornix and the thalamus). It enters the ventricle and runs, forming the choroid plexus and navigating in the temporal horn, the atrium and the body of the lateral ventricle, reaching the foramen of Monro. It supplies the posterior limb of the internal capsule, part of the cerebral peduncle, the optic tract and the lateral geniculated body. The occlusion of this artery can cause hemianesthesia, hemiplegia and hemianopsia.

Anterior Cerebral Artery

The ACA is the smaller branch of the carotid bifurcation. It begins in the medial portion of de silvian fissure and ends in the medial surface of the cerebral hemispheres. In its trajectory, it displaces over the optic chiasm to reach the interhemispheric fissure getting in intimate relation to the corpus callosum. (Fig. 1)

It has two segments related to the anterior communicating artery (ACom), a proximal one, Pre-communicating and distal or post-communicating. The Pre-communicating segment might be hypo plastic; in that case, the ACom has a bigger size, and the contralateral ACA will supply both sides.

The post-communicating segment, or pericallosal, is in contact with the corpus callosum, at the beginning below it, then in front of it, and finally, above the corpus callosum. One of the most important branches of the ACA is the callosomarginal artery, which usually rises at the level of

the genu of the corpus callosum and runs along the cingulum sulcus, parallel to the pericallosal artery (Fig. 2)

The pre-communicating segment of the ACA gives rise to many perforators' branches; one of the most important vessels is the recurrent artery of Heubner, which usually starts in the post-communicating segment and supplies the anterior portion of the caudate nucleus, the anterior two-thirds of the putamen, anterior part of the globus pallidum and the anteroinferior portion of the anterior limb of the internal capsule. Occlusion of this vessel may cause facial-brachial paresis and aphasia if the occlusion is on the dominant hemisphere. Other perforator branches irrigate the dorsal portion of the optic chiasm, the suprachiasmatic region of the hypothalamus, the optic tract and the optic nerve. Obliteration of these branches may cause personality disturbances, intellectual deficit or emotional lability. Cortical branches of the ACA irrigate the cortex and white substance of the medial aspect of the brain from the frontal pole up to the parietal lobe. Also irrigates the medial and basal regions of the frontal lobe. Finally, it also irrigates the superior border of the frontal and anterior part of the parietal lobe. Occlusion of these branches may give contralateral paresis of the inferior limb.

Middle Cerebral Artery

The middle cerebral artery (MCA) is the longest and more complex of the brain's arteries. Its origin is located at the bifurcation of the ICA, and the diameter doubles the ACA. It irrigates the lateral aspect of the brain hemisphere and part of the inferior aspect of the frontal and temporal lobe. (Fig. 3) Four different segments can be found: Sphenoidal (M1) begins from the origin of the MCA in the carotid bifurcation up to the division of the two main trunks before the 90 degrees turn that is done at the level of the insula limen. Insular (M2) is related to the part of the artery that is closely related to the insular lobe. Opercular (M3) is the portion of the artery related to the medial aspect of the front parietal and temporal operculum. Cortical (M4) is formed by the cortical branches once they exit the Sylvian fissure.

The MCA gives supply to most of the convexity of the cerebral hemisphere: The insular lobe, the lateral region of the basal aspect of the frontal lobe, temporal pole and lateral region of the basal aspect of the temporal lobe. The superior border of the cerebral hemisphere is irrigated in the anterior region by the ACA and the posterior one by posterior cerebral artery (PCA). The perforating branches are the lenticular striate arteries. They arise in the M1 segment. Irrigate the superior region of the internal

capsule as well as the anterior limb of the internal capsule, the head of the caudate nucleus and the lateral portion of the globus pallidus.

Obliteration of the MCA could give different clinical manifestations depending on the compromised area. It could give contralateral hemiparesis when the precentral gyrus (motor area) is affected, and this area is where the corticospinal tract begins. Motor aphasia could be present when the Broca area (posteroinferior area of the inferior frontal gyrus and prefrontal area) of the dominant hemisphere is affected, perception aphasia by compromise of the Wernicke area in the temporo parietal or a Gerstmann syndrome (digital agnosia, inability of right-left discrimination, agraphia and acalculia) (Fig.4).

Vertebral-Basilar System

The Vertebral artery arises from the subclavian (SA) and ends at the level of the Ponto medullary sulcus forming the basilar artery (BA). After its origin in the SA, it goes through the transverse process of C6, and it ascends through the transversarium foramina of the cervical spine of C5 to C2, reaching C1, where the artery is related to the posterior arch of this vertebra. Then it perforates the dura next to the foramen magnum. In the endocranium, it ascends up to the point where it joins the contralateral artery to form the BA in front of the ponto-medullaris sulcus1. In the intracranial segment, it gives rise to three important branches, the anterior spinal artery that supplies the anterior two-thirds of the cervical spinal cord, the posterior spinal artery that supplies the posterior third one and finally, the posteroinferior cerebellar artery (PICA) that supplies the sub occipital aspect (inferior aspect) of the cerebellum. During its trajectory, the BA gives rise to small branches that supplies the medulla.

Basilar Artery

The BA is formed by the anastomosis of the two VA in front of the Ponto medullary sulcus of the brain stem and ends in front of the mesencephalon where it divides into terminal branches, the posterior cerebral arteries. As it ascends, the BA gives rise to branches to the brain stem, the anterior cerebellar artery (AICA) that irrigates the petrosal aspect (anterior aspect) of the cerebellum and the superior cerebellar artery (SC) that irrigates the tentorial aspect (superior aspect) of the cerebellum[2].

Posterior Cerebral Artery

The posterior cerebral artery (PCA) initiates at the basilar bifurcation in front of the mesencephalon. It ends in the quadrigeminal cistern giving rise to two terminal branches, the parieto-occipital and the calcarine arteries. It supplies the mesial aspect of the occipital lobe and the basal aspect of the temporal lobe. In its trajectory, it surrounds the mesencephalon, and it joins to the posterior communicating artery (PCom) in the lateral margin of the interpeduncular cistern, going through the crural and ambient cistern to reach the quadrigeminal cistern. It finishes irrigating the posterior region of the hemispheres, especially the basal and mesial aspects of the occipital lobes (Fig.4).

It has 4 segments (Fig.5): Segment P1 (pre-communicating) goes from the basilar bifurcation to the point where it joins the PComm. Most of the time, the P1 caliber is bigger than PComm. Nevertheless, in one-third of the cases, PComm caliber is bigger than P1 (fetal configuration). The III cranial nerve is located below this segment. Segment P2 is at the beginning in the crural cistern related to the cerebral peduncles, then reaches the ambient cistern in relation to the lateral aspect of the mesencephalon medially and the parahippocampal gyrus and dentate gyrus laterally. Segment P3 (quadrigeminal) is located in the quadrigeminal cistern. It ends up giving rise to the two terminal branches, the calcarine and the parieto-occipital arteries. Segment P4 includes the branches that distribute in the cortical surface of the occipital lobe.

It gives rise to three different kinds of branches. Perforators are the central perforators of the diencephalon and mesencephalon, known as the thalamus perforators, mesencephalon perforators and thalamus-geniculated arteries. They supply the most rostral aspect of the mesencephalon and posterior section of the diencephalon (Fig.4).

Ventricular branches such as the posteromedial and posterolateral choroidal arteries. The posteromedial choroidal artery (PMCho) begins in the P1 segment and finishes in the third ventricle accessing it through the posterior aspect of it. In his trajectory, the artery surrounds the mesencephalon, then enters the third ventricle through the roof and ends in the lateral ventricle irrigating the choroid plexus. The posterolateral choroidal artery (PLCho) also begins in the P1 segment and ends in the body of the lateral ventricle. It anastomoses with the AChoA. Cortical branches to the cerebral cortex and the splenium of the corpus callosum. They end up irrigating the basal and medial aspect of the temporal lobe, medial aspect and superior border of the parietal and occipital lobe including the visual cortex.

Circle of Willis

Multiple anastomoses are present in the central nervous system allowing maintaining the cerebral blood flow when one of the vessels is occluded. The most important is the circle of Willis, located in the base of the brain and connects the carotid system with the vertebra-basilar and both carotid systems. Usually, a small flow goes through the circle of Willis, but if one of the arteries is occluded, the flow could be maintained by the rest of the vessels that form the circle. The ICA connects with the PCA through the PCommA. Sometimes the PCommA gives the full supply to the PCA, which is known as the fetal variant. Also, both carotid systems are connected by the AComm (Fig.1)

Another collateral circulation is given through the anastomosis of arteriolar and capillary vessels between the terminal branches at pial level.

In the ventricles, there is another anastomosis between the AChoA, a branch of the ICA, with the PLCho artery that belongs to the posterior circulation.

Finally, the carotid system connects with the external carotid artery through the ophthalmic artery, a branch of the ICA.

Recommendation

The brain is irrigated by two arterial systems: the carotid system (anterior circulation) and vertebro-basilar system (posterior circulation). The *circle of Willis* assures cerebral blood flow in case of obstruction of one of the vessels.

The *carotid system* irrigates almost all the telencephalon and part of the diencephalon. The ACA supplies most of the medial aspect of the cerebral hemisphere and its superior border. The PCA supplies the posterior area of the mesial and basal aspect of the brain and the posterior region of the superior border. The MCA irrigates most of the lateral aspect of the brain as well as part of the basal ganglia.

The *vertebra-basilar system* irrigates the posterior region of the telencephalon, brain stem and cerebellum.

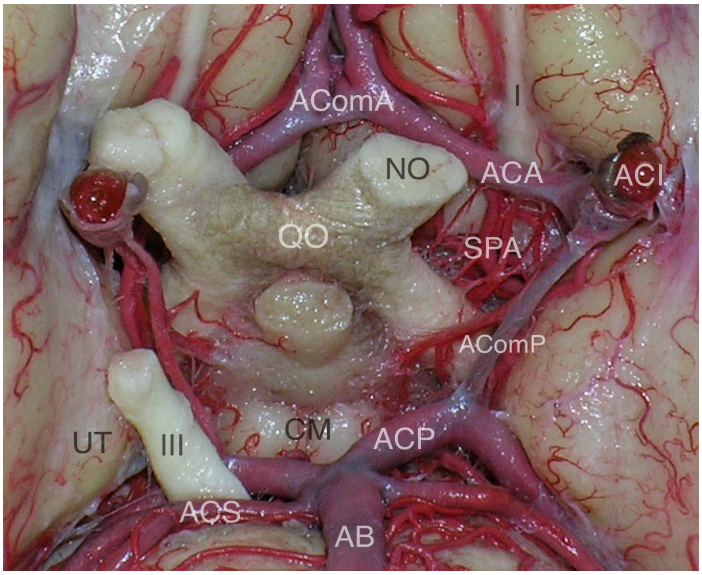

Fig. 1-1 Circle of Willis. Basal cisterns: inferior view. The circle of Willis can be appreciated form by the ACA, AComm, and the ICA with the bifurcation of the two terminal branches, PComm and PCA. The AComm is an artery with many variations in size; its size is inversely proportional to the size of the ACA, connects both carotid systems and is located above the optic chiasm. The PComm connects the carotid system with the vertebro-basilar. Occasionally it can give the full flow directly to the PCA; in that case, is known as fetal configuration. The anterior perforated substance can be seen with the entrance of the perforators that will supply the basal ganglia and internal capsule. The basilar bifurcation can be seen with the two PCA below the mammillary body. Notice the relationship between the III cranial nerve with the PCA above and the PC below this cranial nerve and its relation to the temporal uncus and the PCom; these two structures can be affected by temporal herniation and aneurysms of the communicating segment of the ICA. (AB: basilar artery. ACA: anterior cerebral artery. ACI: internal carotid artery. AComA: anterior communicating artery. PComA: posterior communicating artery. ACP: posterior cerebral artery. ACS: superior cerebellar artery. CM: mammillary body. I: olfactory nerve. III: oculomotor nerve. QO: optic chiasm. UT: temporal uncus).

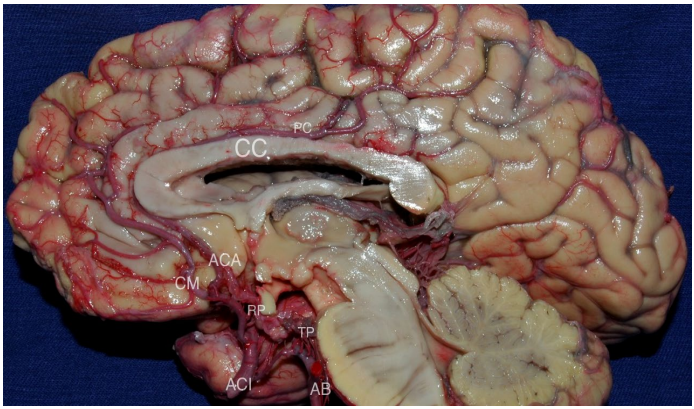

Fig. 1-2. Anterior Cerebral Artery: medial aspect of the brain, the trajectory of the ACA can be seen. Its relationship with the corpus callosum and its branches can be appreciated.
(CC corpus callosum. ACI: internal carotid artery. ACA: anterior cerebral artery. CM: callosal-marginal artery. PC: peri callosal artery. RP: perforator branches. TP: thalamus-perforating arteries. AB: basilar artery).

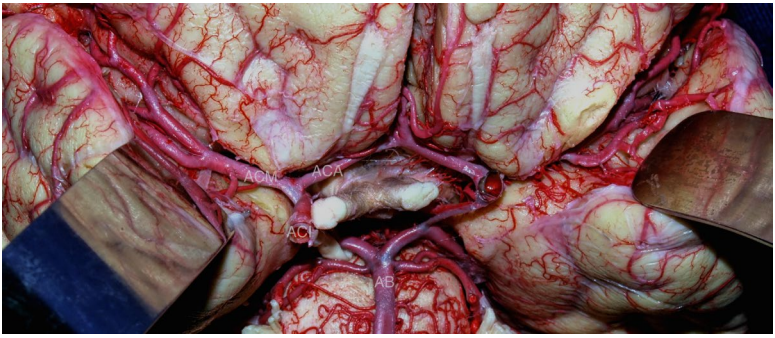

Fig. 1-3 Middle cerebral artery and circle of Willis. Both temporal lobes were retracted to observe the trajectory of the MCA from its beginning in the anterior perforated space up to the sylvian cistern. The bifurcation in the two main trunks can be seen, the superior and inferior, and its relationship with the limen insulae. (AB: basilar artery. ACA: anterior cerebral artery. ACI: internal carotid artery. ACM: middle cerebral artery).

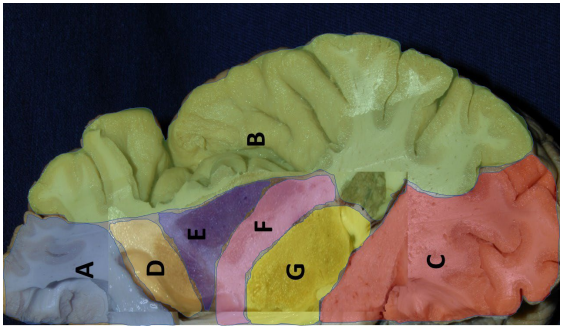

Fig. 1-4 Axial section of the brain through the ganglia base nucleus. The different vascular territories related to cerebral vascularization are depicted. (A: ACA. B: MCA. C: PCA. D: perforators of the ACA. E: lenticulo-estriates arteries and MCA perforators. F: ACho artery territory. G: Thalamus perforators and PMedChoroidal arteries territory).

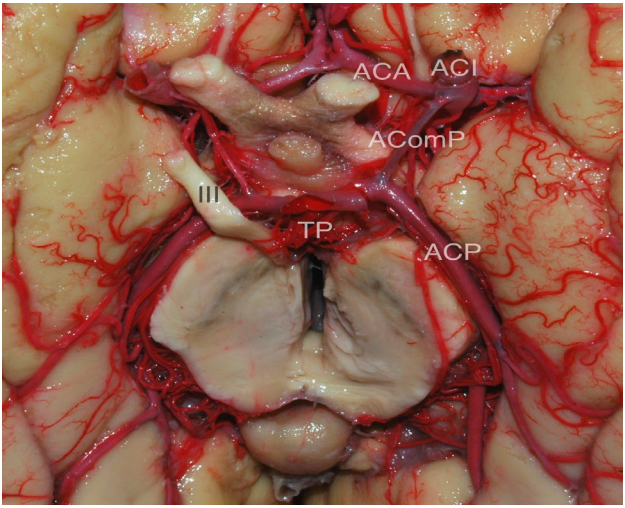

Fig. 1-5 Posterior cerebral artery and circle of Willis. The circle of Willis and the PCA can be seen surrounding the mesencephalon. Note the thalamic-perforating arteries accessing the posterior perforated substance.
(ACA: anterior cerebral artery. ACI: internal carotid artery. ACommP: posterior communicating artery. ACP: posterior cerebral artery. III: oculomotor nerve. TP: thalamic-perforating arteries).

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CHAPTER 2

HAEMORRHAGIC STROKE: EPIDEMIOLOGY, RISKS FACTORS AND CLASSIFICATION

GUSTAVO G. DOMENICONI, EDGAR AMUNDARAIN AND IGNACIO CECCONI

Introduction

Acute stroke is the second cause of death and the first cause of incapacity in the world. Through the increase of life expectancy, in a non-distant future, it could become the main cause in both statistics. Intracranial haemorrhage is the second cause of stroke, counting to up to 10-20%.

Regarding to haemorrhagic stroke, this condition can result as a complication of pre-existing lesion such as AVMs, or a tumour, term known as secondary intracranial haemorrhage. Primary intracranial haemorrhage refers to those in which non clear lesion can be assess or diagnosed, this type of haemorrhagic stroke represents the main cause. This chapter focuses on primary haemorrhagic strokes.

Definitions

Haemorrhagic strokes can be defined as those strokes that present with focal bleeding in the brain parenchyma, because by the rupture of blood vessels that supply the brain cells, which causes the compression of the surrounding tissue. The bleed can cause dissemination of blood in the nearby compartments of the brain such as ventricles and cisterns, and less frequently into the subarachnoid and subdural space. Therefore, the bleeding that happens into the brain, in the intra-axial space, will be defined as Intracerebral haemorrhage (ICH), as opposed to those that happen in the extra-axial tissues that do not compromise encephalic tissue.

Epidemiology

The frequency of age in all strokes has decreased in the past decades and is mainly because of ischemic stroke. Regarding specifically to haemorrhagic strokes, data still remains controversial and contradictory in the different studies. Nevertheless, the global impact of ICH has increased (1990-2010), 47% in terms of the number of people who have been affected by the condition. This is mainly due to the increase of people and data from countries with medium and low income (+22%; 95% CI 5-30%). In the countries with high income the incidence has decreased.

Regarding the contradictory results found in the different studies performed, a possible explanation to that would be the variation in the time of publication of the different studies, among time the number of haemorrhagic strokes due to chronic hypertension has decreased, whereas there has been an increase in those secondary to the use of anticoagulation therapy. When most available studies are combined and after a metanalysis was performed, it concluded that the general incidence of ICH has not changed between 1980 and 2006.

General incidences of haemorrhagic stroke are 24.6 cases, per 100.000 habitant, per year. Varying between, 1.8 and 129.6, in different studies. Asiatic population has double incidence among all ethnics' groups. In the second place comes African population to this point. Also, women are 15% less likely than men to suffer from haemorrhagic stroke. The difference in incidence between regions and ethnics, is related to the different risk factors for ICH among populations, most important being chronic hypertension. Specifically, regarding Asia, a low fruit ingest, high consumption of hydrogenic vegetal oil in Southern Asia, are risk factors for a higher incidence of ICH in this particular region.

All studies have found consistently that age; specifically over 85 have 10 times more risk than those who are between 45 and 54 years old. In the USA, there are 60.000 cases each year, with a mortality rate of 40% on the first month, and 54% percent after a year.

Morbidity is also high after haemorrhagic stroke. According to studies, only 12-33% of patients recover independency after a year of having suffered it. In a 5-year follow-up, and independency rate of 39% was reported.

Risk factors

The correct identification of risk factors regarding haemorrhagic stroke is important in at least three points: It helps to establish the pathophysiology and or cause. Those who are due to modifiable are helpful to prevent the

population. Due to the characteristics of the disease, where treatment and post-bleeding care have had little impact on risk factors, it allows developing prevention politics, that morbidity and mortality rate, development of correct and opportune politics are mandatory to prevent and to decrease incidence of ICH. Finally, there is a relationship between risk factors, subtype of bleeding and prognosis.

It is important to remember that ICH is complex entity, with different subtypes, and therefore, it is likely that risk factors and causes of haemorrhagic stroke are multiple and variable and are actually interrelated. In this chapter we will focus on the different types of risk factors related to the pathology, and to make the reading and understanding of the disease more practical, each will be analysed separately.

Hypertension:

Is the most important risk factor, it is even more significant for haemorrhagic stroke than for ischaemic stroke. It congregates every region and ethnic in the world, and therefore has the biggest importance. In an epidemiological study of reference, was found that those who suffer from hypertension were 3.5 times more likely to suffer from ICH than those who were normotensive. Another metanalysis showed that auto-informed hypertension or a measured arterial pressure over 160/90 mmHg increased the risk of suffering from haemorrhagic stroke over 9 times. Normally chronic hypertension is related to deep localize bleeding. Putamen is affected in 46 to 50 %, Thalamus 18 to 20% and the Caudate nucleus up to 5%, although it can be present in different localizations such as the lobes or the posterior fossa.

The Pathophysiological mechanism predisposes to bleeding and is related to a degenerative process called lipohialinosis. This is a biological process that includes the proliferation of fibroblastic cells, increase in the deposits of macrophages and the replacement of the smooth muscle for collagen in the walls of the small arteriole. This phenomenon reduces the elasticity and increases the risk of rupture.

It is important to define, which rate of hypertension determines whether there is risk for ICH. Based on various studies, it can be stablished that tensional numbers of systolic pressure between 120-140 mmHg, have a significant higher risk for ICH than those individuals who remain below 120 mmHg. Other variables apart from the absolute digits seem to be important as well. The amplitude of pulse seems to be directly related to the risk of haemorrhagic stroke. In hypertensive patients who are under treatment present an ambiguous behaviour. It is not only important to

achieve digits bellow 120 mmHg of systolic pressure, but also that the rate in which the systolic pressure descends determines the risk for ICH.

Therefore, seems to be important, in order to descend the incidence and gravity of ICH, to perform aggressive manoeuvres to descend the digits of arterial pressure. It is recommended that patients remain normotensive (SP less than 120 mmHg).

Cerebral amyloid angiopathy (CAA):

It is the second most common risk factor for haemorrhagic stroke, it summons to up to 10% of the ICHs. The mechanism is the deposit of beta-amyloid peptide, in the middle and external layer of the arteriole's wall. This happens mainly in the cortex. The deposit continues until it affects the muscular layer and predisposes the vessels to micro-aneurisms and fibrinoid necrosis. Because of the distribution of the deposit, these types of strokes are generally but not exclusively in the cortex of the lobes, these are known as lobar intracerebral haemorrhage. The frequency of CAA increases with age, almost half of people studied over the age of 90 shows some signs of this disease. Actual estimations show that almost 50% of intracerebral haemorrhage distributed in a lobar region, are related to CAA. Although these percentage is high for only one risk factor, it is important to assess that over 50% of the remaining ICHs is caused by other risk factors, many of which have not being identified yet. CAA increases 5 times the risk of recurrence after one event. Most of the investigations about CAA focus actually in early identification and risk stratification, regarding possible early markers of the disease. However, the cause of CAA remains today unknown. Other than genetic influences, up to today non modifiable risk factors have been identified, given this circumstance, the opportunity of primary prevention related to this risk factor remain limited.

As mentioned above, older patients are at far most risk of suffering from CAA, this summons up with the fact that this group tend to have a higher incidence of diseases for which anticoagulation therapy is required as part of the treatment, as for example atrial fibrillation. Scores usually utilized to calculate risk of bleeding do not consider the mayor risk of bleeding related to the deposit of amyloid, tending therefore to underestimate the risk of bleeding in such patients. As a result of these findings, in older patients, an even more in those who present neurological impairments such as dementia, MRI scan becomes an important tool to diagnose vascular lesions and should be performed before starting anticoagulation therapy. Mayor criteria to diagnose the presence of CAA is the presence of micro bleeding in the lobes, hemosiderin deposits at the cortex surface

(superficial cortical siderosis) and or hyper intensity in the white matter in posterior cerebral regions.

Smoking:

Smoking habit is strongly related to ischemic stroke. The association between smoking and haemorrhagic stroke is more complicated to stablish. The “Interstroke study” found that smoking is related to ICH when the number of cigarettes consumed is over 10, after that point a linear increase in the risk of bleeding has been observed. In other studies, the relative risk related to smoking was reported to be between 1.2 and 1.5 compared to non-smokers. Although the most studied variable is related to smoking cigarettes, we cannot assure that other methods related to smoking (such as: smoking pipe, cigars, vaping, etc.) are not related to an increased risk of suffering ICH.

Alcoholism:

The so-called protective effects of moderate consumption of alcohol in the prevention of cardiovascular disease are controversial and even more in cerebrovascular diseases. A metanalysis determined that a high alcohol consumption (over 4 drinks a day) was associated with a higher risk, statistically significant of ICH (RR=1.67; IC 95%, 1.25-2.23), being less significant when alcohol consumption is mild and under 2-4 drinks a day.

This association can be explained due to different effects of alcohol. Alcohol consumption was associated with higher risk of hypertension in a positive linear dose-response association in men, and in women was related to a J form dose response relation. Alcohol consumption is also related to hypo fibrinogenemia, lessens platelet function and aggregation, among other alteration factors related to coagulopathy.

Hypercholesterolemia/Hypertriglyceridemia:

Actual bibliography supports the inverse association between high levels of plasmatic cholesterol and lower risk of haemorrhagic stroke. These results are based upon case-control studies and big data bases of informative health-care systems. Plasmatic levels of LDL-C have shown the same tendencies. Not only are higher plasmatic levels of cholesterol related to a lower risk of bleeding, but also to smaller extension of the hematoma, and better neurological outcomes afterwards.

It is interesting to mention that a low LDL-C/HDL-C relation increases the probability of suffering of any cerebrovascular event. Despite the so-described protective effects of cholesterol, the use of statins does not seem to increase the risk of suffering an ICH, and there are reports in different scenarios (such as treatment for hypercholesterolemia or secondary prevention in patient with antecedents of cardiovascular diseases) where it actually decreases the chances of suffering from haemorrhagic stroke. The discrepancies of equals results regarding two different clinical scenarios are hard to explain and it escapes the objectives of these chapter.

Regarding hypertriglyceridemia, it seems to be an association to higher risk of haemorrhagic stroke. Such association has not been so extensively studied as that associated to cholesterol levels. In a recent study, the influence of hypertriglyceridemia shows a valley effect in the incidence of ICH. That means, there is an increase of incidence in those values above or under (205-225 mg/Dl).

Diabetes:

Represents and independent risk factor for cardiovascular disease as well as for ischaemic stroke, however, its association with haemorrhagic stroke has yet not been well stablished. In a recent metanalysis in which analysis from all over the world where included, showed that diabetes increases the risk of suffering from ICH in 1.5 times. A recent clinical trial showed similar results, even when many confounders for cardiovascular risk where adjusted. In diabetic patients followed up for over two years with HbA1c, a linear relation was found between high HbA1c levels and the incidence of ICH. However, the linear association was found with levels above 6.5%. According to these findings, we can summarize that the presence of diabetes predisposes to ICH, and when not properly treated, the risk increases accordingly. The pathophysiological mechanism, for which the risk of haemorrhagic stroke increases, remains still unknown. But it has been found that patients suffering from diabetes have a higher risk of deep bleeding and bigger haematomas.

Sedentary lifestyle:

A sedentary lifestyle increases the risk of cerebrovascular stroke, not only ischaemic, but also haemorrhagic. Many studies and metanalysis were performed that come to this conclusion. However, the evidence about not only the type of physical activity but also the intensity in which the activi-

ty should be performed to prevent the occurrence of stroke has yet not been stablished.

Older studies would differentiate the activities into subcategories such as: intense, moderate, and mild, and how many times a week would be performed. In the actuality we can conclude that recreational activities that implied a moderate intensity such as walking are independently associated with a decreased risk of stroke, these associations are specially reported in women. This protective effect of physical activity is also important in obese and older adults. Therefore, it is recommended that moderate physical activity such as walking will be promoted to help prevent and lower the risk of stroke, especially in women.

Medication (anticoagulants and antiplatelet):

The benefits of the use of blood thinners and antiplatelet, in those patients who had been correctly assessed, overcome largely the risks of mayor bleeding, including haemorrhagic stroke. Nevertheless, it must be taken into consideration, that with anticoagulation, the annual incidence of ICH increases up to 0.8 to 44.4 for 100.000 habitants. Therefore, the clue to decrease the risk of ICH associated with the use of blood thinners and antiplatelet, is to determine the proper and correct indication and those factors that could increase the risk of mayor bleeding, which could contraindicate their use.

In patients suffering from atrial fibrillation, there are two scales to determine the risk for ischaemic stroke: the most commonly used and recommended in the American and European guidelines are CHA2DS2-VASc and the most recently published ATRIA scale. The risk of stroke must be compared to the risk of bleeding, to this end, exists the HAS BLED scale which determines the risk for mayor bleeding with anticoagulation therapy. None of the three scales mentioned above considerate two extremely important risk factors associated with the development of haemorrhagic stroke, which are: the presence of cerebral amyloid angiopathy (CAA) and micro bleeds that can be found when performing a brain MRI. Different studies and a metanalysis have reported that the presences of more than five micro bleeds significantly increase the risk of brain bleeding.

As for anticoagulants or bleed thinners, we must also consider the type of drug we are dealing with, as for new anticoagulants (Apixaban, Dabigatran, and Rivaroxaban) are actually more secure and present a lower risk of bleeding when compared to older anticoagulants such as Warfarin or Acenocoumarin. These findings have an increased rolled specially in the secondary prevention of ischaemic stroke related to atrial fibrillation,

even in patients over 80 years of age. Regarding this last point, antiplatelet are more secure. However, there are precise indications for the use of double antiplatelet agents that increase the risk of bleeding. In the last years, the use of double antiplatelet with AAS and Clopidogrel has shown benefits in the secondary prevention of ischaemic stroke minor or in TIA of high risk. This benefit has to be counterweight with an increased risk for mayor bleeding when treatment must be longer than four weeks.

Genetic risk factors:

Evidence regarding a genetically predisposition for intracerebral bleeding, comes from familiar case studies. Many gene disorders have been identified that might conduce to ICH, and those include the presence of familiar CAA (cerebral amyloid angiopathy) due to mutations in the gen APP, also dominant autosomal cerebral arteriopathy which causes subcortical strokes, and leukoencephalopathy due to mutations in the gen NOTCH3. Nevertheless, these monogenetic disorders are rare, and can explain only a little proportion of the genetic predispose to intracerebral bleeding. It has been thought that the genetic factors that predispose to primary intracerebral bleeding are far more complex, regarding many other not yet correctly identified genes that are also involved. Up until now, only the mutation in the gen APOE has been identified as a solid genetic risk factor that could lead to the presence of ICH.

APOE is considered a strong risk factor for the development of CAA, and it is in part through this underlying etiology, that APOE has been related with the development of intracerebral haemorrhage. Other alteration in the blood vessels due to a mutation in APOE has been discovered.

With further investigations in the genome in which thousands of genes and gene marks can be concomitantly studied, allows a unique opportunity to identify additional genes that can have modest effects. In a close future with the correct tools to modify certain parts of the genome, ICH could be prevented.

Obesity:

Obesity has been stablished as a modifiable risk factor for ICH, taking into consideration that this condition is mostly related to hypertension and diabetes due to insulin resistance, therefore, is not surprising that a reduction in the obesity rate, can lower the risk of ICH as well.

Classification

Anatomic:

Cerebral bleedings happen more frequently in the encephalic lobes, basal ganglia, brain stem (ponce) and in the cerebellum. According to this description, they can be subdivided into three locations: Lobar, 40% Deep bleeds: 45-50% of the cases. Infra tentorial 10% and represent those taking place in the cerebellum, and 5% on the brain stem, mostly in the pons. These figures, however, keep a close relationship with the risk factor implied in the cause of bleeding.

Etiological:

Based on the main risk factor, the ICH can be sub classified in secondary to: Hypertension, CAA, or associated to the used of blood thinners and or due to coagulopathy.

Pathophysiological:

It can be differentiated into *Primary ICH*: In this group belong almost exclusively those haemorrhages caused by hypertension or CAA. And *Secondary ICH*: Here belong all those bleedings that are related to anatomical and functional causes that will develop a characteristically evolution and have specific therapeutic as well.

Recommendations

Intracerebral bleeding (ICH) is an entity characterized by the presence of blood in the cerebral parenchyma, it has different locations and therefore different clinical presentations, consequently, a detailed initial evaluation is mandatory in order to assess and predict the areas of the brain that could be affected, and the precipitant factors of such bleed.

It can be defined as a focal bleeding in the parenchyma caused by the rupture of blood vessels, resulting in the compression of the nearby cerebral tissue. It can be disseminated to other compartments of the brain, such as: ventricles, cisterns, and less frequently, but also observed, subdural or subarachnoid spaces. It is important to note that there is a particular group of bleeding that is denominate as primary, and that can be misinterpreted in the literature as spontaneous. Therapeutics must be followed through according to this specific pathophysiological model.