

## Pathophysiology and clinical aspects of temporal evolution of intracerebral hemorrhage - implication in prognosis and neurorehabilitation

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### Abstract

Over the past 10 years great progress has been made in the diagnosis and treatment of neurological pathology such is stroke. Primary intracerebral hemorrhage (PICH) is a devastating subtype of stroke, caused by acute and spontaneously of the blood in the cerebral parenchyma. Its many causes offer a substantial heterogeneity in terms of clinical appearance, evolution, prognosis and therapeutically resources. Despite of high importance in neurology, the pathophysiological mechanisms of PICH is not complete understand. The aim of this paper is to emphasize the importance of etiological factors and pathophysiological mechanisms in the clinical evolution, prognosis and patient's rehabilitation in PICH

**Key words:** *neurorehabilitation, pathophysiology of intracerebral hemorrhage, prognosis of intracerebral hemorrhage,*

### Introduction

Primary intracerebral hemorrhage (PICH) is an acute and spontaneous blood extravasation in the cerebral parenchyma by vascular rupture. Bleeding may extend into the subarachnoid space or the ventricular system. PICH is clinically the most severe subtype of stroke with a mortality of 35-50% in the first month of evolution [1,2]. The relative frequency of PICH as the first manifestation of cerebral vascular pathology is between 6,5% and 14,5% in western countries [3-5]. The incidence of PICH is clearly dependent on race or ethnic groups, being higher in Afro-Americans, Latin-Americans and populations in the Far East, probably in association with genetic factors, eating habits, arterial hypertension and the socio-economic status [1,2,6]. Existing data also suggests a gender-dependent difference in large PICH study groups: men with a slightly higher incidence than women [1,6]. Older age is associated with an increase in PICH incidence as well as with a worse prognosis, due to the involvement of various vascular cerebral pathophysiological risk factors and the existence of many other comorbidities [7,8]. Moreover, patients with a history of migraine with aura have a higher risk of hemorrhagic stroke due to the presence of vasodilatation mechanism [9-11]. PICH is in itself a form of focal lesion of the central nervous system.

*Anatomo-pathological classification criteria for primary intracerebral hemorrhage and their prognosis*

From the anatomo-pathological point of view, there are several subtypes of PICH determined by localization, possibilities of expansion and clinical evolution [2,12]: putaminal hemorrhage with severe prognosis; lobar hemorrhage (interesting regions of cerebral hemispheres, in ascending order: occipital lobe, temporal lobe and frontal lobe) with better prognosis than putaminal hemorrhage but with higher risk of recurrence; thalamic hemorrhage in which the prognosis is dependent on the size of the lesion (a diameter greater than 3 cm is often fatal); cerebellar hemorrhage- frequently represents a cause of herniation of the cerebellar tonsils; pontine hemorrhage leading to locked in syndrome with a survival rate of 35-45%; caudate hemorrhage in which the extension into lateral ventricle may mimic a subarachnoid hemorrhage, intraventricular hemorrhage with about 50 % mortality rate. Midbrain and medulla oblongata are rarely involved in PICH.

Modern neuroimaging applying the T2\*-weighted MRI sequence, also detects another type of intraparenchymatous hemorrhage: microbleeds (small perivascular bleeding that is clinically silent). In subjects without cerebrovascular suffering, the presence of microbleeds ranges between 4-8,5% [13]. Their association with PICH is evaluated between 47-80% and with ischemic cerebrovascular pathology between 18-78% [13,14]. Although their significance is still uncertain and seems devoid of specificity, microbleeds are generally considered elements that predict PICH [13-15]. Their presence, however, is an aggravating prognostic factor in patients with stroke [16].

### *The etiology of PICH*

There are many conditions in human pathology that increase the risk of PICH. Clinical appearance, clinical evolution and recovery prognosis largely depend on the determinant cause of PICH. *Arterial hypertension* causes approximately 50% [2,12] to 75% [14] of PICH. Hypertensive hemorrhage occurs most commonly in putamen and thalamus (approximately 60%), in the cerebral hemispheres (lobar haematoma approximately 20%), in the cerebellum (13%) and in the pons (7%) [2]. The risk in PICH increases in proportion to the blood pressure values and the duration they have acted on the vascular wall, generating structural changes [2,15]. Another cause for PICH is the *cerebral amyloid angiopathy* (CAA), secondary to the amyloid deposit in the arterial wall of the cerebral parenchyma. CAA is responsible for 12% of PICH, also being a common cause of lobar hemorrhage (30% of cases) in elderly and normotensive patients [2,12,17]. Frequently, in 80% of CAA cases, micro-bleeds are found during the MRI examination [2,18]. The modified Boston criteria for probable CAA diagnosis were validated in 2010 and have a sensitivity of 94,7 % and a specificity of 81,2% [19]. PICH can also be caused by *anticoagulant, antiplatelet and thrombolytic treatment*. Approximately 10% of PICH occur in association with a well controlled and limited anticoagulant therapy [20]. In opposition, antiplatelet therapy is used on a larger scale. However, the risk of PICH is small compared to the benefits that such treatments have in the prophylaxis of myocardial infarction and stroke ([21]. What should be taken into account is the fact that, in the case of PICH, anticoagulant and antiplatelet treatment increases the volume of the hematoma leading to a worse prognosis ( [20,22]. HAS-BLED Score is used for the evaluation of the risk of hemorrhage in patients with atrial fibrillation treated with anticoagulant therapy [23]. Thrombolytic therapy in used in management of cerebral strokes can contribute to the development of an intracerebral hemorrhage. Nonetheless, in such cases, the intracerebral hemorrhage occurs in the ischemic zone and it is not an actual primary intracerebral hemorrhage. Moreover, the incidence of PICH after thrombolytic therapy for myocardial infarction is 0.3-0.8% [24]. *Arterio-venous malformations (AVM), aneurysms and angiomas* can be the root for PICH at any age. There is a tendency for a more visible

clinical manifestation in younger patients compared to elderly patients, whose PICH is often caused by hypertension [12]. AVM have an incidence of approximately 0,14% of the global population. AVM represent congenital anomalies of blood vessel development such as a direct communication between arterial and venous channels without an intervening capillary network [25]. Cavernous angiomas are estimated to be present in about 4% of the population. The presence of remote blood- breakdowns around this kind of lesion is often manifest in patients who relate no history of cerebral hemorrhage [25]. Developmental venous anomalies (venous malformations) have no arterial component. Brain tissue around this venous malformation is usually normal without evidence of hemosiderin staining or gliosis [26]. This malformations have an overall incidence of 2%, as shown by a large autopsy study [27] but rarely cause neurological symptoms [28]. Cerebral aneurysms are found in 4% of the population [29]. While unruptured aneurysms may cause symptoms mainly due to the mass effect, the real danger occur when an aneurysm rupture takes place, leading to subarachnoid hemorrhage. *Ethyl alcohol and drug abuse* (specifically cocaine, heroin and sympathomimetics) significantly increase the risk of PICH. The age of PICH onset for alcohol consumers is younger if the duration of the consumption was longer [30].The relative risk for PICH was 2,4 for ethanol consumers, who exceeded 400 g of ethanol per week. In this situation the PICH are usually lobar [31].

### *Pathophysiology of PICH*

Despite its clinical and therapeutically importance, the pathophysiology of PICH is not well understood. PICH is much more complex than the simple mechanical lesion generated by the penetration of the blood into the brain parenchyma. We propose a mechanism that evolves in three stages. *The first stage* is the primary brain damage. Cerebral angiography has demonstrated that intracerebral hemorrhage usually originates from a single artery and it may continue for many hours or days [32]. Blood from intracerebral hemorrhage accumulates as a foreign mass that mechanically dissects gray and white matter. The hemorrhage expansion occurs along the tracts of the white matter and compresses adjacent brain tissues. All of this acute neuronal destructions are lead to negative clinical manifestation. Associated oxidative stress can further

damage cerebral tissue and can result in long term sequelae and being more important in elderly people that can have various supplementary disorders (as are diabetes mellitus or cognitive dysfunctions due to hypothyroidism) [8,33]. The progression of the hemorrhagic outbreak also affects other vascular structures leading to secondary bleeding sites [2,17,32], meaning that PICH is a dynamic process that progresses in the first 24 hours with an expansion peak of 6 hours [17]. *The next stage* of PICH is the secondary brain damage. Distal to the bleeding point of the artery, parenchymatous territory becomes ischemic due to the decreased perfusion pressure and the formation of platelet plugs. The rupture of other arterioles and capillaries leads to other areas of ischemia. Therefore, the result of a hemorrhagic outbreak is a mosaic of ischemic and hemorrhagic lesions. On the other hand, there is an impairment of the cerebral circulatory autoregulation in the perihematoma area and, as a consequence, the sudden decrease in blood pressure can lead to vasodilatation, which can increase the intracranial pressure and lower the cerebral perfusion pressure even further [17]. All these elements contribute to the disruption of the blood-brain-barrier and to the formation of perihemorrhagic edema. PICH and the accompanying edema may also disrupt or compress adjacent brain tissue, leading to neurological dysfunction. Substantial displacement of brain parenchyma may cause an elevation in intracranial pressure with the potential outcome of total herniation syndromes [34,35]. *The last stage* in the pathophysiology of PICH is represented by the territory brain damage, which is, for the most part, attributed to the presence of intraparenchymal blood and may be dependent on the initial haematoma volume [36]. Many parallel pathophysiological pathways may occur, including: cytotoxicity of the blood components, excitotoxicity, oxidative stress and inflammation [37-41].

Finally, all these pathogenetic mechanisms lead to irreversible disruption of the brain-blood-barrier and of the neurovascular unit with massive brain cell death [41]. Especially mediators of the locally produced inflammation (as a response to the brain lesion) have the capacity to augment the damage caused by PICH. The involvement of inflammatory cells microglia and macrophages is vital for the removal of the damaged tissue from the haematoma. [42]. The blood components

(erythrocytes, plasma proteins, ATP, lipid mediators, cellular membrane fragments) and the components of the necrotic and damaged tissue determine a strong cytotoxic, pro-oxidative and pro-inflammatory insult against adjacent viable brain cells. As in the case of cerebral ischemia, time is very important. The three described stages are succeeded one after another but overlapping of the phases may occur.

#### *Diagnosis*

The diagnosis consists of clinical investigation and imaging. First of all, in an emergency situation such as PICH, focused history and eliciting specific risk factors for stroke like symptoms is important. The ROSIER scale is very helpful. This scale ranges from -2 to +5 points. Any patient scoring greater than 0 has a 90% likelihood of stroke. The ROSIER scale is a rapid stroke assessment tool (sensitivity of 92%, specificity of 86%, positive predictive value 88%) [34]: components with + 1 point each (asymmetrical facial weakness, asymmetrical arm weakness asymmetrical leg weakness speech disturbances, visual field defect); components with - 1 point each (seizure, loss of consciousness).

As for imaging, cranial non-contrast computed tomography (CT) and magnetic resonance imaging (MRI) are both the first line ways to diagnose PICH. Due to the urgency of getting a diagnosis and the rapid acquisition of images, CT is almost always carried out in the first examination [12]. PICH appears as an intraparenchymatous area of high density specifying the location and the extent of the hemorrhage. CT also highlights the brain edema, midline shift, brain herniation and ventricular extension. It is thought to be nearly 100% sensitive for detecting relevant acute hemorrhages [34]. With the hemolysis of the blood its density diminishes and the hemorrhagic outbreak is cleared in about 4 weeks [12]. CT angiography (CTA) has proven to be a useful in detecting aneurysms. Compared to CT, MRI offers structural details and both edema and herniation are better visible. However, the MRI interpretation of the evolution of cerebral hemorrhages is more sophisticated than CT. The temporal evolution of the biochemical changes in the hemorrhagic outbreak offers only a relative staging (i.e. acute, subacute, chronic), as shown in table 1 [25].

**Table 1.** Indicative changes for temporal evolution of PICH of MRI. In the first 3 groups, oxyhemoglobin, deoxyhemoglobin and methemoglobin are intracellular [25].

Biochemical form	Stage	Temporal evolution	T1 weighted image	T2 weighted image
• Oxyhemoglobin	hyperacute	the first hours	=	↑
• Deoxyhemoglobin	acute	hours to days	=, ↓	↓↓
• Methemoglobin	early subacute	first several days	↑↑	↓↓
• Extracellular methemoglobin	subacute to chronic	days to months	↑↑	↑↑

= defines isointensity, ↓ defines hypointensity, ↑ defines hyperintensity

This evolution in time of T1-T2-weighted signal changes requires the additional use of T2\* (or SWI) sequence for a more accurate diagnosis. This way we obtain the specific neuroimaging models for the clinical etiology of PICH.

#### *Prognosis*

PICH is associated with high mortality and unfavorable outcome [36]. There is a large heterogeneity of clinical appearance within PICH depending on etiology, neuro-imaging aspect, localization and lesion extension. The initial clinical appearance is also important for the prognosis. Currently, there are numerous grading scales for assessing prognosis and functional recovery possibilities. Two of these are widely used in intracerebral hemorrhage clinical trials: ICH Score (which predicts 30-days mortality) and FUNC (functional outcome risk stratification) Score, which assesses the risk of functional impairment at 90 days post stroke. The FUNC Score completes the previous scale with the functional prognosis [43,44].

Involvement of this multiple aspects of PICH has been the target of numerous clinical trials for a proper setting of the therapeutic strategies. It balances the clinical and therapeutic reasoning based on “early subjective clinical judgment” (the personal experience of the physician) and the therapeutic implication of the prognostics provided by the “formal scales” and neuroimaging aspect. All this to develop a better understanding of the therapeutic attitude for PICH [45,46]. These studies have found a significant variability in physician prognostic estimation and treatment recommendations for cases of moderate to severe PICH. It was found that medical recommendations for the magnitude and intensity of treatment were altered when they were provided with a valid prognostic score [45]. Two extreme situations have been identified in these

studies. If the prognosis suggested by scores was poor, physicians were more inclined towards therapeutic limitation compared to indication made by subjective clinical judgment. If the prognosis score suggested a favorable outcome, physicians have had a broader and more generous therapeutic initiative [45,46]. The results of these studies suggest that increased use of formal scales may alter physician treatment recommendations – especially in severe cases [45].

#### *Treatment of PICH*

##### *Medical therapy*

PICH is a major medical emergency. The patient should rapidly be evaluated by a team of physicians, who are experienced in this field. Patients have a better prognosis if they are treated in a stroke unit (a neurointensive care). The American Heart Association, American Stroke Association and European Stroke Organization have developed guidelines for the management of PICH [12, 47, 48].

##### *Surgical Treatment*

Surgical treatment in intracerebral hemorrhage has the following reasons: removing blood from the hemorrhagic outbreak (to minimize the cytotoxic, proinflammatory, excitotoxic impact of blood on neighboring brain structures); to prevent brainstem compression by intracranial hernias (cerebellar hemorrhage); to control the increase of intracranial pressure. Despite these rational arguments, the International Surgical Trial in Intracerebral Hemorrhage (STICH) concluded that surgery offered no benefit [49]. However, there are studies that indicated that surgery is beneficial for patients with intraventricular hemorrhage and hydrocephalus. Cerebral hematoma have indication of surgical evacuation if their diameter exceeds 3 cm [49].

Rehabilitation after PICH is an important goal of the treatment aimed to reduce the impairment, to improve independent activities, and return patients to a social life. To optimize plasticity and restoration of function after neural injury, neurorehabilitation be started early and should be given at a high intensity and dose [50]. The rehabilitation methods consists in physical training and brain stimulation. Early and intensive behavioral physical training augments recovery after ICH, and that this training is accompanied by anatomical changes in the neural substrate [51]. Brain stimulation by vagal nerve may increase neuromodulators (like BDNF and prefrontal norepinephrine concentration), that have an important role in brain plasticity [52]. For the patients who have a serious motor impairment providing an exoskeleton can be implemented as component of rehabilitation therapy [53].

### **Conclusion**

Primary intracerebral hemorrhage remains a devastating cause of stroke. The many etiological causes offer a substantial heterogeneity in terms of clinical appearance, evolution, prognosis and therapeutic resources. During primary intracerebral hemorrhage evolution we need to focus on the variable risk factors that can be therapeutically influenced. Deciphering the complexity of the pathogenetic phenomena opens new therapeutic opportunities with important implications in neurorehabilitation. Specific complications that may lead to increased intracranial pressure, deterioration of neurological status and cerebrospinal fluid disorder, should be treated individually. At the level of current medical practice, but also from the analyzed clinical studies, it appears there is a great variability in the prognosis established by physicians due to a subjective clinical impression or due to the use of formal scales, the same substantial variability is also found in treatment recommendation. Therefore, in our opinion, in a patient with intracerebral hemorrhage, all the therapeutic resources should be used, even if the prognosis given by the formal scales or by the physician's experience is severe. This especially in the case of lobar hematoma, thalamo-capsulo-lenticular hemorrhage and cerebellar hematoma.

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