Spontaneous intracerebral hemorrhages

- Pathology -

Date de mise en ligne : Friday 20 February 2015

L'encyclopédie neurochirurgicale

Definition

Spontaneous intracerebral (intraparenchymal) hemorrhages (SICH) are characterized by a non-traumatic bleeding into the brain parenchyma.

They account for 10 to 15% of cerebrovascular accidents (CVA) (stroke), and together with subarachnoid hemorrhage, are categorized as hemorrhagic strokes.

They are primary in most cases, that is, in relation to the rupture of small vessels damaged by high blood pressure (hypertension) or chronic amyloid angiopathy (11). They can also be secondary (20% of the cases) to an underlying macroscopic lesion such as an arterial aneurysm, an arteriovenous malformation, a tumor or related to any cause of coagulopathy. Only primary ICH will be covered in this chapter.

1 - Epidemiology

The annual incidence of primary ICH is between 10 to 20 cases per 100,000 inhabitants. It increases with age (2/3 occur after the age of 75), and is higher among males (12,15,41). Contrary to what is observed for cerebral infarctions, the overall incidence of ICH has not declined in the past decades (45). Epidemiological studies suggest a decrease in the incidence of ICH in patients under 75 years (probably due to a better management of hypertension) and an increase in the elderly (due to amyloid angiopathy and antithrombotic drugs). Finally, the risk of ICHs is increased in the Asian population (45).

2 - Risk Factors (RF)

Known risk factors for primary SICH include (1):

- a- **HBP:** This is the single most important RF, especially in smokers (5). The risk correlates with the severity of hypertension. A good blood pressure control can decrease this risk (21).
- b- **Alcohol consumption** increases the risk of primary SICH by inducing changes in brain vasculature and disrupting hemostasis (25).
- c- **Other RFs** are more anecdotal and include: diabetes mellitus, factor §III mutation, the presence of µ2 and µ4 alleles of the apolopoprotein E gene (1,7,34).

3 - Anatomopathology

a- Causal lesions

Two types of lesions account for the rupture of small cerebral vessels and are both secondary to chronic hypertension: **hypertensive angiopathy and amyloid angiopathy**.

- **Hypertensive angiopathy:** chronic hypertension induces a reduction in arterial compliance. These vessels

which are more rigid, will therefore have a decreased tolerance to potential spurts in blood pressure, thus a tendency to rupture. This phenomenon is observed mainly in small perforating arteries (50-700 ¼m in diameter) as reflected in the topographic distribution of the hematoma (see Anatomy) (42). There are often several sites of rupture, characterized by a breach in the elastic layer, atrophy of smooth muscle and cellular degeneration. This is often associated with atherosclerotic lesions. Historically in 1868, Charcot and Bouchard attributed the vascular rupture to the presence of micro aneurysms (called Charcot-Bouchard microaneurysms). However, electron microscopic studies have actually shown that these lesions are sub-adventitial hemorrhages, outdating the concept of microaneurysms (10,42).

- **Amyloid angiopathy**: it is characterized by the presence of ²-amyloid deposits in small and medium size arteries, thus inducing degenerative lesions of the arterial wall. These lesions are mainly located in the cortical leptomeningeal arteries and the cerebellum, hence explaining the topographic predilection of the hematoma at these sites.

b-The hematoma

The blood usually clots within the cleavage planes of the white matter, with a relatively limited neuronal destruction. However, under the influence of different toxins released in-situ, peri-lesional edema, neuronal damage and infiltration by macrophages and neutrophils occurs (32).

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Anatomy

Primary SICHs are located near small perforating arteries [thalamus and basal ganglia (50%), brainstem (mainly the pons) and cerebellum (20%)] or at the cortico-subcortical level [in case of amyloid angiopathy (30%)] (32). In case of deep hematoma, ependymal disruption may occur with the extravasation of blood in the ventricular system leading to intraventricular hemorrhage (IVH). IVH as we will see later is a major factor for the severity of the hematoma justifying the use of specific therapeutic measures.

Pathophysiology

Vascular rupture occurs within small vessels and diffuses into the parenchyma.

Nota Bene: Contrary to what was initially thought, the hematoma often continues to increase volume for several hours after its occurrence, usually within 3 hours of the onset of bleeding, but this may continue for 12 to 24 hours (23). Thus 26% of patients have an increase in size of the hematoma within the hour of diagnosis, and 12% in the first 24 hours (6). Moreover, the production from the clot of osmotically active proteins into adjacent parenchyma quickly induces the appearance of early edema (47).

Secondarily, the disruption of the blood-brain barrier, dysfunction of various ionic channels and neuronal death induces cytotoxic and vasogenic edema (48). The induction of this secondary edema seems to be related to the toxicity of the degradation products of the hematoma such as iron, and not in connection with an ischemic event as originally thought of (47,48,49). This is important because most pharmacological trials are derived from this concept (including trials testing the iron chelators, such as deferoxamine). This peri-lesional edema occurs mainly in the first 24 hours, however it evolves slowly to reach a maximum volume 5-6 days after the onset of bleeding (14,22).

The increased volume of the hematoma and peri-lesional edema over several hours clearly explains the progressive

neurological deterioration often observed during the first hours after the onset of symptoms.

In case of ventricular bleeding, the blood clots may cause an obstruction of the CSF flow leading to hydrocephalus. This is generally rapid and responsible for significant mortality. Secondarily, the breakdown products of the IVH will exert significant toxicity on the ependyma, which can lead to impaired absorption of CSF and thus to communicating hydrocephalus (19).

Clinical picture

A clinical picture of neurologic symptoms of sudden onset should primarily evoke the diagnosis of a CVA but there are no signs specific for the hemorrhagic type.

The clinical features depend on the location and extension of the hematoma.

1 - The manifestations of intracranial hypertension (ICHTN) are common and classical: headache, vomiting and impaired alertness to coma (to be evaluated by the GCS). They are due to the direct or indirect compression of the thalamus and reticular formation (39, 30, 39).

2 - A meningeal syndrome can be observed in case of subarachnoid or intraventricular extension (29).

3 - Deep ICH (thalamus, putamen, caudate nucleus) by compressing the internal capsule, may cause contro-lateral hemiplegia (43).

4 - Lesions of the subcortical white matter can interrupt the activity of different cortical regions causing various dysfunctions or neurological deficit (including but not limited to): aphasia, homonymous hemianopia, hemiplegia, frontal syndrome ... (43)

5 - Brainstem lesions may include (but not limited to): gaze abnormality, cranial nerves lesions, contralateral hemiplegia ... (35)

6 - Cerebellar hemorrhage causes cerebellar syndrome (35).

None of these signs are specifi, the diagnosis is made on imaging.

Almost a quarter of patients will have a deteriorating level of consciousness in the early hours of the treatment: when it occurs within the first 3 hours after onset of symptoms, it is most often due an increase in the volume of the hematoma. When it occurs within 24-48 hours, it is usually due to an increase in the peri-lesional edema (27,36).

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Imaging

1/Techniques

Non-contrasted Computed Tomography (CT) Scan remains the gold standard for the diagnosis of ICH. However, MRI T2 * has the same sensitivity and has the advantage of being able to differentially diagnose it from an ischemic lesion. Both techniques can therefore be used, with the choice depending largely on the availability of machines (I, A) (8). It is worth noting that in case of early imaging (less than 3 hours), the bleeding may still be active. The identification of patients with active bleeding and therefore a risk of neurological deterioration could be of therapeutic interest although this attitude has not yet been validated (IIb, B). Active bleeding can be demonstrated by the extravasation of contrast product into the hematoma, visible on both CT and MRI angiographies (3,16).

2 / Radiological semiology (25)

a-CT

During the acute phase, the ICH appears as a spontaneous intraparenchymal hyperdensity, exerting a mass effect on adjacent structures. A hypertensive cause is suspected with deep seated hematoma (Figure 1).

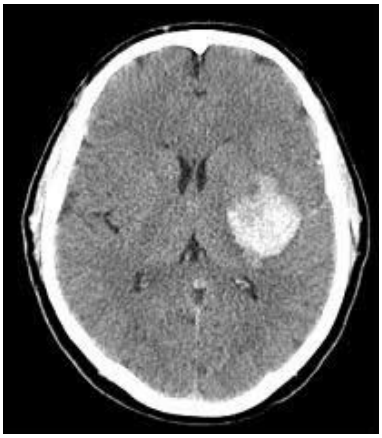

Figure 1: Left capsular and thalamic spontaneous intraparenchymal hematoma whose topography is suggestive of a hypertensive cause.

When the hematoma is lobar, it does not preclude a hypertensive cause but amyloid angiopathy is more likely in older patients (Figure 2).

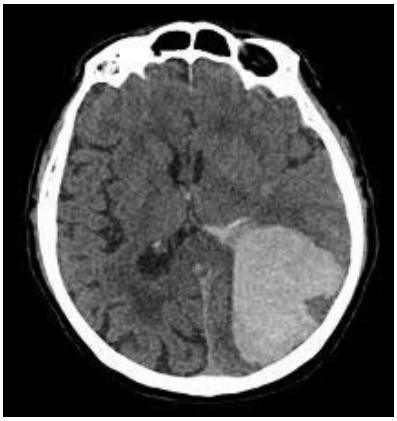

Figure 2: Left parietal-occipital lobar hematoma, suggestive of amyloid angiopathy in a hypertensive and / or aged patient. The cortical nature and its large volume is an indication for surgery.

From Day 3 a ring of hypodensity appears reflecting an increase in the peri-lesional edema. Secondary hemoglobin degradation will cause a change in the density of the hematoma: the hyperdensity will decrease from the periphery to the center as from D4-D5. From the 2nd to the 9th week the hyperdensity decreases and is replaced by an iso- and then a hypodensity. It then remains as a hypodense "scar".

b-MRI

The topography and morphology of the ICH on the MRI are of course superimposable to the CT description. The paramagnetic properties of the hemoglobin degradation products produces a complex MRI signal change with time, which we will briefly describe (Table 1):

	T1 Sequence	**T2 Sequence**
Acute : 8-72h	Isointense	Hypointense
Early Subacute (D3-D7)	Isointense with peripheral hypersignal	Hypointense
Late SubAcute (First Week-Month)	Hyperintense	Hyperintense peripheral hyposignal
Late (Month-Years)	Hypointense	Hypointense

Table 1 : Evolution of MRI signal of the hematoma with time according to MRI sequence used

- **In the Acute stage** (8 to 72H), the signal will be determined by the presence of intracellular deoxyhemoglobin: the hematoma will appear as isointense on T1 and hypointense on T2. This T2 hypointensity is even more pronounced on T2 gradient echo (T2 *), which makes it the reference sequence for the early MRI diagnosis.
- **In the Early Subacute Stage** (D3-D7, Figure 3a and b): the intracellular methemoglobin will cause a peripheral hyperintensity on T1 weighted images and hypointensity on T2 weighted images.

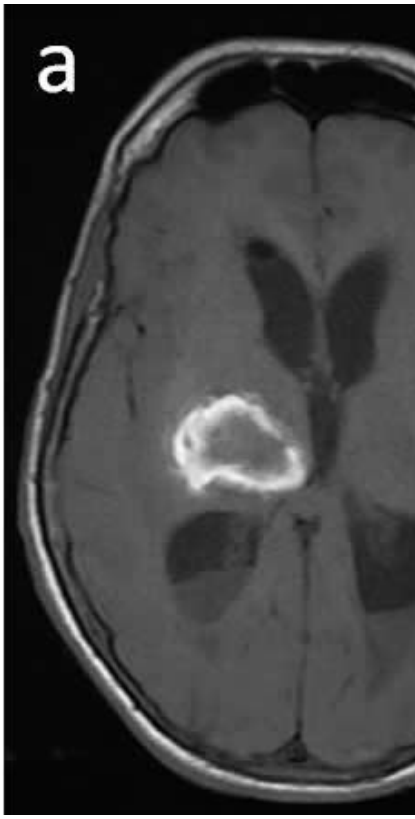

Figure 3: MRI axial cut of a right capsular and thalamic hematoma in the early subacute phase (D3-D7). On T1W1 -the hematoma appears as a central isointensity with a hyperintense rim (a).On T2W1, the hematoma appears hypointense (b).

- **In the Late Subacute Stage** (first week- month, Figure 4a and b), T1 hyperintensity and a central T2 hyperintensity with hypointense peripheral borders in relation to the presence of extracellular methemoglobin.

Figure 4: MRI axial cuts of a cortico-subcortical hematoma in the late subacute phase (weeks-months). T1W1-, hematoma begins to appear hyperintense T1 (a). In T2W1, the hematoma is hyperintense with a hypointense peripheral ring (b).

- **Late-stage** (month-year), hypointensity on both T1 and T2 related to hemosiderin deposits.

3/Diagnosis of secondary ICH (differential diagnosis)

a-Etiology of secondary ICH

Faced with ICH one should exclude a lesion underlying the hematoma such as: arterial aneurysm, arteriovenous malformation, dural fistula, cavernoma, venous angioma, cerebral venous thrombosis, brain tumor, cerebral vasculitis.

b-Techniques

MRA and CTA are sufficiently sensitive and specific to detect an underlying cause, and are therefore indicated as first-line examinations (31). In the event of a strong clinical index of suspicion or any doubt about the MRA or CTA findings, conventional angiography which is the gold standard should be performed (31). If there is a very strong index of suspicion, these tests may be repeated remotely.

c-Indications

When should a secondary cause for ICH be suspected and when should vascular imaging be done? The following criteria were considered discriminative to request for these complementary tests (IIa, B) (31.50):

- Context: Patient under 45 years with a negative history of hypertension.
- Clinically: neurological symptoms (headache, deficit ...) preceding the SICH.
- Radiologically: Associated subarachnoid hemorrhage.
- Lobar ICH: superficial, supratentorial.
- Isolated intraventricular hemorrhage.

Prognostic factors

The mortality rate at six months is between 23 and 58%, and almost half of survivors will live a dependent life (26,40,44). Prognostic factors of death in the short term are as follows (9.20):

- advanced age.
- an initial low GCS score.
- the volume of ICH, which can be determined by the formula ABC/2 (see section on score).
- an increase in the volume of the hematoma.
- an associated IVH of which the severity directly correlates to mortality. This can be evaluated using the Graeb's score (see section on score).

For example, a patient with a GCS less than 9 and an ICH volume greater than 60 ml has a one month mortality risk of 90%, whereas a patient with a GCS score of above 9 with a hematoma of less than 30 ml carries a one month mortality risk of 17% (4).

Scores

1 / Calculation of the hematoma volume (Figure 5)

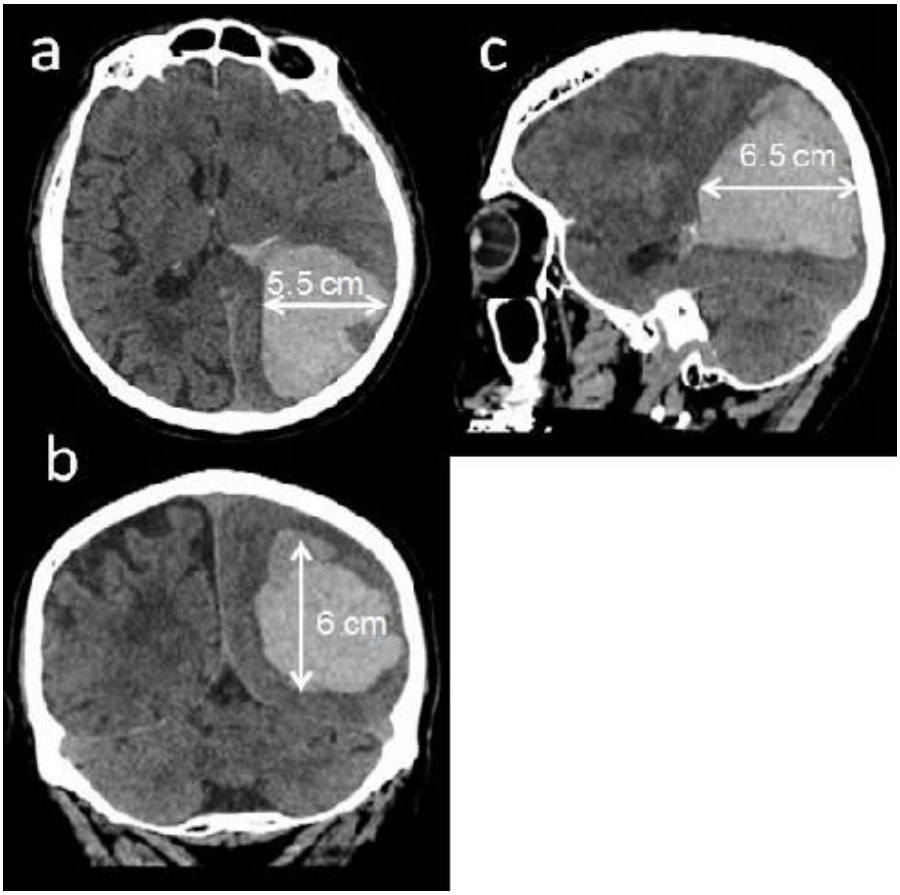

Figure 5a, b, c: Calculation of the volume of the hematoma according to the / 2 ABC rule, or A, B and C are the greatest diameters of the hematoma in the 3 planes. Here is A = 5.5 cm, B = C = 6 cm and 6.5 cm, so an estimated volume was 107.5 ml.

The volume of the hematoma can simply calculated using the following formula (4):

Where A, B and C are the largest diameter of the hematoma in centimeter in 3 the spatial planes.

2 / Graeb Score (Figure 6) (17)

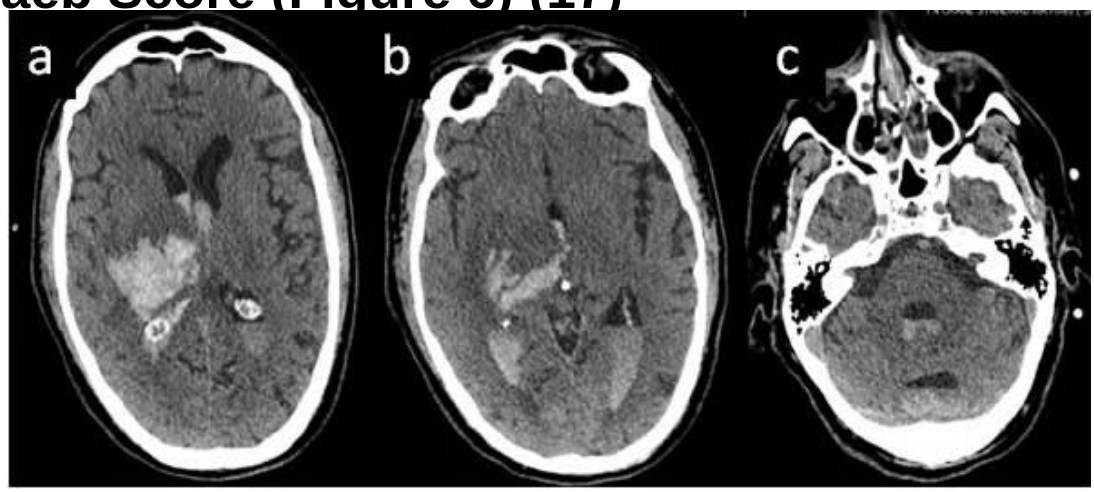

Figure 6 a, b and c: spontaneous capsule-thalamic hematoma with right ventricular extension. Graeb score = 8/12.

Is designed to evaluate the severity of the IVH. It is quoted on 12 and the components are:

A-Lateral ventricles (Right and Left lateral ventricles scored separately):
1 = trace of blood or moderate bleeding.
2 = less than half the ventricle filled with blood.
3 = more than half of the ventricle filled with blood.
4 = fully filled with blood and dilated ventricle.

B-Third and fourth ventricles (Third and Fourth ventricles scored separately):
1 = blood present, size normal
2 = filled with blood and expanded

Graeb score = right ventricular score + left ventricular score + 3th ventricular score + 4th ventricular score

3/ Mortality Prognostic Score (20)

The following score based on independent prognostic factors of death, enables us to determine the risk of mortality at 1 month after the initial episode. There is a linear relationship between the score and the risk of death.
At 0, the risk of death is zero. At 6, the risk is more than 80%.
Method of calculation:
a-GCS score:
3-4 =2 points
5-12 = 1 point
13-15 = 0 point
b- ICH Volume, cm3 :
e30 : 1 point
<30 : 0 point
c-Intraventricular Hemorrhage:
Yes: 1 point
No : 0 point
d- Infratentorial Origin of Hemorrhage:
Yes : 1 point
No : 0 point
e-Age, years:
e80 : 1 point
<80 : 0 point
Total Score: 0-6
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Treatment options

The principles of treatment described below are from the 2010 recommendations of the American Heart Association and American Stroke Association (31).

1 / Management.

In contrast to the current general attitude, the decision of therapeutic abstention and resuscitation should not be made until at least 48 hours of appropriate and intensive care. Given the absence of perfectly reliable predictive factors, any patient with SICH, even seemingly severe cases, should benefit from intensive care. However, this recommendation does not apply when the indication for non-resuscitative care is related to the patient's past history (such as untreatable neoplasia, major organ failure ...) or a patient in a state of apparent brain death. Reevaluation is then necessary after 48H and the decision whether to continue or discontinue care should be taken during a multidisciplinary meeting.

- The patient should be initially admitted in a neurovascular intensive care unit or even a neurointensive care with trained and competent personnel in the management of this pathology (I, B).

2 / Medical Treatment

a- A normal blood sugar should be maintained (insulinotherapy protocol) (I, C), and if possible hyperthermia should be avoided.

b-Antiepileptic treatment

Any symptomatic epileptic crisis should be treated and the treatment continued for several months (I, A). Prophylaxis is not indicated (III, B).

c- Blood Pressure Control

The current recommendations are:

- If the systolic blood pressure (SBP) is greater than 200 mmHg or Mean Arterial Pressure (MAP) is greater than 150 mmHg, intravenous antihypertensive therapy (eg nicardipine IV) should be given rapidly and BP (blood pressure) be monitored every 5 minutes.
- If the SBP e 180 mm Hg or MAP e 130mmHg and there is a strong likelihood of increased intracranial pressure, it is advisable to monitor the intracranial pressure (ICP) and control the BP with IV antihypertensive drugs in order to maintain a cerebral perfusion pressure (CPP) e 60 mmHg.
- If the SBP e 180 mmHg or MAP e 130mmHg without signs of intracranial hypertension, set up an IV antihypertensive treatment accompanied by clinical monitoring.
- In general, for patients with SBP between 150 and 220 mmHg, reducing it to around 140 mmHg, seems reasonable provided it is not deleterious on the CPP (IIa, B).

d-Any patient with a **deficiency in coagulation factors or thrombocytopenia should** have a rapid correction of the deficit (I, C). Specific cases:

- Patients on vitamin K antagonist (VKA): This is a frequent occurrence (12-14% of SICH (36)), imposing specific measures: stop oral anticoagulant, immediate correction of the vitamin K dependent deficient coagulation factor by PPSB[Prothrombin-Proconvertin-Stuart Factor-Antihemophilic Factor B] (Kascadil for example) associated with a parenteral injection of vitamin K (with delayed effect) (I, C). The objective is to obtain an INR of 1.
- Patients on antiplatelet agents: immediately stop the antiplatelet. The administration of platelets is not indicated, unless surgery is planned (IIb, B).

e-Prevention of thromboembolic complications:

- Stockings combined with intermittent pneumatic compression (I, B).
- Preventive anticoagulation: it must be considered between D1 and D4 in a bedridden patient, provided there is evidence of cessation of bleeding (on control images) (IIb, B).

3 / Neurosurgical Management

a-Intracranial Pressure (ICP) Monitoring

There is no data in the literature confirming the benefit of ICP monitoring in ICH in terms of functional outcome and mortality. The proposed indications are an extrapolation of the indications defined for head trauma. ICP Monitoring may be proposed in the following situations:

GCS d 8, signs of temporal herniation (mass effect), hydrocephalus or IVH on the CT Scan (IIb, C).

The choice of using a fiberoptic ICP device or an External Ventricular Drain (EVD) depends on the situation. An ICP monitoring device with less complications should be preferred except in cases of hydrocephalus or IVH where only the EVD allows for an effective ICP control.

The ICP must be controlled so as to obtain a CPP between 50 and 70 mmHg.

b-Intraventricular Hemorrhage(IVH)

Occurring in approximately 45% of the cases with SICH, it constitutes a major factor for the severity of the ICH and is a subject for intense research (19). The current standard of treatment of IVH is EVD to control hydrocephalus. However EVD does not enable a rapid drainage of the IVH, and does not seem to improve the functional outcome (33). It was therefore proposed to inject via the EVD catheter a fibrinolytic agent (tPA or urokinase) to lyse the clot and thus accelerate the resolution of IVH. A recent meta-analysis of observational studies showed that intraventricular fibrinolysis (IVF) markedly decreased mortality and improved functional outcome, without increasing complications (13). However, no good quality randomized clinical trial has been so far published, and IVF cannot be strongly recommended, but its use decided upon on a case-by-case basis (IIa, B).

c- Surgical Treatment.

In most cases of ICH, surgical evacuation is not indicated (IIb, C). There are however some special cases:

- Cerebellar ICH compressing the brainstem or causing obstructive hydrocephalus in a patient with neurologic deterioration. This indication is almost unquestionable (I, B) (Figure 7). EVD alone is not recommended.

- In case of supratentorial ICH, a recent meta-analysis on individual data suggests a benefit of surgery in the following situations (IIa, B) (18):
- Patients under age 69
- GCS between 8 and 12
- Hematoma volume between 20 and 50 ml
- No associated IVH
- Surgery performed within 8 hours of onset of symptoms
- ICH located less than a centimeter from the cortex (Figure 2).

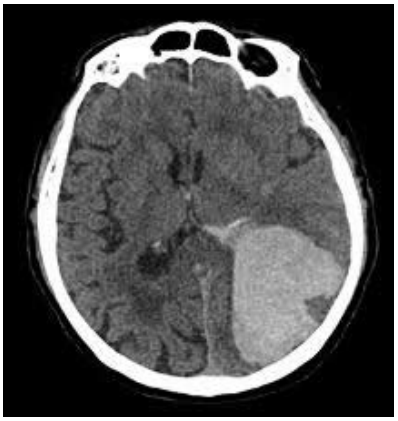

Figure 2: Left parietal-occipital lobar hematoma, suggestive of amyloid angiopathy in a hypertensive and / or aged patient. The cortical nature and its large volume is an indication for surgery.

The surgical procedure, which would not elaborated on here, must be performed under standard neurosurgical conditions, that is : by a conventional craniotomy. The authors recommend not to completely evacuate the hematoma (but at least 70%) in order to reduce the risk of rebleeding from the walls of the cavity. Currently, endoscopy or stereotactic techniques (associated or not with fibrinolytics) have not demonstrated their effectiveness and are under research (IIb, B).

4 / Long-Term Management

a-Rehabilitation

Any patient with an ICH should be appropriately rehabilitated as soon as possible in a specialized center (IIa, B).

b-Prevention of recurrence

The prevention of recurrences is based on:

- Treatment of arterial hypertension; the target blood pressure should be <140/90 mmHg (I, A). But it is likely that lowering of blood pressure is also beneficial in non-hypertensive subjects.
- Resumption of anticoagulants: it depends on their underlying indication and the topography of the ICH. In case of non-valvular atrial fibrillation at high risk of embolism, the resumption of VKAs may be considered if the ICH is deep (no argument for amyloid angiopathy) and if the predisposing factors for ICH (notably hypertension) are controlled (IIa, B).
- Avoiding excessive alcohol abuse seems also to decrease the risk of recurrence (IIa, B). ++++

Prognosis

The mortality rate at six months is between 23 and 58%, and almost half of the survivors will live a dependent life (26,40,44). Recurrence rates are between 2.1 and 3.7% per patient per year. The risk of recurrence is much higher when the site of the first hematoma is lobar (indicative of a probable underlying amyloid angiopathy) than when its topography is suggestive of a hypertensive hematoma (2.46).

Prospects

Therapeutic possibilities in the current management of ICH are unfortunately very limited. It is however reasonable to remain hopeful on the following domains:

- Prevention is essential and rests on a good control of hypertension -the main risk factor for ICH, and the proper use of antithrombotic drugs.
- Restricting an increase in the volume of the hematoma in the early hours, using hemostatic agents. Up to now, one trial has been conducted using recombinant Factor VIIa, which unfortunately failed to demonstrate any functional benefit (28). A new trial is underway selecting patients with documented active bleeding.
- Controlling the secondary effects of cytotoxic edema. Iron chelators, such as deferoxamine, are promising, as well as some anti-oxidant molecules. Their efficacy in humans remains to be determined.
- Given the toxicity of blood on the brain parenchyma, special attention is given to various techniques for the draining of the hematoma. Except for rare indications, open surgery has not proven beneficial. But it is reasonable to think that the development of minimally invasive techniques (stereotactic or endoscopy), associated with agents to lyse the clot (whose neurotoxicity remains to be determined) are of considerable hope in the treatment of ICH . ++++

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