Spontaneous intracerebral and intracerebellar hematomas

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Objective

This chapter aims to summarize the pathophysiology of spontaneous intracerebral and intracerebellar hematomas (SICH) while focusing on contemporary thought on inhibition of hematoma propagation and future directions of clinical research in the field.

ICH can be classified into primary and secondary forms. Primary ICH occurs in the absence of a pre-existing structural abnormality while secondary ICH is due to a congenital or acquired lesion. (The most common type of secondary ICH caused by a ruptured aneurysm or arteriovenous malformation is detailed in different presentations.)

Modern literature review - Recent clinical and research developments

Epidemiology. Spontaneous ICH is the most feared form of stroke with a mortality rate of 25-55%. Due to aging of the population more and more elderly people require oral anticoagulation (OAC) to prevent thromboembolic complications of atrial fibrillation, deep venous thrombosis (DVT), heart valve replacement etc.

Incidence of ICH ranges from 10-20/100 000 population/year; its occurrence is about ten fold more frequent in OAC-treated patients, up to 1,7%/treatment-year –although this incidence is strictly age-dependent and primarily refers to patients over 60.

ICH represents about 70% of all OAC-associated bleedings, subdural haematoma is the second most frequent (over 20%), while subarachnoid haemorrhage is rare –its incidence is practically unaffected by OAC.

ICH in patients on OAC is associated with a mortality rate of over 65% a finding well explained by more rapid haematoma-accumulation and enduring progression of its size in comparison with ICH occurring in patients without OAC (progression over 33% of the original ICH occurs in 56 vs. 26% respectively).

Pathophysiological considerations identify the same underlying conditions for all spontaneous ICH: risk factors include age, hypertension, previous stroke, cerebral amyloid angiopathy and concomitant use of antiplatelet drugs while OAC contributes to the development of ICH as an exacerbating agent. This theory is supported by the fact that small petechial or micro-bleedings can be found even in asymptomatic patients harboring the aforementioned risk factors and predilection areas are the same for OAC-ICH and ICH.

Since Charcot and Bouchard miliary aneurysms of small perforating arteries are held accountable for at least some of the ICH from the pathological point of view but arteritis-like structural changes as well as true microdissection of the vessels also play a substantial role.

Although it has been investigated less extensively, some studies indicate that antiplatelet drugs may also contribute to a higher frequency of ICH: regular dose aspirin was reported to increase mortality and contribute to poorer short term outcome in patents with ICH, while others proved antiplatelet therapy an independent predictor of 30D mortality. Nevertheless, most recent reports do not suggest that antiplatelet therapy could lead to hematoma growth or adverse outcome.

A special form of spontaneous ICH is associated with thrombolytic therapy: the ten times higher risk of ICH in these patients should be considered as a price we pay for the
significant better outcome observed in the majority of patients suffering from ischemic stroke.

**Symptoms and signs, diagnosis.** ICH is primarily localized -in decreasing frequency of accordance- in the putamen, subcortical white matter, cerebellum, thalamus and brainstem (pons). The most common symptoms and signs include: abrupt onset of headache (with or without vomiting) with hemiparesis, hemihypaesthesia, cerebellar and/or cranial nerve involvement that are ultimately associated with the location of ICH. Gradual deterioration is frequently noticed and explained with continued ICH-propagation. Coma is primarily associated with large ICH in the putamen or thalamus, and usually indicative of poor outcome. However, in the case of cerebellar ICH coma is not necessarily associated with irreversible deterioration. The **diagnosis** is made by plain CT (ICH becomes isodense in 2-3 weeks and resolves in 10-12 weeks).

**Therapeutic considerations.** Current treatment of ICH is primarily **conservative**: reversal of anticoagulation and maintenance of adequate cerebral perfusion is of crucial importance. The role for **surgery** is rather questionable: the International Surgical Trial in ICH (STICH) has proven that for patients in coma, surgery is probably harmful, and patients with supratentorial ICH show no benefit from early haematoma evacuation (within 24hrs of randomization), although a subgroup of patients with lobar bleedings may benefit from surgery – a theory now being evaluated in STICH-II. Nevertheless, surgery is well justified in cerebellar hematomas with a diameter over 3cm or when the lesion compresses the outlets of the 4th ventricle leading to hydrocephalus. The most important goal is a prompt **reversal of the OAC** that is provision of normal hemostasis in order to halt the progression of the haematoma and associated deterioration. To this end, as it is detailed in **Table 1** several tools could be used: **vitamin K** normalizes the INR values with a considerable delay thereby it can not be used in monotherapy in the acute setting; **fresh frozen plasma (FFP)** contains all F required although its vitamin-K dependent F level is unreliably variable and the occasionally large volume required may lead to circulatory overload and raised ICP. **Prothrombin complex concentrates (PCC)** provide all F in a small volume without a delay required for thawing but may induce thrombosis and disseminated intravascular coagulopathy. While a considerable hope was associated with the **FAST-trial** assessing the beneficial effects of **recombinant activated FVII**, it turned out that although the agent proved to inhibit the growth of ICH this effect has not been translated into better outcome. Further, activated FVII increased the risk of the occurrence of arterial thromboembolic complications. In light of above a **proposed protocol for immediate reversal of OAC** might include 10mg iv. Vitamin K and PCC with or without FFP to achieve physiological INR, followed by meticulous monitoring of haemostasis and repeated administration of Vitamin K particularly when a prolonged coumarin-effect is considered.
Table 1 Current tools in haemostasis

<table>
<thead>
<tr>
<th>Agent</th>
<th>Mechanism of action</th>
<th>Dose required</th>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin K</td>
<td>activates prothrombin, FVII,IX,X</td>
<td>5-20mg, iv. preferred over sc.</td>
<td>Cheep, delayed action, can be used for days</td>
<td>Delayed action: inadequate for acute reversal of OAC</td>
</tr>
<tr>
<td>PCC</td>
<td>Contains prothrombin, FVII,IX,X, protein C,S,Z in concentrated form</td>
<td>1 IU of F IX/kg body weight increases the level of plasma F IX by 1 IU/dL: 50-150ml</td>
<td>Prompt action, all factors in small volume, rapid reversal of OAC</td>
<td>Risk of thrombosis and DIC</td>
</tr>
<tr>
<td>FFP</td>
<td>All factors in non-concentrated form</td>
<td>1 mL of FFP/kg body weight increases the levels of coagulation factors by 1 to 2 IU/dL.</td>
<td>Contains all factors</td>
<td>Delay due to thawing, F-level is not reliable, circulatory overload</td>
</tr>
<tr>
<td>Activated FVII</td>
<td>Activated FVII</td>
<td>5 to 320 ug/kg</td>
<td>Prompt action, documented reduction in haematoma growth</td>
<td>No documented change in outcome Increased arterial thromboembolism</td>
</tr>
<tr>
<td>Surgery</td>
<td>Halt haematoma growth, provide surgical haemostasis</td>
<td>Within 2-24 hrs to reduce haematoma growth</td>
<td>Prompt reduction of ICP, prevention of haematoma growth</td>
<td>No benefit except a subset of patients</td>
</tr>
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</table>

Future questions and direction

Although theoretically inhibition of hematoma growth would be the gold standard in the treatment of SICH, unfortunately, so far none of the studies testing such approaches have found significant benefit in outcome. The future of safe prevention of ICH lays in the introduction of new therapeutic agents as well as close monitoring of OAC therapy. Patient education and feedback to family practitioners should also be emphasized. The role of surgical treatment will be clarified in the near future by reports on the STICH-II trial.

Conclusions - take home message

In sum, in the treatment of ICH the “commonsense” approach is suggested to both save life and resources, also considering that age over 60, GCS under 8, rapid hematoma growth with intraventricular expansion and pre-existing significant comorbidity are indicators of poor outcome.
Large cerebellar hematomas with or without hydrocephalus should require surgical treatment while some forms of superficial lobar bleedings may also benefit from surgery.

The aging population requires more frequent use of OAC thereby OAC-related ICH will represent a major challenge neurosurgeons will face in the forthcoming years. Therapeutic interventions should target prompt reversal of OAC-therapy in order to provide haemostasis and prevent haematoma-growth. This goal is currently best achieved by PCC with or without FFP and Vitamin K.

Further research should focus on the development of novel tools to monitor the whole haemostatic machinery and on the establishment of the role of surgical interventions in the treatment of ICH.

**Key references, recommended reading**


