Intracranial haemorrhage in children and adults with haemophilia A and B: a literature review of the last 20 years

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Abstract

Intracranial haemorrhage (ICH) is the most serious event in haemophiliacs, resulting in high rates of mortality and disability. Although the use of a prophylaxis regimen has improved outcomes, the mortality caused by ICH is still around 20%. ICH is more frequent at two different ages: in childhood (mostly in children aged ≤2 years) and in adulthood (with known risk factors such as hypertension and age ≥60 years). Our review shows how ICH remains one of the worst problems of patients with haemophilia. Greater attention to risk factors and early symptoms, together with an appropriate early prophylaxis, may reduce the risk of severe intracranial haemorrhagic events.

Keywords: haemophilia, intracranial haemorrhage in haemophilia patients, risk factors for intracranial haemorrhage, intracranial haemorrhage management.

Introduction

Haemophilia A and B are rare X-linked recessive bleeding diseases caused by a deficiency of blood factors VIII (FVIII) for haemophilia A and IX (FIX) for haemophilia B. They only affect males; females are carriers. Depending on the FVIII or FIX concentration, these coagulation disorders are divided into: severe, when levels in the plasma are less than 1%; moderate, when levels are 1-4%; or mild, when levels are 5-40%[1,2].

Spontaneous bleeding into muscles and joints are the typical symptoms of haemophilia, but it is intracranial haemorrhage (ICH) which is the most serious event that can occur in haemophiliacs, resulting in high rates of mortality and disability[3,4]. Mortality caused by ICH is still around 20%[5], and is higher in younger children and in developing countries[6]. Incidence of ICH in haemophiliac neonates is 40-80 times higher than in neonates without congenital bleeding disorders; nearly half of these episodes occur in the first days of life, in most of the cases related to traumatic delivery. Clinical signs of ICH in newborns are difficult to assess and treatment is consequently delayed and associated with increased disability and mortality[4,7]. In adult patients without haemophilia, the major risk factor for ICH is hypertension but, unlike in the past, when people with haemophilia were considered at low risk of cardiovascular events, recent studies have shown that hypertension is the first risk factor for ICH in these patients as well, and cardiovascular diseases are commonly present[4,8,9]. The international registries performed in different developed countries have shown that in males the incidence of ICH is estimated to be between 13.9-38.6/100,000 subjects[10,11], from 10 to 20 times greater in patients with haemophilia, for whom the reported incidence is between 290-540/100,000[5,10].

Intracranial haemorrhage is usually considered to be more frequent at two different ages: in childhood (mostly in children aged ≤2 years) and in adulthood (with known risk factors such as hypertension and age ≥60 years). Over the years, the real frequency of ICH in haemophiliac neonates has been a subject of discussion among clinicians. Two reviews published in the late 1960s and 1970s reported only a few cases of ICH in newborns: 1 out of 192 in the study of Baehner *et al.*[12] and 3 out of 2,500 in the work by Eyser *et al.*[13] Data were not supported by subsequent studies. In fact, Ljung *et al.*[14] reported 7 cases of ICH in 140 children with haemophilia A and B, 5 of whom were neonates, while a review of the literature performed by Kulkarni *et al.*[15] in 1999 showed that 102 neonates with haemophilia had a total of 109 cranial bleeds, among which 71 were ICH events often associated with late neurological deficits.

The aim of our work here is to review all reports on cerebral bleeding in haemophilia A and B patients published from January 1998 to June 2018, with special reference to risk factors, management, and outcomes of intracranial haemorrhages.

Materials and methods

A MEDLINE search using the key terms "cerebral bleeding", "intracranial haemorrhage", "head bleeding", AND "haemophilia" OR "coagulation defects", "coagulation disorders", revealed a total of 517 reports published between January 1948 and June 2018; 236 of these were excluded because they dated from before 1998. Among the remaining 281 studies, 62 describe intracranial haemorrhage in haemophiliacs A and B, 29 are case reports which were excluded from our review, while the remaining 33 articles (24 of which involve only paediatric patients) comprise reviews, surveys/registries alongside clinical trials, and these were considered in our analysis.

A total of 219 articles published in the last 20 years have been excluded from our review for the following reasons: 1) the reported data on ICH occurred in patients suffering from different coagulation defects from haemophilia; 2) ICH episodes were related to acquired diseases or to anticoagulation; 3) articles only focused on the effectiveness and safety of the haemostatic treatments used in haemorrhage cases, without any characterisation of ICH; 4) articles were not written in English. Case reports were not taken into account due to the difficulty in standardising the data obtained.

The review examined the remaining 62 reports published from January 1998 to June 2018. Two groups of relevant studies on intracranial haemorrhage in haemophilia patients were subsequently assessed: 1) ICH in paediatric patients; 2) ICH in adult patients. In the latter, the studies considered sometimes included some paediatric patients, but it was not always possible to evaluate them separately.

Results

Thirty-three studies from over the last twenty years (from January 1998 to June 2018) were eligible for our literature review. These studies reported epidemiology, management, and/or outcomes of intracranial bleeding in adult and paediatric patients with haemophilia A and B.

Intracranial haemorrhage in paediatric patients

Intracranial haemorrhage in newborns and children with haemophilia is one of the most serious adverse events that may occur in this population. The causes of ICH in newborns are often associated with delivery. In a recent study published by Kulkarni *et al.*[16], ICH related to delivery represented 30% of all 46 cerebral bleeds, second only to spontaneous events. So far, comparisons among the different modes of delivery have not provided a definitive answer to the question as to which represents a lower risk of ICH for haemophiliac children. Nazir *et al.*[17] enrolled 163 children with haemophilia A, and only 5 of them experienced at least one episode of ICH, equally divided among babies born by vaginal delivery, by instrumental delivery, or by caesarean section. Conversely, in their systematic review and meta-analysis, Davies and Kadir[18] showed that caesarean section is associated with a reduced risk of ICH if compared with a spontaneous vaginal delivery (odds ratio [OR]: 0.34; 95% confidence interval [CI]: 0.14-0.83), while the highest risk is due to assisted vaginal delivery (forceps or vacuum), which increases the risk of ICH in haemophiliac newborns over 4-fold (OR: 4.39; 95% CI: 1.46-13.7) compared with a spontaneous vaginal delivery. These results should be discussed with pregnant women who are haemophilia carriers in order to plan an appropriate delivery. Witmer[19] evaluated 3,133 males with haemophilia hospitalised in 43 tertiary paediatric care hospitals in the United States, 236 of whom experienced one or more ICH events (total number of events=271). Over 50% of the patients experienced an ICH occurrence under two years of age; the estimated mortality rate of 2.5% was similar to that in the general paediatric population presenting ICH. This result was probably due to both the early start of prophylaxis in children with severe haemophilia and the standard of care adopted when ICH was suspected. Even if mortality was reduced, the risk of relapses or severe sequelae remained unchanged in the patients who had a first haemorrhagic event. In a multicentre study performed by Andersson *et al.*[20] on a total of 1,515 children and adolescents with haemophilia A or B, 92.3% of whom were aged 17 years or under, 60 ICH cases were reported overall. Among these, only 5 ICH events occurred in patients treated with full or partial prophylaxis; the remaining episodes were recorded in either patients on no prophylaxis or in those who had not yet been diagnosed with a bleeding disorder. Twenty-nine ICH cases (48.4%) were diagnosed in patients aged 5 years or under with known haemophilia in whom trauma was the first cause of ICH. The mortality rate was almost 3-fold higher than that reported by Witmer[19]. This study confirmed the important role of early prophylaxis in preventing bleeding. Conversely, as previously reported in a Turkish study published by Patiroglu *et al.*[21] in 2011, the causes of ICH diagnosed in 18 children with coagulation disorders were either traumatic (57.9%) or spontaneous (42.1%), but no deaths were recorded; 22.2% subsequently showed motor deficit and a decrease in intellectual functions. Among these, 7 patients suffered from haemophilia A or B; each child had one haemorrhagic event, but no single data on the causes or sequelae were reported. Bladen *et al.*[22] considered 283 children with severe haemophilia A and B, 26 of whom developed an ICH. The mortality rate (15.4%) and neurological impairment (23.1%) were very high when compared to other similar studies. Due to these results, the authors stated that children with haemophilia and ICH should receive continued follow up for at least ten years / to the age of ten years in order to identify any educational or physical rehabilitation needs. A more recent British study performed by Chalmers *et al.*[23] from 2003 to 2015 on a cohort of young patients aged 16 years or under with inherited bleeding disorders also reached the same conclusions as those discussed above. The occurrence of ICH is often spontaneous, being higher in children aged 2 years or under and in those without prophylaxis. In a previous review, Nagel *et al.*[24] tried to define an algorithm for the management of children (aged 3-18 years) with haemophilia and suspected ICH, based on disease grade (mild, moderate,

severe) and the presence or absence of trauma, in order to reduce whenever possible the unnecessary exposure to radiation associated with a computed tomography scan, and to optimise early treatment. A European observational cohort study performed on twelve Haemophilia Centres by Richards *et al.*[25] to define the rate of and the risk factors for neonatal bleeding included a total of 508 young patients. ICH episodes occurred in 18 babies within their first twenty-eight days of life and were associated with long-term neurological defects in 0.4% of cases. As reported by Davies and Kadir[18], assisted vaginal delivery (forceps or vacuum) proved to be the risk factor for neonatal cerebral bleeding in this study as well, while the maternal awareness of being a haemophilia carrier along with mild haemophilia seemed to be protective in reducing haemorrhagic risk. A few years before the study by Chalmers *et al.*[23], Witmer *et al.*[26] had described the important role of prophylaxis. In their case-control study[26], performed on 10,262 patients with haemophilia aged 2 years or over, 199 patients experienced ICH. Prophylaxis was shown to be associated with a significant reduction in the risk of cerebral bleeding events in subjects without viral infections (OR: 0.52; 95% CI: 0.34-0.81) or inhibitors (OR: 0.50; 95% CI: 0.32-0.77). An Italian study published by Zanon *et al.*[4] also showed that the highest rate of ICH was observed among babies (24.4 per 1,000; 95% CI: 12.7-47.0, in patients ≤1 year of age and 14.9, 95% CI: 7.1-31.4, in the second year of life); 4 bleeds were due to traumatic delivery. Witmer *et al.*[26] tried to put forward suggestions about ICH management based on their observations. However, unlike Nagel *et al.*[24], the comparison was made between patients with or without inhibitors. Vaginal delivery and early start of prophylaxis after the first bleeding episode were suggested to prevent ICH during childbirth and the first two years of life.

Severity of haemophilia is the most important risk factor for ICH in children. Andersson *et al.*[20] only reported cases of severe haemophilia and emphasised the role of prophylaxis in reducing the risk of ICH. Data were confirmed by Bladen *et al.*[22], whose study, performed on 1,111 patients with inherited bleeding diseases, showed that all the ICH episodes involving haemophilia children occurred in patients with severe disease. Chalmers *et al.*[23] described 54 ICH events in patients with haemophilia A and B, 94.4% of whom presented a severe coagulation disease. In two other studies[16,21], intracranial bleeding occurred in patients with severe haemophilia in 71.4-76% of cases; the majority of them were spontaneous haemorrhages, while in the remaining children with non-severe disease the cause of ICH was often due to trauma.

The acute management of ICH events has only been discussed in a few reports[21,23], while more importance has been given to the cause of bleeding and long-term sequelae. However, all the authors described the use of coagulation factor concentrates for approximately 15 days, often without specifying what dosage of FVIII was administered per day, whilst neurosurgery was used solely in the most severe cases to evacuate the haematoma. Patiroglu *et al.*[21] reported 7 ICH episodes in haemophilia patients, and suggested a conservative replacement with coagulation factor concentrates; 80-100% correction for three days followed by 50-60% correction for another eleven days, if possible.

The characteristics of the 24 studies including clinical trials, reviews and registries/surveys performed on paediatric patients with haemophilia A or B are summarised in Table I[15-25,27-39].

Intracranial haemorrhage in adult patients

Nuss *et al.*[40] reported 88 ICH episodes in a cohort of over 3,000 patients with haemophilia A and B. In 22% of the cases, these haemorrhagic events were due to trauma, while in the remaining patients the only factors associated with ICH were the severity of haemophilia, the presence of inhibitors, and older age. HIV infection proved to be related to ICH only in Caucasians. No data are available on either the concomitant use of drugs that can interfere with normal haemostasis or comorbid conditions, such as thrombocytopenia or hypertension, often related to intracranial bleeding, especially in the case of mild haemophiliac patients as reported in other studies. The recent INSIGHT Study[41] recorded the mortality rate due to ICH in a population of 2,709 patients with non-severe haemophilia A; 12% of reported deaths were caused by intracranial bleeding. The patients involved were relatively young and had no clear comorbidities associated with an increased risk of haemorrhage. This information differs from that reported in the study by Zanon *et al.*[4] where, in an Italian population of 88 patients with a total of 112 ICH events, the related risk factors for ICH in adults were: age over fifty years, the severity of haemophilia, the presence of inhibitors and hepatitis C virus (HCV) infection, and on-demand treatment, alongside hypertension in the case of mild haemophiliacs.

In the Zanon *et al.* study[4], the mortality rate related to intracranial bleeding was high, especially in the patients with inhibitors (50%), while 22.7% of the patients who survived had disabling sequelae. A large study performed by Witmar *et al.*[26] focused its attention on the haemostatic treatment given at the moment of the ICH. Among the over 10,000 enrolled patients, the prophylactic therapy with coagulation factor concentrates was more frequent in the younger patients with severe haemophilia, while the adults were often treated only on demand. A significant statistical

Table I - Characteristics of twenty-four studies on only paediatric patients (clinical trials, reviews and registries/surveys).

Ref. (n)	Authors	Year	Type of haemophilia	Patients (*n)	Age of patients	ICH (n)
23	Chalmers *et al.*	2018	A/B	54	≤2yrs	54
20	Andersson *et al.*	2017	A/B	1,515	≤22yrs	60
16	Kulkarni *et al.*	2017	A/B	547	≤2yrs	46
22	Bladen *et al.*	2016	A/B	283	0-16+ yrs	26
17	Nazir *et al.*	2016	A	163	2 wks-18 yrs	5
18	Davies *et al.*	2016	A/B	3,018	0-30 days	79
27	Liu *et al.*	2015	A	70 (total)	1-18 yrs	1
19	Witmer	2015	A/B	3,133	<21 yrs	271
28	Moorehead *et al.*	2013	A	58	0-30 days	9
29	Morales *et al.*	2013	A	10	NA	10
24	Nagel *et al.*	2013	A/B	NA	3-18 yrs	
25	Richards *et al.*	2012	A/B	508	NA	4
21	Patiroglu *et al.*	2011	A/B	7	3 wks -13 yrs	7
30	Kenet *et al.*	2010	A/B	864	0-2 yrs	49
31	Kulkarni *et al.*	2009	A/B	580	0-2 yrs	
32	Bladen *et al.*	2009	A	6	4-12 yrs	6
33	Mishra *et al.*	2008	A/B	38	0-22 yrs	
34	Smith *et al.*	2008	A/B	20	0-7 days	3
35	Traivaree *et al.*	2007	A/B	43	0-17 yrs	11
36	Tarantino *et al.*	2007	A/B	580	NA	17
37	Revel-Vilk *et al.*	2004	A/B	172	0-3 yrs	18
38	Kulkarni *et al.*	1999	A/B	NA	NA	
39	Nelson *et al.*	1999	A/B	NA	NA	
15	Kulkarni *et al.*	1999	A/B	102	0-1 month	109
	Total			**11,669**§		**676**§

ICH: Intracranial haemorrhage; NA: not available; wks: weeks; yrs: years. *Only patients with haemophilia A or B. §Cumulative number, including the reviews; cases may be repeated among different reports.

difference between the intracranial bleeding rates occurred in these different groups of patients showed the importance of appropriate prophylaxis in preventing haemorrhages. Therefore, another significant risk factor for ICH was a previous haemorrhagic episode; in some cases, the recurrence occurred in those patients who had refused a subsequent prophylactic treatment after the first event. In their single centre experience, Cho *et al.*[42] reported 6 ICH events occurred in five adult patients. Among the risk factors, also described in other reports, HCV/human immunodeficiency virus (HIV) infection was present in 80% of subjects, and hypertension in 40%; all the patients suffered from severe haemophilia. A limitation of this study is the very small number of cases.

The severity of disease is universally considered one of the most important risk factors for ICH, but while severe haemophilia is reported in the majority of children, exceeding 90% in babies under two years of age[23], in adult patients, this percentage decreases to between 50-74.4%[4,5,26].

Loomans *et al.*[41] only described 17 ICH events occurring in non-severe patients whose mean age was 38 years; 76.5% of these cases were spontaneous and, besides the known coagulation defect, there were no other clear risk factors for bleeding. Zanon *et al.*[4] and Witmar *et al.*[5] separately reported approximately 25% of total ICH occurrences in patients with mild or moderate grade events in whom cerebral bleeding had been related to age, viral infections, presence of inhibitors, and uncontrolled hypertension.

Only a few studies have described the management of ICH. In his review, Ljung[3] highlights the need to treat patients with FVIII or FIX concentrates for at least two weeks, without further specification, and he also reports on few cases of patients treated with antifibrinolytics to reduce bleeding. In the Italian Study[4], 45.5% of patients underwent neurosurgery to evacuate the haematoma; such data have not been provided in the other published reports. Plasmaderived or recombinant coagulation

Table II - Characteristics of nine studies on patients (clinical trials, reviews and registries/surveys).

Ref (n)	Authors	Year	Type of haemophilia	Patients (*n)	Age of patients	ICH (n)
41	Loomans *et al.*	2017	A	2,709	0-80+ yrs	17 (all fatal)
42	Cho *et al.*	2016	A	10	NA	12
4	Zanon *et al.*	2012	A/B	88	0-70+ yrs	112
26	Witmer *et al.*	2011	A/B	10,262	2-41+ yrs	199
3	Ljung	2008	A/B	10,976	0-50+ yrs	503
43	Ghosh *et al.*	2005	A/B	600	NA	43
5	Stieltjes *et al.*	2005	A/B	4,000	0-50+ yrs	123
44	Antunes *et al.*	2003	A/B	401	0-49 yrs	45
40	Nuss *et al.*	2001	A/B	3,269	0-50+ yrs	88
	Total			**29,046**§		**1,054**§

ICH: Intracranial haemorrhage; Yrs: years; NA: not available. *Only patients with haemophilia A or B. §Cumulative number, including the reviews; cases may be repeated among different reports.

factor concentrates were used for 1-4 weeks in patients without inhibitors, while those who presented allo-antibodies were treated with recombinant activated FVII (rFVIIa) for 1-21 days. Plasmatic porcine anti-haemophilic factor was used only in one case to treat a first episode of intracranial bleeding in a patient who would subsequently have a further episode which was managed with rFVIIa.

In their report evaluating 43 ICH episodes in 37 haemophiliac patients from developing countries, Ghosh *et al.*[43] suggest a conservative replacement treatment with coagulation factor concentrates: 100% correction, for three days followed by 50-60% correction for another seven days, combined with antifibrinolytics for at least thirty days.

The characteristics of the 9 studies, including clinical trials, reviews and registries/surveys, which considered adult patients are summarised in Table II[3-5,26,40-44].

Discussion

This review shows that the risk factors for ICH in haemophilia patients have not changed over the last twenty years. In the paediatric population, ICH episodes are more frequently observed in children aged 2 years or under with severe haemophilia who are still not on prophylaxis. The protective role of early treatment with coagulation factor concentrate has been recently reported by Andersson *et al.*[20] and confirms the recommendations from international guidelines on haemophilia management. When to start a prophylaxis regimen in children is still a subject of debate, especially due to the problems in infusing the youngest patients. In some hospitals, a central venous catheter is usually considered to bypass this problem. In addition to the absence of prophylaxis, another important risk factor for ICH in the paediatric population is the mode of delivery. No significant differences between caesarean or spontaneous delivery have been reported, but the use of assisted modes of delivery such as forceps or vacuum increases the number and severity of haemorrhages. In cases of known foetal haemophilia, delivery should take place in the presence of a haemophilia expert to guarantee the best management of the newborn.

Similarly, in adults with haemophilia, the risk factors for ICH are the severity of disease and the absence of prophylaxis, although these are not the only causes of bleeding. The presence of inhibitors against FVIII/FIX or of infection diseases such as HIV and HCV have often been described in patients with ICH. Arterial hypertension has been shown to be involved in cerebral bleeding, especially in mild haemophiliacs.

Based on these results, we can put forward some simple and feasible suggestions for avoiding or managing an ICH.

- *Women haemophilia carriers*: in case of pregnancy, we suggest early genetic counselling and a prenatal test to evaluate the status of the foetus. If the child is an affected male, pregnancy and delivery should be managed under the supervision of an expert in coagulation disease.
- *Delivery:* the choice between spontaneous or caesarean delivery should be taken jointly by the different specialists involved (gynaecologist, obstetrician, haemophilia expert, anaesthetist, etc.) after assessing the status of the mother, the foetus, and the type of medical institution in which the birth is expected to take place. Assisted modes of delivery such as forceps and vacuum should be avoided due to the high risk of causing intracranial bleeding in children with haemophilia.
- *Children with known haemophilia*: in case of newborns with moderate or severe haemophilia, prophylaxis should be started as soon as possible to reduce the risk of ICH, which is very high in children aged 2 years or under.

- *Children with previously unknown haemophilia:* in cases of children with previously unknown haemophilia, who have been diagnosed after an ICH, we suggest giving immediate prophylaxis treatment to prevent further bleeding episodes, which are more frequent during the first two years of life.
- *Adult patients with haemophilia without inhibitors:* in adults with haemophilia without inhibitors, life-long prophylactic treatment should always be considered after an episode of ICH. We suggest careful evaluation and monitoring of risk factors such as hypertension, especially in mild haemophiliacs treated only on demand[45,46]. Close and constant monitoring should be performed in patients with HCV and/or HIV infections, and a secondary prophylaxis should be considered when necessary.
- *Adult patients with haemophilia with inhibitors:* in haemophiliac adults with inhibitors, we suggest treatment with by-passing agents (rFVIIa, activated prothrombin complex concentrate [aPCC]) at the early onset of symptoms; these should be continued at full dose or substituted for emicizumab after an ICH episode[47-49].

Conclusions

Our review shows how ICH remains one of the worst problems of patients with haemophilia. Greater attention to risk factors and early symptoms, together with the most appropriate prophylaxis, may reduce the risk of severe intracranial haemorrhagic events.

Acknowledgements

All of the Authors meet the International Committee of Medical Journal Editors criteria for authorship for this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval of the version to be published.

The Authors declare no conflicts of interest.

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Arrived: 18 December 2018 - Revision accepted: 22 January 2019
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