Abstract

Background: Intracerebral Hemorrhage (ICH) is one of the most feared complications after brain tumor surgery. Postoperative hemorrhage has been described in presence of a reduction of Factor XIII (FXIII) with normal routine coagulation tests in different fields. The primary objective was to evaluate the influence of perioperative FXIII levels on ICH after brain surgery.

Methods: A prospective, observational, 18-month study was conducted at a third-level hospital in Spain. It included all consecutive adults (18 years of age or older) operated on elective brain tumor surgery with postoperative stay in the Neurointensive Care Unit (N-ICU). Informed consent from all participants and ethical approval were obtained. Younger than 18 years of age, informed refusal, death in the OR, incomplete blood sample or non-tumoral tissue were exclusion criteria.
Results: The study included 109 patients.ICH was finally confirmed in 39 of them (35.78%). Inferential analysis determined statistical association between length of stay in ICU (p<0.01) and male group (p<0.03) with ICH. The average of FXIII was lower in patients who suffered from ICH, specially in B sample (A 71.2%, B 51.57%, C 52.14%). Statistical analysis determined FXIII deficiency (FXIIIID) (<70%) after brain tumor surgery increased ICH (A p<0.073, B and C p<0.01). FXIII baseline variation was also associated to ICH (FXIII A-B and A-C p<0.01, FXIII B-C 0.282). However, standard coagulation was not associated with either ICH or FXIIIID.

Conclusion: Acquired FXIIIID (<70%) after brain tumor surgery increased ICH, so it could be considered a risk marker of hemorrhage. ICH was also associated with baseline variation, male gender and prolonged stay in ICU. Normal standard coagulation tests did not exclude FXIII disorder. Detect on time FXIIIID and replacement treatment could become a therapeutic target in future studies.

Three blood samples evaluated FXIII levels (A-presurgical, B-postsurgical and C-24 hours after surgery). ICH, as a primary outcome variable, was defined as bleeding that generates radiological signs of intracranial hypertension either by volume or by mass effect on the routine CT scan 24 hours after surgery. The influence of tumoral data and standard coagulation were also analyzed. Chi-square (χ²) and Fisher’s exact tests, Mann-Whitney U and T-Tests and multiple regression were used for inferential analysis.

Abbreviations

aTTPA: activated Thromboplastin Time; CT: Computerized Tomography; D: Deficiency; Fb: Fibrinogen; FXIII: Factor XIII; G6PDD: Glucose-6-Phosphate Dehydrogenase Deficiency; Hb: Hemoglobin; HBP: High Blood Pressure; ICH: Intracerebral Hemorrhage; INR: International Normalized Ratio; MSUH: Miguel Servet University Hospital; MR: Magnetic Resonance; N-ICU: Neurointensive Care Unit; SD: Standard Deviation; OR: Operation Room; PA: Prothrombin Activity

Background

Cancer incidence is increasing globally, being a leading cause of death worldwide [1-3]. Though brain tumors are uncommon, they cause morbidity and mortality disproportionate to their incidence [4]. Despite individualized management and optimal surgical measures, removal of a brain tumor carries a higher risk of Intracerebral Hemorrhage (ICH)[5,6]. Sometimes unexplained, it is likely the most feared complication leading to poor functional prognosis, even risk of death [7-9].

Functional integrity of hemostatic system and normal standard coagulation tests, are both required for safe neurosurgical procedures.

Congenital FXIII deficiency (FXIIIID), not detected in those routine clotting tests, is associated with moderate to severe bleeding complications. Fibrin clot strength depends mainly on FXIII, a tetrameric pro–transglaminase enzyme, consisting of A and B chains, which once activated by thrombin cross-links fibrin monomers and enhances clot resistance against fibrinolysis. Congenital deficiency, a rare autosomal recessive disorder carries a higher incidence of severe bleeding, in particular ICH (20–30%)[10,11].

Moreover, other hemostatic disorders could also be developed during cancer surgery (by consumption due to bleeding)[12-14]. Acquired FXIIIID is much more common, but probably underdiagnosed because patients rarely bleed spontaneously. It usually occurs under surgical aggression and stress conditions, sometimes in presence of inhibitory autoantibodies against FXIII subunits [15-17]. Normal range of FXIII is over 70–140%.

Over the last years, several studies have measured FXIII activity after surgical bleeding [16–22]. Gerlach R. et al.[10,15] demonstrated ICH after intracranial surgery but, unfortunately, there are no data in patients with brain tumor. FXIII concentrate (plasma–derived factor concentrate) and recombinant FXIII–A would be the two most safety and current forms of replacement in congenital disorder, without consistent evidence in acquired one [16–24].

Considering increasing incidence of cancer and poor functional prognosis after ICH, the objective of this prospective study is to describe the incidence of FXIIIID and evaluate the influence of perioperative FXIII levels on ICH after brain tumor surgery.

Material and methods

A prospective, observational, 18-month study (July 2013–December 2014) was conducted in the Neurointensive Care Unit (N–ICU) at Miguel Servet University Hospital (MSUH), a single third–level center in the north of Spain. The study included all consecutive adults (18 years of age and older) operated on elective brain tumor surgery in the neurosurgical operating room (OR) at MSUH by four trained and experienced neurosurgeons with immediate postoperative stay in the N–ICU. Written informed consent was obtained from all participants. Younger than 18 years of age, informed refusal, dead people in the OR, incomplete coagulation test or non–tumoral tissue were exclusion criteria.

Three blood samples were drawn from a jugular central venous catheter placed prior to surgery (A-presurgery or baseline, B–postsurgery and C–24 hours after surgery).

After plasma freezing at ~20°C, photometric assay was the method to measure FXIII. It is based on ammonia release in the first step of transglaminase reaction of FXIII. The kit available was Berichrom® FXIII (Dade Behring, Marburg, Germany). A plasma–blank sample would be used to avoid overestimated FXIII in severely deficient activity [25]. FXIII normal range was considered 70–140%. The automated hemostasis analyzer was BCS® XP System. Competence and quality management of medical laboratory was accredited by ISO 15189: 2012 certification.

ICH, as a primary outcome variable, was defined as bleeding that generates radiological signs of intracranial hypertension either by volume or by mass effect on the routine head Computerized Tomography (CT) scan 24 hours after surgery, assessed by the same radiologist.

Filiation (age, gender), medical history (High Blood
Perioperative management of antiplatelet and anticoagulant agents was considered.

To determine association between qualitative variables Pearson Chi–square test ($\chi^2$) or Fisher’s exact test were used. Mann–Whitney U-test and T-Test were considered to establish differences and correlation between quantitative variables and multiple regression between the dependent variable and the independent variables. P-value <0.05 was considered significant for confidence interval of 95%.

Data collection worksheets were stored and analyzed by SPSS® Statistic Software 21.0.0. Each participant was assigned a registration number to to data anonymization.

Informed consent was required and Ethical approval was obtained from Ethics Committee of Clinical Investigation in Aragon (CEICA, nº CP14/2013).

Results

A total of 120 patients were operated on neurosurgery during 18 months, but 11 of them were excluded (9 for incomplete blood sample and 2 for non-tumoral tissue). Finally, 109 patients were included, 69 males (63.30%) and 40 females (36.70%), with a mean age of 54.60 ± 14.75 years. Group aged 50–69 years was the most prevalent (55.04%) versus ≤50y.o (21.10%) and metastases tumor (10.09%). There were different histological types of brain tumor, being high-grade glioma the most prevalent (39.44%) followed by meningioma (27.52%). The least common was mesenchymal one (4.58%). The average of volume tumor, calculated in preoperative magnetic resonance (MR), was 30,78ml ± 34,37, the largest one was 201,66ml and the smallest one 5ml. Subtotal removal (≥90%) was possible in more than 85%. During the stay in ICU, neurological focality (24,77%) and sepsis (10,09%) were the most prevalent complications after ICH. All patients were operated with normal hemogram and standard coagulation values and only one patient suffered from inherited hemostatis disorder: Glucose–6-Phosphate–Dehydrogenase Deficiency (G6PD). Blood transfusion was required in 14 patients (8 of them as prophilaxis) and 5 patients needed hemostatic agents (3 with concomitant blood transfusion).

All patients were discharged from the ICU, except two of them with a severe FXIIIID who died in ICU as a result of massive ICH (Table 1).

ICH was finally confirmed in 39 patients (35.78%). The average of FXIII was lower in patients who suffered from ICH, specially in postsurgery samples (sample A: 77,52% without ICH versus 71,2% with ICH, sample B: 70,14% vs 51,57%, sample C: 69,68% vs 52,14%). Maximum value of FXIII (it coincides in patients with ICH) was 30ml 25 23 0,06. Minimum value of FXIII (it coincides in patients with ICH) was A:155,70%, B:126,50% and C:131% and minimum (it coincides in patients with ICH) was A:69,68% vs 52,14%, sample C: 69,68% vs 52,14%).

Table 1: Clinical and tumoral data and ICH.

<table>
<thead>
<tr>
<th>Age ≤50y.o</th>
<th>&gt;50y.o</th>
<th>Gender Male</th>
<th>Female</th>
<th>Hypertension HBP</th>
<th>No HBP</th>
<th>Tobacco Yes</th>
<th>No</th>
<th>Preoperative complications Seizures</th>
<th>Hydrocephalus</th>
<th>Headache</th>
<th>Ischemia</th>
<th>Neurologic Deficit</th>
<th>Sepsis</th>
<th>P value Fisher</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>22</td>
<td>30</td>
<td>31</td>
<td>6</td>
<td>13</td>
<td>4</td>
<td>11</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6</td>
<td>0.06</td>
</tr>
</tbody>
</table>

Inferential analysis determined that neither age, HBP, cancer and tobacco history nor tumoral data and standard coagulation were statistically associated with ICH, unlike male group (po,030 $\chi^2$). ICH also increased significantly length of

stay in ICU (p<0.01). There was no correlation between FXIII levels and standard coagulation. Male with previous G6PDD, who also suffered from ICH, had a severe presurgery FXIIID (A: 38% B: 83,30% C: 65,1%) (Tables 2-4).

Inferential analysis confirmed that FXIIID (<70%) after brain tumor surgery increased ICH (both samples B and C p<0.01 Mann Whitney U Test) and absence of association in those cases without ICH. FXIII baseline variation was also significant (FXIII A-B and A-C p<0.01, FXIII B-C p0,282 T-Test) (Tables 5,6). Finally, there was an absence of lineal relationship between FXIII levels and standard coagulation (Table 7).

**Discussion**

This is one of the few prospective studies in the literature to evaluate acquired FXIIID and its clinical effects after surgical aggression in a tumor state and the first that demonstrates increased ICH in presence of FXIIID or baseline variation after brain tumor surgery.

Until a few years ago, there was no evidence about FXIII and ICH in neurosurgical procedures. Gerlach, et al. published the first and the most consistent study about postoperative hemorrhage in neurosurgical patients with decreased FXIII activity. A retrospective review [12] of 1,264, neurosurgical operations demonstrated that all patients (n=8) with postoperative FXIIID had a severe ICH. Two years later, FXIII levels were tested preoperatively and postoperatively in a prospective 876-patient study [10]. Of the 39 patients with an ICH (33.3%) had a postoperative FXIII <60% compared with 61 (7%) without hematoma (p<0.01, Fisher’s exact test). The relative risk of developing ICH was therefore increased 6.4-fold in those patients. In 2004, other retrospective 296-patient study [6] confirmed thrombocytopenia and other hemostatic disorders were frequently associated with ICH after meningioma surgery. In conclusion, decreased perioperative FXIII increased risk of ICH in neurosurgical patients,

so extending coagulation tests and specific replacement therapy were recommended to prevent bleeding and improve patient outcome [26,27–30].

Despite FXIIID interest is increasing in all surgical fields, especially to prevent cerebral hematoma, there is a lack of studies after neurosurgery and none of them after brain tumor surgery. In the present study, FXIII levels were considered to be analyzed in three different moments to evaluate their real influence and variation before and after surgery.

Most patients who suffered from ICH had FXIIID (<70%). However, the inferential analysis only determined statistical association with postsurgery levels, especially sample B. It is likely to be the nearest and the most related sample to surgical aggression, bleeding, consumption and it could be considered the most interesting one in case of replacement treatment.

Despite lack of association between ICH and presurgery FXIII levels, it should be noted that 39,45% patients had FXIII levels <70% and 46,51% of them suffered from ICH. Measuring preoperative levels in our study was interesting because baseline variation was also statistically significant and because it resembles what literature confirms: acquired FXIIID is underdiagnosed being prevalence unknown nowadays. So, although most people do not have preoperative FXIIID, it could be useful to prevent bleeding in case of important postsurgery variation.

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**Table 2: Age and ICH.**

<table>
<thead>
<tr>
<th>AGE (years)</th>
<th>CH</th>
<th>No ICH</th>
<th>Total</th>
<th>χ²</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 70</td>
<td>7</td>
<td>50-69</td>
<td>30-49</td>
<td>≤ 29</td>
</tr>
<tr>
<td>No ICH</td>
<td>8</td>
<td>40</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td>Total</td>
<td>15</td>
<td>60</td>
<td>22</td>
<td>12</td>
</tr>
</tbody>
</table>

**Table 3: Gender and ICH.**

<table>
<thead>
<tr>
<th>Gender</th>
<th>CH</th>
<th>No ICH</th>
<th>Total</th>
<th>χ²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>30</td>
<td>9</td>
<td>39</td>
<td>0,030</td>
</tr>
<tr>
<td>Female</td>
<td>39</td>
<td>31</td>
<td>70</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>69</td>
<td>40</td>
<td>109</td>
<td></td>
</tr>
</tbody>
</table>

**Table 4: Histopathology and ICH.**

<table>
<thead>
<tr>
<th>Tumor origin</th>
<th>CH</th>
<th>No ICH</th>
<th>Mann Whitney U Test (p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td>25</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Recurrence</td>
<td>50</td>
<td>17</td>
<td>3</td>
</tr>
<tr>
<td>Metastases</td>
<td>75</td>
<td>23</td>
<td>11</td>
</tr>
<tr>
<td>Total</td>
<td>150</td>
<td>50</td>
<td>39</td>
</tr>
</tbody>
</table>

**Table 5: FXIII and ICH.**

<table>
<thead>
<tr>
<th>A- FXIII</th>
<th>CH</th>
<th>No ICH</th>
<th>Mann Whitney U Test (p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;70%</td>
<td>20</td>
<td>23</td>
<td>0.073</td>
</tr>
<tr>
<td>&gt;70%</td>
<td>19</td>
<td>47</td>
<td></td>
</tr>
<tr>
<td>FXIII Mean</td>
<td>71.2%</td>
<td>77.52%</td>
<td></td>
</tr>
<tr>
<td>B-FXIII</td>
<td>CH</td>
<td>No ICH</td>
<td>Mann Whitney U Test (p value)</td>
</tr>
<tr>
<td>&lt;70%</td>
<td>31</td>
<td>32</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>&gt;70%</td>
<td>8</td>
<td>38</td>
<td></td>
</tr>
<tr>
<td>FXIII Mean</td>
<td>51.57%</td>
<td>70.14%</td>
<td></td>
</tr>
<tr>
<td>C-FXIII</td>
<td>CH</td>
<td>No ICH</td>
<td>Mann Whitney U Test (p value)</td>
</tr>
<tr>
<td>&lt;70%</td>
<td>34</td>
<td>33</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>&gt;70%</td>
<td>5</td>
<td>37</td>
<td></td>
</tr>
<tr>
<td>FXIII Mean</td>
<td>52.14%</td>
<td>69.68%</td>
<td></td>
</tr>
</tbody>
</table>

**Table 6: FXIII baseline variation.**

<table>
<thead>
<tr>
<th>T-Test (p value)</th>
<th>A-B FXIII</th>
<th>A-C FXIII</th>
<th>B-C FXIII</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>0.282</td>
<td></td>
</tr>
</tbody>
</table>

**Table 7: Standard coagulation and FXIII.**

<table>
<thead>
<tr>
<th>Standard coagulation</th>
<th>FXIII</th>
<th>A</th>
<th>B</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb</td>
<td>0,132</td>
<td>0,29</td>
<td>0,075</td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>0,155</td>
<td>0,095</td>
<td>0,106</td>
<td></td>
</tr>
<tr>
<td>PA</td>
<td>0,220</td>
<td>0,189</td>
<td>0,432</td>
<td></td>
</tr>
<tr>
<td>aTTP</td>
<td>0,417</td>
<td>0,276</td>
<td>0,098</td>
<td></td>
</tr>
<tr>
<td>INR</td>
<td>0,199</td>
<td>0,287</td>
<td>0,414</td>
<td></td>
</tr>
<tr>
<td>Fb</td>
<td>0,202</td>
<td>0,495</td>
<td>0,183</td>
<td></td>
</tr>
</tbody>
</table>

**Citation:** Jordan EV, Puertas AN, Pellejero JC, Goixart LS, Ruiz JR, et al. (2021) Role of perioperative Factor XIII in intracerebral hemorrhage after brain tumor surgery: A prospective study. Arch Hematol Case Rep Rev 6(1): 007-012. DOI: https://dx.doi.org/10.17352/ahcrr.000031
Given the absence of association between routine coagulation and hemogram parameters with ICH and FXIII levels, essential for the integrity of the hemostatic system in high-risk bleeding surgery, it is recommended to measured FXIII levels to prevent ICH in neurosurgical procedures [15,19,20,23,24,26–29].

Most blood transfusions were considered empiric as prophylaxis of bleeding during surgery because Hb range and standard coagulation were normal and most of these patients did not suffer from ICH or need another transfusion. Nobody received prophylaxis or treatment with FXIII concentrate or recombinant.

Main limitations were sample size and single-center study, so it is difficult to generalize statistical results at the moment. Lack of established criteria in the literature lead to measure the main variable in an objective way by neuroradiologists and neurosurgeons, avoiding evacuation criteria, controversial between studies.

Filiation and tumoral features included were similar to general population as well as cardiovascular risk factors analysed. Literature review didn’t find studies evaluating association between gender and ICH after brain tumor surgery to explain why males were at greater risk of bleeding but it is well known that prevalence of cardiovascular disease and spontaneous ICH increases in males, so it could explain the association found [1–4,25,31–33]. However, it would be advisable to analyze many individual risk factors to determine the true influence of gender on perioperative ICH [25,27,31,32,33].

Further randomized studies with a larger sample size and more bleeding risk factors analysed are required to conclude FXIIID increased ICH after brain tumor surgery and to evaluate replacement treatment as a therapeutic target.

Conclusion

Acquired FXIIID (<70%) after brain tumor surgery increased ICH, so it could be considered a risk marker of hemorrhage. ICH was also associated with baseline variation, male gender and prolonged stay in ICU. Normal standard coagulation tests did not exclude FXIII disorder. Detect on time FXIIID and replacement treatment could become a therapeutic target in future studies.

Declarations

Ethics approval and consent to participate: Written informed consent was required for all participants. Comité de Ética de Investigación de la Comunidad de Aragón (CEICA) approved the study (NºCP14/2015).

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Author’s contributions

EVJ: main author, design, methodology and writing

ANP: coordination and design

JCP: collection and analysis of neurosurgery data

CRL: statistical analysis

NFM: blood sample analysis

LSG: visualization, writing-review, expert in brain injury

MQD: visualization, writing-review and editing

JCL: visualization, writing-review and editing.

References


