Chronic Subdural Hematoma: Role of Vascular Endothelial Growth Factor and Craniotomy in Pathophysiology and Prevention of Recurrence

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Abstract
Current body of evidence suggests that the maintenance or enlargement of chronic subdural hematoma (cSDH) is caused by multiple factors. Inflammatory and vascular endothelial growth factor (VEGF)–induced accumulation of hematoma plays an important role in pathophysiology of cSDH. If neomembrane is implicated in the propagation of inflammatory mediators, excision of the culprit membrane becomes essential to treat and prevent recurrence of cSDH. This retrospective study was conducted in a service hospital where 48 cases of cSDH were operated in 2 years. Patients were evaluated clinically and radiologically. Surgical procedure offered included burr hole craniotomy (BHC), twist drill craniotomy (TDC), or craniotomy (Cr) with excision of neomembrane. Cr was offered whenever there was suspicion or evidence of reaccumulation, solid or calcified hematoma formation, nonobliteration of the subdural space, or numerous thick membranes as were demonstrated in imaging. In Cr maximum part of outer neomembrane was excised and margins were coagulated. The excised outer neomembrane was sent for immunohistochemical examination to assess the VEGF expression. Depending on the VEGF expression as seen on the microscope, these expressions were grouped into weak, moderate, or strong VEGF expression. The study showed that cSDH patients with neomembrane formation benefit from Cr. The strong VEGF expression from the excised neomembrane further strengthens the proinflammatory VEGF theory propagation of cSDH. It further proves that excision of the culprit membrane is essential to prevent recurrences.

Keywords
► chronic subdural hematoma
► vascular endothelial growth factor
► neomembrane

Introduction
A chronic subdural hematoma (cSDH) is defined as chronic (> 3 weeks) intracranial bleeding between the dura mater (which adheres to the skull) and the arachnoid mater (which envelops the brain). The underlying cause of cSDH is usually traumatic tearing of the bridging veins that connect the brain surface with the dura mater.¹ The incidence of cSDH is estimated at 1.7–18 per 100,000 people, rising up to 58 per 100,000 people in patients older than 65.²–⁴ As the population continues to mature, incidence is expected to double by the year 2030.⁵,⁶ The reported recurrence rates range from 2.3 to 33%.⁷–¹⁰ Many theories attempt to explain the pathophysiology of cSDH. They include osmotic, oncotic, microbleed, anticoagulant and profibrinolytic, and the inflammatory and growth factor theories. Current body of evidence suggests that the cause can be attributed to probably a mixture of all the aforementioned mechanisms. Barring the osmotic and oncotic theories, all other
Materials and Methods
This retrospective study was conducted in a service hospital where 48 patients of cSDH were operated in period of 2 years from June 2014 to October 2016. Patients were evaluated clinically and radiologically. Patients were offered surgical intervention, with definitive evidence of increasing mass effect clinically and radiologically. Surgical procedure offered included burr hole craniotomy (BHC), twist drill craniotomy (TDC), or craniotomy (Cr) with excision of neomembrane. Cr was offered whenever there was suspicion or evidence of reaccumulation, solid or calcified hematoma formation, nonobliteration of the subdural space, or numerous thick membranes as were demonstrated in imaging. In Cr, free bone flap was raised, durotomy was done circumferentially pedicled at the skull base region, maximum part of outer membrane was excised, and margins were coagulated. Inner layer of neomembrane was excised without tearing off or coagulating the adherent surface veins (►Figs. 1, 2). The excised outer neomembrane was sent for immunohistochemical examination to assess the VEGF expression (►Fig. 3). Depending on the VEGF expression as seen on the microscope, these expressions were grouped into weak, moderate, or strong VEGF expression (►Figs. 4–6). All operated cases were followed up for 6 months. Complications arising from each procedure were recorded and treated.

Observation
Out of a total of 48 patients, 22 underwent Cr with evacuation of hematoma and excision of neomembrane. Twenty-four patients underwent BHC and two underwent TDC (►Table 1). None of them undergoing Cr developed recurrence whereas 17% in BHC and 50% in TDC group developed recurrence (►Table 2). In the Cr group 82% showed high whereas 18% showed moderate expression of VEGF concentration in the excised specimen of outer neomembrane. TDC was offered as a lifesaving emergency in neurologically compromised patient with poor general condition. Out of two patients, one expired within 48 hours postoperatively due to associated comorbidities. Morbidity was in the form of superficial wound gaping that was treated with secondary suturing (►Table 3).

Inference
This study is of elementary importance as it establishes a clear relationship between VEGF expression and hematoma enlargement in cSDH. Eighty-two percent showed high VEGF expression, which supports the hypothesis that VEGF-induced proinflammatory state causes progressive hematoma enlargement. Also, we found that Cr with excision of neomembrane prevents recurrence.

Discussion
It was Virchow who performed the first empirical study on the dura mater of cSDH, thereby suggesting an inflammatory pathology. During the last few years, a growing body of evidence has been accumulated, which points to an involvement of angiogenic mechanisms in the propagation of cSDH. Secretion of VEGF from local sources, including cells within hematoma fluid and the parietal membrane, may well be considered an important pathophysiologic factor resulting from the proinflammatory environment in the cSDH cavity. A high secretion rate of VEGF in hematoma fluid will lead to continuous formation of immature, fragile blood vessels, which are prone to hemorrhagic events.

It becomes evident that on the one side we have a proinflammatory secreting and extravasation mechanisms leading to increase in the SDH volume and countering them in the anti-inflammatory mechanism with breakdown and clearance processes trying to counter the same. Probably in some patients the latter mechanisms may become more prevailing, thereby reducing the VEGF expression. This could
be one of the reasons explaining the lack of high VEGF expression among all patients with cSDH. It is also probable that abnormal angiogenesis leads to formation of leaky and anatomically weak structures susceptible to rupture following trivial trauma and even transient rise in intracranial pressure, thereby potentiating the vicious cycle. This could explain why most patients with cSDH deny any history of trauma.

Suzuki and colleagues have demonstrated complete clearance of SDH in a case of glioblastoma multiforme using bevacizumab.\textsuperscript{18} Although the present study does not exclude contribution of other factors, the use of compounds...
to interfere with the action of VEGF, such as receptor blockers or inhibitors of the second messenger pathways, may well be considered a worthwhile approach for clinical testing in cSDH, which, despite being a benign disease, is nevertheless accompanied by a high rate of mortality in the predominantly affected group of old patients.19

Table 1 Showing all case and their VEGF expression

<table>
<thead>
<tr>
<th>VEGF expression</th>
<th>Cases</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>18</td>
<td>82</td>
</tr>
<tr>
<td>Moderate</td>
<td>03</td>
<td>14</td>
</tr>
<tr>
<td>Low</td>
<td>01</td>
<td>04</td>
</tr>
</tbody>
</table>

Abbreviation: VEGF, vascular endothelial growth factor.

Table 2 Showing the percentage of recurrence

<table>
<thead>
<tr>
<th>Type of surgery</th>
<th>Case</th>
<th>Recurrence</th>
<th>Percentage recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>BHC</td>
<td>24</td>
<td>04</td>
<td>17</td>
</tr>
<tr>
<td>Cr</td>
<td>22</td>
<td>00</td>
<td>00</td>
</tr>
<tr>
<td>TDC</td>
<td>02</td>
<td>01</td>
<td>50</td>
</tr>
</tbody>
</table>

Abbreviations: BHC, burr hole craniotomy; Cr, craniotomy; TDC, twist drill craniotomy.

References
8 Nakaguchi H, Tanishima T, Yoshimasu N. Factors in the natural history of chronic subdural hematomas that influence their postoperative recurrence. J Neurosurg 2001;95(02):256–262

