Physiopathogenesis of subdural hematomas

Part 2: Inhibition of growth of experimental hematomas with dexamethasone

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A previously described experimental hematoma model, achieved by the subcutaneous injection of 12 ml of autologous hemolyzed blood clotted in situ, was made in 33 rats. Seventeen animals served as controls; the other 16 received daily intramuscular injections of dexamethasone. After an initial decrease in size, 47% of the lesions in the control animals enlarged to a mean weight of 12.1 ± 2.5 gm, while the lesions in the 16 steroid-treated rats weighed 3.2 ± 0.70 gm (p < 0.01). Histologically, lesions from the steroid group showed absence of neomembrane formation. These data offer further support to the theory that the neomembrane development and subsequent enlargement of subdural hematomas is due to inflammatory reactions of tissues in contact with large blood clots.

KEY WORDS • experimental hematoma • dexamethasone • neomembrane

In Part 1 of this study we described the development of a subdural hematoma model in the subcutaneous tissues of rats. The lesions were induced by the autologous hemolyzed blood or autologous fresh whole blood, but not by the use of injected plasma clotted in situ. The clinical behavior and histological features of this animal model were found to be virtually identical to those seen in human subdural hematomas. Subsequent biochemical analysis of their liquid contents showed remarkable similarities to human samples previously reported.

During our previous experiments we showed that the characteristic enlargement of the lesions seemed to be strongly dependent on inflammatory reactions. The purpose of this paper is to describe a successful attempt to inhibit the neomembrane formation and subsequent enlargement of similarly injected autologous hemolyzed whole blood implants clotted in situ.

Materials and Methods

We used 33 Sprague-Dawley female rats, weighing 300 to 350 gm. Blood was drawn from all animals by direct cardiac punctures under anesthesia into a plastic syringe as previously described. This procedure was repeated at 1-week intervals until 12 ml per
FIG. 1. Weight of lesions at autopsy. The control lesions with liquid central cavity (open dots) weighed $12.1 \pm 2.5$ gm, the solid control lesions (solid dots) weighed $5.0 \pm 0.41$ gm; the difference between them was significant at $p < 0.01$. The steroid-treated lesions weighed $3.2 \pm 0.70$ gm; the difference between the solid lesions of both groups was $p < 0.001$.

animal had been collected. The citrated blood was stored in the plastic syringes at $-20^\circ$ C. One week after the last cardiac puncture was performed, the blood was thawed at room temperature. The rats were then anesthetized with Metofane (methoxyflurane) and their dorsal skin was shaved and cleansed.

One ml of 0.1 M CaCl$_2$ solution which contained 5 units of thrombin was passed through a 0.22-$\mu$ millipore filter directly into the blood in the syringes; this mixture was then injected rapidly into the high dorsal subcutaneous tissue where it clotted.

Sixteen rats then immediately received one intramuscular injection of 1 mg/kg methylprednisolone (Depo-Medrol) and subsequent daily intramuscular injections of dexamethasone (Decadron) at a dosage of 0.5 mg/kg. The other 17 rats did not receive any medications. All animals were sacrificed 9 days after implantation. The lesions obtained at autopsy were placed in 10% buffered formalin for 2 days. They were then carefully dissected, weighed, and photographed. Coronal sections were stained with hematoxylin and eosin and Mallory's trichrome. The histological samples were examined by neuropathologists at this institution.

FIG. 2. Upper: Cross section of a control lesion. The neomembrane is seen between arrows. $S =$ subcutaneous tissues; $C =$ clot cavity. H & E, $\times 44$. Lower: Same as above. $\times 117$. 
Results

During the first 4 days after clot implantation, no differences could be seen between the groups; all lesions seemed to diminish in size. By the fifth day, however, 47% of the lesions in the control animals began enlarging and continued to do so until the experiment was ended on the ninth day. The lesions in the animals that received daily dexamethasone injections, however, continued to decrease in size and none showed any clinical evidence of enlargement.

At autopsy, gross differences could be seen between the two groups. The lesions of the steroid-treated group were thin, small clots, with no surrounding capsule, while those from the untreated group were much larger and encapsulated. When the lesions were sectioned, those that had enlarged clinically showed a central cavity filled with light brown fluid. In contrast, all the lesions from the steroid-treated group were solid.

The lesions fell into three distinct weight groups. The control lesions with a central cavity weighed 12.1 ± 2.5 gm, while those control lesions that remained solid weighed 5.0 ± 0.41 gm. This weight difference is statistically significant at the p < 0.01 level. In sharp contrast, the lesions in the 16 steroid-treated animals weighed even less than the solid lesions in the controls, 3.2 ± 0.70 gm. This weight difference between the solid lesions of the treated and control animals was highly significant at the p < 0.001 level (Fig. 1). The fact that none of the steroid-treated lesions had a liquid center cavity, while 47% of the controls did, was tested using contingency tables for small unequal samples. This difference was significant at the p < 0.02 level.

The histological features of the lesions were also quite different. All of the control lesions showed a thick fibroblastic neomembrane while lesions in the steroid-treated animals showed little fibroblastic reaction with only patchy areas of a very thin neomembrane (Figs. 2 and 3).

Discussion

The dramatic inhibition of these experimental lesions by the use of corticosteroids lends further support to the theory that the neomembrane formation and subse-
quent enlargement of this hematoma model are directly related to inflammatory phenomena.

Recently Bender and Christoff \(^1\) reported their experience with the medical treatment of over 100 patients with chronic subdural hematomas. They asserted that the use of corticosteroids seemed to accelerate the patient's recovery, resulting in a shorter, less complicated hospitalization. The results achieved in our animal model with the use of corticosteroids offer the first experimental explanation to their empirical therapeutic observation in man.

With this supporting evidence at hand, we offer the following theory to explain the pathogenesis of chronic subdural hematomas. It seems that minimal head trauma in individuals with predisposing factors \(^6\) produces subdural venous bleeding. The accumulated blood coagulates and in the first few days after trauma, clot retraction and serum leakage reduce the initial clot volume. At this point a critical minimum residual size is apparently required for the process to continue. \(^8\)

Products derived from the breakdown of solid blood elements trigger inflammatory responses in the surrounding meningeal membranes, \(^4\) which promote a fibroblastic reaction that infiltrates the clot surface through the fibrin fibers. Meanwhile, plasminogen activators within the clot and arising from the meninges \(^13-17\) initiate the fibrinolytic liquefaction that creates the center cavity. In the ongoing inflammatory process, neo-capillaries are formed within the fibroblastic membrane. These thin-walled vessels permit the exit of plasma to the interstitial space of the neo-membrane and into the cavity. It appears that the enhanced permeability of the capillaries contributes to the enlargement of the lesions. \(^3,4-8\)

Possibly this process is mediated by kinin, bradykinin, and other vasoactive substances described in inflammatory processes elsewhere. \(^10,16\) The chemical characteristics of subdural hygromas in infants studied by Gitlin \(^3\) and those effusions obtained from our rat model \(^8\) have shown lower total protein levels with higher albumin-gamma globulin ratios than those of blood. This peculiar dilution can be explained by assuming an influx of interstitial fluid, which has a very low protein content with similarly altered albumin-gamma globulin ratios. \(^11,14,18\) Further support to this concept of plasma exudation causing enlargement comes from studies using albumin \(^19\) and other radioactive tracers, which have been shown to penetrate into the liquid cavity of human subdural hematomas, apparently not by simple diffusion. \(^9,15,19,20\)

In previous experiments we have shown that in both reforming subdural hematomas in man and experimental hematomas in rats, active fibrinolysis takes place. \(^7,8\) We do not know if the inflammatory reactions and the fibrinolytic mechanisms are interdependent, or if they occur simultaneously but separately. Theoretically, the reactions here described would apply to large extravascular collections of clotted blood regardless of the type of tissue in which they occur. Hence, hemispherically shaped intracerebral hematomas and spinal epidural hematomas \(^5,6\) of sufficient size would conceivably follow the same course. Future experiments with this animal model may help to determine the optimal anti-inflammatory agent, dosage, and duration of therapy required to achieve a complete clot absorption.

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