Pathological findings in acute experimental spinal cord trauma

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This study shows that spinal cord pathology secondary to acute trauma in monkeys evolves with stepwise sequential changes. The acute damage is more central than peripheral. Depending on the amount of trauma, the subacute damage may be limited to central gray necrosis or may progress or evolve to include the neighboring white matter. These pathological changes may be taking place even in the presence of clinical improvement.

KEY WORDS · spinal cord injury · monkey · gray matter · white matter · hemorrhage · necrosis

HUMAN cord pathology has been categorized in such terms as “initial phase,” “ischemic phase,” and “repair phase.” Little attention has been paid to the amount of trauma. With the recent revival of Allen’s 1911 experiments on spinal trauma,2 reports have appeared that discuss the merits of various treatments in reducing spinal cord damage, such as hypothermia,1,2 steroids,6 hyperosmotic agents,8 and myelotomy.14,18 Studies of graded, progressively severe cases of cord trauma have been lacking, and the following experimental studies were carried out to supply this information.

Materials and Methods

Thirty-two rhesus monkeys which weighed 4 to 8 kg were anesthetized with intramuscular phencyclidine hydrochloride (1 mg/kg) initially and sodium pentobarbital as required for maintenance. Endotracheal tubes were placed and respirations assisted as needed. The posterior operative site from the fourth thoracic to the third lumbar vertebrae was clipped and shaved, scrubbed with surgical soap, and sprayed with betadine. After sterile draping, a midline longitudinal incision was deepened to the muscle layers over the dorsal-lumbar region. The muscles were stripped bilaterally from the spinous processes and posterior laminae of the eleventh and twelfth thoracic and first lumbar vertebrae. Hemostasis was accomplished with the electrocoagulator and bone wax. A three-space laminectomy was carried out to expose the dural sac. Uniform spinal cord trauma was delivered to a 0.32 × 0.32 cm area of the dural surface by the method described by Allen8 and Freeman and Wright.8 Over the cord impounder, a glass tube was fitted so that various weights could be dropped from 20 cm. The weights were 10, 15, 20, and 25 gm in cylinder form, which were dropped from 20 cm onto the impounder on the dura. The weights were immediately retrieved back up the tube by pulling a thread attached to each cylinder. This prevented any bouncing, and lesions due to a single blow were produced in the spinal cord.

The animals were randomly divided into
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four groups of eight each. In each group of animals, the weights were changed so that forces of 200 gm-cm (gram-centimeter), 300 gm-cm, 400 gm-cm, and 500 gm-cm were inflicted on the spinal cords. The muscle and skin were closed in layers over the cord lesion. Then, each group of animals was randomly divided again into acute and subacute categories. At 6 hours after injury, the acute animals were sacrificed with large doses of pentobarbital. At 5 or 6 days, the subacute animals were sacrificed. At autopsy, the laminectomy sites were reopened and extended proximally and distally to include an additional segment. The spinal cord was excised with the dura intact and placed in formalin after the dura had been removed under microscopic dissection. After the tissues had been fixed for 3 or 4 days, the cords were imbedded in paraffin. Microscopic sections were taken not only through the lesion but also proximal and distal to it. Hematoxylin and eosin was the routine stain, but myelin stains were used on occasions.

The final sections of each animal were centered on the pathological lesion, with prefixes of “P” and “D” attached to those slides that were more proximal and distal cross sections of the cord. The microscopic pathology was graded without knowing the amount of trauma. Edema, diapedesis, petechial hemorrhage, flame hemorrhage, and globular hematoma were all graded at a low power of magnification as slight, moderate, and severe in the acute animals. Edema, demyelination, necrosis, hemorrhage, and vascular deformity were all similarly recorded for the subacute animals. In both acute and subacute groups, high power microscopic evaluation included, first, polymorphonuclear leukocyte (PMN) infiltration into the vessel walls, the pia arachnoid and the areas of necrosis; and, second, both axonal and neuronal swelling and necrosis. The average change for any given trauma is recorded in the table of results. A cord that best represented the trend of progressive damage in each group is shown in the photographs.

The subacute animals also had clinical neurological testings, as we have done in similar experiments. Only motor performance was recorded; sensory examination was not considered objective. Functional levels were:

0 = able to run with little or no deficit
1 = able to stand, walk, and run, even though spastic
2 = good movements of limbs which enabled the animal to right and stand but not walk
3 = minimal perceptible voluntary movements of limbs
4 = complete paraplegia with no voluntary movements.

The animal’s functional status was judged without knowledge of the trauma sustained. The functional level was recorded just before sacrifice.

Results

The predominant pattern in progressively severe spinal cord trauma is a central-to-peripheral spread of the pathology. The central gray matter is involved before the peripheral gray; the more central white matter shows changes before the peripheral white matter. Even though the results have been placed in Table 1, an understanding of the progressive pathological changes is best appreciated by viewing the cord sections in their sequence in Figs. 1 through 4.

Clinical and Pathological Effects of Graded Trauma

**Application of 200 gm-cm Force.** In the acute phase, all that was seen was very mild edema and a few small gray matter hematomas (Fig. 1 left). On occasion, a minimal inflammatory response was present in the vessel walls, Diapedesis, hematomas, or extensive necrosis were minimal to absent in the early specimens. Over the next 5 to 6 days, these animals remained neurologically intact, and the only common pathological lesion found in the subacute phase was a small area of posterior gray necrosis. These small hematomas and necrotic areas were always centrally placed posterior to the central canal. They were of the size noted in Fig. 3 left in half the animals; in the other half, the lesions were smaller or absent. As the trauma was progressively increased, this same area was more severely involved than other areas (Figs. 1 right, 2, 3, and 4).

**Application of 300 gm-cm Force.** In this group the acute phase showed definite but mild diapedesis of all elements of blood, petechial and flame hematomas, and
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TABLE 1

<table>
<thead>
<tr>
<th>Condition of spinal cord after varying degrees of trauma</th>
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<tbody>
<tr>
<td>Amount of Trauma (gm-cm)</td>
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<td>Clinical Condition</td>
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<tr>
<td>Average Clinical Grade*</td>
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</table>

<table>
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<tr>
<th>Acute Pathology (low power)</th>
<th>edema</th>
<th>diapedesis</th>
<th>petechial hemorrhages</th>
<th>flame hemorrhages</th>
<th>hematoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weakness Paraparesis</td>
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<td>2</td>
<td>3</td>
<td>4</td>
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</table>

<table>
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<tr>
<th>Acute Pathology (high power)</th>
<th>PMN in vessel walls</th>
<th>PMN in pia-arachnoid</th>
<th>inflammatory necrosis</th>
<th>neuronal swelling</th>
<th>neuronal necrosis</th>
<th>axonal swelling</th>
<th>axonal necrosis</th>
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<tbody>
<tr>
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<td>3</td>
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<th>Subacute Pathology (low power)</th>
<th>edema</th>
<th>vascular deformation</th>
<th>demyelinization</th>
<th>necrosis</th>
<th>hemorrhages</th>
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<tr>
<td>*</td>
<td>1</td>
<td>1</td>
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* The grading of the pathology is: 0 = absent, 1 = mild, 2 = moderate, 3 = severe, 4 = very severe. PMN = polymorphocyte.

edema. The small hemorrhages, instead of being occasional or single within one section, were now multiple. These hemorrhages were nearly exclusively in the gray matter. White matter changes consisted of increased edema and occasional axonal swelling, most of which occurred in the white matter that bordered on the gray. The peripheral white and gray were normal. In the subacute animals, the cords on the surface would appear normal except for dilatation and engorgement of the dorsal veins. On cross section, an area of central necrosis or hematoma was present. The central necrosis involved approximately one-fourth of the total gray. The PMN infiltrate not only involved the necrotic, hemorrhagic area but also many of the vessels. Adjacent neurons appeared dying or dead and adjacent medial white matter was edematous with swollen axons. The more posterior lateral and far anterior gray matter and the peripheral white matter were normal. Animals with these pathologic findings had little neurologic deficit, as all of them ran and climbed easily with minimal clumsiness.

Application of 400 gm-cm Force. In this group the pathological and clinical picture had definitely changed. In the cross sections of the cords from the acute animals, the gray matter architecture was altered with debris, fluid, and hemorrhage. Severe vascular diapedesis was more prominent, for nearly every intact vessel within the cord had a moderate ring of red cells about it. Larger flame-
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shaped hemorrhages and a definite hematoma were present in one of the four acute animals, while the other three were like that shown in Fig. 2 left and had simple multiple small hemorrhages. Several vacuolated spaces, felt to represent edema, were seen throughout the cord. An inflammatory response was apparent in the vessel walls and the pia; swelling of the neurons and axons was present but mild; and often many of the gray matter neurons were stained very pink with hematoxin and eosin, which suggested early necrosis of the cells. In the spinal cords taken at 5 to 6 days, where the clinical picture was that of a marked paraparesis, the pathology had progressed to severe necrosis, demyelination, edema, and vessel breakdown (Fig. 4 left). The central architecture was barely maintained at this time period. Only the periphery of the spinal cord was preserved, which probably carried through the injured area those few functional transmissions that were observed in the animal.

Application of 500 gm-cm Force. The ani-

Fig. 1. Spinal cord sections taken from monkeys 5 to 6 hours after trauma. Left: A spinal cord that sustained a 200 gm-cm force. Right: A spinal cord that sustained a 300 gm-cm force.

Fig. 2. Spinal cord sections 5 to 6 hours after trauma. Left: After 400 gm-cm force. Right: After 500 gm-cm force. Note the stepwise increase in gray matter hemorrhages from one to multiple, the increase in edema from minimal to severe, and the development of central necrosis with the heavier blows.
mals in this group had complete paraplegia. In the acute cords, the edema and tissue separation had extended to involve the entire cord. In the center of the cord, large flame-shaped hemorrhages and generous edematous and necrotic areas were present (Fig. 2 right). In the subacute phase at less than 1 week, the center of the cord had completely disappeared and was replaced by fluid, debris, and inflammatory cells (Fig. 4 right). This necrotic and inflammatory material appeared under pressure when the specimens were cut. Only an outside shell of cord was preserved, and even this was thinned in the area of the traumatic blow. There were marked changes in the vessels, both superficial and deep. Most often, the arteries and veins were dilated more than was normal, indicating absences of vasomotor tone. On high power magnification, there were many polymorphocytes in the arterial walls, a diapedesis of all blood elements about the remaining capillaries, and fragmentation and dilatation of the larger veins. Axonal and neuronal swelling was severe. The tissue which stained most consistently was the peripheral glial substances.

Central Necrotic Hematoma Areas

The central necrotic hematoma areas extended proximally and distally from the site of impact. For a 200 gm-cm force, the longi-

Fig. 3. Sections of monkey cords from the area of maximum damage 5 to 6 days after trauma. *Left:* After 200 gm-cm force. *Right:* After 300 gm-cm force.

Fig. 4. Cord sections in the area of maximum damage 5 to 6 days after injury. *Left:* After 400 gm-cm force. *Right:* After 500 gm-cm force. Note the progressive development in the size of the central necrosis and the increase in white matter pathology as the amount of trauma is advanced.
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tudinal limit of this demarcated pathology was usually 2 cm; for 300 gm-cm, it was 3 cm; for 400 gm-cm, 4 cm; for 500 gm-cm, 5 cm or more. The two ends of the necrotic hematoma tapered to small points just posterior to the central canal. Surrounding the central necrotic area there were pathological changes in the adjacent gray and white matter. These changes tapered, too. In the more severe lesions wherein paraplegia was produced, early myelin fragmentation in the appropriate white matter tract could be occasionally traced further proximally and distally.

Discussion

In human disease or damage to the spinal cord, the greatest neurological loss is initially and the deficit may improve with time. The pathological picture is the reverse. Even in the face of improved neurological function, the gross pathological picture shows evolution or progression for 5 to 7 days from central to peripheral microscopic and gross pathological involvement.

The various degrees of progression of the cord trauma from a small central necrotic area (Fig. 3 left) to extensive central as well as peripheral necrosis (Fig. 4 right) is dependent on the severity of the traumatic blow. Why the center of the cord is more vulnerable is not clear. The anatomy, cell metabolism, arterial supply, and venous drainage all probably contribute to a cumulative effect.

The anatomy of the cord may explain the pathological findings on the basis of two different observations. The first is the difference between gray and white matter. The gray, which is centrally situated, consists of neurons with mostly short axonal and dendritic processes and mesh of supportive glial structures. This tissue can easily be separated by fluid or blood. In contrast, the white matter is made up of long, tightly packed, fiber tracts which are not so easily separated. The second possibility centers on the maximum pressure point with tissue surrounded by a non-elastic membrane. The pia mater surrounds the cord with the single large invagination at the anteromedian fissure and bounds firmly the cord tissue. With any trauma there is edema and swelling, but the cord can not significantly enlarge because of the tough encasing pia. Instead, there is an increase in intrapial or intramedullary pressure. As formulated by McVeigh in 1923, the maximum pressure is concentrated in that geographic area most central to all surrounding pia with respect to both outer sheath and invagination. This area is behind the central canal; indeed, on reviewing all the research on cord trauma as well as our own (Figs. 3 and 4), the initial necrosis is there. However, both anatomical explanations may be important and the pathology may be based on a combination.

The metabolic rate and the demand for blood differs greatly between gray and white matter. In the cortex, the gray matter flow is five to six times greater than white matter, and spinal cord white matter flow is much less than cortical white matter; so the difference between the two is probably even greater. An injured tissue has even greater metabolic demands; the metabolic demands may exceed the available blood flow, and central gray necrosis ensue. But because the most anterior aspects of the gray are spared (Figs. 3 and 4), the metabolic and flow difference is certainly not the sole factor involved.

The arterial blood supply is affected by the trauma, with small vessel diapedesis initially and with an inflammatory response over the next hours and days. There is a prolonged circulation time. Experiments on microcirculation in experimental cord trauma have demonstrated focal arterial constriction and intra-arterial emboli. Progressive impairment of the arterial supply to the spinal cord by surgical clipping has been proven in animals to cause ischemic and necrotic changes in the spinal cord. Thus, if traumatic impairment of the blood supply were also progressive, and studies by Fairholm and Turnbull suggest this thesis, then the resultant pathological change could be similar to those observed.

The venous outflow of the circulation is also affected. Grossly, the changes in the veins are more apparent than those in the arteries. The proven changes in both blood flow and vasomotor tone in this type of experimental model all indicate that major flow delay is on the venous side of the circulation. Also, there is other evidence that venous insufficiency alone produces cavitation in the central gray of the cord. Since the venous drainage is from the internal parts of
INCREASE IN SEVERITY OF TRAUMA

5-6 hrs.
- small hemorrhage
  - minimal edema

5-6 days
- Small central necrosis
  - and cavity
  - minimal edema

200
- several small hemorrhages
  - moderate edema

300
- multiple hemorrhages
  - extensive edema

400
Large, multiple hemorrhages
  - severe edema
  - central necrosis

500 g/m²
- extensive central hematoma cavity
  - white necrosis
  - minimal peripheral glia
  - spared

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the cord to the periphery, it is logical to assume that outflow insufficiency would be most detrimental where the vessels are the thinnest at the deep capillary-venous junctions. Progressive edema, diapedesis, and hemorrhage could all occur depending on the post-traumatic integrity of the local vessel walls and on the dammed-up intravascular pressure in a damaged venous system.

Thus the pathophysiology of spinal cord damage is probably the total of many factors. The reasons for the exact sequence of pathological changes, however, are not clearly understood. For example, are the vascular changes, arterial and venous, secondary to primary nervous tissue damage instead of the reverse, as we have suggested? Certainly that sequence is possible even though current data\textsuperscript{1,2,4,6,10,12,17,20} imply that the vascular pathology is primary. A second question centers on which word, progression or evolution, more accurately defines the observed pathophysiologic events from acute to subacute. Because early dorsal myelotomy and intramedullary decompression did prevent the white matter changes in certain experimental animals,\textsuperscript{8,10,18} the word "progression" was most often, but not exclusively, used. Current laboratory work on cord blood flow, enzyme changes, and electrical activity may help answer some of the questions raised by this study.

Conclusions

Our studies on increasingly severe injuries to the spinal cord in monkeys lead to the following conclusions.

First, the development of demonstrable spinal cord pathology does not parallel the clinical neurological condition. While there may be improvement in the clinical findings, the pathological changes seem to progress in severity for about 1 week.

Second, spinal cord changes are initially more prominent in the center of the cord, even when the traumatic blow is delivered to the surface. Generally, they start as small gray matter hemorrhages and edema, and progress through central necrosis, adjacent white matter edema, and demyelination, to finally involve the entire cord.

Third, the location and progression of the injured area of the spinal cord is dependent on the amount of trauma delivered. In minimal trauma where the animal recovers, the changes are only central. In moderate trauma with significant paresis, the changes engulf the central area and involve the adjacent white matter. In severe blows with a resultant paralysis, the changes spread to include the entire medullary substance.

References

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