OBSERVATIONS ON MYELINATION OF HUMAN SPINAL CORD
AND SOME EFFECTS OF PARTURITIONAL TRANSECTION

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ABSTRACT

The changing pattern of myelination in the spinal cords of 9 normal infants aged between 2 and 8 months was contrasted with the patterns of myelination in cervical and thoracic spinal cords of 3 infants who survived parturitional lower cervical spinal cord transection for 6, 9 and 11 months. The ascending tracts in all the normal spinal cords were densely myelinated. The corticospinal tracts were less myelinated than the fasicuuli proprii in the cervical cord up to 4 months of age and in the lumbar cord up to 7 months of age. In 2 infants aged 8 months no difference between myelin staining of corticospinal tracts and fasicuuli proprii were seen in either cervical or lumbar spinal cord. In contrast, the corticospinal tracts of the cervical spinal cord rostral to, and the spino-cerebellar and spinothalamic tracts caudal to the transection were distinctly less myelinated than fasicuuli proprii. It is proposed that these observations represent examples of delayed or decreased myelination as a result of absence of the peripheral connections of the axons in the central nervous system of infants. The impact of function and other factors upon myelination of axons is emphasized.

INTRODUCTION

Myelination of axons is a complex process affected by axonal function (14, 20), axonal growth (11, 15, 17), malnutrition (6, 8, 15, 17), hypothyroidism (5), and drugs (15, 25, 26), among other factors. Since axon caliber and myelin sheath thickness in developing rodents are linearly related (11, 15, 17), and nerve fiber sizes in adult peripheral nerve can be altered by increasing (7) or decreasing their function (23, 24, 28), one might predict that alteration of function in a nerve tract in the developing animal would influence the extent of myelination of that tract. In fact, caliber of nerve fibers and thickness of myelin sheaths are less in the optic nerves of mice raised in the dark (14) and in the homolateral dorsal spinal columns of rats subjected to sciatic neurectomy in the suckling period (20). Therefore, nerve function might be expected to influence fiber size and extent of myelination in the human infant nervous system.

Deprivation of output of axons, as after axonal section and prevention of re-
connection, not only affects the ultimate caliber of the regenerated nerve fiber, but also the remaining proximal portion of the axon in the peripheral nervous system (23, 24, 28). We surmise that spinal cord transection (18) in infants represents an example in humans of deprivation of the output function of the axon, and could result in decreased myelination. However, data on the pattern of myelination of the human spinal cord after birth are scanty despite extensive investigation of myelination of cerebral hemispheres and brain stem (2, 4, 9, 19, 21, 29), and most of these papers do not mention the state of health of the infants prior to death. Langworthy noted that the pyramidal tracts in both cervical and lumbar spinal cord were less well myelinated than the ascending tracts in a 2 month old infant and commented that progression of myelination in the pyramidal tract is from rostral to caudal (21). Keene and Hewer examined the spinal cords from 3, 7 and 9 month old infants and observed incompletely myelinated pyramidal tracts in the 9 month old infant with fully myelinated ascending tracts; but they do not specify to which level of the spinal cord they refer (19). Bok demonstrated partially myelinated cortico-spinal tracts in cervical and lumbar spinal cord of a 5 month old infant (2). Hence, the present study was undertaken to evaluate the pattern and timing of myelination of the human spinal cord as seen in luxol fast blue stained preparations and to contrast them with the extent of myelination in the spinal cords of 3 infants who survived parturitional cervical spinal cord transection for 6, 9 and 11 months.

MATERIALS AND METHODS

The spinal cords from 2 groups of infants who had been autopsied at The Children’s Hospital Medical Center were examined.

Infants with Normal Spinal Cords

Spinal cords of 6 presumably healthy full-term infants dying of "crib death" between the ages of 2 and 7 months, and of 3 infants between the ages of 6 and 8 months who were clinically ill less than 6 weeks, were examined. The diagnoses of these latter 3 children were Letterer-Siwe’s disease, α-antitrypsin deficiency and acute monocytic leukemia. The ages, weights and other pertinent clinical and post-mortem data are shown in Table 1. Ten micron thick sections of paraffin-embedded mid-cervical, mid-thoracic and lumbar spinal cord were stained with a combined Luxol fast blue and hematoxylin and eosin stains to demonstrate myelin and cell bodies, and with Bodian’s stain for axons. The extent of myelination of spinal cord tracts was assessed by inspection of the depth of color on the Luxol fast blue-stained preparations. In all instances the results are based on a comparison with the color of the fasciculi proprii in the same section. No evidence of long-standing damage was found in the remainder of the central nervous system.

Infants with Parturitional Spinal Cord Transection

In the files of the Pathology Department at The Children’s Hospital Medical Center between 1930 and 1972, we were able to find 4 infants who had sustained a complete cervical spinal cord transection during a breech delivery and who had survived for 4, 6, 9 and 11 months after birth. Three of these infants had spinal cords and brains available for study in a way similar to the normal spinal cords. The other infant died in 1930, aged 4 months,
and only pictures and a microscopic description could be found (3). Other data on these infants is shown in Table 2 and given in references #1 and #3.

RESULTS

Infants with Normal Spinal Cords

The corticospinal tracts were less myelinated than the fasciculi proprii in the cervical segment in 3 out of 5 (Table 1, Fig. 1), and in the lumbar segment in all 4 of the spinal cords available from infants between 2 and 5 months of age (Table 1, Fig. 2). No differences in staining quality between ascending (except dorsal funiculi which were always more densely stained at all ages), fasciculi proprii, and descending tracts were seen in the cervical segment of 4 infants 6–8 months of age (Table 1, Fig. 3); but in 2 of these 4 infants the lumbar corticospinal tracts were less myelinated than the fasciculi proprii (Table 1, Fig. 4). No differences in density of axons were noted between ascending and descending tracts, although axons in corticospinal tracts were smaller than those in ascending tracts. Beyond 8 months of age no differences in myelin staining of fasciculi proprii, lateral and ventral ascending and descending tracts in cervical or lumbar

<table>
<thead>
<tr>
<th>Age (months)</th>
<th>Crown-heel length (cm)</th>
<th>Body weight (kg)</th>
<th>Brain weight (g)</th>
<th>Clinical data</th>
<th>Intensity of myelin staining of corticospinal tracts compared to fasciculi proprii</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>47.5</td>
<td>3.5</td>
<td>460</td>
<td>&quot;Crib death&quot;, low Apgar at birth and seizures.</td>
<td>paller paller</td>
</tr>
<tr>
<td>2½</td>
<td>60.0</td>
<td>6.6</td>
<td>(head circ. 60 cm)</td>
<td>&quot;Crib death&quot;</td>
<td>paller n.e.*</td>
</tr>
<tr>
<td>3</td>
<td>66.0</td>
<td>12 (est)</td>
<td>660</td>
<td>&quot;Crib death&quot;</td>
<td>same paller</td>
</tr>
<tr>
<td>3</td>
<td>61.0</td>
<td>5</td>
<td>830</td>
<td>&quot;Crib death&quot;. On ventilator for last 4 days of life.</td>
<td>paller paller</td>
</tr>
<tr>
<td>4</td>
<td>64.0</td>
<td>7</td>
<td>728</td>
<td>&quot;Crib death&quot;</td>
<td>paller paller</td>
</tr>
<tr>
<td>6</td>
<td>39.0</td>
<td>6 (est)</td>
<td>740</td>
<td>Letterer-Siwe's disease, respiratory distress 10 days, treated Velban 1 day.</td>
<td>same paller</td>
</tr>
<tr>
<td>7</td>
<td>69.0</td>
<td>&quot;fairly well nourished&quot;</td>
<td>730</td>
<td>Accidental strangulation 2 days prior to death, on ventilator for last 2 days of life.</td>
<td>same paller</td>
</tr>
<tr>
<td>8</td>
<td>68.0</td>
<td>8</td>
<td>740</td>
<td>Alpha-1 antitrypsin deficiency, ill for last 6 weeks of life.</td>
<td>same same</td>
</tr>
<tr>
<td>8</td>
<td>65.5</td>
<td>7.7 (est)</td>
<td>880</td>
<td>Acute monocytic leukemia of 2 weeks duration, died of intracerebral hemorrhage.</td>
<td>same same</td>
</tr>
</tbody>
</table>

* Not examined.
cord were detected. The myelin in the spino-cerebellar tracts stained in a manner similar to that of the fasciculi proprii in all these infants (Fig. 1). At term, the spino-cerebellar tracts are not as densely stained as the fasciculi proprii (21, 29). The ascending tracts and the fasciculus proprius in all the infants in this study appeared well myelinated.

**Infants with Parturitional Spinal Cord Transection**

In the 3 infants surviving perinatal lower cervical spinal cord transection for 6, 9 and 11 months, the crossed and uncrossed corticospinal tracts in the upper cervical spinal cord, several segments above the level of the transection, were less myelinated than expected (Figs. 5, 6 and 7). The spino-cerebellar and spino-thalamic tracts in the thoracic spinal cord (several segments below the transection) were also less myelinated than expected (Figs. 8 and 9). The density of axons in these tracts did not differ from that seen in controls in 2 of the 3 infants (Fig. 10). The exception was the 11 month old infant, in whom the density of axons in the corticospinal tract of the cervical spinal cord seemed slightly decreased. The ascending tracts, above the transection, except for lateral tractus cuneatus, and the descending tracts below the transection, were appropriately degenerated. Myelin staining of corticospinal tracts in the medulla and pons was similar to that of controls in all 3 cases. At the levels of spinal cord examined, anterior horn cells were normal and, except for the appropriately degenerated systems and the region of the transection (18), the size and shape of the spinal cords were normal and no increase in glial cells or fibers was found.

The brain weights, body weights and body length of all 3 infants were each in the third percentile for age, but none of the infants was obviously malnourished (Table 2). Each infant died of bronchopneumonia. No evidence of delayed myelination was found in the cerebral hemispheres. Two of the 3 infants had other minor abnormalities in the cerebral hemispheres such as old small borderzone infarcts in the cerebral cortex in the 11 month old infant and some hypertrophic astrocytes and amphophilic globules in white matter of the 6 month old infant.

**DISCUSSION**

From 6 months of age onwards in our normal infants myelin staining of corticospinal tracts, fasciculi proprii and lateral and ventral ascending tracts in the cervical spinal cord was the same. In fact, in 1 of the 3 month old infants no difference in density of myelin staining of corticospinal tracts from fasciculi proprii in cervical spinal cord could be seen. The spino-cerebellar tract was myelinated by 2 months of postnatal age in our material and in Langworthy's case (21). The lumbar corticospinal tracts were not as densely stained until 6 to 8 months of postnatal age. These observations are in agreement with the observation of centrifugal progression of myelination in the motor tracts by Yakovlev (29), Cajal (4), Keene and Heuer (19) and others (9, 21).

In the 3 infants surviving cervical spinal cord transection by 6 months or
more the lateral corticospinal tracts in the cervical spinal cord above the transection were less myelinated than the fasciculi proprii; whereas, the axon density was similar for the two tracts in 2 of the 3 infants. In the 4 month old infant reported by Byers (3), pale corticospinal tracts above the level of transection may or may not be abnormal, but the pale corticospinal tracts in each cervical spinal cord of a 5 (12) and a 9 (22) month old infant and the pale spino cerebellar tract of the 5 month old infant's thoracic cord are abnormal, according to our observations of infants in this age group. We interpret these findings to indicate that there is delayed myelination in the tracts interrupted distally in the infants who survived parturitional spinal cord transection.

Two of the 3 infants in this report had minor lesions in the cerebral hemispheres; but the pyramidal tracts within the brain stem were normal, suggesting that the changes were not secondary to lesions above the transection. Other evidence for delayed myelination rather than degeneration of axons is the presence of a normal density of axons in two of our three cases, and the pallor of myelin staining of the spino cerebellar and spinothalamic tracts below the transection.

The vascular supply to the cervical spinal cord in infants and children is most frequently derived from arteries accompanying C 6, C 7 and C 8 roots and ascends to the junction of the vertebral arteries (10). These roots are close to the region of the transection; however, no neuronal loss was detected at the levels of spinal cord under discussion; and again, an apparently normal axon population would mediate against the changes being secondary to vascular insufficiency. Lesions of the vertebral arteries are frequently found in infants dying in the newborn period (30); however, no abnormality of vertebral arteries was found in the infant in which a careful search was made (1).

Generalized inanition can be associated with delayed myelination in humans and rodents (5, 6, 8, 15); therefore, chronic illness may be a reason for delayed

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Fig. 1. Cervical spinal cord from a normal 2 month old infant. Note dense staining of ascending tracts including dorsal spino cerebellar and pale staining of lateral and ventral corticospinal tracts compared to fasciculi proprii. (Hematoxylin and eosin and Luxol fast blue stain, × 9).

Fig. 2. Lumbar spinal cord from same infant as Figure 1. Note pale staining of lateral corticospinal tracts indicating incomplete myelination. (Hematoxylin and eosin and Luxol fast blue stain, × 9).

Fig. 3. Cervical spinal cord from a normal 3 month old infant. The density of staining of the lateral corticospinal tracts is indistinguishable from that of the fasciculi proprii. (Hematoxylin and eosin and Luxol fast blue stain, × 9).

Fig. 4. Lumbar spinal cord from a normal 7 month old infant. Note persistent slight pallor of lateral corticospinal tracts as compared to fasciculi proprii. (Hematoxylin and eosin and Luxol fast blue stain, × 9).

Fig. 5. High spinal cervical cord from 6 month old infant with neonatally transected spinal cord. Note slight pallor of staining of lateral and ventral corticospinal tracts as compared with fasciculi proprii and compare with Figure 3. The degenerated ascending dorsal and lateral columns are striking. Note similarity to Figure 5, ref. 22 and Figure 21b, ref. 12. The density of axons in the lateral and ventral corticospinal tracts does not differ from that in the normal spinal cords suggesting that the deficiency of myelin is not due to fiber degeneration. (Hematoxylin and eosin and Luxol fast blue stain, × 9).

Fig. 6. High cervical spinal cord from 9 month old infant about 7 segments above site of neonatal transection. Lateral and ventral corticospinal tracts are distinctly paler than the fasciculi proprii and tractus cuneatus and are similar to Figure 1. The ascending tracts are appropriately degenerated. (Hematoxylin and eosin and Luxol fast blue stain, × 9).
myelination of tracts actively myelinating at the time of the illness. However, in the infants examined by us, the remainder of the white matter of the cerebral hemispheres was not undermyelinated, and the infants, although they had multiple respiratory infections did not appear severely malnourished.

In rodents, a close relationships exists between axonal growth and myelin sheath formation (11, 15) although this relationship can be altered by undernutrition (15, 17). In humans a relationship between myelin sheath thickness and axon diameter also exists (13). In our material it was not possible to assess the size of the individual axons and myelin sheaths in the tracts because of the methods of preparation of the tissues.
Fig. 10. Cervical spinal cord from 9 month old infant at same level as Figure 5. Note presence of axons in lateral corticospinal tract (L) and absence in dorsal spinocerebellar (D) tract. The pial surface of the spinal cord is towards the left. (Bodian stain for axons, × 168).

TABLE 2
Data on Patients Surviving Parturitional Spinal Cord Transection

<table>
<thead>
<tr>
<th>Age months</th>
<th>C-H cms.</th>
<th>C-R cms.</th>
<th>Body weight kg.</th>
<th>Brain weight g.</th>
<th>Level of transection</th>
</tr>
</thead>
<tbody>
<tr>
<td>4(1)</td>
<td>64</td>
<td>—</td>
<td>&quot;well-nourished&quot;</td>
<td>608</td>
<td>C7-T1</td>
</tr>
<tr>
<td>6</td>
<td>70</td>
<td>47</td>
<td>5.5</td>
<td>605</td>
<td>C7-C5</td>
</tr>
<tr>
<td>8(1)</td>
<td>50</td>
<td>46</td>
<td>7.5</td>
<td>700</td>
<td>C7-T1</td>
</tr>
<tr>
<td>11</td>
<td>70</td>
<td>46</td>
<td>7.2</td>
<td>995</td>
<td>C5-T1</td>
</tr>
</tbody>
</table>

(after fixation)

Function is thought to be a significant factor in development of the nervous system including myelogenesis. Experimentally delayed myelination of optic nerves has been produced in mice deprived of light (14). Also, delayed myelination of homolateral dorsal column with smaller axons has been found in suckling rats following sciatic nerve transection (20). Volkmar and Greenough have shown that branching of dendrites in rat occipital cortex is greater in rats raised in a complex environment (27). This suggests that deprivation of input to a neuron leads to decreased growth of its axon and its myelin sheath.

Function is an important factor in determining the caliber of regenerated nerve fibers after crushing of the adult peripheral nerve (23, 24, 28). Nerve fibers in regenerating nerves which were prevented from establishing peripheral connections had more numerous and smaller fibers than those permitted to establish a peripheral connection (23, 24, 28). In addition, the nerve fibers proximal to the crush atrophied in the nerves prevented from functioning (24,
In our human infants the corticospinal tracts rostral to and the dorsal spinocebellar and spinothalamic tracts distal to the crush represent a situation similar to the above experiments; that is, the nerve fibers were unable to establish peripheral connections. Therefore, one might expect that the axons in these tracts would be smaller than usual and this may account for the lesser extent of myelination reported here. It may also be that the apparently fewer axons noted in the proximal corticospinal tract of the 11 month old represent atrophy as well as failure of expansion of these axons. Weiss et al's (28) and Sanders and Young's (23, 24) experiments were conducted on adult rats and rabbits so that the problems of growth and development are superimposed in our human infants. The tracts that are less myelinated in the infants with crushed spinal cords are those that are not or are incompletely myelinated at the time of birth. We therefore propose that deprivation of peripheral connections in the myelinating spinal cord results in slower myelination of those tracts that are not myelinated at the time of interruption.

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