DYSTOPTIC MYELINATION WITH HYPERTROPHY OF PYRAMIDAL TRACT

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ABSTRACT

In a case of hypertrophy of the pyramidal tract the cross section of the hypertrophic pyramids was 174% of controls with an increase (148%) in the total population of myelinated fibers. However, there was no commensurate increase in the density of Betz cells. Confined to the hypertrophic tract there was a peculiar anomaly consisting of tubes of thick myelin sheaths that encompassed columns of glial nuclei instead of axons. This type of change, along with the clinical data, may indicate that the lesion originated in the perinatal period when myelin formation is in progress and is susceptible to derangement.

INTRODUCTION

Hypertrophy of the pyramidal tract is a rare condition of puzzling pathogenesis. In a review of the literature Scales and Collins (34) found only 11 reports on a total of 17 cases, in addition to one of their own. Most patients had a history of infantile hemiplegia. An increased volume of the contralateral pyramids was interpreted as compensatory hypertrophy of the undamaged pyramidal tract (8, 29, 43, 44), a phenomenon that may depend on the existence of uncrossed pyramidal fibers descending in the ipsilateral tract (13, 40). Relatively well preserved voluntary movements of the paretic extremities were attributed to the hypertrophy or hyperplasia of such uncrossed fibers (34, 41, 43). There is consensus that hypertrophy of the pyramidal tract develops only if the contralateral tract is damaged early in life; yet, the morphologic basis of this phenomenon and the mechanism of the assumed adaptive process remain debated. In the following a new case is described with counts of Betz cells and of myelinated fibers in the pyramidal tract using thin sections of plastic embedded tissue. In addition a peculiar anomaly of myelin formation in the hypertrophied tract is reported, that is myelin sheaths encompassing columns of glia cells instead of axons.

CASE REPORT

This 62-year old man suffered from infantile cerebral palsy with slight left-sided hemiparesis. His first neurological examination was at the age of 26 years because of sudden onset of epileptic convulsions which began in the left arm. There was no record of difficulties during

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his gestation or in the perinatal period; frequent headaches as a child were the only complaints. Neurologic examination disclosed hyperactive reflexes on the left side with atrophy and muscular weakness of the left arm and a shorter and weaker left leg. In addition, there was a left facial paresis, said to date from earliest childhood. Anticonvulsive therapy reduced the frequency of seizures and the patient was capable of hard manual labour all his life, working as a stonemason and in road construction; he was capable of riding a bicycle. In his last years he suffered from chronic asthma-like bronchitis. Two weeks prior to his death he was found dyspeptic and unconscious at home, and he died in persistent coma. Necropsy revealed a severe generalized arteriosclerosis and sclerotic coronary heart disease with old myocardial infarctions and parietal thrombi in the left atrium and in the left ventricle. A fresh thrombus was found in the left renal artery with a resultant renal infarct, and there were peripheral pulmonary emboli, pulmonary congestion and bronchopneumonia.

Thin neomembranes covered the inner surface of the right cerebral hemispheric dura mater. Gross inspection of the right cerebral hemisphere revealed a depressed area, $5 \times 1.5$ cm, in the fronto-central region just above the Sylvian fissure, covered by slightly thickened leptomeninges. The left cerebral hemisphere showed a small occipital surface defect, and a markedly softened area measuring $3 \times 4$ cm in the post-central region with localized subarachnoidal bleeding. The pons was asymmetrical, the pyramids differed greatly in size; the left was expanded while the right was shrunken.

On coronal sections a large, partly collapsed cavity was found replacing most of the frontal cortex over the convexity and part of that of the insula. The distented frontal horn of the right ventricle was separated from the cavity by a 1 mm thick gli-oependymal membrane. No abnormalities were found in the cortex at the edges of the defect. The left hemisphere showed a recent large hemorrhagic infarct in the area of supply of the middle cerebral artery including the lateral surface of the frontal and temporal operculum, insula, head of the caudate nucleus, the putamen, and the white matter of the parietal lobe. The precentral region was spared. The small cavity in the occipital cortex was covered by an intact molecular layer. The asymmetries of the brain stem consisted of a reduction of the descending tracts in the flattened right half of the pons with crowding of the pontocerebellar fibers. At the medullary level the right pyramid was atrophic (about $3 \times 2$ mm) and the left was enlarged, measuring $6 \times 5$ mm. It extended across the midline, deflecting the ventral fissure, and dislocated the left inferior olivary nucleus dorsally (Fig. 1).

Microscopic examination of the large lesion of the right frontal lobe revealed a cavity lined by old gliosis containing foci of dense collagen. Neither reactive astrocytes, macrophages or proliferating vessels were seen. The small cortical defect in the left occipital region was of relatively recent origin and showed signs of subsiding organisation. The large hemorrhagic infarct of the left hemisphere was in early organisation with fresh hemorrhages, eosinophil degeneration of neurons, foamy macrophages and proliferation of glia cells and blood vessels.

**METHODS**

Betz cells were counted in cresyl violet-stained paraffin sections $5 \mu$ thick. A Betz cell was defined as a giant pyramidal cell in layer V, more than $20 \mu$ in width (3). Cell diameters were checked using an ocular-micrometer. For the counts segments of motor cortex of exactly 1 cm length were marked off on the slides and all nucleoli of cells fitting the above definition were counted. Six to eleven equivalent levels of the motor cortex were counted per case.

The area of the pyramids was measured at the midolivary level in enlarged photographs of slices of formalin fixed tissue, using a planimeter. Calibration was by means of a metric scale photographed together with the specimen. Subsequently the entire tissue of each pyramid was dissected into a series of approximately 30 numbered blocks; the location of each block was registered on a chart. Blocks were rinsed in 0.1% cacodylate-buffer, postfixed in buffered 2% osmic acid and embedded in Durcupan-ACM-Fluka. Semithin sections (1 $\mu$) were cut on a LKB-ultramicrotome and stained with toluidine-blue. From each pyramid four blocks from equivalent registered locations within the tract were selected. From each of these blocks three roughly equidistant high power fields were photographed. All profiles of myelinated fibers visible within two exactly calibrated ($0.0025 \text{ mm}^2$) squares drawn on a standard
Fig. 1. The hypertrophic left pyramid deflects the median fissure and dislocates the homolateral inferior olivary nucleus dorsally. The right pyramid is atrophic. Klüver-Barrera stain, 4 ×.

template of transparent foil were counted. For each pyramid 24 squares were counted. The total population of myelinated fibers of each pyramid was calculated from mean fiber numbers per mm² and the area of the pyramid. Control experiments with measured tissue cubes showed no significant volume-change of formaldehyde-fixed tissue during plastic-embedding. Ultrathin sections were made from the hypertrophic and the contralateral atrophic pyramid and from pyramids of three controls. After contrasting with uranyl-acetate and lead-nitrate they were studied in a Philips 201 electron microscope.

Five cases used for controls were between 58 and 83 years old; two of them suffered from carcinoma of the pancreas, the others had carcinoma of the stomach, chronic myeloid leukemia and combustions respectively. The brains were without pathologic changes, except for microscopic teleangiectasia in the basal ganglia in one and microinfarcts of the left caudate nucleus in another. There were no lesions in the motor cortex or in the pyramidal tract.

RESULTS

Cross-sectional areas of tracts and calculated total myelinated fiber populations are shown in Table 1. There was a significant enlargement of the left pyramid, its area being 174% of the mean of controls. Hypertrophy was also evident from the dorsal displacement of the homolateral inferior olivary nucleus. The total number of myelinated fibers in the hypertrophied pyramid was 148% of the mean of controls. Fiber packing was slightly decreased. A quantitative analysis of fiber diameters was not done, but subjective compar-
ison of the hypertrophic pyramid with the controls in semithin and in ultrathin sections disclosed no detectable difference in fiber calibers nor evident shifts in fiber spectra. The thickest fibers in the hypertrophic tract were of approximately same calibers as the thickest fibers in controls. The increase in total fiber numbers of the hypertrophic pyramid did not correspond to a proportional increase in the density of Betz cells in the ipsilateral precentral gyrus, as shown in Table 2.

On conducting these studies we became aware of fairly frequent profiles of myelin sheaths encompassing glial nuclei. These were seen only in the hypertrophic tract; not a single one could be found in the contralateral atrophic pyramid nor in any of the controls. Each of the semithin sections measuring about 1 mm² showed an average of 3 to 6 profiles of nuclei and cell bodies, presumably oligodendroglial, surrounded by myelin sheaths. The nuclei were round or oval with a maximum diameter up to 7 microns. The nucleolus was clear with dense aggregates of chromatin at the nuclear membrane. Nucleoli were not prominent. Sometimes the nucleus was excentric in relation to the sheath, being encompassed by a large homogeneous cell body that stained weakly with toluidine-blue. Cell borders were indistinct. At the times there was a cleavage between cell body and the inner surface of the sheath. The sheaths were usually thick and regular in profile, but flaring or relatively thin sheaths were also seen.

Electron microscopy of myelinated cells (Fig. 2) disclosed poor preservation of the formalin-fixed autopsy tissue. The relatively dense, uniform cytoplasm contained swollen and disintegrating mitochondria, numerous fragments of ribosomal aggregates, sparsely distributed vesicles, and cisternal elements of a granular endoplasmic reticulum. Lysosomes were not definitely identified but some cells showed compact myelin-like and loose concentric lamellar cytoplasmic inclusions. Some of these were discernible even with the light microscope. Glial fibers were absent. The cell membrane could be traced only for parts of the cell's circumference; longer segments of a distinct plasma membrane traced the innermost lamella of the myelin sheath. The

### TABLE 1

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<thead>
<tr>
<th>Area of Fiber Counts in The Medullary Pyramid</th>
<th>Case</th>
<th>Mean of controls</th>
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<tbody>
<tr>
<td></td>
<td>Left (hypertrophic pyramid)</td>
<td>Right (atrophic pyramid)</td>
</tr>
<tr>
<td>Area in mm² ± SD</td>
<td>23.7</td>
<td>6.0</td>
</tr>
<tr>
<td>Fibers per mm² in thousands ± SD</td>
<td>58.5 ± 9.9</td>
<td>55.4 ± 10.6</td>
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<tr>
<td>Total fibers in million ± SD</td>
<td>1.39 ± 0.24</td>
<td>0.33 ± 0.06</td>
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### TABLE 2

<table>
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<tr>
<th>Density of Betz Cells in Precentral Gyrus</th>
<th>Case</th>
<th>Mean of controls</th>
</tr>
</thead>
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<tr>
<td>Nucleoli of Betz cells (arbitrary 10 mm of central region, 5 μ sections) ± SD</td>
<td>20.2 ± 5.0</td>
<td>18.7 ± 7.5</td>
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Fig. 2 (Top) Four profiles of myelin sheaths containing glial nuclei in semithin sections; one of the cells includes small myelin figures within the cytoplasm \(1360 \times\). (Middle) A glia cell occupies nearly the entire space within the myelin sheath \(8400 \times\). This myelin sheath encompasses 3 structures: a central perikaryon; a lamellar cell process abutting the inner surface of the sheath which may or may not belong to the perikaryon; and a round profile with fibrillar material thought to be astrocytic \(18220 \times\).
myelin sheaths were of uniform thickness, although splitting of lamellae was common, evidently from poor fixation. The thickness of the sheaths that encompassed cells corresponded to medium sized or thick fibers in the tract; compact myelin sheaths with up to 50 major dense lines were counted. Structures equivalent to internal or external mesaxons could not be identified. In one instance three components were distinguished within one sheath namely a central cell body with nucleus, secondly a cell process encompassing this cell, lining the inner surface of the sheath, and, thirdly, a round profile of another cell process containing abundant filaments, suggestive of an astrocytic process (Fig. 2). All other myelinated cells contained no such filaments.

An effort was made to determine the longitudinal extension of the myelinated cells and their sheaths from reconstruction of fibers cut in series approximately parallel to their axes. These disclosed tubular sheaths of varying caliber containing columns of nuclei. The longest segment that could be studied contained 6 nuclei within the same myelin tube (Fig. 3). No information could be obtained on the configuration of the terminal poles of such tubes.

DISCUSSION

The hypertrophy of the pyramidal tract in our case was documented by a significant enlargement of the area of the tract in crosssection compared with three normal controls, as well as by dorsal displacement of the homolateral inferior olivary nucleus. The area of the pyramid in our control cases (13.6 mm²) compares well with the mean value of 11 mm² (6.5–14.1) found by DeMyer (9) in frozen sections of 21 subjects. Duncan (10) recorded 17.2 to 26.2 mm² for both pyramids in formalin fixed specimens, and Lassen and Rasmussen (25) noted pyramids from 10.9 to 11.7 mm² in size from sections corrected for shrinkage. Measurements of hypertrophied pyramids were mostly done on embedded material and are not directly comparable. In the cases of Verhaart (43) and van der Bruggen (41) the size of the hypertrophied tract was only slightly above normal. The 30.2 mm² recorded by Scales and Collins (34) was clearly abnormal.

An increase in the number of fibers in the hypertrophied tract, as in the present case, was similar to that found by van der Bruggen (41) and Scales and Collins (34); the latter authors generally recorded higher numbers for both hypertrophic tract and controls, evidently due to differences in their counting technique. Verhaart (42, 43), in contrast, emphasized that there was only a relative preponderance of the medium-sized and the large fibers; however, the pyramids of his cases were not much larger than normal. The use of semithin sections of plastic embedded material in the present study permitted positive identification of even the thinnest myelinated fibers. According to DeMyer (9) the total axonal populations of 21 pyramidal tracts of normal brains varied between 0.75 and 1.39 million, approximately 6% of the fibers being nonmyelinated. The highest number of myelinated fibers recorded in his series was 1.26 millions, still below the 1.39 millions found in
the hypertrophic pyramidal tract of our case. Yet, the increase in fiber number (148%) was much less than the increase in the area of the tract (174%), due to a reduced packing density of the fibers.

No previous assessment of the Betz cell population is on record although van der Bruggen (41) postulated that there should be more Betz cells in such
cases. The density of Betz cells in the present case failed to disclose a significant increase. We have no data for determining whether the motor strip was larger than normal, although this did not appear to be the case. These findings do not rule out an increase in the number of fibers in the pyramid, as Betz cells account only for a minor part of the fiber population of the pyramidal tract (23) giving origin especially to the thickest fibers (24). Theoretically an increase in the number of thick fibers may cause hypertrophy of the tract since fibers thicker than 10 μ occupy 18% of the volume of the tract even though they comprise only 1.73% of the total fiber population (23). However, neither a significant increase in the number of Betz cells nor a relative preponderance of thicker fibers was found. Hence, if there is compensatory hyperplasia it must receive only little contribution from the Betz cells and their neurites.

A previously unrecorded aspect of the hypertrophic pyramid was the considerable number of myelin sheaths that contained glial cell bodies, presumably oligodendroglia, instead of axons. This phenomenon was virtually restricted to the hypertrophied tract. Myelination of structures other than axons is uncommon. Nerve cell perikarya of peripheral ganglia, especially that of the VIIIth nerve may be encompassed by myelin sheaths in several species (16, 27, 28, 30, 31, 33, 35, 38). There are also scattered observations on myelinated neuronal perikarya within the central nervous system, i.e. in the habenular nuclei of the frog (19), cerebellar granule cells in toads, mice and man (32, 37), and about nerve cells in the spinal cords of the mouse (5) and the monkey (1). Myelinated nerve cells were also seen repeatedly in tissue culture (11, 17, 20, 21, 22).

Reports on myelin sheaths about non-neuronal elements are still less frequent. Haug (15) reports an incidental myelinated glial nucleus in the white matter of a cat, and Leonhardt (26) found groups of myelinated oligodendroglia cells in the median eminence of rabbits. Dystopic myelination of glial cells may be found, on occasion, in experimental lesions including glial scars in the rat cerebral cortex (36), in secondary fiber degeneration in the chicken optic tectum (14), in crush injury of the rat optic nerve (39) and in lesions of the corpus callosum in cyanide intoxication (18). Myelination of astrocytic processes may develop following dorsal root section in the cat (2) and within experimentally produced gliosis in the rabbit cerebral cortex (4). Myelination of complex structures that include synapses, dendrites, astrocytic and oligodendroglial processes was observed following cryogenic injury of the rat cerebral cortex (7).

The present observations record dystopic myelination as a component, perhaps characteristic, of a human disease. Possibly this feature and the clinical record may date the lesion to early infancy, when the process of myelin formation is still active and is susceptible to derangement. The only other comparable observation in man is myelination of astrocytic processes in status marmoratus (6); this begins early in development. However, recent studies of early stages of status marmoratus tend to de-emphasize dystopic myelination as a cause of the abnormal myelin pattern in this disease (12).

Whether dystopic myelination is the cause of or is a critical factor in
producing the hypertrophy of the tract remains uncertain. Myelinated columns of glial cells undoubtedly did add to the sum of myelinated "fibers"; these structures were usually of large caliber. Yet their exact frequency could not be determined as many of them may have been cut at levels that did not include nuclei. It appears unlikely, though, that there were enough of them to account for a 174% increase in the volume of the tract. More likely, the increase in volume resulted from a combination of several factors including dystopic myelination, reduced packing density of the fibers, and a "compensatory" hyperplasia of fiber population.

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REFERENCES


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