Remyelination in the Human Central Nervous System

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Abstract. Remyelination, albeit incomplete, has been demonstrated in human central nervous system (CNS). However, information about the initial stage and the final extent of such remyelination is not available. We describe the morphologic findings of a demyelinating lesion with evidence of early remyelination in a biopsy obtained from a 15-year-old boy about two weeks after the onset of neurologic symptoms. The demyelinated area appeared hypercellular with a relatively large number of oligodendrocytes frequently seen in the process of new myelin formation. In addition to the usual reactive changes, the astrocytes were often seen to contain otherwise normal-looking oligodendrocytes within their cytoplasm. In the ensuing months, the patient made apparently total functional recovery accompanied by nearly complete resolution of the white matter lesions demonstrated by the subsequent magnetic resonance studies. These observations suggested that the initial remyelination seen in the biopsy eventually succeeded in producing extensive remyelination in the lesion. Although the exact nature of the demyelinating disorder in our patient remains undetermined, this study indicates that clinically significant remyelination is possible in human CNS. Also, our findings appeared strikingly similar to those described in certain experimental animal models in which widespread remyelination is known to occur.

Key Words: Astrocyte; Demyelination; Multiple sclerosis; Oligodendrocyte; Remyelination.

INTRODUCTION

The occurrence of remyelination in human central nervous system (CNS) has been convincingly demonstrated by morphologic studies of multiple sclerosis (MS) lesions (1–4). Usually a small number of remyelinated axons, recognized by abnormally thin myelin sheaths, are seen in chronic MS plaques. More recently, studies of acute MS lesions at autopsy have shown formation of new myelin in the presence of ongoing myelin destruction (5, 6). However, the fate of such attempted remyelination in a given lesion is obviously not possible to determine from these studies. It is now generally assumed that remyelination in human CNS, when it occurs, is incomplete and usually confined to the periphery of the plaques. The clinical significance of such limited remyelination is yet to be established, although it has been suggested that thinly remyelinated axons at the plaque margins may play a critical role in continuous conduction by the demyelinated axons (7).

In this report, we describe the morphologic features of a demyelinated lesion with an early stage of remyelination in a biopsy obtained about two weeks after the onset of symptoms. Subsequent clinical follow-up and magnetic resonance (MR) studies strongly suggested that a significant degree of remyelination had occurred in this patient. We believe that this case provides a rare opportunity to document the morphologic details during the initial stage of remyelination in human CNS. Also, we analyze these findings in light of the present understanding of CNS remyelination, which is largely based on experimental observations.

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Fig. 1. Sequential MRI studies showing coronal slightly T2 weighted images (TR = 2,500-3,000 millisecond (ms); TE = 25–30 ms) through posterior (occipital) horns of the lateral ventricles. A. (Initial study) shows increased signal intensity in subcortical white matter and around occipital horns. Bx indicates approximate site of biopsy. B. (At 16 days) and C (at two months) show progressive resolution of lesions. D. (At 18 months) shows nearly complete resolution of lesion with only residual periventricular component.

CASE REPORT

A 15-year-old boy was admitted to the hospital with complaints of headache and progressive binocular visual loss of two weeks' duration. About a week earlier, the patient had had flu-like symptoms characterized by low grade fever, nausea, vomiting, diarrhea, cervical lymphadenopathy and orthostatic light-headedness. There were no symptoms referable to motor and general sensory functions. There was no history of trauma or exposure to toxic substances.

On examination, the patient was alert and afebrile with normal vital signs. Visual acuity was reduced to hand motion bilaterally. Color vision was absent. Pupillary function was normal. There was no afferent pupillary defect. The visual fields were
Fig. 2. A. Biopsy showing demyelination sharply demarcated from intact white matter. LFB-PAS, x60. B. Relative sparing of axons in demyelinated area. Bielschowsky, x350. C. Demyelinated area showing hypercellularity with mitoses in reactive astrocytes. H&E, x400.

highly constricted on both sides with a relatively more dense right homonymous hemianopia. The fundi were normal. Optokinetic response was blunted in all planes. Oculomotor function was otherwise normal. There were no motor or sensory deficits. The plantar responses were normal.

Extensive laboratory examination including throat culture, serology, and urine toxicology screen showed no abnormality. Cerebrospinal fluid (CSF) was under normal pressure, colorless and revealed the following: one lymphocyte/mm³; glucose 55 mg/dl (serum glucose 95 mg/dl); total protein 122 mg/dl; myelin basic protein 15.6 ng/ml (normal 1–5 ng/ml); IgG/albumin ratio of 0.09. Oligoclonal banding was absent. An electroencephalogram showed diffuse slow activity, more so in the left hemisphere. Computerized tomography (CT) with intravenous contrast material demonstrated bilateral hypodense lesions in the white matter of the occipital and posterior parietal regions. The periphery of the lesions showed ring-like enhancement. The magnetic resonance imaging (MRI) demonstrated lesions in the same region with more precise localization (Fig. 1A).
A CT-guided stereotactic needle biopsy was obtained from the left occipital lesion two days after admission. The pathologic findings of the biopsy are described below. The patient was treated with intravenous methyl prednisolone (250 mg every six hours) for three days followed by oral prednisone 100 mg per day, tapered over the ensuing two weeks.

There was progressive improvement in the patient’s visual function. Two weeks after admission, his corrected visual acuity measured 20/20 bilaterally. The color vision remained impaired and his visual field test demonstrated a relative right homonymous hemianopia. Subsequent follow-up at about nine months after the onset of initial symptoms demonstrated complete resolution of the visual field deficit and return of color vision. The patient returned to full participation in academic and extracurricular activities without experiencing any difficulty and remains symptom-free about two years after the initial illness. The MRI obtained at 16 days (Fig. 1B), and at two months (Fig. 1C) showed progressive decrease in the white matter lesions compared to those in the initial study (Fig. 1A). The MRI obtained 18 months after the initial study showed nearly complete resolution of the lesions with minimal residual periventricular component (Fig. 1D).

PATHOLOGIC STUDY

A portion of the biopsy specimen was embedded in paraffin and the sections were stained by hematoxylin and eosin (H&E), luxol fast blue (LFB)-PAS and Bielschow-
sky methods. For electron microscopy (EM), the specimen was immersed in 4% glutaraldehyde immediately after removal and was processed in the usual manner.

The tissue consisted of white matter with a sharply demarcated area of demyelination (Fig. 2A) with relative preservation of axons (Figs. 2B, 7). In paraffin-embedded sections, the lesion appeared quite cellular with some degree of pleomorphism and many mitoses particularly in reactive astrocytes (Fig. 2C) and occasionally in small mononuclear cells, presumably oligodendrocytes. No lymphocytic infiltration, perivascular or otherwise, was seen.

In addition to a variable number of reactive astrocytes and macrophages containing myelin debris, many oligodendrocytes were seen throughout the lesion (Fig. 3). These cells contained large nuclei and relatively dark cytoplasm with abundant rough endoplasmic reticulum and microtubules but no glial filaments (Figs. 3, 4), thus conforming to the morphologic criteria of oligodendrocytes (8). They were often seen in small clusters and displayed delicate processes. These tongue-like processes frequently invested naked axons to a variable extent initiating the formation of myelin (Figs. 4–6). The newly formed myelin sheaths were thin but compact and consisted of up to five or six lamellae. The presence of aberrant cytoplasmic loops in these sheaths was a common feature (Fig. 6B). Such early myelination was seen only in a small proportion of the demyelinated axons (Fig. 7).

The reactive astrocytes displayed large cytoplasmic area containing various organelles including filaments and often lipid droplets (Figs. 3, 8). Slender and often branching processes of these cells closely resembled those of oligodendrocytes and
Fig. 5. Oblique section of axons (Ax) showing partial investment by slender cell processes (O) presumably from oligodendrocytes. ×32,500.

were seen in between naked axons, sometimes completely enclosing them (Fig. 8). In addition, large reactive astrocytes contained the cell body of an oligodendrocyte within the cytoplasm (Fig. 9). Sometimes two oligodendrocytes were seen in the same astrocyte. These internalized oligodendrocytes appeared viable with a smooth cell surface separated from the astrocytic cytoplasm by a narrow space occasionally, with formation of rudimentary junctions (Fig. 9). Otherwise, these apparently engulfed oligodendrocytes were morphologically identical to those forming myelin elsewhere in the lesion. Whether or not the internalized oligodendrocytes represented the entire cell bodies could not be determined. This interesting phenomenon was observed frequently at the fine structural level and occasionally, with the light microscope as well (Fig. 3).

DISCUSSION

The precise nature of this apparently monophasic demyelinating lesion remains unknown. Although the morphologic features are indistinguishable from those seen in acute multiple sclerosis (MS), such a diagnosis in our patient cannot be confirmed at this time. On the other hand, an antecedent history of flu-like symptoms might raise the possibility of postinfectious demyelination despite the absence of perivascular lymphocytes in this limited biopsy sample. Regardless of the etiology, the white matter changes seen on MRI in this patient clearly represented areas of demyelination with evidence of early remyelination as demonstrated in the CT-guided stereotactic biopsy from one of the lesions. Obviously, it is not possible to ascertain the final outcome of this attempted remyelination without subsequent biopsy studies from

Fig. 6. Cross section of axons showing partial (A) and complete (B) investment by cytoplasmic processes with formation of thin but compact myelin sheath in B. Arrows indicate overlapping cytoplasmic loops. × 24,000.

the same lesion. However, based on the follow-up MRI which showed dramatic resolution of the white matter lesions accompanied by functional recovery, it seems reasonable to assume that the initial remyelinating process seen in the biopsy eventually succeeded in producing substantial regeneration of myelin. Areas of high signal intensity detected by MRI in MS patients often correlate poorly with neurologic deficits and sometimes remain asymptomatic (9–13). On follow-up with MRI, some of these lesions have been shown to decrease in size or even disappear (12, 13). In the absence of histologic verification, it is not possible to determine whether such areas predominantly represent demyelination or simply reflect large areas of transitory edema associated with small foci of inflammatory myelin destruction during
the early stage of MS lesions. Therefore, mere resolution of these unverified high signal lesions on subsequent MRI cannot be regarded as definitive evidence of remyelination.

Remyelination in the CNS has been studied in a variety of animals under many experimental conditions (14–21). In addition to CNS myelin derived from oligodendrocytes, remyelination of CNS axons by Schwann cells has been observed in several models similar to that described in human CNS in MS (22, 23). Also, there seems to be a wide range of variation in the degree of remyelination in different models. For example, in immune-mediated demyelination produced by chronic experimental allergic encephalomyelitis (EAE) or Theiler's murine encephalomyelitis virus (TMEV), the extent of remyelination has been found to be much less compared to that in the lesions induced by Cuprizone (biscycloaldehydrazone) or by a certain strain of mouse hepatitis virus (MHV) in which immunologic mechanisms are not implicated (24). Whether or not a similar relationship exists between the nature of demyelination and the degree of remyelination in humans is not known. The morphologic features of early remyelination in the biopsy from our patient were similar in many respects to those seen in certain experimental models, especially in Cuprizone-treated young mice (19). The stage of remyelination observed in our patient's biopsy taken about two weeks after the onset of symptoms seemed to correspond to that seen in these mice at one week following Cuprizone-induced demyelination. Such a similarity is particularly noteworthy since spontaneous widespread remyelination is known to occur in these animals by six or seven weeks following the experimentally induced demyelination.
Lack of significant remyelination in human CNS has long been attributed mainly to astrocytic gliosis in the lesions and an inability of mature oligodendrocytes to multiply. However, recent studies of active MS lesions have shown that there is no paucity of oligodendrocytes in such lesions. As described in this report, there seems to be an increased number of oligodendrocytes in lesions with ongoing demyelination suggesting a proliferation of oligodendrocytes that survived the initial pathologic process (3, 5, 6, 8). Active multiplication of oligodendrocytes has also been demonstrated in experimental animals under pathologic conditions including demyelination induced by Cuprizone or MHV (19, 23, 26). As mentioned before, extensive remyelination occurs in these non-immune mediated demyelinating lesions. Autoradiographic study of these lesions following administration of tritiated thymidine indicated that the oligodendrocytes responsible for new myelin formation are derived as a result of recent multiplication. What triggers the proliferation and differentiation of oligodendrocytes in a demyelinating lesion is not known. Rodriguez et al (24) have recently shown that proliferation of oligodendrocytes and remyelination could be greatly enhanced in TMEV induced demyelination in mice by treatment with serum from syngeneic animals immunized with homogenized spinal cord. These and similar observations in chronic EAE animals treated with myelin basic protein and galactocerebroside (20, 27) are particularly interesting since significant remyelination is not commonly seen in these models. These observations raise the possibility of the therapeutic use of such agents to stimulate remyelination in MS.

The histologic appearance of this lesion containing oligodendrocytes and reactive astrocytes with mitoses closely simulated that of a neoplasm. Indeed, the difficulty
Fig. 9. An internalized oligodendrocyte within the cytoplasm of an astrocyte (the same cell illustrated in Fig. 8). $\times 12,600$. Inset: a narrow space separates oligodendrocyte (O) from astrocyte (A). Arrows indicate a rudimentary junctional device. $\times 31,000$.

In differentiating an active MS lesion from a glioma, especially in a limited biopsy specimen, has been recently emphasized (28). Reactive astrocytosis is usually held responsible for inhibiting CNS remyelination by establishing a barrier between the axons and oligodendrocytes. This seems to be the case in long-standing demyelinated lesions such as in MS or chronic EAE (20). However, in a recent lesion as described in this study, investment of the naked axons by astrocytic processes apparently had no significant adverse effect on remyelination. A similar observation has been made in studies of certain animals in which remyelination occurs following experimentally induced demyelination (19, 21). Therefore, the role of astrocytes in impeding remyelination seems to vary under different conditions.

A remarkable feature of the reactive astrocytes observed in this study was the presence of oligodendrocytes within their cytoplasm. This interesting phenomenon has apparently been overlooked until recently when Prineas et al reported it in acute MS lesions (6). They interpreted this finding as representing phagocytosis of new oligodendrocytes by astrocytes and suggested that this may be an additional factor in limiting remyelination in MS. Detailed morphologic description of this phenomenon is not available and a similar finding has apparently not been reported in experimental animals. The fine structural observations in this study do not seem to indicate that internalization of these otherwise intact oligodendrocytes by astrocytes represents true phagocytosis. Also, the number of the sequestered oligodendrocytes in this lesion apparently was not large enough to impede remyelination. Further studies are needed before any significance can be assigned to this newly recognized phenomenon.

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Remyelination is often considered as a possible explanation for remission in MS. To our knowledge, clinically significant functional recovery as a result of remyelination has not been documented in humans. Clinical and MRI findings similar to those described in our patient have been reported, however, without pathological verification of the lesion (29). The present study, therefore, is significant in that it provides evidence, albeit indirect, that, contrary to the traditional views, substantial remyelination is possible in human CNS. It also raises the question whether remyelination to a similar extent can occur in MS, especially during the initial episodes. Obviously, this question remains unresolved since the nature of the demyelinating lesion in our patient is not known. With the advent of MRI and increasing use of stereotactic biopsy technique, similar correlative studies of MS and other demyelinating disorders may shed light on this important question.

REFERENCES


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