Cellular Inflammation in Nonarteritic Anterior Ischemic Optic Neuropathy and Its Primate Model

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Objective: To correlate potential inflammatory responses in nonarteritic anterior ischemic optic neuropathy (NAION) with a lesion possessing many physiologic and histologic similarities from a model of nonhuman primate NAION (pNAION).

Methods: Using immunohistochemistry and confocal microscopic analysis, we evaluated the relative numbers of inflammatory cell types in the single available clinical specimen of early NAION (21 days after event). We correlated this with the temporal inflammatory response occurring in optic nerve tissue at different times following pNAION induction.

Results: In pNAION, there is a previously unsuspected infiltration of polymorphonuclear leukocytes occurring almost immediately after infarct induction, followed by invasion of ED1+ extrinsic macrophages, which peaks 5 weeks after infarct. Intrinsic microglia accumulate up to 70 days after induction in the area of primary axonal loss. The analyzed human NAION specimen was similar to 21-day pNAION tissue, with extrinsic macrophages and intrinsic microglial cells in the region of focal axon loss.

Conclusions: Cellular inflammation plays a major early role following white-matter (optic nerve) infarct, with both polymorphonuclear leukocyte and macrophage function involved in debris elimination and tissue remodeling. The optic nerve in NAION and its primate model are associated with early cellular inflammation, previously unsuspected, that may contribute to postinfarct optic nerve damage.

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The optic nerve (ON) is a central nervous system (CNS) white-matter tract composed of retinal ganglion cell axons and supporting glia. The retinal ganglion cell axons synapse in the lateral geniculate nuclei.

Nonarteritic anterior ischemic optic neuropathy (NAION) is the leading cause of sudden ON-related vision loss in the developed world, with an incidence in the United States from 3 to 10 cases per 100,000 population per year. There is currently no effective treatment for this condition, largely because little is known about its pathophysiology and early cellular changes following onset. The reason for this lack of knowledge is that few histopathologically studied cases of acute NAION exist and partially because until recently no relevant NAION animal models existed.

In 2003, our laboratory developed the first reproducible murine model of human NAION (rAION). This model is generated by laser activation of the photosensitive dye rose bengal. Following induction in this model, pathologic assessment including immunohistochemical analysis reveals not only ischemia but also an early significant inflammatory response in the infarct region that may contribute to subsequent ON damage. Using a technique similar to that used to induce rAION, our laboratory recently developed a nonhuman primate (NHP) model of NAION (pNAION). This model is clinically, electrophysiologically, and angiographically identical to human NAION and has the added advantage of identifying primate-specific responses to ON ischemia. Although no early histologic findings have been reported in this model, late histologic findings (5-9 weeks after induction of pNAION) show changes consistent with an isolated optic neuropathy. Immunohistochemical evaluation of affected ONs in this model reveals a consistent late inflammatory response in the region of the infarct similar to that observed in rAION.

Currently, NAION-associated ON damage is theorized to result from thrombotic or hypoperfusion ischemia, which pro-
duces tissue edema in the confined space of the ON sheath. This process results in a compartment syndrome, with additional vascular compromise, similar to that which occurs in other CNS white-matter strokes.4 Thus, NAION may be considered a stroke of the ON, similar to white-matter strokes elsewhere in the brain.3 A complex temporal and sequential cellular inflammatory response has been identified in cortical lesions following middle cerebral artery occlusion.7 Nonarteritic anterior ischemic optic neuropathy should therefore result in inflammatory responses similar to those of other CNS regions. Although histologic examination of recently infarcted CNS white matter reveals both ischemic changes and postischemic inflammation that may have an important role in the evolving brain ischemic final injury,9 early human NAION pathology has been described in very few reports. One study digitally analyzed the region of the ischemic lesion in a patient who died 20 days after developing NAION and found an infarct confined to the region of the lamina cribrosa (the junctional region between the retina and the ON).9 Although these investigators did not detect pathologic evidence of an inflammatory response in this region, they did not use any specialized stains to identify inflammatory cells. A large retrospective histopathologic review of 193 eyes with presumed ischemic optic neuropathy of different etiologies was performed by Knox et al.8 In none of these cases had an ophthalmic examination been performed just before the patient’s death, although in 23 of 193 cases (11.9%), there was a history of acute vision loss, and in a small number of these cases, death occurred shortly after the occurrence of an acute systemic vascular event. In these acute cases, focal ischemic edema was associated with foamy macrophages (ie, gitter cells), but similar to the single human study,9 no immunohistochemical stains were used to assess inflammation in the areas of ON damage.8

The question of human NAION-associated inflammation is relevant to potential treatment. An early post-NAION inflammatory response could cause persistent or even progressive nerve dysfunction. If this latter effect occurs, early treatments aimed at selectively reducing the inflammatory response could theoretically result in improved visual outcome in patients with NAION.

The aims of this study were 3-fold: (1) to determine, using the ON of the patient who died shortly after developing well-documented NAION9 and whose ON tissue was provided to us, whether inflammation is a prominent feature of early human NAION as opposed to a generalized epiphenomenon that occurs only in the later stages of CNS ischemia; (2) to determine whether the pNAION model shows early inflammatory changes similar to those observed in our rAION model; and (3) to compare the relative timing and type of observed inflammatory response in the pNAION model with any inflammation identified in the human specimen, using tissue from pNAION-affected animals at different times following induction of pNAION, thus enabling us to capture the timing and potential range of different immune responses that may occur during the development and progression of isolated ON infarction in humans and other Old World primates.

**METHODS**

Institutional review board exemption was obtained from the University of Maryland at Baltimore Institutional Review Board. Tissue from an individual with masked identity was obtained (see the “Human Material” subsection). All animal procedures were performed on tissues obtained from work generated via an approved University of Maryland at Baltimore Institutional Animal Care and Use Committee proposal.

**HUMAN MATERIAL**

The clinical material from an individual with NAION was derived from prepared ON tissue from the previously reported case of a 70-year-old white man with a history of systemic hypertension, coronary artery disease, congestive heart failure, atrial fibrillation, peripheral vascular disease, and renal failure.7 The patient had experienced sudden, painless loss of vision in the left eye 2 days after a thromboembolectomy performed for a femoral-popliteal thromboembolism with postoperative anemia. There were no intraoperative complications and specifically no history of acute hypotension; however, during the next 48 hours, the patient’s hematocrit level substantially decreased, requiring transfusion with 4 U of packed red blood cells. Two days later (the fourth day following the thromboembolectomy), the patient complained of visual difficulties in his left eye, at which time NAION of the left eye was diagnosed. Final visual acuity was reported as 9/200 in the affected eye, associated with an inferior altitudinal field defect by confrontation, a relative afferent pupillary defect, and left optic disc swelling with small, peripapillary retinal hemorrhages. The Westergren erythrocyte sedimentation rate (typically elevated in arteritic cases of AION) was 21 mm/h (normal for age). The patient died 20 days later of complications of renal failure, pancreatitis, and hypercalcemia. The patient’s affected eye was removed 12 hours postmortem, formalin fixed, paraffin embedded, and serially sectioned in the coronal plane at 6-µm steps. Two unstained tissue cross-sections of the ON immediately posterior to the globe were sent to us by the authors7 for immunohistochemical analysis. Normal human ON pathology samples from the William Richard Green Ocular Pathology Laboratory of the Wilmer Eye Institute, The Johns Hopkins Hospital, were used for comparison.

**NONHUMAN PRIMATE MATERIAL**

Male rhesus macaques (NHPs; weight, 5-10 kg each; age range, 3-10 y) were obtained from commercial sources. Animals were eliminated from the study if they had any history of eye disease or inflammatory disorders. We induced pNAION as previously reported,3 using rose bengal (0.5 mL/kg of 5.0 mM in Dulbecco phosphate-buffered saline) and 7 to 10 seconds of ON exposure to 200 mW/1.06-mm-diameter 532 nm laser light from a frequency-doubled yttrium-aluminum-garnet laser (Iridex, Mountain City, California). Optic nerve.eye tissues were obtained from animals euthanized at various times after induction. Tissues were fixed either in 4% paraformaldehyde-phosphate buffered saline and embedded in paraffin and sectioned at 7 µm or embedded in optimal cutting temperature compound, frozen in liquid nitrogen, and sectioned at 10 µm. The Table shows the different times from induction and relative lesion severity.

<table>
<thead>
<tr>
<th>Time after Induction (h)</th>
<th>Lesion Severity</th>
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<tbody>
<tr>
<td>3</td>
<td>Mild</td>
</tr>
<tr>
<td>6</td>
<td>Moderate</td>
</tr>
<tr>
<td>12</td>
<td>Severe</td>
</tr>
<tr>
<td>24</td>
<td>Extensive</td>
</tr>
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Paraffin-embedded ON tissue specimens were deparaffinized in xylene and graded alcohols and incubated with 5% block-
ing serum in phosphate-buffered saline for 3 hours. All tissue samples were then incubated with up to 3 primary antibodies overnight at 4°C. Antigen retrieval was performed using a boiling citrate buffer protocol (http://www.ihcworld.com/_protocols/epitope_retrieval/citrate_buffer.htm). Sections were bleached to eliminate nonspecific autofluorescence (Poly sciences, Warrenton, Pennsylvania).

The marker ED1 (CD68) recognizes a membrane protein that is present on newly synthesized (extrinsic) macrophages and monocytes. We used a mouse monoclonal antibody against human ED1 (CD68) (clone KP1; Dako, Glostrup, Denmark). Rabbit polyclonal antibody against Iba-1 (Wako, Richmond, Virginia) recognizes the ionized calcium-binding receptor membrane protein expressed in macrophages and microglia and acts as a general marker for all inflammatory cells. The marker SMI312 (Sternberg Monoclonals, Inc, Lutherville, Maryland) is a cocktail of mouse monoclonal antibodies that recognizes neurofilaments and is a useful marker for intact axons. Myeloperoxidase recognizes polymorphonuclear leukocytes (PMNs) and immature monocytes. We used a rabbit polyclonal antibody against human myeloperoxidase (Dako).

Following blocking in 3% donkey serum–phosphate-buffered saline, sections were incubated in primary antibodies overnight at 40°C, followed by incubation with appropriate donkey secondary Cy3 or Cy5 fluorescent-labeled antibodies (1:1000) (Jackson ImmunoRes, West Grove, Pennsylvania), overnight at 4°C. Antigen retrieval was performed using a boil- ing serum in phosphate-buffered saline for 30 seconds and mounted with a custom-generated fluorescent mounting medium. Sections were visualized with an E900 fluorescent digital confocal microscope (Olympus, Tokyo, Japan).

RESULTS

Cross-sections of normal human ON revealed no evidence of tissue disruption with standard hematoxylin-eosin staining (Figure 1A), immunostaining with Iba1 and SM312 (Figure 1B), or immunostaining with Iba1 and ED1 (Figure 1C). Eosinophilic axons were present in organized bundles surrounded by fibrovascular pial septae (Figure 1A). The axons stained positively with SM312 (Figure 1B).

Immunohistochemistry revealed that Iba1+ cells were scattered randomly throughout the axon bundles of the nerve (Figure 1B), but there were only rare ED1+ cells in the normal ON sections (Figure 1C). This photograph was the basis for the initial report of the lack of inflammation within the affected ON. Using this photograph, we subdivided the unaffected cross-section of the nerve into 5 different zones on the basis of the level of structural morphology and nuclear staining pattern. The zones were an area of normal nerve tissue (zone 1), the infarct (zone 3), 2 areas with some tissue damage adjacent to the infarct (the penumbra and zones 2 and 5), and a central area containing a central vessel supplying the nerve (zone 4).

The results of SMI312, ED1, and Iba1 immunostaining of the affected ON section revealed significant differences in the number of intact axons as well as of Iba1+/ED1− cells and Iba1+/ED1+ cells in the different subregions (Figure 3). Specifically, Iba1+/ED1− cells (presumably intrinsic microglia) were present in all areas, whereas Iba1+/ED1+ cells (presumably extrinsic macrophages) were present in the area of the infarct (zone 3)

<table>
<thead>
<tr>
<th>Animal Identifier</th>
<th>Time From Lesion Onset, d</th>
<th>Approximate Optic Nerve Axonal Loss, %</th>
<th>Note</th>
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<tbody>
<tr>
<td>SH (OS)</td>
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<td>0</td>
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<td>...</td>
</tr>
<tr>
<td>Q10 (OS)</td>
<td>7</td>
<td>50</td>
<td>...</td>
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<tr>
<td>Q10 (OD)</td>
<td>21</td>
<td>50</td>
<td>Similar time to clinical specimen</td>
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<tr>
<td>D6LR</td>
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<td>...</td>
</tr>
<tr>
<td>P25 (OD)</td>
<td>70</td>
<td>80</td>
<td>Maximal lesion</td>
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Abbreviation: pNAION, nonarteritic anterior ischemic optic neuropathy in a nonhuman primate.
[Figure 3B]) and in the penumbral regions (zones 2, 4, and 5 [Figure 3C]) but not in the normal region (zone 1 [Figure 3A]). These differences were not apparent in the hematoxylin-eosin–stained section. Similarly, SMI312 staining was variable, depending on the region stained. Staining was relatively normal in the normal area of the nerve (zone 1), with evenly distributed neurofilaments (Figure 3D). In contrast, the SMI312 signal was markedly attenuated in the region of the primary infarct (zone 3 [Figure 3E]) and in the penumbral regions (zones 3 and 5 [Figure 3F]), indicating severe axon disruption.

Timed specimens of NHPs with pNAION enabled detailed histologic analysis of the changes that occur in both the overall structure of the retina/ON junction and the degree to which infarct-associated edema and inflammation alter these structures. Figure 4 shows hematoxylin-eosin–stained sections of the specimens used for immunohistochemistry. Confocal microscopic evaluation of the nature of the inflammatory process was performed using immunostaining for PMNs (myeloperoxidase), total inflammatory cells (macrophages plus PMNs plus microglia; Iba1), and recently generated extrinsic macrophages (ED1). Similar to the clinical specimen, SMI312 immunostaining was performed to identify normal axon elements. Myeloperoxidase+/PMN identity was confirmed using tissue from a recent infarct. Results from these specimens revealed the temporal wave nature of inflammatory processes present in the affected tissue (Figure 5). Specific
nearly, in the naive ON, Iba1+/ED1−/myeloperoxidase− cells were randomly scattered throughout the nerve (Figures 5A, D, and G). Three days after induction, there was an accumulation of myeloperoxidase+/PMNs, but only a few ED1+/extrinsic macrophages were present (Figures 5B, E, and H). By 1 week after induction, the number of PMNs had drastically decreased, but large numbers of extrinsic macrophages were apparent (Figure 5I).

Analysis of inflammatory cell types in affected ONs at later time points was also revealing (Figure 6). At 21 to 70 days after induction, there was focal loss of SMI312 immunoreactivity (Figures 6A-C, arrowheads), indicating the focal nature of the ON infarct, with accumulation of Iba1+ immunopositive cells in the region of axonal loss. Myeloperoxidase+ cells were notably absent 21 to 70 days after induction (Figures 6D-F), with an apparent peak number of ED1+ immunopositive cells at 35 days (Figures 6H, arrows). Fewer but still detectable numbers of ED1+ extrinsic macrophages were present 70 days after induction (Figure 6I, arrows), suggesting that, like other regions of the CNS, replenishment from the extrinsic macrophage population occurs in the infarct region long term.

On the basis of the relative expression of the different cell populations disclosed by immunohistochemistry and confocal analysis, we can summarize the qualitative time-associated (temporal) map of cellular expression in the affected nerve following induction of pNAION. Following ON infarct, there is early invasion of PMNs into the infarct region (compare Figures 5 and 6), with elimination or disappearance of these cells after 1 week after induction. Extrinsic macrophages, distinguished by ED1+ immunopositivity, begin to appear by 3 days after induction and reach a maximum expression by 35 days. Thereafter, these cells decrease in number in the infarct region. The total number of inflammatory cells, distinguishable by Iba1 immunostaining, continues to accumulate up to the latest date examined. There is also evidence of continued extrinsic macrophage invasion, albeit at a lower rate. Thus, cellular inflammation is a prominent early feature of focal ON infarct.

**COMMENT**

Nonarteritic anterior ischemic optic neuropathy remains a perplexing disorder with respect to its pathogenesis. It generally is believed that the final common pathway in NAION is reduced blood flow to the anterior ON, leading to ischemia; however, the precise mechanism by which this occurs is unclear and probably is multifactorial, including the development of a compartment syndrome, embolism, and vascular dysregulation. Regardless, because the ON is a CNS white-matter tract, NAION behaves as a pure CNS white-matter stroke, thus, identification of the immune responses in NAION has implications not only.
for treatment of NAION but also for understanding the physiologic responses that likely occur in other white-matter infarcts and preventing the dysfunction that occurs from such infarcts.

Previous results implicated cellular inflammation as a major component in rodent models of NAION and in mixed infarct models; however, the inflammatory response in rodents may be different not only between rats and mice but also from that of primates. In addition, the anatomy of the retina/ON junction is markedly different between primates and rodents, and this may contribute to additional response differences between these species. In the rat middle cerebral artery occlusion model, ED1+/Iba1+ cells, which presumably represent blood-borne macrophages, are present in the ischemic zone during the first week of the insult, whereas Iba1+/ED1− cells, representing intrinsic microglia, are present in high numbers in the penumbral area. A rat NAION model similar to that used to generate pNAION revealed early recruitment of extrinsic macrophages in the ischemic infarct core followed by postischemic inflammation with macrophage infiltration into the ON.

Cellular inflammation was reported in late stages of pNAION by Chen et al. These investigators postulated that the inflammation that occurs in these models of white-matter stroke may have 2 opposing roles. Inflammation

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**Figure 5.** Identification of inflammatory cells in region of infarct shortly after induction of nonarteritic anterior ischemic optic neuropathy (NAION) in a nonhuman primate (pNAION). Antibodies used against Iba1 (green), SMI312 (red), ED1 (red), and myeloperoxidase (Myelo, green) are indicated on each horizontal panel series. A, D, and G, Control (naive) optic nerve. B, E, and H, Three days after induction. C, F, and I, Seven days after induction. A-C, Total inflammatory cell numbers. A, The naive nerve has numerous Iba1+ cells scattered throughout the optic nerve structure, with normal axon numbers and staining. B, Three days after induction, there is focal Iba1+ cell accumulation, with slight focal reduction of SMI312 immunopositivity. C, One week after induction, there is marked loss of SMI312 immunopositivity, with increased focal accumulation of Iba1+ inflammatory cells (arrowheads). D, In the control nerve, few if any polymorphonuclear lymphocytes (PMNs) are present. E, Three days after induction, PMNs are present as a focal accumulation in the region of optic nerve damage (arrows). F, The PMN numbers are greatly decreased 1 week after induction (arrow). G, Few if any extrinsic macrophages (in red) are present in the naive optic nerve, which has strong Iba1+ cellular immunostaining. H, Three days after induction, there are a few Iba1+/ED1+ cells (ie, extrinsic macrophages) in the affected optic nerve region (arrows). I, One week after induction, there are a large number of extrinsic macrophages (arrows) in the affected region. Bar=20 µm.
may result in increased destruction of adjacent axons,\textsuperscript{18} which may contribute to the poor visual outcome in many patients with NAION. On the other hand, extrinsic macrophages may enhance neuron survival and axonal regeneration\textsuperscript{19,20} and may play a role in phagocytosis and removal of myelin debris.

An additional objective of this study was to determine whether there was evidence of inflammation present in the ON in the only pathologically examined case of clinically proven early human NAION. The initial report of the histologic findings in this study suggested that there was no increase in the cellular inflammatory component; however, no immunohistologic analysis was performed. In addition, because of the vagaries of small-sample tissue analysis, it is possible to miss specific regions of interest. This occurred in 2 of our primate samples and was identified only by axon immunostaining, which revealed the lesion site.

Re-analysis of tissue from the single available case of acute NAION, with autopsy tissue obtained 20 days after onset of visual symptoms, identified 5 different zones within the ON, with evidence of inflammation both within the area of infarction and in the penumbral region. The inflammation was demonstrable by specialized staining that revealed the accumulation of Iba1+/ED1+ cells representing extrinsic macrophages in ischemic areas of the ON, with accumulation of Iba1+/ED1− cells; that is, intrinsic microglia in the area as well as in the penumbral regions. The loss of SMI312 immunoreactivity in both the central lesion and presumed penumbral regions revealed the severity of the NAION infarct. In fact, this ON probably had greater than 65% axon loss, as determined

**Figure 6.** Longer-term (21-70 days) changes in inflammatory cell populations in optic nerves with induction of nonarteritic anterior ischemic optic neuropathy (NAION) in a nonhuman primate (pNAION). Antibodies used against Iba1 (green), SMI312 (red), ED1 (red), and myeloperoxidase (Myelo, green) are indicated on each horizontal panel series. A, D, and G, Sections from nerve 21 days after infarct. B, E, and H, Sections from nerve 35 days after infarct. C, F, and I, Sections from nerve 70 days after infarct. A-C, Marker SMI312/Iba1 immunostaining. There is focal axon loss (arrowheads), with an Iba1+ cellular infiltrate within the region of loss. D-F, Myelo/ED1 immunostaining. A few Myelo+ cells (green) are visible at 21 days (D, arrowheads), but only punctuate (noncellular) staining is seen at 35 and 70 days. G-I, Marker ED1/Iba1 immunostaining. The ED1+ cells are present in all sections (arrows), with the largest number of ED1+ cells seen at 35 days. Bar=20 µm.
from the lack of neurofilament staining. The extrinsic macrophages and microglial cells likely represent intrinsic ON damage, implying both microglial activation and extrinsic macrophage invasion following ON ischemia. We postulate that after infarct, recently generated blood-borne ED1+ macrophages likely reach the ON via adjacent vessels that originate from the posterior ciliary arteries and possibly the central retinal artery.

There are several limitations to the initial part of this study. First, the findings were from a single pathologic specimen. Second, the specimen was obtained from a patient 20 days after the onset of visual symptoms. Thus, we have no way of knowing what changes may have been present before this time or might have occurred subsequent to it. A final potential limitation is that artifacts during tissue processing could have occurred that would affect our interpretation. Despite these limitations, we believe our findings regarding the presence of a significant inflammatory response in a typical case of acute NAION to be valid. There is a surprising similarity between the patterns of cellular inflammatory response in rodent CNS ischemia and those in primate ischemic optic neuropathy.

A considerable advantage is gained in using the NHP model of NAION because the similarity between physiologic responses in humans and NHPs makes it likely that findings generated by the pNAION model will correlate with tissue responses seen in the human condition. Early ON edema is a factor in both the primate model and tissue obtained in this clinical case.35 In the primate model, tissue edema increases during the first week following pNAION induction (compare Figure 4, panels B and C, with panel A), with hemorrhage seen at both 3 days and 7 days but not earlier, suggesting that ischemia is followed by later perfusion and release of blood cells from damaged vessels. Polymorphonuclear leukocytes are the earliest cellular response element seen in the tissue and are maximal at 3 days but not earlier, suggesting that ischemia is followed by perivascular invasion and release of blood cells during the first week after induction. This rapid PMN response decreases, with no detectable PMNs in the area of the primary lesion by 2 weeks after induction.

Following PMN invasion, there is a strong microglial response, as well as invasion by extrinsic macrophages. Both immune populations are detectable by immunostaining. Despite the resolution of ON edema, extrinsic macrophages continue to accumulate during the entire period of analysis, suggesting that even after reconstitution of the blood-brain barrier, there is long-term infiltration of systemic macrophages to the lesion site, with microglial conversion similar to that seen in other systems.21-23 Extrinsic macrophages are detectable by 3 days after induction, with a maximal response at 35 days after induction. These findings correlate quite well with the data obtained from the human clinical sample because both extrinsic macrophages and intrinsic microglial elements appear to be concentrated in the clinical disease-affected region in a manner similar to that seen at 21 and 35 days after induction. A caveat of this analysis is that correlation must be between similarly affected regions. This comparison is considerably enhanced by using the SMI immunostaining, which enabled direct identification of axon loss.

The results of this study reveal that, similar to other CNS lesions, both human NAION and pNAION are associated with an early and complicated immunologic response that suggests that inflammation may indeed play a major role in the physiology of ON damage from anterior ON ischemia. The inflammatory response continues for long periods, with accumulation of the classic gitter cells only in the final stages of the disease.

As in other CNS white-matter infarcts, inflammation could cause damage not only in the area of the infarct but also in the penumbral regions adjacent to the infarct, presumably by inhibiting axon regeneration and remyelination as well as by enhancing glial scar formation.24 Microglial inflammation may also result in oligodendrocyte death and increased retinal ganglion cell loss, apart from the primary ischemic insult.25 Alternatively, selective ocular inflammation may also play a recuperative role in preventing retinal ganglion cell death.26 Our findings, coupled with previous studies, suggest that precise, early, selective anti-inflammatory treatment, such as has been shown in the case of tumor necrosis factor-α inhibition in ocular hypertension,25 may be useful in cases of acute NAION to help limit visual loss and enhance recovery. More global inflammatory inhibitors, such as corticosteroids, have not been shown to enhance clinical recovery from CNS infarcts,27-29 and their use is highly debatable in NAION treatment, showing minimal, if any, improvement.30,31

Because NAION may not be just a “compartmental” disease but may also have etiologies related to other conditions, such as embolism or vascular dysregulation, our findings by no means exclude other potential treatments for NAION; however, these results may provide some clues as to some of the phenomena that occur in this as yet untreatable disease and, with the appropriate models, suggest avenues for treatment by modulating the associated inflammatory response that appears to accompany infarction in this condition.

In summary, both an autopsy specimen from a patient with acute NAION and multiple specimens from ONs in primates in which anterior ON ischemia (pNAION) has been induced, reveal early inflammation via testing using selective immunohistochemical stains. In the future, clinical studies designed to determine the presence of an inflammatory component must include such stains, rather than relying on nonspecific histologic methods, as has heretofore been the rule. The NHP model may be of considerable future help in validating the timing and presence of inflammation. This model may also be useful in elucidating mechanisms of response, treatment, and recovery in both ON and other CNS-associated white-matter infarcts.

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