Ischemia and Multiple Sclerosis: Perfusion MR Imaging Provides Insight into an Underexplored Pathophysiology

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Ocular Manifestations of Cat-Scratch Disease: Role of MR Imaging

In this issue of the AJNR, Schmalfuss et al report the MR imaging features of optic neuropathy due to cat scratch disease (CSD). MR imaging in five of nine patients with CSD demonstrated abnormal contrast enhancement of the optic nerve disk and a short segment of optic nerve just behind the globe. Attempting to understand the MR imaging findings in CSD requires insight into the pathogenesis of CSD and its ocular manifestations, particularly CSD neuroretinitis.

CSD is almost always a self-limited systemic illness, and usually presents as a benign tender lymphadenitis involving the lymph nodes draining dermal or conjunctival sites of inoculation. The disease was first reported in 1950 by Debré et al (1). Since then, despite numerous reports on CSD, and despite clinical, epidemiologic, serologic, and pathologic studies that have suggested an infectious pathogen, the causative agent of the CSD had eluded detection until 1983, when Wear et al (2) at the Armed Forces Institute of Pathology (AFIP) identified a small pleomorphic Gram-negative bacillus from lymph nodes of seven of eight patients who were positive for CSD. The bacilli were clearly seen with the Warthin-Starry (WS) silver impregnation stain. The bacilli were found to be very small at the limit of the resolving power of the light microscope, although the WS silver impregnation stain resulted in coating the organisms, making them appear larger and easier to see (2). The bacilli were shortly identified in skin at the primary inoculation site (3) and in the conjunctiva of patients with Parinaud oculoglandular syndrome (4).

Initial attempts to isolate and culture this pleomorphic Gram-negative bacilli were unsuccessful until 1988, when English et al (5) at AFIP were successful in isolation and cultivation of a pleomorphic Gram-negative bacillus from lymph nodes of 10 patients with clinically or histopathologically proven CSD. This causative agent became known as the “cat-scratch disease bacillus” and when Brenner et al (6) described, the new genus Afipia, the CSD bacillus was given the name Afipia felis. Afipia, derived from the abbreviation AFIP, where the type strain of the type species was isolated. They reported that the CSD bacillus and five cat scratch-like strains represent separate species in the new genus Afipia.

Despite the identification of Afipia felis, as the causative agent of CSD, the pathogenesis of CSD remained incomplete until new information emerged in early 1990s, when Relman's study concerning the etiology of bacillary angiomatosis in AIDS-related syndromes identified Rochalimaea quintana, the causative agent of trench fever as a pathogen (7). This study led to the isolation and characterization of another agent, Rochalimaea henselae, and its role as an etiologic agent in bacillary angiomatosis (8, 9). In 1992, Regnery et al (10) reported that R henselae has been found in blood or tissues of patients with bacillary angiomatosis, peliosis hepatitis, and in patients with fever alone or fever associated with HIV-related syndromes. The similarities between CSD and bacillary angiomatosis had led them and other scientists to speculate that they were possibly caused by the same organism (8–10). Regnery et al (10) reported that 88% of their patients with clinically suspected CSD had high serum titers to R henselae antigen. They concluded that serologic assays based on R henselae might be useful for diagnosis of CSD. Studies by Perkins et al (11), based on serologic and polymerase chain reaction (PCR) assays also, seemed to refute A felis, formerly known as the “cat scratch bacillus,” and suggested that Rochalimaea species may be responsible for most cases of CSD. In 1993, Dolan et al (12) were able to culture R henselae from lymph nodes of two patients suspected of having CSD, confirming that it was the most likely causative agent of CSD. Finally, as genotypic studies of the genera Rochalimaea and Grahamea revealed their close homology to Bartonella bacilliformis and their remoteness from the Richettsiales, the genera Bartonella and Rochalimaea were united (13). The name Bartonella was preferred because it had nomenclatural priority over Rochalimaea. Bartonella henselae an intracellular bacillus is now considered the principle cause of CSD (14). Other pathogens such as Bartonella elizabethae, or A felis might be the cause in small percentage of CSD patients in whom no evidence of B henselae can be found (15, 16).

The disease is transmitted by the bite or scratch of an infected cat or kitten. The cat flea has also been shown to be a possible transmission vector among humans (14). The infected individual often develops an erythematous papule, vesicle, or pustule at the site of inoculation followed by a systemic reaction within few days. The symptoms include regional lymphadenitis, fever, chills, malaise, night sweats, headache, and fatigue. Less commonly, more severe and disseminated form of the disease may develop, associated with encephalopathy, aseptic meningitis, neuroretinitis, optic neuritis, granulomatous hepatitis, pneumonia, pleural and pericardial effusions, and other widespread systemic disease (14, 15).
The eye can be involved either with the primary inoculation complex, resulting in the so-called Parinaud oculoglandular syndrome (14–16) or by hematogenous spread, leading to an array of ocular and neuro-ophthalmic complications (14–17). The POS represents the regional lymphadenopathy associated with conjunctival or eyelid infection. The main ocular manifestations of disseminated CSD are neuroretinitis, papillitis, and optic neuritis. Other ocular complications include vitritis, pars planitis, focal retinal vasculitis, focal choroiditis, peripapillary angiomatous lesions, optic disk edema and secondary macular detachment, and branch retinal arteriolar or venular occlusions (15, 17). In one series, isolated foci of retinitis and choroiditis were the most common ocular manifestation of CSD (17). An idiopathic form of anterior optic neuropathy with a macular star figure, the so-called stellate maculopathy, is referred to as Leber stellate neuroretinitis or idiopathic optic neuritis with stellate maculopathy of Leber. This entity, which was identified by Leber in 1916, is now considered to be a commonly manifestation of CSD. The term “neuroretinitis” evolved to include the common finding of disk edema with the macular star (17, 18). In 1977, Gass (18) first noted the association of neuroretinitis with CSD in a young child. He observed that the fundamental disorder was an exudative optic neuritis with transudation into an apparently normal macula. Histopathologically, the macular star is caused by the microglial ingestion of the lipid-rich exudate in the outer plexiform layer of Henle (15). The optic nerve head is the principal target of acute neuroretinitis. Massive inflammation of the optic nerve head may be seen in eyes of patient with ocular CSD (17). The disease affects the permeability of the capillaries in the depth of the optic nerve head (18). Fluorescein angiography will show vascular leakage from the optic nerve head (17, 18). Bartonella organisms are known to invade vascular endothelium (17). Endothelial damage stimulates thrombogenic mediators with resulting obliterator vasculitis and branch retinal artery or vein occlusion (15–17). Neuroretinitis, papillitis, and optic neuritis are the main neuro-ophthalmic syndromes in CSD. The optic nerve swelling usually resolves spontaneously in 2–8 weeks, with most patients recovering normal vision (15).

With regard to the CSD neuroretinitis, the abnormal enhancement on MR imaging is likely due to disruption of vasculature at the optic disk. In addition, alteration in the capillaries (obliterator vasculitis) may also contribute to the MR imaging findings. The results of Schmalfuss et al’s work in this issue of the AJNR allow us to include CSD where abnormal optic disk-short segment retro-laminar optic nerve is seen on MR imaging. This MR imaging finding in the context of disk edema and stellate maculopathy should be considered characteristics of CSD. It is important, however, to keep in mind that other entities, such as papillitis, granulomatous, neuroretinitis (toxoplasmosis, syphilis, sarcoid, Lyme disease, leptospirosis), xanthogranuloma, and noninfectious causes of neuroretinitis, including ischemic optic neuropathy, may demonstrate similar MR imaging findings. Optic disk enhancement in multiple sclerosis is unlikely because the disk is composed of nonmyelinated axons; nonetheless, short-segment retrolaminar involvement may be seen in MS along with, short-segment involvement in the intracanalicular or intracranial segments of optic nerve. Whether the MR imaging findings described by Schmalfuss et al will be specific for CSD neuroretinitis remains uncertain.

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Is Current Imaging Good Enough to Differentiate Radiation-Induced Brain Injury from Tumor Recurrence?

Differentiating radiation-induced brain injury from tumor recurrence is a challenging problem. This is important in the current medical environment, where therapeutic strategies for CNS disorders are moving toward minimally invasive procedures. On many clinical occasions, imaging is the only reference for choosing an appropriate therapeutic strategy and for evaluating the therapeutic result. Gliomas, particularly those of high grade, contain heterogeneous tissue components with tumor necrosis. Their clinical and pathologic behaviors are different from that of radiation-induced necrosis. They may share similar imaging characters, although the management strategy and outcome of tumor necrosis and radiation necrosis are obviously different.

In the current issue of AJNR, Asao et al present a series of 20 brain tumor lesions in 17 patients and in most (14/17) they were initially high grade (grade III and IV astrocytic tumors). At the time of study, 12 lesions in 10 patients developed radiation necrosis, and the other eight lesions of seven patients were tumor recurrence. By drawing five regions of interest on trace DWI and apparent diffusion coefficients (ADC) maps within these lesions, they observed that radiation necrosis usually showed heterogeneity on DWI, and often included spotty, marked hypointensity visually on DWI. The maximum ADC values were significantly lower for the recurrence group than for the necrosis group. With this observation, the authors concluded that DWI was useful in differentiating recurrent neoplasm from radiation necrosis.

The message conveyed in the article is similar to that from an article published last year in the AJNR (1). Clinically, the results may be applicable to many tumors with classic imaging manifestations, or to tumors with massive necrosis either radiation-induced or nonradiation-induced. For cases with mixture of tissue components or with an evolving necrotic process or tumor progression, the dilemma, however, remains. Unfortunately, that is the most common situation.

After reading these articles, some questions remain. Can overall signal intensities and their corresponding ADC values represent tissue characteristics? Is the spatial resolution of our current imaging technique (DWI, PWI, MR spectroscopy) high enough to deal with the tissue heterogeneity? Does current metabolic imaging provide enough specificity (2, 3)? Although we have many sophisticated imaging tools at our disposal, the questions we face are even more complicated. It is clear that the complexity of different tissue component in brain tumors and the relative ineffectiveness of current therapies make these questions even more problematic. The real challenge is to find a biomarker of tumor recurrence that can be identified in its early stage.

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USPIOs to Enhance the Diagnostic Potential of Ultrasound in Tumor and Other Inflammatory Lesions

The article “Iron Particles Enhance Visualization of Experimental Gliomas by High-Resolution Sonography,” which appears in this issue of the AJNR, focuses on a potential new use of contrast enhanced ultrasonography (US) with iron oxide–based contrast agents in brain tumors. Our laboratory, for instance, has used MR imaging and histologic studies to image iron particles that target inflammation in the CNS such as in brain tumors (1–4). In the current report, the authors used iron oxide particles to enhance sonography imaging.

More specifically, a brain tumor model (surgical inoculation of C6 glioma) was used. Three groups with 12 rats each were studied: (1) gadolinium diethylenetriamine pentaacetic acid contrast; (2) superparamagnetic iron (IO) 24 hours before scanning; and (3) no contrast. An MR imaging study was obtained 11 days after tumor inoculation in the 36 animals. Immediately after scanning, the brains were extracted and placed in saline for US. Subsequently the tissue was observed histologically by using different stains to detect tumor, iron particles, and macrophages. The authors conclude that IO contrast improves tumor definition with IO-enhanced US.

The authors present an interesting and new application for IO in neurosurgery. Cavernous angiomas are a good clinical example of how a tumor that contains iron particles as part of the lesion may look
Ischemia and Multiple Sclerosis: Perfusion MR Imaging Provides Insight into an Underexplored Pathophysiology

The past two decades have been an exciting period in the field of MR imaging of multiple sclerosis (MS), because it has provided the tools required to answer new questions and to generate and address new hypotheses. In the late 1980s, MR imaging was shown to be the best technology for providing sensitive and objective measures of the mostly subclinical disease of MS. MR imaging became fundamental in evaluating the disease in clinical trials, including its utilization as primary outcome measure in phase II trials. MR studies of MS at the time of a clinically isolated syndrome (CIS) provided objective criteria and a new basis for determining dissemination in space and time that have been recently incorporated into the “McDonald” criteria for diagnosis and that can be used to expedite the diagnosis after a CIS (1). Multiple quantitative MR methodologies (e.g., magnetization transfer and diffusion-based imaging) were instrumental in establishing the prevalence and importance of the “invisible” disease in the normal-appearing white matter (NAWM), and more recently the normal-appearing gray matter (2). In the late 1990s, the MS community was reoriented to the importance of early axonal injury in MS. Axonal injury and transection are now thought to be in part the previously missing links in understanding disability and progression that could not be accounted for by demyelination alone (3). MR spectroscopy confirmed axonal injury in vivo based on reduced n-acetylaspartate, and MR-based atrophy measures now provide a relatively simple, practical measure of the destructive, mostly irreversible injury that can be detected even in early MS.

We did not have to wait long for another stimulating development in MS that already has important implications for imaging. On the basis of neuropathologic studies from biopsy material, Lucchinetti et al (4) suggested that MS is best characterized as a heterogeneous disease that is relatively homogeneous within individuals. A new classification was proposed such that MS would fit neatly into four categories. The underlying pathology in MS in all four types remained chronic T lymphocyte–mediated inflammation, accompanied by activated macrophages and microglia and their toxic products (pattern I). But additional amplification factors generate patterns II–IV (5). Pattern II could be characterized by deposition of immunoglobulins and components of activated complement (resembling an antibody-mediated process); pattern III by distal dying back oligodendrogliopathy (DDBO) with oligodendrocyte apoptosis; and pattern

Overall, the article presents an attractive idea that is worth pursuing in clinical settings of tumor and/or inflammatory lesions.

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IV, relatively rare, by degeneration and oligodendrocyte death in the periplaque white matter (5). One obvious implication of this classification is that, if the underlying pathology is heterogeneous, the one treatment fits all approach is not likely to be optimal. In addition, there has been an interesting attempt (but not as neat) to relate MS variants and possibly MS phenotype to this classification scheme, for example Devic’s neuromyelitis optica with pattern II and Balo concentric sclerosis and lesions with ill-defined contours to pattern III. It should be noted that this classification scheme is not free from healthy controversy and may be best described as a working and stimulating model.

From an imager’s perspective, this is all very pleasing, because there may finally be a path to understanding the striking MR imaging heterogeneity we see in the clinic when evaluating “MS.” For example, some individuals show numerous tiny focal lesions, others multiple large “punched-out” lesions, still others have lesions with ill-defined borders. We do not know whether these varied appearances reflect a different host response to a common insult or the heterogeneity is primary, related to etiology, pathogenesis, or comorbid factors. Attempts to relate MR imaging features to pathology have to date been stimulating, but direct histopathology-MR imaging material is limited.

Although all the patterns are interesting, pattern III may now have special attraction for imagers, because this pattern has been associated with hypoxia (5). The characteristic DDBO of pattern III was described in demyelination and specific toxic demyelinations from agents that interfere with cellular energy metabolism such as cuprizone, and this pathology is also found in acute white matter stroke (5). In stroke and a subset of MS lesions with DDBO, there is profound expression of an hypoxia-inducible factor called HIF 12 α, an antigen recognized as a marker of hypoxic tissue damage (5). Mechanisms responsible for this metabolic state resembling hypoxia could be secondary to microcirculation disturbances, and/or toxic metabolites, such as those interfering with mitochondrial energy metabolism. In acute inflammation, edema and locally constrained tissue may be the basis for circulatory disturbances. Possibly more important, inflammatory changes in the vessel wall with activation of a clotting cascade, or direct endothelial damage, may contribute to this injury. Toxic disturbances from liberated excitotoxins, reactive oxygen species, and nitric oxide intermediates may also contribute to DDOR, metabolic injury, and ischemic states in MS.

This brings us back to MR imaging. MR imaging is an important technique for the evaluation of vascular abnormalities and assessment of the microcirculation based on perfusion imaging, but, apart from attempts to understand the blood-brain-barrier, the microcirculation has received only little attention in MS. The report by Ge et al in this issue of the AJNR has special significance in view of the background pathophysiology highlighted by Luchinetti et al, Lassman, and others, not just because of the possible relationship of ischemia to MS, but also related to the potential for helping us understand normal and disturbed regulatory events at the capillary and postcapillary level in MS. In Ge et al’s study, dynamic susceptibility contrast MR imaging was used to evaluate focal MS lesions in patients with relapsing MS. An important methodologic detail is that perfusion measures were referenced to control white matter, by using the arterial input function, rather than contralateral NAWM. This is important because the latter has been shown by the same group (6) and others (7) to be abnormal in MS and therefore a suboptimal reference tissue. Perfusion measures of cerebral blood flow (CBF), cerebral blood volume (CBV), and mean transit time (MTT) were analyzed in 75 lesions from 17 patients with the NAWM of 17 MR imaging negative control subjects as reference.

MTT values were found to be significantly prolonged for the enhancing and nonenhancing MS lesions and importantly for the NAWM in MS patients compared with normal control white matter. With an eye toward determining whether perfusion measures would segregate focal lesions into perfusion types, a cluster analysis was performed, which resulted in three clusters, with two nonenhancing lesion subtypes (called class 1 and class 2), and a cluster of enhancing lesions. Compared with the enhancing lesions, the nonenhancing lesion cluster—called class 1—had relatively low CBV and calculated CBF compared with nonenhancing class 2 lesions characterized by relatively high CBV and CBF.

This perfusion-based differentiation would not be apparent by conventional T2-weighted imaging. The magnitude of the prolonged MTT and reduced CBF indicating perfusion deficits for all these focal lesion clusters and the NAWM is provocative in itself and especially so in view of the new pathology literature and the direction it is leading us in determining factors in MS relevant to the microcirculation and ischemia. The authors interpret their findings as a primary vascular pathology rather than reflecting decreased metabolic demand. They also speculate regarding increased CBF in enhancing lesions compared with contralateral tissue (increased perfusion beyond a baseline ischemic background accompanying inflammation). This finding is more difficult to interpret but is not entirely unexpected, in view of the known vasoactive factors associated with inflammation and supported by recent studies showing increased perfusion weeks before gadolinium enhancement (7). Whether class 2 lesions represent a pre-enhancing stage of early inflammatory activity as suggested will require longitudinal confirmation.

The results of Ge et al suggest that microcirculatory disturbances can be detected with surprisingly high frequency in MS. There are many unanswered and new questions. We do not know to what extent if any the perfusion patterns demonstrated by Ge et al correlate with those of DDBO or type III patterns. One recent study suggests that type III lesions may not be exclusively limited to a subset of MS patients.
but may in fact represent an early stage in formation of most MS lesions associated with acute exacerbation (8). This study did not relate perfusion findings to lesion size, lesion duration, treatment status, or presence or absence of T1 black holes, which are a well-defined, more severely injured subset of T2-hyperintense lesions. There is literature suggesting hypometabolism in MS, a factor which needs to be accounted for in interpreting these results and relevant to discussion of perfusion abnormalities as representing a primary rather than secondary pathology. Most intriguing, as suggested by the authors, are possibilities for in vivo microperfusion measures in understanding the vasoactive components of inflammation, and the effect of more targeted therapy on these, because the endothelium of the microvasculature and the release of vasoactive molecules are certainly central components of the early inflammatory cascade in MS. We need to know when these perfusion deficits first occur, how they progress, and specifically whether they present in the earliest stages of disease, for example at the time of a CIS.

Future studies will determine how perfusion measures will be used in demyelinating disease in the reading room. For now there is the opportunity with high-resolution perfusion MR imaging, diffusion MR imaging, and cellular and molecular imaging to look specifically at the normal and abnormal processes occurring at the endothelial level in MS. This will bring us closer to understanding the effects of intervention, including treatments targeting cellular migration and and CNS surveillance, vasoreactivity, and the specific “good” and “bad” components of the inflammatory events in MS. This work by Ge et al provokes us to look at the microscopic pathology of MS by MR imaging in new ways. Whether perfusion abnormalities are cause or effect, we are delivered to a fork in the road of considerable interest.

**When Is the Abnormal Normal?**

Whenever there is a new advance in imaging or a new medical procedure, the inevitable problem arises regarding what can be considered normal. Radiologists the world over were either pleased or dismayed when the advent of high-resolution CT imaging made possible the visualization of the stapedius muscle and the individual cochlear and vestibular branches of the 8th cranial nerve. And when innovations in the treatment of glioblastomas made possible the delivery of tumor specific radiation-laden antibodies into a surgically created cavity, the next question that needed to be answered was what was the normal enhancement pattern for radiation necrosis following these procedures, as the enhancement pattern was strikingly different compared with regional radiation therapy. A similar need has arisen with the rising popularity and prevalence of percutaneous vertebroplasty, as there are patients who present postprocedure with back pain that may or may not be related to the level already treated.

To this point, there has not been any description of what MR findings can be considered normal in a vertebral body that has undergone vertebroplasty. In light of the invasiveness of the procedure, as well as the potential effects of the heat and pressure generated during the procedure, it seems likely that some changes would be inevitable. The spectrum of normal postprocedure findings is important to know when evaluating the treated patient who returns with pain, because the significance of edema or additional height loss within the treated level can affect whether to retreat these patients at the same level. Dansie et al’s article, “MR Imaging Findings After Successful Vertebroplasty,” in this issue of the *AJNR*, is an excellent study that addresses these issues, and, although it leaves open the door for further studies, it should be useful to vertebroplasty practitioners wrestling with the occasional patient who returns with pain and has vertebral body edema and height loss at a previously treated level. The important point that is made by this study is that the presence of such findings, which are certainly abnormal in most patients, can be seen in postvertebroplasty patients whose pain is coming from a different location, potentially saving patients from additional, ultimately unnecessary, and unsuccessful repeat procedures.

It is unreasonable, however, to conclude from the data presented in this article that painful refractures

**References**


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at a previously treated level do not occur. In my experience, I have seen at least one patient whose pain was definitely originating from such an instance, and there is a case report in the literature describing a refracture with cement extrusion that had to be surgically stabilized. These types of cases, however, are likely quite rare, and, on the basis of this study, most vertebroplasty patients who re-present with vertebral body edema and compression at that site will not be symptomatic from that level, despite the MR imaging appearance.

Regardless of whether some treated vertebral bodies require retreatment for pain relief, the strong data in this article should make all spine interventionalists hesitate before proceeding with such a course of action. Adjacent level fractures are a commonly encountered phenomenon and can be problematic when adjacent to a previously treated level with edema or height loss, a situation where it can be easy to rationalize retreatment of the initial level at the same time as the vertebroplasty of the adjacent one. It is interesting that, in this article, all of these patients were successfully treated with vertebroplasty of the adjacent level only. Pain coming from a previously treated level appears to be almost a diagnosis of exclusion, and certainly another source of pain, such as additional level fracture or facet disease, should be extensively sought and treated before considering a repeat vertebroplasty.

One hopes that the authors and others might use this article as a starting point when considering follow-up studies to confirm and further the work presented here. A large study comparing follow-up MR images in all vertebroplasty patients, whether pain-free or not, would be an excellent companion study, as would descriptions of cases of painful refracture that were successfully retreated.

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