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AJNR

Progress in Understanding Creutzfeldt-Jakob Disease

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AJNR Am J Neuroradiol 2002, 23 (7) 1070-1072
<http://www.ajnr.org/content/23/7/1070>

This information is current as
of October 3, 2023.

The Abnormal Annulus Fibrosus: Can We Infer the Acuteness of an Annular Injury?

Few issues in neuroimaging are as controversial as the nomenclature used to describe abnormalities of the lumbosacral spine. What immediately comes to mind are the variations in the labeling of various degrees of disk abnormalities (eg, herniation, bulge, protrusion, extrusion). With better MR resolution and a wider understanding of the nature of the disk disease and its manifestations, we are often faced with the task of trying to associate a finding in the disk complex with the underlying pathophysiology. Added to this is the spectrum of abnormalities of the annulus fibrosus and the associated signal intensity changes within the annulus.

Faced with an MR abnormality in the annulus such as a high signal intensity on a T2-weighted image or enhancement on a contrast-enhanced T1-weighted image, one often asks whether these abnormalities represent only acute or subacute changes or whether they are chronic and persistent. In this issue of the *AJNR*, Munter et al (page 1105) address this issue by analyzing findings in a cohort of 18 patients who had what they defined as annular tears and who underwent follow-up MR studies over a period of 3–64 months. Simply stated, such a study would answer the following important question: If a signal intensity abnormality is present in the posterior annulus, can one say if that represents an acute finding? In addition to affecting the diagnosis and patient care, this observation has clear medical-legal implications. That is, a plaintiff's attorney may posit that a given annular abnormality represents an acute finding that is traceable to a recent mishap such as a slip and fall or a fender bender.

In Munter et al's paper, 29 annular tears in the authors' 18 patients formed the basis of the investigation. Twenty-seven tears were seen at the time of the first study; of those, 25 were radial tears, and two were transverse tears. The persistence of high signal intensity in most tears and the persistence of abnormal annular enhancement in all patients who received gadolinium-based contrast agent over the period of the sequential studies (which lasted years in some cases) makes a strong argument that such findings on a given image are not necessarily acute.

As with many retrospective clinical investigations, certain problems exist, and some questions are left unanswered. The authors acknowledge the limitations of their study; some are worth additional com-

ment. Namely, the authors retrieved cases by finding the words *annular tear* in old reports; one does not know how many other patients may have such tears that were never mentioned in the original report. Because such patients were not included in the study group, a prospective study would probably have allowed the identification of more patients, increasing the statistical power of the study. The uniform protocol of a prospective study would have allowed the administration of contrast material in all patients, both during the initial study and at follow-up, not just in some patients as in this situation. A prospective study might have allowed for a more uniform follow-up period. The study would have been strengthened and it may have revealed more insights into the clinical importance of annular signal intensity abnormalities if the authors had prospectively evaluated more patients. Their conclusions would have been more cogent had they classified their injuries as radial, concentric, or transverse tears, depending on the extent and location of the signal intensity abnormality. Specifically, these tears could have been correlated with the presence of a normal nucleus pulposus and the presence of degrees of disk bulges or protrusions. As opposed to annular tears, which are commonly associated with disk degeneration, transverse or concentric tears might be expected to appear the same or show little change over time.

Although this article raises a number of questions, it is a valuable starting point for further investigation of the importance of these signal intensity abnormalities on T2-weighted images. It would be of interest to have others examine this issue with a controlled series; however, in the meantime, we have a report to which we can refer when we are confronted with the issue of whether hyperintensity in the annulus is necessarily related to a relatively recent event. The dating of an injury based on abnormal signal intensity or contrast enhancement in an annular tear at follow-up imaging appears to be impossible unless an initial MR image depicts the absence of those findings. Even then, the sensitivity of MR imaging for annular tears remains uncertain. In any event, overinterpretation of the clinical importance of these MR findings is to be avoided.

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Progress in Understanding Creutzfeldt-Jakob Disease

The neurodegenerative diseases are experiencing a new lease on life. New treatments, such as anticholinesterases for Alzheimer disease, have become available, with several other promising drugs under assessment. Considerable progress has been achieved in the understanding of the underlying molecular and genetic basis of dementing diseases, but perhaps the most unexpected development has been the increasing contribution of imaging to this understanding. Medical progress increasingly requires a multidisciplinary approach. This paradigm is well illustrated by Creutzfeldt-Jakob disease (CJD), with imaging playing an increasingly important role in case definition and elucidating the cause of this disease. In this issue of the *AJNR*, Murata et al (page 1164), using diffusion-weighted imaging, provide important insights into the early diagnosis of CJD and how the disease may spread in the brain.

CJD is one of the transmissible spongiform encephalopathies, a rare but important group of diseases affecting humans and other animals, characterized by fatal progressive neurologic illness, unusual neuropathologic changes, and an unconventional transmissible causal agent. A number of subtypes of CJD are recognized, including sporadic CJD (sCJD, the most common form worldwide), familial CJD (fCJD, rare), iatrogenic CJD (iCJD, increasingly rare; from cadaveric hormone-related transmission or neurosurgical procedures), and the recently described variant CJD (vCJD). In some countries, CJD is a notifiable disease monitored by dedicated national CJD surveillance units.

An unusual feature of the agent causing CJD is its relative resistance to many routine sterilization procedures, including standard autoclaving. For many years, this transmissible agent resisted characterization. However, in his groundbreaking work for which he won a Nobel Prize, Stanley Prusiner proposed that the transmissible agent in CJD and related diseases was a protein (PrP^{Sc}). This protein or prion catalyses the conversion of a normal native protein (PrP^C) into the isomeric PrP^{Sc} form (the prion hypothesis [1]). The neuropathologic changes of CJD are spongiform change, neuronal loss, and astrocytic proliferation, associated with deposition of the PrP^{Sc} protein throughout the brain.

sCJD most commonly affects patients who are between 60 and 75 years of age. It presents clinically with a rapidly progressive dementing illness, culminating in akinetic mutism. Neurologic features observed during the illness reflect widespread neuronal damage and include myoclonus, cerebellar ataxia, pyramidal and extrapyramidal signs, and cortical blindness. The role of investigations in the diagnosis of CJD has been comprehensively reviewed (2). Until recently, the clinical diagnosis has relied on identification of appropriate clinical features supported by characteristic EEG changes (periodic triphasic sharp wave complexes or periodic synchronous discharge or both, seen in two thirds of patients) and CSF protein

electrophoresis findings (raised 14-3-3 protein, sensitivity and specificity of 85–90%).

Characteristic, usually symmetrical, hyperintensity (relative to cortical gray matter signal intensity) of the caudate head and putamen has been described in 67–79% of sCJD cases on MR images, with varying specificity (3, 4). Some investigators have proposed that these findings should be incorporated into the diagnostic criteria for sCJD. However, false-positive imaging results can occur, partly because the normal putamen is sometimes hyperintense relative to the cortical gray matter with some pulse sequences (particularly proton density-weighted images) and also because overlap of appearances exists with other conditions (although these are usually clinically distinct from sCJD). Other gray matter structures may be affected in sCJD, including the hippocampus, periaqueductal gray matter, and thalamus (although in sCJD, the signal intensity in the thalamus remains lower than that in the putamen).

These basal ganglionic changes have been shown on T2-weighted, proton density-weighted, fluid-attenuated inversion recovery, and diffusion-weighted images. Several of the described abnormalities, particularly the earlier features of cortical hyperintensity, are best seen on fluid-attenuated inversion recovery and diffusion-weighted images. The superiority of diffusion-weighted imaging over other sequences, including fluid-attenuated inversion recovery imaging, in detecting basal ganglionic changes and cortical changes is not a new concept in cases of sCJD and has been previously documented in two small case series (5, 6). T1-weighted imaging results are usually normal in cases of sCJD, and contrast enhancement does not occur.

MR imaging research in association with CJD has been hampered by the rarity of the disease. Murata et al (7) have overcome this by grouping imaging from different subtypes of CJD with differing degrees of diagnostic certainty. Clinical criteria (history, EEG, and CSF analysis) in cases of CJD are not 100% accurate (7), which is why so much interest has been generated in MR imaging as a means to further improve diagnostic accuracy noninvasively. It is unknown whether it is valid to group sporadic and genetic cases of CJD together when assessing MR imaging results. That most of their genetic cases had an atypical clinical course and absent EEG changes adds weight to the growing evidence that they are distinct diseases. This limits the validity of extrapolating their results. When imaging studies lack the accepted criterion standard of pathologic confirmation, the methodology of image assessment becomes more critical. When possible, the scales used for image assessment should be validated by simple inter- and intraobserver studies, preferably including comparison with control cases. The methods can then be more easily reproduced by other centers and the findings fairly and independently validated.

Despite these limitations, the article by Murata et al is an important one. It is the first substantial study to chart the progression of changes in CJD with serial diffusion-weighted imaging. In their study of 13 patients, they convincingly confirmed that diffusion-weighted imaging is considerably more sensitive to basal ganglionic changes than are other sequences, including fluid-attenuated inversion recovery imaging, particularly during the earlier stages of the illness. They also documented progressive changes, with spread of signal intensity changes from caudate head to putamen. They then present the interesting hypothesis that this may reflect synaptic spread through gray matter bridges between the caudate head and the putamen. Despite the rather heterogeneous CJD case mix, Murata et al made a number of other important observations. Cortical diffusion restriction on diffusion-weighted images has previously been thought to be a very transient phenomenon. However, they documented several cases in which this had persisted for several weeks, potentially distinguishing the changes from infarction. In addition, it seems that during the early stages of the clinical disease, asymmetrical signal intensity changes are more prevalent than previously thought, and this has important implications in the interpretation of MR images performed early in cases of rapidly progressive dementia.

MR imaging has played an even more important role in the diagnosis of the most recently discovered subtype of CJD, vCJD. This form of CJD is clinically and neuropathologically distinct from sCJD and has been causally linked to bovine spongiform encephalopathy ("mad cow disease") in cattle. One hundred seventeen cases of probable or definite vCJD have been diagnosed to date through the UK National CJD Surveillance Unit (Western General Hospital, Edinburgh, Scotland). vCJD is characterized by younger age at time of onset (median, 29 years, although a confirmed case has been identified recently in a 74-year-old man), longer duration of disease (median, 14 months), and a clinical picture differing from that of sCJD (8). The presenting symptoms are usually nonspecific, with sensory symptoms (sensation of cold, paraesthesia, or pain) and psychiatric symptoms (withdrawal, depression, fleeting delusions) occurring commonly, and the nonspecific nature of these symptoms often leads to late diagnosis. Other neurologic features include cerebellar signs, abnormal eye movement, and involuntary movements (myoclonus, chorea, dystonia).

The histopathology of vCJD is also distinct from that of sCJD, with astrocytosis and neuronal loss being particularly prominent in the thalamus and with characteristic florid plaques seen in the cerebral cortex. In cases of vCJD, the EEG and CSF 14-3-3 have a much lower sensitivity than in cases of sCJD. Tonsil biopsy may be useful but is invasive and has yet to be

fully validated in a large group of patients. Criteria for the *in vivo* diagnosis of probable vCJD have been defined, and MR imaging now plays a pivotal role.

In the past, the diagnosis of vCJD has often been delayed and made only post mortem, but recent studies have shown that in cases of vCJD, MR imaging shows a characteristic distribution of symmetrical hyperintensity in the pulvinar of the thalamus. The degree of hyperintensity is greater than that seen in the putamen or cortical gray matter and is known as the pulvinar sign of vCJD (9). The pulvinar hyperintensity is best appreciated on axial images on which the thalamus, basal ganglia, and cortex can all be compared on a single section (10). The sign was originally described on T2-weighted and proton density-weighted images and was 80% sensitive and 100% specific in the appropriate patient group (11), but the sensitivity has increased to greater than 90% with improvements in MR imaging technology, particularly with wider availability of fluid-attenuated inversion recovery imaging. Very limited data are available regarding diffusion-weighted imaging in cases of vCJD, with only four of the first 100 cases having included diffusion-weighted imaging. Therefore, the value of this sequence in association with vCJD remains unclear. Quantification studies of the pulvinar sign are currently in progress, and serial studies using diffusion-weighted imaging as performed by Murata et al may also provide insights into how this disease enters the brain from the digestive system.

Although the differential diagnosis of hyperintensity in the thalamus is extensive, the presence of high signal intensity limited to the pulvinar of the thalamus in conditions other than vCJD is extremely rare. To date, those conditions with true pulvinar hyperintensity have all remained clinically clearly distinct from vCJD. Hyperintensity is also seen in the dorsomedial nuclei of the thalamus in 60–80% of cases of vCJD (depending on pulse sequence performed). However, unlike sCJD characteristics, cerebral atrophy is not prominent.

Although CJD is a rare disease, it has generated great interest, particularly because of the discovery that it may be transmitted iatrogenically, and more recently, from animals to humans by food products, with subsequent enormous commercial and political consequences. To date, it has remained a uniformly fatal disease with no specific treatment. From an imaging perspective, it is also unusual, with the recent discovery of characteristic deep gray matter nuclei changes, which are surprisingly sensitive and specific for the disease. Many unanswered questions remain regarding the pathogenesis and imaging of CJD, and because of the rarity of the disease, it is unlikely that major progress will be made without coordinated multicenter collaboration. However, diffusion-weighted imaging offers an exciting new and useful way of following the clinical course and is

beginning to help our understanding of the pathogenesis of this disease.

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Neuroradiology and Drug Abuse: A Picture Is Worth a Thousand Words

Drug abuse continues to be the scourge of the modern world, affecting the destitute and underprivileged, as well as the most affluent in all countries. In the current issue of the *AJNR*, Aydin et al (page 1173) describe and catalogue the neuroradiologic findings of a form of drug abuse, chronic toluene inhalation, as depicted on MR images.

In this article, the authors document abnormalities in the white matter tracts and in the thalami of chronic toluene abusers and detail the concordance of the MR findings with the results of the neurologic examination. In the study population, in which the average patient age was 17.5 years, the neurologic signs and symptoms included insomnia and forgetfulness in 83%, tremors in 54%, ataxia and disturbed cerebellar test performance in 49%, rigidity in 24%, and dysarthria in 10%. The authors also found that the severity of the white matter disease is correlated with the duration of abuse. In addition, the following neuroradiologic findings were seen on the MR images: 1) hyperintensities in the cerebellum, brain stem, and upper cervical cord at T2-weighted imaging; 2) generalized atrophy of the brain; 3) thinning of the corpus callosum; and 4) abnormalities in the substantia nigra, the red nucleus, and the hippocampus. MR findings of severe abnormalities in what should be pristine adolescent brains are truly disturbing. It is also important to remember that this type of drug abuse is certainly prevalent in the United States and Europe. This sobering thought may spur some of us on to fulfill our social responsibilities.

I certainly hope that, when each of us writes or reads a scientific paper, we strive to accomplish more than just describe a disease process. Our work should offer concrete benefit for human beings. As neurora-

diologists, what can we do to combat drug abuse? Clearly, images can serve as a powerful deterrent. For example, I remember being in grade school, when images from an anti-smoking campaign showed the difference between healthy lungs and smokers' lungs.

However, perhaps the strongest testament to the power of a radiologic image is conveyed by the noted cardiologist and Nobel Prize winner Evgeni Chazov (1). He describes the situation in communist Mongolia in 1984 when the country was ruled by the aging Yumjaagiyn Tsendenbal, who according to Chazov, lost his mental faculties and left all decision making to his rude power-hungry wife. Removing the leader was not that easy, and the members of the government were reluctant to move against Tsendenbal, although they understood his limited mental capacity. His ouster was facilitated by sending Tsendenbal for a health check-up that included CT of the brain. Needless to say, the images showed severe atrophy. Chazov showed the CT scan, along with a CT scan of normal brain for comparison, to the members of the Mongolian politburo. After seeing the severe atrophy of Comrade Tsendenbal's brain, they quickly deposed him.

All neuroradiologists know that cerebral atrophy does not necessarily connote dementia. Also, I do not know whether the change in governmental leadership has improved the welfare of the Mongolian people. Nevertheless, the fact remains that a single neuroradiologic image is powerful enough to bring about a change in the leadership of a communist country.

I am far from advocating the platonic aphorism that we make mistakes only because of ignorance. Clearly, neuroradiology cannot conquer the problem of drug abuse. MR images cannot solve life's chal-

lenges (eg, homelessness, stark poverty, orphanhood) that perhaps led the child and adolescent subjects of the current study to turn to drugs. Nevertheless, the episode described earlier demonstrates how powerful a single neuroradiologic image can be. We can only hope that work such as the current article that demonstrates the damage inflicted on young brains by drug abuse can be used to influence young minds. Perhaps showing a 14-year-old youth that his brain

will look like that of an 85-year-old man may convince him not to start sniffing glue.

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