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# The Promises and Challenges of Rigorous Research

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# Letters

## Diffusion-weighted Monitoring of Conservatively Treated Pyogenic Brain Abscesses: A Marker for Antibacterial Treatment Efficacy

We were highly interested in Cartes-Zumelzu et al's article (1) on the value of the diffusion-weighted (DW) image monitoring in conservatively treated pyogenic brain abscesses published in the September 2004 issue of the *AJNR*. As Chen and Chung's editorial (2) in the same issue highlighted, accurate and early indices on antibacterial treatment efficacy are crucial to optimize the therapeutic strategy.

A few years ago, we published the observation of a 14-year-old boy presenting with a pyogenic frontal brain abscess brain that was not immediately treated surgically and showed two components that evolved with time on serial DW images (3). Newly reformatted images of this case are shown in Figures 1 and 2. The patient presented with a febrile meningeal syndrome and biologic markers for sepsis. We observed a strong time dependence of both signal intensity and apparent diffusion coefficient (ADC) values of the abscess throughout serial DW image monitoring. In the initial phase of the disease course a hyperintense material completely filled the abscess cavity, in which the ADC was

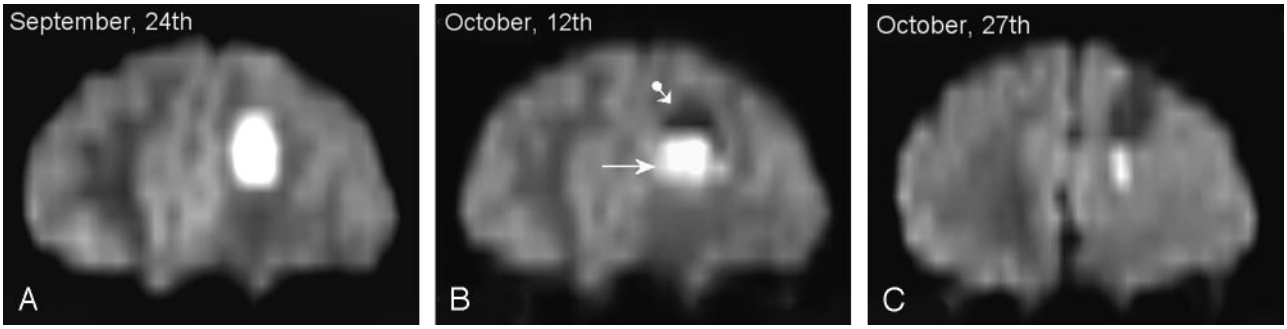


FIG 1. Patient 1. Frontal reformats of serial DW trace images.

*A,* Status at admission: complete filling of the abscess cavity by hyperintense material. Hyperintensity was mainly due to true diffusion weighting effect (see Fig 2A, -B).

*B*, Status 3 weeks later: appearance of two components with a sharply delineating interface. Hyperintensity at the time was mainly due to T2-weighted shine-through effect (see Fig 2C, -D).

*C,* Status 5 weeks later: further decrease in size of the hyperintense component after stereotactic drainage. The patient had clinically recovered at the time.

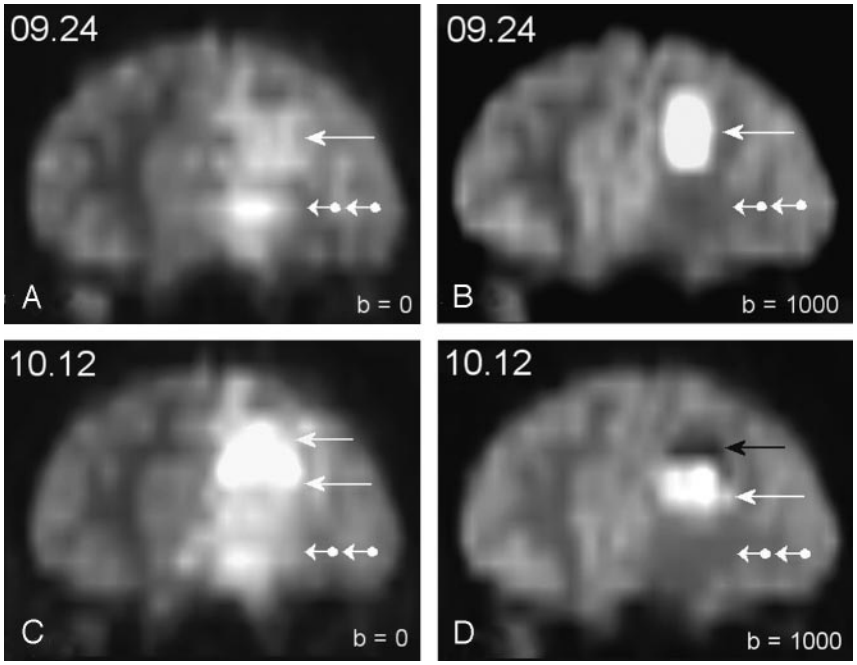


FIG 2. Patient 1. T2-weighted shine-through effect in the hyperintense component.

*A* and *B,* Status at admission. *A,* Frontal reformat of the T2-W image of the echo-planar imaging (EPI)–spin-echo (SE)–DW sequence with *b* factor = 0. Left frontal parenchyma displayed hyperintensity. Inferior area (*double-ball arrowhead*) seemed very slightly brighter than the superior one (*arrow*). *B,* Similar image after application of the diffusion-sensitizing gradients at *b* factor = 1000 s/mm$^2$. The inferior area became hypointense and corresponded to vasogenic interstitial edema with mean ADC values at 1480 mm$^2$/s. Superior area remained hyperintense because of prominent diffusion-weighting effect with a mean ADC at 650. Mean ADC was 780 in the contralateral normal brain tissue.

*C* and *D,* Status at 3 weeks. *C,* Frontal reformat of the T2-weighted image of the EPI-SE-DW sequence (*b* = 0). Left frontal parenchyma is still hyperintense, with little change when compared with panel *A,* except for more perceptible hyperintensity within superior areas (*arrows*) when compared to inferior areas (*double-ball arrowhead*). *D,* Similar image after application of the diffusion-sensitizing gradients at *b* = 1000. Inferior area of vasogenic edema displayed similar hypointensity as on admission (see panel *B*). A sharply delineated interface has appeared within the superior area separating a very hypointense upper area (*black arrow*) in which mean ADC value was measured at 2320 and a lower one (*white arrow*) with persistent hyperintensity in which mean ADC value was 1130. The upper area corresponded to fluid supernatant and the lower area to shrinking purulent core in which fibrinolysis has decreased the restriction to the water diffusion within pus when compared with the initial status (see panel *B*). The T2-weighted shine-through effect was thus far mainly responsible for hyperintensity in this subarea, and not the true diffusion weighting effect.

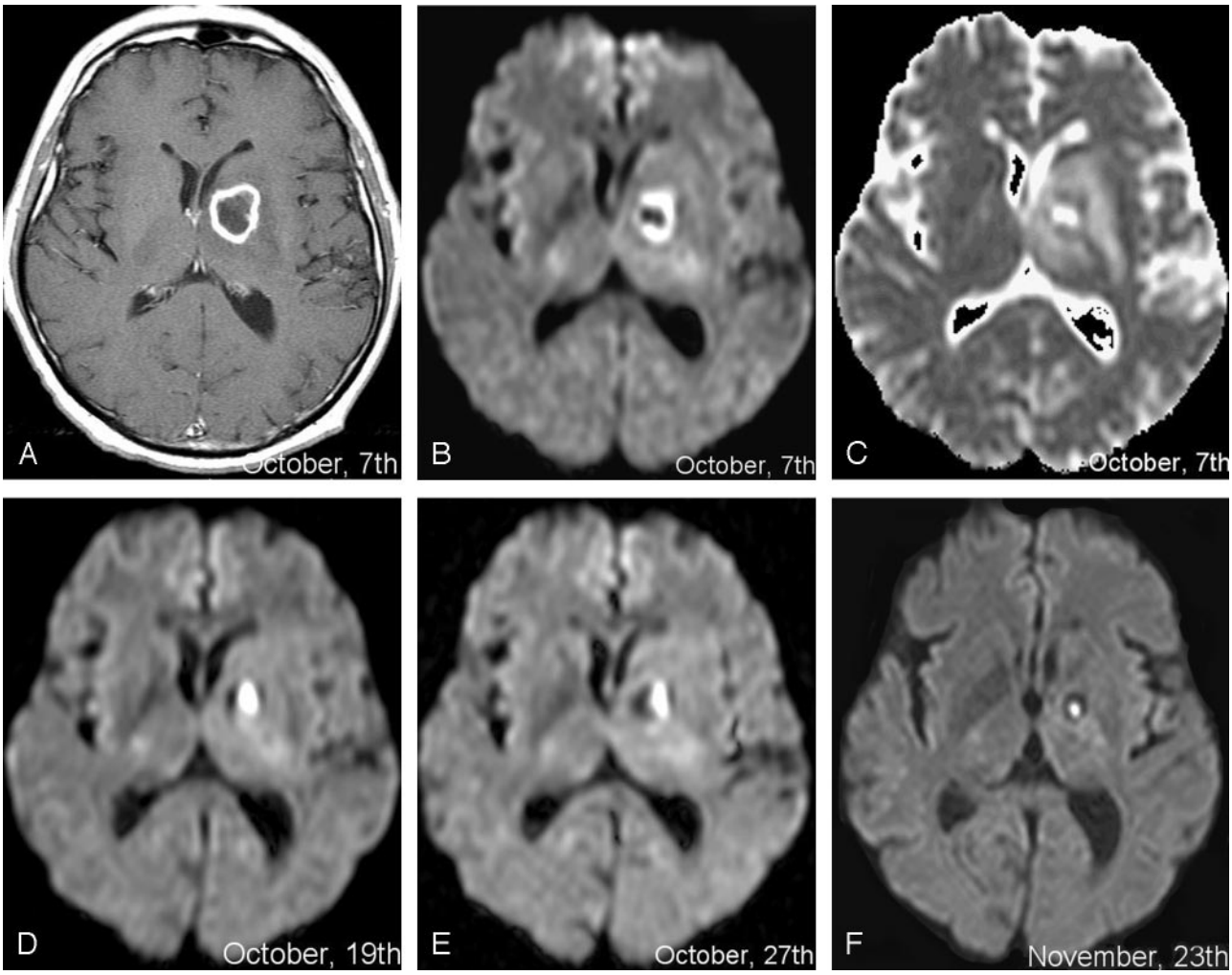


FIG 3. Patient 2.

*A–C,* Initial MR examination at admission. *A,* Postcontrast T1-weighted image shows a left-sided ring-like lesion with central cystic necrosis and enhanced peripheral margins. *B,* DW trace image shows sharply delineated central hypointensity and peripheral hyperintensity of the lesion. The pattern is up to now undescribed in pyogenic abscesses. *C,* ADC-mapped image shows strongly increased ADC values within the center of the lesion (mean, 2320) and moderately increased ones within the peripheral ring (mean, 1210). Mean ADC value in normal contra lateral mirror area was 830.

*D–F,* Serial follow-up DW images after stereotactic drainage and during consolidation antibiotic treatment. *D,* Lesion pattern has inverted when compared with the pretherapeutic status (Fig 2*B*): central area has now become hyperintense and peripheral one has become hypointense. *E* and *F,* Shrinkage of the central hyperintense component over time is obvious.

decreased when compared with contralateral normal brain tissue (Figs 1A, 2B). The strong hyperintensity in the homogeneous core was thus far prominently due to true diffusion-weighting because only moderate hypersignal intensity was observed on corresponding T2-weighted images (Fig 2A). Shortly after the initiation of empirical antibiotic therapy, a sharply delineated hypo-/hyperintense interface between pus sediment and fluid supernatant appeared (Fig 1B). The ADC values of the hyperintense component had then become slightly elevated when compared with normal brain tissue, thereby suggesting the prominence of the T2-weighted shine-through effect in the hyperintensity of the lesion (Fig 2D). Delayed stereotactic drainage confirmed the presence of thick pus containing neutrophilic pyocytes but failed to identify the causative organism. A second follow-up examination after drainage revealed further shrinking of the hyperintense component (Fig 1C).

We recently observed a 61-year-old man with non-Hodgkin lymphoma who complained from tiredness, atypical sensory disturbances of the four extremities, and gait disturbances without fever. Initial MR examination demonstrated the presence of a left-sided deep nodular lesion. Intensely enhanced margins surrounded a central area of cystic necrosis (Fig 3A). DW trace images revealed a sharply delineated hypo-/hyperinterface with ringlike pattern (Fig 3B). The peripheral component was hyperintense, but had slightly elevated ADC values when compared with normal brain tissue (Fig 3C), just as the shrinking hyperintense core in the previous patient. The central component was hypointense with highly elevated ADC values, which has not been described yet in brain abscesses involving pyogens. Empirical antibiotic therapy was unsuccessful. Stereotactic biopsy evacuated purulent material containing neutrophilic pyocytes. The causative germ remained unidentified. Antibiotic treatment was continued after drainage, and serial follow-up MR examinations were performed (Fig 3D–F). The first follow-up examination performed 2 days after stereotactic procedure showed inverted hypo-/hyper-ring pattern with central hyperintensity and peripheral hypointensity (Fig 3D). Further examinations demonstrated the progressive shrinkage of hyperintense core and the persistence of hypointense margins (Fig 2E, -F).

The two cases highlight the diagnostic value of the sharply

delineated hypo/hyper interface sign on DW trace images of pyogenic cerebral abscesses. Slightly elevated ADC values were measured within the hyperintense shrinking component when hypo- and hyperintense components were present concomitantly, reflecting the overweighing of the true diffusion-weighted effect by the T2-weighted shine-through effect. Perhaps the combination of both features (sharply delineated hypo-/hyperinterface plus slightly elevated ADC within hyperintense component) is to become a clue to the diagnosis of abscess. Moreover, the shrinkage of the hyperintense content on serial DW images paralleled the efficacy of the antimicrobial treatment in the two patients, thereby assessing the clinical value of the DW monitoring of brain abscesses under antibiotic therapy.

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## References

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## The Promises and Challenges of Rigorous Research

Dr. Cartes-Zumelzu and colleagues (1) are to be commended for investigating diffusion-weighted imaging to monitor therapy of brain abscesses. Despite the limited specificity of DW imaging in the diagnosis of abscesses, its use in the surveillance of treated abscesses may demonstrate sufficient accuracy to guide therapy as the number of pathologic processes within an abscess cavity after evacuation is usually limited to pus resorption or reaccumulation, or to intracavitary hemorrhage. Detecting these changes before their appearance on conventional imaging and before the patient deteriorates and requires reintervention could lead to earlier preventive drainages and improved outcomes.

To prove the incremental value of DW imaging over conventional MR imaging in improving patient mortality and morbidity in a rigorous study offers a challenge. Such a study would be fraught with difficulties inherent in the variability of patient presentations, clinical courses and individual responses to treatment.

The details and design of Cartes-Zumelzu et al's study deserve further evaluation. There are apparent mistakes in Table 2. Patient 2 is mentioned twice, in part *A* as having one drainage of the two abscesses and in part B as having one drainage of a single abscess. Patient 3 is omitted from the table, although the text states that drainage was performed on one of two abscesses. Inconsistencies are present in part B of the table in labeling times of follow-up imaging and placement of values into incorrect boxes. For example, the fourth follow-up in Table 2B shows "D" as the value when "D" represents drainage, not a time value. The DW imaging is listed as 1.17 when only high and low categories are possible. This puts in doubt the reliability of the table and, as a result, the entire table needs re-explanation.

No relationship is demonstrated between apparent diffusion coefficient (ADC) and DW values. Specifically, low DW is associated with ADC values of 0.51–2.95. High DW is associated with ADC values of 0.36–1.17, which is a near-complete overlap. Even if trends are considered, the independent behavior of ADC and DW is apparent. A fall of ADC from 2.61 to 1.57 is not reflected in a the change of DW from low to high in patient 7, whereas a rise of 0.41 to 0.51 converts DW from high to low in the second abscess of patient 6.

The authors do not state which value, DW or ADC, was used as the primary factor in the decision whether to perform drainage or to declare therapy successful. If both values were considered, how were inconsistencies between the two resolved, in light of the independent behavior of the two? Did the authors use a predefined threshold of ADC or a percentage fall as their decision threshold? The reader deserves a precise answer to this question.

Scrutiny of Table 2 and the results section reveals multiple violations of the presumed protocol to drain abscesses with low/falling ADC and observing ones with high/rising ADC. Patient 7 demonstrated a fall in ADC from 2.61 to 1.57 and the second abscess in patient 2 from Table 2A had ADC change from 1.12 down to 0.46, yet neither patient was drained. No further imaging was performed for either patient despite a falling ADC, presumably an unfavorable sign. For patient 2 in Table 2A, the first abscess showed a rising ADC, yet drainage was performed despite this good imaging sign, an apparent contradiction of the very hypothesis of the study.

The study is shortchanged into being simply narrative and descriptive in its methodology by the lack of statistical analysis of the numerical results generated.

Clear, reproducible, a priori definition of the decision threshold, adherence to the predefined protocol and accurate reporting of results would significantly improve the study. The current study appears to be flawed and, by itself, does not support use of DW in abscess imaging.

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## Reference

1. Cartes-Zumelzu FW, Stavrou I, Castillo M, et al. **Diffusion-weighted imaging in the assessment of brain abscess therapy.** *AJNR Am J Neuroradiol* 2004;25:1310–1317

## Conventional T1-Weighted Imaging in the Diagnosis and Assessment of Brain Abscesses

For several years now, radiologists have known the utility of diffusion-weighted (DW) imaging in differentiating brain abscesses from cystic/necrotic brain tumors.

In "Diffusion-Weighted Imaging in the Assessment of Brain Abscesses Therapy," Cartes-Zumelzu et al (1) discuss the extension of this technique to using DW imaging to assess abscess response to therapy. In the article, the authors state, "with contrast-enhanced T1-weighted imaging the differentiation of purulent fluid from serous fluid inside the abscess cavity is not possible." They further conclude, "findings in successfully and unsuccessfully treated brain abscesses were similar on conventional MR images and did not allow for their differentiation." In my experience this is not always the case. Clearly, DW imaging is a very useful technique to assess the therapeutic response of the abscess cavity, however this may also be done by careful inspection of routine contrast-enhanced T1-

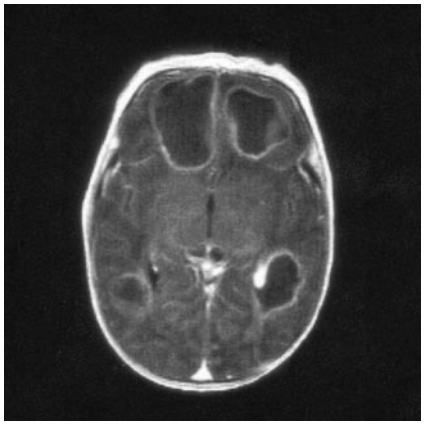

FIG. 1. Axial contrast-enhanced T1-weighted image.

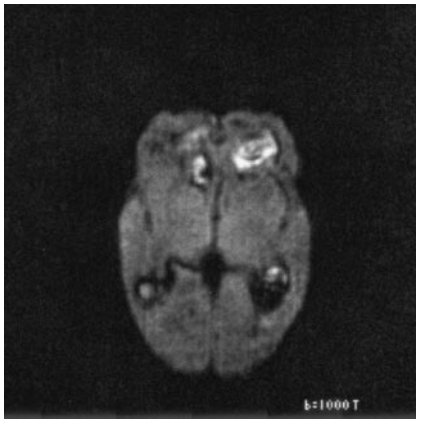


FIG. 2. Axial DW image.

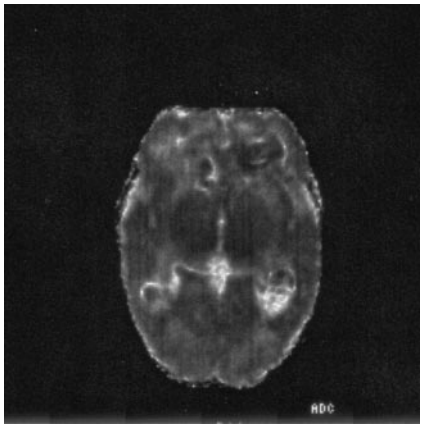


FIG. 3. Axial ADC map.

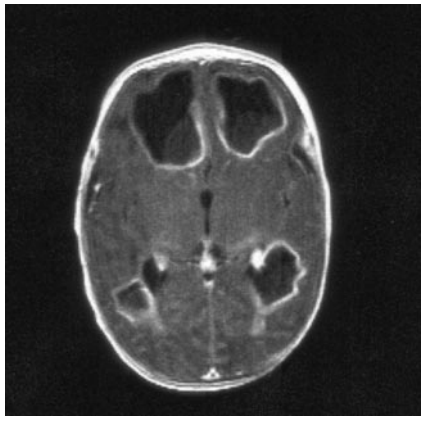

FIG. 4. Axial contrast-enhanced T1-weighted image.

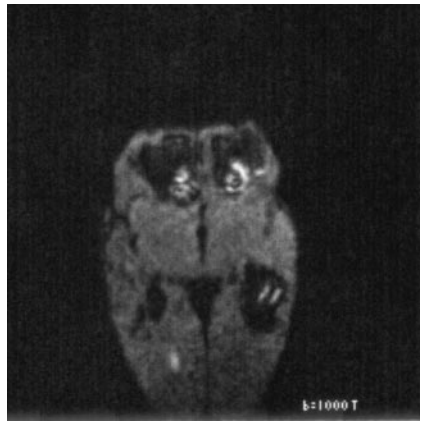


FIG. 5. Axial DW image.

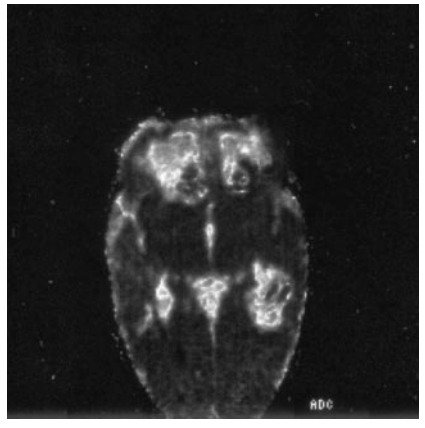


FIG. 6. Axial ADC image.

weighted images. I have included an example to illustrate this point. The images presented are from a child of 3 weeks of age with Gram-negative rod meningitis.

On the initial images (Figs 1–3) multiple abscesses were noted in both frontal and parietal lobes bilaterally, which were homogeneously low (but not CSF) signal intensity with peripheral enhancement on post-contrast T1-weighted images. They appeared hyperintense on DW imaging and demonstrated corresponding hypointensity on the apparent diffusion coefficient (ADC) map.

Following 11 days of antibiotic therapy (ampicillin and gentamicin) the patient was reimaged (Figs 4–6). Again ring-enhancing lesions were noted on the post-contrast T1-weighted images. But, unlike the initial images, the collections were heterogeneous with two discrete components. The dependent portion was again hypointense (but not CSF in signal intensity) and again demonstrated restricted diffusion. The

nondependent portion, however, became isointense to CSF and was no longer hyperintense on DW imaging and was hypointense on the ADC map. Thus, the postcontrast T1-weighted images demonstrated essentially the same information (albeit a bit more subtle) as the DW image. This in no way diminishes the use of diffusion sequences in diagnosing and following brain abscesses, but merely points out the usefulness of conventional T1-weighted images.

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## In Re: Diffusion-Weighted Imaging in the Assessment of Brain Abscesses Therapy

We are pleased that our article "Diffusion-Weighted Imaging in the Assessment of Brain Abscesses Therapy" has resulted in several letters to the editor, and here we will attempt to address the issues raised in those letters.

We agree with Dr. Khramov in that to prove the value of diffusion-weighted (DW) imaging in management of cerebral abscesses would require a more rigorous investigation than ours. Our study was comprised of our "limited" experience in seven patients, a fact that should lead no reader to believe that our investigation is a definite one but, rather, an enthusiastic beginning for what is a complex clinical issue. We hope that our findings will lead other investigators to pursue this exciting issue with more depth. We thank Dr. Khramov for pointing out what can be explained by a typographical error in Table 2. The patient identified as 2 on part B of the table should actually be patient 3. We sincerely apologize for overlooking this mistake. In addition, Dr. Khramov is correct in pointing out other errors in Table 2, particularly where the columns appear to have "shifted" (this resulted in confusion regarding the results listed in the columns labeled "time" and "DWI"). To cast doubt on our results and integrity on the basis of typographical mistakes, however, is unwarranted.

Dr. Khramov goes on to question the relationship between apparent diffusion coefficient (ADC) and DW imaging values. As we stated in our article, the mean ADC in untreated abscesses (representing the initial MR study) was 0.52 (range, $0.36–0.75 \times 10^{-3}$ mm$^2$/s), and all abscesses had high signal intensity on DW imaging, probably because of restricted diffusion. These findings in our small series correlate with previous experience, our own experience, and that of others. ADC values measured after surgical drainage (first follow-up) showed considerable variations ($0.51–2.95 \times 10^{-3}$ mm$^2$/s), which we believe reflect the contents of the drained cavities (a combination of artificial CSF, antibiotics, fluids, and hemorrhage). The heterogeneity of the cavities may have accounted for the overlap in the values we obtained.

Furthermore, Dr. Khramov is correct in pointing out that we did not state whether DW imaging, ADC, or both was the deciding value for performing drainage. We did not seek to establish a threshold ADC but cautiously concluded that signal intensity changes on DW imaging (in the correct clinical and laboratory settings) may detect the reappearance of pus before conventional MR imaging. The lack of clinical deterioration and decreasing C-reactive protein in patient 7 explains surgery was not performed again. In patient 2, it is obvious that, despite relatively decreasing ADC values (less restriction) in the abscess cavity, his C-reactive protein continued to rise, he was showing a lack of clinical improvement, and the DW image showed very high signal intensity, all factors that lead to repeat surgery. Therefore, we are well aware of the complexity in the management of these patients and are not advocating the use of DW imaging/ADC independent of the other clinical parameters. We do not agree with Dr. Khramov's claim that these tendencies contradict our hypothesis. To say that our "early" experience is simply narrative and that our study is flawed represents, in our opinion, a lack of understanding of the complexity involved in managing these type of patients.

The second letter takes a more benign tone. Dr. Duprez tells

**TABLE 2a: Signal intensities on DWI and ADC values on initial and subsequent MR scans in 4 patients who underwent one abscess drainage**

| Patient # | MR examinations | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Initial MRI | | | | 1. Follow-up | | | | | 2. Follow-up | | | | | 3. Follow-up | | | |
| | ADC | DWI | CRP | | Time | ADC | DWI | CRP | | Time | ADC | DWI | CRP | Time | ADC | DWI | CRP | |
| 1 | 0.42 | high | 0.5 | D | 4 | 0.87 | low | 0.5 | | 14 | 2.19 | low | 0.5 | 26 | 2.25 | low | 0.5 | |
| 2 | 0.53 | high | 0.5 | | 13 | 0.81 | high | 1.7 | D | 21 | 2.76 | low | 0.9 | | | | | |
| | 0.52 | high | | | | 1.12 | high | | | | 0.46 | high | | | | | | |
| 6 | 0.36 | high | | | 7 | 0.60 | low | | | 14 | 1.68 | low | | | | | | |
| | 0.41 | high | | D | | 0.51 | low | | | | 1.39 | low | | | | | | |
| 7 | 0.67 | high | 3.0 | D | 14 | 2.61 | low | 2.2 | | 28 | 1.57 | low | 1.0 | | | | | |

ADC = $\times 10^{-3}$ mm$^2$sec, DWI = signal intensity on DWI, Time = time interval (days) after the drainage, CRP = C reactive protein, D = surgical intervention/drainage

**TABLE 2b: Signal intensities on DWI and ADC values on initial and subsequent MR scans in 2 patients who underwent two abscess drainages**

| # | Initial MRI | | | | 1. Follow-up | | | | 2. Follow-up | | | | 3. Follow-up | | | | 4. Follow-up | | | | 5. Follow-up | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | ADC | DWI | CRP | | Time | ADC | DWI | CRP | Time | ADC | DWI | CRP | Time | ADC | DWI | CRP | | Time | ADC | DWI | CRP | Time | ADC | DWI |
| 3 | 0.52 | high | 2.3 | D | 4 | 2.56 | low | 1.6 | 13 | 1.16 | high | 3.4 | 18 | 0.76 | high | | D | 11 | 1.17 | high | | 7 | 2.66 | low |
| 5 | 0.48 | high | 2.3 | D | 10 | 2.95 | low | 3.18 | 16 | 2.58 | iso | 2.5 | 26 | 0.75 | high | | D | 2 | 1.21 | low | | | | |

ADC = $\times 10^{-3}$ mm$^2$sec, DWI = signal intensity on DWI, Time = time interval (days) after the drainage, CRP = C reactive protein, D = surgical intervention/drainage

us about a patient who is interesting because a partially treated abscess showed increasing ADC values despite aspiration that confirmed the presence of pus. It is impossible to know what changes in the microenvironment of the pus are introduced by antibiotics (it is not even clear whether antibiotics truly penetrate through the abscess capsule into the pus) or to what extent T2 relaxation effects may account for these findings. Antibiotics must have an effect on the pus, because in many partially treated abscesses the responsible microorganism is never isolated from aspirated pus. In his second patient, high ADC was also found in the pus of another partially treated abscess. The role (if any) that bacteria play in the signal intensity characteristics of abscesses remains to be elucidated. In addition, these two cases also show the complex interplay between signal intensity characteristics on DW imaging and T2 relaxation effects. Dr. Duprez also calls our attention to the different signal intensities between the peripheral and central aspects of the lesions. Although we did not mention this observation in our article, just by glancing at our illustrations one can observe a hypo-/hyperinterface (such as the one he mentions) on the DW image in untreated abscesses and in the recurrent abscess shown in Figure 4. This interface, however, is absent in the successfully treated abscesses. We thank Dr. Duprez for pointing out this finding and agree with him in that the resolution of this signal intensity interface may signify successful therapy.

In the third letter, Dr. Holz presents a patient with multiple cerebral abscesses showing changing DW imaging characteristics after 11 days of antibiotic therapy. Similar to our findings, successful therapy was evidenced by decreasing diffusion restriction in the cavities (at least the frontal ones in his patient). He is correct in saying that the findings are also seen on the T1-weighted images, but we would venture that they are easier to appreciate on the DW image. Also, in accordance with the observations made by Dr. Duprez, we also believe that the signal intensity interface at the margins of the abscesses became less distinct with therapy.

We thank the authors of the three letters for bringing to our attention some problems in our article and for pointing out other DW imaging features of treated abscesses that we did not mention.

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