Original article

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7 tesla T_2*-weighted MRI as a tool to improve detection of focal cortical dysplasia

Tim J. Veersema [1], Pieter van Eijsden [1], Peter H. Gosselaar [1], Jeroen Hendrikse [2], Jaco J.M. Zwanenburg [2], Wim G.M. Spliet [3], Eleonora Aronica [4], Kees P.J. Braun [1], Cyrille H. Ferrier [1]

[1] Department of Neurology and Neurosurgery, Brain Center Rudolg Magnus, University Medical Center Utrecht
[2] Department of Radiology, University Medical Center Utrecht
[3] Department of Pathology, University Medical Center Utrecht
[4] Academic Medical Center, Department of Pathology, Amsterdam, The Netherlands

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ABSTRACT – Focal cortical dysplasia is one of the most common underlying pathologies in patients who undergo surgery for refractory epilepsy. Absence of a MRI-visible lesion necessitates additional diagnostic tests and is a predictor of poor surgical outcome. We describe a series of six patients with refractory epilepsy due to histopathologically-confirmed focal cortical dysplasia, for whom pre-surgical 7 tesla T_2*-weighted MRI was acquired. In four of six patients, T_2* sequences showed areas of marked superficial hypointensity, co-localizing with the epileptogenic lesion. 7 tesla T_2* hypointensities overlying focal cortical dysplasia may represent leptomeningeal venous vascular abnormalities associated with the underlying dysplastic cortex. Adding T_2* sequences to the MRI protocol may aid in the detection of focal cortical dysplasias.

Key words: epilepsy, FCD, cortical localization, susceptibility weighted, ultra-high field, magnetic resonance imaging

Focal cortical dysplasia (FCD) is one of the most common underlying pathologies in patients who undergo surgery for refractory epilepsy. A substantial percentage of these lesions is not visible using routine 1.5 tesla (T) or 3T MRI; 37% for FCD type I and 15% for type FCD type II in a review of surgical series from 2000 to 2008, and 36% and 2%, respectively, in a 2000-2007 UCLA series of 97 patients (Lerner *et al.,* 2009). No visible lesion on MRI is a predictor of poor surgical outcome and necessitates additional diagnostic studies which may include invasive intracranial electrode registration (Téllez-Zenteno *et al.,* 2010). Advances in imaging techniques are expected to improve the detection of epileptogenic lesions.

Correspondence:
Tim J. Veersema
Universitair Medisch Centrum Utrecht,
Internal post number G03.232,
PO Box 85500, 3508 GA Utrecht,
The Netherlands
<T.J.Veersema@umcutrecht.nl>

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Susceptibility-based contrast MRI sequences are sensitive to the susceptibility effect created by the paramagnetic property of deoxyhaemoglobin in blood, and thus augment the visibility of the cerebral venous microvasculature (Haacke *et al.*, 2009). Sequences such as T_2* and susceptibility-weighted imaging (SWI) have proven useful in the detection and characterization of a variety of cerebral vascular abnormalities (*e.g.* Sturge-Weber syndrome and cavernous malformations), as well as haemorrhagic, calcified or iron-containing lesions (Mittal *et al.*, 2009). Reports on susceptibility-based contrast sequences in epilepsy patients are limited and mostly describe the benefits for detection and characterization of calcified lesions, and not for the detection of otherwise inconspicuous lesions, such as FCD (Saini *et al.*, 2009). In this series, we illustrate the potential of the T_2* MRI sequence at 7 tesla (T) in assisting the detection of FCD.

Methods

We retrospectively selected six consecutive patients from the Dutch Epilepsy Surgery Program with refractory epilepsy due to histopathologically-confirmed FCD, for whom T_2* images at 7T were acquired presurgically between November 2008 and November 2014. These patients either had lesions suggestive of FCD on 3T (n=2) or had normal 3T MRI, with semiology, electroencephalogram, and telemetry findings strongly suggesting a structural focal abnormality (n=4). 3T MRI was deemed normal if no indications for structural abnormalities were identified on assessment by expert neuroradiologists and during review by the Dutch Epilepsy Surgery Program board, which includes neurosurgeons, neurologists, and neuroradiologists with expertise in the field of epilepsy. 3T MRI-negative patients underwent additional presurgical evaluation, including 7T MRI and PET, SPECT, or MEG, in order to localize the epileptogenic zone. In addition, 7T MRI was used to further characterize the lesions for the two subjects with lesions on 3T.

The 7T MRI protocol included (conventional) 3D FLAIR, 3D double inversion recovery, 3D T_1 and 3D T_2-weighted sequences, and a previously described T_2*-weighted sequence (Zwanenburg *et al.*, 2011). Parameters used for the gradient echo T_2* MRI were: isotropic 0.5-mm resolution, echo time of 27 ms, flip angle of 24°, repetition time of 57-93 ms (shortest possible), with EPI and flow compensation. For two patients, scans were acquired with 0.6-mm resolution (isotropic), echo time of 20 ms, flip angle of 20°, and repetition time of 25-26 ms. Images were acquired on a Phillips 7T system (Philips Healthcare, Cleveland, OH, USA) with a volume transmit and 16- or 32-channel receive head coil (Nova Medical, Wilmington, MA, USA).

7T T_2* images were reviewed for abnormalities co-localizing with epileptogenic zones. To aid visual detection of hypointense structures, minimum intensity projections of T_2* sequences were constructed with 5-mm slab thickness. Following resective surgery, tissues were histopathologically classified according to ILAE guidelines (Blümcke *et al.*, 2011).

Informed consent was obtained for performing 7T MRI and the use of patient data. The report complies with the declaration of Helsinki.

In addition, we reviewed 7T T_2* images of eight control subjects (four male and four female; age: 27±4) (previously published by Zwanenburg *et al.* [2011]).

Case series

Four of six patients had normal 3T MRI findings; in two of these, conventional 7T MRI sequences (T_1, T_2, double inversion recovery, and FLAIR) revealed a lesion suggestive of FCD. In two other patients, abnormalities were seen both on 3T and 7T images. All six patients underwent resective surgery and had histopathological confirmation of FCD (ILAE type Ib in Patient II, type IIa in Patient V and VI, type IIb in Patient I and IV, and mild malformation of cortical development type 2 in Patient III). In four of these patients (Patients I and II [*figure 1A*] and Patients III and IV [*figure 1B*]), 7T T_2* showed areas containing marked hypointensities with a branched, partly tortuous configuration, and a signal compatible with venous blood, suggestive of increased venous vasculature in the sulci neighbouring the malformed cortex.

Because the described T_2* signal changes appeared to be located in the leptomeningeal tissue or subarachnoid space overlying the malformed cortex, we looked for a histopathological correlate in the leptomeninges of the operated patients. Unfortunately, due to the locations of the malformations, in the lower part of a sulcus and interhemispheric, respectively, en-bloc resection with intact leptomeningeal structures was only possible in one patient (Patient III). This lesion was classified as mMCD type 2, with fibrotic and thick meninges containing prominent vascular structures (*figure 2*).

In summary, hypointensities on T_2* were identified in four of six consecutive patients with histologically-confirmed FCD, for whom 7T T_2* images where available. *Table 1* lists clinical and imaging characteristics of all six patients.

On 7T T_2* images and corresponding minimum intensity projections of eight healthy volunteers, symmetric venous leptomeningeal vascular structures

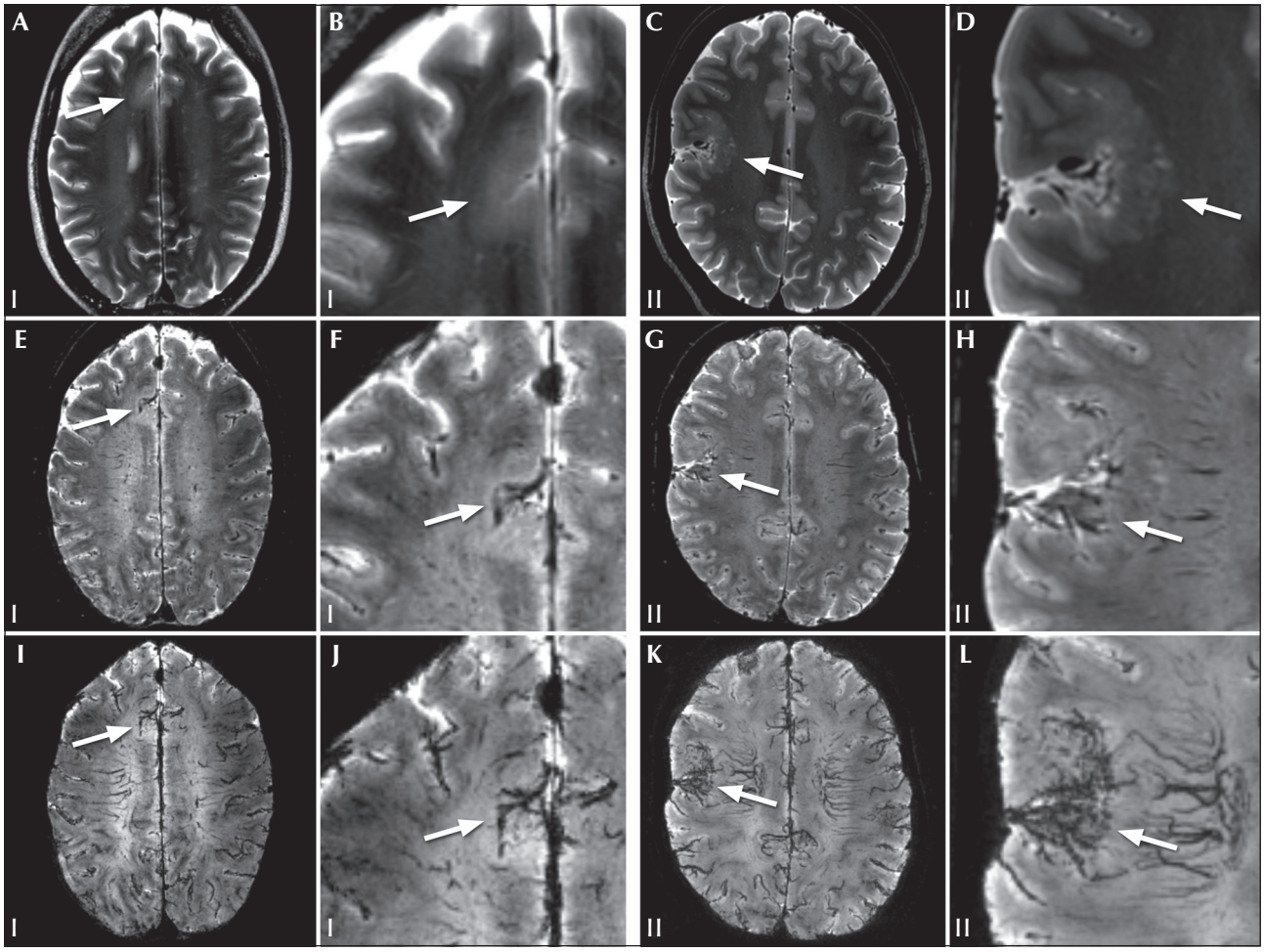

Figure 1A. (A) MRI findings of patients with confirmed FCD and T_2* signal changes; 7T T_2 (A-D), T_2* (E-H) and T_2* minimum intensity projection (I-L) transverse reconstructions. Lesions are depicted in detail in (B), (D), (F), (H), (J) and (L). Patient I; FCD ILAE type IIb (A, B, E, F, I, J). No lesion was identified on 3T MRI and subtle grey-white matter junction blurring was seen on 7T T_2 weighted MRI (A, B). On T_2* (E, F), the neighbouring sulcus appears to contain prominent vasculature. T_2* minimum intensity projection (I, J) aids in the visual detection. Patient II; FCD ILAE type Ib (C, D, G, H, K, L). T_2 -weighted MRI (C, D) shows grey-white matter junction blurring and cortical thickening indicative of FCD. In the same area, T_2* (G, H) shows a wide sulcus with prominent vascular structures. T_2* minimum intensity projection (K, L) strongly emphasizes the increased vasculature.

were clearly visible but the phenomenon described above was not identified (*figure 3* for 7T T_2* images of a healthy subject).

Discussion

We describe the observation of 7T T_2* hypointensities overlying pathologically-confirmed (*n*=4) epileptogenic malformations of cortical development. We propose that these signal abnormalities reveal a pathological change in the leptomeningeal venous vasculature. The location in sulci and on the cortical surface, the configuration, and a T_2* signal compatible with venous blood all support this hypothesis. The origin of the observed T_2* hypointensities could be either, or a combination, of the following:

– (1) Increased blood volume may be the result of increased vascular diameter or density in the context of a developmental anomaly of the leptomeningeal vasculature, parallel to the developmental malformation of the underlying cortex. The leptomeningeal vascular network is formed from a gestational age of eight weeks, starting as the pial capillary anastomotic plexus which produces penetrating vessels into the cortex (Marín-Padilla, 2012). It is conceivable that, in addition to immaturity and abnormal migration of neurons, the vascular network may show analogous abnormalities in dysplastic cortex, resulting in abnormal configuration of superficial cortical vasculature.

– (2) Paroxysmal increased metabolic demand associated with epileptic activity (la Fougère *et al.*, 2009) may lead to reactive vascular changes in the form of

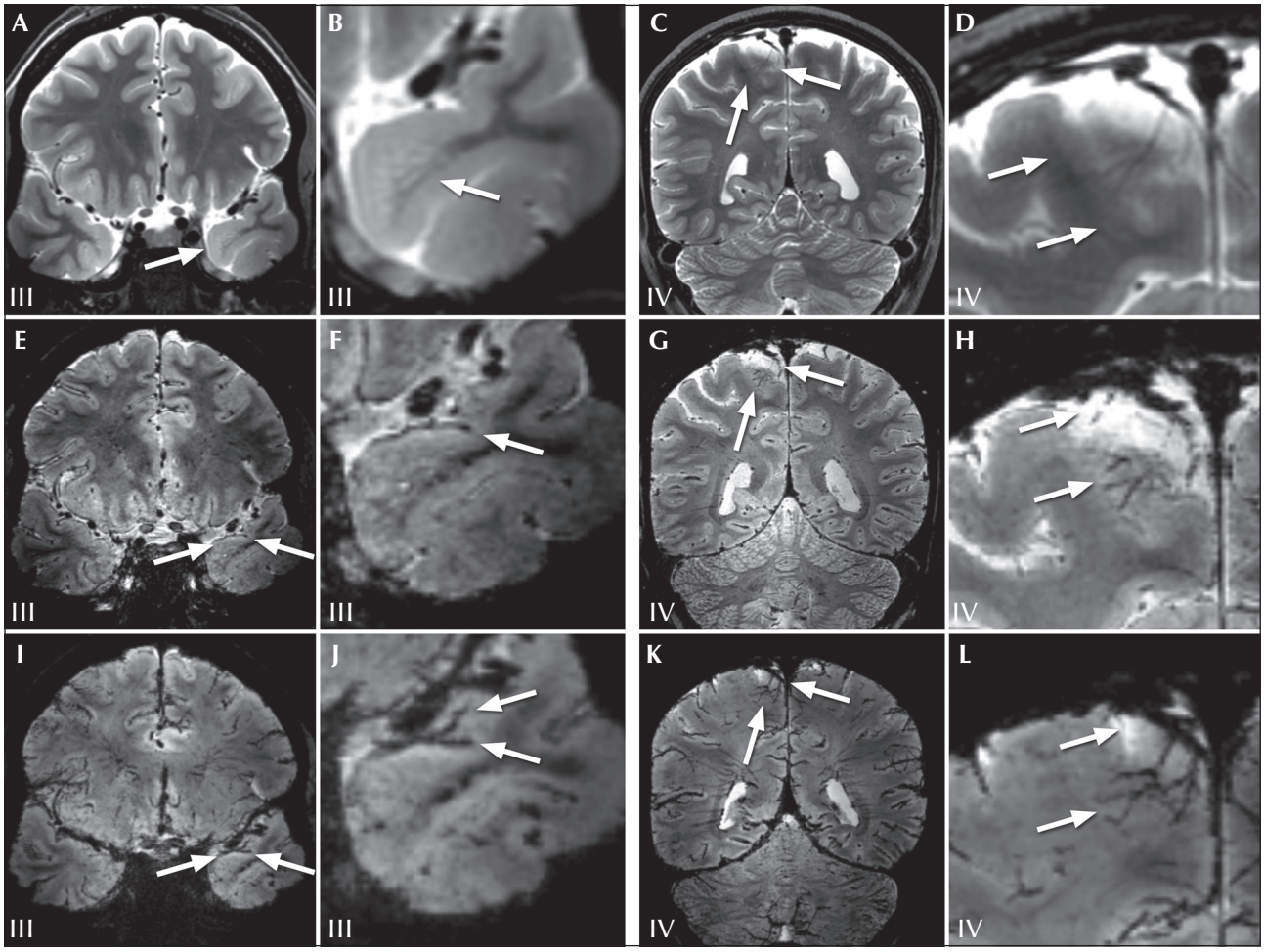

Figure 1B. (B) MRI findings of patients with confirmed FCD and T_2* signal changes. 7T T_2 (A-D), T_2* (E-H), and T_2* minimum intensity projection (I-L) coronal reconstructions. Lesions are depicted in detail in (B), (D), (F), (H), (J) and (L). Patient III; mild malformation of cortical development type 2 (A, B, E, F, I, J). On T_2 (A, B), blurring and subcortical hyperintensity represent developmental malformation. T_2* (E, F) shows a wide Sylvian fissure but no clearly appreciable vascular changes. On T_2* minimum intensity projection (I, J), there appears to be an increase in vascular signal in the superior temporal pole. Patient IV (C, D, G, H, K, L); FCD ILAE type IIb. On T_2 (C, D), there is a notable large central parasagittal extracerebral space containing a large vein, but without evident dysplastic characteristics, however, on T_2* (G, H), the large vein and smaller vasculature that drains from the dysplastic cortex (as confirmed by histological examination) is observed. (K, L) Image enhancement on T_2* minimum intensity projection.

hypervascularisation. An increase in venous vascular diameter or density results in a greater deoxygenated blood volume per voxel and concomitant T_2* changes.

– (3) A focal increase in deoxyhaemoglobin may be explained by altered hemodynamics. Other studies have shown that interictal hypometabolism was associated with decreased perfusion on arterial spin labelling MRI (Pendse *et al.*, 2010), while cortical activation is generally linked to positive blood oxygen-dependent signal changes caused by an increase in oxygenated blood (Logothetis *et al.*, 2001). Decreased perfusion in epileptogenic lesions may lead to an interictal increase in venous deoxyhaemoglobin, visible as T_2* hypointensity.

The clinical relevance of the described phenomenon is that it might be indicative of underlying epileptogenic cortex and even be distinctive in cases where conventional MRI sequences reveal no abnormalities.

Two additional patients with refractory epilepsy evaluated in our centre had clinical and electrophysiological characteristics indicative of a structural seizure focus, but no supportive findings on 3 and 7T MRI. Retrospective review of 7T MRI T_2* images showed hypointensities that might have provided clues for

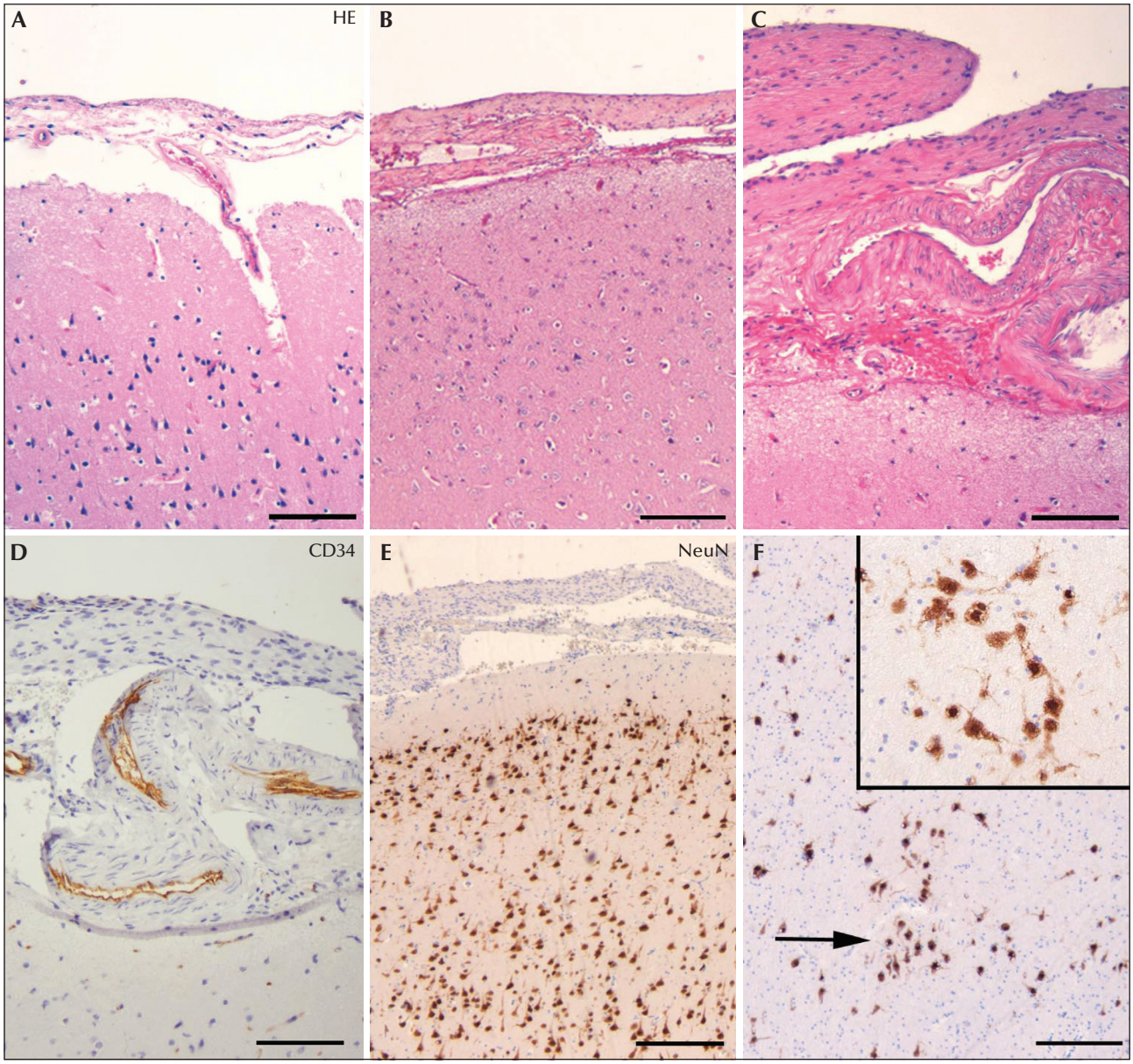

Figure 2. Histology. (A) Normal neocortex (HE: haematoxylin and eosin). (B-C) HE and (D) CD34 of neocortex from Patient III with thick (focally fibrotic) leptomeninges and prominent vascular structures. (E-F) NeuN of neocortex from Patient III without cortical dyslamination, but with microscopic neuronal clusters (arrow; insert in F) and excess of neurons of normal morphology in the deep white matter (isolated mild malformations of cortical development; mMCD type 2). Scale bar in A, B, E, F: 320 μm; C, D: 160 μm.

localizing the seizure focus (data not shown). Lack of concordance between other ancillary diagnostic results prevented surgical treatment.

Comparison of *T2**-weighted sequences acquired at 7T and at lower field strength was not possible since this sequence is not routinely performed with 1.5 or 3T MRI for epilepsy patients in our centre. Fine vascular structures should be more detectable on 7T systems because of the higher spatial resolution and the positive relationship between field strength and T_2* effects (Haacke *et al.*, 2009). Because of the type of pathology and the as yet experimental nature of 7T MRI, it is difficult to obtain *T2** images in large groups of patients in order to assess the presence of the described phenomenon.

An important limitation is that we report a qualitative analysis of the T_2* signal change. Furthermore, histopathological validation of changes in

Table 1. Characteristics of patients with confirmed or suspected FCD and abnormal findings on T_2*.

Patient no.	Sex/age	Semiology	Surface EEG ictal epileptiform discharges	Surface EEG interictal epileptiform discharges	Electrocorticography	3T MRI (T_1, T_2, Flair)	7T MRI conventional sequences (T_1, T_2, FLAIR, DIR/WMS)	T_2* 7T	SPECT/PET	Surgery	Histopathology (ILAE classification)	Outcome (Engel Score)
I	♀/45	CPS, hypermotor	R frontal parasagittal	R front parasagittal	Continuous spiking; R frontal parasagittal.	No abnormalities	Subtle blurring, hyperintensity on DIR R front parasagittal	Hypointensities; R front parasagittal	No abnormalities (PET)	R Partial lobectomy frontal parasagittal	FCD IIb	1A + 1yr
II	♀/22	SPS, sensory L mouth/jaw	no epileptiform discharges	no epileptiform discharges	Bursts and continuous spiking; R inferior frontocentral.	R inferior frontocentral G/W blurring, cortical thickening		Hypointensities; R inferior frontocentral	n/a	R inferior frontocentral lesionectomy	FCD Ib	2B + 2yr
III	♀/25	SPS, olfactory, gustatory and experiential auras	L temporal	Bilateral fronto-temporal	Sporadic spiking; mesiotemporal and antero-temporal. Continuous spiking; baso-temporal.	L anterior temporal pole G/W blurring, subcortical hyperintensity on FLAIR, T_2, DIR		Hypointensities; superior anterior temporal pole	n/a	L anterior temporal lobectomy + amygdalohippocampectomy	mMCD type 2 (no hippocampal sclerosis)	1B + 3yr
IV	♀/12	SPS, Left leg sensorimotor	Centro-parietal midline	Centro-parietal midline	Continuous spiking; R medial pre- and post-central.	No abnormalities		Hypointensities in wide sulcus R central	No abnormalities (PET)	R pre-central lesionectomy	FCD IIb	1A - 1/2yr

Table 1. (*Continued*)

Patient no.	Sex/age	Semiology	Surface EEG ictal epileptiform discharges	Surface EEG interictal epileptiform discharges	Electrocorticography	3T MRI (T_1, T_2, Flair)	7T MRI conventional sequences (T_1, T_2, FLAIR, DIR/WMS)	T_2* 7T	SPECT/PET	Surgery	Histopathology (ILAE classification)	Outcome (Engel Score)
V	♂/15	CPS, left motor. secondary GS: left sided tonic-clonic seizures	R fronto-central	R posterior temporal	Continuous spiking; R baso-temporo-occipital.	No abnormalities		No abnormalities	R baso-temporo-occipital hypometabolism (PET)	R baso-temporo-occiptal lesionectomy	FCD IIa	1A - 1yr
VI	♂/7	CPS, R hand automatisms	R frontal	R frontal parasagittal	Continuous spiking; R frontal parasagittal.	No abnormalities	R frontal small area with subtle blurring of G/W boundary, subtle white matter hyperintensity (T_2)	No abnormalities	No abnormalities (PET)	R Front lesionectomy	FCD IIa	1A+ 1/4 yr

EEG: electroencephalogram; DIR: double inversion recovery; L: left; R: right. CPS: complex partial seizures; SPS: simple partial seizures; TCS: tonic-clonic seizures; GS: generalized seizures; G/W: grey-white matter junction; HS: hippocampal sclerosis; FCD: focal cortical dysplasia; mMCD: mild malformation of cortical development; N/a: not applicable; Engel scores 1A+: completely seizure-free since surgery, continued use of anti-epileptic drugs; 1A-: completely seizure-free since surgery, anti-epileptic drugs discontinued; 1B+: non-disabling simple partial seizures only, continued use of anti-epileptic drugs; 2B+: rare disabling seizures, continued use of anti-epileptic drugs.

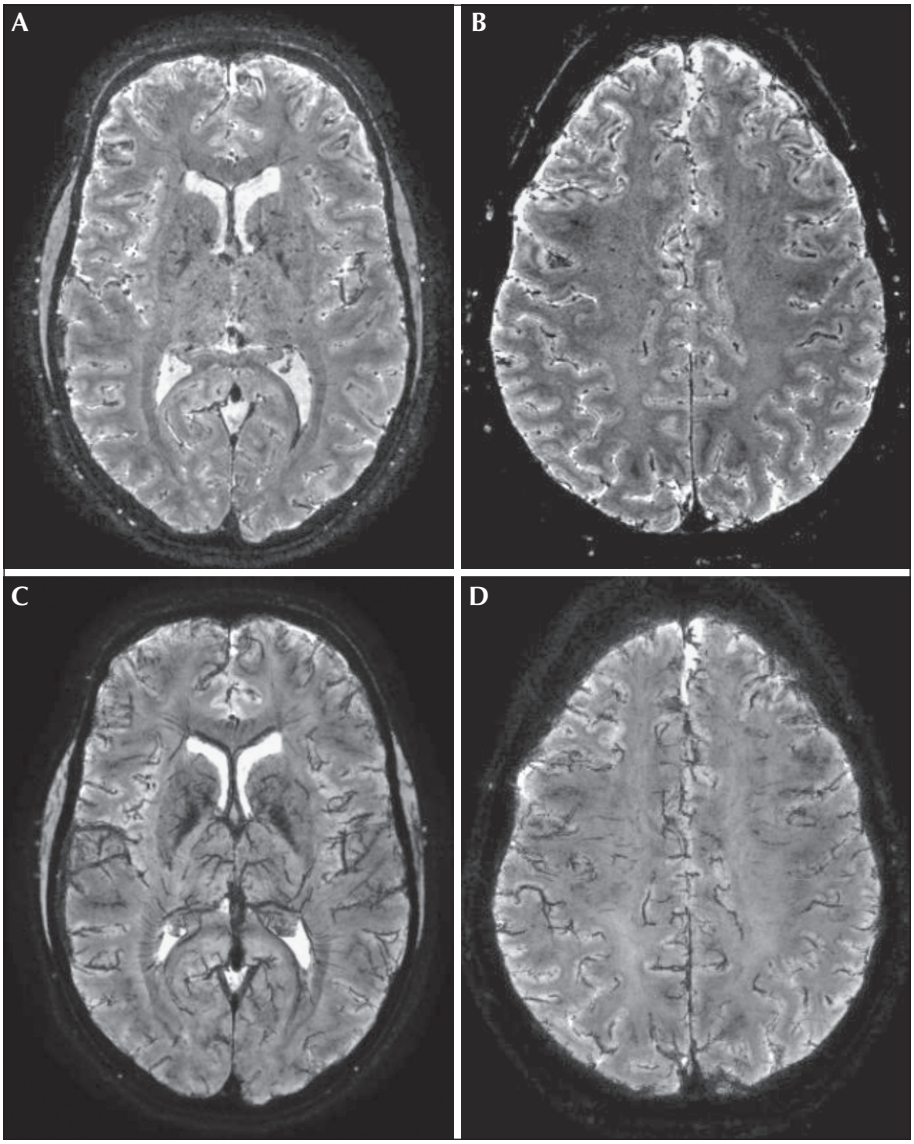

Figure 3. Transverse 7T T_2* images of a healthy subject. T_2*-weighted images showing transverse slices parallel to the anterior commissure-posterior commissure line at the level of the foramen of Monroe (A) and at the level of the cingulate sulcus (B). (A, B) Minimum intensity projections with 5-mm slab thickness at the level of (C) and (D), respectively. These images show the normal appearance of venous cerebral vasculature in a healthy subject.

leptomeningeal tissues is limited, because leptomeninges could only be assessed in one surgical specimen. While the impression of increased vasculature on T_2* images is congruent with the leptomeningeal histological findings (thick and fibrosed meninges containing large caliber vessels), this may be a non-specific finding in patients with epilepsy. To elucidate the histopathological substrate for this potential marker of subtle epileptogenic lesions and assess its clinical relevance, studies on larger groups of patients are needed, including histopathological analysis of leptomeningeal vascular structures.

Despite its limitations, this case series suggests that it may be worthwhile to further explore the possibilities of using T_2* sequences at 7T, and possibly also at lower field strength, to improve the detection of FCD in patients with refractory epilepsy.

Conclusion

We report a novel, 7T MR T_2* finding co-localizing with FCD. This hypointense signal may indicate an increase in vascular prominence in the leptomeningeal vascular

network overlying the dysplastic cortex. Adding T_2*-weighted sequences to the 7T MRI protocol may aid in the detection of FCDs and guide effective epilepsy surgery, while obviating the need for additional (invasive) diagnostic tests. □

Supplementary data.
Summary didactic slides are available on the www.epilepticdisorders.com website.

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References

Blümcke I, Thom M, Aronica E, *et al*. The clinicopathologic spectrum of focal cortical dysplasias: a consensus classification proposed by an ad hoc Task Force of the ILAE Diagnostic Methods Commission. *Epilepsia* 2011; 52: 158-74.

Haacke EM, Mittal S, Wu Z, Neelavalli J, Cheng Y-CN. Susceptibility-weighted imaging: technical aspects and clinical applications, part 1. *AJNR Am J Neuroradiol* 2009; 30: 19-30.

la Fougère C, Rominger A, Förster S, Geisler J, Bartenstein P. PET and SPECT in epilepsy: a critical review. *Epilepsy Behav* 2009; 15: 50-5.

Lerner JT, Salamon N, Hauptman JS, *et al*. Assessment and surgical outcomes for mild type I and severe type II cortical dysplasia: a critical review and the UCLA experience. *Epilepsia* 2009; 50: 1310-35.

Logothetis NK, Pauls J, Augath M, Trinath T, Oeltermann A. Neurophysiological investigation of the basis of the fMRI signal. *Nature* 2001; 412: 150-7.

Marín-Padilla M. The human brain intracerebral microvascular system: development and structure. *Front Neuroanat* 2012; 6: 38.

Mittal S, Wu Z, Neelavalli J, Haacke EM. Susceptibility-weighted imaging: technical aspects and clinical applications, part 2. *AJNR Am J Neuroradiol* 2009; 30: 232-52.

Pendse N, Wissmeyer M, Altrichter S, *et al*. Interictal arterial spin-labeling MRI perfusion in intractable epilepsy. *J Neuroradiol* 2010; 37: 60-3.

Saini J, Kesavadas C, Thomas B, *et al*. Susceptibility weighted imaging in the diagnostic evaluation of patients with intractable epilepsy. *Epilepsia* 2009; 50: 1462-73.

Téllez-Zenteno JF, Hernández Ronquillo L, Moien-Afshari F, Wiebe S. Surgical outcomes in lesional and non-lesional epilepsy: a systematic review and meta-analysis. *Epilepsy Res* 2010; 89: 310-8.

Zwanenburg JJM, Versluis MJ, Luijten PR, Petridou N. Fast high resolution whole brain T2* weighted imaging using echo planar imaging at 7 T. *Neuroimage* 2011; 56: 1902-7.

TEST YOURSELF

(1) How effective is MRI in the detection of focal cortical dysplasia?

(2) On T_2* weighted MRI sequences, which intracranial structures are visualized as hypointense?

(3) What can be identified using T_2* weighted sequences that might aid in the detection of cortical dysplasias?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".