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SHORT COMMUNICATION

Tracing of Neuronal Connections in the Human Brain by Magnetic Resonance Imaging *in vivo*

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Abstract

Axon degeneration after disruption of fibre tracts in the mammalian nervous system is accompanied by myelin breakdown which leads to changes in its magnetic resonance properties. In two patients with pure motor strokes due to small ischaemic lesions restricted to the internal capsule, magnetic resonance imaging disclosed a narrow band of pathological signal increase descending band-like into the brain stem and ascending to the precentral gyrus, which corresponded to the well-known path of the pyramidal tract. The findings suggest that in man anterograde and possibly retrograde fibre degeneration can be traced *in vivo* by conventional magnetic resonance imaging techniques. Critical conditions are the presence of small, strategically located lesions, appropriate choice of imaging plane, and the interval between time of lesion and of imaging. This demonstration may open a new era for functional neuroanatomy of man.

The introduction of neuroanatomical techniques to trace fibre connections has revolutionized our knowledge of the brain. However, the information obtained is derived mainly from non-human species. In particular the use of the more novel techniques such as that of retrograde labelling by horseradish peroxidase or anterograde labelling by means of radioactive amino acids, has been entirely restricted to experimental animals (Heimer and RoBards, 1981). The human brain is a good deal more complex and many of the clinical syndromes in man have no counterpart in animals. The complexity of the syndromes which result from particular lesions in the human brain suggest that many regions of the brain are affected secondarily. Unfortunately, however, there are only very few techniques to trace the connections from the obviously lesioned parts of the human brain to other areas (Dejerine, 1895/1901; Mesulam, 1979; Miklossy and Van der Loos, 1987). Such information is not only of great anatomical interest but also essential for sound clinico-pathological correlations.

In the rat sciatic nerve, after transsection and subsequent myelin breakdown, magnetic resonance (MR) spectroscopy has been shown to detect increases in water content by changes in the longitudinal and transverse relaxation times (T1 and T2); that is, tissue-specific MR parameters corresponding to tissue water content (Jolesz et al., 1984). It is to be expected that such changes can be visualized by MR imaging. Therefore, we have attempted to study fibre degeneration in the living human brain, choosing a well-identified, substantial neural pathway such as the pyramidal tract. From a population of stroke patients we selected two cases presenting with motor strokes following infarction in the territory of the anterior choroidal artery (Decroix et al., 1986). Cranial computed tomography (CCT) had revealed small lesions confined to the posterior limb of the internal capsule and the overlying coronal radiation, respectively, measuring about 5×16 mm and 11×10 mm in the horizontal plane (Figs 1a and 2a). The lesions were located at positions intersecting the course of the pyramidal tract, as confirmed by projection of CCT scans onto corresponding sections of the stereotaxic atlas of Talairach and Tournoux (1988).

MR imaging in both patients showed pathological signals in addition to the defect seen in CCT (Figs 1a and 2a), extending from it caudally in a band-like fashion down to the level of the foramen magnum (Fig. 1b). A band-like signal increase extending *towards* the cortex (precentral gyrus) was seen in the second patient 7 months after the stroke (Fig. 2b and c). In the first patient, this band could be followed not more than 2 cm towards the cortex, even at unusual inclinations of the imaging plane (Fig. 1b).

There can be little doubt that these bands represent the degenerating pyramidal tract. Their topography corresponds to that fibre system (Nieuwenhuys et al., 1988) since the signals can be followed coursing from precentral gyrus (Fig. 2b and c) through the posterior limb of

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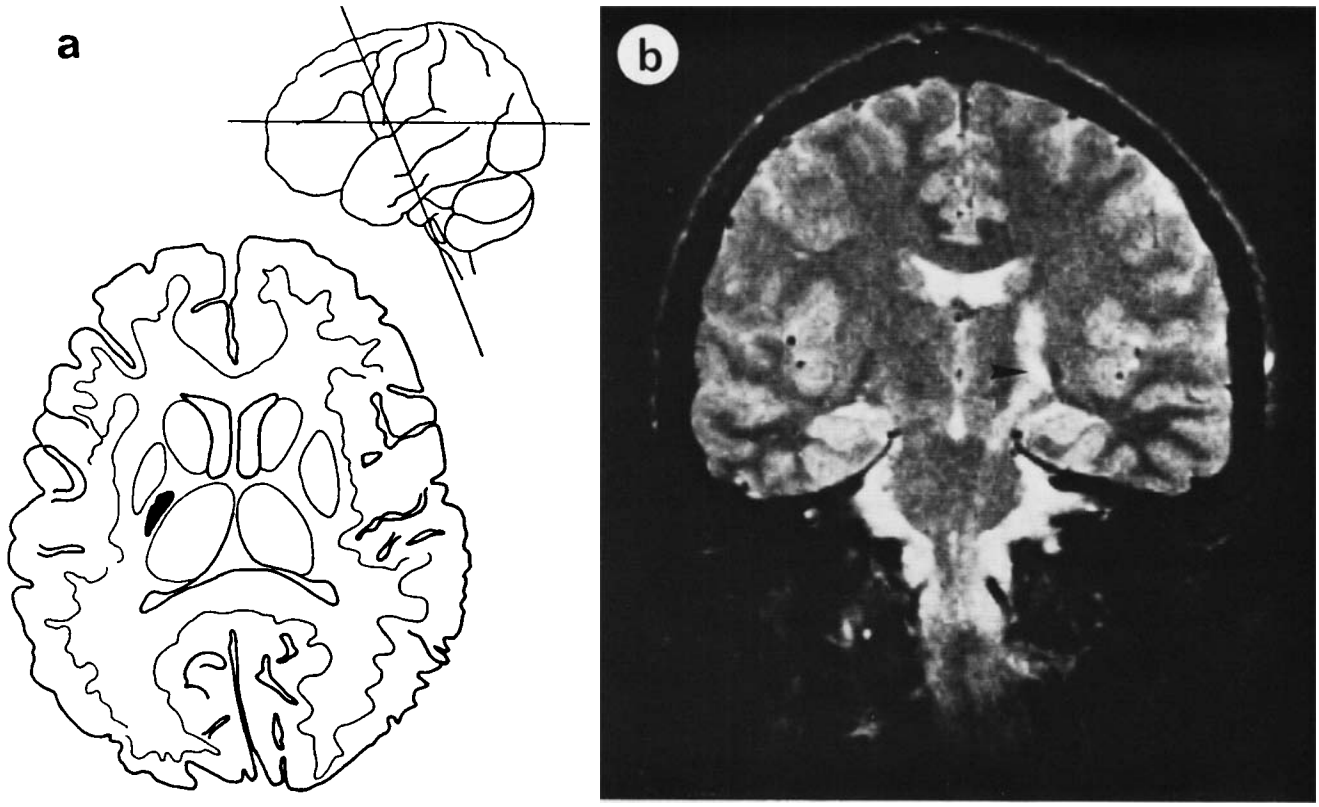

FIG. 1. (a) Diagnostic imaging in a 19-year-old male who had suddenly become hemiplegic but recovered almost completely. The ischemic infarct was thought to be due to an embolus from the heart. The drawing from horizontal sections of cranial computed tomography (CCT) 7 months after the stroke shows the small lesion (solid black) confined to the posterior limb of the left internal capsule. Note that in the occipital region an asymmetry is present; this is not caused by skewed positioning of the patient, but represents an obviously congenital anatomical variant. In the insert the horizontal plane of section in CCT and the oblique frontal plane of the magnetic resonance (MR) image, pictured in b, are marked.

(b) MR image 4 months after onset (T2 weighted with repetition time (TR) of 3000 ms and echo time (TE) of 90 ms, slice thickness 4 mm) shows the original stroke as abnormal, bright signal (arrow). Imaging was performed at 1.0 Tesla with conventional spin echo pulse sequences (Magnetom®, Siemens). A band of signal increase extends about 2 cm toward the cortex from the lesion site. More extensively, the hyperintense band courses down to the brain stem pyramids and across the pyramidal decussation. These pathological signals are considered to represent retrograde and anterograde degeneration in the pyramidal tract.

the internal capsule, the midbrain peduncle, and the pons and medulla to the pyramidal decussation (Fig. 1b). Also, their identification as degenerating fibre tracts, interrupted in the posterior limb of the internal capsule, is supported by the MR properties of increased T1- and T2-values due to increased water, that is, proton content, corresponding to experimental MR spectroscopy findings (Jolesz et al., 1984). Further, the band of pathological signal in patient 1 had not been present in an early MR examination (17 days after onset), while it was identical on two subsequent examinations at 4 and 7 months after the stroke. When examined again 16 months later, they were no longer obvious. At that time the slight abnormalities at the site of the tract could not be recognized as of pathological importance without prior knowledge. This time course of appearance of the pathological MR signals is paralleled in histopathological studies by the appearance of myelin breakdown products during fibre degeneration within a limited time span between 4 months and 20 months after lesion (Miklossy and Van der Loos, 1987).

Previous attempts to show pyramidal tract degeneration in MR imaging were compromised by three factors. First, non-selective large hemispheric lesions encompassed additional fibre systems other than the pyramidal tract (DeWitt et al., 1987; Cobb and Mehringer, 1987). Second, signal changes along the tract were described in T1-weighted images as *hypo*intensities (Kuhn et al., 1988). True degeneration in MR imaging should always show up as *hyper*intensity due to the experimentally shown prolongation of T2- as well as of T1-relaxation time (Jolesz et al., 1984). The latter is reflected in the proton density weighted image (see Fig. 2c). Most likely, the *hypo*intense signals represent tissue loss, that is, the cysts or atrophies seen after completed degeneration (Kuhn et al., 1988). Third, the MR imaging was performed up to 29 years after the stroke (Kuhn et al., 1988). Our results, in accordance with histopathology (Miklossy and Van der Loos, 1987), indicate that the myelin breakdown process appearing as increased signal intensity is confined to a narrow window of time of about 4–20 months after the lesion.

As in both patients the motor deficit was clinically predominant, the main damage seems to have affected pyramidal tract fibres. One might speculate that the signals extending from the lesion sites towards the cortex may represent *retrograde* degeneration of fibres originating in the anterior bank of the central sulcus, that is, the pyramidal tract (see Murray and Coulter, 1981). Since the motor cortex is intensely connected also with the thalamus (Jones, 1985) this question cannot be settled on the basis of the present evidence. It seems, however,

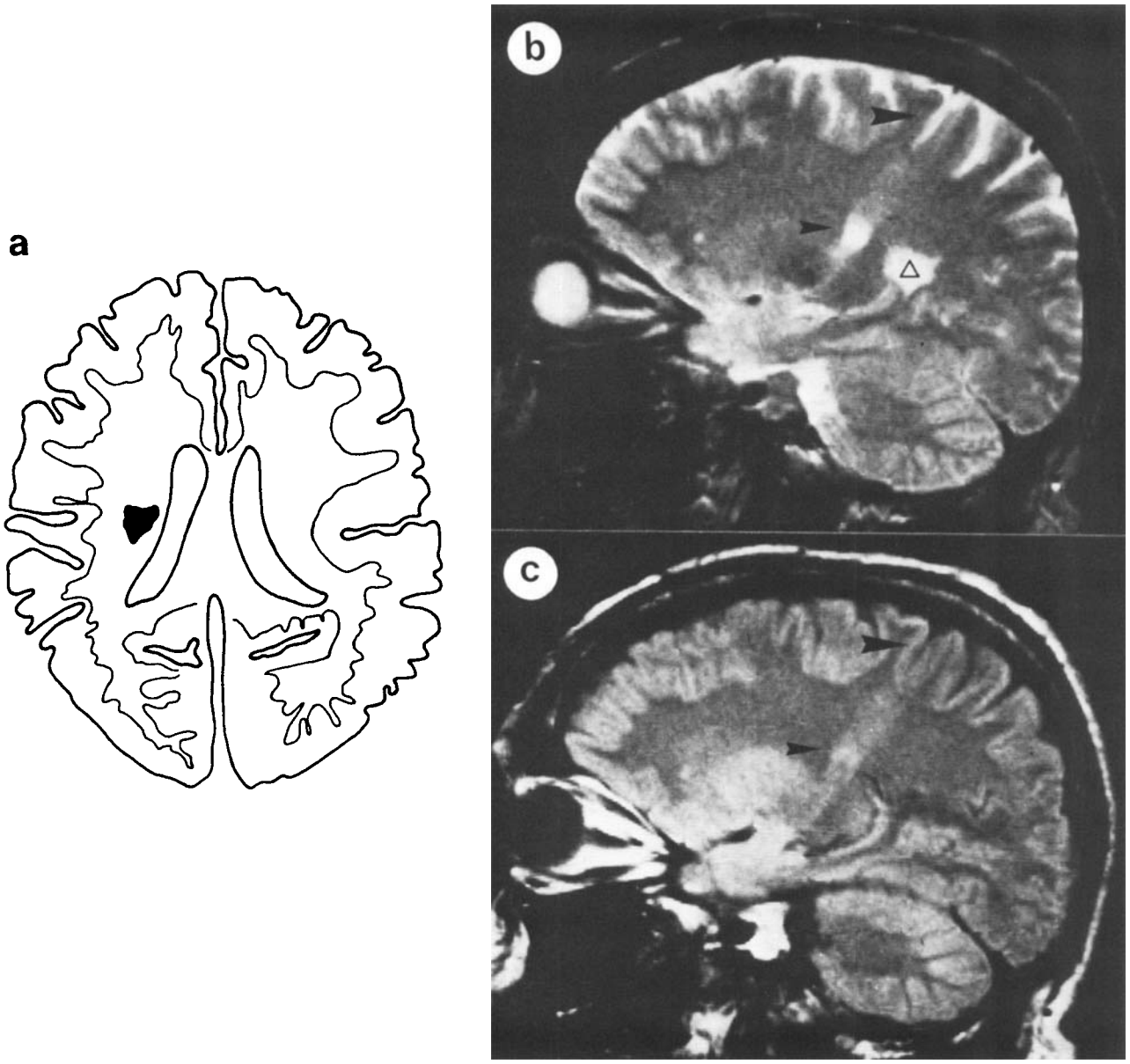

FIG. 2. (a) Lesion site (solid black) in the dorsal part of the posterior limb of the internal capsule according to cranial computed tomography (horizontal scan) of a 51-year-old male who 4 months before the CCT had suddenly developed a right-sided ataxic hemiparesis.

(b and c) Magnetic resonance images 7 months after the stroke show the original infarct (small arrow) and a band of signal descending from it but also ascending towards the central sulcus (large arrow). The latter may correspond to retrograde degeneration of the pyramidal tract. The bright region on image 2b (T2 weighted with repetition time (TR) of 3000 ms and echo time (TE) of 90 ms, slice thickness 6 mm) is part of the lateral ventricle (triangle). Image 2c is the corresponding proton density image (TR=3000 ms, TE=25 ms). The imaging plane was 24 mm left of the midsagittal plane, other imaging conditions were as in patient 1. Structures were identified according to Talairach and Tournoux (1988) and Nieuwenhuys et al. (1988).

reasonable to assume that MR imaging should pick up signs of myelin breakdown irrespective of direction of degeneration, anterograde as well as retrograde.

In conclusion, we suggest that the study of the sequelae of such small strategically situated lesions is a unique tool for human neuroanatomy. Further studies on fibre tracts less extensive than the pyramidal tract may have to use more sensitive methods to detect the signal changes. In our own experience, they may go unnoticed unless an imaging plane is chosen with optimal comparison between normal and abnormal tissue over an extended course. This approach of an 'experimental' neuroanatomy may yield new insights into neural connectivity in the human brain which have not much advanced since the last century (Dejerine, 1895/1901; Nieuwenhuys et al., 1988). More importantly, through these *in vivo* anatomical studies, clinical correlations may be

possible for syndromes that are regarded as unique to man. To give just a few examples, studies of aphasia, apraxia, and achromatopsia rarely, if at all, can be based on results from animal experimentation.

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Abbreviations

CCT cranial computed tomography
MR magnetic resonance
T1 longitudinal relaxation time
T2 transverse relaxation time
TE echo time
TR repetition time

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