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Three-dimensional anisotropy contrast magnetic resonance axonography to predict the prognosis for motor function in patients suffering from stroke

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Object. The purpose of this study was to assess how early wallerian degeneration in the corticospinal tracts of patients who had suffered from stroke was detected using three-dimensional anisotropy contrast (3D-AC) magnetic resonance (MR) axonography and to explore the possibility of predicting the prognosis for motor function in these patients.

Methods. Ten healthy volunteers and 16 stroke patients with hemiparesis were studied using MR images including 3D-AC MR axonography images obtained using a 1.5-tesla MR imaging system. The axonography was performed using an echoplanar imaging method. All patients underwent MR studies 2, 3, and 10 weeks after stroke onset. To detect wallerian degeneration, the diffusion anisotropy in the corticospinal tracts at the level of the upper pons was evaluated on axial images. These MR findings were compared with the patients' motor functions, which were classified according to the Brunnstrom criteria 12 weeks after the onset of stroke.

In all patients with poor recovery (Brunnstrom Stages I–IV), wallerian degeneration, which was demonstrated as a reduction in diffusion anisotropy on axonography images, could be observed in the corticospinal tracts; this degeneration was not found in patients with good recovery (Stages V and VI). Axonography could be used to detect degeneration between 2 and 3 weeks after stroke onset. On conventional T_2-weighted MR images, hyperintense areas indicating wallerian degeneration were not detected until 10 weeks after stroke onset.

Conclusions. With the aid of 3D-AC MR axonography, wallerian degeneration can be detected in the corticospinal tracts during the early stage of stroke (2–3 weeks after onset), much earlier than it can be detected using T_2-weighted MR imaging. The procedure of 3D-AC MR axonography may be useful in predicting motor function prognosis in stroke patients.

Key Words • stroke • hemiparesis • wallerian degeneration • three-dimensional anisotropy contrast magnetic resonance axonography • diffusion-weighted imaging

In the majority of patients suffering from stroke in whom there is wallerian degeneration in corticospinal tracts, there is a poor prognosis for motor function.[17–19] Therefore, to predict prognosis for motor function in stroke patients it seems useful to determine whether there is wallerian degeneration in the corticospinal tracts during the early stage of stroke. To assess this degeneration during that time period, it may be best to estimate changes in diffusion anisotropy in the corticospinal tracts quantitatively.

Although several methods are available to quantitate diffusion anisotropy,[10,11,16] it is important to maintain an anatomical resolution that preserves the quality of the final image in clinical situations. Diffusion-weighted imaging performed using an isotropic motion-probing gradient (isotropic diffusion-weighted imaging) is useless to evaluate diffusion anisotropy, whereas using a one-directional motion-probing gradient (anisotropic diffusion-weighted imaging) provides no information on diffusion in other directions. Trace imaging does not allow us to determine the direction of diffusion anisotropy. Although a full tensor analysis is theoretically a good method to quantitate diffusion anisotropy, it requires a complex mathematical algorithm that invariably results in degradation of image quality and is extremely difficult to perform practically, especially in patients experiencing the acute stage of stroke. The 3D-AC MR axonography method can provide directional information on anisotropic apparent diffusion as a true color contrast and with exquisitely high anatomical resolution.[14] Hence, in clinical situations, we believe

Abbreviations used in this paper: MR = magnetic resonance; 3D-AC = three-dimensional anisotropy contrast.

TABLE 1

*Summary of clinical data obtained in 16 stroke patients with hemiparesis**

Case No.	Age (yrs), Sex	Stroke Type	Brunnstrom Stage	
			At Admission	12 Wks After Admission
good recovery group				
1	76, F	infarction	I	V
2	73, M	infarction	II	VI
3	69, M	ICH	III	V
4	57, F	ICH	III	VI
5	66, F	ICH	II	VI
6	76, F	ICH	III	VI
7	72, M	ICH	II	V
8	62, F	ICH	II	V
poor recovery group				
9	50, M	infarction	I	II
10	70, M	infarction	III	II
11	88, M	infarction	I	I
12	87, F	infarction	II	II
13	88, F	ICH	II	II
14	68, M	ICH	I	I
15	34, F	ICH	II	III
16	52, M	ICH	I	II

* There were no significant differences in age, sex, type of stroke, and Brunnstrom stage at admission between patient groups with good and poor recovery (Fisher exact probability method and Mann–Whitney U-test). Abbreviation: ICH = intracerebral hemorrhage.

that 3D-AC MR axonography is the best method to detect wallerian degeneration.[3,7,12–14] To apply 3D-AC MR axonography to routine clinical examinations, however, one must use ultrafast imaging methods such as echoplanar imaging, instead of conventional spin-echo sequences, to minimize the pixel misalignment that results from patient movement and to reduce imaging time.

This study was conducted to assess how early wallerian degeneration in stroke patients can be detected by 3D-AC MR axonography performed using echoplanar imaging and to explore whether the prognosis for motor function can be predicted during the early stage of stroke.

Clinical Material and Methods

Healthy Volunteers and Patients

This study was performed according to the human research guidelines of the Internal Review Board of Suibarago General Hospital. Ten healthy volunteers and 16 stroke patients with supratentorial lesions (cerebral infarction in six patients and intracerebral hemorrhage in 10 patients) were recruited for our study. A clinical summary of the 16 patients with hemiparesis is shown in Table 1. The mean age of the patients was 68 years (range 34–88 years). All patients suffered from severe hemiparesis at the time of admission.

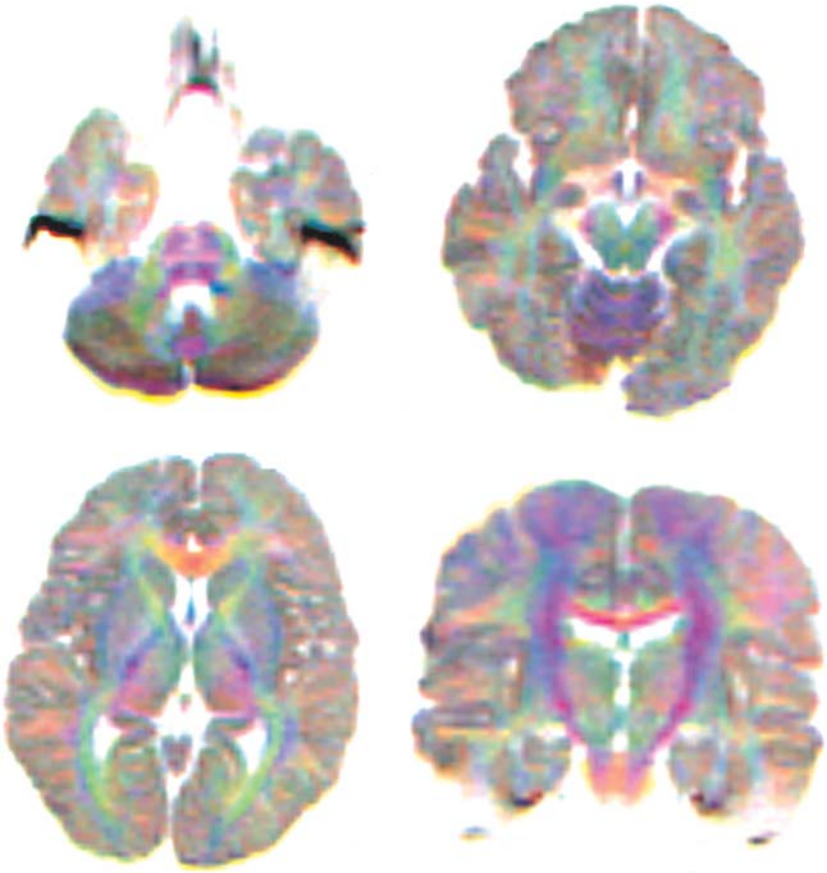

FIG. 1. Representative 3D-AC MR axonography images obtained in healthy volunteers. The hues of each direction are as follows: right to left, red; anterior to posterior (up–down), green; orthogonal to the axial imaging plane, blue. Note that the corpus callosum, optic radiation, and corticospinal tract display red, green, and blue, respectively.

Data Collection

A 1.5-tesla whole-body MR system (Signa Horizon; General Electric Medical Systems, Milwaukee, WI) was used to perform all studies. A single-shot echoplanar technique was used to obtain anisotropic diffusion-weighted images for 3D-AC MR axonography. All patients underwent conventional MR imaging and 3D-AC MR axonography 2, 3, and 10 weeks after stroke onset. The parameters for the diffusion-weighted images were as follows: TR 10,000 msec; TE 96.8 msec; two acquisitions; matrix size 128 × 128, field of view 300 × 190 mm; slice thickness 5 mm; and no gap between slices. Three anisotropic diffusion-weighted images of identical volume, representing each of the orthogonal axes, were obtained using a b value of 750 sec/mm^2. The total imaging time for each study was approximately 80 seconds.

Motor Function

Outcomes of motor function were assessed by clinical follow-up examination 12 weeks after onset of stroke. All patients were classified into one of five mutually exclusive categories according to Brunnstrom criteria[2] at admission and at 12 weeks after stroke onset. At the 12th week, patients classified as being in Brunnstrom Stage V or VI and those in Stages I to IV were assigned to a good recovery and poor recovery group, respectively.

Processing of the 3D-AC Image

The 3D-AC MR axonography images were obtained using a method reported previously.[12–14] These images provide sensitive MR imaging contrast for axonal information by displaying qualitative information (directional) through spectral frequency (color) and quantitative information (relative density) through the intensity of each color that appears simultaneously within the same pixel. The colors assigned to each direction were as follows: right to left, red; anterior to posterior (up–down), green; and orthogonal to the axial imaging plane, blue. Computer software (GE Yokogawa Medical Systems, Hino, Tokyo, Japan) was used to produce the 3D-AC MR axonography images, and image analyses were conducted using a personal computer.

Diffusion Anisotropy in the Corticospinal Tracts

Normal corticospinal tracts displayed a rich blue color in the upper pons on 3D-AC MR axonography images due to fibers in that area that course orthogonal to the axial imaging plane (Fig. 1). Diffusion anisotropy in the corticospinal tract was evaluated at the level of the upper pons with the aid of axial images obtained using 3D-AC MR axonography to minimize the direct influence of lesions, such as diamagnetic susceptibility of intracerebral hematomas. The diffusion anisotropy in the corticospinal tracts was evaluated using axial images and by referring to the mean trichromatic coefficients of five areas consisting of 4 × 4 pixels involving corticospinal tracts on each side of the upper pons (Fig. 2). To evaluate deterioration in axonal function following stroke, we used ratios (percentages) composed of each factor of the trichromatic coefficients of the ipsilateral corticospinal tract and the corresponding contralateral tract. Patients in whom the trichromatic coefficient ratios were less than 90% were defined as having wallerian degeneration.

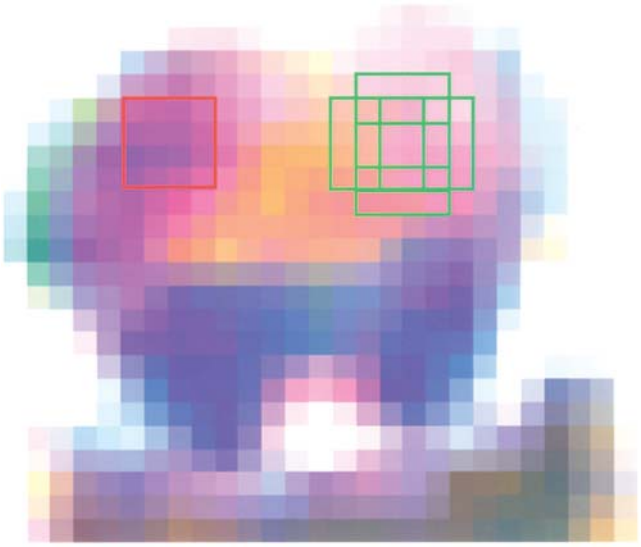

FIG. 2. Enlarged axial 3D-AC MR axonography image of the upper pons. The laterality of diffusion anisotropy in the corticospinal and corticopontine tracts was statistically evaluated by using axial images and referring to the mean trichromatic coefficients of five areas *(green squares)* consisting of 4 × 4 pixels including these tracts *(red square)* on each side of the upper pons.

Statistical Analysis

A Mann–Whitney U-test was used to determine statistical differences in age, the ratios of coefficients, and the distribution of Brunnstrom stages between patient groups with good recovery and poor recovery. The Fisher exact probability test was used to examine differences in the distribution of sex and type of stroke between the two groups. A paired t-test was used to assess changes in the ratios of coefficients from 2 to 3 weeks after stroke onset. Values are expressed as the means ± standard deviations. In the analyses, probability values less than 0.01 were considered statistically significant.

Results

Findings of 3D-AC MR Axonography in Healthy Volunteers

Representative 3D-AC MR axonography images of healthy human brains are shown in Fig. 1. In 10 healthy volunteers, differences in all trichromatic coefficients (red, green, and blue) between the right and left corticospinal tracts at the upper pons level were less than 10%.

Findings of 3D-AC MR Axonography in Stroke Patients

Representative 3D-AC MR axonography images of wallerian degeneration are shown in Fig. 3 *upper*. A reduction in the blue factor of the trichromatic coefficients, which signals a reduction in diffusion anisotropy in the direction orthogonal to the axial imaging plane, was observed in the left corticospinal tract. In eight patients with good recovery, there was no significant difference in any

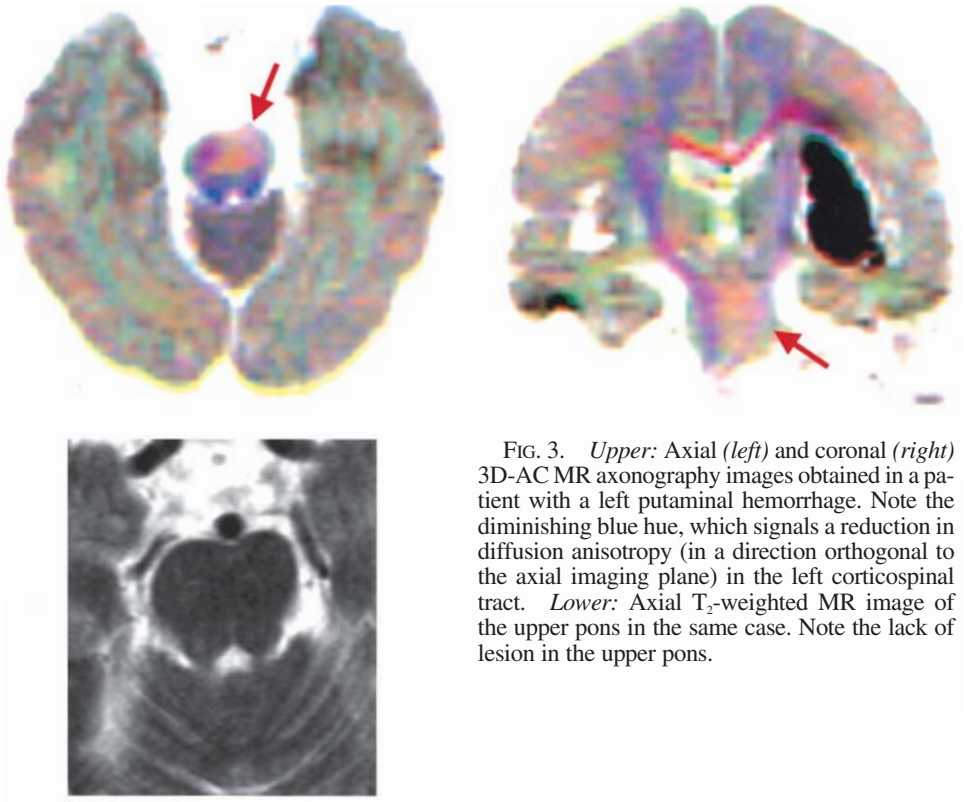

FIG. 3. *Upper:* Axial *(left)* and coronal *(right)* 3D-AC MR axonography images obtained in a patient with a left putaminal hemorrhage. Note the diminishing blue hue, which signals a reduction in diffusion anisotropy (in a direction orthogonal to the axial imaging plane) in the left corticospinal tract. *Lower:* Axial T_2-weighted MR image of the upper pons in the same case. Note the lack of lesion in the upper pons.

factor of the trichromatic coefficients between the right and left corticospinal tracts (Fig. 4 *left*) until the 10th week after onset of stroke. No significant change was observed in the ratios of each factor of the trichromatic coefficients from 2 to 3 weeks after onset. On the other hand, in all eight patients who experienced a poor recovery, wallerian degeneration, that is, a decreased ($< 90\%$) blue factor ratio of trichromatic coefficients, was found 3 weeks after stroke onset; in one patient degeneration was detected as early as 2 weeks after stroke onset (Fig. 4 *right*). The blue factor ratios in this group also significantly decreased from 2 to 3 weeks after stroke occurred. Although 2 weeks after stroke onset there was no significant difference in blue factor ratios between the two patient groups, 3 weeks after onset the mean ratio in patients with poor recovery was significantly smaller than that found in patients with good recovery. On the other hand, no ratio for red and green factors of the trichromatic coefficients was less than 90% at any time point.

Findings of T_2-Weighted MR Imaging in Stroke Patients

On conventional T_2-weighted MR images, abnormal findings, that is, the appearance of hyperintense areas indicating wallerian degeneration, were not detected less than 10 weeks after stroke occurred (Fig. 3 *lower*).

Discussion

The method of 3D-AC MR axonography detected wallerian degeneration as a reduction in diffusion anisotropy in the corticospinal tracts between 2 and 3 weeks after onset of stroke; that is, the appearance of hemiparesis indicated that degeneration had occurred.

In patients with spinal cord injury, histological examinations have been used to detect wallerian degeneration in the dorsal column 8 days after injury and in the lateral column, including the corticospinal tract, 12 days after injury. Conventional MR imaging did not reveal these changes.[1] Even histopathological examination barely demonstrated wallerian degeneration in patients' brains after cerebral infarction within 4 days of onset of stroke, but it revealed degeneration as axonal breakdown 8 days after onset.[8,9] On the other hand, myelin structure has been observed to be preserved as late as 52 days after sectioning.[6] Hence, we believe that the reduction in anisotropy in the corticospinal tract revealed by 3D-AC MR axonography reflects a manifestation of axonal dysfunction rather than myelin degeneration.

The series of changes following wallerian degeneration, that is, depression of the lipid/protein ratio due to myelin lipid breakdown, gliosis, and changes in tissue water content, result in a hyperintense signal on T_2-weighted MR images.[5] The hyperintense appearance of these lesions, due to wallerian degeneration, can usually be detected on T_2-weighted MR images 2 months after stroke has occurred.[4,5,15] In this study, although wallerian degeneration could not be detected as high-intensity lesions of the ipsilateral corticospinal tract on T_2-weighted images obtained 10 weeks after onset of stroke, 3D-AC MR axonography revealed the occurrence of wallerian degeneration much earlier. Furthermore, all patients in whom wallerian de-

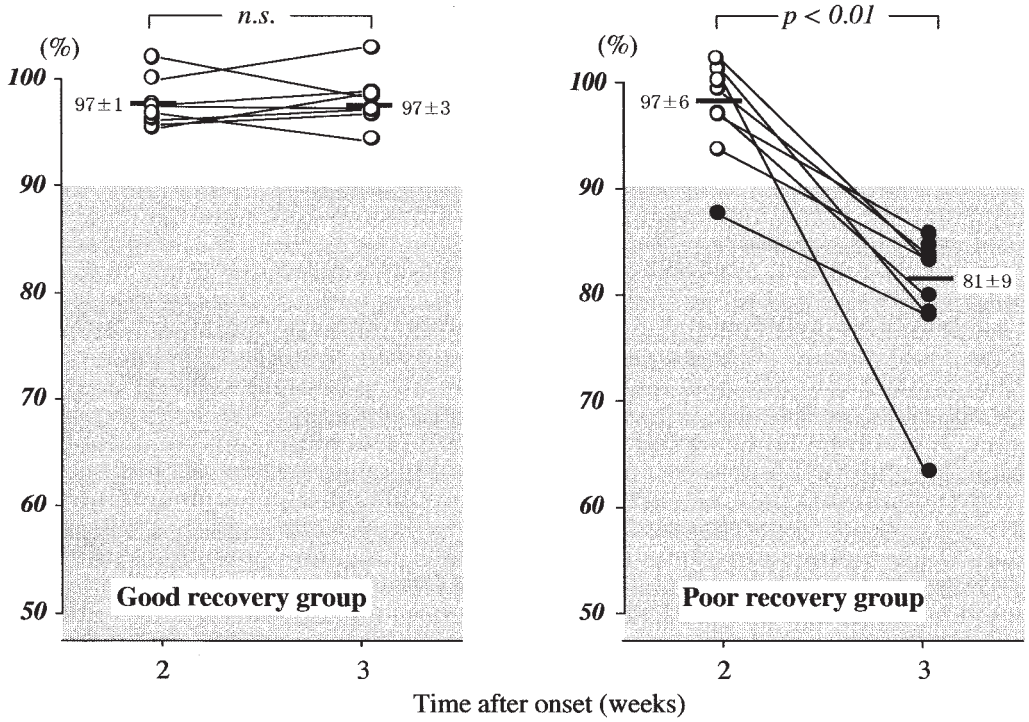

FIG. 4. Graphs indicating changes in the blue coefficient ratio in patients with good recovery *(left)* and those with poor recovery *(right)* from 2 to 3 weeks after onset. Although in patients with good recovery no significant difference was found in the ratio between 2 and 3 weeks after stroke onset, in patients with poor recovery the ratios 3 weeks after onset were significantly lower than those 2 weeks after onset. Wallerian degeneration *(closed circles)* was detected in all patients with poor recovery 3 weeks and in one patient 2 weeks after stroke occurred, whereas it was not found in any patient with good recovery. n.s. = not significant.

generation was detected in the corticospinal tracts by using 3D-AC MR axonography had a poor outcome of motor function; all patients in whom no degeneration was detected had a good recovery. Hence, 3D-AC MR axonography images may be a useful tool to predict motor function prognosis in patients during the early stage of stroke. Furthermore, it may have substantial applications in other neurosurgical fields, particularly spinal cord injury.[7,12,13]

Although it is obvious that, because of its high contrast resolution capability, 3D-AC MR axonography is a useful tool for diagnoses of central nervous system disease and for the development of treatment strategies in patients with these disorders,[14] there are several problems in applying this method to routine clinical study. With the use of echoplanar imaging instead of conventional spin-echo pulse sequences, however, almost all problems can be resolved; that is, motion artifacts can be minimized and imaging time can be reduced. Three-dimensional anisotropy contrast MR axonography is expected to become an invaluable tool in the neurological and neurosurgical fields, especially in spinal cord imaging.[7,12,13]

Conclusions

Three-dimensional anisotropy contrast MR axonography performed using echoplanar imaging demonstrated wallerian degeneration during the early stage of stroke, between 2 and 3 weeks after onset. In addition, 3D-AC MR axonography may be a useful tool for the prediction of prognosis for motor function in stroke patients.

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