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Diffusion Tensor Images in Children with Early-Treated, Chronic, Malignant Phenylketonuric: Correlation with Intelligence Assessment

Steven Shinn-Fong Peng, Wen-Yih Isaac Tseng, Yin-Hsiu Chien,
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BACKGROUND AND PURPOSE: Diffusion tensor (DT) images can provide information about the nature of white matter changes, including axonal loss and demyelination. We applied DT imaging to verify white matter changes in patients with malignant phenylketonuria (PKU) and to correlate the findings with clinical intelligence quotients (IQs).

METHODS: We compared DT images with T2-weighted images in 12 patients with early-treated, chronic, stable malignant PKU and 12 age-matched control subjects. DT parameters included first, second, and third eigenvalues (EV1–3), apparent diffusion coefficients (ADCs), and fractional anisotropy (FA). Regions of interest were placed the frontoparietal, parieto-occipital, frontal and central white matter and in the anterior and posterior corpus callosum. Eight patients older than 3 years underwent IQ assessment including verbal, performance, and full-scale IQ tests.

RESULTS: In the eight patients older than 3 years, no definite abnormal signal intensity changes were found on T2-weighted images. EV2, EV3, and FA of the parieto-occipital white matter were significantly different in patients and control subjects older than 3 years. EV3 and ADC of the parieto-occipital white matter were significantly and negatively correlated with verbal IQ ($r = -0.79$, $P = .04$) and performance IQ ($r = -0.93$, $P = .03$). FA of the parieto-occipital central white matter was positively correlated with verbal IQ ($r = 0.75$, $P = .05$).

CONCLUSION: Though treated early, patients with chronic, stable malignant PKU had abnormal DT findings in the parieto-occipital central white matter. EV2, EV3, and FA maps are potential tools for demonstrating brain changes due to malignant PKU.

Phenylketonuria (PKU) is the most frequent inborn error of amino acid metabolism. PKU originates from a multiplicity of mutations causing a broad spectrum of clinical and metabolic phenotypes. Among these, classic PKU results from deficiency of phenylalanine hydroxylase and is the most common (1–4). Unlike the classic type, malignant PKU is a rare disease caused by a deficiency in dihydropteridine reductase. The primary neuropathologic findings of PKU are diffuse abnormalities in the cerebral white matter (5,

6). The most obvious neuropathologic finding in PKU is pallor on myelin staining; this is often associated with gliosis in the brain (5–7). The myelin lamellae usually splay, and vacuoles form within the myelin sheath. Eventually, the myelin sheaths are permanently damaged and lost. Even with dietary control starting early in life, PKU patients of all ages have neuropsychological deficits, including deficient abstract reasoning, executive functioning, and information processing (8, 9). On MR examination, T2-weighted images reveal symmetrical hyperintense lesions in the periventricular white matter in classic PKU. These MR abnormalities are not correlated with the intelligence quotient (IQ) and less remarkable in malignant PKU patients whose blood levels of phenylalanine are usually not elevated (10–21).

Studies of diffusion-weighted MR imaging have shown changes in trace apparent diffusion coefficients (ADCs) and tortuosity, which is a parameter characterizing diffusion in tissues that increases when ADC decreases (10, 22) in PKU. In the white matter, microstructures of the tissue, such as myelin attenu-

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ation and fiber size, are believed to affect diffusional movement. Previous diffusion tensor (DT) MR imaging studies in infants (23, 24) revealed that relative anisotropy increases with brain maturation. DT images can provide information about the nature of white matter changes, including axonal loss and demyelination (25). The purpose of this study was to evaluate 1) brain changes in malignant PKU on DT images and 2) the relationship between different DT imaging parameters and the intellectual development of patients with PKU.

Methods

The ethics committee in our hospital approved this study. Informed consent was obtained from the families of all patients and control subjects. We included 12 patients (four boys, eight girls) aged 0.5–130 months (mean, 69 ± 51 months) with chronic, stable malignant PKU diagnosed by means of urine pterine analysis and tetrahydrobiopterine loading tests. All patients were identified during neonatal screening. Genotypic characterization at the 6-PTPS locus was performed. The patients were treated with a standard protocol including a low-phenylalanine diet, tetrahydrobiopterine, levodopa, and 5-hydroxytryptophan supplementation since the neonatal period. Blood levels of all patients with malignant PKU were within normal limits at the time of MR examination.

We assigned patients to two groups: one group of four patients who were younger than 3 years (13 ± 14 months) and one group of eight who were older than 3 years (106 ± 21 months). The latter group underwent intelligence assessment conducted by using the Chinese version of the Wechsler Intelligence Scale for Children–Revised (26).

The control group included 12 age-matched, unrelated subjects (four boys and eight girls) who were referred for MR examination because of headache (eight patients) or a neck mass (four patients). The ages of control subjects matched to PKU patients younger than 24 months did not differ by more than 1 month, and the control subjects matched to patients older than 24 months did not differ by more than 10 months. All control subjects were free of neurologic deficits and had normal brain MR images. We assigned the control subjects to two groups: one group of four who were younger than 3 years (15 ± 16 months) and one group of eight who were older than 3 years (102 ± 20 months). There was no significant difference in the ages of the study groups and the control groups, for both the older children ($P = .8746$, Mann-Whitney rank-sum test) and the younger children ($P = .5590$, Mann-Whitney rank-sum test).

All patients and control subjects underwent MR examinations by using a 1.5-T MR machine (Sonata; Siemens, Erlangen, Germany) with the same parameters. Axial fast spin-echo (FSE) T2-weighted images were obtained (TR/TE/NEX = 4330/100/1, echo train length = 11, matrix size = 256×256 , field of view = 14×14 to 20×20 , section thickness = 4–5 mm with gap of 1–1.5 mm). DT images were acquired with diffusion encoding gradients in six directions, ie, $\{1, \pm 1, 0\}$, $\{0, \pm 1, 1\}$, $\{\pm 1, 0, 1\}$, and diffusion sensitivity $b = 1500$ s/mm². Imaging parameters included the following: 240/124/5, matrix size = 128×128 , field of view = 14×14 to 20×20 , and section thickness = 4–5 mm with gap of 1–1.5 mm.

In all patients and control subjects, maps of the first, second, and third eigenvalues (EV1, EV2, EV3, respectively), trace ADC, and fractional anisotropy (FA) were generated according to the method previously described (27). In summary, diagonalization of the DT gave the first, second, and third eigenvectors and the corresponding EV1, EV2, and EV3, respectively. The trace ADC represented the mean diffusivity of water molecules; this was quantified as the mean of the three eigenvalues. FA was quantified as the standard deviations of the eigenvalues of the DT normalized by the magnitudes of the

three eigenvectors of the DT. Additionally, color maps of the orientations of the first eigenvectors of the DTs were rendered and used as road maps for defining five regions of interest (ROIs) in the frontoparietal, parieto-occipital, and frontal and central white matter and also in the anterior and posterior corpus callosum. Diffusion indices in these five ROIs were quantified and compared between the study group and control group by using the Mann-Whitney rank-sum test. In the eight PKU patients older than 3 years, results of intelligence assessment, including verbal IQ (VIQ), performance IQ (PIQ), and full-scale IQ (FSIQ), were correlated with all diffusion indices in the five ROIs by using the Spearman rank-order correlation test. A P value less than or equal to .05 was considered to indicate a significant difference.

Results

Conventional MR Images

T2-weighted MR images revealed focal high signal intensity in the bilateral parieto-occipital and central white matter in all four patients and control subjects younger than 3 years. These signal intensity changes in the parieto-occipital and central white matter were not discrete and similar to those found in the unmyelinated parieto-occipital white matter of children. In the other eight patients, no definite signal intensity changes were found on the axial FSE T2-weighted images.

Diffusion-Weighted and DT Images

None of the patients with malignant PKU had decreased ADC, as compared with the control groups. Occasionally, a slight increase in ADC was found, but the difference between the study and control groups was not significant. In the eight PKU patients older than 3 years, EV2 (0.5961 ± 0.0483) and EV3 (0.4006 ± 0.0545) of the parieto-occipital and central white matter were significantly larger than the EV2 (0.5263 ± 0.0449) and EV3 (0.3473 ± 0.0503) of the control group ($P < .05$) (Figs 1 and 2, Table 1). FA of the parieto-occipital and central white matter (0.3206 ± 0.0528) was significantly smaller in the older PKU group than the control group (0.3954 ± 0.0788). However, EV1 and ADC in the parieto-occipital and central white matter were not significantly different between the study and control groups older than 3 years. In the frontal, frontoparietal, and central white matter and also in the anterior and posterior portions of the corpus callosum, the difference in all DT image parameters was not significant between PKU patients and control subjects older than 3 years. In the four patients younger than 3 years, DT indices did not differ significantly from those of the control group (Table 2). FA values of patients younger than 3 years were as follows: frontoparietal, 0.29428 ± 0.15618 ; parieto-occipital, 0.19254 ± 0.11905 ; frontal, 0.181095 ± 0.090107 ; anterior corpus callosum, 0.328969 ± 0.151884 ; and posterior corpus callosum, 0.330658 ± 0.16969 . In comparison, FA values in the younger control group were as follows: frontoparietal, 0.315707 ± 0.169711 ; parieto-occipital, 0.248352 ± 0.127141 ; frontal, 0.241654 ± 0.15065 ; anterior corpus callosum,

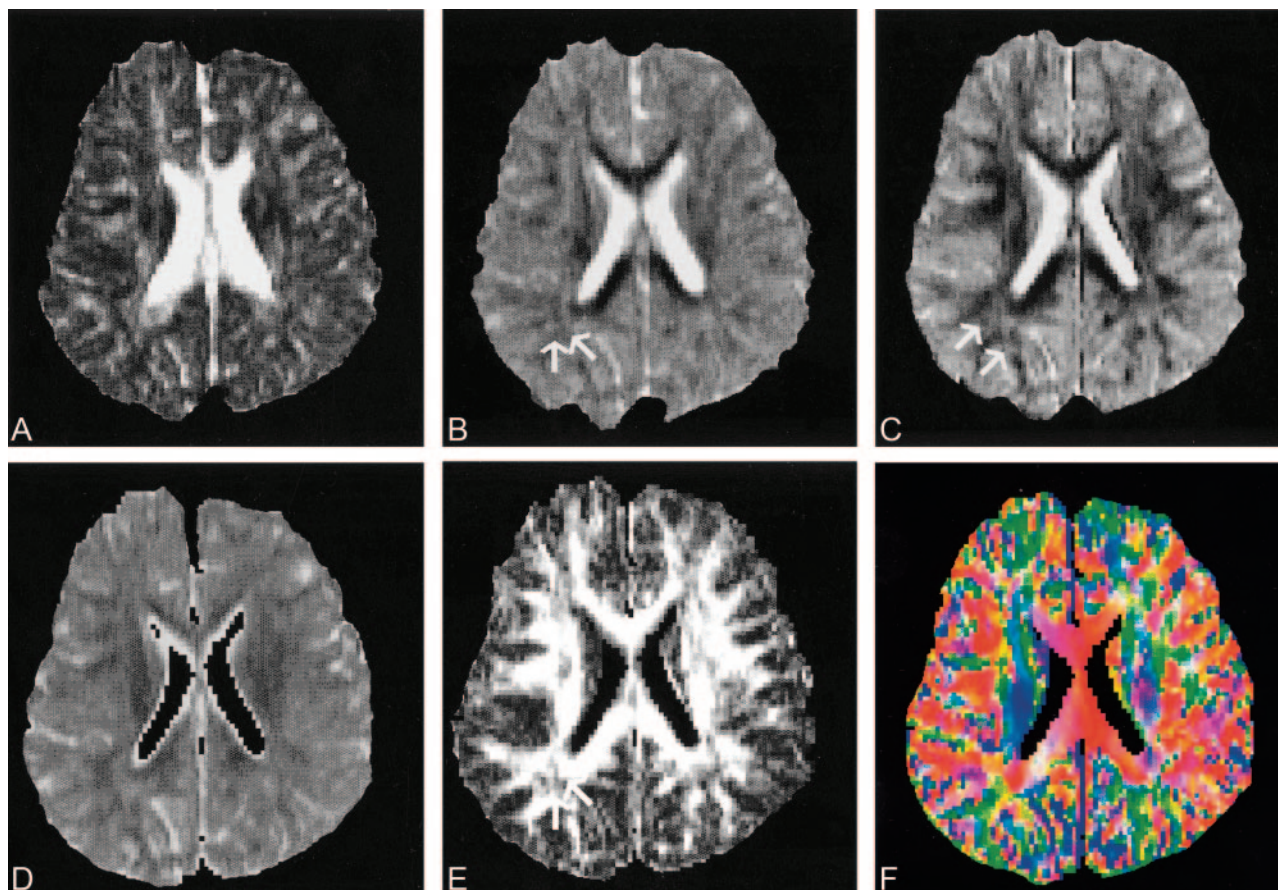


FIG 1. Control subject aged 27 months. Maps of the brain at the level of the lateral ventricular bodies show the right parietal-occipital central white matter with ROIs in the frontoparietal, parietal-occipital, frontal central white matter and in the anterior and posterior corpus callosum.

A, EV1; B, EV2; C, EV3; D, trace ADC; E, FA index.

F, Color-coded fiber orientation. Left-right, anterior-posterior, and superior-inferior directions are associated with pure red, green, and blue, respectively. Combinations of these colors represent oblique fibers.

0.359111 ± 0.198671 ; and posterior corpus callosal, 0.323026 ± 0.191233 .

Correlation between IQ and DT Images

For seven of eight patients receiving assessment of intelligence, VIQ (81 ± 18), PIQ (75 ± 18), and FSIQ (76 ± 19) were subnormal. EV3 and ADC of the parieto-occipital white matter were significantly correlated with VIQ ($r = -0.79$, $P = .04$) and PIQ ($r = -0.93$, $P = .03$), respectively. ADC and FA in the parieto-occipital white matter had borderline correlations with FSIQ ($r = -0.76$, $P = .05$) and VIQ ($r = 0.75$, $P = .05$), respectively. No significant correlation existed between DT image indices at the other ROIs and all IQ results.

Discussion

Our results indicate that EV2, EV3, and FA of the parieto-occipital white matter were significantly different between study and control groups older than 3 years. EV2 and EV3 were significantly larger and FA was smaller in older patients with malignant PKU compared with control subjects. Although treated

early, these patients with chronic, stable malignant PKU still had abnormal findings in the parieto-occipital central white matter on DT images. In addition, EV3 and ADC of the parieto-occipital white matter were significantly and negatively correlated with VIQ and PIQ, respectively. FA of the parietal and central white matter was positively correlated with VIQ. However, the trace ADC of the parieto-occipital and central white matter was negatively correlated with FSIQ.

PKU is an autosomal recessive disorder that causes a broad spectrum of clinical and metabolic phenotypes ranging from classic PKU to mild hyperphenylalaninemia (1–4). Classic PKU is the most common type of PKU and induced by a deficiency of phenylalanine hydroxylase. Malignant PKU is a rare variant caused by dihydropteridine reductase deficiency, which induces hyperphenylalaninemia and deficiency in neurotransmitters such as 3,4-dihydroxyphenylalanine and 5-hydroxytryptophan. Such a defect not only prevents the transformation of phenylalanine to tyrosine but also blocks the biosynthesis of dopamine, norepinephrine, and serotonin, causing severe neurologic disturbances (15). Retarded development and intellectual impairment are the most consistent clin-

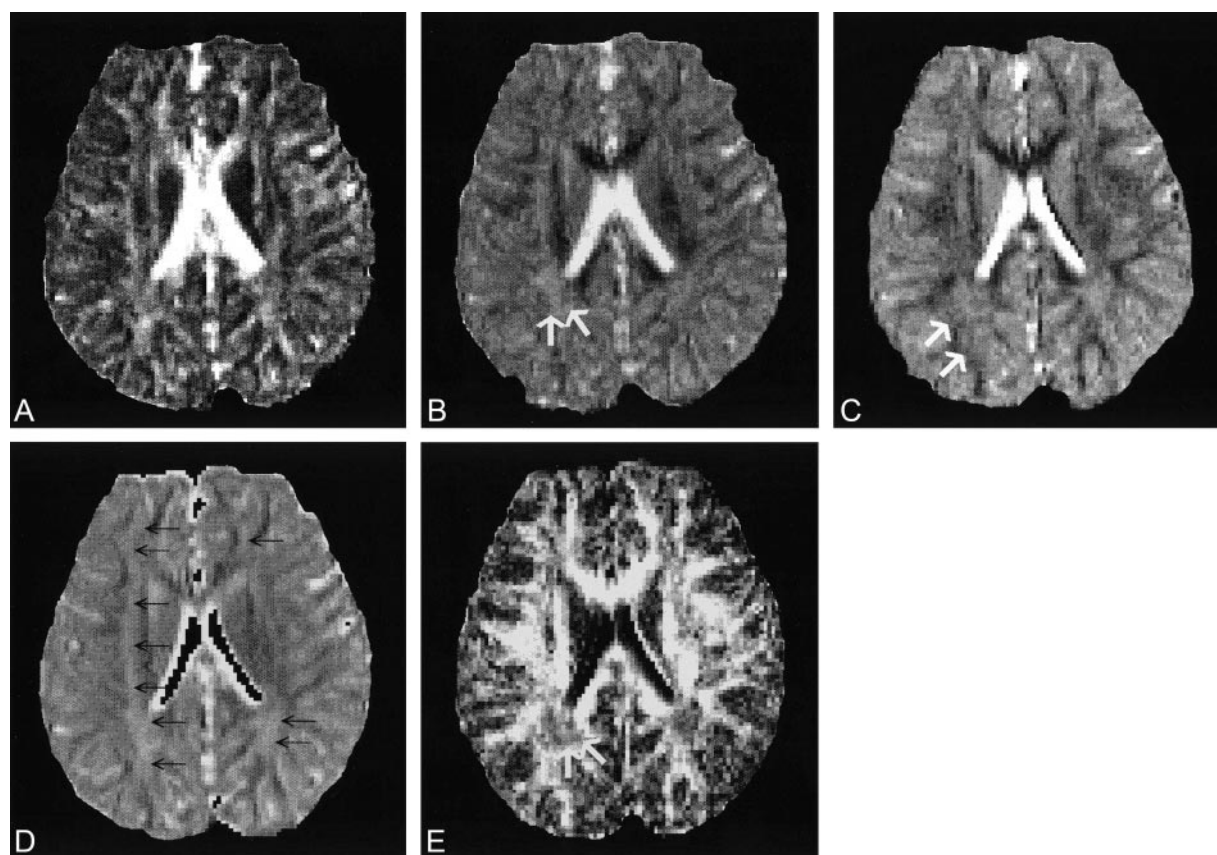


FIG 2. PKU patient aged 25 months. Cerebral maps at the level of lateral ventricular bodies.

A, EV1.

B, EV2 increases in the bilateral frontal and parietal-occipital central parenchyma, more prominently in the right parietal-occipital central areas (arrows). High-EV2 area is more extensive in bilateral parietal-occipital central areas than in areas shown in Figure 1B.

C, High EV3 is prominent in parietal-occipital central areas, more on the right (arrows) than the left.

D, ADCs are diffusely increased, slightly in the bilateral frontal, right frontoparietal, and bilateral parietal-occipital central parenchyma (arrows); the difference is not significant.

E, FA is reduced in parietal-occipital central white matter, more on the right (arrows) than the left.

TABLE 1: Results of the Mann-Whitney rank-sum test in patients and control subjects older than 3 years

Position	P Value				
	EV1	EV2	EV3	ADC	FA
Frontoparietal central white matter	.37	.49	.79	.64	.56
Parieto-occipital central white	.37	.02	.04	.16	.02
Superiofrontal central white matter	.43	1.00	.64	.87	.79
Anterior portion of corpus callosum	.27	.10	.19	.13	.08
Posterior portion of corpus callosum	.27	.71	.79	>.99	.96

TABLE 2: Results of the Mann-Whitney rank-sum test in patients and control subjects younger than 3 years

Position	P Value				
	EV1	EV2	EV3	ADC	FA
Frontoparietal central white matter	.66	>.99	>.99	>.99	>.99
Parieto-occipital central white	>.99	.38	.66	.38	.38
Superiofrontal central white matter	.66	>.99	>.99	>.99	>.99
Anterior portion of corpus callosum	.66	>.99	.66	.66	.66
Posterior portion of corpus callosum	>.99	.38	.38	.19	.66

ical findings in patients with PKU, although no single clinical risk factor is sufficient to explain the brain manifestations by itself (28).

MR imaging studies on early, late, and untreated

classic PKU show frequent findings of white matter abnormalities, even in neurologically asymptomatic patients (17–21, 29). MR findings in malignant PKU are usually normal or almost normal (13). However,

subtle or different MR imaging findings, including subcortical cystlike lesions and abnormal signal intensities in the periventricular white matter, are also found (11–15, 30). Our patients with malignant PKU, like well-treated PKU patients, had subtle or equivocal findings on FSE T2-weighted images. In our study, DT images were more sensitive than FSE T2-weighted images for detecting abnormalities in the normal-appearing white matter of PKU patients. In addition, DT images can provide additional quantitative MR parameters for assessing and monitoring patients with malignant PKU.

Pathologic changes include impaired myelination, intramyelinic vacuoles, and gliosis (6, 7, 31). Myelin proteins degrade rapidly, especially in the regions that become myelinated late in life, such as parieto-occipital periventricular white matter (7). Previous studies of diffusion-weighted images have shown that water molecules in PKU lesions are more restricted as a result of the deformed myelin structure (22). In comparison, DT images provide more diffusion parameters that help to reveal the underlying microscopic structural changes. We found no significant difference in EV1 in malignant PKU, but we did find a significant increase in EV2 and EV3 in malignant PKU. This may be due to an increased sideways diffusion within the intramyelinic vacuoles. However, diffusion along the main axonal direction did not change significantly in our patients with chronic, stable malignant PKU. Although water molecules are not confined to the intracellular spaces in either patients with malignant PKU or control subjects, sideways diffusion is more prominent in patients than controls. The water molecules in the parieto-occipital areas were more randomly mobile in the patients than in the control subjects, and this caused FA to decrease. The changes in EV2, EV3, and FA might have been explained by changes in structures of myelin sheaths, which presumably have geometric changes in malignant PKU. However, changes in ADCs can still be important in revealing acute changes, including relatively recent increases in intracellular water content; however, our cases did not have significant ADC changes. None of our patients had high blood levels of phenylalanine, though changes in DT image indices were significant in patients older than 3 years but not in those younger than 3. The failure to find significant changes in DT image indices in the younger group could have been due to small number of patients and the narrow range of DT imaging parameters, including anisotropy in these patients whose cerebral white matters were undergoing active myelination.

MR image abnormalities did not seem to be correlated with IQ or clinical stage (18–20). Our results indicated that changes in DT indices, including EV2, EV3, and FA, are significant in patients without remarkable conventional MR imaging findings. In addition, our data also indicated that changes in VIQ, PIQ, and FSIQ were related to alterations of diffusion indices in the parieto-occipital white matter. These correlations probably reflected diffuse, pathologic white matter abnormalities, which may exert their effect by disrupting

association fibers. EV3 of the parieto-occipital white matter was particularly more sensitive than conventional MR images in demonstrating white matter changes in malignant PKU and significantly correlated with their intellectual impairment.

Color schemes demonstrating the anisotropy of white matter are helpful in distinguishing adjacent tracts with the same signal intensity on conventional MR images. However, technical problems still existed in the present study. To compare malignant patients and control subjects, ROIs were chosen by using anatomic landmarks shown on color maps of DT images rather than the corresponding T2-weighted abnormalities. Consequently, some ROIs inevitably contained both normal and abnormal tissue on color maps. In addition, the selected ROIs were limited to the supratentorial and central white matter because DT images are greatly distorted in the posterior fossa owing to inhomogeneity of the magnetic fields.

Conclusion

Our findings indicate that EV2, EV3, and FA maps are more sensitive than conventional MR images for demonstrating brain changes in malignant PKU. DT imaging can also provide overview images helpful in guiding localization for MR spectroscopy and quantitative imaging follow-up of malignant PKU. However, pathogenesis and clinical correlation of the lesions identified in this study warrant further investigation.

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