AJNR

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AJNR Am J Neuroradiol 2001, 22 (8) 1583-1586
http://www.ajnr.org/content/22/8/1583

AJNR Am J Neuroradiol 22:1583–1586, September 2001

Case Report

Diffusion-Weighted Imaging of White Matter Abnormalities in Patients with Phenylketonuria

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Summary: Phenylketonuria (PKU) is an autosomal recessive disorder caused by a deficiency of the enzyme phenylalanine hydroxylase (EC 1.14.16.1). Affected patients develop elevated plasma and tissue levels of phenylalanine and its related ketoacids. Untreated patients usually exhibit severe mental retardation and poor motor function, with characteristic T2 white matter signal abnormalities on conventional MR images. In the present study, we performed diffusion-weighted imaging in three PKU patients. All three patients demonstrated significantly restricted diffusion in all white matter areas examined.

Phenylketonuria (PKU) is the most common congenital disorder of amino acid metabolism. Since its first description by Folling in 1934 (1), PKU has been extensively studied, and its clinical (2, 3), pathologic (4, 5), and MR imaging characteristics have been well defined (6–11). Although the characteristic T2 white matter changes and MR spectroscopy abnormalities have been repeatedly shown, no study has been performed, to our knowledge, to examine diffusion-weighted imaging of these patients. Diffusion imaging may provide information about the nature of parenchymal changes producing T2 changes and provide an additional quantitative MR parameter for assessing and monitoring patients with PKU. The purpose of our study was to investigate white matter abnormalities in PKU patients by using quantitative diffusion measurements and to compare these measurements with those obtained from the white matter of healthy subjects.

Case Reports

We investigated one pediatric and two adult patients with classic PKU by using a 1.5-T General Electric (Milwaukee, WI) echo-speed imager. Cranial MR imaging was performed with the following imaging sequences: 1) axial T2-weighted fast spin-echo (FSE) (3000/105/1 [TR/TE/excitation]), field of view (FOV) = 22 cm, matrix (MAT) = 256 × 256, and 5-mm contiguous sections; 2) axial fluid-attenuated inversion-recovery (FLAIR) (10,000/150/2200/1 [TR/TE/TI/excitation]), FOV = 22 cm, MAT = 256 × 256, and 5-mm contiguous sections; 3) axial echo-planar diffusion images (7000/110/1 [TR/TE/excitation]), FOV = 22 cm, and MAT = 128 × 128. Diffusion images were obtained with diffusion gradients (b = 0 and 1000) in each of the cardinal planes. Apparent diffusion coefficient (ADC) maps were calculated in each of the cardinal directions and averaged to produce an average ADC map (ADC_{av}). Diffusion images were also obtained for six healthy volunteers (four men and two women ranging in age from 29 to 36 years).

Eight regions of interest (ROIs) within cerebral white matter were examined on the ADC_{av} maps with a commercially available software package. ROIs were placed according to anatomic landmarks to exclude partial-voluming with CSF and gray matter and allow a reliable comparison of ADC values between PKU patients and healthy volunteers. ROIs were drawn within bilateral frontal white matter, occipital white matter, and centrum semiovale as well as the splenium and genu of the corpus callosum. ADC_{av} values within ROIs were compared between the three subjects and six healthy adults by using a standard *t* test.

The first case was a 27-year-old man with a recent diagnosis of PKU (Fig 1). Blood spot phenylalanine when he was 4 days old had been borderline (elevated at ~4 mg/dL [~240 micromoles/L]), and he was not treated with diet. Owing to a history of mild behavior problems, learning disability, and abnormal newborn screening in the past, he was referred for evaluation. Serum phenylalanine level was 20.5 mg/dL (1241 μmol/L with a normal range of 41–86 μmol/L) with a tyrosine of 35 μmol/L (normal 43–123 μmol/L). At the time of the imaging study, he had had variable compliance with dietary restriction of his phenylalanine intake. Blood phenylalanine levels ranged from 2.3–13.8 mg/dL (desired therapeutic range 2–10 mg/dL).

The second case was a 21-year-old man with a diagnosis of PKU at birth. Early history showed good compliance with dietary restrictions including intake of PKU formula. As a teen with normal intellect and mental status, his blood phenylalanine levels ranged from 8–19.4 mg/dL. Over the year prior to imaging, he improved his dietary compliance to limit his phenylalanine levels to the desirable range of 2–6 mg/dL.

The third case was a 7-year-old girl with a diagnosis of classic PKU at birth. Dietary compliance was adequate during the first year of life, but formula intake and diet control were poor until the age of 7 years, when her level was found to be greater than 20 mg/dL. After reestablishing appropriate formula intake, her dietary compliance and phenylalanine levels improved to the range of 4–12 mg/dL. She had normal intelligence and behavior. Her phenylalanine levels during the 2 weeks prior to imaging were 4–20 mg/dL.

All PKU patients demonstrated MR imaging white matter T2 hyperintensities that were seen on T2-weighted FSE and FLAIR images. For all patients, findings were most conspicuous on the FLAIR and diffusion-weighted images. None of the participants demonstrated significant volume loss. Cases 1 and 2 showed greater white matter involvement than did case

Received June 21, 2000; accepted after revision March 23, 2001.

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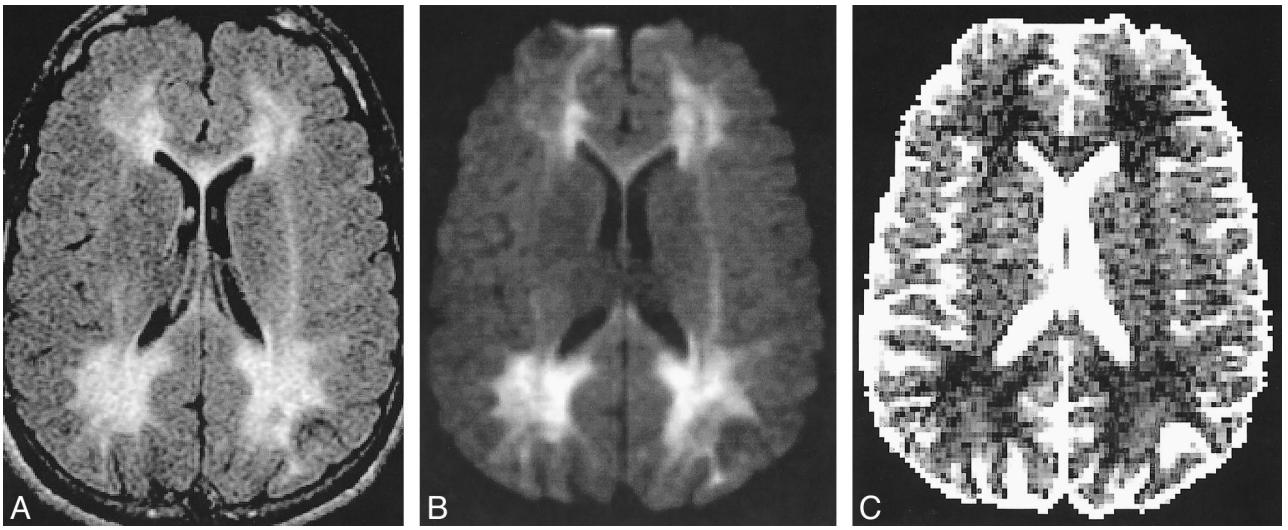

FIG 1. Case 1: a 27-year-old man was screened at birth and was found to have a borderline phenylalanine level.
A–C, FLAIR (*A*), trace diffusion-weighted (*B*), and ADC_{av} (*C*) images show extensive white matter abnormalities with restricted diffusion.

TABLE 1: Comparison of ADC_{av} values for all brain regions for cases 1, 2, and 3

Brain Region	Case 1 ADC_{av}	Case 2 ADC_{av}	Case 3 ADC_{av}
Occipital white matter	0.524×10^{-3}	0.517×10^{-3}	0.667×10^{-3}
Splenium	0.629×10^{-3}	0.615×10^{-3}	0.649×10^{-3}
Genu	0.587×10^{-3}	0.427×10^{-3}	0.672×10^{-3}
Frontal white matter	$0.519.5 \times 10^{-3}$	$0.620.5 \times 10^{-3}$	0.702×10^{-3}
Corona radiata	$0.475.5 \times 10^{-3}$	$0.514.5 \times 10^{-3}$	0.735×10^{-3}

TABLE 2: Comparison of mean ADC_{av} values between healthy subjects and PKU patients in the occipital white matter, splenium, genu of the corpus callosum, frontal white matter, and corona radiata

Brain Region	Normal Mean ADC_{av}	PKU Mean ADC_{av}	*t* Test
Occipital white matter	$0.836 \times 10^{-3} \pm 0.047 \times 10^{-3}$	$0.580 \times 10^{-3} \pm 0.091 \times 10^{-3}$	$P < .0003$
Splenium	$0.880 \times 10^{-3} \pm 0.042 \times 10^{-3}$	$0.631 \times 10^{-3} \pm 0.033 \times 10^{-3}$	$P < .0001$
Genu	$0.861 \times 10^{-3} \pm 0.078 \times 10^{-3}$	$0.562 \times 10^{-3} \pm 0.149 \times 10^{-3}$	$P < .03$
Frontal white matter	$0.086 \times 10^{-3} \pm 0.039 \times 10^{-3}$	$0.614 \times 10^{-3} \pm 0.085 \times 10^{-3}$	$P < .001$
Corona radiata	$0.686 \times 10^{-3} \pm 0.046 \times 10^{-3}$	$0.575 \times 10^{-3} \pm 0.122 \times 10^{-3}$	$P < .05$

3 on all imaging sequences. Correspondingly, cases 1 and 2 demonstrated the most severely restricted ADC values, as shown in Table 1. PKU patients had significantly reduced diffusion in all of the brain regions tested as compared with the healthy volunteers. Mean ADC_{av} values for healthy and PKU subjects for each brain region are shown in Table 2.

Discussion

PKU is an inborn error of metabolism that most commonly stems from mutations in the phenylalanine hydroxylase gene that is found on chromosome 12 at the locus 12q24.1 (3, 12). It is transmitted as an autosomal recessive disorder with considerable variability in incidence among different ethnic populations. In the United States, the incidence is approximately 1 in 10,000 with an incidence of 1 in 8000 among Caucasians and 1 in 50,000 among African Americans (3, 12). Classic PKU arises from a severe deficiency of phenylalanine hydroxylase that limits the hepatic hydroxylation of phenylalanine to tyrosine (2, 3). Untreated patients typically develop a characteristic clinical picture that may include mental retardation, seizures, growth retardation, hyperreflexia, eczematous dermatitis, and hypopigmentation (2, 3, 12). Treatment consists of dietary control with restricted intake of phenylalanine through the use of special medical formulas or foods (13).

Although gray matter changes in cortical layering, tissue mass (atrophy), and reduced dendritic arborization have been reported, the primary neuropathologic finding of PKU is that of diffuse abnormalities within white matter (3, 5, 14). Reduction in brain size is largely due to white matter volume loss. Specific white matter abnormalities include delayed or defective myelination, diffuse white matter vacuolization (status spongiosis), demyelination, and gliosis (3–5, 14). Malamud (5)

suggested that findings varied between older and younger patients, with older patients tending to show more changes of demyelination and younger patients showing more changes of status spongiosis. It remains unclear whether the white matter changes in PKU represent a failure of myelin production, destruction of myelin, or a combination of both processes. Studies in animal models of PKU suggest that there is increased myelin turnover (15). This suggests that an ongoing decrease in the formation of myelin and/or increase in the destruction of myelin occurred in the model animals.

Although characteristic white matter MR spectroscopic and positron emission tomography glucose metabolism changes have been reported in PKU (11, 16), neuroimaging of PKU has focused largely on the MR imaging T2 abnormalities. Multiple studies have demonstrated T2 hyperintensities that are most commonly seen in the periventricular parietal and occipital regions (6–11, 17). In more severely affected patients, extensive confluent areas of abnormally increased T2 signal intensity can be seen extending to the frontal and subcortical white matter. T2 white matter abnormalities have been shown to be reversible, with improvement in metabolic control and reduced serum phenylalanine levels from dietary restriction (6, 9). The quantitative relationship between the level of T2 abnormality within white matter and the extent of clinical disease remains unclear. While white matter changes have been shown in some reports to correlate with blood levels of phenylalanine (6, 9), the degree of white matter abnormality has not shown consistent correlation with measures of IQ, dietary control, visual evoked potential, or neuropsychological testing (7, 8, 10, 11, 17).

The etiology of T2 hyperintensities in PKU remains unclear. Several authors have suggested that T2 hyperintensities reflect increased water within white matter of patients with PKU (10, 17). The increased white matter water content has been suggested to reflect edema associated with the myelination or to reflect gliosis within the tissue. Studies of T2 relaximetry suggest a bimodal distribution of T2 relaxation within abnormal white matter of PKU patients (10, 17). Authors of these studies suggest that these findings reflect two pools of water within abnormal white matter of patients with PKU (10, 17). One pool represents the water within normal white matter, with the second pool representing water that is either in the extracellular space or within intralamellar portions of abnormal myelin sheaths.

The findings of the present study demonstrated restricted diffusion of water within areas of abnormal white matter in patients with PKU. The relationship of these findings to those of previous studies is unclear. The restricted diffusion seen in the present study would suggest that the T2 prolongation found on conventional images is unlikely to reflect increased extracellular fluid. Increased extracellular fluid, such as that seen in vasogenic-related edema, should produce increased, rather than restricted, diffusion (18). Additionally, it would seem unlikely that the restricted diffusion in our patients reflects only demyelination. The demyelination seen in association with multiple sclerosis tends to produce relatively increased diffusion values rather than restricted diffusion (19). Impaired or delayed myelination might be expected to produce relatively increased diffusion, as diffusion values typically drop in the developing brain white matter as it becomes increasingly myelinated (20). However, the changes of impaired myelination in PKU are likely to reflect a different process than occurs in normal or delayed myelination seen in other disease processes. Restricted diffusion seen in the present study may reflect the presence of status spongiosis change within the white matter, as has been described in prior pathologic studies. This explanation seems unlikely, as protons within vacuoles should be freely diffusing; however, the presence of a large number of small vacuoles may increase the barriers to diffusion within the tissue. Alternatively, it may reflect water within or associated with abnormal myelin sheaths related to increased myelin turnover. Protons within vacuoles or within partially destroyed portions of myelin sheath may not be as mobile as those seen in free water. This may account for the relatively restricted diffusion in these regions seen in the present study.

The authors recognize some technical limitations to the present study. ROIs were chosen using anatomic markers rather than corresponding T2 abnormalities to allow for comparisons between patients and control subjects. Consequently, some ROIs contained both normal and abnormal tissue on T2-weighted images. This primarily occurred in case 3, in which fewer white matter abnormalities existed. Cases 1 and 2 had diffuse white matter disease that essentially filled all of the ROIs drawn. Additionally, owing to the extensive involvement in cases 1 and 2, evaluation of the diffusion abnormality in normal-appearing white matter on T2-weighted imaging was not possible in these patients. However, the ADC values in case 3 were closer to those of healthy subjects, suggesting that the worst diffusion abnormalities corresponded to T2 abnormalities.

Our results are preliminary and warrant further study to delineate the potential variables that may produce restricted diffusion. The diffusion findings need to be evaluated in a larger number of patients to determine their reliability and sensitivity compared with conventional MR imaging. Further investigation needs to be performed to determine the sensitivity of diffusion imaging for detecting abnormalities in normal-appearing white matter of PKU patients on T2-weighted images. Additionally, it is not known if the diffusion images seen in our study are reversible in a fashion similar to those seen with the T2 changes when the diet is well controlled (6, 9). The diffusion results should also be correlated with other clinical factors, such as

neuropsychological testing, IQ, visual evoked potentials, dietary compliance, and blood or CSF phenylalanine, tyrosine, and branched-chain amino acid levels.

In conclusion, three patients with a history of PKU demonstrated decreased diffusion within their white matter. Changes of restricted diffusion suggest that T2 abnormalities shown by previous authors are not consistent with extracellular edema that would more likely appear as increased diffusion. The exact etiology of the restricted diffusion in these cases and the T2 changes associated with PKU remain unclear. Further study is needed to determine the relationship between the diffusion findings, conventional imaging, and clinical parameters in patients with PKU.

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