MR Imaging of Phenylketonuria

Cranial MR imaging was performed on nine patients (13–27 years old) with classical phenylketonuria in order to define the spectrum of abnormal findings and to determine if these could be related to clinical or biochemical findings. MR abnormalities consistent with demyelination were found in varying degrees in a distribution corresponding to previous histopathologic studies. Specifically, increased signal was seen on T2-weighted sequences, most marked in the periventricular deep cerebral white matter. These changes were more prominent posteriorly, especially about the optic radiations. Comparison with clinical history and MR findings in this small series revealed that patients with adequate dietary control of phenylalanine levels had less severe white matter abnormalities than did patients with poorly controlled phenylalanine intake.

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Classical phenylketonuria (PKU) represents an autosomal recessive defect in phenylalanine hydroxylase conversion of phenylalanine (PA) to tyrosine, which results in hyperphenylalaninemia [1]. Patients whose dietary intake of PA is unrestricted develop poor motor function and are profoundly retarded. Restricting dietary PA intake in early childhood prevents these neurologic manifestations [2]. More recently, with recognition of more subtle abnormalities, longer-term dietary control has been advocated [2], although this is not uniformly accepted. Neurohistopathologic findings in untreated patients consist primarily of abnormalities of white matter tracts [3, 4]. The present study was undertaken to evaluate the MR appearance in classical PKU and search for any relationship between the MR findings and dietary treatment history.

Materials and Methods

Nine patients (13–27 years old) with classical PKU were selected from three clinical groups that were formulated on the basis of dietary control as measured by historical serum PA levels. Each group contained three patients (see Table 1). All patients had been diagnosed within the first few days of life and begun on some form of dietary control. In the first group (I), patients were maintained continuously on good dietary control from the time of diagnosis, with serum PA levels remaining generally less than 10 mg/dl. In the second group (II), patients were maintained on good dietary control in early childhood (serum PA levels < 10 mg/dl) but were withdrawn from dietary restrictions at ages ranging from 6 to 12 years, after which serum PA levels rose to 15–30 mg/dl. The third group (III) consisted of patients with a clinical history of poor dietary control throughout their lives as determined by serum PA levels that regularly were in the 20–30 mg/dl range, although none was completely untreated in early childhood. One of the patients from this group is the subject of a previous case report [5].

MR imaging was performed on a 1.5-T magnet (General Electric, Milwaukee, WI) using spin-echo T1-weighted 600/20/1 (TR/TE/excitations) sequences, proton-density-weighted 2700/30/1 sequences, and T2-weighted 2700/80/1 sequences. MR scans were independently evaluated by three radiologists who were unaware of the patients' clinical status. The evaluation included a grading of the white matter signal. T2-weighted sequences were rated...
TABLE 1: Summary of Patient Data (n = 9)

<table>
<thead>
<tr>
<th>Group/Patient No.</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Age at Start of Therapy</th>
<th>Age at End of Therapy</th>
<th>Average PA Levels on Therapy (mg/dl)</th>
<th>Current PA Level (mg/dl)</th>
<th>Current Degree of White Matter Abnormality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>14</td>
<td>M</td>
<td>Neonate</td>
<td>Not ended</td>
<td>&lt;10</td>
<td>&lt;10</td>
<td>Minimal</td>
</tr>
<tr>
<td>2</td>
<td>16</td>
<td>F</td>
<td>Neonate</td>
<td>Not ended</td>
<td>&lt;10</td>
<td>&lt;10</td>
<td>Normal</td>
</tr>
<tr>
<td>3</td>
<td>21</td>
<td>F</td>
<td>Neonate</td>
<td>Not ended</td>
<td>&lt;10</td>
<td>&lt;10</td>
<td>Mild</td>
</tr>
<tr>
<td>Group II</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>17</td>
<td>M</td>
<td>Neonate</td>
<td>6 years</td>
<td>&lt;15</td>
<td>&gt;20</td>
<td>Moderate</td>
</tr>
<tr>
<td>5</td>
<td>21</td>
<td>F</td>
<td>Neonate</td>
<td>12 years</td>
<td>&lt;10</td>
<td>&gt;20</td>
<td>Minimal</td>
</tr>
<tr>
<td>6</td>
<td>21</td>
<td>F</td>
<td>Neonate</td>
<td>8 years</td>
<td>&lt;10</td>
<td>&gt;15</td>
<td>Moderate</td>
</tr>
<tr>
<td>Group III</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>20</td>
<td>F</td>
<td>Neonate</td>
<td>Not ended</td>
<td>&gt;20</td>
<td>&gt;20</td>
<td>Mild</td>
</tr>
<tr>
<td>8</td>
<td>27</td>
<td>F</td>
<td>Neonate</td>
<td>8 years</td>
<td>&gt;20</td>
<td>&gt;20</td>
<td>Moderate</td>
</tr>
<tr>
<td>9</td>
<td>21</td>
<td>M</td>
<td>6 weeks</td>
<td>6 years</td>
<td>&gt;20</td>
<td>&gt;20</td>
<td>Severe</td>
</tr>
</tbody>
</table>

Note.—PA = phenylalanine.

from 0 (normal) to 3 (markedly increased signal, assigned to those areas equaling the most severely affected white matter seen in the series of patients). Grading was performed at six locations in the cerebral white matter: (1) white matter adjacent to the frontal horns, (2) body of the lateral ventricles, (3) perialarial white matter, (4) centrum semiovale, (5) subcortical white matter, and (6) optic radiations. Final ratings for each location was the average of the rating assigned by the three evaluating radiologists. A severity score was obtained for each patient by summing the averaged values obtained at the six locations. Comparisons were made with the clinical history, including dietary grouping.

Results

The most common MR finding was that of patchy to confluent increased signal in the cerebral white matter on the T2-weighted sequence, seen most prominently in the perialarial region and about the optic radiations (Figs. 1, 2, 3A). Increased signal on T2-weighted scans was seen extending into the corona radiata (Fig. 3B) and subcortical white matter in the more severely affected patients. The signal intensity was less marked on the proton density sequence. In areas with the highest signal intensity on T2-weighted scans there was some concomitant decrease in signal on the T1-weighted sequence. There was a general gradation of severity with a greater degree of signal abnormality posteriorly than anteriorly, and more centrally than peripherally. Overall, the white matter changes were symmetric.

Mild ventriculomegaly was seen in one patient who had minimal white matter abnormality and in another who had minimal ventricular prominence. One patient, who had the most marked signal changes in the white matter, demonstrated a mild decrease in white matter volume. In only one patient were abnormalities seen in the brainstem, specifically the punctate foci of increased signal on a T2-weighted sequence in the midbrain. No other abnormalities in the brainstem or cerebellum were present.

All patients in this series demonstrated normal neurologic and intellectual function, except one patient in the poorly treated group whose IQ was in the borderline mentally retarded range and who had a mild tremor. For each patient a total severity score was obtained by adding the scores (scale from 0 to 3).

Fig. 1.—Case 4: 17-year-old boy. T2-weighted SE (2700/80/2) axial MR image at level of basal ganglia shows moderate signal increase in posterior periventricular white matter about the optic radiations (arrows). Less severe changes are seen anteriorly.

Fig. 2.—Case 9: 21-year-old man. T2-weighted SE (2700/80/2) axial MR image at level of basal ganglia shows marked signal increase in posterior periventricular white matter about the optic radiations (arrows). Less severe changes are seen anteriorly.
Fig. 3.—Case 6: 21-year-old woman.
A, T2-weighted SE (2700/80) axial MR image shows moderate confluent increased signal in periatrial white matter. Less severe changes are seen in white matter anteriorly around frontal horns.
B, T2-weighted SE (2700/80) axial MR image shows moderate patchy confluent increased signal in corona radiata (arrows).

Fig. 4.—Averaged cerebral white matter severity scores as shown on T2-weighted MR sequences, and arranged in vertical columns by dietary groups (I = continuously good treatment; II = good early treatment, which was stopped; III = continuously poor treatment). See text for further explanation.

Discussion

Classical PKU represents a defect in the phenylalanine hydroxylase enzyme. Treatment consists of dietary restriction of PA, optimally maintaining the serum PA levels to <10 mg/dl. Untreated patients demonstrate poor neurologic development and are profoundly retarded [6]. In the past, dietary control was discontinued at ages 5–6 years. More recently, most centers have recommended long-term dietary control, though some questions as to the length of term persist [4].

Pathologic studies in untreated patients report white matter degeneration ranging from spongiosis to areas of frank demyelination [3, 4]. These findings are most common in the deep cerebral white matter, optic tracts, and fornix. Cerebral white matter MR findings in the present study are consistent with spongiosis and demyelination. Attempts to look for similar findings in the optic tracts and fornix were limited by the resolution allowed by the imaging method and by the protocol employed. Lack of structural changes, such as atrophy, in our patients, compared with previous pathologic studies, is likely attributable to the increased severity of disease among the untreated subjects studied in the pathologic series [3, 4]. Although some patients in the present series had suboptimal dietary control, none was completely untreated in early childhood, as was the case in many earlier studies.

The only brainstem abnormality (punctate foci of increased signal on a T2-weighted sequence) in one patient is of uncertain significance. A recent report (Elster AD, Richardson DN. Paper presented at the annual meeting of the American Society of Neuroradiology, Los Angeles, March 1990) suggests that this appearance is a normal variant representing prominent perivascular spaces.

Radiologic reports of PKU have been few. In 1981 Behbehani et al. [7] reported cranial CT findings in 14 patients with classical PKU (six untreated until ages 2–8 years old). They demonstrated white matter disease in only two patients and the authors believed that the findings were most likely attributable to neonatal asphyxia in one and prior pneumococcal meningitis in the second. We recently reported characteristic cranial MR findings in a case of PKU [5]. The findings in this series demonstrate the same pattern as the original case, although with varying degrees of severity. A similar white matter appearance has recently been reported (Pearsen KD, et al. Paper presented at the annual meeting of the RSNA, Chicago, November 1989). This study found no relationship between the extent of white matter disease and IQ or diet.
No attempt was made to correlate IQ with MR findings in the present study.

Although the number of patients in the present study is insufficient for statistical significance, a general trend appears evident. Patients in the poorly treated group (III) and the early treatment termination group (II) had more significant white matter abnormalities than did those in the continuous treatment group (I). The one exception was a patient in group II who had minimal findings. However, in this patient, dietary restriction was discontinued later in life (at age 12) than it was in the other two members of the group (at ages 6 and 8, respectively).

In conclusion, classical PKU seems to be associated with MR changes in cerebral white matter consistent with the spongiosis and demyelination that is described pathologically. In our series, the degree of MR abnormality seemed to be less severe than in those who received good dietary control of PA levels. Although further study will be necessary to correlate the clinical significance of these findings, this study suggests a role for MR in evaluating adequacy of dietary control in patients with PKU and in addressing the issues surrounding discontinuation of PA restriction.

REFERENCES


The reader’s attention is directed to the commentary on this article, which appears on pages 413–416.