Brain MRI Abnormalities in Phenylketonuria
An Update on MR Imaging and MR Volumetry*

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Abstract
Phenylketonuria (PKU), a systemic metabolic disease that mainly involves cerebral white matter, is the most common congenital disorder of amino acid metabolism. Untreated patients usually exhibit epilepsy, microcephaly, severe mental retardation, and hyperactive behavior. In this review, the most important neuroradiologic findings in PKU regarding MR imaging and MR volumetry are summarized.

Key Words: Phenylketonuria · White matter diseases · MR imaging · MR volumetry · Diffusion-weighted MR imaging

Hirnveränderungen bei Phenylketonurie: Ein Update mit Blick auf MR-Tomographie und MR-Volumetrie

Zusammenfassung
Die Phenylketonurie (PKU), eine systemische metabolische Erkrankung, die hauptsächlich die weiße Hirnsubstanz schädigt, ist eine der häufigsten kongenitalen Störungen des Aminosäurestoffwechsels. Unbehandelte Patienten zeigen meist eine Epilepsie, Mikrozephalie, schwere mentale Retardierung und hyperaktives Verhalten. In dieser Übersicht fassen wir die wichtigsten neuroradiologischen Befunde bei PKU zusammen.

Schlüsselwörter: Phenylketonurie · Erkrankungen der weißen Substanz · MR-Tomographie · MR-Volumetrie · Diffusions MRT

Epidemiologic, Clinical and Histopathologic Aspects of Phenylketonuria
Phenylketonuria (PKU) is an inborn error of amino acid metabolism that results from mutations in the phenylalanine hydroxylase (PAH, EC 1.14.16.1) gene located on chromosome 12 at the locus 12q24.1 [1]. The disease is transmitted as an autosomal recessive disorder with considerable variability in incidence among different ethnic populations. In the USA, the incidence is approximately 1 in 10,000 persons, ranging between 1 in 8,000 persons among Caucasians and 1 in 50,000 among African Americans [1]. PKU arises from a severe PAH deficiency that limits the hepatic hydroxylation of phenylalanine (Phe) to tyrosine [1] (Figure 1). In affected patients, plasma and tissue levels of Phe and its related ketoacids are elevated. Untreated patients typically develop a characteristic clinical picture that may include mental retardation, seizures, growth retardation, hyper-
reflexia, eczematous dermatitis, and hypopigmentation [2]. Brain pathology of untreated patients is characterized by reduced brain weight and hypo- and demyelination of cerebral white matter [2]. 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, 4]. 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 spongiosus), demyelination, and gliosis [3, 4]. Malamud [3] 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 spongiosus. Generally, 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.

**Dietary Treatment**

By the application of a Phe-restricted diet beginning in the first days of life, the phenotype of untreated PKU can be prevented. This requires severely restricting or eliminating foods high in Phe, such as breast milk, meat, chicken, fish, nuts, cheese and other dairy products. Starchy foods such as potatoes, bread, pasta, and corn must be monitored. Babies who are diagnosed with PKU must immediately be put on a special milk/formula substitute (diet powder). Later in life, the diet continues to exclude Phe-containing foods.

If PKU is diagnosed early enough, an affected newborn can grow up with normal brain development, but only by eating a special diet low in Phe for the rest of his or her life. Many diet foods and diet soft drinks that contain the sweetener aspartame must also be avoided, as aspartame consists of two amino acids: Phe and aspartic acid [5]. Supplementary infant formulas are used in these patients to provide the amino acids and other necessary nutrients that would otherwise be lacking in a protein-free diet. Since Phe is necessary for the synthesis of many proteins, it is required but levels must be strictly controlled. In addition, tyrosine, which is normally derived from Phe, must be supplemented.

The link between histopathologic and MR imaging findings in PKU and clinical features is not clearly understood yet. This might be one reason for the fact that treatment policies for PKU are quite different among European countries, ranging from the French practice to discontinue diet at 5 years of age to the British recommendation for a lifelong diet [4]. Treatment policies in the US and Canada revealed similar inconsistencies [5]. According to German guidelines, our patient group underwent dietary treatment until the age of 18 years.

**Conventional MR Imaging**

The typical MR imaging features of early-treated PKU are hyperintensities on T2-weighted or FLAIR images that are located mainly in the occipital-parietal regions; in more severe cases they may extend into the frontal and parietal lobes, including the arcuate fibers [6] (Figure 2). The abnormal MR signal is most markedly found in the Phe-sensitive oligodendrocytes, which are located in brain areas that normally myelinate postpartum, e.g., in the subcortical and periventricular white matter, in the corpus callosum, in the optic tract, and in the forebrain. Rarely, basal ganglia, brain stem, and cerebellum are affected [4, 7, 8]. In a study with early-treated PKU patients, who were systematically evaluated using MR imaging, Pietz et al. [9] reported marked diffuse cortical atrophy in three of 51 patients (5.9%).

T2 white matter abnormalities have been shown to be reversible, with improvement in metabolic control and reduced serum Phe levels from dietary restriction [10, 11], but 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 Phe, the degree of