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White matter pathology in phenylketonuria ☆

Peter J. Anderson [a,b,*], Vincenzo Leuzzi [c]

[a] Department of Psychology, The University of Melbourne, Melbourne, Vic. 3010, Australia
[b] Critical Care and Neurosciences, Murdoch Childrens Research Institute, Melbourne, Vic., Australia
[c] Department of Child Neurology and Psychiatry, La Sapienza Università di Roma, Italy

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ABSTRACT

Early-treated phenylketonuria (PKU) is associated with a range of neuropsychological impairments. Proposed mechanisms for these impairments include dopamine depletion and white matter pathology. Neuroimaging studies demonstrate high-signal intensity in the periventricular white matter in most PKU patients, which can extend into subcortical and frontal regions in more severe cases. A review of histopathology and neuroimaging studies reveals that diffuse white matter pathology in untreated PKU patients is likely to reflect hypomyelination (lack of myelin formation), while in early-treated patients white matter abnormalities observed on magnetic resonance imaging (MRI) is likely to reflect intramyelinic edema. Research demonstrates that this pathology is associated with metabolic control and may be reversed with adherence to a strict low-phenylalanine (Phe) diet. While the functional significance of white matter pathology in PKU is not certain, there is some evidence that these abnormalities are associated with functional impairments when the pathology extends into subcortical and frontal regions.

Introduction

Phenylketonuria (PKU[1]; OMIM 261600 and 261630) is an inborn error of metabolism associated with diffuse brain pathology. The consequences are usually severe when this metabolic condition is left untreated; however, white matter pathology is common even in early diagnosed and treated individuals. PKU appears to principally affect cortical and subcortical white matter, although there is emerging evidence that this condition also influences cortical development, in particular dendritic growth and dendritic spine density [1]. Little is known about the cortical changes related to early-treated PKU in humans as dendritic abnormalities are not easily detectable with current neuroimaging paradigms. However, some recent studies have reported volumetric reductions in gray matter structures including the motor cortex, thalamus, and hippocampus [2,3]. In contrast, considerable human research has examined how PKU impacts white matter development, and this literature will be the focus of this review.

Histopathology

While human histopathology studies are limited to small numbers of selective samples of different ages, these studies can provide important insights into the specific neuropathology associated with PKU. The brains of untreated PKU patients generally show impaired myelination, reflected by pallor of the white matter on myelin stains [1,4]. Astrocystic gliosis is usually present in these affected white matter tracts [5]. In animal models of PKU, studies have demonstrated that oligodendrocytes (i.e., cells that assemble and maintain myelin) fail to form myelin in response to high-phenylalanine (Phe) levels [6]. For example, rats placed on a hyperphenylalanemia diet display increased turnover of myelin components and inhibited myelin synthesis [7], which is similar to the disturbed myelin metabolism observed in a mouse mutant deficient of phenylalanine hydroxylase (PAH; EC 1.14.16.1) [8]. Given that elevated Phe is a symptom of untreated or poorly treated PKU, the impaired myelination observed in these individuals is probably due to a toxic effect of high-Phe levels on oligodendroglia [4].

In utero the fetus with PKU of a mother heterozygous of PKU does not experience the elevated Phe levels associated with this metabolic disorder, and brain development up to birth is thought to proceed normally. After birth, Phe levels rise quickly and from this point forward are considered neurotoxic for subsequent brain development. This view is consistent with the location of white matter

☆ *References to electronic databases:* Phenylketonuria, OMIM 261600 and 261630. Phenylalanine hydroxylase, EC 1.14.16.1.
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* Corresponding author. Address: Department of Psychology, The University of Melbourne, Melbourne, Vic. 3010, Australia. Fax: +61 3 9345 4840.
E-mail address: peterja@unimelb.edu.au (P.J. Anderson).
[1] *Abbreviations used:* PKU, phenylketonuria; Phe, phenylalanine; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; VEP, visual evoked potentials; SEP, somatosensory evoked potentials; DTI, diffusion tensor imaging; CSF, cerebrospinal fluid; ADC, apparent diffusion coefficient; MW, myelin water; FA, fractional anisotropy; BBB, blood–brain barrier; IQ, intelligence quotient.

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lesions in untreated PKU, which generally occur in regions in which myelination occurs postnatally [4,6]. As a consequence, it has been proposed that oligodendrocytes in regions that myelinate post-birth (e.g., optic tract, corpus callosum, subcortical white matter, and periventricular white matter) are vulnerable to high-Phe levels post-birth, while oligodendrocytes associated with white matter tracts that myelinate pre-birth (e.g., internal capsule and brainstem) are resistant to elevated Phe levels post-birth [4]. If this is the case, one would expect that offspring from untreated or poorly treated maternal PKU pregnancies would show myelination abnormalities in the internal capsule, brainstem, and other early myelinating tracts. However, to date, there is limited supporting evidence. A neuroimaging study reported no myelination abnormalities in offspring without PKU, although significant changes to the corpus callosum were observed [9]. Further, an autopsy report on an infant whose mother had poorly controlled maternal PKU and died at 4 months of age revealed age-appropriate myelination in early myelinating tracts including the brainstem, spinal cord, and cerebellum, but myelination was delayed in tracts that commence myelination late in the third trimester, such as the optic radiation [10].

Dyer [4] argues that white matter pathology in untreated PKU is a developmental process whereby elevated Phe levels stall the myelination process, resulting in severe hypomyelination. Mild and transient involvement of white matter tracts that myelinate post-birth has been suggested also in early-treated PKU patients. However, in early-treated patients myelination is thought to proceed normally, or close to normal, and the lesions are likely to reflect demyelination or dysmyelination. In other words, white matter lesions in untreated PKU is likely to be due to reduced myelin formation, while lesions in well-controlled patients is considered a function of loss or impairment of previously assembled myelin [4].

In the lack of neuropathological confirmation, this attractive model can be explored in light of the data collected in vivo in PKU patients by magnetic resonance imaging (MRI) examination and neurophysiological and clinical studies.

Structural MRI

Probably the first report of white matter abnormality in treated PKU patients using conventional MRI was in 1989 [11]. This case report described two young adults displaying neurological deterioration (years after diet discontinuation) who on T_2 weighted images exhibited increased signal intensity in periventricular white matter.

This report was followed by a series of studies published in the early 1990s, which investigated neuroanatomical changes in treated PKU patients using structural MRI. An influential paper was published in the *Lancet* by Thompson et al. [12]. This case series described seven treated patients who displayed neurological deterioration in adolescence or early adulthood. Six of these patients underwent MRI and all were identified as having white matter abnormalities on T_2 weighted images, specifically high-signal intensity in periventricular white matter. While the size and distribution of these high-signal intensity changes varied between subjects, it was more common in posterior temporal and occipital white matter. The abnormal high-signal areas were thought to indicate "increased water content and/or an alteration in the macromolecular environment of water" in the cerebral white matter. Thompson et al. [12] also described one young adult who had serial MRI scans at age 23, 24, and 25 (two scans, with a repeat scan taken after resumption of treatment). The white matter abnormalities observed on brain scans at 23 and 24 years of age were similar, and during this period this patient remained stable. Between 24 and 25 years of age this patient showed marked clinical deterioration, which interestingly coincided with "striking MRI changes". A follow-up assessment was undertaken 2 months after resuming a strict low-Phe diet, neurological symptoms improved, and the severity of white matter changes diminished.

At roughly the same time Pearsen et al. [13] published the findings of an MRI study involving 17 PKU patients (age range: 9–35 years), nine of which were early-treated and six of these were still following a low-Phe diet. All but one of these patients had "symmetric high-signal intensity in the periventricular white matter of the posterior cerebral hemispheres, with extension into the frontal lobes in advanced cases only". No white matter abnormalities were identified in other brain regions and the basal ganglia appeared unaffected in all cases; however, mild cortical atrophy was seen in eight patients.

The findings of these early reports have been replicated in larger and more representative samples, and also in quite young and well-controlled children [14–26]. The largest cohort study using MRI scanned 77 adolescent and adult PKU patients (recruitment rate of 78%), with suitable images obtained for 74 cases [18]. The majority of the participants ($n = 70$) were early-treated (treatment commenced within 2 months), and most discontinued treatment at age 14 years. Some degree of white matter abnormality was observed in 71 (of 74) scans, with one normal scan and two with "equivocal changes". The MRI abnormalities were less severe for younger participants who were still on treatment in comparison to those who were off treatment.

In summary, the prevalence for white matter abnormalities is high [18,24], with most early-treated patients exhibiting at least mild high-signal intensity in the periventricular white matter [15,18,23]. The prevalence of the white matter abnormalities tends to be higher and more severe in older children [15,18], those who are off treatment [15,18,24], or those with high-Phe levels [15,17,18,22–24,27]. Further studies have also demonstrated that in more severe cases the white matter abnormalities can extend into subcortical regions [15–17,24], posterior limb of the internal capsule into the cerebral peduncles [17], brain stem [22], and cerebellum [22].

A major limitation of these studies is the reliance on qualitative measurements of pathology. Furthermore, the imaging sequences vary across studies, as do the protocols for assessing the presence and severity of white matter abnormalities. Finally, the majority of subjects examined by a number of these published studies (see Table 1) were in their second decade of life or older and longitudinal studies are still lacking. So, as the information based on structural studies is concerned, the age of the onset and the *natural* outcome of MRI white matter abnormalities remain to be explored. In spite of these constraints, the picture emerging from the literature of the last 20 years is striking, showing that over 90% of all PKU patients suffer from white matter abnormalities (Table 1), which were not associated with obvious neurological alterations.

Table 1
Cumulative data on structural white matter MRI abnormality in PKU without neurological deterioration.

Patients	312
Age range (years)	0.9–49
</> 11 years, *n*	23/172 (available data for 195/312)
PKU (Phe > 600 μM), *n*	300
Hphe (Phe < 600 μM), *n*	12
Early/late detected, *n*	254/58
On/off diet, *n*	107/205
Cognitive functioning (normal/abnormal), *n*	96/59 (available data for 165/312)
MRI white matter pathology (normal/abnormal), *n*	22 (7%)/290 (93%)

Data summarize patients reported in Refs. [13,14,16–26]. Numbers should be accepted with prudence, considering that it is not totally possible to rule out repeated enrollment of the same patient in more than one paper.