2. Physical Evidence for Altered Brain Function in PKU

Summary

- Scientists are currently gathering physical evidence to determine whether the current standard therapy involving a Phe-restricted diet and meeting blood Phe targets can still lead to changes in the brain.
  - Some of the physical evidence scientists have gathered involves brain scans. So far, the evidence shows that a large percentage of people with PKU may have some visible brain abnormalities, even when on diet. There is a reasonable correlation between the amount of brain abnormalities and life time Phe levels, the higher the Phe levels the more brain abnormalities.
  - However, it's not yet clear what these changes mean in terms of brain function.
    - Some researchers think that these changes may cause problems in how fast you can process information.
    - However, less than half of the people who have displayed brain abnormalities show any impairment in mental abilities, and these impairments are subtle.
    - The bottom line is that much more research is needed to understand the nature and impact of these brain-scan visual abnormalities in diet-controlled PKU.
  - Another form of physical evidence found that people with PKU may have lower levels of certain brain chemicals called neurotransmitters.
    - **The defective enzyme in PKU, PAH, has the job of changing some of the Phe you eat into a different amino acid called tyrosine (Tyr). Tyr is used to make a brain neurotransmitter (messenger) chemical called dopamine. Evidence suggests that changes in PAH function in PKU can cause lower amounts of dopamine in the brain.**
    - Some symptoms of low dopamine include drastic mood swings, difficulty paying attention and sleep disturbances.
  - Bear in mind that it is hard to do these studies, so there aren't that many documented cases. More physical evidence is needed to draw any conclusions. The jury is still out, but the evidence is piling up.

Altered brain white matter: Sophisticated imaging technology such as magnetic resonance imagining (MRI) has allowed scientists to take a peek at the brains of PKU patients. A recent review of MRI evidence in PKU has shown that 93% of the 312 brains of PKU patients investigated by MRI, 107 of which were still on a PKU diet*, showed abnormal white matter.[5] The white matter is mostly made up nerve fibers in your brain that send electrical signals to process information. It is called white matter because it appears white, mainly because of a white-colored insulating layer on your nerve fibers called the myelin sheath.

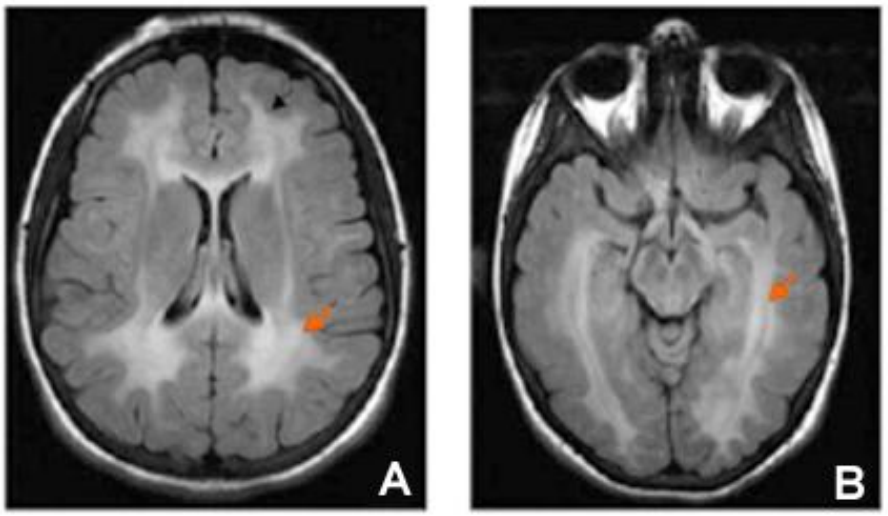
It's not yet clear what these changes mean in terms of brain function, but changes in white matter may cause information to be sent more slowly, causing thinking problems and slower information processing. It is worth mentioning that even though nearly all of the PKU patients studied thus far have been seen to have white matter abnormalities, only 38% of those studied showed any impairment of mental abilities, most of which were

subtle in nature.[5] Thus, much more research is required to understand the nature and impact of white matter pathology in PKU.

What is sure is that there is a reasonable association between the lifetime blood Phe levels and the amount of white matter abnormalities observed (the higher the Phe, the more abnormalities observed).[5] There is also preliminary evidence suggesting that a certain degree of white matter abnormality can be reversed if a stricter control of blood Phe levels is obtained for a prolonged period of time.[5]

Here is an example of an MRI showing white matter abnormalities in a 15-year-old girl early-treated and still on diet* who, despite having white matter abnormalities, presented normal mental and neurological development:[6]

*Authors of the publications only stated that the subjects were on a PKU diet; they did not report their lifetime blood Phe averages. It is assumed that these individuals were in metabolic control of their PKU.



Orange arrows show the "lighter area" of white matter abnormality in a diet-treated 15-year-old girl with PKU and normal mental and neurological development. [6]
A) represents white matter abnormalities in the frontal lobe of the brain.
B) represents white matter abnormalities in the temporal lobe of the brain.

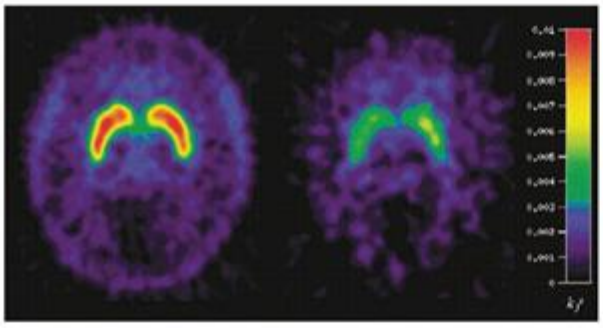
Reduced levels of brain neurotransmitters: Scientific evidence suggests that higher-than-normal blood phenylalanine (Phe) levels can reduce neurotransmitter levels in the brain of a person with PKU.[7] The defective enzyme in PKU, phenylalanine hydroxylase (PAH), has the job of changing some of the Phe you eat into a different amino acid called tyrosine (Tyr). Tyr is used to make a brain neurotransmitter (messenger) chemical called dopamine. Evidence suggests that changes in PAH function in PKU can cause lower amounts of dopamine in the brain.

Decreased dopamine levels may cause problems with motor function (controlling your muscles) and emotional state. Symptoms of low dopamine include drastic mood swings,

decreased libido (sex drive), difficulty paying attention and sleep disturbances. Illnesses such as Parkinson's disease and attention deficit/hyperactivity disorder (ADHD) have been linked to low dopamine levels in the general population. Although there is no evidence suggesting a higher incidence of Parkinson's disease in the PKU population, there is evidence of a higher frequency of ADHD-like symptoms in PKU.[8]

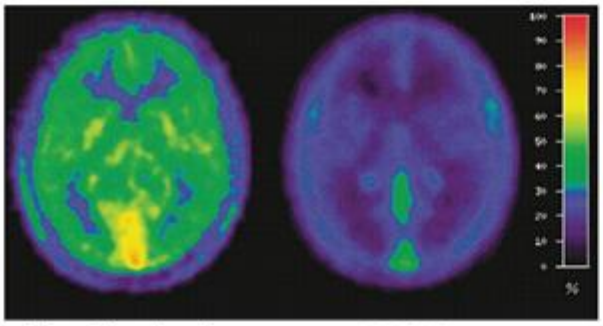
The following image shows that FDOPA (a fluorescent version of a chemical that is turned into dopamine in the brain) is not transported into or used by the brain of a person with PKU in the same way as by unaffected individuals. The fluorescent version was used so that it could easily be seen in the images.[9] The image of the PKU brain is an overall average obtained from imaging 7 patients with PKU (2 males, 5 females; age 21 to 27 years) selected to have no impairment in intellectual or neurologic function. The PKU patients imaged had adhered to a Phe-restricted diet until the age of 15 to 18 years, then abandoned the diet afterwards. The normal control group image was obtained from the average of 7 age-matched, healthy male volunteers (age 23 to 34 years).

FDOPA levels in the brain



In people with PKU, less FDOPA is taken up into the brain compared with unaffected people.

Use of FDOPA in the brain



In people with PKU, less FDOPA is used in the brain compared with unaffected people.

Unaffected people PKU