BAHAN AJAR IV

Phenylketonurias (Phenylalanine Hydroxylase Deficiency)

Nama Mata Kuliah/Bobot SKS	: Sistem Neuropsikiatri / 8 SKS
Standar Kompetensi	: area kompetensi 5: landasan ilmiah kedokteran
Kompetensi Dasar	: menerapkan ilmu kedokteran klinik pada sistem neuropsikiatri
Indikator	: menegakkan diagnosis dan melakukan penatalaksanaan awal sebelum dirujuk sebagai kasus emergensi
Level Kompetensi	: 1
Alokasi Waktu	: 1 x 50 menit

1. Tujuan Instruksional Umum (TIU) :

Mampu mengenali dan mendiagnosis penyakit-penyakit genetik dan kongenital serta melakukan penangan sesuai dengan tingkat kompetensi yang ditentukan, dan melakukan rujukan bila perlu.

2. Tujuan Instruksional Khusus (TIK) :

a. Mampu menyebutkan patogenesis terjadinya Fenilketonuria
b. Mampu melakukan promosi kesehatan dan pencegahan Fenilketonuria

Isi Materi;

BAB I

PENDAHULUAN

Phenylketonuria (PKU) is an inborn error of metabolism involving impaired metabolism of the amino acid phenylalanine. Phenylketonuria is caused by absent or virtually absent phenylalanine hydroxylase (PAH) enzyme activity.

Phenylketonurias is the most frequent of the aminoacidurias disease and occur of the late infantile and early childhood period. Since its discovery by Følling in 1934, it has remained the classic example of an aminoaciduria and illustrates three principles of medical genetics: first, it is inherited as an autosomal recessive trait; second, it exemplifies Garrod's cardinal principle of gene action, in which genetic factors specify chemical reactions as well as biochemical individuality; third, PKU is expressed only in an environment that contains an abundance of L-phenylalanine. Thus, as predicted by Galton, the ultimate phenotype is a product of "nature and nurture".

Patophysiology, Signs, and Symptoms

At birth, the typical PKU infant is believed to have a normal nervous system. The disease appears later, only after long exposure of the nervous system to phenylalanine (PA), because the homozygous infant lacks the means of protecting the nervous system. However, if the mother is homozygous with high PA levels in the blood during pregnancy, the CNS is damaged in utero and the heterozygous infant is mentally defective from birth.

The damage done to the brain if PKU is untreated during the first months of life is not reversible. It is critical to control the diet of infants with PKU very carefully so that the brain has an opportunity to develop normally. Affected children who are detected at birth and treated are much less likely to develop neurological problems or have seizures and intellectual disability (though such clinical disorders are still possible.)

In the classic form of PKU, the *impairment of psychomotor development* can usually be recognized in the latter part of the first year, when expected performance lags. By 5 to 6 years in an untreated child, when the IQ can be estimated, it is usually less than 20, occasionally 20 to 50, and exceptionally above 50. *Hyperactivity*, aggressivity, self-injurious behavior—including severe injury to the eyes, clumsy gait, fine tremor of the hands, poor coordination, odd posturings, *repetitious digital mannerisms* and other so-called rhythmias, and slight corticospinal tract signs stand out as the main clinical manifestations. Athetosis, dystonia, and frank cerebellar ataxia have been described but must be rare. Also, seizures occur in a small minority of severely affected patients (abnormal EEG finding), taking the form at first of flexor spasms and later of absence and grand mal attacks. The majority of PKU patients are blue-eyed and fair in skin and hair color, and their skin is rough and dry and subject to eczema. A musty or mousy body odor (because of phenylacetic acid

excretion) can often be detected. Two-thirds are slightly microcephalic. The fundi are normal, and there is no visceral enlargement or skeletal abnormality. In untreated phenylketonuria (PKU), deficiency of phenylalanine hydroxylase (PAH) results in elevated blood phenylalanine (Phe) concentrations and severe mental retardation.

There are some people living in the community with asymptomatic PKU and normal intelligence. Adult onset PKU is rare and if found, they developed a progressive spastic paraparesis, some with mild dementia. The phenylalanine levels were at values that reflect total or partial enzyme deficiency.

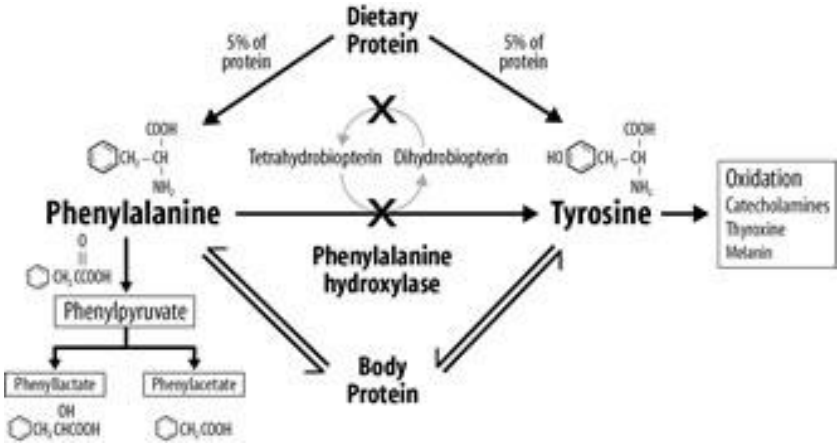

Figure 1. Metabolism of phenylalanin

Phenylalanine (phe) metabolism in phenylketonuria (PKU). As indicated by the "X", PKU results from mutations (over 800 have been identified) that affect the hepatic phe hydroxylase (PAH) enzyme needed for the hydroxylation of the indispensable amino acid phe to tyrosine. PKU may also result from mutations in the recycling of the essential PAH cofactor tetrahydrobiopterin. Due to these mutations which reduce the conversion of phe to tyrosine, phe accumulates in blood and is transaminated and decarboxylated into many compounds which appear in blood and urine; three of the compounds which are measured clinically are shown. Tyrosine, a precursor for multiple biological products, becomes an indispensable AA and must be provided by the diet for those with PKU. Under physiological conditions PAH catalyzes about 75% of the phe input from the diet and protein catabolism.

Diagnosis

The finding of *high levels of serum phenylalanine* (above 15 mg/dL) and of *phenylpyruvic acid in the blood*, *CSF*, *and urine* is diagnostic of PKU. The level is normal at birth and rises only after the first few days. But screening by the Guthrie (ferric chloride) test will reliably identify the patient at risk. The addition of 3 to 5 drops of 10 percent ferric chloride to 1 mL of urine is a simple and informative test. It yields an emerald-green color that reaches peak intensity in 3 to 4 min and fades in 20 to 40 min. In contrast, the green-brown color in the urine of patients with histidinemia is permanent.

Pathologic examination shows poor staining of myelin in the cerebral hemispheres. This can be visualized by MRI in untreated children. Another instructive feature is that the pigmented nuclei (substantia nigra, locus ceruleus, dorsal vagal motor) fail to acquire dark coloration because of a block in the production of neuromelanin. Reduction in size of cortical neurons and their dendritic arborizations is said to be demonstrable in some cases.

Treatment

If instituted in infancy, diets low but not totally lacking in PA can improve intellectual development (blood level should be maintained at 5 to 10 mg/dL). Careful dietary management may result in completely normal intellectual development. Once the neurologic picture unfolds, diet has little or no effect on the mental status but may improve behavior. Prolonged dietary treatment has many untoward effects and should be supervised by physicians and nutritionists experienced in its use; if too restricted, it may retard growth. This is particularly important, as it has been shown that intellectual impairment is greatest among children who were the earliest to abandon their diets, permitting the PA concentration to rise above 15 mg/dL, and least in children who maintained dietary control

the longest. Continued dietary treatment is probably necessary, but the degree of restriction of PA may be relaxed once the nervous system is fully developed. The precise degree of allowed restriction of dietary PA restriction is not known but many children, having been raised on a low PA diet, will have little or no difficulty in maintaining the restrictions into adulthood.

Bibliography

1. Adam’s and Victor’s 9th edition

2. de Groot MJ, Hoeskma M, Blau N, Reijingoud DJ, van Spronsen FJ. 2010. Pathogenesis of cognitive dysfunction in phenylketonuria: review of hypotheses. Mol Genet Metab. (99) 86-89

3. Ney DM. Metabolism and metabolic disease focus group. Department of Nutritional Sciences