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Personal view

Phenylketonuria: central nervous system and microbiome interaction

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Abstract

Phenylketonuria (PKU) is an autosomal recessive inborn error of metabolism characterized by increased phenylalanine (Phe) levels causing an inadequate neurodevelopment; the treatment of PKU is a Phe-restricting diet, and as such it can modulate the intestinal microbiome of the individual, generating central nervous system secondary disturbances that, added to the baseline disturbance, can influence the outcome of the disease.

Keywords

Phenylalanine, phenylketonuria, microbiome, glial cells, neurogenesis.

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Introduction

Phenylketonuria (PKU) is an autosomal recessive inborn error of metabolism characterized by dysfunctional or absent enzyme activity (phenylalanine [Phe] hydroxylase), altering the Phe primary pathway, increasing its levels and decreasing tyrosine levels, causing a decreased production of catecholaminergic neurotransmitters necessary for the adequate development of the individual [1, 2].

PKU treatment is the restriction of Phe from the diet, to avoid the production of phenylacetic acid and phenyllactic acid which would cause a detrimen-

tal effect on the central nervous system (CNS) secondary to: inflammatory response, oxidative stress and neurotransmitter synthesis disruption [1]; such changes affect white matter formation, posteriorly observed as disturbance of the cognitive functions in PKU individuals when compared to non-PKU individuals [2].

CNS and phenylketonuria

Glial cells are the most abundant cells of the CNS: the most numerous are astrocytes having a role in neurotransmission maintenance and brain development of the infant [3].

The increased Phe levels disrupt the normal flux of amino acids causing decreased protein synthesis with posterior repercussion on CNS development [1]. Wesonga et al. in 2016 observed that PKU patients with proper follow-up and treatment adherence had decreased white matter levels when compared to a control group [2].

Microbiome and CNS

Glial cell synthesis reaches a peak by 36-40 weeks of life, but gliogenesis occurs predominantly during the postnatal period; different factors influence the fetal life outcome, such as microbiome signals [4]. Microbiome modifications disrupt the normal CNS glial cells development, interfering with myelination of areas and leading to inadequate behavior/conduct disorders. Hoban et al. observed that microbiome changes can affect prefrontal cortex myelination [5], changes critical during the neurodevelopmental phase of the individual.

Microbiome composition interacts with CNS plasticity via the synthesis of brain-derived neurotrophic factor and synaptophysin, both involved in neuronal survival, synapsis plasticity and synapsis maturation [6].

Phenylketonuria diet and microbiome

Diet properties, such as plant-based versus animal-based, or the quantity of complex polysaccharides and fibers, are factors that modify the intestinal microbiome of an individual; depending on the substrates availability from the diet, specific taxa of bacteria generate diverse end-products such as volatile fatty acids, secondary bile acids, and others, affecting the microbiome environment and the health outcomes for the individual [7].

The backbone treatment in PKU is a Phe-restricted diet, achieved with low Phe formulas, generating microbiome modification in PKU patients when compared to healthy individuals. Pinheiro De Oliveira et al. in 2016 [8] reported such observation in a small sample research; PKU patients had higher levels of *Bacteroidetes* when compared to the control group. The dominant microbial phyla determine the outcome of nutrients obtained from the diet and specific compound utilization/degradation [9].

Microbiome and CNS interaction in phenylketonuria

Behavior and cognitive disturbance on PKU patients present neurotransmission disturbances because of Phe elevated levels [1, 2]. PKU treatment is a Phe-restricted diet, characterized by specific formulas and diet restriction after diagnosis [1]. Those interventions can modify the person's microbiome [8], induce neurogenesis and neuronal plasticity disturbance [5, 6]. Microbiome modifications depend on substrate availability [7], the posterior modification can diminish substrate availability with an increased intake. Neurotransmission depends on amino acids availability and so it's related to Phe levels and diet intake. When Phe levels regain their normal values, if amino acid levels remain inadequate, neurotransmission continues to be affected [9].

Conclusion

PKU affects brain development as an immediate effect of the elevated Phe levels and toxic compounds, and Phe-restricted diet induces microbiome changes that modify the availability of different amino acids for a proper neurotransmitter synthesis.

Declaration of interest

The Author declares that there is no conflict of interest. No funding was received for this paper.

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