Slightly imperfect: long-term cognitive outcomes of phenylketonuria

If left untreated, phenylketonuria (PKU) results in severe brain damage and lifelong mental impairment. Deficiencies in the actions of the enzyme phenylalanine hydroxylase results in the dual defects of high phenylalanine and low tyrosine levels. Newborn screening and early dietary management have nearly eradicated these harmful effects – almost, but not quite.

Louise Crossley and Peter Anderson clarify what it means to undergo lifelong treatment for PKU in terms of behavioral and cognitive function. The effects of the underlying disease are still apparent even in patients who undergo optimal therapy. PKU patients exhibit subtle signs of neuropsychological defects such as slower reaction time, memory impairment and lower academic achievement.

Why do these patients manifest so many subtle deficiencies despite treatment? To begin with, Crossley and Anderson examine the cognitive and behavioral outcomes for patients who receive early treatment. The first part of the article provides a comprehensive overview of how PKU patients compare with normal individuals, in terms of IQ, motor functioning, information processing, language, and other parameters. The key pattern that emerges from this detailed analysis is that the disease has subtle effects across all outcomes.

In the final part of the article, the authors explain how these neurocognitive deficits come about. Two complementary theories address this issue. The prefrontal dysfunction hypothesis suggests that low tyrosine levels result in depletion of dopamine, thus affecting the brain prefrontal cortex. This theory explains the multiple difficulties faced by PKU patients in the cognitive functions governed by this part of the brain; however, it cannot account for deficits in other cognitive domains. The white matter hypothesis provides an explanation for these additional observations. Those with high phenylalanine levels often have diffuse abnormalities in white matter as a result of dysmyelination. This impairs the speed of neural transmission, compromising other functional pathways within the brain.

What does this mean for the PKU patient? In general, most have a good quality of life and have to contend with only minor neuropsychological deficits. “Considerable variability exists in the PKU population with some individuals exhibiting exceptional cognitive abilities,” state Crossley and Anderson. In conclusion, they emphasize that “Close surveillance in relation to cognitive functioning, academic performance, and behavior of PKU patients is required, especially during childhood.”

References