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COMMENT

Looking back at the neonatal period in early-treated phenylketonuric patients

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Current research on the clinical outcome of phenylketonuria (PKU) patients has mainly explored the possible consequences of late exposure to high phenylalanine (Phe) levels in early-treated adult and elderly patients. However, despite the progressively earlier diagnosis and treatment of PKU, the neonatal and infancy periods remain the most vulnerable periods of the brain to Phe, which may cause permanent impairment of early- and late-emerging cognitive functions. The few studies that have measured Phe exposure during the first month of life, before metabolic control is achieved, confirm Phe exposure during the first month as a factor contributing to the final outcome of the disease.

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Phenylketonuria (PKU; OMIM #261600) is an inborn error of amino acid metabolism due to defects of the phenylalanine hydroxylase (PAH) enzyme (EC 1.14.16.1), which converts phenylalanine (Phe) to tyrosine.[1] Due to the neurotoxicity of Phe, which accumulates in brain tissue and biological fluid as a consequence of PAH defects, PKU is essentially a neurological disorder. Moreover, the selective age-related vulnerability of the brain to Phe makes PKU a prototypical model of neurodevelopmental metabolic disease.

Neonatal screening and early treatment with a Phe-restricted diet have radically changed the natural history of the disease. With the exception of age at treatment onset[2] and metabolic control quality (an estimation of brain exposure to high Phe levels), no other factors affecting the clinical outcome of the disease have been unequivocally identified.[3,4]

Since untreated PKU results in an impairment in higher cortical functions, the clinical monitoring of early-treated patients has been based on the assessment of neurocognitive functioning, as measured by intelligence quotient (IQ) and/or neuropsychological tests designed to explore several specific cognitive skills.

Despite normalization of the clinical phenotype with early and continuous treatment, considerable variability in neurological outcome, which is unexplained by the aforementioned variables, affects PKU subjects as a group.[5] In particular, (1) an undetermined, but relatively high, percentage of early-treated PKU patients have an IQ score lower than expected (with respect to controls or unaffected relatives)[6–8] and (2) clinically relevant neuropsychological impairment is found in about 25% of early and continuously treated PKU subjects.[8,9] The consequences of this alteration on quality of life, everyday executive functioning, and the adaptive skills of adults with PKU are not easy to evaluate and have been conversely emphasized by different authors.[9,10]

Among the early factors that may affect disease outcome, the latency in the attainment of a stable reduction in blood Phe to within the recommended range (currently 120–360 µmol/L) during the neonatal period has not been sufficiently explored in studies on PKU. As a matter of fact, in most cohort studies and metanalyses, the age at treatment onset, rather than the age at metabolic control achievement, was considered as a biomarker of the duration of early exposure to high Phe levels. In terms of clinical recommendations, the American College of Medical Genetics and Genomics stated that "initiation of treatment for PKU should be undertaken as early as possible, preferably within the first week of life with a goal of having blood Phe in the treatment range within the first 2 weeks of life."[11] European guidelines recommend starting dietary treatment early (by 10 days of age), and while they do not set a recommended age for the achievement of metabolic control, they are explicit that it should happen as soon as possible.[12,13]

While it is reasonable to believe that age at diet onset and age at metabolic control achievement are strongly correlated, several circumstances may result in a discrepancy between these two targets. Mild hyperphenylalaninemia may be an example: with a borderline level of blood Phe (with respect to the current diagnostic threshold) and while awaiting genetic confirmation, clinicians may decide to monitor the Phe trend rather than promptly starting diet therapy in order to avoid the risk of unnecessary treatment and an unconfirmed diagnosis. Moreover, sometimes the psychological impact of the diagnosis on the neonate's parents or caregivers may transiently undermine their capability to acquaint themselves with the procedures required for dietary treatment. Finally, the difficulties of the family in obtaining the required nutritional products due to local bureaucratic procedures should not be underestimated.

The critical importance of early metabolic control was proven by Smith et al. in 1990,[2] with the finding of a negative linear effect of age at treatment onset on childhood IQ at the age of 4 years. Extraordinarily rapid brain connectivity development in this early phase of neonatal and infant development makes the child's brain particularly vulnerable to neurotoxic effects of Phe, as evidenced by the persistent alterations in the postnatal developing

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component of visual and auditory evoked potentials in clinically normal PKU infants who started dietary therapy after the third week of life.[14] Moreover, in a longitudinal study on early executive function development in PKU subjects from 6 months to 7 years with controlled Phe levels (blood Phe 240–600 µmol/L), Diamond et al. detected a selective impairment in both working memory and inhibitory control in very young patients, which was related to Phe levels during the first month of life.[15] A rapid increase and fluctuation in Phe levels may contribute to undermining brain development in this early stage.[15,16]

In this issue, Lieburg and colleagues[17] contributed to this topic with a retrospective study aimed at assessing the effect of neonatal Phe exposure on IQ assessed in late childhood or adolescence. The authors enrolled a cohort of early- and continuously-treated young PKU patients with optimal metabolic control throughout the entire follow-up. To quantify both the Phe concentration and duration of Phe exposure as a single comprehensive measurement, the authors computed the area under the curve (AUC) of total blood Phe levels and blood Phe levels exceeding 360 µmol/L during the first month of life and 10-day subperiods, i.e., 0–10, 10–20, and 20–30 days, respectively. They found a negative correlation between the total AUC and the AUC above 360 µmol/L and IQ at the age of 10 years (range 6–18 years). Interestingly, neither the delay in days before metabolic control achievement nor diagnostic Phe values were independently related to outcome, suggesting the importance of the interaction between them. The influence of other explicative variables, such as lifetime metabolic control and Phe levels at the time of clinical assessment, was ruled out by the statistical analysis. The correlation between the AUC of the 10-day subperiods and IQ is also interesting, but its independent effect on outcome needs further confirmation. Despite being treated early and continuously, this patient cohort showed large variability in IQ, a finding that is generally consistent with other studies.

With regard to other possible factors that act during this early stage of brain development and influence outcome, the lowering of target levels of blood Phe closer to normal values (120 µmol/L) for optimal metabolic control remains an option. A low level of blood Phe may be more protective for young children in general or for those more vulnerable to Phe. A previous study by Jahia et al.[18] showed that cognitive performance of PKU patients with lifetime blood Phe <240 µmol/L at the age of 10 years overlapped with that of controls and was significantly better in several neuropsychological tasks than patients with blood Phe levels between 240 and 360 µmol/L, who in turn were less impaired than patients with lifetime Phe >360 µmol/L. Accordingly, several other metabolic measures, such as concurrent Phe, Phe variation, and lifetime and concurrent Phe:Tyr, were related to the accuracy and speed of a number of cognitive tasks and to each other. A few other studies reported similar results.[19,20] Both these studies addressed the problematic and unresolved distinction between hyperphenylalaninemias that require treatment and those that do not. Consensus-based guidelines/recommendations need to establish rigid decisional thresholds in order to direct each PKU patient to the safer therapeutic range. However, a continuous effect (as opposed to a threshold effect) between Phe levels that are far from normal levels and consequent transient and/or persistent neurological impairment cannot be ruled out, and neither can an age-specific (or individual-specific) gradient, which is probably the most realistic scenario.

In conclusion, while PKU research is mainly centered on identifying early and late predictive biomarkers and outcomes in adult and elderly PKU patients,[10,21,22] studying the very early period of life and early stages of the neonatal brain, when the cerebral circuitry necessary for the implementation of future complex skills is developing, may contribute to better understanding and improving the final outcome of PKU.

PKU is one of the most frequent rare diseases, affecting about 100,000 patients in countries with advanced healthcare systems. However, for many other rare diseases or even for more non-rare diseases, international cooperation has been developed to improve knowledge of the disease by implementing registries and supranational collaborative studies, which have contributed to better understanding critical disease aspects. In contrast, present studies on PKU are single-center studies or collaborative studies with <100 patients. Even 60 years after the implementation of neonatal PKU screening, present institutional research on PKU is still plagued by the paucity of systematic longitudinal studies and small sample sizes. The most problematic clinical aspects of the disease could be more appropriately addressed by a common collaborative effort.

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