Tyrosine monitoring in children with early and continuously treated phenylketonuria: results of an international practice survey

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Abstract

Investigations into the biochemical markers associated with executive function (EF) impairment in children with early and continuously treated phenylketonuria (ECT-PKU), remains largely phenylalanine-only focused. Despite experimental data showing that a high phenylalanine:tyrosine (phe:tyr ratio) is more strongly associated with EF deficit than phe alone. A high phe:tyr ratio is hypothesized to lead to a reduction in dopamine synthesis within the brain, which in turn results in the development of EF impairment. This paper provides a snapshot of current practice in the monitoring and/or treatment of tyrosine levels in children with PKU, across 12 countries from Australasia, USA and Europe. Tyrosine monitoring in this population has increased over the last five years, with over 80% of clinics surveyed reporting routine monitoring of tyrosine levels in infancy alongside phe levels. 25% of clinics surveyed reported actively treating/managing tyrosine levels (with supplemental tyrosine above that contained in PKU formulas) to ensure tyrosine levels remain within normal ranges. Anecdotally, supplemental tyrosine has been reported to remediate symptoms of both Attention Deficit Hyperactivity Disorder and depression in this population. EF assessment of children with ECT-PKU was likewise highly variable, with 50% of clinics surveyed reporting routine assessments of intellectual function. However when function was assessed, test instruments chosen tended towards global measures of IQ prior to school entry, rather than specific assessment of EF development. Further investigation of the role of tyrosine, its relationship with phe and EF development, is needed to establish whether routine tyrosine monitoring and increased supplementation is recommended.
One sentence synopsis: The treatment of child patients with PKU with supplemental tyrosine to normalize tyrosine levels and/or remediate executive function impairment is an emerging practice in some metabolic clinics.

Keywords: Phenylketonuria; executive function; phenylalanine; tyrosine; phe:tyr ratio; dopamine
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PKU detection in the neonatal period and the medically prescribed dietary treatment has resulted in one of the great success stories from last century for the effective prevention of neurological disability. Improvements in dietary management and formulas since the 1960’s have been associated with steadily improving outcomes in intellectual functioning, as measured by standard I.Q. scores. Children with early and continuously treated PKU born from 1980’s onwards, should develop an I.Q. within the normal range (Burgard, 2000).

Despite these improvements, children with early and continuously treated phenylketonuria (ECT-PKU) continue to be at increased risk for developing certain executive function (EF) deficits. EF directs purposeful, adaptive behaviors and the regulation of mood. EF specifically encompasses skills in integration of information across time and space, task switching, self monitoring, abstract and predictive reasoning, and working memory. The current population of children with ECT-PKU continue to show high levels of EF impairment, particularly in processing speed and working memory, resulting in a diagnosis of Attention Deficit Disorder diagnosis up to five times the norm (Antshel & Waisbren, 2003; Arnold et al., 2004; Huijbregts et al., 2002a).

Most studies indicate that EF worsens with higher exposure to phe and that high levels of phe, earlier in childhood and across longer periods of time, correlate with steadily worsening EF (for a review and meta-analysis see Waisbren et al., 2007). Secondary problems arising from the biochemistry associated with PKU are thought to primarily affect the dopaminergic systems in the brain due to the disruption of the
metabolism of phe to tyrosine, a precursor to dopamine (Diamond, 1997). Experimental
data suggests that high phe in concert with low tyrosine (a high phe:tyr ratio) may better explain EF deficits in children with PKU than phe levels alone (Diamond et al., 1997; Luciana et al., 2001; Sharman et al., 2009; 2010). However, the potential role, of the phe:tyr ratio on brain development has yet to be extensively researched because the focus of most studies involves phe only measures, i.e. concurrently, historically, or both (e.g., Antshel & Waisbren, 2003; Arnold et al., 2004; Huijbregts et al., 2002ab).

**Clinical applications of the dopamine hypothesis**

The phe:tyr ratio in the non-PKU population is approximately 1:1 (Hilton et al., 1986) whereas phe:tyr ratios in the PKU population generally start at around 2.5:1 and can increase to well above 10:1 (Chace et al., 1998). Sharman et al. (2010) recently reported a clinical level of lifetime phe:tyr ratio that was associated with impaired EF. In this sample of children (n=13; age range 10 – 17 years), a phe:tyr ratio above 6:1 was significantly and strongly associated with executive function impairment. Further, improved EF was observed in children with the lowest lifetime phe:tyr ratios.

**Tyrosine and EF**

A question remains as to why a high phe:tyr ratio is strongly related to EF impairments, given that low tyrosine on its own has not yet shown such an association. Mixed results have emerged from past ECT-PKU studies that included increased tyrosine supplementation as a variable (see Cochrane review: Poustie and Rutherford, 1999). It is also important to note that some researchers have questioned the validity of tyrosine treatment (van Spronsen et al., 2001). Nonetheless, there are emerging reports that treatment with tyrosine (over and above that contained in PKU formula) is specifically
being used as an adjunct therapy to improve the EF of children with PKU who display deficits. For example, Posner et al. (2009) describe the successful use of supplemental tyrosine to remediate ADHD symptoms in a child with PKU.

Current Clinical Practice

Despite the emerging evidence regarding the potential role of tyrosine in the development of neuropsychological deficits in children with PKU, the extent to which the phe:tyr ratio and/or tyrosine levels are routinely monitored and/or treated in this population of children is largely unknown. Given this possible gap between current understanding and actual practice at the clinical level, the purpose of the following survey was to collect a brief snapshot of tyrosine monitoring and management in children receiving treatment for PKU in metabolic clinics.

Method

A short (20 question) web-based survey was developed to capture information about current clinical practice in the measurement and/or treatment of tyrosine levels in children with PKU, as well as any anecdotal information from clinics as to the perceived usefulness of tyrosine screening and treatment.

Procedure

The survey was emailed directly to all metabolic clinics across Australia and New Zealand where the research team is based. The same survey was also sent to the SSIEM National President/Secretary of each member nation requesting that the survey be forwarded to the clinics in their region that managed children with PKU.

Participants
In total, 20 clinics from 12 countries responded to the survey. Clinics were given the option to identify from which country they were responding. Those respondents who chose to identify their country of origin were located in Australia, Austria, Canada, Ireland, Italy, New Zealand, Spain, Sweden, Switzerland and the United States of America. Surveys were completed by the consultant metabolic physician (n=17) or metabolic dietician (n=3). The median number of children managed by each clinic was 60 (Mean = 105); with a range of 12 – 500.

Results

Current Phe-screening protocols

As a reference point in terms of consistency of screening protocols for children with PKU internationally, clinics were first asked to indicate both their recommendations to patients regarding frequency of phe- monitoring and the actual frequency of phe-monitoring for each age range. Questions regarding phe and tyrosine monitoring were split into three age groups according to the Australian Society for Inborn Errors of Metabolism [ASIEM] guidelines (Infants 0 – 12 months; Children 1 – 12 years; Adolescents 12 – 18 years).

Agreement between clinics in recommended frequency of phe- monitoring was high. During infancy, 80% of clinics both recommended and reported adherence to phe-monitoring every 1 – 2 weeks, the remaining 20% of clinics recommended and received monthly phe- monitoring. Phe monitoring during childhood was decreased to monthly by the majority (75%) of clinics. The beginning of attrition from recommended screening frequency in some patients/parents began during childhood, with 40% of patients providing blood samples less frequently than requested. By adolescence,
80% of clinics recommended monthly phe-monitoring, the remainder quarterly, however, on average, only 30% of adolescents adhered to the recommended frequency of phe-monitoring.

42% of clinics nominated either their own country’s guidelines or international guidelines as their primary reference point regarding “safe” phe levels recommended to patients. 15% of clinics cited their “own guidelines” and/or “clinical experience” as their reference point. The remaining clinics listed the cut-offs they used but did not nominate where those figures came from (i.e. formal guidelines). One clinic acknowledged they were unsure of the reference and another noted that they disagreed with the National Institutes of Health [NIH; 2000] consensus statement regarding appropriate phe levels.

Biochemical markers and cognitive outcomes

Clinicians were also asked to nominate which biochemical markers they believed best predicted cognitive outcomes in children with PKU. Clinicians were able to select more than one option (i.e. these results will not sum to 100). 55% of clinics stated they believed that lifetime phe levels best predicted cognitive outcomes in children with PKU; 55% nominated phe levels prior to age 12 years; 5% stated phe:tyr ratio and 15% nominated that all biochemical markers (phe and tyr across childhood) as important to a similar degree.

Tyrosine monitoring/treatment

In comparison to phe-monitoring practices, frequency of tyrosine monitoring was highly variable, both within countries and internationally. Tyrosine monitoring at least monthly has clearly been on the rise during the last 5 years, with over 80% of clinics now routinely monitoring tyrosine levels in infancy. Figure 1 shows the comparison of
tyrosine monitoring practices from over 5 years ago, compared to the during the last 2 years.

25% of clinics reported that they supplemented paediatric patients with tyrosine over and above that contained in PKU formula if their tyrosine levels dropped below “normal” levels. Clinics that recommended optimal tyrosine levels to patients stated they did so, on the basis of: the normal reference point from laboratory; published data; and clinical concerns regarding neurotransmitter function.

Clinical situations/scenarios that were described as requiring supplemental tyrosine treatment included those with persistently low tyrosine levels; and younger children with optimal phe levels. One clinic nominated 1 gram tyrosine per day as a practical start, other clinics used the “smallest amount” or “whatever” was necessary to shift the tyrosine level back into normal range. The only contraindications to tyrosine supplementation noted were if the patient was allergic to tyrosine (sic); or if dietary control was already good.

*Reported side effects/benefits of tyrosine supplementation*

Those clinics who used supplemental tyrosine reported no noticeable adverse effects; likewise most reported no clinical improvement apart from one physician who noted that tyrosine supplementation appeared to improve mood *if* the patient had been exhibiting signs of depression in the first place. One clinic made the observation that in
their experience, if PKU formula was adhered to and phe levels within guidelines, tyrosine regulation was not observed to be necessary.

Neuropsychological data

50% of clinics reported routine assessments of cognitive function and/or psychological function during childhood. The other 50% reported no routine assessments. Assessments were mostly global measures of IQ and conducted prior to school entry.

Discussion

This practice survey provides a snapshot of current clinical practice, primarily to ascertain current protocols regarding tyrosine monitoring/treatment in children with ECT-PKU and any anecdotal information from clinics regarding their experience with the same. Whilst some caution in interpreting this data is warranted because results will not generalize to all clinics, the findings suggest that tyrosine screening and treatment practices are highly variable both internationally and within countries. This finding is consistent with recent practice surveys (van Spronsen et al., 2009). Approximately half the clinics surveyed did not routinely assess cognitive/neuropsychological function in their patients, and when they did, the test instruments chosen may not include those specific measures of EF known to be the primary deficit now observed in children early and continuously treated for PKU.

Whilst the veracity of tyrosine supplementation to a) restore poor tyrosine levels to normal or b) improve (lower) the phe:tyr ratio has yet to be convincingly demonstrated, 25% of metabolic clinics from our practice survey were pursuing this as a treatment strategy for patients. As some clinics are already utilising this treatment
strategy, further research is needed to determine if, and to what extent, manipulating tyrosine levels back to normal or to improve the phe:tyr ratio, is advisable as an additional treatment strategy for patients with PKU.
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References


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