Phenylketonuria (PKU) has been associated with neurocognitive deficits possibly due to: (1) the direct effects of hyperphenylalaninaemia, (2) the indirect reduction of neurotransmitter and (3) defective protein synthesis, (4) white and grey matter anomalies and/or (5) oxidative stress caused by a defective phenylalanine hydroxylase (PAH) enzyme. It has been reported that children with PKU who are treated early and continuously with a phenylalanine (Phe)-restricted diet and/or have lowered blood Phe, have improved neurocognitive outcomes.

Sapropterin (KUVAN®, BioMarin Pharmaceutical Inc., Novato CA USA), a synthetically-prepared salt of naturally occurring tetrahydrobiopterin (BH4) and a co-factor for PAH, is known to reduce blood phenylalanine (Phe) in BH4-responsive patients [2]. Sapropterin treatment is associated with improvements in both working memory and brain activation [3]. It is not known if sapropterin is associated with improvements to other executive function domains in patients with PKU.

The executive cognitive functions are a collection of mental processes responsible for purposeful, goal-directed, problem-solving behavior [1]. The Behavior Rating Inventory of Executive Function® (BRIEF) assessment measures the extent to which corresponding reports problems with the various domains of executive functioning (e.g., Inhibit, Shift, Emotional Control, Self-Monitor, Initiate, Working Memory, Plan/ Organize, Task Monitor, Organization of Materials). BRIEF is a reliable and validated diagnostic tool for the evaluation and treatment of executive control dysfunctions when used in conjunction with psychological, neuropsychological, and other clinical assessments.

**METHODS**

A retrospective chart review was performed using data from twenty-nine (29) patients with PKU at the PKU Program and Metabolic Screening Coordination Centre for New Brunswick, Moncton, New Brunswick, Canada and at the Ann & Robert H. Lurie Children’s Hospital of Chicago, Chicago IL, United States. For patients in New Brunswick (Moncton Clinic), blood Phe is collected at home or during clinics using capillary blood directly deposited on filter paper cards. These are sent out by mail to the IWK Health Centre Lab in Nova Scotia for analyses using Tandem Mass spectrometry. For patients in Lurie Children’s Hospital, blood samples for blood Phe are collected at home or during clinic using capillary blood directly deposited on filter paper cards. The filter cards are sent to a laboratory and analyzed using ion chromatography.

All patients were tested, by self-evaluation and/or by evaluation by an informant, using a BRIEF assessment and some patients had multiple assessments. After the screening test(s), sapropterin was administered a dosage of 10-20 mg/kg per day (mean: 19.6 mg/kg/day) to each patient (according to the standard of care) before patients were again evaluated with a final BRIEF assessment. Some patients had multiple pre- and post-sapropterin BRIEF assessments and not all sub-assessments were conducted with each patient. All BRIEF T-scores were adjusted for age and gender. BRIEF scores ≤ 50 are considered normal, scores > 50 ≤ 65 are considered indicative of mildly elevated and areas of concern, and scores > 65 are considered abnormally elevated and clinically significant.

Pre-sapropterin and post-sapropterin BRIEF assessment percentile scores were compared and significance was assessed by paired t-test. For correlation of self-reported vs. informant-reported scores and their corresponding differences, a two sample t-test was performed. For factor analysis, a regression analysis was performed. P-values < 0.05 are considered significant.

**RESULTS**

Table 2 and Figure 1 shows the averaged BRIEF results of the pre-sapropterin, post-sapropterin, and the difference between the two mean scores. Most of the differences were statistically different and some of the subjects showed improvements up to 50 percentile points while others showed declines in the post-sapropterin percentiles of up to 18 percentile points. The overall average delta percentile was -4.0 ± 1.7 percentile.

For sapropterin treatment, metabolic and cognitive benefits were noted in 50% of patients, with improvements in both working memory and brain activation [3]. It is not known if sapropterin is associated with improvements to other executive function domains in patients with PKU.

**OUTCOMES PER PKU SEVERITY**

Subjects with non-classic/other PKU showed general improvement in post-sapropterin Global Executive Composite BRIEF scores (range: 2 to -27 percentile changes, N=10). Ten subjects with classic PKU also showed improvements in post-sapropterin Global Executive Composite BRIEF scores (range: -3 to -29 percentile changes, N=10), whereas seven others with classic PKU did not show improvement in global executive composite scores (range: 0 to 11, N=7).

**CONCLUSION**

The data suggests that sapropterin at a mean dose of 19.6 mg/kg/day is associated with improvements in executive function domains in patients with PKU when evaluated using the BRIEF assessment.

*The data show a consistent pattern of generally higher pre-sapropterin BRIEF scores and generally lower post-sapropterin BRIEF scores for each of the cognitive domains (Figure 1).*

*The average post-sapropterin BRIEF assessment showed clinical improvement (average percentile range: -1.1% to -7.2%). However, specific patients with PKU show up to a 50% improvement in certain executive function scores after taking sapropterin (Table 2).*

*Impairments of executive function are one of the most consistent findings of persons with PKU [4]. Sapropterin treatment might be useful for some individuals with PKU to optimize care and improve quality of life.*

*Except for Inhibit (significant for duration of sapropterin exposure) and Metacognition Index (significant for baseline Phe pre-sapropterin), the results were not significantly affected by any one single factor: i.e., age, at screen, duration of sapropterin exposure, pre-sapropterin Phe, Post-sapropterin Phe, or PKU type (Table 3). This suggests that some other factor (or combination of factors) predict sapropterin patient benefit. Further research is warranted on lifetime Phe exposure, longer duration of sapropterin exposure, index of dietary control, and/or the type of patient with PKU whose executive function is likely to benefit from sapropterin treatment – especially because some patients with classic PKU showed a post-sapropterin benefit in their Global Executive Composite scores.*

**REFERENCES**


