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Is BRIEF a useful instrument in day to day care of patients with phenylketonuria?

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ABSTRACT

Objectives: Despite early and continuous treatment many patients with phenylketonuria (PKU) still experience neurocognitive problems. Most problems have been observed in the domain of executive functioning (EF). For regular monitoring of EF, the use of the Behavior Rating Inventory of Executive Function (BRIEF) has been proposed. The aim of this study was to investigate whether the BRIEF is indeed a useful screening instrument in monitoring of adults with PKU.

Study design: Adult PKU patients (n = 55; mean age 28.3 ± 6.2 years) filled out the BRIEF-A (higher scores = poorer EF) and performed computerized tasks measuring executive functions (inhibition, cognitive flexibility, and working memory). The outcome of the BRIEF-A questionnaire was compared with the neurocognitive outcome as measured by three tasks from the Amsterdam Neuropsychological Tasks (ANT).

Results: Forty-two percent of the PKU patients scored in the borderline/clinical range of the BRIEF-A. Six of the 55 patients (11%) scored >1 SD above the normative mean, mostly on the Metacognition Index. With respect to ANT measurements, patients mainly showed deficits in inhibitory control (34–36%) and cognitive flexibility (31–40%) as compared to the general Dutch population. No significant correlations between the two methods were found, which was confirmed with the Bland–Altman approach where no agreement between the two methods was observed. Only with respect to inhibitory control, patients scored significantly worse on both BRIEF-A and ANT classifications. No other associations between classification according to the BRIEF-A and classifications according to the ANT tasks were found.

Conclusions: Patients reporting EF problems in daily life are not necessarily those that present with core EF deficits. The results of this study suggest that regular self-administration of the BRIEF-A is not a sufficient way to monitor EF in adult PKU patients.

Abbreviations: PKU, phenylketonuria; PAH, phenylalanine hydroxylase; Phe, phenylalanine; Tyr, tyrosine; EF, executive functions; BRIEF, Behavior Rating Inventory of Executive Function; ANT, Amsterdam Neuropsychological Tasks; BRIEF-A, Behavior Rating Inventory of Executive Function – Adult version; BRI, Behavioral Regulation Index; MI, Metacognition Index; GEC, Global Executive Composite; SSV, Shifting Attentional Set Visual; SAD, Sustained Attention Dots; FI, Feature Identification.

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1. Introduction

Phenylketonuria (PKU; OMIM 261600) is an inborn error of phenylalanine metabolism [1,2], affecting about 1 in 18,000 newborns in The Netherlands [3]. PKU is caused by a mutation within the gene encoding the hepatic enzyme phenylalanine hydroxylase (PAH), normally converting phenylalanine (Phe) into tyrosine (Tyr). Biochemically, the defect is characterized by increased blood and tissue concentrations of Phe and normal to decreased Tyr concentrations.

Untreated PKU is characterized by neurological and behavioral problems, such as severe mental retardation, epilepsy, developmental delays, and anxiety disorders [4,5]. Outcome is clearly related to blood Phe concentrations [6,7]. Since the introduction of the neonatal screening for PKU in 1974 in The Netherlands, early diagnosis and treatment are feasible and have reduced most of the neurological problems [2].

Current treatment mainly consists of a Phe-restricted diet reducing the intake of natural protein with, in addition, a synthetic amino acid mixture devoid of Phe and enriched with Tyr. Some patients benefit from large doses of the natural cofactor of PAH by treatment with tetrahydrobiopterin (BH_4) [2]. Even with early and continuous treatment and Phe levels within the target range, PKU patients still score 4–8 IQ points lower and present with neurocognitive, social, and emotional problems compared to the general population [8–10]. Most problems in PKU patients have been observed in the domain of executive functions (EF) [11].

EF encompasses complex brain processes responsible for the management of neurocognitive functions, which control goal-oriented behavior and problem solving abilities. Problems with EF can express themselves in decreased concentration, learning problems, impulsivity, and inappropriate behavior due to alterations in the prefrontal cortex and associated brain regions [11–13]. An article of Waisbren and White in this journal suggested the Behavior Rating Inventory of Executive Function (BRIEF) as a reliable screening method to identify and monitor aspects of daily executive dysfunctioning in patients with PKU [14]. The BRIEF is an easy and frequently used standardized questionnaire to assess executive functioning and can also be administered by non-psychologists. However, there is little agreement about the domains of impairment in studies with early-treated PKU patients using the BRIEF [15–17], while there is also only one known study that has compared the BRIEF with neuropsychological measurements of EF in PKU [15]. In that study four different EF measures (i.e., Contingency Naming Test, Rey Complex Figure, Tower of London, and Controlled Oral Word Association Test) were compared with scales of the BRIEF. Only very modest correlations between the BRIEF and scores on these paper-and-pencil tasks were shown, indicating that different constructs within EF were measured.

Therefore, in the current study we compared the BRIEF-A questionnaire with the neurocognitive outcome as measured by the Amsterdam Neuropsychological Tasks (ANT, De Sonneville [18]), a computerized test battery that has been used in a series of studies examining neurocognitive functioning in early and continuously treated PKU patients of different ages [19–28]. The ANT has consistently shown Phe-related EF problems in PKU. However, performing the ANT is time consuming and the test battery can only be administered by trained professionals. This, in turn, may be particularly problematic for adults with PKU, who generally visit the clinic less frequently than children. Therefore, a questionnaire such as the BRIEF, which is relatively easy and quick to fill out, and which is able to signal EF-problems, could indicate whether more intensive and specific neuropsychological testing is required. The central, underlying question of this study is whether the BRIEF-A is a useful screening or monitoring instrument in day to day care of adults with PKU.

2. Material and methods

2.1. Participants

Fifty-five Dutch adult PKU patients (25 male, 30 female) participated in this study. All patients were born after the introduction of the neonatal screening in The Netherlands in 1974 and were screened for PKU within one week after birth. Patients were treated early (<1 month after birth) and continuously, at least up to 12 years of age. In The Netherlands, target Phe concentrations between 120 and 360 μmol/L are recommended for the first 12 years of life, however during adolescence and adulthood most patients exceeded the recommended upper target Phe concentrations. The average age of the patients was 28.3 years (SD 6.2 years, range 18.7 to 40.0 years). Concurrent Phe (658 ± 347, range 66–1550 μmol/L) and Tyr (50 ± 18, range 24–94 μmol/L) concentrations on the day of testing were available for 53 out of 55 patients.

All patients met the National Institutes for Health (NIH) diagnostic criteria for hyperphenylalaninemia (HPA) or PKU. Treatment consisted of a Phe-restricted diet and/or BH_4 administration. Patients with IQ below 80, medical conditions other than PKU with known effects on neurocognitive and social functioning or usage of medication that could influence neurocognitive functioning were excluded from participation in this study.

Patients from six university medical centers in The Netherlands were included: University Medical Center Groningen, Academic Medical Center Amsterdam, Maastricht University Medical Center, Radboud University Medical Center Nijmegen, Erasmus University Medical Center Rotterdam and University Medical Center Utrecht. This study is part of the PKU-COBESO study, which examines cognitive functions, behavioral problems and social functioning in early and continuously treated PKU patients in relation to metabolic control [26]. National approval has been given by the medical ethics committee of the University Medical Center Groningen in The Netherlands and the study has been registered in the CCMO Register (NL38932.042.11). Participants gave written informed consent to participate in the study after procedures had been fully explained. All procedures were performed according to standardized protocols.

2.2. Measurements

The Behavior Rating Inventory of Executive Function — Adult version (BRIEF-A) was used to measure executive functioning in daily life of the adult PKU patients [29,30]. The questionnaire consists of 75 questions, assessing nine subdomains of executive functioning: inhibit, shift (Cognitive Flexibility), emotional control, self-regulation, initiate, working memory, plan/organize, organization of materials, and monitor. The four subdomains inhibit, shift, emotional control and self-regulation together determine the Behavioral Regulation Index (BRI). Furthermore, the combined scores of the other five mentioned executive functions represent the Metacognition Index (MI). The Global Executive Composite (GEC) is the total score of all nine subdomains and represents the overall executive functioning in daily life.

Individuals with a T-score ≤ 50 are considered to have normal executive functions based on a healthy Dutch and Flemish population between 18 and 65 years old. A T-score between 50 and 65 is regarded as increased or borderline, and a T-score above 65 indicates clinical significance (clinical range). In this study 23 out of the 55 patients (42%) had a score in the borderline/clinical range (T-score > 50). However, in order to be able to optimally compare the BRIEF-A and the ANT, a score of 1 SD above the normative mean was used for both tests in our main analyses. Thus, for these analyses a T-score ≥ 60 was used to make a distinction between patients with normal EF and patients with problems in executive functioning.

For the present study, three tasks from the computerized test battery ANT were included to measure the executive functioning of the