Molecular Genetics and Metabolism 99 (2010) S96–S99

Contents lists available at ScienceDirect

Molecular Genetics and Metabolism

journal homepage: www.elsevier.com/locate/ymgme

Screening for cognitive and social–emotional problems in individuals with PKU: Tools for use in the metabolic clinic ☆

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ARTICLE INFO

Article history:
Received 21 September 2009
Received in revised form 25 September 2009
Accepted 5 October 2009

Keywords:
Phenylketonuria
PKU
Assessment
Outcomes
Psychology
Cognition
Emotion
Social

ABSTRACT

Cognitive deficits, learning difficulties, and emotional problems occur at significantly higher rates in individuals with phenylketonuria (PKU) than in the general population. The relationship between elevated blood phenylalanine (Phe) levels and the severity of these problems often remain unrecognized. Children and adults with PKU require ongoing screening so that referrals to psychologists or psychiatrists familiar with metabolic disorders can be made when necessary for in-depth evaluation and treatment. To identify screening instruments that can be used by non-psychologists as well as psychologists, a group of 10 psychologists and a psychiatrist in the United States with expertise in neuropsychological assessment and PKU proposed a Uniform Assessment Method for PKU. Questionnaires were selected that reliably detect problems in adaptive behavior, executive function, and emotional well-being, representing the most vulnerable areas for individuals with PKU. These questionnaires are appropriate for individuals from infancy through adulthood, may be administered in less than 1 h, have computerized scoring accessibility, have no practice effects, and are available in Spanish and English. In addition to assessing function at a single point in time, the screening measures may be administered at each clinic visit to assess changes in function related to metabolic status or treatment (e.g., Phe-restricted diet, food supplements). The following questionnaires comprise the Uniform Assessment Method for PKU: for 0–2 years, Adaptive Behavior Assessment System – Second Edition (ABAS-II); for 2–17 years, Behavior Rating Inventory of Executive Function (BRIEF) and Behavior Assessment System for Children – Second Edition (BASC-II); and for adults, BRIEF, Beck Anxiety Inventory (BAI), and Beck Depression Inventory – Second Edition (BDI-II). In addition to long-term monitoring of outcomes in PKU, this uniform screening approach facilitates PKU research, as data may be pooled across multiple clinics using a consistent battery of assessment measures.

Introduction

Untreated phenylketonuria (PKU; OMIM 261600 and 261630)[1] results in mental retardation, microcephaly, autistic behavior, eczema, and seizures [1]. Newborn screening for this metabolic disorder and the introduction of a low-phenylalanine (Phe) therapeutic diet for infants diagnosed with PKU prevents the most serious consequences. This nearly 50-year-old PKU management strategy is still considered the standard of care and is hailed as a success story for treatment of inborn errors of metabolism. However, cognitive and social–emotional problems occur at higher frequencies in the PKU population than in the general population, even in early- and continuously-treated individuals.

Although cognitive problems are observed in other chronic disease populations such as type 1 diabetes (T1D) [2,3] and early-treated hydrocephalus [4], individuals with PKU fare significantly less well. A study comparing PKU with diabetes demonstrated that the PKU group ($n = 38$) had a significantly ($P < 0.006$) higher frequency of treatment for attentional dysfunction (26%) [5]. Another study comparing early-treated children with PKU ($n = 44$) and children with early-treated hydrocephalus ($n = 45$) to healthy controls ($n = 80$) demonstrated that a significantly higher proportion of

☆ *References to electronic databases:* Phenylketonuria, OMIM 261600 and 261630.*Financial disclosures:* D. A. White and S. Waisbren serve as consultants for BioMarin Pharmaceutical Inc.

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[1] *Abbreviations used:* PKU, phenylketonuria; Phe, phenylalanine; ABAS-II, Adaptive Behavior Assessment System-Second Edition; BRIEF, Behavior Rating Inventory of Executive Function; BASC-II, Behavior Assessment System for Children-Second Edition; BAI, Beck Anxiety Inventory; BDI-II, Beck Depression Inventory-Second Edition; GAC, General Adaptive Composite; GEC, Global Executive Composite; ISCI, Inhibitory Self-Control; FI, Flexibility; EMI, Emergent Metacognition; ADHD, Attention Deficit Hyperactivity Disorder; BRIEF-A, BRIEF Adult Version.

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doi:10.1016/j.ymgme.2009.10.006

individuals in the PKU group (21%) received scores in the severe deficit range in terms of executive functioning compared to the hydrocephalus (18%) and control group (5%) [6].

Other studies highlight the frequency of executive function deficits [7,8], school problems [9,10], and social–emotional issues [11–13] in individuals with PKU. Historically, these cognitive and social–emotional problems have been under-diagnosed or insufficiently treated in many metabolic clinics. In addition, access to psychologists familiar with metabolic disorders is limited in many metabolic clinics.

A group of 10 psychologists and a psychiatrist in the United States addressed the need to develop a uniform psychological assessment battery of tests that could be administered by non-psychologists as well as psychologists to reliably screen for cognitive and social–emotional problems in individuals with PKU. This assessment battery supplements current treatment assessments based on blood Phe measurements and provides information on treatment outcomes, including effectiveness of diet prescriptions, medications, and psychological interventions. The uniform assessment tools selected also permit the detection of modest changes in function over time and provide adequate normative data so that individuals at risk may be reliably identified.

The group of professionals selecting tests for the uniform assessment battery used the following criteria:

- Applicability for all ages.
- Inclusion of psychological domains with deficits known to occur in PKU.
- Ease of administration and scoring by non-psychologists.
- Published reliability and validity of data.
- Up-to-date normative samples.
- No practice effects.
- Brief administration time.
- Cost efficiency.

The resulting Uniform Assessment Method for PKU can be administered every time an individual with PKU attends a metabolic clinic to assess changes in function that may be related to treatment strategies or Phe levels. The age of the individual with PKU is taken into consideration because standard scores (not raw scores) are used. Table 1 lists the domains assessed and the names of the instruments to be used for each age group.

Adaptive Behavior Assessment System – Second Edition (ABAS-II) [14]

The ABAS-II is the only instrument selected for infants 0–2 years of age. There are 193 items that can be completed in approximately 20 min. The ABAS-II standardization samples include 1350 respondents for the infant-preschool parent/primary caregiver form. Reliability coefficients are approximately 0.90, and inter–rater correlations are high (generally above 0.80 for each scale). In terms of validity, correlations between the ABAS-II and the Vineland adaptive behavior scales are moderate to high, with a correlation of 0.70 between the ABAS-II general adaptive composite (GAC) and the Vineland adaptive behavior composite. The correlation between the ABAS-II GAC and the Behavior Assessment System for Children – Second Edition (BASC-II) Adaptive Skills Composite is 0.80.

Table 1
Uniform assessment method for PKU summary.

Psychological domain	Infants (0–2 years)	Children (3–17 years)	Adults (⩾18 years)
Adaptive behavior	ABAS-II	–	–
Executive functioning	–	BRIEF-P or BRIEF	BRIEF-A
Social/emotional functioning	–	BASC-II	BAI, BDI-II

ABAS-II, Adaptive Behavior Assessment System – Second Edition; BRIEF, Behavior Rating Inventory of Executive Function; BRIEF-P, Behavior Rating Inventory of Executive Function Preschool Version; BRIEF-A, Behavior Rating Inventory of Executive Function Adult Version; BASC-II, Behavior Assessment System for Children – Second Edition; BAI, Beck Anxiety Inventory; BDI-II, Beck Depression Inventory – Second Edition.

Behavior Assessment System for Children – Second Edition (BASC-II) [15]

The BASC-II is designed to evaluate the behavior and self-perceptions of children and young adults ages 2–25 years. In the Uniform Assessment Method for PKU, the BASC-II will be administered for children 2–17 years of age. Forms for parents and teachers and a self-report form are available. The Parent Rating Scale uses a four-choice format ranging from "never" to "almost always." It requires 10–20 min to complete and is written at a fourth-grade reading level in English and Spanish. The Parent Rating Scale contains 134 items for the Preschool Form (ages 2–5 years), 160 items for the Child Form (ages 6–11 years), and 150 items for the Adolescent Form (ages 12–21). The BASC-II has three validity scales: F Index (Negativity), L Index ("Faking Good"), and V Index (Implausibility). These scales comprise the Consistency Index and Response Pattern Index. The manual provides acceptable raw scores for each of these validity indices.

The clinical scales include Hyperactivity, Aggression, Conduct Problems (ages 6–21 only), Anxiety, Depression, Somatization, Attention Problems, Learning Problems (ages 6–21 only), Atypicality, and Withdrawal. The Adaptive Scales include Adaptability, Social Skills, Leadership, Study Skills (ages 6–21 only), and Functional Communication. High scores indicate negative or undesirable characteristics. Clinical scale scores of 60–69 place a child in the At-Risk range, and scores $\geqslant 70$ are clinically significant. For the Adaptive Scales, scores of 31–40 are considered At-Risk and scores $\leqslant 30$ are clinically significant. Factor analysis led to the following composites: Externalizing Problems, Internalizing Problems, Adaptive Skills, and Behavioral Symptoms Index.

Internal consistency alpha coefficients and test–retest coefficients are generally above 0.80 for all scales. Inter–rater reliability is adequate, with correlations higher for younger children. Correlations with other tests are in the expected directions and indicate adequate validity.

Behavior Rating Inventory of Executive Function (BRIEF) [16]

The BRIEF can be completed in 10–15 min and was selected for children 2–17 years of age and for adults. The inventory provides theoretically and empirically derived clinical scales that measure aspects of executive function. The clinical scales form broader indices of behavior and cognition and an overall score, the Global Executive Composite (GEC). Two additional scales (Inconsistency and Negativity) provide measures of the validity of responses. Parent response forms are available for Preschool and School-Aged Children, and a self-report form and an informant response form are available for adults, which permits consistent assessment across a broad age range. All forms are standardized on normative samples representing diversity in terms of race/ethnicity, age, and geographical population density.

Rater responses are scored on a 1–3 scale, with 1 corresponding to Never (N), 2 corresponding to Sometimes (S), and 3 corresponding to Often (O). The sum of the raw score for each scale is converted to a *T*-score. Percentile scores and confidence intervals are

provided in age-specific tables. A *T*-score of 50 is the mean of the *T*-score distribution, and a score of 65 represents 1.5 standard deviations above the mean. *T*-scores of $\geqslant$65 represent the recommended threshold for an "abnormally elevated" score which is considered "clinically significant."

The BRIEF-P is designed for children aged 2–5 years and 11 months, and it is completed by parents/guardians or teachers. This questionnaire contains 63 items within five scales: Inhibit, Shift, Emotional Control, Working Memory, and Plan/Organization. The clinical scales form the broad indices of Inhibitory Self-Control (ISCI), Flexibility (FI), and Emergent Metacognition (EMI), as well as the overall composite score (GEC). The BRIEF-P is standardized on a normative sample of 460 children. The questionnaire has adequate internal consistency, with $\alpha = 0.95$ for the GEC and $\geqslant$0.90 for each of the clinical scales and indices. Test–retest stability is 0.90 for the GEC over an average interval of 4.5 weeks. In terms of validity, the BRIEF-P Working Memory scale and the Plan/Organize scale are highly correlated with an ADHD questionnaire ($r = 0.88$, 0.86, $P < 0.001$). More than 70% of children with diagnoses of ADHD and autism spectrum disorder received "clinically significant" *T*-scores ($\geqslant$65), whereas less than 7% of children in a control group received scores in this range. A score of <8 on the Inconsistency Scale and a score of <4 on the Negativity Scale indicate validity of responses.

The BRIEF for School-Aged Children aged 5–18 years contains 86 items within eight scales: Inhibit, Shift, Emotional Control, Initiate, Working Memory, Plan/Organize, Organization of Materials, and Monitor. These scales form two indices, Behavioral Regulation and Metacognition, and the overall GEC. The questionnaire is standardized on a normative sample of 1419 children. A score of >6 on the Inconsistency Scale and a score of >5 on the Negativity Scale possibly invalidate the responses (or indicate severe executive function deficits, as might occur in severe traumatic brain injury or autism). Internal consistency is between 0.80 and 0.98 on all scales and indices. Test–retest reliability is above 0.80 over a 2-week period for the Behavioral Regulation Index, the Metacognition Index, and the GEC. In terms of validity, the Behavioral Regulation index has a correlation of 0.70 with the ADHD Rating Scale (Hyperactivity/Impulsivity). Scale scores on the BRIEF correlate significantly with other measures of general behavioral function but are generally unrelated to scores on tests of emotional function.

The BRIEF Adult Version (BRIEF-A) assesses patients aged 18–90 years with a minimum fifth-grade reading level. The BRIEF-A has 75 items measuring nine clinical scales: Inhibit, Shift, Emotional Control, Self-Monitor, Initiate, Working Memory, Plan/Organize, Task Monitor, and Organization of Materials. Three validity scales are used: Negativity, Infrequency, and Inconsistency. The clinical scales form two indices: Behavioral Regulation and Metacognition. In addition, an overall summary score (GEC) is calculated. Scores of $\geqslant$6 on the Negativity Scale, of $\geqslant$3 on the Infrequency Scale, and of $\geqslant$8 on the Inconsistency Scale are considered elevated and indicate a need to determine if the responses are valid. The BRIEF-A is standardized on a normative sample obtained throughout the United States via Internet sampling methodology. A total of 1196 adults completed the self-report form and 1215 adults completed the informant form. Gender accounts for less than 2% of the variance in any scale. Age-related differences are found on all self-report form scales except the Self-Monitor Scale, with younger adults reporting greater difficulties. Therefore, separate norms are provided for eight age categories. Alpha coefficients for internal consistency are above 0.80 on all scales, with somewhat higher scores for the Informant than self-report form. Test–retest stability over an average of 4 weeks is adequate for all scales. Correlations with neuropsychological tests of executive function are as high as 0.87 for the Informant Form, and all are above 0.50 for the GEC.

Beck Anxiety Inventory (BAI) [17]

The BAI is a 21-item scale measuring anxiety in adults and adolescents. Requiring 5–10 min to complete, the questionnaire requests that respondents endorse statements related to 21 symptoms, such as "unable to relax," "heart pounding," or "feeling hot," that can be divided into four categories: Neurophysiological, Subjective, Panic, and Autonomic. Items are rated on a 4-point scale (0–3), indicating the extent to which the respondent is bothered by each symptom during the past week, including today. Total scores are interpreted as follows: 0–7 minimal anxiety, 8–15 mild anxiety, 16–25 moderate anxiety, and 26–63 severe anxiety. The BAI can be administered orally. The BAI was developed through administration to 1086 psychiatric outpatients. Test items to responses from a subsample of 160 outpatients were used for reliability and validity analyses. Internal reliability is 0.92 (Cronbach coefficient alpha) and the test–retest correlation is 0.75 after 1 week. In terms of validity, the BAI correlates at or above 0.51 with other measures of self-reported and clinically rated anxiety. Although depression and anxiety often occur in combination, respondents with a primary diagnosis of anxiety had a median BAI score of 24 (range 2–58), whereas respondents with a primary diagnosis of depression had a median BAI score of 13 (range 1–31).

Beck Depression Inventory – Second Edition (BDI-II) [18]

The BDI-II is a 21-item self-report measure of depression in adults and adolescents aged 13 years and older. This questionnaire requires 5–10 min to complete and asks that respondents endorse the "most characteristic" statements covering the past 2 weeks, including today. The questionnaire can be administered orally. The BDI-II is scored by summing the ratings of the 21 items, which are rated on a 4-point scale (0–3). If multiple statements are endorsed, the highest rating is used. Scores are interpreted as follows: 0–13 minimal, 14–19 mild, 20–28 moderate, 29–63 severe depression. The test is standardized on 500 outpatients with diagnosed emotional disorders (ages 13–86 years and including 53% with confirmed depression). A student sample of 120 college students serves as a comparative normal group. Test–retest correlations and internal consistency for the overall BDI-II score is $\geqslant$0.92 for the outpatient and student samples. In terms of validity, respondents tended to endorse an average of 1.4 items more on the BDI-II than on the older version of the questionnaire (which did not include items related to "agitation," "worthlessness," "concentration difficult," and "loss of energy").

After administering the BDI-II, the clinician must review the response to item 9: "Suicidal Thoughts or Wishes." If the respondent endorsed statements 2 or 3, he or she needs to be referred immediately to the medical doctor or psychologist to ensure that appropriate protections are in place, including hospitalization if the respondent is at risk for self-injury or suicide. By using this assessment, metabolic clinics will ensure that referrals occur when appropriate, although a psychologist may not be on staff.

Conclusions

The person administering the Uniform Assessment Method for PKU communicates the results of the evaluation through a written report generated from computerized scoring or a template created for this purpose. When a non-psychologist administers and scores the questionnaires, no specific recommendations regarding psychological interventions should be made other than referral to an appropriate professional for further evaluation if needed.

The Uniform Assessment Method addresses the need for ongoing psychological and behavioral monitoring of individuals with

PKU, but it does not replace neuropsychological evaluations, psychiatric assessments, or behavioral analyses. Instead, it provides a reliable and valid method for tracking changes in function that may be related to variations in metabolic status, age, or modifications in treatment such as decreased protein allotment, introduction of low-protein foods, or medications (e.g., hyperactivity medication). Collaborative outcome research as well as prospective and retrospective studies, meta-analyses, and follow-up registries also will be enhanced by using the Uniform Assessment Method.

The initial meeting of the 10 psychologists and one psychiatrist led to the establishment of a Genetics and Metabolism Psychology Network. This network hosts a website (www.gmpsych.org) with more detailed descriptions of each of the tests comprising the Uniform Assessment Method for PKU. In addition, the website will provide templates for reporting results to families and clinicians, as well as recommendations for a core battery of neuropsychological tests to be administered and interpreted by psychologists who are conducting in-depth evaluations of individuals with PKU and other metabolic or genetic disorders.

It is our hope that this article and the Network website will facilitate more thorough monitoring of the development of cognitive and social–emotional functioning in children with PKU, as well as earlier identification of children at risk for serious difficulties. In addition, we hope that these efforts will facilitate the identification of adults with significant cognitive and social–emotional problems. Through timely identification, children and adults with PKU will be more likely to receive needed referrals for comprehensive psychological and/or psychiatric evaluations and to receive treatment recommendations that will permit them to achieve their full potentials.

Acknowledgments

We wish to acknowledge the invaluable contributions made by the professionals who consulted with us to develop the Uniform Assessment Method for PKU, including Kevin Antshel, Deborah Bilder, Virdette Brumm, Nancy Cantor, Shawn Christ, Hillary Lee Feldman, Jennifer Gentile, Mitzie Grant, Darren Janzen, Mina Nguyen, Rani Singh, and Wendy Packman. We also wish to acknowledge BioMarin Pharmaceutical Inc. for facilitating the gathering of these professionals to develop the Uniform Assessment Method for PKU.

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