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Content Validity of the ADHD Rating Scale (ADHD RS-IV) and Adult ADHD Self-Report Scale (ASRS) in Phenylketonuria

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Abstract

The ADHD Rating Scale (ADHD RS-IV; parent report) and Adult ADHD Self-Rating Scale (ASRS; self-report) are validated instruments for measuring symptoms of attention-deficit/hyperactivity disorder (ADHD). The objectives of this study were to elicit descriptions of phenylketonuria (PKU) symptoms and assess content validity of these instruments in PKU. Parents (N = 15) of children with PKU (≥8 years old) and adults with PKU (N=13) described PKU-related symptoms and commented on the scale's clarity, comprehensiveness, and relevance to their experience with PKU. Most of the adults (84.6%) and all of the children were on a phenylalanine-restricted diet, according to respondent report. The inattentiveness symptoms reported by participants mapped to the inattentive items of the questionnaires. Most participants felt the inattentive items were clear and relevant to their experience. Despite study design limitations, these results demonstrate the relevance of assessing inattentiveness in PKU, and both instruments achieved content validity for inattentive subscale items.

Keywords

phenylketonuria, metabolic disorder, attention-deficit/hyperactivity disorder, inattentiveness, content validity

Introduction

Phenylketonuria (PKU; *Online Mendelian Inheritance in Man* [OMIM] 261600 and 261630) is the most common inherited metabolic disorder, occurring in 1:10,000 to 1:15,000 births.[1] This autosomal recessive condition is caused by a functional deficit in the phenylalanine (Phe) hydroxylase enzyme, which subsequently impairs the conversion of Phe into tyrosine.[2] If untreated, Phe accumulates in the serum and brain, leading to severe intellectual disability, language and social skill deficits, seizures, and disruptive behavior.[3,4] Since the onset of newborn screening in 1964, PKU is routinely identified at birth, dietary intervention is initiated immediately, and these neurologically devastating complications are prevented. Children and adults with PKU are managed in the outpatient genetics clinic setting, where they receive Phe monitoring, nutritional support, and pharmacologic intervention, when appropriate. Not surprisingly, a dramatic decline in PKU treatment adherence commonly occurs during adolescence and persists into adulthood.

Individuals with early-treated PKU experience normal intellectual functioning with mean IQs typically falling within normal limits. However, neurocognitive symptoms continue to be observed in early-treated patients, even among those who adhere closely to dietary treatment.[5-7] Even modest elevations in Phe levels may impair high-level executive functioning.[8-10] Among the common concerns encompassed within executive functioning are reduced attention span[11-15] and hyperactivity/impulsivity.[16-18] In a 2003 study designed to document the

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symptom dimensions of attention-deficit/hyperactivity disorder (ADHD) in children with PKU, Antshel and Waisbren demonstrated that ADHD inattentive symptoms occur significantly more often in children aged 7 to 16 years old with PKU when compared to their unaffected siblings[19] using the ADHD Rating Scale IV (ADHD RS-IV).[20] Moreover, ADHD symptoms and treatment (stimulants) have been reported in children with PKU; the presence of both appears to correlate with higher Phe levels.[21] Although the exact mechanism underlying ADHD symptoms associated with PKU is unknown, it has been hypothesized that reduced tyrosine levels in PKU may lead to impaired dopamine and norepinephrine production in the central nervous system.[22,23] Similarly, ADHD has been linked to dopaminergic and adrenergic pathways in the prefrontal cortex.[24,25]

Although ADHD rating scales have been designed to measure the presence and treatment response of ADHD symptoms in the general population,[26-29] their appropriateness and relevance for measuring symptoms associated with PKU have yet to be established. Content validation of ADHD self-report and parent-report rating scales for the PKU population would provide PKU clinic teams with tools to incorporate ADHD screening into routine clinical care. This also comprises a necessary step for the inclusion of clinically relevant neurocognitive outcomes among designated end points in pharmaceutical trials of Phe-lowering medication. In this context, *content validity* refers to an instrument's capacity to collect meaningful and accurate data that are relevant to individuals with PKU.[30,31]

The objectives of this study were (a) to obtain descriptions of PKU symptoms in children (reported by parents) and adults with PKU and (b) to evaluate the content validity of 2 widely used ADHD symptom rating scales, ADHD RS-IV (parent report) and self-report Adult Self-Rating Scale (ASRS), for children and adults with PKU.

Methods

Participants

In this cross-sectional study, adults with PKU and parents of children 8 to 17 years old with PKU were recruited either before/during the 2012 National PKU Conference in Cherry Hill, New Jersey, or via e-mail and foundation/social networking Web sites. Saturation of concepts was used to determine when a sufficient number of participants were interviewed. *Saturation* is defined as the point at which no substantially new themes, descriptions of a concept, or terms are introduced. The number of patients needed to reach saturation is largely driven by the complexity of a concept and the diversity of the population.[30] This study was approved by the Ethical & Independent Review Services (E&I) Institutional Review Board (http://www.eandireview.com/).

Eligibility

Potential participants were screened via telephone for eligibility. Participants met the following inclusion criteria: diagnosed with PKU (or had a child diagnosed with PKU); able to read, speak, and understand English; willing and able to participate in a 90-minute one-on-one interview session including audio-recording; and willing to provide written informed consent. An individual was excluded if he or she (or his or her child) was a participant in a research study related to PKU at the time of the interview; taking sapropterin currently or during the 3 months preceding screening; or unable to participate fully in the interview. Inclusion and exclusion criteria closely approximated those of a pharmaceutical clinical trial that investigated the neurocognitive effects of sapropterin, a Phe-reducing medication that received Food and Drug Administration (FDA) approval for PKU in 2007.[32] Most individuals taking this medication continue to require dietary Phe restriction and protein replacement formula to maintain adequate metabolic control. Information regarding the age at diagnosis for PKU or ADHD diagnosis/treatment history was not collected during screening or used as exclusionary criteria to mirror the clinical trial.

Study Design

Interviewers trained in qualitative research methods and PKU symptoms conducted semistructured one-on-one interviews with adult participants having PKU and parents of children with PKU. Written informed consent was obtained from all participants at the onset of the interview. Interviews were conducted in 2 phases. During phase 1, interviewers asked open-ended concept elicitation questions about diagnosis, symptoms, and impacts of PKU. Following this open-ended discussion, participants completed the appropriate questionnaire (adult participants: ASRS; parent participants: ADHD RS-IV). During phase 2, interviewers asked questions regarding the clarity, comprehensiveness, and relevance for each rating scale item, instructions, recall periods, and response options. All interviews were conducted in English and were digitally recorded. Participants then completed a sociodemographic questionnaire and provided information regarding PKU diagnosis and treatment. For interviews conducted via telephone, interview materials were mailed in advance and participants were instructed to keep the envelope containing the ADHD rating scale sealed until prompted to open it during the interview.

Measures

Adult ADHD Self-Report Scale. The Adult ADHD Self-Report Scale (ASRS) is a self-report, 18-question scale developed by the World Health Organization to assess the frequency of ADHD symptoms and behaviors in adults.[33] The recall period is the past month. Each question on the ASRS maps directly to 1 ADHD symptom criterion in the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM*; Fourth Edition, Text Revision).[34] The questions are divided into inattention (questions 1-9) and hyperactive/impulsive (Questions 10-18) symptom subscales. The ASRS has demonstrated high internal consistency and concurrent validity when compared to the investigator-rated ADHD RS-IV[35] and has been used

extensively in clinical trials to measure treatment response in ADHD.[36,37]

ADHD Rating Scale IV. The ADHD RS-IV assesses children's ADHD symptoms and is designed for completion by a parent, guardian, or grandparent. The scale includes 18 questions assessing the frequency of ADHD symptoms and behaviors in children over the preceding month. Like the ASRS, the scale is consistent with the *DSM* (Fourth Edition) ADHD criteria, has inattentive and hyperactivity/impulsivity subscales, and individual items correspond to specific ADHD criterion.[38] The ADHD RS-IV has demonstrated strong reliability and validity[20,39] and is often used to measure symptom change in response to ADHD treatment.[40-42] The ADHD RS-IV differs from the ASRS in that items on the latter are focused on adults (versus children), and the ASRS is designed for adult self-report (versus parent, guardian, or grandparent).

Analyses

Descriptive statistics were used to summarize the sociodemographic and clinical data collected during the interview. All interview audio-recordings were transcribed. The qualitative data were analyzed using ATLAS.ti software.[43] Two researchers coded the transcripts, and a third researcher reviewed all coded transcripts for accuracy and consistency. The coded text yielded qualitative tables and descriptive statistics that identify and categorize concepts. Concepts were analyzed for the presence of novel information in successive interviews and concept saturation.

Results

Participant Characteristics

Thirteen adults with PKU and 15 parents of children with PKU participated in the interviews. Table 1 describes the sociodemographic and clinical characteristics of adult and parent participants and parent participants' children. The adult participants comprised 8 (61.5%) women and 5 (38.5%) men; their mean age was 34.8 $\pm$ 8.3 years (range: 24-46 years). Most adults achieved either a college (46.2%) or postgraduate degree (15.4%). All adults were diagnosed with PKU within the first 3 weeks of life. Most (84.6%) adults adhered to a modified PKU diet by limiting Phe intake and/or consuming PKU formula/medical foods.

Six parents of children (aged 8-12) and 9 parents of adolescents (aged 13-17) diagnosed with PKU participated in the study. The majority of the parents achieved either a college (33.3%) or a postgraduate degree (26.7%). Twelve children were diagnosed with PKU during the first 3 weeks of life; 1 child born outside the United States was diagnosed at 3 years of age. All children were on a low Phe diet, and 14 children took PKU formula regularly. One child, off formula, took an amino acid supplement.

One adult and 2 children were reported to have been diagnosed with attention-deficient disorder (ADD) and/or ADHD (Table 1). All 3 took ADHD medication; the adult's medication was unknown, and the children were taking methylphenidate.

Participant-Elicited PKU Effects

Sixty-two distinct symptoms (23 physical, 21 cognitive, and 18 emotional) were reported by adult participants. Content saturation was achieved with no novel PKU symptoms emerging in the final adult interview. Physical, cognitive, and a third grouping of emotional/behavioral/social symptoms were reported by 92%, 85%, and 92% of adults, respectively (bolded values in Table 2). Frequently reported symptoms were difficulty concentrating (85%), difficulty paying attention (54%), and tiredness/fatigue (46%). All adults endorsed symptom variability, which was typically attributed to seasonal changes, stress, lack of sleep, and/or high Phe levels. High Phe levels were reportedly caused by eating inappropriate foods, not consuming the recommended amount of formula, or not consuming formula steadily throughout the day.

Forty-four distinct symptoms (12 physical, 17 cognitive, and 15 emotional) were observed by parent participants and reported as PKU related. Concept saturation was achieved on all 3 symptom domains. Physical, cognitive, and emotional/behavioral/social symptoms were reported by 67%, 87%, and 80% of parents, respectively (bolded values in Table 2). Frequently reported symptoms by parents were difficulty concentrating (60%), difficulty paying attention (33%), and skin rashes/eczema (33%). Most parents (93%) reported variability in their children's PKU symptoms attributed to lack of sleep and/or high Phe levels. High Phe levels were caused by high Phe content in food choices, inappropriate timing of formula consumption, and a busy/stressful schedule.

Adult Participants: The ASRS

Figure 1 depicts the participant-elicited, PKU-related inattentive symptoms and the individual ASRS inattentiveness subscale items. Figure 2 illustrates participant-elicited, PKU-related symptoms that correspond to hyperactivity/impulsivity subscale items. Eight inattentiveness symptoms were elicited, and each inattentiveness symptom was endorsed by at least 2 and up to 11 adult participants. In contrast, only 3 hyperactive/impulsive symptoms were elicited, each with a generally lower frequency of endorsement.

ASRS Interviews. All adult participants demonstrated understanding of the meaning of inattentiveness and hyperactivity/impulsivity subscale questions by providing examples for each subscale item. The majority (77%) of the participants endorsed the relevance of the inattentiveness questions for adults with PKU. Five participants noted that the following inattentiveness questions could also apply to adults without PKU: "doing a boring project," "repetitive work," "details of a project,"

Table 1. Sociodemographic and Clinical Characteristics of Adult and Parent Interview Participants and the Parents of Children With PKU.

	Adult Participants, n = 13	Parents of Children With PKU, n = 15	Children With PKU, n = 15
Age, mean (SD), range	34.8 (8.3), 24-46	47.7 (7.3), 35-67	12.9 (3.1), 8-17
Male, n (%)	5 (38.5)	2 (13.3)	7 (46.7)
Race			
White, n (%)	13 (100)	14 (93.3)	14 (93.3)
Other, n (%)	0 (0)	1 (6.7)	1 (6.7)
Marital status			
Single, n (%)	5 (38.5)	–	
Married, n (%)	7 (53.9)	12 (80.0)	
Divorced, n (%)	1 (7.7)	2 (13.3)	
Separated, n (%)	–	1 (6.7)	
Current living/domestic situation			
Living alone, n (%)	4 (30.8)	1 (6.7)	
Living with a spouse, partner, family, or friends, n (%)	9 (69.2)	14 (93.3)	
Employment status			
Full-time work, n (%)	10 (76.9)	6 (40.0)	
Part-time work, n (%)	1 (7.7)	6 (40.0)	
Homemaker, n (%)	2 (15.4)	3 (20.0)	
Highest level of education			
Secondary/high school, n (%)	–	1 (6.7)	
Some college, n (%)	5 (38.5)	5 (33.3)	
College degree, n (%)	6 (46.2)	5 (33.3)	
Postgraduate degree, n (%)	2 (15.4)	4 (26.7)	
Other existing diagnoses[a]			
Attention-deficit hyperactivity disorder (ADHD), n (%)	–		1 (6.7)
Attention-deficit disorder (ADD), n (%)	1 (7.7)		2 (13.3)
Autism, n (%)	–		1 (6.7)
Learning disability, n (%)	3 (23.1)		3 (20)
Intellectual Disability, n (%)	1 (7.7)		1 (6.7)
Seizures, n (%)	1 (7.7)		1 (6.7)
Skin rashes or eczema, n (%)	2 (15.4)		4 (26.7)
Anxiety, n (%)	1 (7.7)		–
Depression, n (%)	1 (7.7)		–
Other mental health problem[b], n (%)	1 (7.7)		–
Other health problem[c], n (%)	1 (7.7)		–
None, n (%)	5 (38.5)		7 (46.7)
On a Phe restricted diet, n (%)	11 (84.6)		15 (100)

Abbreviations: PKU, phenylketonuria; PHE, phenylalanine; SD, standard deviation.
[a]Not mutually exclusive.
[b]Participant noted "seasonal affect disorder—still under diagnosing."
[c]Participant noted "gastrointestinal issues."

"misplacing things," "distracted," and "remembering appointments."

The majority (69%) of participants reported that all hyperactive/impulsivity questions were relevant to PKU. Four participants thought the following hyperactivity/impulsivity questions were unrelated to PKU: "fidgeting or squirming," "leaving seat in meetings," "feeling restless/fidgety," "talking too much," "difficulty waiting turn," and "interrupting others."

All 13 (100%) adult participants understood the intended meaning of the ASRS instructions and response options. Seven (54%) participants answered based on the correct recall period of 1 month. Three (23%) participants skipped the instructions, and 3 (23%) participants revealed that when responding to ASRS questions they incorporated longer recall periods (ie, 6 weeks, summer, and several months).

Parent Participants: The ADHD RS-IV

The ADHD RS-IV is completed by a parent (or grandparent/guardian), and the items have been designed to apply to children's activities. Figures 1 and 2 depict the symptoms observed by parents that correspond to concepts measured in the ADHD RS-IV's inattentiveness and hyperactivity/impulsivity subscales, respectively. As with adult participants, 7 inattentiveness symptoms were observed by at least 2 and up to 9 parents. Six hyperactivity/impulsivity symptoms were elicited, with generally weaker endorsement by 1 to 4 parent participants.

Table 2. Key Adult- and Parent-Reported Symptoms of PKU.

Key Symptoms[a]	Adult Reported (n = 13), n (%)	Parent reported for Child <18 Years Old, (n = 15), n (%)
Physical symptoms	**12 (92%)**	**10 (67%)**
Tiredness/fatigue	6 (46%)	4 (27%)
Skin rashes/eczema	3 (23%)	5 (33%)
Headaches/migraine	4 (31%)	1 (7%)
Tremor or jerking movements in the extremities/seizures	3 (23%)	2 (13%)
Hunger	3 (23%)	3 (20%)
Abnormal body odor	3 (23%)	1 (7%)
Difficulty sleeping	3 (23%)	0 (0%)
Cognitive symptoms	**11 (85%)**	**13 (87%)**
Difficulty concentrating	11 (85%)	9 (60%)
Difficulty paying attention	7 (54%)	5 (33%)
Difficulty focusing	5 (38%)	3 (20%)
Becoming bored quickly	3 (23%)	4 (27%)
Forgetful/poor memory	4 (31%)	2 (13%)
Difficulty staying focused on a single activity/distractible	3 (23%)	2 (13%)
Slow response time/processing slowly	2 (15%)	3 (20%)
Emotional, behavioral, or social symptoms	**12 (92%)**	**12 (80%)**
Frustration	5 (38%)	0 (0%)
Anxiety/nervousness	5 (38%)	1 (7%)
Irritability/agitation	5 (38%)	4 (27%)
Anger/short tempered/easily upset	4 (31%)	3 (20%)
Active	3 (23%)	4 (27%)
Moodiness/crankiness	3 (23%)	3 (20%)
Bounces from one activity to another	3 (23%)	3 (20%)
Difficulty in social situations	1 (8%)	4 (27%)
Low motivation/lazy	3 (23%)	0 (0%)
Stress	3 (23%)	0 (0%)
Behavioral issues	0 (0%)	3 (20%)

Abbreviation: PKU, phenylketonuria.
[a]Key symptoms had at least 3 endorsements from either the adult group or the parent group.
Bolded values represent the percentage in each column who reported any Physical, Cognitive, or Emotional, behavioral, or social symptom, respectively.

ADHD RS-IV interviews. Three (20%) parents reported that all ADHD RS-IV questions were relevant to their child with PKU, 8 (53%) reported that only some questions were relevant, and 4 (27%) reported that no questions were relevant to their child. All but 1 parent felt the questions were easily understood and were able to provide examples for each item. The remaining parent reported that English was his second language and requested interviewer clarification for "fidgets with hands or feet," "on the go," and "easily distracted," which most likely reflects the use of 2 less common English words (*fidgets* and *distracted*) and an idiom (*on the go*). Following this clarification, this parent was able to complete the ADHD RS-IV in its entirety.

The majority (73%) of the participants felt all inattentiveness questions were relevant to children with PKU. Three participants thought one of the following subscale items was irrelevant to PKU: "attention to schoolwork," "not listening when spoken to," and "avoiding tasks requiring sustained mental effort." Three participants noted that some questions were not specific to PKU, including "easily distracted" and "forgetfulness."

Approximately half (53%) of parent participants endorsed the relevance of all hyperactivity/impulsivity questions for children with PKU. Forty percent identified at least one of the following items was irrelevant to PKU: "runs/climbs," "difficulty playing quietly," "driven by a motor," "talks excessively," and "difficulty awaiting turn." Eight (53%) parents commented that several of the hyperactive/impulsive questions describe normal childhood behavior and are not specific to PKU, including "difficulty listening when being spoken to," "talking excessively," "difficulty awaiting turn," and "blurting out answers." Two participants felt that "runs/climbs in inappropriate situations" is relevant to young children but not to adolescents. In addition, 5 parents reported difficulty responding to questions about in-school behavior because they had not observed their child at school.

The ADHD RS-IV instructions and response options were understood by all parents, and all parents noted the intended recall period of 1 month. Most parents reported behavior they observed over the preceding month (n = 8, 53%) or during the most recent school year (n = 5, 33%).

Discussion

This investigation found strong evidence to support the content validity of the ASRS and ADHD RS-IV inattentiveness subscales for children ≥8 years old and adults with PKU. However, the tools' hyperactivity/impulsivity subscales appeared less relevant for this population. A key strength for the inattentiveness subscales was the significant overlap between inattentiveness symptoms elicited from participants and the content of the inattentiveness subscale items. Both instruments' inattentiveness subscale items were considered relevant, comprehensive, and clear by both participant groups. These results are consistent with the existing literature on executive function deficits in PKU.[18,25]

One purpose of this study was to describe the experience of PKU symptoms in children and adults with PKU, irrespective of concurrent PKU treatment status (ie, on diet, off diet, Phe levels, and formula/medical foods consumption). All adults and most parents endorsed symptom variability, which was typically attributed to seasonal changes, stress, lack of sleep, and/or high Phe levels. It can be difficult to differentiate the effects of short-/long-term blood phenylalanine fluctuations and the cumulative effect of lifelong Phe concentrations.[44-49] Even those with early and continuously treated PKU have been reported to experience higher than expected rates of neuropsychiatric symptoms and cognitive impairment although generally at lower rates than for those with early-treated PKU who had discontinued diet.

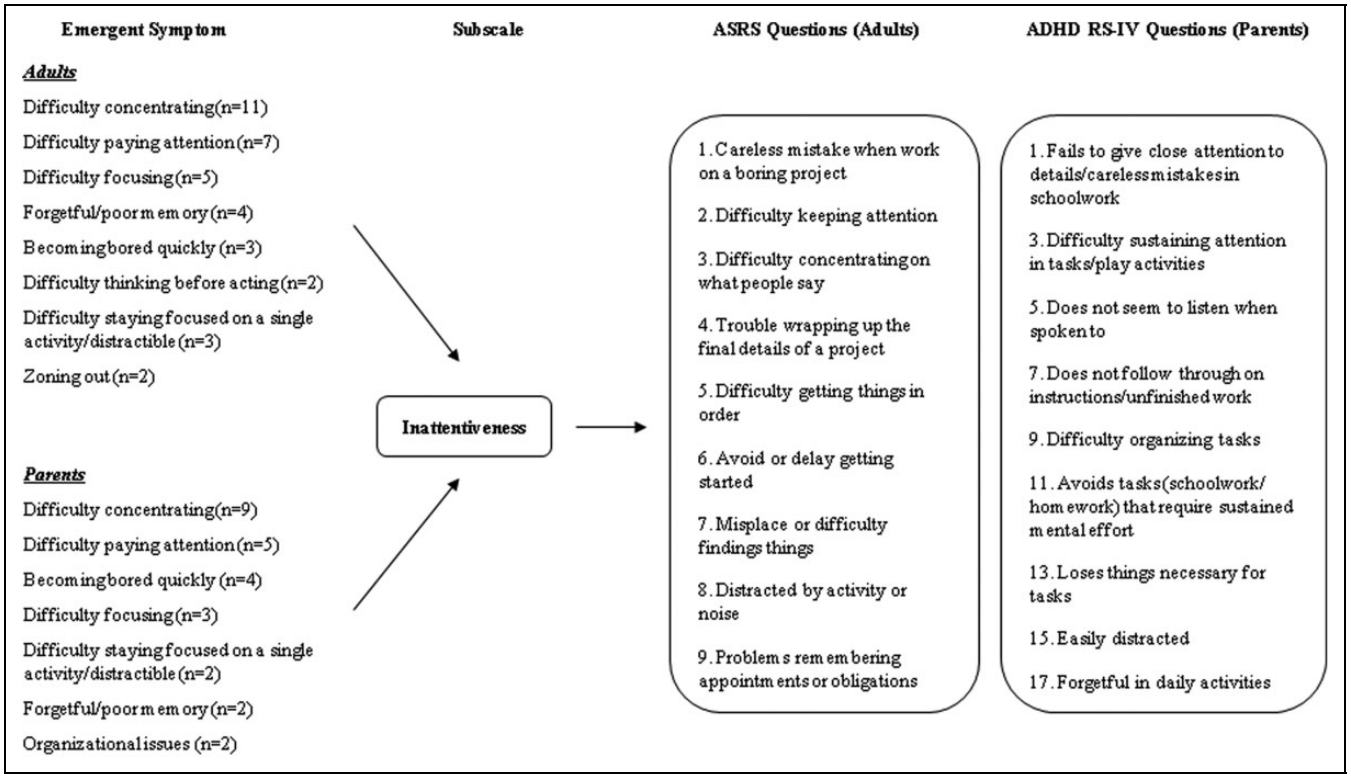

Figure 1. Inattentive symptoms reported by adults and parents of children with phenylketonuria (PKU).

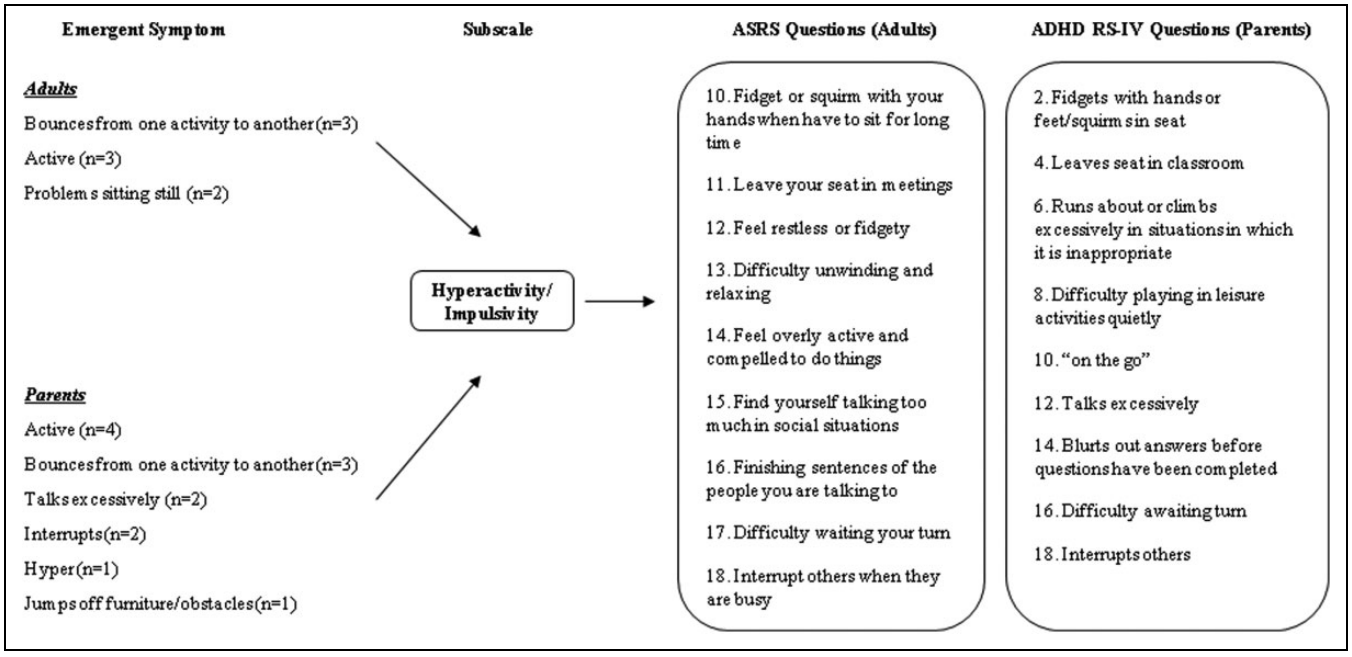

Figure 2. Hyperactive/impulsive symptoms reported by adults and parents of children with phenylketonuria (PKU).

The relatively low number of hyperactivity/impulsivity symptoms was also unsurprising as previous reports of these symptoms had been limited to children[16-18,50] and associated with the discontinuation of dietary treatment.[6] Like the typical developmental course of ADHD, hyperactivity and impulsivity were more frequently noted in children. Indeed, a sensitivity analysis of our results focused only on the 6 parents of the youngest children (aged 8-12) found that a greater percentage

(67%) of the parent endorsements of the hyperactivity/impulsivity symptoms in Figure 2 were from these children's parents compared to 52% of the parents' reports of inattentiveness symptoms in Figure 1; however, this sample size is very limited. Nonetheless, a small number of hyperactivity/impulsivity symptoms emerged from both the adolescents' parents and the adults with PKU.

Limitations to this study include the potential for selection bias and the timing (summer break) of the in-person parent interviews, and this may limit the reliability of these study results. As a rare condition, PKU poses the challenge of recruiting an adequate number of participants into a qualitative research study without immediate treatment benefit. The national PKU conference provided an opportunity to recruit eligible adult and parent participants who, through their attendance, had already demonstrated an interest in PKU treatment. With the majority of the participants recruited from sources that may have yielded more highly motivated participants (national PKU conference, social media, etc.), it is possible that the findings from these limited sample sizes may not be representative of the whole population of patients with PKU. Although effective, this strategy lends itself toward enrolling participants with a high degree of awareness of PKU-related conditions. This awareness and higher socioeconomic status (SES), as suggested by educational attainment, may lead to better metabolic control. High SES, in particular, can improve access to low-Phe medical foods, protein-replacement formula, and specialty medical care. As a cross-sectional qualitative study, sociodemographic and clinical data were collected by self-report at the completion of the interview. Due to the nature of the interview setting, details on specific factors that are likely to affect executive function were not known in the sampled cohort, including participant treatment history, such as compliance or discontinuation of PKU diet over time, Phe levels (current and recent), intelligence/IQ, family history of ADHD, learning disabilities, response rate to stimulants, and so on. Moreover, the use of self-reported symptoms from adults with PKU may be questionable if these informants do not have clear insights and assessments of their functioning. Finally, the plural interview modes for parent participants (in-person and telephone) posed another potential limitation, given the preference for in-person interviews in qualitative research. However, the telephone interview extended participation beyond conference attendees and were conducted during the school year, optimizing parents' ability to observe their child's symptoms.

The enrollment of 1 adult with PKU and 2 parents of children with PKU with a comorbid diagnosis of ADD and/or ADHD is also a potential limitation, as these 3 participants may have been more likely to report symptoms related to the investigated instruments. Nonetheless, a sensitivity analysis of the saturation results after removing these 3 participants' data revealed that all of the symptoms in Table 2 were also endorsed by the remaining participants, without self-reported AD(H)D. Given that the purpose of this study was to investigate symptoms experienced by individuals with PKU and the usefulness of the ASRS/ADHD-RS IV measurement tools, selecting for or excluding participants with an existing AD(H)D diagnosis would bias our sample and limit the generalizability of our results for PKU population overall.

The prominence of inattentive symptoms and their relevance to the inattentive subscale items provide meaningful insight into PKU's cognitive phenotype from a psychiatric perspective. Although examined within the context of an underlying medical etiology (PKU), these inattentive symptoms were well captured by rating scales designed to assess idiopathic ADHD, a condition with which psychiatrists are quite familiar. The ASRS and ADHD RS-IV have been used extensively to measure treatment response in ADHD. Although this study's results support the use of these tools to assess inattentive symptoms in individuals with PKU, further research is necessary in the quantitative realm to identify the tools' psychometric properties (ie, reliability, construct validity, measurement of change) in the context of PKU.[51]

Treatment options are becoming increasingly available for inherited metabolic conditions. Many of these disorders are associated with neuropsychiatric phenotypes described in the literature through studies that used extensive neuropsychological batteries. Yet, these batteries are impractical to use routinely in busy clinical settings and do not provided definitive, clinically relevant outcome measures to obtain an FDA indication. Subsequently, pharmaceutical studies use disease-associated biomarkers as end points rather than neuropsychiatric outcomes, even when psychiatric symptoms (such as in PKU) are the most clinically relevant manifestation of the disorder. The results of this study offer promise that neuropsychiatric complications of inherited metabolic disorders can be measured with existing rating scales for related psychiatric conditions and if used in the clinical setting can hopefully lead to increased identification and treatment of symptoms and increased success in adaptive function (daily life skills) for individuals with PKU, including school performance in children.

Author's Note

Priscilla Auguste was formerly at Evidera, Bethesda, MD, USA. Kim Hart Mooney and Suyash Prasad were formerly at BioMarin Pharmaceutical, Novato, CA, USA.

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