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RESEARCH REPORT

Treatment Adherence and Psychological Wellbeing in Maternal Carers of Children with Phenylketonuria (PKU)

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Abstract Phenylketonuria (PKU), a rare metabolic disorder, causes cognitive impairment unless treated with a strict, protein-restricted diet, but few studies have examined the relationship between treatment compliance and parental wellbeing. In the present study, 46 primary caregivers of children with PKU completed measures of psychological distress, parenting stress (related to caring for a child with an illness), resilience, perceived social support and child dependency. Treatment adherence was assessed using the proportion of blood phenylalanine concentrations within target range in the preceding year. Results indicated that 59% of caregivers showed clinical levels of psychological distress, which was predicted by their parenting stress and resilience. Whilst the proportion of blood phenylalanine concentrations in range was not associated with parental distress, it was predicted by child age and caregiver's perceived support from family. Despite experiencing high levels of distress, the results indicated that caregivers' ability to adhere to treatment was not affected. Interventions to reduce parenting stress and boost caregiver resilience may have a positive effect on parental wellbeing. Additionally, interventions to promote treatment adherence benefit parents of older children, with a focus on promoting support from family members. Further research with larger sample sizes and longitudinal designs is needed to further establish causal mechanisms.

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Introduction

Phenylketonuria (PKU, OMIM 261600) is a rare genetic disorder in which the amino acid phenylalanine (phe) is insufficiently metabolised. Although phe accumulation causes severe and irreversible cognitive impairment, this can be prevented by a lifelong protein-restricted diet. Parents have to supervise their child's nutritional intake and facilitate regular sampling of blood phe concentrations (Smith et al. 1993). Given the effort required for treatment adherence and the consequences of poor compliance, caring for a child with PKU brings additional challenges (Awiszus and Unger 1990) that potentially affect parental wellbeing, with increased depression and anxiety reported in some parents of children with PKU (Gundaz et al. 2015; Mahmoudi-Gharaei et al. 2011), but not others (Fidika et al. 2013; Kazak et al. 1988; Ten Hoedt et al. 2011).

To support parents of children with PKU, it is important to understand the determinants of their psychological wellbeing. Fidika et al. (2013) found parental quality of life (QoL) was predicted by family stress and perceived social support, whilst Ten Hoedt et al. (2011) noted that health-related QoL was affected by emotional support and

loss of friendship. Whilst QoL was lower for parents with younger children due to greater parental responsibility for dietary adherence, Gundaz et al. (2015) found that parental anxiety and depression were not associated with child age.

There is little data on parental psychological wellbeing and treatment adherence. Reber et al. (1987) found no significant difference in external life stress between parents of children with good and poor metabolic control; Fehrenback and Peterson (1989) observed that parental anxiety and depression were not significantly associated with metabolic control. However, associations between parental wellbeing and treatment adherence have been identified in other lifelong metabolic conditions. In childhood diabetes, increased maternal depressive symptoms were associated with less parental monitoring, itself associated with poorer adherence and metabolic control (MacKey et al. 2014).

The aims of the current study were to (1) examine the psychological impact of parenting a child with PKU, (2) examine influences on parental psychological wellbeing and (3) examine the relationship between parental wellbeing and treatment adherence. It was hypothesised that parents would have high levels of psychological distress, which would be predicted by their parenting stress (related to caring for a child with an illness), resilience, perceived social support and level of child dependency. It was also hypothesised that treatment adherence would be associated with parental psychological distress and other parent factors (resilience, perceived social support and child dependency).

Method

Participants

Primary caregivers of children with PKU attending three metabolic clinics in the North West UK (Manchester, Liverpool and Bradford) were invited to participate. Caregivers were eligible to participate if their child was between 0 and 16 years old and diagnosed with PKU at birth. Caregivers were excluded if they could not comprehend English or if there were any other significant health problems or caring responsibilities that could affect their psychological wellbeing.

Measures

Psychological Distress

The 12-item *General Health Questionnaire-12* (GHQ-12; Goldberg and Williams 1988) was used to assess caregiver psychological distress. Higher scores suggest higher levels of distress (anxiety and depression), and scores over 12 indicate distress within the clinical range (Goldberg et al. 1997). The GHQ-12 has good psychometric properties (Goldberg and Williams 1988) and good internal consistency in the current study ($\alpha = 0.87$).

Parenting Stress

The *Pediatric Inventory for Parents* (PIP; Streisand et al. 2001) was used to measure caregiver stress related to caring for a child with an illness. The PIP is a self-report measure with four subscales (communication, medical care, emotional distress and role function) and overall total difficulty and total frequency scores. The total scores were used in the present study, and both had good internal consistency ($\alpha = 0.94$ and 0.95).

Resilience

Caregiver resilience was assessed using the *Resilience Scale for Adults* (RSA; Friborg et al. 2006), a self-report measure with six subscales (perception of self, planned future, social competency, structured style, family cohesion and social resources) and a total score. Higher scores indicate increased protective resilience. The RSA has good psychometric properties (Windle et al. 2011), and internal consistency in the present study was high ($\alpha = 0.88$).

Social Support

Perceived social support was assessed using the *Multidimensional Scale of Perceived Social Support* (MSPSS; Zimet et al. 1988), a self-report measure with three subscales (family, friends and significant other) and a total score. The MSPSS has strong psychometric properties (Zimet et al. 1990) and good internal consistency in the current study (family $\alpha = 0.92$, friends $\alpha = 0.93$, significant other $\alpha = 0.97$ and total scale $\alpha = 0.90$).

Child Dependency

A seven-point Likert-style question was developed to assess how much the child depended on their caregiver to adhere to the recommended dietary treatment using two opposing statements ('My child has managed their diet on their own' and 'My child has relied on me to help them stick to a protein-restricted diet'). Participants were required to select an option box closest to the end statement that best described their child best over the previous weeks.

Treatment Adherence

Two measures of treatment adherence were used: (1) the proportion of blood phe concentrations within target range

in the preceding year and (2) the proportion of required blood samples submitted in the preceding year, with information taken from existing medical records. Blood samples had been routinely collected using Guthrie card blood spots or venous samples and analysed using tandem mass spectrometry or Thermo high-performance liquid chromatography.

All three PKU clinics used the National Society for PKU recommendations (NSPKU 2014) for target blood phe concentrations and frequency of blood sampling, i.e. acceptable blood phe ranges of 120–360 μmol/L for 0–5-year-olds, 120–480 μmol/L for over 5-year-olds and 120–700 μmol/L for adults. However, one of the clinics accepted 100–400 μmol/L for 0–5-year-olds, 100–500 μmol/L for over 5-year-olds and up to 700 μmol/L for adolescents (from around 14 years old). Two clinics requested weekly blood samples for 0–5-year-olds, fortnightly samples for over 5-year-olds and monthly samples for adolescents and adults. The third clinic requested weekly samples for 0–2-year-olds, fortnightly samples for 2–5-year-olds and monthly samples for over 5-year-olds. In addition to these minimum requirements, patients were asked to provide additional blood samples on a case-by-case basis, for example, during periods of illness or when blood phe levels were high, and these were necessarily included in the data used for the present study as it was not feasible to disaggregate the data to remove these additional samples.

Demographic information (caregiver date of birth, gender, language, relationship to child, highest qualification and average family income) was also collected.

Procedure

Clinical teams at the PKU clinics identified eligible caregivers by reviewing patient notes and databases. Invitation packs (including participant information sheets, consent forms and the study questionnaires) were posted to eligible caregivers alongside a freepost envelope. If caregivers returned incomplete questionnaires, they were followed up with a phone call. An opt-out form was available for caregivers to complete if they did not want to participate. If caregivers did not respond to their initial invitation pack, a reminder pack was sent. In addition to postal invitation, researchers [EM and KC] attended PKU clinics, and the study was advertised on posters displayed in PKU clinics and social media (Facebook) and via NSPKU and clinic newsletters. On return of the questionnaires, participants received a £5 shopping voucher. Ethical approval was granted by the NHS Greater Manchester Central Research Ethics Committee (REC reference number: 15/NW/0454). The study, which was also approved by the University of Manchester Research Subcommittee and the Manchester, Liverpool and Bradford NHS Research and Development departments, was conducted in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration (1975, 2000 revision). Informed written consent was obtained from all participants.

Statistical Analysis

Average score substitution was used for minor missing data on GHQ-12 and/or PIP. As one participant had an incomplete PIP, she/he was excluded from analyses involving this measure. Assumptions of normality were met for all variables, except MSPSS significant other subscale and the child dependency scale, which were negatively skewed. Pearson's and Spearman's correlations were therefore used, depending on data distribution, to examine associations between demographic variables, caregiver measures and treatment adherence. Although multiple correlational analyses were performed, Bonferroni corrections were not utilised (Nakagawa 2004) with attention paid to the post hoc effect size of significant results. Multiple regression analysis was used to examine the predictors of parental psychological distress (GHQ-12 score) and exploratory regression analyses to explore predictors of parenting stress (frequency and difficulty) and treatment adherence. With minimum $N = 10$ participants per predictor variable to prevent overfitting, four predictor variables were included in the regression models using $p = 0.05$ for all analyses. All analyses were performed using IBM SPSS 20.

Results

Forty-six (24%) of 192 invited caregivers participated, mean age 36 years and 11 months (SD = 8 years and 4 months, range = 22 years to 66 years and 2 months), with 28/94 from Manchester, 6/44 from Liverpool and 12/54 from Bradford, comprising of 44 mothers (96%), one father (2%) and one grandmother (2%). Two caregivers completed questionnaires for two siblings with PKU, and for the purposes of analysis, one child from each sibling pair was selected at random. Twenty-nine (63%) of the children were male and 17 (37%) were female, with a mean age of 6 years and 11 months (SD = 4 years and 10 months, range = 4 months to 15 years and 10 months). English was the caregivers' first language, with the exception of one mother (Punjabi). Educational attainment included General Certificate of Secondary Education (GCSE) ($N = 10/22\%$), A Levels ($N = 8/17\%$), diploma ($N = 4/9\%$), degrees (N = 13/28%), masters ($n = 5/11\%$) and

doctorate ($N = 1/2\%$) [no information $N = 5/11\%$]. Thirty-six (78%) caregivers reported a mean income of £37,157 (SD = £24,598; range = £6,500–100,000).

The mean GHQ-12 score was 13.09 (see Table 1) with 27 caregivers (59%) scoring above the clinical cut-off score of 12, indicative of clinically significant anxiety and depression. The mean care dependency score was 5.78, indicating that as might be expected given their age, the children were highly dependent on their carers for dietary treatment adherence.

Caregiver psychological distress and stress related to caring for a child with an illness were strongly and negatively associated with caregiver level of resilience (see Table 2). Levels of psychological distress and parenting stress were positively correlated. Conversely, level of psychological distress was not significantly associated with perceived social support, child dependency or demographic factors (caregiver and child age, caregiver qualifications and household income).

Whilst there was a moderate negative correlation between caregivers' stress related to caring for a child with an illness (both frequency and difficulty) and perceived support from friends, it was not significantly correlated with their perceived support from family or significant other. Although level of child dependency was moderately and positively associated with stress difficulty score, it was not associated with stress frequency score. Finally, stress was not significantly associated with demographic factors.

Regarding treatment adherence, the percentage of blood phe concentrations in target range was moderately negatively correlated with parent and child age and moderately positively correlated with caregivers' perceived support from family, but was not associated with caregivers' perceived support from friends or significant other, child dependency, resilience, psychological distress, stress related to caring for a child with an illness or other demographic factors. Percentage of blood samples submitted was moderately negatively associated with the proportion of blood phe concentrations in target range but was not correlated with any other variables.

Table 1 Descriptive statistics for caregiver measures and treatment adherence

Measure	*N*	Mean (SD)	Range of data (scale range)
GHQ-12	46	13.09 (5.09)	5–27 (0–36)[a]
PIP total frequency	45	102.04 (25.92)	50–158 (42–210)
PIP total difficulty	45	99.98 (30.79)	45–169 (42–210)
RSA	46	167.46 (24.12)	114–227 (33–231)
MSPSS friend	46	19.61 (6.62)	4–28 (4–28)
MSPSS family	46	20.93 (5.78)	7–28 (4–28)
MSPSS sig. other	46	21.57 (7.51)	4–28 (4–28)
MSPSS total	46	62.11 (14.785)	27–84 (12–84)
Care dependency	46	5.78 (2.086)	1–7 (1–7)
% phe in target	46	69.09 (23.992)	0–100
% blood samples	46	107.17 (60.484)	8–333

[a] Scores over 12 indicate distress within the clinical range

Multiple regression analysis was used to identify predictors of parental psychological wellbeing using the variables that were hypothesised to influence GHQ-12 score (Table 3). As parenting stress frequency and difficulty scores were highly intercorrelated ($r = 0.93$), only the latter was used.

When parenting stress, resilience, perceived social support and child dependency were entered simultaneously, the regression model explained 36.7% of the variance in GHQ-12 score. Caregivers' parenting stress and resilience independently accounted for significant variance ($\beta = 0.061$ and $-0.0.08$, $p = 0.032$ and 0.049, respectively), but perceived social support and child dependency did not ($p = 0.497$ and 0.673, respectively). Exploratory regression analyses were used to examine predictors of parenting stress (frequency and difficulty, Table 4). Given the close relationship between child dependency and age (Spearman's $\rho = -0.63$), age was entered first to determine whether child dependency could explain additional variance. Perceived support from friends was entered rather than total social support, given the higher correlation with parenting stress.

Child age did not significantly predict parenting stress related to caring for a child with an illness (frequency or difficulty). Whilst caregivers' level of resilience explained significant variance in PIP difficulty and frequency after accounting for child age ($\beta = -0.677$ and -0.538, $p = <0.001$ and 0.001, respectively), perceived support from friends and level of child dependency did not.

When examining predictors of the proportion of blood phe concentrations within target range (Table 4), child age was entered first, given previously reported associations with metabolic control (MacDonald et al. 2010). Parental age was not selected as a predictor variable given the high correlation with child age ($r = 0.73$), and perceived support from family was used rather than total social support score given the stronger correlation with percentage of blood phe concentrations in target range. Child age accounted for significant variance in the proportion of blood phe concentrations in target range ($\beta = -1.879$, $p = 0.009$, $r^2 = 0.147$), followed by perceived social support ($\beta = 1.844$, $p = 0.002$). Inclusion of perceived support from family, parental wellbeing and level of child depen-

Table 2 Correlations between demographic variables, caregiver measures and treatment adherence

	1	2	3	4	5	6	7	8	9	10	11	12	13	14
1. Parent age														
2. Child age	0.73**													
3. Parent qualification	0.20	0.01												
4. Parent income	0.29	0.15	0.65**											
5. MSPSS total	−0.02	0.00	−0.07	0.27										
6. MSPSS friend	0.15	0.27	−0.11	0.12	0.72**									
7. MSPSS family	−0.08	−0.04	−0.18	−0.04	0.71**	0.30*								
8. MSPSS sig. other	−0.18[a]	−0.26[a]	0.14[a]	0.57**[a]	0.76**[a]	0.34*[a]	0.42**[a]							
9. Child dependency	−0.34*[a]	−0.63**[a]	0.06[a]	−0.09[a]	−0.28[a]	−0.45**[a]	−0.19[a]	−0.02[a]						
10. RSA total	0.09	0.11	0.17	0.21	0.52**	0.41**	0.30*	0.40**[a]	−0.24[a]					
11. GHQ-12	−0.06	−0.05	0.18	0.01	−0.19	−0.16	−0.09	−0.16[a]	0.16[a]	−0.54**				
12. PIP frequency	0.08	−0.08	0.03	−0.16	−0.30*	−0.37*	−0.18	−0.21[a]	0.27[a]	−0.62**	0.51**			
13. PIP difficulty	−0.04	−0.14	0.04	−0.24	−0.29	−0.39**	−0.2	−0.16[a]	0.30*[a]	−0.63**	0.55**	0.93**		
14. % phe in target	−0.36*	−0.38**	−0.13	−0.03	0.11	−0.16	0.43**	0.19[a]	0.19[a]	−0.04	−0.09	−0.10	−0.08	
15. % blood samples	0.14	0.13	0.15	−0.02	0.13	0.26	−0.04	−0.02[a]	−0.20[a]	0.17	−0.10	0.04	0.06	−0.43**

Note: *$p < 0.05$, **$p < 0.01$

[a] Spearman's rho correlation, all other correlations are Pearson's

Table 3 Multiple regression analysis using parenting stress, resilience, social support and child dependency to predict caregiver psychological distress

Enter	*B*	SE B	*p*	R^2	*F* change
Parenting stress: difficulty	0.061	0.027	0.032		
Resilience	−0.08	0.039	0.049		
Social support: total	0.035	0.051	0.497		
Child dependency	0.145	0.341	0.673	0.367	5.791**

Note: $^{**}p < 0.01$
Criterion variable: GHQ total score

Table 4 Hierarchical regression analyses predicting parenting stress (difficulty and frequency) and the proportion of blood phe concentrations within target range

Criterion variable: PIP difficulty					
Enter	*B*	SE B	*p*	R^2	*F* change
1. Age	−0.875	0.946	0.360	0.019	0.855
2. Age	0.536	0.988	0.590		
Social support: friends	−0.649	0.638	0.316		
Resilience	−0.677	0.177	<0.001		
Child dependency	2.495	2.528	0.330	0.435	7.713**
Criterion variable: PIP frequency					
Enter	*B*	SE B	*p*	R^2	*F* change
1. Age	−0.413	0.802	0.609	0.006	0.265
2. Age	1.014	0.833	0.231		
Social support: friends	−0.537	0.539	0.324		
Resilience	−0.538	0.149	0.001		
Child dependency	3.062	2.133	0.159	0.433	7.642**
Enter	*B*	*SE B*	*p*	R^2	*F change*
1. Age	−1.879	0.683	0.009	0.147	7.571**
2. Age	−1.249	0.835	0.143		
Social support: family	1.844	0.547	0.002		
Parental wellbeing	−0.432	0.612	0.484		
Child dependency	2.02	2.01	0.321	0.341	5.309**
Enter	*B*	*SE B*	*p*	R^2	*F change*
1. Age	−1.807	0.623	0.006		
Social support: family	1.706	0.529	0.002		
Parental wellbeing	−0.320	0.601	0.597	0.325	6.741**

Note: $^{**}p < 0.01$

dency in the regression model increased the percentage of variance explained from 14.7 to 34.1%, but age was no longer significant after adjusting for the other variables ($p = 0.143$). In another model that excluded child dependency and included child age, social support from family and parental distress (Table 4), child age and social support explained significant independent variance, whilst the inclusion of child dependency only explained an additional 1.6% of the variance in the proportion of blood phe levels in target range (r^2 [including child dependency] = 0.341; r^2 [excluding child dependency] = 0.325).

Discussion

As predicted, caregivers had high levels of clinically significant psychological distress, reflecting the additional challenges of caring for a child with PKU. This is consistent with previous research in both PKU and other disorders (Gundaz et al. 2015; Mahmoudi-Gharaei et al. 2011; Cousino and Hazen 2013). Increased resilience was also associated with reduced psychological distress in the present study. In contrast to earlier studies (Fidika et al. 2013; Ten Hoedt et al. 2011), caregivers' psychological

distress was not associated with their perceived social support in the present study.

In the present study, level of dependency on the caregiver for dietary adherence was not associated with level of psychological distress. Although it correlated with parenting stress difficulty, it was not a significant predictor when entered with other variables. In addition, child age and caregiver wellbeing were not significantly associated, which is congruent with Gundaz et al. (2015), but not with other studies reporting an association between child age and parental quality of life (Fidika et al. 2013; Ten Hoedt et al. 2011).

Contrary to prediction, caregiver levels of psychological distress, parenting stress and resilience were not associated with treatment adherence. Although at variance with other metabolic conditions such as type 1 diabetes (Driscoll et al. 2010; MacKey et al. 2014; Skocic et al. 2012; Whittemore et al. 2012), this is consistent with previous research in PKU (Fehrenback and Peterson 1989; Reber et al. 1987) and implies that experiencing increased levels of psychological distress does not affect adherence to treatment.

As per previous research (MacDonald et al. 2010), child age accounted for nearly 15% of the variance in blood phe concentration data, but child dependency was not significantly correlated with treatment adherence, suggesting that other factors around food and lifestyle may be involved (Levy and Waisbren 1994). After accounting for age, higher levels of caregiver's perceived support from family predicted better metabolic control, consistent with other metabolic conditions (Miller and DiMatteo 2013). Such increased family support may negotiate the challenges of dietary adherence, for example, through greater assistance with meeting the child's dietary needs and making necessary adjustments. Finally, socioeconomic factors were not associated with parental wellbeing or treatment adherence.

Limitations

In the present study, it was identified that using proportion of required blood samples submitted had limitations as an estimate of treatment adherence, because it was not possible to obtain the number of additional samples requested. The correlation between the proportion of submitted samples and the proportion of phe concentrations in target range ($r = -0.43$) indicated that more samples were requested when metabolic control was poor, suggesting that using the proportion of blood samples as a measure of treatment adherence should be treated with caution. However, exploratory t-tests were carried out to examine differences between children with 100% blood samples submitted and children with less than 100%, with no significant differences for any caregiver or demographic variable. Other limitations include the cross-sectional design of the study and the lack of an appropriate control group, whilst acknowledging the difficulties involved in identifying the latter.

Implications for Clinical Practice

The current findings highlight consideration of the psychological impact of parenting a child with PKU and the need for appropriate support to caregivers, such as referral to appropriate psychological services or support groups (Awiszus and Unger 1990). With regards to treatment adherence, interventions to promote dietary compliance may be particularly important for older children, as metabolic control decreases with age. In addition, interventions such as family therapy, involving communication training and cognitive restructuring to promote metabolic control (Wysocki et al. 2006), may be required.

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Synopsis

This study identified that for parents of children with phenylketonuria, parental psychological wellbeing was predicted by parenting stress and resilience, whereas treatment adherence was predicted by child age and perceived support from family.

Compliance with Ethics Guidelines

Conflict of Interest

Emma Medford, Dougal Hare, Katie Carpenter, Stewart Rust, Simon Jones, and Anja Wittkowski declare that they have no conflict of interest.

Informed Consent

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 (5). Informed consent was obtained from all participants for being included in the study.

Details of the Contributions of Individual Authors

Emma Medford contributed to identifying the research question, designing and planning the research, all aspects of the method section, and the majority of the writing of the article. She was the main researchers on this project.

Dougal Hare contributed to identifying the research question, designing and planning the research, and writing the article.

Katie Carpenter contributed to identifying the research question, deciding on the scope of the research and data collection.

Stewart Rust contributed to identifying the research question and designing and planning the research.

Simon Jones contributed to identifying the research question and designing and planning the research.

Anja Wittkowski contributed to the statistical analysis and writing the article. She oversaw the research process and the writing of the final manuscript.

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