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RESEARCH REPORT

Treatment Adherence in Type 1 Hereditary Tyrosinaemia (HT1): A Mixed-Method Investigation into the Beliefs, Attitudes and Behaviour of Adolescent Patients, Their Families and Their Health-Care Team

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Abstract *Background*: Type 1 hereditary tyrosinaemia (HT1) is a rare metabolic disorder caused by an enzymatic defect in the metabolism of the amino acid tyrosine. Primary treatment for HT1 is nitisinone (Orfadin) in conjunction with a low-tyrosine/phenylalanine diet. The appropriate use of nitisinone medication and adhering to specialist diet is thus central to the successful management of HT1.

Objective: To date, no published research has examined adherence (to medication and diet) and factors that influence it in the context of HT1. This study aimed to ascertain the extent to which non-adherence is a problem in this patient population, identify perceived barriers and facilitators to treatment adherence and explore the role of illness beliefs and treatment perceptions in treatment management.

Methods: The present study used a combination of qualitative interviews and quantitative survey methods with patients, carers and health-care professionals (HCPs).

Results: This study found adherence to medication to be high amongst patients with HT1 and their carers who administer it. However, adherence to diet was reported to be much lower. A key factor influencing adherence to diet was age, with adolescents reported to have most difficulty adhering.

Conclusions: The results indicate that adherence to dietary instructions becomes more problematic as children with HT1 grow older. Greater involvement in managing their condition and in their consultation at an early stage may have a positive impact on future adherence by increasing their investment and understanding of the treatment regime, potentially making adherence rates more stable and less influenced by moving through different life stages.

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Introduction

Type 1 hereditary tyrosinaemia (HT1) is an ultra-orphan disease caused by an enzymatic defect in the metabolism of the amino acid tyrosine. It typically presents in infancy as failure to thrive and, if left untreated, can lead to progressive liver and kidney dysfunction as well as neurological crisis and death (Sniderman King et al. 2006).

HT1 has an estimated incidence of 1 case in every 100,000 births (Sniderman King et al. 2006). The latest prevalence estimate available from Orphanet is 1 per 2,000,000 people (Orphanet 2007). Although HT1 is uncommon in all populations, there is considerable variation in its incidence according to region and ethnic background. For example, at a centre for hereditary metabolic disorders in the UK, the frequency of HT1 was

approximately 100 times higher amongst individuals of Pakistani origin compared with those of European descent (3.7 per million vs. 0.04 per million, respectively), and a difference attributed to a high rate of consanguineous marriages amongst Pakistani parents (Hutchesson et al. 1998). Additionally, overall incidence is much higher in Quebec, Canada (1 in 16,000), due to a founder mutation in the French-Canadian population (Sniderman King et al. 2006).

The primary treatment for HT1 is currently nitisinone (Orfadin), which works by inhibiting enzymes that convert excess tyrosine into urea. Nitisinone treatment is orally administered and taken in conjunction with a low-tyrosine/phenylalanine diet. Research has shown that if nitisinone treatment is started before 2 months of age, 4-year survival rates are increased to 94% compared to 29% with a controlled diet alone (Sobi 2010). The appropriate use of nitisinone medication and adhering to a specialist diet is thus central to the successful management of HT1.

There is little research regarding adherence to medication or diet in HT1; however, available research indicates that adherence may be suboptimal, particularly with regard to dietary restrictions (Masurel-Paulet et al. 2008; Wisse et al. 2012). Published research across a range of chronic conditions has shown that treatment regimen adherence is suboptimal across chronic illnesses (Sabaté 2003) and is significantly lower in adolescence (Dean et al. 2010; Salema et al. 2011).

Patients' perceptions and beliefs are consistently found to be important predictors of non-adherence (Nunes et al. 2009). For example, perceptions relating to the *cause* of the illness, its *nature* or identity, its *duration*, the personal *consequences* of suffering from it and the extent to which the illness can be *controlled* or cured, influence disease management (Broadbent et al. 2006). Patients' beliefs around the *necessity* of treatment and *concerns* about taking it also affect their adherence (Horne et al. 1999). Interventions focusing on changing these beliefs have been shown to be effective at improving adherence in the long term (e.g. Petrie et al. 2012).

To date, however, no published research has examined adherence challenges and support needs in the context of HT1 specifically. The present study used a combination of qualitative and quantitative research methods with patients, carers and health-care professionals (HCPs) to (a) ascertain the extent to which non-adherence is a problem in this patient population, (b) identify perceived barriers and facilitators to treatment adherence and (c) explore the role of illness beliefs and treatment perceptions in relation to treatment management. As this is such a small patient group, it was decided to run the study in two countries.

Methods

Sample

HCPs

HCPs from key sites in the UK (Birmingham, Manchester and Bradford) and France (Paris, Lyon and Marseille), who were involved in the care of patients with HT1, were identified and invited to take part in the qualitative arm of the study.

Patients

A total of 40 families with HT1 were identified across the research sites in the UK (Birmingham, Manchester and Bradford) and 37 families in France (Paris, Lyon and Marseille). Convenience sampling was employed, whereby all eligible patients (or their carers if under 12) at research sites in the UK and France were invited to participate in the study. Patients were excluded from the study if they were either under the age of 12, had received a liver transplant or had severe or profound intellectual impairments and learning difficulties. Additionally patients and carers who could not communicate in English or French fluently were excluded from the study.

Procedure

In the UK, ethical approval for the study was obtained from the Fulham Research Ethics Committee and the R&D department in each NHS site. French ethical approval was obtained from the equivalent research committees for the sites in France (CPP[1], CCTIRS[2], CNIL[3] and the CNOM[4]).

Eligible patients were identified by the lead physician at each site, informed about the research project and asked to provide consent for the research team to contact them regarding participation in the study. Those who expressed an interest were sent the study information sheet along with the questionnaire and a stamped addressed envelope for return of the questionnaire and signed consent form.

Qualitative Research

Semi-structured interviews were conducted in English or French, recorded and transcribed verbatim. The French

[0] Comité de Protection des Personnes – ethics committee in France.
[0] Comité consultatif sur le Traitement de l'Information en matière de Santé – a consultative committee specialising in health which gives advice to the data protection committee for medical projects.
[0] Commission nationale de l'informatique et des libertés – data protection committee.
[0] The French physician organisation.

interviews were translated into English for data analysis. Translations were reviewed by the interviewer in france for validity prior to data analysis.

The qualitative data was analysed using a framework analysis approach (Richie And Spencer 1994), which involves identifying key themes in the data in relation to the specific questions/issues driving the research (Gale et al. 2013).

Quantitative Research

The self-report questionnaire contained questions covering the following:

- Socio-demographic and disease-related information: Patients/carers were asked to indicate their gender, age, main language spoken, employment status, duration of diagnosis, details of treatments currently used for HT1 and any comorbid illnesses.
- Persistence to medication: A single item 'are you still using your prescribed medication?' was used to measure treatment persistence. Participants were asked to indicate yes or no.
- Adherence to medication was measured by a 6-item version of the Medication Adherence Report Scale (MARS) (Horne and Weinman 2002), a reliable and valid self-report measure of non-adherence.
- Adherence to dietary instructions was measured by four items. A single item devised for the study asked patients and carers to rate on a 5-point scale how well they thought they (patients) or their child (carers) usually adhered to dietary instructions. Response options ranged from 1 (not at all) to 5 (completely), with higher scores indicating higher adherence. Two items adapted from the MARS were included (I forget to stick to my diet regime and I stop adhering to my special diet regime for a while). In addition, participants were asked to state the number of days over the past week that they had not deviated from the recommended diet.
- Beliefs about medication: The Beliefs about Medicine Questionnaire (BMQ) (Horne et al. 1999) is a reliable and valid 10-item scale. Five items assess beliefs about the necessity of medication, and five assess concerns about medication.
- Illness perceptions: The Brief Illness Perception Questionnaire (BIPQ) was used to assess patients' and carers' cognitive and emotional representations of illness with a single item representing each illness perception (Broadbent et al. 2006).
- Mood: Anxiety was measured using the General Anxiety Disorder Assessment (GAD-2) (Kroenke et al. 2007). The PHQ 2 (Kroenke et al. 2003) was used to screen for depression.
- Social support: Perceptions of social support were assessed using the Medical Outcomes Study Social Support Survey (MOS-SSS) (Sherbourne and Stewart 1991).
- Relationship with physician: Four items were devised for the study to measure satisfaction and confidence in the physician. Participants were asked to rate their perceptions of care on a scale from 0 to 10, with higher scores indicating more positive perceptions of care (see Table 2).

Unless otherwise stated, the questions were scored in line with published recommendations.

Data were analysed using IBM SPSS Statistics version 21. Descriptive statistics were performed on all data. Pearson's correlations were used to explore relationships between variables, and t-tests were used to assess differences between patient and carer samples.

Results

Sample Characteristics

Qualitative interviews were conducted with four patients, nine carers and eight HCPs (three doctors, two dieticians, two specialist nurses, and one pharmacist).

A total of 27 participants, 22 (81%) who were adult carers and 5 (19%) patients, returned completed questionnaires. The demographic and clinical characteristics of the patient and carer sample who completed the demographic questionnaire are shown in Table 1. The majority of carers were female (15; 68%) with a mean age of 38 (SD = 8.9).

Due to the low response rate of this study, the quantitative data lacked the power to detect predictors of adherence. Data from the quantitative survey and qualitative interviews were thus combined to allow us to further explore and interpret trends identified through the statistical analyses.

Psychological Well-Being and Social Support

The majority of participants reported levels of anxiety and depression that were under the threshold for clinical caseness; however, 4 (15%) participants had scores on the GAD2 of >3, and 6 (22%) participants had scores of ≥2 on the PHQ2 that warrant clinical caseness. Patients reported more depressive symptoms than carers; conversely carers reported more symptoms of anxiety than patients. However these differences did not reach statistical significance.

Table 1 Demographic and clinical characteristics of the sample

			Overall ($n = 27$)	Patients ($n = 5$)	Carers ($n = 22$)
Country	UK	*n* (%)	10 (37.0)	2 (40.0)	8 (36.4)
	France	*n* (%)	17 (63.0)	3 (60.0)	14 (63.6)
Patient/Carer Gender	Male	*n* (%)	11 (40.7)	2 (40.0)	9 (40.9)
	Female	*n* (%)	16 (59.3)	3 (60.0)	13 (59.1)
Patient/Carer age		Mean (SD)	13.1 (4.3)	16.8 (4.2)	9.3 (4.4)
First language	English	*n* (%)	7 (25.9)	1 (20.0)	6 (27.3)
	French	*n* (%)	12 (44.4)	2 (40.0)	10 (45.5)
	Moroccan	*n* (%)	1 (3.7)	0	1 (4.5)
	Arabic	*n* (%)	3 (11.1)	1 (20.0)	2 (9.1)
	Russian	*n* (%)	1 (3.7)	0	1 (4.5)
	Gujarati	*n* (%)	1 (3.7)	0	1 (4.5)
	Punjabi	*n* (%)	2 (7.4)	1 (20.0)	1 (4.5)
Employment	Full time	*n* (%)	10 (37.0)	1 (20.0)	9 (40.9)
	Part time	*n* (%)	3 (11.1)	0	3 (13.6)
	Self-employed	*n* (%)	3 (11.1)	0	3 (13.6)
	Student	*n* (%)	4 (14.8)	3 (60.0)	1 (4.5)
	Unemployed	*n* (%)	3 (11.1)	0	3 (13.6)
	Other	*n* (%)	4 (14.8)	1 (20.0)	3 (13.6)
Duration of diagnosis		Mean (SD)	12.7 (3.8)	16.2 (3.2)	9.2 (4.3)
Prescribed nutritional supplements		*n* (%)	26 (96.3)	5 (100)	21 (95.5)
Prescribed co-medicines		*n* (%)	6 (22.2)	2 (40.0)	4 (18.2)

Table 2 Psychological well-being, social support and relationship with physicians

Psychological well-being and social support	Overall ($n = 27$) Mean (SD)	Patients ($n = 5$) Mean (SD)	Carers ($n = 22$) Mean (SD)
GAD2 anxiety	1.6 (1.7)	0.4 (0.9)	1.9 (1.7)
PHQ2 depression	0.9 (1.3)	1.8 (1.7)	0.8 (1.1)
MOS-SSS emotional/informational support	3.3 (0.9)	3.9 (0.9)	3.1 (0.9)
MOS-SSS tangible support	3.3 (0.9)	3.8 (0.8)	3.1 (0.9)
MOS-SSS affectionate support	4.2 (0.9)	5.0 (0.0)	4.1 (0.9)*
MOS-SSS positive social support	4.1 (0.8)	4.5 (0.5)	3.9 (0.9)
Relationship with physicians			
How satisfied are you with the care you/your child receives from your/their doctor	8.0 (1.7)	7.8 (1.9)	8.1 (1.7)
How likely is it that you would talk to your/your child's doctor if you had queries about your/your child's condition and the treatments you/they have been asked to use?	7.5 (2.4)	6.6 (1.5)	7.7 (2.5)
How much confidence do you have in your/your child's doctor with regard to tyrosinaemia?	8.0 (2.0)	7.2 (2.3)	8.2 (2.0)
How much do you think your physician understands you and your/your child's condition?	8.0 (2.0)	7.2 (2.6)	7.7 (2.0)

*$p < 0.005$

Descriptive statistics for depression, anxiety and social support are shown in Table 2.

The qualitative research amongst patients and carers found that the social and emotional impact of the condition was more evident in carers than patients. The diagnosis of HT1 was particularly devastating. Carers' descriptions of their concerns may explain the increased anxiety they reported. Primarily, there was concern for the present and future health of the child. In addition, carers were concerned for the child's emotional well-being, such as

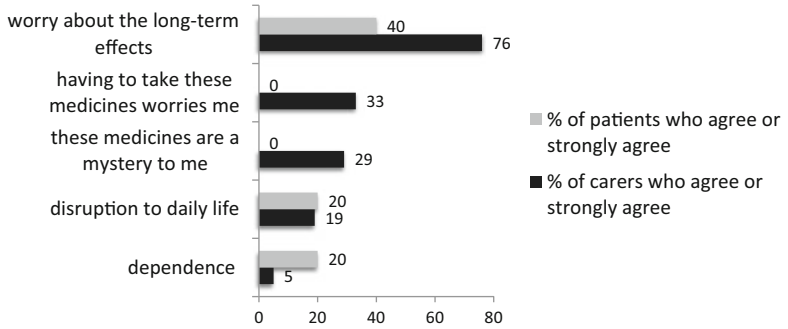

Fig. 1 Types of concerns held by patients and carers about nitisinone

their feelings of social exclusion and of being different. Feelings of isolation were common amongst carers, particularly at the time of diagnosis. This was attributed to the rarity of the condition and therefore the lack of available information and support.

> "I feel like we've been left a lot of the time to fend for ourselves" Carer 001, parent of a 10-year-old

Some carers often reported feelings of stress, anxiety and of being emotionally overwhelmed by the change in lifestyle and the difficulty of caring for a child with this condition. Carers often felt guilty because the condition is genetic, and one carer reported experiences of stigma and discrimination within her community. HCPs also reported that several parents seemed to experience a sense of stigma surrounding the condition and appeared reluctant to openly acknowledge that their child had a serious medical condition, to avoid setting them apart from other children.

Relationship with HCPs

Overall, participants reported a high level of satisfaction with their doctor and confidence in their doctor with regard to HT1 (see Table 2). Ratings were slightly lower amongst patients than carers; however, no significant differences were found.

The qualitative research confirms this level of satisfaction with HCPs in general, with patients perceiving HCPs as knowledgeable and reporting satisfaction with the support they had received. However, some carers reported unmet needs, such as beliefs that HCPs lacked understanding of the psychosocial impact of the condition and the difficulties involved in maintaining adherence to diet and managing the condition on a day-to-day basis. Carers also felt that HCPs should provide greater opportunities for the child to ask questions.

> "I don't think his consultants [and] dieticians explain it to him because he's a child and they see him as a child so they don't want to like bombard him with all the scientific information" Carer 004, parent of a 14-year-old

Perceptions of Illness and Treatment

All participants reported high beliefs in necessity for treatment (>scale midpoint), and these were significantly higher amongst carers than patients (carers: mean 4.6 (SD = 0.5); patients: mean 3.9 (SD = 0.3), $t = 3.455$; $p = 0.002$). Over half of the participants ($n = 16$; 59%) reported high concerns about their medication, in particular long-term effects (>scale midpoint); see Fig. 1. Descriptive statistics are shown in Table 3. Overall, participants perceived treatment to be helpful in controlling HT1; however, carers were significantly more convinced than patients that treatment was helpful (IPQ treatment control, carers: mean = 9.3 (SD = 0.9); patients: mean = 7.8 (SD = 1.4); $t = 2.920$; $p = 0.007$).

Adherence

Overall a high level of adherence to medication was reported, with a mean score of 29.1 (SD = 2.4) on the MARS. The mean number of days per week patients reported non-adherence was 0.1 (SD = 0.6). Patients reported lower adherence on all scales compared to carers. Only four carers (18%) scored <30 on the MARS (see Table 4), compared to 4 (100%) of patients (one patient had missing data). Adherence to medication was uniformly high

Table 3 Beliefs about illness and treatment

	Overall ($n = 27$) Mean (SD)	Patients ($n = 5$) Mean (SD)	Carers ($n = 22$) Mean (SD)
BMQ necessity (range = 1–5)	4.5 (0.5)	3.9 (0.3)	4.6 (0.5)*
BMQ concerns (range = 1–5)	2.7 (0.7)	2.4 (0.4)	2.8 (0.7)
IPQ consequences (range = 0–10)	6.8 (2.1)	6.6 (2.1)	6.8 (2.1)
IPQ timeline (range = 0–10)	8.9 (1.9)	9.4 (1.3)	8.8 (2.0)
IPQ personal control (range = 0–10)	6.6 (2.6)	6.0 (2.3)	6.7 (2.7)
IPQ treatment control (range = 0–10)	9.0 (1.2)	7.8 (1.4)	9.3 (0.9)**
IPQ identity (range = 0–10)	4.1 (2.9)	4.4 (3.8)	4.0 (2.8)
IPQ concern (range = 0–10)	8.1 (1.8)	7.4 (1.8)	8.3 (1.7)
IPQ coherence (range = 0–10)	7.5 (1.9)	6.4 (1.5)	7.8 (1.9)
IPQ emotional representations (range = 0–10)	7.1 (1.8)	6.4 (1.1)	7.2 (1.9)

*$p < 0.005$; **$p < 0.01$

Table 4 Adherence to medication and dietary recommendations

	Overall ($n = 27$) Mean (SD)	Patients ($n = 5$) Mean (SD)	Carers ($n = 22$) Mean (SD)
Medication MARS total	29.1 (2.4)	25.5 (5.1)	29.8 (0.4)
Medication MARS forget to take medication	4.4 (1.0)	2.6 (0.9)	4.9 (0.4)*
Medication MARS alter the dose of medication	4.9 (0.4)	4.5 (1.0)	5.0 (0.2)
Medication MARS stop taking medication	4.9 (0.4)	4.5 (1.0)	5.0 (0.0)
Medication MARS decide to miss out a dose	4.9 (0.6)	4.3 (1.0)	5.0 (0.0)
Medication MARS take less medication than instructed	4.9 (0.4)	4.5 (1.0)	5.0 (0.0)
Medication MARS take more medication than instructed	5.0 (0.0)	5.0 (0.0)	5.0 (0.0)
Medication Number of days non-adherent	0.1 (0.6)	1.0 (1.7)	0.0 (0.0)
Diet how well do you comply with instructions	4.1 (0.8)	3.0 (1.0)	4.3 (0.7)*
Diet adherence total (2 items)	7.8 (2.4)	6.0 (3.2)	8.1 (2.2)
Diet-forget to stick to diet regimen	3.7 (1.3)	2.8 (1.7)	3.9 (1.1)
Diet-stop adhering for a while	4.0 (1.3)	3.3 (1.5)	4.2 (1.2)
Diet number of days non-adherent	0.7 (1.2)	2.3 (2.1)	0.4 (0.8)

*$p = < 0.005$

on all MARS scales measuring intentional non-adherence (e.g. altering the dose intentionally). The findings show that patients were significantly more likely to report unintentional non-adherence (e.g. forgetting) than carers (patients mean (SD) = 2.6 (0.9); carers mean (SD) = 4.9 (0.4); $t = 5.562$; $p = 0.004$).

There was greater variation in rates of adherence to dietary recommendations. Overall non-adherence was reported on a mean of 0.7 day/week, with more days of non-adherence reported by patients (mean = 2.3 day/week; SD = 2.1) than carers (mean = 0.4 day/week; SD = 0.8). Carers reported a higher level of adherence to dietary instructions than patients (mean (SD) = 4.3 (0.7) amongst carers; 3.0 (1.0) amongst patients ($t = 2.821$; $p = 0.010$).

The qualitative research amongst patients, carers and HCPs supported this finding that adherence to dietary restrictions and protein supplements was often less successful than adherence to nitisinone.

> "The biggest problem is compliance with the diet rather than compliance with the medicines and in general they're relatively compliant with the medicine but diet less so" Physician, Birmingham

Factors Associated with Adherence to Diet and Medication

Illness Experience and Perceptions

Carers of older children and those who had been diagnosed for a longer period of time reported higher adherence to medication ($r = 0.436$, $p = 0.048$; $r = 0.456$, $p = 0.038$, respectively). Carers who believed that their child's illness would last a long time (IPQ Timeline: $r = 0.472$, $p = 0.036$) and those who attributed fewer symptoms to HT1 (IPQ Identity: $r = -0.496$, $p = 0.026$) were more adherent to medication. There was a significant positive correlation between concerns about HT1 and adherence to dietary recommendations (IPQ concern: $r = 0.399$; $p = 0.048$). Those who were more concerned about HT1 reported higher adherence. Amongst carers, anxiety was inversely correlated with adherence to medication (GAD2: $r = -0.547$, $p = 0.013$), with a similar trend for depression (PHQ2: $r = -0.419$, $p = 0.066$).

Interviews with patients and carers suggest that the perception of consequences of non-adherence, such as experiencing symptoms after eating protein, can also be a driver for better adherence. Indeed, HCPs noted that if the patient eats restricted foods, they don't immediately become ill, which can lead both patients and their carers to believe that full adherence to dietary recommendations is not necessary.

HCPs felt that a lack of understanding about the condition, its seriousness and the role of diet and medication was linked to non-adherent behaviour.

Treatment Perceptions and Experiences

In the sample as a whole, there was a significant positive correlation between BMQ necessity beliefs and adherence to treatment, indicating that those who were more convinced of the necessity of nitisinone were more adherent ($r = 0.494$; $p = 0.014$). The qualitative interviews amongst patients and carers found that participants were convinced that treatment was effective at controlling the condition and maintaining good health. Adherence was driven by a strong perceived need for treatment (both medication and dietary restrictions).

> "She has got to have her medicine, if she doesn't have it, she will become poorly". Carer 002, parent of a 10-year-old

Adherence to treatment was also significantly associated with a stronger belief that treatment can successfully control HT1 (IPQ treatment control: $r = 0.533$; $p = 0.007$).

In addition, the unpleasant taste of protein supplement drinks was reported by many participants as a particular difficulty, especially for parents of small children, who were often adamant in their refusal to take them.

Patient and Family Factors

A significant inverse correlation was found between child age and adherence within the overall sample ($r = -0.634$; $p = 0.0001$) and amongst the carers ($r = -0.526$; $p = 0.012$), indicating that both carers and patients experience increasing difficulty with adherence to dietary recommendations as the patient grows older. As children grow older, social situations, including school dinner times, posed particular difficulties. Problems arise as children grow older because they become more independent and become aware of the differences between their own diet and those of their family or peers and start to take control of their own medication/eating habits. HCPs also suggested that since patients have no recollection of being unwell, they don't always perceive that they have a serious condition.

> "I've found him in the middle of the night, some nights, coming down to fridge and you'll go what are you doing? And he goes I want some ham". Carer 003, parent of 3- and 6-year-olds

The qualitative interviews amongst patients and carers and HCPs suggest that establishing a daily routine and advanced planning are important for adherence. For example, ensuring adequate supplies of medicines or dietary supplements and preparation for being away from home seem to be important for successful adherence in this population.

Although many had good support networks, both carers and patients talked of a lack of understanding from others about the severity and potential consequences of the condition and the importance of adhering to a strict diet.

> "And then telling people, they kind of just went, Oh she's vegan … there was no real understanding". Carer 001, parent of a 10-year-old

Discussion

This mixed-method study amongst patients with HT1, their carers and HCPs provided valuable insight into the extent of adherence to treatment recommendations, namely, diet and medication (nitisinone). Findings from the qualitative and quantitative phases revealed that reported adherence to nitisinone was high. However, adherence to dietary recommendations was more problematic. These findings support previous research which indicates that adherence to dietary restrictions may be suboptimal (Masurel-Paulet et al. 2008; Wisse et al. 2012).

Patients reported lower levels of adherence to medication and dietary restrictions than carers. This finding may be influenced by carers' strong perceived necessity for treatment, whereas patients were more likely to have doubts about their personal necessity for treatment and were less convinced than carers that their treatment was effective in controlling their condition. In addition those carers who perceived their children's illness to have a chronic timeline and those who attributed fewer symptoms to HT1 were more adherent. Although it is not possible to determine causal relationships due to the cross-sectional design of the study, it is important to consider that the latter finding may be a consequence of, rather than a cause of, high adherence. In addition, carers who reported higher levels of anxiety and depression were less adherent to their children's medication regime. These differences between carers and patients provide insight into key factors to target amongst patients to support their continued adherence into adolescence and adulthood.

The results indicate that adherence to dietary instructions becomes more problematic as children with HT1 grow older. Published research across a range of chronic conditions has shown that treatment regimen adherence is significantly lower in adolescence than in adult populations (Dean et al. 2010; Salema et al. 2011). One explanation for this could be the unique physical, social and emotional challenges experienced by all young people during adolescence, thus making the management of a strict treatment regime seem like an additional and often unnecessary burden that sets them apart from their peers (Salema et al. 2011). In addition, it was reported that young patients are often not actively involved in their consultations with HCPs. Greater involvement in managing their condition and in their consultation at these early stages (as appropriate) may have a positive impact on future adherence by increasing their investment and understanding of the treatment regime, potentially making it more stable and less influenced by moving through different life stages.

The study has several limitations including a very small sample size, particularly for the quantitative phase of the research. The small sample size and lack of variation in adherence mean that the findings of this study should be interpreted with caution, as the study lacked power to detect predictors of adherence. Also, due to the small sample size and anonymity of the survey responses, it was not possible to explore potential similarities and/or differences in the response pattern of patient/carer dyads. Since patients in this study typically reported lower levels of adherence than carers, this could be an interesting avenue to explore in future research. Additionally, since a cross-sectional design was employed, it was not possible to infer the direction of relationships. It should also be considered that self-report measures of adherence may be prone to bias. However, despite the small sample, the present study successfully gained insight from a range of perspectives into the experiences of living with or caring for someone with HT1 through a mixed-method approach. Mixed-method research designs are often used to expand the scope of enquiry by accessing a wider range of data (O'Cathain and Thomas 2006) and are ideal in areas where there is currently little information such as the study of rare diseases.

Recommendations and Conclusions

Additional research, using prospective designs and larger samples, is required to track and examine levels of adherence and barriers to/strategies for maintaining adherence as children and adolescence grow older and reach adulthood. In addition, it is important for HCPs to provide practical and emotional support for both parents and children to facilitate adherence to dietary restrictions, with a focus on social situations and when away from home (e.g. psychological support to address stigma and address feelings of being different to others; practical support to plan for risk situations and facilitate appropriate food choices). Children should also be encouraged to ask questions about their condition and their treatment regimen, with a view to making them more actively involved in their care, while they still have the full support of their carer. Greater support may be needed when transitioning from child to adult services, with recognition of the potential psychosocial factors that may influence an unhelpful change in behaviours relating to medication and dietary management.

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Disclaimer

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Take-Home Message

Patients with HT1 and their carers need greater support adhering to the low tyrosine/phenylalanine diet necessary for successful management of this condition, through education and increased involvement in consultations.

Compliance with Ethics Guidelines

The submitting authors have circulated the article and secured final approval of the version to be peer-reviewed from all co-authors prior to article submission. We can also conclude:

- Absence of previous similar or simultaneous publications.
- That all authors have inspected and approved the manuscript.
- That all authors have made a substantial contribution to the work (all authors should have been involved in (a) conception and design, or analysis and interpretation of data, and (b) drafting the article or revising it critically for important intellectual content).
- All authors have agreement to submission.

Conflict of Interest

Dr Sumaira Malik, Dr Sinead NiMhurchadha, Dr Christina Jackson and Dr Lina Eliasson PhD are all employed by Atlantis Healthcare, which received funds from Swedish Orphan Biovitrum AB to carry out this project.

Professor John Weinman has received consulting fees from Swedish Orphan Biovitrum AB, to carry out this project and attend scientific meetings.

Dr Sandrine Roche has received Professor Weinman is also a part time employee of Atlantis Healthcare. Support from Swedish Orphan Biovitrum AB, to attend scientific meetings and to carry out data collection for this study in France.

Professor John H. Walter has received support from Swedish Orphan Biovitrum AB, to attend scientific meetings.

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 patients prior to inclusion in the study.

Details of the contributions of individual authors:

SM: study conception and design, data collection, analysis and interpretation and drafting of the manuscript. SNM: data collection, analysis and interpretation and drafting of the manuscript. CJ and LE: data interpretation and critical revision of the manuscript. Prof JW: study conception and design and critical revision of the manuscript. SR: data collection and critical revision of the manuscript. JW: data collection and critical revision of the manuscript. All authors gave final approval of the version to be published.

References

Broadbent E, Petrie KJ, Main J, Weinman J (2006) The brief illness perception questionnaire. J Psychosom Res 60:631–637

Dean AJ, Walters J, Hall A (2010) A systematic review of interventions to enhance medication adherence in children and adolescents with chronic illness. Arch Disease Child 95:717–723

Gale NK, Heath G, Cameron E, Rashid S, Redwood S (2013) Using the framework method for the analysis of qualitative data in multi-disciplinary health research. BMC Med Res Methodol 13:117. doi:10.1186/1471-2288-13-117

Horne R, Weinman J (2002) Self-regulation and self-management in asthma: exploring the role of illness perceptions and treatment beliefs in explaining non-adherence to preventer medication. Psychol Health 17:17–32

Horne R, Weinman J, Hankins M (1999) The beliefs about medicines questionnaire: the development and evaluation of a new method for assessing the cognitive representation of medication. Psychol Health 14:1–24

Hutchesson A, Bundey S, Preece MA, Hall SK, Green A (1998) A comparison of disease and gene frequencies of inborn errors of metabolism among different ethnic groups in the West Midlands, UK. J Med Genet 35:5

Kroenke K, Spitzer RL, Williams JB (2003) The Patient Health Questionnaire-2: validity of a two-item depression screener. Med Care 41:1284–1292

Kroenke K, Spitzer RL, Williams JB, Monahan PO, Löwe B (2007) Anxiety disorders in primary care: prevalence, impairment, comorbidity, and detection. Ann Intern Med 146:317–325

Masurel-Paulet A, Poggi-Bach J, Rolland MO, Bernard O, Guffon N, Dobbelaere D, Sarles J, de Baulny HO, Touati G (2008) NTBC treatment in tyrosinaemia type I: long-term outcome in French patients. J Inherit Metab Dis 31:81–87

Nunes V, Neilson J, O'flynn N, Calvert N, Kuntze S, Smithson H et al (2009) Clinical guidelines and evidence review for medicines adherence: involving patients in decisions about prescribed medicines and supporting adherence. National Collaborating Centre for Primary Care and Royal College of General Practitioners, London, p 364

O'Cathain A, Thomas K (2006) Combining qualitative and quantitative methods. Qual Health Care 3:102–111

Orphanet (2007) Tyrosinemia type 1. http://www.orpha.net/consor/cgi-bin/Disease_Search.php?lng=EN&data_id=3494

Petrie KJ, Perry K, Broadbent E, Weinman J (2012) A text message programme designed to modify patients' illness and treatment beliefs improves self-reported adherence to asthma preventer medication. Br J Health Psychol 17:74–84

Richie J, Spencer L (1994) Qualitative data analysis for applied policy research. In: Burgess RABA (ed) Analysing qualitative data. Routledge, London, pp 173–194

Sabaté E (2003) Adherence to long-term therapies: evidence for action. World Health Organization, Geneva

Salema NEM, Elliott RA, Glazebrook C (2011) A systematic review of adherence-enhancing interventions in adolescents taking long-term medicines. J Adolesc Health 49:455–466

Sherbourne CD, Stewart AL (1991) The MOS social support survey. Soc Sci Med 32:705–714

Sniderman King L, Trahms C, Scott C (2006) Tyrosinemia type 1. SourceGeneReviews™[Internet]. Seattle (WA): University of Washington, Seattle

SOBI (2010) NTBC Study: Swedish Orphan AB Report No. 2000 010 02

Wisse RP, Wittebol-Post D, Visser G, van der Lelij A (2012) Corneal depositions in tyrosinaemia type I during treatment with Nitisinone. BMJ Case Rep. doi:10.1136/bcr-2012-006301