Defining tetrahydrobiopterin responsiveness in phenylketonuria: survey results from 38 countries

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ABSTRACT

Background: A subset of patients with phenylketonuria benefit from treatment with tetrahydrobiopterin (BH_4), although there is no consensus on the definition of BH_4 responsiveness. The aim of this study therefore was to gain insight into the definitions of long-term BH_4 responsiveness being used around the world.
Methods: We performed a web-based survey targeting healthcare professionals involved in the treatment of PKU patients. Data were analysed according to geographical region (Europe, USA/Canada, other).
Results: We analysed 166 responses. Long-term BH_4 responsiveness was commonly defined using natural protein tolerance (95.6%), improvement of metabolic control (73.5%) and increase in quality of life (48.2%). When a specific value for a reduction in phenylalanine concentrations was reported ($n = 89$), 30% and 20% were most frequently used as cut-off values (76% and 19% of respondents, respectively). When a specific relative increase in natural protein tolerance was used to define long-term BH_4 responsiveness ($n = 71$), respondents most commonly reported cut-off values of 30% and 100% (28% of respondents in both cases). Respondents from USA/Canada ($n = 50$) generally used less strict cut-off values compared to Europe ($n = 96$). Furthermore, respondents working within the same center answered differently.
Conclusion: The results of this study suggest a very heterogeneous situation on the topic of defining long-term BH_4 responsiveness, not only at a worldwide level but also within centers. Developing a strong evidence- and consensus-based definition would improve the quality of BH_4 treatment.

Abbreviations: BH4, tetrahydrobiopterin; PAH, phenylalanine hydroxylase; Phe, phenylalanine; PKU, phenylketonuria; USA, United States of America.

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1. Introduction

Phenylketonuria (PKU, MIM 261600) is an inborn error of amino acid metabolism caused by a deficiency of the enzyme phenylalanine (Phe) hydroxylase (PAH) [1]. If left untreated, PKU causes high blood Phe concentrations, leading to severe intellectual disability and behavioural problems. Therefore, limiting dietary Phe intake through a natural protein-restricted diet is essential. Together with the intake of amino acid supplements, this life-long treatment is effective in preventing most complications associated with untreated PKU. However, the treatment for PKU may pose a high burden for patients and caregivers, and can be hard to maintain, especially after childhood [2]. Moreover, outcome in some treated PKU patients is still suboptimal [3].

Besides the dietary treatment, the pharmacological chaperone tetrahydrobiopterin (BH_4) is beneficial for a subset of PKU patients. In BH_4-responsive patients, treatment with BH_4 increases residual PAH activity, which results in a decrease in blood Phe concentrations and/or an increase in natural protein tolerance [4]. Considering not all PKU patients respond to BH_4, it is important to appropriately select patients with PKU who benefit from long-term BH_4 treatment. Evaluating eligibility for treatment with BH_4 is typically done by performing a BH_4 testing period or treatment trial to assess its effects. However, there is on-going debate on how BH_4 responsiveness should be defined, i.e. which effects of BH_4 treatment justify long-term treatment. This debate is also reflected by differences in the recommendations in the two major international PKU guidelines [5,6]. Specifically, the European guidelines define BH_4 responsiveness as an increase of 100% or more in natural protein tolerance or improved biochemical control (>75% of phenylalanine levels in target range), whereas the American guidelines state that clinical judgement is required to determine BH_4 responsiveness.

To harmonize treatment for PKU patients and ensure appropriate use of BH_4, it is important to have a uniform definition of BH_4 responsiveness that can be used by healthcare professionals worldwide. Therefore, it is necessary to have a good overview of the definitions of BH_4 responsiveness that are currently used, and to assess the extent of agreement on this topic. We therefore performed an international survey among healthcare professionals working in the field of PKU.

2. Methods

2.1. General information

We performed a survey using a web-based questionnaire targeting healthcare professionals involved in the care of PKU patients. The medical ethical committee of the University Medical Center Groningen ascertained that our study protocol was not clinical research with test subjects as meant in the Dutch Medical Research act involving human subjects, and therefore did not find it necessary to review the protocol. The CHERRIES checklist for reporting results of internet e-surveys was used to draft this manuscript [7]. Compliance with this checklist is described in Supplementary material 1, where additional methodological information can be found as well.

2.2. Questionnaire development

A first draft of the questionnaire was developed by RAFE, AMJvW and FJvS. All other authors were given the opportunity to comment on this version. With these comments a second version of the questionnaire was developed, which was used for this survey (Supplementary material 2). Adaptive questioning was implemented to present specific follow-up questions depending on previous answers. Consequently, respondents who indicated that their centre did not use BH_4 as a treatment option for PKU patients received no questions concerning their definition of BH_4 responsiveness. The survey contained, depending on the responses, between 4 and 19 closed, semi-closed and open questions. Qualtrics (https://www.qualtrics.com/) was used to record survey responses. The technical functionality was tested by RAFE and AMJvW. The survey was available in English only.

2.3. Questionnaire distribution

The survey was open to everyone with access to the anonymous survey link. This link was distributed per email to healthcare professionals involved with PKU patients via the Metab-L and SSIEM mailing lists. In the invitation email, the goal of the study as well as the approximate time it would take to complete the survey was mentioned. A reminder was sent two weeks after the first invitation. After five more weeks, a second reminder was sent, specifically targeting SSIEM members from countries from which no response had yet been received. All invitees were encouraged to forward the invitation email to colleagues. Data were collected from March 8 to May 23, 2019.

2.4. Data analysis

Only complete questionnaires were analysed. IP addresses, location data (latitude and longitude), survey starting dates and times, and respondent names and main functions were checked to control for multiple entries from the same individual. Multiple responses per center were allowed because entries from different healthcare professionals working in the same center sometimes gave markedly different answers to the questionnaire. Since some answers to open questions covering the same subtopic overlapped, we analysed the overall survey results per subtopic and not per specific question. The following additional measures that were taken to enable analysis of the dataset: [1] if a respondent gave the same answer multiple times in different open questions, redundant answers were removed; [2] if a respondent gave a range for a cut-off value, the lowest number in that range was used; [3] answers regarding dietary intake given as mg Phe were converted into grams natural protein (using a conversion factor of 50 mg Phe for 1 g of natural protein); [4] since we aimed to analyse general healthcare practices, answers that were related to specific cases were not analysed; [5] answers that were unrelated to defining BH_4 responsiveness were removed; [6] responses to open questions were grouped.

Data were analysed using descriptive statistics and grouped according to geographical region (total, Europe, the United States of America (USA)/Canada). Differences between Europe and USA/Canada were assessed using Fisher's exact test, and cut-off values were considered as ordinal variables. IBS SPSS was used for all analyses.

3. Results

3.1. Responses

Three-hundred and forty different visitors clicked on the link in the invitation email, of whom 326 completed the first page of the survey (participation rate of 95.9%). Two-hundred and seventeen participants completed the entire questionnaire (completion rate of 66.6%).

3.2. Participants

Of the 217 respondents who completed the questionnaire, 50 respondents indicated that their center did not use BH_4 treatment. These responses came from Chile, Costa Rica, the Czech Republic, Finland, Ireland, Japan, Lebanon, Moldova, the Netherlands, Philippines, Serbia, Sri Lanka and Sweden (all $n = 1$); Croatia, France, Iran, Pakistan, Poland and Spain (all $n = 2$); Australia, Greece and USA (all $n = 3$); and the United Kingdom ($n = 16$). These responses were not used in further analyses. Additionally, one response was excluded from the analyses since it did not provide clear information.

Of the 166 remaining responses from 38 countries, 96 responses came from Europe (22 countries), 50 responses from USA/Canada (two countries), and 20 responses from other parts of the world (14

countries) (Supplementary material 3). We received more than one response from 26 centres (Supplementary material 3). Almost all respondents were either a physician (67.1%) or a dietician (25.7%). The distribution of physicians and dieticians differed in Europe compared to USA/Canada: in Europe, 81% of respondents were physicians, and 14% were dieticians; in USA/Canada, 40% were physicians, and 52% were dieticians.

3.3. Definitions of long-term BH_4 responsiveness

Table 1 shows the main criteria respondents used for defining long-term BH_4 responsiveness. Almost all respondents indicated using an increase in natural protein tolerance to define long-term BH_4 responsiveness, although improvement of metabolic control and increase in quality of life were also commonly used. The use of other criteria included neurocognitive and neurodevelopmental improvement.

For an increase in natural protein tolerance ($n = 157$, Supplementary materials 4), most respondents (52.2%) used a relative increase in natural protein tolerance to define long-term BH_4 responsiveness. When respondents used a specific cut-off value for this criterion, cut-off values of 30% and 100% were most often used, followed by 50% and 20% (Table 2). When respondents used a specific cut-off value for an absolute increase in natural protein tolerance measured in grams (28.0%), the most common cut-off value was 5 g (range: 0.2 to 20 g). When respondents used a specific cut-off value for an absolute increase in natural protein tolerance per kilograms bodyweight (13.4%), the most common cut-off value was 0.5 g per kilogram (range: 0.05–30 g per kg). Furthermore, most respondents (75.6%) stated that as long as blood Phe concentrations stay within target range, any increase in Phe concentrations is allowed when increasing natural protein intake.

For an improvement in metabolic control ($n = 122$, Supplementary materials 5), most respondents (73.0%) indicated that patients must show a specific reduction in Phe concentrations to be considered as long-term BH_4 responsive. The cut-off value of 30% was most often used, but the use of 20% as cut-off value was not uncommon (Table 3). Alternatively, respondents defined long-term BH_4 responsiveness using the target range of blood Phe concentrations (51.6%), mostly requiring a specific percentage of Phe concentrations to be within the target range. The most common cut-off values for this were 75%, 70% and 80%.

Regarding respondents who used an increase in quality of life to define BH_4 responsiveness ($n = 80$, Supplementary materials 6), only a small proportion measured quality of life using questionnaires (11%). For most respondents, the increase in quality of life was judged by the patients and/or family/parents (91%) and/or by (someone of) the patient's healthcare team (36%).

3.4. Differences between Europe and USA/Canada

Several differences were found between respondents from Europe versus USA/Canada. Improvement of metabolic control and increase in quality of life were significantly more often used in USA/Canada to define long-term BH_4 responsiveness ($p < 0.001$ and $p = 0.02$, respectively). Respondents from USA/Canada more often used stable Phe concentrations ($p = 0.01$) and tended to more commonly use a specific reduction in Phe concentrations ($p = 0.09$) to define BH_4 responsiveness compared to responders from Europe. The cut-off values for a specific percentage reduction in Phe concentrations differed ($p = 0.04$), with Europe using more strict cut-off values. This was also the case for the cut-off values for a relative increase in natural protein tolerance ($p < 0.001$). Separate analyses for physicians and dieticians, revealed an overall similar picture (Supplementary material 7), although many differences between Europe and USA/Canada were no longer significant in these smaller subgroups.

Table 2
Cut-off values for an increase in natural protein tolerance that respondents used to define long-term BH_4 responsiveness.

Cut-off value	Total ($n = 71$)	Europe ($n = 45$)	USA/Canada ($n = 18$)	Other ($n = 8$)
10%	6%	4%	11%	0%
15%	1%	0%	6%	0%
20%	11%	7%	6%	50%
25%	3%	0%	11%	0%
30%	28%	20%	61%	0%
40%	4%	4%	0%	13%
50%	15%	18%	6%	25%
70%	1%	2%	0%	0%
100%	28%	42%	0%	13%
150%	1%	2%	0%	0%

Table 3
Cut-off values for a decrease in phenylalanine concentrations that respondents used to define long-term BH_4 responsiveness.

Cut-off value	Total ($n = 89$)	Europe ($n = 42$)	USA/Canada ($n = 39$)	Other ($n = 9$)
20%	19%	10%	26%	33%
25%	2%	5%	0%	0%
30%	76%	86%	71%	56%
50%	2%	0%	3%	11%

3.5. Differences within centres

To gain a general impression of the consensus on defining BH_4 responsiveness within the 26 centres from which we received more than one response, we investigated three aspects: [1] the use of general criteria (such as metabolic control, natural protein tolerance, and quality of life); [2] the use of a cut-off value (%) for a decrease in Phe concentrations; and [3] the use of a cut-off value (%) for a relative increase in natural protein tolerance. We found that within 21 of the 26 centres, not all respondents used the same general criteria to assess BH_4 responsiveness. Furthermore, in 11 centres some but not all respondents used a specific percentage decrease in Phe concentrations to define BH_4 responsiveness, and in four centres different cut-off values were used by different healthcare professionals working within the same centre. Similarly, in six centres, some but not all respondents used a specific cut-off value for a relative increase in natural protein tolerance, and in four

Table 1
Main criteria respondents used to define long-term BH_4 responsiveness. Comparisons between Europe and USA/Canada were made using Fisher's exact test.

Main criterion	Total ($n = 166$)	Europe ($n = 96$)	USA/Canada ($n = 50$)	Other ($n = 20$)
Improvement of metabolic control	73.5%	67%	94%***	55%
Increase in natural protein tolerance	94.6%	95%	94%	95%
Increase in quality of life	48.2%	38%	58%*	75%
Other	3.6%	2%	6%	5%

*$p < 0.05$; *** $p < 0.001$.

centres different cut-off values were used by healthcare professionals working within the same centre. Differences within centers were observed both within the same profession (among physicians and among dieticians) and between different professions.

3.6. Confidence and guidelines

Most respondents indicated they felt 'very confident' (18.1%) or 'somewhat confident' (65.1%) about the definition(s) of BH_4 responsiveness they use, and only 16.9% of respondents felt 'not so confident'. Nevertheless, the majority of participants responded that they would 'definitely' (48.8%) or 'probably' (31.9%) be helped by a guideline that gives a better definition. However, 13.9% indicated that they 'might or might not' be helped, and 4.2% and 1.2% said they would 'probably' or 'definitely' not be helped by such a guideline.

4. Discussion

With this study, we aimed to get a better picture of the definitions of long-term BH_4 responsiveness that are used worldwide. Our main finding is the overall lack of consensus regarding this topic among healthcare professionals. This is evident at a worldwide level, but also on a regional level (within Europe and USA/Canada), and even within centres. Despite these large differences, healthcare professionals are remarkably confident about their own definition of long-term BH_4 responsiveness, although, conversely, most stated that they would be helped by a guideline that gives a better definition.

Firstly, we will discuss the strengths and limitations of our study. The main strength is the large number of respondents. As opposed to several recent practice surveys for PKU [8–12], we did not focus on a specific country or region. As a result, we received responses from many different countries around the world, making this the largest practice survey reported about PKU. We especially received many responses from Europe and USA/Canada, enabling us to investigate certain differences between these regions. The limitations of this study are largely related to the general limitations of performing a survey. Firstly, both questions and answers (to open-ended questions) may have been wrongly interpreted. Specifically, some of the reported cut-off values for an absolute increase in natural protein tolerance per kilograms bodyweight seemed extremely unrealistic (e.g. a cut-off value of 30 g per kilogram bodyweight). Furthermore, a selection bias is certainly present, with respect to both the individual respondents and the countries from which we received responses. However, due to the large number of respondents, we estimate that these limitations do not have a large influence on the main conclusions of this study.

It is clear that little agreement exists on the definition of long-term BH_4 responsiveness. Applying the often-used arbitrary cut-off value of 70% to define consensus in the total group of respondents, consensus only exists for the use of metabolic control and natural protein tolerance as criteria for defining long-term BH_4 responsiveness. Specific aspects, such as cut-off values, were all used by less than 70% of the total group of respondents. Moreover, our results show large differences between healthcare professionals who work within the same centre. Illustrative for the lack of consensus was the use of quality of life: around half of the respondents used this criterion to define long-term BH_4 responsiveness. These findings are in contrast with the general feeling of confidence that the respondents had regarding their own definition of BH_4 responsiveness. Ironically, with over 83% of respondents answering that they felt somewhat to very confident, few other questions in our survey were answered with a similarly high level of agreement.

This survey also shows that the definition of BH_4 responsiveness from the 2017 European guidelines for PKU have not yet been implemented in all European countries [13]. These guidelines define BH_4 responsiveness as an increase of 100% or more in natural protein tolerance or improved biochemical control (>75% of phenylalanine levels in target range). Only 20% of the European respondents used the first part of this definition, and an even smaller proportion (5%) used the second part. As stressed previously [14], more insights into the adherence to the European PKU guidelines is needed, and reasons for lack of adherence (e.g. lack of awareness or disagreement) should be investigated. Moreover, our findings indicate the need of an implementation trajectory to improve the application of guidelines [15].

Comparisons between Europe and USA/Canada showed some significant differences. Perhaps most interesting are the differences regarding cut-off values, indicating that professionals in USA/Canada generally use less strict cut-off values. Although the cause of this is not clear, it may be related to the PKU guidelines from the American College of Medical Genetics and Genomics, which were published in 2014 [5]. These guidelines do not give a specific definition of BH_4 responsiveness, leaving it to the clinician to judge which precise effects are significant and thus define BH_4 responsiveness. This freedom possibly leads to the use of relatively low cut-off values and, more or less by definition, results in a more heterogeneous situation.

Reaching more consensus on this subject would be preferable for multiple reasons. Firstly, this would lead to equality in access to BH_4 treatment regardless of the country or center in which the patient is treated, or the healthcare professional by whom the patient is treated. Secondly, it promotes cost-effective treatment, avoiding unnecessary prescription of this expensive treatment to those who do not benefit. Thirdly, reaching more consensus would facilitate the development of an optimal testing regime for BH_4 responsiveness, since the effectiveness of such a regime depends on the definition [16]. Lastly, reaching consensus on the definition of BH_4 responsiveness may serve as a framework for defining effectiveness of new PKU treatment modalities that could partly or wholly replace dietary treatment. This includes pharmacological treatment with pegvaliase, especially since recently published recommendations on this treatment state that 'clinically meaningful efficacy benefit should be determined by the treating clinician' [17], similar to the American recommendations for BH_4 treatment.

Although most respondents answered they felt confident about their definition of BH_4 responsiveness, a majority also indicated that they would be helped with a guideline that gives a better definition of BH_4 responsiveness. Ideally, such a definition of BH_4 responsiveness should be evidence-based. To this end, firstly, the evidence on long-term effects of BH_4 treatment needs to be reviewed. While it is known that BH_4 treatment can decrease Phe concentrations and increase natural protein tolerance [18], it is unclear how changes in these parameters are related to secondary outcomes, such as quality of life, neurocognitive functioning, nutritional status, and anthropomorphic measures. A systematic review on this topic could give valuable insights into the long-term benefits of BH_4 treatment and how these benefits relate to the level of BH_4 responsiveness. While it is likely that the currently available evidence is not sufficient to provide clear-cut answers, such a review would serve as a solid basis to develop an evidence- and consensus-based definition of long-term BH_4 responsiveness. Furthermore, it is also crucial that a new definition of BH_4 responsiveness is useful in daily practice. To that aim, the outcomes of this survey, reporting on a large variety of definitions of BH_4 responsiveness that are currently used, may be of help.

5. Conclusion

The results of this large worldwide practice survey show a very heterogeneous picture regarding the definition of BH_4 responsiveness that healthcare professionals use in daily practice. Considering the implications of the large differences in definitions of BH_4 responsiveness that were observed, even within centres, it is clear that an evidence- and consensus-based definition of long-term BH_4 responsiveness should be developed to improve the quality of BH_4 treatment in PKU patients.

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Contributors' statement

Roeland Evers conceptualized the study, collected the data, carried out the analyses, and was the lead writer of the initial manuscript. Annemiek van Wegberg conceptualized the study, collected the data, and was the second lead writer of the manuscript. Francjan van Spronsen conceptualized the study, and coordinated the project. All authors designed the study, interpreted the data, critically reviewed the manuscript, approved of the final manuscript as submitted, and agree to be accountable for all aspects of the work.

Declaration of Competing Interest

RAFE has received financial support from Biomarin for attending symposia. AMJvW has received a research grant form Nutricia, honoraria from Biomarin as speaker, and travel grants from Nutricia and Vitaflo. AMB has received a speakers fee from Nutricia and has been a member of advisory boards for Biomarin. MG received honoraria and was a consultant for: Nutricia International/Danone, Merck-Serono, Mead Johnson, BioMarin and Vitaflo. JCR has been a member of the European Nutritionist Expert Panel [Biomarin], the Advisory Board for Applied Pharma Research and Nutricia, and received honoraria as a speaker from APR, Merck Serono, Biomarin, Nutricia, Vitaflo, Cambrooke, PIAM and Lifediet. FJvS is a member of scientific advisory boards for PKU and aminoacid defects that are supported by Agios, Applied Pharma Research, Arla Food Int, BioMarin, Eurocept, Homology, Lucane, Nestle-Codexis Alliance, Nutricia, orphan Europe, Rivium Medical BV, Vivet, has received research grants from Alexion, BioMarin, Beatrix Research Fund, Codexis, ESPKU, NPKUA, NPKUV, Nutricia, Sobi, Tyrosinemia Foundation, Vitaflo, ZONMW, and has received honoraria as a consultant and speaker from Applied Pharma Research, Biomarin, MendeliKABS, Nutricia, Pluvia, SoBi, and Vitaflo. AM is an advisory board member for ELEMENT, Danone-Nutricia, Arla, and Applied Pharma Research, and has received research funding and honoraria from Applied Pharma Research, Nutricia, and Vitaflo International. All other authors reported no conflicts of interest.

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Appendix A. Supplementary data

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