J Inherit Metab Dis (2012) 35:823–829
DOI 10.1007/s10545-011-9429-y

ORIGINAL ARTICLE

Heterogeneity of follow-up procedures in French and Belgian patients with treated hereditary tyrosinemia type 1: results of a questionnaire and proposed guidelines

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Received: 21 June 2011 / Revised: 17 November 2011 / Accepted: 21 November 2011 / Published online: 14 December 2011

Abstract The 1991 introduction of 2-(2-nitro-4-trifluoromethylbenzyol)-1,3 cyclohexanedione (NTBC) as a treatment for hereditary tyrosinemia type 1 (HT-1), a disorder of tyrosine catabolism, has radically modified the natural history of this disorder. Despite the dramatic improvements in survival, outcomes and quality of life seen with NTBC treatment, HT-1 remains a chronic disorder with several long-term complications, including, a persistent (albeit low) risk of hepatocellular carcinoma and suboptimal neuropsychological outcomes. There remain unsolved key-questions concerning the long-term outcomes of patients with HT-1, which closely depend on the quality of follow-up in these patients. In the absence of published guidelines, we investigated the follow-up methods used for French and

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Communicated by: James V. Leonard

Electronic supplementary material The online version of this article (doi:10.1007/s10545-011-9429-y) contains supplementary material, which is available to authorized users.

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Belgian patients with HT-1. A simple questionnaire providing a rapid overview of follow-up procedures was sent to the 19 physicians in charge of HT-1 patients treated with NTBC and low-tyrosine diet in France and Belgium. Several areas of heterogeneity (especially liver imaging, slit lamp examination, neuropsychological evaluation and maximal plasma tyrosine level accepted) were observed. In an attempt to improve long-term management and outcome of patients with HT-1, we proposed follow-up recommendations.

Introduction

Hereditary tyrosinemia type 1 (HT-1) is a rare disorder affecting the catabolism of the amino acid tyrosine due to a deficiency of the fumarylacetoacetate hydrolase (FAH) enzyme encoded by the *FAH* gene (Grompe 2001). The natural history of HT-1 has drastically changed since the introduction of 2-(2-nitro-4-trifluoro-methylbenzyol)-1,3 cyclohexanedione (NTBC; nitisinone [Orfadin®]) for its treatment in 1991 (Lindstedt et al. 1992). Prior to the availability of NTBC, the outcome for patients with HT-1 was poor with death usually occurring by the age of ten years, typically from liver failure, neurological crisis, or hepatocellular carcinoma (HCC) (van Spronsen et al. 1994). The combination of NTBC treatment plus a low-tyrosine diet has resulted in a ≥90% survival rate, normal growth, improved liver function, prevention of cirrhosis, and correction of proximal renal tubular dysfunction (McKiernan 2006). However, despite 20 years since the introduction of NTBC, several long-term outcome issues remain unsolved despite appropriate patient treatment (Masurel-Paulet et al. 2008). These, for example, concern 1) neuropsychological impairment (De Laet et al. 2011) possibly related to chronic toxicity of elevated tyrosine plasma levels, 2) the optimal plasma NTBC dosage, 3) evaluation of the risk for HCC, and 4) management of potential pregnancies in treated women. A first step toward answering these central questions encompasses an evaluation of patient follow-up methods. In the absence of available follow-up guidelines for patients with HT-1, we investigated follow-up methods and the ways in which patients with HT-1 who were treated with NTBC and a low-tyrosine diet were followed in different treatment centers in France or Belgium using a simple questionnaire that assessed the methods used by physicians in the follow-up of patients with HT-1.

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Materials and methods

Participants

All 19 French and Belgian physicians who were recorded in the NTBC database were sent a simple questionnaire that assessed the follow-up methods of HT-1 patients treated with NTBC and low-tyrosine diet. Of the physicians who were sent the questionnaire, ten were metabolic physicians, six were hepatologists and three were general pediatricians.

Outline of the questionnaire

Based on the follow-up protocol used at Robert Debré University Hospital (Paris, France), we asked the participants whether or not they were following patients with HT-1 using similar methods. The following parameters were addressed:

1- Number of patients and age distribution.
2- Frequency of the clinical and/or dietary follow-up.
3- Hepatic follow-up including blood tests (glucose, protein, albumin, bilirubin, biliary acids, aspartate transaminase [AST], alanine transaminase [ALT], alkaline phosphatases, γ-glutamyltransferase, α-fetoprotein [α-FP], prothrombin time), and liver imaging using ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI).
4- Renal follow-up including blood tests (blood electrolytes, serum creatinine, blood urea nitrogen, uric acid, calcium, phosphate), and urine tests (protein, glucose, electrolytes, calcium, phosphate).
5- Nutritional follow-up including blood tests (complete blood count, iron, cholesterol, triglycerides, vitamin A, D, E, B_{12} and folates, copper, zinc, selenium [micronutrients]), X-ray bone age test and osteodensitometry.
6- Metabolic follow-up including blood tests (amino acids, NTBC plasma level, porphobilinogen synthase activity in erythrocytes), and urine tests (amino acids, δ-aminolevulinate, succinylacetone).
7- "Toxicity" follow-up including the evaluation of eye (slit lamp examination) and brain toxicity (neuropsychological evaluation).
8- Treatment and compliance follow-up included measurements of the minimal target plasma level of NTBC as well as the maximal plasma tyrosine level that were deemed "acceptable" by each physician.

The replies from the physicians were collated and an overview regarding the follow-up procedures practiced by

physicians in France and Belgium for patients with HT-1 was determined. No statistical analyses of these results were conducted.

Results

Number of patients with HT-1 followed

In each department, one to 11 patients with HT-1 were followed, sometimes by several physicians in a given department; each physician followed one to nine patients. As a whole, a total of 100 patients with HT-1 were recorded; however, the total number of patients with HT-1 receiving treatment in France and Belgium is approximately 75 according to the NTBC database which raises the possibility of a given patient being recorded more than once. It was not possible to solve this question since the questionnaires were anonymous.

Frequency of the clinical and/or dietary follow-up

Fifty percent of the physicians questioned used a written follow-up protocol. The frequency of clinical examinations performed varied with age. Patients aged less than 3 years were examined from once every 2 weeks to once every 3 months. After the age of 3, the frequency of clinical examinations varied from one to four times a year (with the majority of patients visiting once every 3–4 months). The frequency of dietitian visits also varied with age with a range from one to four times a year.

Hepatic follow-up

Supplementary Table 1 details the frequency and type of hepatic tests conducted by physicians during the follow-up of patients with HT-1. As observed, hepatic follow-up was relatively homogeneous in terms of the biological tests conducted. Noticeably, all the physicians were monitoring serum α-FP levels. Conversely, some variations were observed between physicians with regards to liver imaging follow-up procedures with ultrasound performed by 100% of the physicians, CT by 69% of the physicians, and MRI by 31% of the physicians.

Renal follow-up

Supplementary Table 2 details the frequency and type of renal tests conducted by physicians during the follow-up of patients with HT-1. As observed, renal follow-up was also homogeneous with glomerular and tubular dysfunction monitored by 100% and 85% of the physicians respectively.

Nutritional follow-up

The frequency and type of nutritional tests conducted by physicians during the follow-up of patients with HT-1 is detailed in Supplementary Table 3. These tests were relatively homogeneous among centers with very little variation in the frequency and type of tests conducted.

Metabolic follow-up

Supplementary Table 4 details the frequency and type of metabolic tests conducted by physicians during the follow-up of patients with HT-1. As observed, metabolic follow-up tests were mostly homogeneous: all physicians monitored tyrosine plasma levels (plasma amino acids) and 95% of them measured urinary succinylacetone. However, only 69% (13 out of 19) of physicians monitored plasma NTBC levels.

"Toxicity" follow-up

Slit lamp examination was performed by 79% of the physicians. However, neuropsychological evaluations were only performed by 42% of the physicians. The reduced frequency of neuropsychological evaluations conducted was usually due to the unavailability of a qualified psychologist.

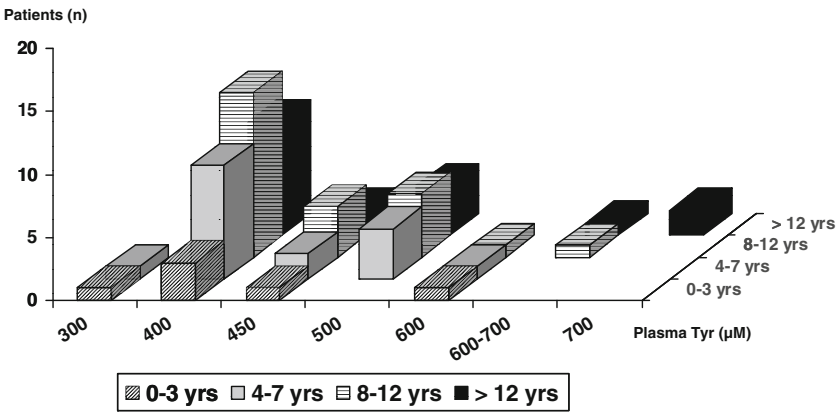

Fig. 1 The maximum tyrosine (Tyr) plasma levels in patients with hereditary tyrosinemia type 1 accepted by physicians in France and Belgium and the variation in acceptance observed with age. n, number of patients; yrs, years

Table 1 Proposed follow-up guidelines in treated HT-1 patients. Various exams performed during the follow-up

Hepatic workup	Renal workup	Metabolic workup	Nutritional workup	Miscellaneous
Glucose	Blood electrolytes	Plasma amino acids (especially tyrosine[a] and phenylalanine levels)	Complete blood count	Liver ultrasound
Protein/albumin	BUN/SCr	Urinary amino acids	Blood iron, ferritin	Liver imaging (MRI if possible, or CT)
Bilirubin	Blood uric acid	Urinary δ-aminolevulinate	Blood cholesterol/TGs	NTBC plasma level
AST/ALT	Blood Ca/P	Urinary succinylacetone	Blood vitamins A D E	Slit lamp examination
Alkaline phosphatases	Proteinuria		Blood B_{12}/folates	Osteodensitometry
γ-GT	Glucosuria		Blood micronutrients	Neuropsychological evaluation
α-FP	Urine electrolytes			
Coagulation tests (PT, aPTT, coagulation factors)	Urine Ca/P			

[a] objective tyrosine level between 400 and 500 μM; α-FP, α-fetoprotein; aPTT, activated partial thromboplastin time; γ-GT , γ-glutamyltransferase; ALT, alanine transaminase; AST, aspartate transaminase; BUN, blood urea nitrogen; Ca, calcium levels; P, phosphate levels; PT, prothrombin time; SCr, serum creatinine; TG, triglycerides

Treatment and compliance follow-up goals

Among the 13 physicians who were measuring NTBC plasma levels, only ten answered on what they considered the minimal target plasma level of NTBC required in patients with HT-1 receiving NTBC. For 30% of the physicians, the desirable minimal target plasma level of NTBC was 30 μM, for 20% of the physicians it was 40 μM, for 20% of the physicians it was 50 μM, and for the remaining physicians (30%) there was no indication of what they considered the minimal target for NTBC plasma level. Similarly, the maximal "acceptable" plasma tyrosine level varied among the physicians (Fig. 1). For 52.5% of the patients, the maximal tyrosine level accepted by the physicians questioned was 400 μM, whereas it was 300 μM for 3%, 450 μM for 14%, 500 μM for 20%, 600 μM for 4.5%, between 600 and 700 μM for 3%, and 700 μM for the remaining 3% of patients (Supplementary Fig. 1). When age was considered, there were also great variations (Supplementary Fig. 2) with levels over 600 μM tolerated for the oldest patients.

Discussion

Despite the progress in the management of patients with HT-1 observed since the introduction of NTBC treatment, these patients still often develop several chronic complications including chronic hepatopathy with a high risk of hepatocellular carcinoma (HCC) and mild neuropsychological impairment (De Laet et al. 2011). In order to evaluate and/or prevent these complications, a rigorous, high-quality and long-term follow-up of patients with HT-1 is required. The aim of this simple questionnaire sent to 19 physicians in charge of patients with HT-1 treated by NTBC and a low-

Table 2 Proposed guidelines for monitoring in HT1 patients during the first year after the start of NTBC

Evaluation	Initiation of therapy (baseline)	M1	M2	M3	M6	M9	M12
Clinical evaluation	+	+	+	+	+	+	+
Hepatic workup	+	+	+	+	+	+	+
Liver ultrasound	+	+			+		+
Liver imaging[a]	+				+		+
Renal workup	+	+	+	+	+	+	+
Metabolic workup	+	+	+	+	+	+	+
NTBC plasma level[b]	+	+	+	+	+	+	+
Nutritional workup	+			+	+	+	+
Slit lamp	+						+
Neuropsychological evaluation[c]	+						+

[a] if available prefer MRI to CT;
[b] to assess appropriate dosage (objectives: 40–60 μM);
[c] according to local settings;
M, months

Table 3 Proposed guidelines for monitoring in HT1 patients after the first year of NTBC with normal α-FP **AND** liver imaging

Evaluation	Every 4–6 months	Every 6 months	Other
Clinical evaluation	+		
Hepatic workup	+		
Liver ultrasound		+	
Liver imaging			+[a]
Renal workup		+	
Metabolic workup	+		
NTBC plasma level		+[b]	
Nutritional workup		+[c]	
Slit lamp			+[a]
Neuropsychological evaluation			+[a, d]
Osteodensitometry			+[d, e]

[a]yearly; [b]could be performed more frequently in case of insufficient levels; [c]frequency individually varying from every 6 months to once a year; [d] according to local settings; [e]twice a year

tyrosine diet was not to analyze the individual follow-up of every patient with HT-1 (which should definitely be done in the near future) but to provide an overview of the follow-up procedures currently in practice and the variability between treatment centers in France and Belgium. The preliminary data recorded in this report highlight that follow-up methods are not homogeneous between study centers in France or Belgium. Discrepancies were observed in liver imaging frequency and methods (CT or MRI). Similarly, NTBC plasma levels were not measured by 31% of the physicians and when it was, the minimal target level accepted varied from 30 μM to 50 μM. Also, the maximal plasma tyrosine levels accepted by physicians varied largely from 300 to 700 μM. With respect to the monitoring of NTBC toxicity, slit lamp examination and neuropsychological evaluations were not performed by 21% and 58% of physicians, respectively.

Hepatocellular carcinoma is a major concern in patients with HT-1 and is tightly associated with a secondary increase in α-FP and/or persistently elevated levels of α-FP (with long-term absence of normalization) despite optimal therapy with NTBC (Koelink et al. 2006). Our results show that α-FP levels were monitored at least twice a year by all the physicians surveyed. This is sensible as patients with elevated α-FP levels despite optimal therapy have a high risk of developing HCC (Koelink et al. 2006). Furthermore, all physicians surveyed were utilizing liver ultrasound at least once a year. This should be recommended as standard follow-up practice as liver ultrasound is ideal for detecting adenomas and subsequent HCC (Mohan et al. 1999). However, it has also been suggested that the optimal way for monitoring for adenomas was with liver MRI (Mohan et al. 1999), which 31% of the physicians surveyed were regularly doing. Furthermore, in France it is recommended that adult patients with uncomplicated cirrhosis monitor α-FP levels and undergo liver ultrasound every 6 months (http://www.tncd.org, http://www.has-sante.fr). Since cirrhosis is frequently associated with HT-1, we recommend that evaluations of liver tumor should be conducted at least twice a year in patients with HT-1.

We recommend that NTBC plasma level is regularly monitored since inter-patient variability in drug metabolism

Table 4 Proposed guidelines for monitoring in HT1 patients after the first year of NTBC with abnormal α-FP and/or abnormal liver imaging

Evaluation	Every 3 months	Every 6 months	Other
Clinical evaluation	+		
Hepatic workup	+		
Liver ultrasound		+[a]	
Liver imaging		+[a]	
Renal workup		+	
Metabolic workup	+		
NTBC plasma level		+[b]	
Nutritional workup			+[c]
Slit lamp			+[d]
Neuropsychological evaluation			+[d, e]
Osteodensitometry			+[e, f]

[a]alternate liver ultrasound and liver imaging every 3 months; [b]could be performed more frequently in case of insufficient levels; [c]frequency individually varying from every 6 months to once a year; [d]yearly; [e]according to local settings; [f]twice a year

was observed: at similar NTBC dosage (1 mg/kg/day) NTBC concentrations varied in the range of 25 to 75 μM (personal communication). It was proposed to maintain NTBC concentration between 40 and 60 μM since these concentrations should theoretically provide a 99% inhibition of the 4-hydroxyphenylpyruvate dioxygenase (Ellis et al. 1995) but in a few patients, this target NTBC concentration has been associated to mildly elevated urinary succinylacetone excretion (personal communication). Therefore, long-term studies will be indispensable to determine the optimal (minimal) NTBC dosage needed to prevent the production of hepatotoxic metabolites.

Recent data has emerged regarding long-term neuropsychological impairment in patients with HT-1, especially schooling difficulties and learning disabilities (De Laet et al. 2011, Masurel-Paulet et al. 2008). Even though the pathophysiology remains unclear, neuropsychological impairment in patients with HT-1 may at least be partly related to high plasma tyrosine levels (Mamunes et al. 1976). Thus, we believe that not only is regular monitoring of plasma tyrosine levels crucial but the absence of a consensus on the maximal "acceptable" tyrosine level (as observed in our questionnaire) is potentially deleterious for the patients. We believe it is reasonable to aim for a tyrosine level between 400 and 500 μM, as suggested in previous publications (Grompe 2001, Masurel-Paulet et al. 2008, Sniderman King et al. 1993). Such a range has indeed not been associated with the development of complications in oculocutaneous tyrosinemia and has been compatible with normal growth in HT-1 patients.

Elevated plasma tyrosine levels may also be associated with ophthalmological complications, namely corneal opacities, especially in patients with poor dietary compliance (Ahmad et al. 2002). In keeping with this, yearly ophthalmological follow-up with a slit lamp examination is warranted to search for corneal opacities that may sometimes be reversible with appropriate dietary intervention and monitoring (Gissen et al. 2003).

The lack of consistency in the follow-up as demonstrated by our data was an incentive to propose follow-up guidelines. These guidelines are based on our personal experience as well as extensive (albeit scarce) literature review (Couce et al. 2010, Grompe 2001, Sniderman King et al. 1993) and are detailed in Table 1 to 4. Briefly, we propose that HT-1 patients should be divided into two groups after the first year of NTBC treatment (during which they should be thoroughly followed monthly for the first 3 months and every 3 months thereafter; liver imaging being performed every 6 months, Table 2). The first group concerns patients with rapid normalization of α-FP as well as normal liver imaging after the first year of NTBC. These patients should be followed every 4 to 6 months (clinical, hepatic, renal, metabolic) with liver imaging that should be performed annually (Table 3). The other group concerns patients with a persistently high α-FP and/or abnormal liver imaging (adenomas). These patients should be more frequently followed with clinical, biological (hepatic, metabolic) follow-up every 3 months (renal biological workup every 6 months) and imaging performed every 6 months with alternating liver ultrasound and liver imaging every 3 months (Table 4). In each group (Tables 3 and 4), liver ultrasound should be performed every 6 months and slit lamp examination should be performed yearly. NTBC plasma level should be assessed twice a year. Nutritional workup should be performed at least once a year. According to local settings, osteodensitometry and neuropsychological evaluation may also be performed.

Conclusions and perspectives

Whereas agreement may be difficult to achieve in the absence of suitable studies to provide a sound evidence base for the recommendations, these proposed guidelines (even if provisional) could help to promptly identify possible complications of the disease or treatment toxicity and thus improve long-term outcomes of HT-1 patients.

Acknowledgments We thank Simone Boniface of *in*Science Communications, a Wolters Kluwer business, who provided assistance with English-language editing. This assistance was funded by Swedish Orphan Biovitrum.

Competing interests MS has received speaker (part of this work has been presented in July 2010 at the 2nd Symposium on Tyrosinemia Type I in Saint Petersburg) and consultant (2009) honoraria from Swedish Orphan Biovitrum.

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