

# High prevalence of complementary and alternative medicine use in patients with genetically proven mitochondrial disorders

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**Abstract** Despite major advances in understanding the pathophysiology of mitochondrial diseases, clinical management of these conditions remains largely supportive, and no effective treatment is available. We therefore assumed that the burden of disease combined with the lack of adequate treatment leaves open a big market for complementary and alternative medicine use. The objective of this study was to evaluate the use and perceived effectiveness of complementary and alternative medicine in children and adults with genetically proven mitochondrial disease. The reported use was surprisingly high, with 88 % of children and 91 % of adults having used some kind of complementary and alternative medicine in the last 2 years. Also, the mean cost of these treatments was impressive, being €489/year for children and €359/year for adult patients. Over-the-counter remedies (e.g., food supplements, homeopathy) and self-help techniques

(e.g., Reiki, yoga) were the most frequently used complementary and alternative therapies in our cohort: 54 % of children and 60 % of adults reported the various complementary and alternative medicine therapies to be effective. Given the fact that currently no effective treatment exists, further research toward the different therapies is needed, as our study clearly demonstrates that such therapies are highly sought after by affected patients.

## Introduction

Disorders of the mitochondrial oxidative phosphorylation (OXPHOS) system are rare disorders that can present with virtually any clinical symptom. Underlying mutations can be found in nuclear genes as well as in the maternally inherited

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mitochondrial genome (Taylor and Turnbull 2005; Koopman et al. 2012; DiMauro et al. 2013). Despite major advances in understanding the pathophysiology of mitochondrial diseases, clinical management remains largely supportive, and no effective treatment is available (Pfeffer et al. 2013). Often, high-dose multivitamin cocktails are prescribed to patients, but there are no studies supporting the effectiveness, with the exception of some reported cases of coenzyme Q10 deficiency responding to therapy (Emmanuele et al. 2012).

Complementary and alternative medicine (CAM) refers to a group of diverse medical health care systems, practices, and products that are not considered to be part of conventional medicine. Renowned therapies, such as homeopathy, acupuncture, yoga, and herbal supplements, fall within this spectrum of therapies. They can be assigned to four major groups: alternative medical systems, mind–body interventions, biologically based therapies, and energy therapies (National Center for Complementary and Alternative Medicine: What are the major types of complementary and alternative medicine? Retrieved from: <http://nccam.nih.gov/health/whatisacam>; NCCAM 2013). Once such a treatment modality is used alongside conventional therapy, it is defined as complementary, whereas that same therapy is called alternative when it substitutes mainstream care.

In recent years, CAM therapies have become quite popular, with approximately one third of all adult and pediatric patients using CAM (Madsen et al. 2003; Tindle et al. 2005; Vlioger et al. 2006). There is growing interest in the use of CAM in different pediatric and adult patient populations, especially in pediatric oncology patients, where usage ranges between 20 and 60 % are reported (Bishop et al. 2010; Singendonk et al. 2013). For these patient groups, evidence-based treatment protocols exist and have shown such therapies to be effective, which is in striking contrast to the group of patients with mitochondrial disorders. We therefore assume that the burden of disease combined with the lack of adequate treatment for mitochondrial disorders leaves open a big market for CAM due to the helplessness of affected patients. The objective of this study was to evaluate the use and perceived effectiveness of CAM in children and adults with genetically proven mitochondrial disease.

## Methods

### Patients

All adult patients and caretakers of pediatric patients with a genetically proven diagnosis of a mitochondrial disorder regularly attending the outpatient clinics of Pediatrics or Internal Medicine at the Nijmegen Centre for Mitochondrial Disorders (NCMD) received an informational letter and questionnaire by postal service. (Caretakers of) patients with an insufficient

knowledge of the Dutch language were not recruited. Patients with the mitochondrial m.3243A>G mutation were recruited for a separate study. Patients attending mainly other specialists [e.g., patients with Leber's hereditary optic neuropathy (LHON) or chronic progressive external ophthalmoplegia (CPEO) phenotype attending the ophthalmology department] were not included.

### Study design

This is a single-center study investigating the prevalence of CAM use by means of a questionnaire consisting of 21 questions, requiring approximately 20 min to complete. The instrument was modified from a previous Dutch study assessing CAM use among pediatric oncology patients and was filled in anonymously by adult patients or by caretakers of pediatric patients (referred to as children or pediatric patients in the further course of this manuscript) (Singendonk et al. 2013). The questionnaire was approved by the ethics committee of the Radboud UMC Nijmegen (*Commissie mensgebonden onderzoek*, CMO Arnhem-Nijmegen). It contained questions about the patient's gender, age, and ethnic background. From the four major domains in CAM as defined by the National Center for Complementary and Alternative Medicine, the 16 most popular modalities in The Netherlands were listed (NCCAM 2013). Additionally, patients could mention other, not listed, CAM therapies. They were asked about any CAM therapies they had used in the past 2 years, their reasons for using it, the costs of the treatment, and the perceived effectiveness of the modalities used. CAM therapies were subdivided into three categories: over-the-counter remedies, self-help techniques, and therapies as prescribed by a CAM therapist/physician. Additionally, communication with the treating metabolic physician regarding CAM use was evaluated, and participants were asked about the desirability of advice on and the availability of CAM modalities in the hospital setting. Finally, patients were asked about the necessity of research on CAM therapies and possible willingness to participate in future clinical trials.

## Results

In total, questionnaires were sent to 38 pediatric and 46 adult patients; 24 (63 %) and 33 (72 %) questionnaires, respectively, were returned. As some questionnaires were only partially completed, our analyses report different numbers per question. Results are rounded to integer. Demographic and disease baseline characteristics are shown in Table 1. Patient age ranged from 2 to 16 (median 8.6) years in pediatric and from 19 to 66 (median 41.7) years in adult patients. Gender was

**Table 1** Demographics, disease baseline characteristics, and use of different complementary and alternative medicine (CAM) therapies among patients with mitochondrial disorders

	Children ( <i>N</i> =24); <i>n</i> (%)	Adults ( <i>N</i> =33); <i>n</i> (%)
Median age in years (range)	8.6 (2–16)	41.7 (19–66)
Male	16 (67)	16 (48)
Time since diagnosis		
<1 year	4 (16.7)	3 (9.09)
1–5 years	8 (33.3)	10 (30.30)
5–10 years	8 (33.3)	9 (27.27)
>10 years	4 (16.7)	11 (33.33)
All types of CAM	21 (88)	30 (91)
Over-the-counter remedies	19 (79)	25 (76)
Food supplements	15 (63)	23 (70)
Homeopathy	12 (50)	9 (27)
Herbal remedies	5 (21)	0 (0)
Other	5 (21)	4 (12)
Self-help techniques	8 (33)	14 (42)
Massage or Reiki	5 (21)	6 (18)
Others	3 (12.50)	4 (12)
Relaxation exercise	2 (8)	2 (6)
Meditation or yoga	1 (4)	6 (18)
Aroma therapy	1 (4)	6 (18)
Visualization or hypnosis	0 (0)	3 (3)
Healing ceremony	0 (0)	0 (0)

equally distributed amongst adult patients; in the pediatric population, boys dominated (67 %).

#### CAM use and costs

Eighty-eight percent of children (C) and 91 % of adults (A) used at least one type of CAM therapy within the 2 years prior to the study. The most common type both in children and adults was over-the-counter remedies (C 79 %, A 76 %), with food supplements being the most popular (C 63 %, A 70 %), followed by various products of homeopathic origin (C 50 %, A 27 %). Food supplements were the only CAM therapies reported to be prescribed by a metabolic physician and were prescribed for 73 % of children and 60 % of adults using them. Self-help techniques were reported to be used frequently by both children (33 %) and adults (42 %), most commonly massage or Reiki (C 21 %, A 18 %), and in adults also meditation or yoga (each 18 %); 38 % of children and 21 % of adults had visited a CAM therapist within the prior 2 years. For children, homeopathy (25 %) and manual-based therapies (21 %) were prescribed most frequently by the consulted CAM therapist, followed by phytotherapy (17 %). Adults most commonly were advised to use manual-based therapy (21 %), phytotherapy (9 %), and Chinese medicine, including acupuncture (6 %). Among patients using CAM, 46 % of children and 29 % of adults already used CAM therapy before diagnosis of their mitochondrial disease; 31 % (A 29 %)

started within 1 year after diagnosis, and 23 % (A 43 %) >1 year after diagnosis. Patients had spent €0–1,000 on CAM per year [mean €489/year (C) and €359/year (A)].

#### Perceived effectiveness

The combined analysis of all different types of CAM shows that 54 % of children and 60 % of adults reported the various CAM therapies to be very or somewhat effective (Table 2); 21 % of children and 17 % of adults reported them to be ineffective; the remainder were unsure. The group of self-help techniques yielded the highest percentage of children and adults rating the therapy as very effective (C 55 %, A 67 %). A detailed analysis of the particular types of CAM therapies used is shown in Supplementary Tables 1 (C) and 2 (A).

#### Reasons for CAM use

All participants were asked if they used CAM therapy for a specific symptom associated with mitochondrial disease or to improve general well-being. They were able to choose between four given options: tiredness or low energy, muscle pain or cramps, general well-being, or other. The most reported reason in children was to improve general well-being (44 %); adults reported tiredness or low energy (38 %) to be the most important reason. The primary motivation for children was to improve the immunity and general condition (17 %), followed

**Table 2** Perceived effectiveness of complementary and alternative medical (CAM) therapies among patients with mitochondrial disorders

	Over-the-counter remedies, <i>n</i> (%)	Self-help techniques, <i>n</i> (%)	Prescribed by CAM physician/therapist, <i>n</i> (%)	All types of CAM, <i>n</i> (%)
Children ( <i>n</i> )	35	11	17	63
Very effective	7 (20)	6 (55)	11 (65)	24 (38)
Somewhat effective	9 (26)	1 (9)	0 (0)	10 (16)
Not effective	9 (26)	1 (9)	3 (18)	13 (21)
Unknown	10 (29)	3 (27)	3 (18)	16 (25)
Adults <i>n</i>	60	24	11	95
Very effective	6 (10)	16 (67)	4 (36)	26 (27)
Somewhat effective	20 (33)	5 (21)	5 (45)	30 (32)
Not effective	13 (22)	1 (4)	2 (18)	16 (17)
Unknown	21 (35)	2 (8)	0 (0)	23 (24)

by suggested by family or friends (13 %) and the wish to get better (10 %). Among adults, the wish to get better and to improve immunity and general condition was equally reported, with 24 % each as their primary motivations, followed by more control over own life and disease (19 %).

#### Communication with treating metabolic physician

About one third of children (33 %) and slightly more adults (38 %) stated that they had communicated their CAM use with their treating metabolic physician. The most common response of the metabolic physician was positive both for children (63 %) and adults (100 %) or neutral (25 % and 0 %, respectively). Communication was always (C 100 %) or most commonly (A 67 %) initiated by the patient.

#### Attitudes towards research

Future research about CAM therapies was rated as important or very important by 87 % of children and 81 % of adults. Subsequently, 48 % of children and 80 % of adults were willing to participate in a future trial. Advice about CAM therapies by the treating metabolic physician was also rated important by both children (83 %) and adults (89 %).

## Discussion

In recent years, CAM therapies have become popular, with approximately one third of all adult and pediatric patients using CAM (Madsen et al. 2003; Tindle et al. 2005; Vlioger et al. 2006). Our study is the first to report on CAM use in children and adults with genetically proven mitochondrial disease. The reported use of CAM in our patient population was surprisingly high, with 88 % of children and 91 % of adults having used some type of CAM in the last 2 years

(Table 1). Also the mean paid for these treatments was impressive, being €489/year for children and €359/year for adults. The high percentage of CAM use found in our study is most likely due to the combination of lack of effective treatment for these diseases and of the disease having a great impact on the daily quality of life due to symptoms such as tiredness, low energy, and muscle pain and cramps, as reported by participants in our study. This helplessness and the lack of evidence-based alternatives leaves open a large market for non-evidence-based CAM use in patients with mitochondrial disease. Comparable rates of CAM use (~80 %) have been reported in pediatric patients with Duchenne or Becker muscular dystrophy (Nabukera et al. 2012). For patients with lysosomal storage disorders, the use of CAM reported in one single-center study was lower: C 8 %/A 45 % for type I Gaucher disease, C 50 %/A 41 % of Fabry disease, and C 33 %/A 47 % of type B Niemann–Pick patients (Balwani et al. 2009). Due to the very limited number of studies and the small number of patients included in that study, the reasons for the differences in CAM use can only be speculative. Most likely, the most important reason is that, in contrast to our patient group, treatments are available for both Duchenne/Becker muscular dystrophy and for several lysosomal storage disorders, which are at least able to slow down the the progressive and disabling course of those diseases.

In our study, 54 % of children and 60 % of adults reported the various CAM therapies to be effective (very effective C 38 %, A 16 %, somewhat effective C 27 %, A 32 %; Table 2). Over-the-counter remedies (e.g., food supplements, homeopathy) and self-help techniques (e.g., Reiki, yoga) were the most frequently used (Table 1). Vitamin supplements such as riboflavin, coenzyme Q10, and thiamine, were not perceived as being effective by most patients (Supplementary Tables 1 and 2). This is an interesting finding and in line with studies that failed to prove the efficacy of vitamin supplements in mitochondrial disease (Pfeffer et al. 2013). Additionally, there is no consensus among physicians prescribing these vitamins

(mostly as a mitochondrial cocktail) as to which supplements are most effective and at what dosages (Parikh et al. 2009, 2013). However, the Mitochondrial Medicine Society advises in their opinion statement that a therapeutic trial of coenzyme Q10, along with other antioxidants, should be attempted based on clinical experience and judgment (Parikh et al. 2009).

In contrast, the effectiveness of self-help techniques such as massage or yoga was rated positively (Supplementary Tables 1 and 2). We assume that the perceived benefits of self-help techniques are both physical and psychological, as patients feel that they can achieve muscular relaxation while positively influencing the course of disease. One should also take into account that patients paid up to €1,000/year for such therapies, and this might also improve the perceived level of effectiveness. It is difficult to compare data evaluating the perceived effectiveness with similar data for other disorders. Singendonk et al. (2013) reported the perceived effectiveness as being even higher: 75 % of their study participants perceived CAM as effective (very effective 49 %, somewhat effective 26 %). There are no directly comparable data for an identical cohort of adult patients. The study evaluating CAM use in Duchenne patients did not report data on this issue, and for the lysosomal group, data were presented only per CAM therapy as a rating on a Likert scale, which makes a comparison impossible (Balwani et al. 2009, Nabukera et al. 2012).

In general, CAM is mostly considered to be “soft” and “natural” therapy by patients and often by their treating physician. However, CAM can have numerous side effects, ranging from mechanical injuries and infections by acupuncture needles, to contact dermatitis due to herbal remedies (Niggemann and Grüber 2003). Our study did not evaluate potential side effects of CAM. It is difficult to estimate the (long-term) side effects of vitamin supplements, but for the other most frequently used CAM therapy—self-helping techniques such as yoga or massage—no serious side effects are expected.

A strength of this study is the use of a validated, standardized questionnaire according to the recent European guidelines on standardization of CAM questionnaires, making it possible to compare the results of this study to previous studies using the same type of survey (Quandt et al. 2009). Since mitochondrial diseases are very rare and the genetic background is often not known, a study group of 57 patients including 24 children might be a representative cohort. However, being a single-center study is a limitation; therefore, the prevalence of and need for information, and attitude toward research reported by our participants, might be overestimated for the general population with mitochondrial disease. Furthermore, as this was a questionnaire-based study, respondent bias is likely to have an impact, possibly leading to over- or underestimation of treatment effects.

Given the lack of any effective treatment for mitochondrial disorders and the perceived effectiveness of CAM therapies reported in this study, more awareness and further research on this issue is needed. Accordingly, 87 % of caretakers of children and 81 % of adults rated further research on CAM therapies as important, and a high percentage (C 48 %, A 80 %) was willing to participate in future studies. Especially when taking into account that modern disease management is a continuous challenge that can only be successful when the patient and the treating physician are partners, further high-quality, multicenter, randomized, and (if possible), double-blind studies are needed to improve the quality of life for children and adults with mitochondrial disorders. Ideally, these should be performed in international collaboration and make use of standardized data collection in order to harmonize data and streamline research. To evaluate the effect of CAM (and other interventions) in upcoming treatment studies, standardized and validated questionnaires evaluating fatigue and quality of life (e.g., KIDSCREEN 52, Pediatric Evaluation of Disabilities Inventory, PedsQL Multidimensional Fatigue Scale) are available and should be used (Koene et al. 2013).

In conclusion, the prevalence of CAM use was very high (~90 %) in our cohort of children and adults with genetically proven mitochondrial disorders. The reported effectiveness for the different types of CAM therapy varied greatly, with self-help techniques rated most effective. Given the fact that no effective treatments exist for these disorders, further research into different CAM therapies is needed, and—as our study clearly demonstrates—is highly sought after by affected patients.

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**Conflict of interest** None.

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