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A Delphi clinical practice protocol for the management of very long chain acyl-CoA dehydrogenase deficiency

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Abstract

Introduction—Very long chain acyl-CoA dehydrogenase (VLCAD) deficiency is a disorder of oxidation of long chain fat, and can present as cardiomyopathy or fasting intolerance in the first months to years of life, or as myopathy in later childhood to adulthood. Expanded newborn screening has identified a relatively high incidence of this disorder (1:31,500), but there is a dearth of evidence-based outcomes data to guide the development of clinical practice protocols. This consensus protocol is intended to assist clinicians in the diagnosis and management of screen-positive newborns for VLCAD deficiency until evidence-based guidelines are available.

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Method—The Oxford Centre for Evidence-based Medicine system was used to grade the literature review and create recommendations graded from A (evidence level of randomized clinical trials) to D (expert opinion). Delphi was used as the consensus tool. A panel of 14 experts (including clinicians, diagnostic laboratory directors and researchers) completed three rounds of survey questions and had a face-to-face meeting.

Result—Panelists reviewed the initial evaluation of the screen-positive infant, diagnostic testing and management of diagnosed patients. Grade C and D consensus recommendations were made in each of these three areas. The panel did not reach consensus on all issues, particularly in the dietary management of asymptomatic infants diagnosed by newborn screening.

Keywords

Very long chain acyl-CoA dehydrogenase; deficiency (VLCAD); Fatty acid oxidation; Delphi; Clinical practice protocol; Newborn screening

Introduction

Very long chain acyl-CoA dehydrogenase (VLCAD) deficiency (OMIM 201475, EC 1.3.99.13) is an inborn error of mitochondrial β-oxidation. Three phenotypes have been described: a “severe” form manifesting cardiac arrhythmia, cardiomyoapthy and hepatopathy that presents between the first hours to the early years of life (VLCAD-C), and two “milder” forms including a hepatic form manifesting hypoketotic hypoglycemia and presenting in infancy or early childhood (VLCAD-H) and a myopathic form with exercise intolerance, myalgia and rhabdomyolysis presenting in later childhood or adulthood (VLCAD-M) [1].

Patients with VLCAD deficiency were traditionally diagnosed after developing symptoms of the disorder. However expanded newborn screening now provides pre-symptomatic diagnosis in infants, typically through elevation of C14:1 acylcarnitine and other acylcarnitines [2]. Previously believed to be rare, newborn screening has identified an incidence as high as 1:31,500 births [3]. However, there is a paucity of data regarding which infants are at risk for neonatal or childhood symptoms, the extent to which symptoms can be prevented by early diagnosis and treatment, or which treatments are likely to be most efficacious. Until these questions are answered through clinical studies there is a need for consensus guidelines for clinicians for the diagnosis and management of infants who are screen-positive for VLCAD deficiency.

Method

A review of the literature was undertaken to grade the quality of the available evidence using the Oxford Centre for Evidence Based Medicine method, grading the evidence from 1 (systematic reviews with homogeneity of randomized controlled trials) to 5 (expert opinion without explicit critical appraisal). According to the Oxford Center guidelines, these levels were used to create Grades of Recommendations from A (consistent level 1 evidence) to D (level 5 evidence) [4].

Delphi was selected for the consensus tool. Delphi was developed by the Rand Corporation for forecasting when there is insufficient data to make an evidence-based decision [5]. It is described as “harnessing the opinions of an often diverse group of experts on practice-related problems” [6]. It is coming under increasing use in medicine for the development of clinical practice protocols (including a recent protocol for the diagnosis and management of 3-methylcrotonyl CoA carboxylase deficiency) [7].

The Delphi method uses a panel of experts who review the available literature, then complete a survey on the issue in question. The surveys are scored to determine the mean response; panelists are informed of the mean score for each item and then have the opportunity to change their responses on a second round of questions. After the second round a face to face meeting is held to consider items which failed to reach consensus.

Sixteen experts in inborn errors of metabolism were asked to serve on the panel. Fifteen agreed and fourteen completed the project. Panelist selection can be an important source of bias [8]. To minimize this bias, panelists were selected from a broad geographic distribution and included clinicians, diagnostic laboratory directors and researchers. Online survey software from Question Pro™ was used. Responses were coded on a five point Likert scale from strongly agree to strongly disagree, and responses were assigned a numerical score (strongly agree = 1, agree = 2, neutral = 3, disagree = 4, strongly disagree = 5). Consensus was reached for an item when the mean score was ≤2 or ≥4, or when at least 67% of the panelists concurred as agree or disagree. Consensus was not reached for all items during the face to face meeting. After the meeting final consensus scores were based on a third survey round.

Results

Evaluating the screen-positive infant

Initial medical evaluation (Recommendation Grade D, case report and expert opinion based)—This panel endorses the ACT sheet recommendations made by the American College of Medical Genetics for evaluating the infant who is screen-positive for VLCAD deficiency (http://www.acmg.net/resources/policies/ACT/ACT_sheet_C14-C14_1_5-2-06_ljo.pdf) [9] (Consensus score 2.0, 93% consensus). These recommendations include evaluating the screen-positive infant for poor feeding, hypotonia, hepatomegaly, arrhythmia or cardiac decompensation and initiating diagnostic testing. If the screen-positive infant does not appear well this panel recommends the following additional evaluations: cardiology evaluation for arrhythmia or cardiomyopathy, glucose, electrolytes, ammonia, lactate, liver function tests, creatine kinase and plasma carnitine. (consensus score 1.1–1.8, 69–100% consensus).

The ACT sheets do not provide additional guidance for management of infants who do not appear ill at the time of the initial evaluation. This panel considered whether diet alterations are indicated while awaiting the results of confirmatory testing. Evidence was sought regarding any potential relationships between screening metabolite levels and risk for neonatal complications. One study noted that newborn screen C14:1 level greater than 1 μmol/l were likely to represent a true positive result [10], but to date there are insufficient data to determine if the initial metabolite levels can predict neonatal risk. Panelists recommended that screen-positive infants should feed at least every 3–4 h around the clock (consensus score 1.2, 100% consensus). In the absence of data the panel had more difficulty coming to consensus regarding whether other feeding changes were indicated; at this time a marginal consensus did not recommend changes in dietary content in well-appearing screen-positive infants while awaiting confirmatory testing (consensus score 2.3, 67% agree). However, some panelists reported that a profoundly abnormal level of C14:1 on newborn screen might well prompt them to consider prophylactically changing feeds to a higher medium chain triglyceride (MCT) content formula in bottle-fed infants or supplementing breast-fed infants with MCT. Clinical studies are urgently needed to determine if infants at higher risk for the VLCAD-C phenotype can be identified on NBS and if they would benefit from long chain triglyceride (LCT) restriction/MCT supplementation even before the diagnosis is confirmed.

Confirming the diagnosis

This panel also endorses the American College of Medical Genetics algorithm for biochemical genetics laboratory follow-up of the screen-positive infant: http://www.acmg.net/resources/policies/ACT/Visio-C14-1_(4-19-06).pdf [11] (Consensus score 1.8, 93% agree).

Plasma acylcarnitine analysis (Recommendation Grade C, case series based)—Although in some cases the follow-up acylcarnitine analysis alone may confirm diagnosis, metabolite studies alone can not yet reliably predict which infants are at risk for the severe VLCAD-C phenotype. Further, it appears that C14:1 levels tend to fall over time even in affected infants, such that several infants have now been described who had normal follow-up biochemical testing but who were later diagnosed with VLCAD deficiency [3,12,13]. Thus, this panel unanimously agreed that normal biochemical testing on follow-up does not rule-out the disorder (consensus score 1.2, 100% agree), and that the diagnosis should be confirmed by DNA analysis and/or enzyme assay or fatty acid oxidation probe studies (consensus score 1, 100% agree).

Confirmatory diagnostic testing (DNA analysis, fatty acid oxidation probe or enzyme assay) (Recommendation Grade C, Case series based)—In addition to verifying diagnosis, it is important to identify those infants at risk for the severe phenotype as expeditiously as possible. DNA analysis is usually helpful in confirming diagnosis and can sometimes be helpful predicting phenotype; preliminary data suggest that infants homozygous for two null mutations are more likely to have a VLCAD-C severe infantile presentation, while those having two mis-sense mutations are more likely to have a VLCAD-H (fasting intolerance) or VLCAD-M (myopathic) phenotype [1,14,15]. However, there are a large number of mutations associated with this disorder [14,16], such that many mutations or combinations represent novel findings. Two apparently affected infants having one detectable mutation and one apparent carrier infant with no detectable mutations have been identified [10,17].

Preliminary data suggest that fatty acid oxidation probe profiles having the most significant elevation of C16 (compared to C12–14) are more likely to have a severe phenotype [18], however, this test typically requires a skin biopsy, an invasive study that can take months to provide an answer and must be weighed against the understanding that the positive predictive value for an abnormal C14:1 can be as low as 25% [19]. Enzyme assay in lymphocytes is currently available in Europe and is expected to be available in the United States in the near future. Preliminary data suggest affected infants with mild or moderate phenotypes are more likely to have residual enzyme activity in the range of 6–12% [10,15], but the full range of genotype/enzyme/phenotype correlation has not yet been described in infants ascertained through newborn screening.

Based on these data and the current unavailability of lymphocyte enzyme assay in the United States, the panel agreed that diagnostic testing was indicated, but did not agree on a recommended sequence of testing (DNA first, enzyme assay/FAO probe first, or simultaneous testing).

Treatment of the affected infant

Diet (Recommendation Grade D (case report and expert opinion based)

Fasting interval: Panelists unanimously agreed that prevention of catabolic fasting stress is a key aspect of dietary treatment. However, there was not one fixed recommendation for maximum fasting interval in infancy. Panelists used a variety of schedules including weight based schedules, for example: maximum fasting time 1 h per kg body wt, up to 8 h at 8 kg,

or age based schedules (q 3–4 h for first 4 months, then maximum fasting time per age in months up to 12 h by 12 months.) No single schedule was considered superior. There are no data supporting any specific safe fasting interval in well infants, and no specific genotype/phenotype correlations or metabolic markers have been investigated which might predict safe overnight fasting tolerance. During intercurrent illnesses the panel recommended extra care, with some consideration given to cutting permitted fasting intervals in half (consensus score 1.8, 84% consensus).

Feeding/formula choice: Regarding dietary prescription in infancy, panelists selected recommendations from the following choices: breast-feeding, breast-feeding supplemented with MCT, standard infant formula, MCT-enriched infant formula (approximately 50% of fat as MCT, e.g. Pregestamil, Special Care Advance, etc.), and maximally MCT-enriched formulas (e.g. Portagen or Monogen). As current maximally MCT-enriched formulas are designed for infants older than 12 months of age and alone might not meet essential fatty acid or other nutritional requirements for infants, it is important to consider the nutritional implications of using these formulas in infants and to seek nutritional assistance to ensure adequate provision of the infant's nutritional needs.

For non-screened infants and children diagnosed because of symptoms, cardiomyopathy has been successfully treated in some cases using maximally MCT-enriched formula [20,21]. In one case a child improved after being changed from a MCT-enriched infant formula (55% MCT) to a maximally MCT-enriched formula [22]. However, to date most infants diagnosed by NBS have been well; one screened infant presented with hypoglycemia and cardiovascular collapse (without cardiomyopathy) at 4 days of age [3], and another with hypoketotic hypoglycemia during an intercurrent illness at age 3 months [10]. In addition to protocols to prevent catabolism during intercurrent illnesses, various feeding regimens have been reported to be successful in preventing symptoms in infants diagnosed by newborn screening, including standard infant or higher MCT formula, breast-feeding with or without MCT supplementation, and after infancy low fat diets with MCT supplementation [3,15]. However, among infants with the “milder” phenotypes, metabolite/genotype/phenotype correlations can not yet fully predict which patients are even at risk to develop symptoms in childhood, and no studies have been conducted to determine if dietary restriction could possibly contribute to catabolism in some circumstances. Additional study is clearly needed regarding the optimal dietary prescription in severely affected children, and attention must be given to meeting essential fatty acid needs.

VLCAD-C (Severe Infantile Phenotype), <12 months of age—breast-fed

Asymptomatic: For breast-fed infants believed by DNA or probe/enzyme to be at risk for the severe phenotype but who do not yet demonstrate evidence of cardiac pathology, there was no consensus regarding a single dietary prescription strategy. The medium chain fat content of breast milk approximates a MCT-enriched infant formula, but still contains more LCT/less MCT than a maximally MCT-enriched formula. A majority of panelists (54%) would not recommend stopping breast-feeding so long as cardiac function remains normal, while 30% of panelists recommended stopping breast-feeding in favor of a maximally MCT-enriched formula (the remaining 16% remained “neutral”) (Table 1). Some panelists recommended supplementing breast-feeding with MCT, but this did not reach the level of a consensus recommendation. Additional data are needed regarding whether or not the MCT content of breast milk is sufficient to treat latent disease in infants predicted to be at risk for the VLCAD-C phenotype on enzyme assay or DNA, or whether breast-feeding should be discontinued in favor of a maximally MCT-enriched formula prophylactically.

Symptomatic (Cardiac Pathology: For breast-fed infants who demonstrate evidence of cardiac pathology, there was consensus that feedings should be changed to a maximally MCT-enriched formula (consensus score 1.8, 85% agree)(Table 1).

VLCAD-C (Severe infantile phenotype) <12 months—bottle fed

Asymptomatic: For bottle-fed asymptomatic infants, there was consensus that the formula should be changed (consensus score 1.8, 77% consensus). (Table 1) A majority of panelists would select a maximally MCT-enriched formula (compared to a MCT-enriched formula), but this did not reach the level of a consensus recommendation (consensus score 2.3 64% consensus) the remainder who recommended changing formula suggested a MCT-enriched formula. Additional data are needed to ascertain if the use of MCT-enriched formula is a safe choice to prevent symptoms, or if maximally MCT-enriched formula is indicated.

Symptomatic (Cardiac Pathology): For bottle-fed infants with any evidence of cardiac pathology, there was consensus that the formula should be changed to a maximally MCT-enriched formula (consensus score 1.8, 86% consensus) (Table 1).

VLCAD-C (Severe infantile phenotype)—after 12 months

Asymptomatic: There was unanimous agreement that dietary modification in older children should include at least some degree of LCT restriction and MCT supplementation. For asymptomatic high-risk children there was no single consensus on the recommended amount of LCT or MCT, but restriction of LCT to approximately 10% of calories with supplementation of at least 20% of calories as MCT received a majority of responses (57% agree, 11% disagree, remainder neutral). Outcomes data are needed regarding the optimal dietary management that will prevent development of symptoms and/or essential fatty acid deficiencies.

Cardiac Pathology: For children with evidence of cardiac pathology, there was consensus that diet should be modified to restrict LCT and supplement MCT. There was a slender consensus regarding dietary prescription for providing 10% of calories from LCT with at least 20% of calories from MCT (69% agree, 11% disagree and 20% chose “neutral”). The safety and efficacy of this restriction has not been studied.

VLCAD- H or VLCAD-M (“Mild” phenotype) <12 months of age—breast-fed

Asymptomatic: For affected asymptomatic infants believed by DNA or probe/enzyme studies to be at risk for a “milder” phenotype, 93% of respondents recommended continuing breast-feedings (consensus score 1.7). (Table 2). Among the panelists, 36% would consider adding MCT supplements to the breast-fed child's diet, but a plurality (42%) disagreed with this choice.

Symptomatic (VLCAD-H): If the infant demonstrated symptoms of fasting intolerance, there was a marginal consensus for supplementation of breast-feeds with MCT or a MCT enriched formula (consensus score 2.5, 71% consensus), although 21% preferred supplementing or replacing breast-feeds with a maximally MCT enriched formula (Table 2). It is not known whether dietary composition plays as important a therapeutic role as the prevention of catabolic stress in this phenotype.

VLCAD-H or VLCAD-M (“Mild” phenotype)<12 months of age—bottle-fed

Asymptomatic: For the asymptomatic bottle-fed infant, a majority recommended some alteration of the formula to increase MCT intake, but the recommendation did not reach consensus (consensus score 2.6, 64% consensus) (Table 2). About half preferred a MCT-

enriched formula and the other half a maximally MCT-enriched formula, but the matter did not reach consensus and further data is required.

Symptomatic (VLCAD-H): If the bottle-fed infant presented with or manifest fasting intolerance, a majority would change to a formula higher in MCT content (consensus score 2.6, 64%) (Table 2) but this did not reach consensus. Panelists who would chane formula were fairly evenly split between choosing a MCT-enriched formula vs a maximally MCT-enriched formula. The role of dietary composition vs prevention of fasting stress in preventing symptoms requires further study.

Asymptomatic VLCAD-H or VLCAD M ("mild" phenotype)—after 12 months of age—For the asymptomatic child, 93% of panelists agreed that some dietary modification should be offered (consensus score 1.1). The most popular option was an age-appropriate "heart-healthy" diet supplemented with MCT (consensus score 2.5, 75% consensus); some panelists recommended more stringent LCT restriction but this did not come to consensus. (Table 2) The role of long chain fat consumption in the development of later-onset myopathy is not known. The possibility that a highly restricted or less palatable diet could contribute to catabolism or essential fatty acid deficiencies also merits consideration.

Symptomatic VLCAD-H—after 12 months of age—For children with a history of fasting intolerance there was strong consensus that some dietary modification was indicated in addition to fasting prevention (consensus score 1.1, 92% consensus). The most commonly recommended option was for an age-appropriate "heart-healthy" diet with MCT supplementation (consensus score 2.3, 71% consensus). Up to half of panelists would consider more stringent LCT restriction but this did not come to consensus; among those who chose this option the most popular option was to provide half of fat calories from LCT and half from MCT.

Symptomatic VLCAD-M (myopathy)—after 12 months of age—For children manifesting myopathic symptoms/rhabdomyolysis, there was strong consensus that diet modifications should be offered (consensus score 1.1, 92% consensus). The most popular recommendation was an age-adjusted heart-healthy diet supplemented with MCT (consensus score 2.2, 78% consensus). However up to 41% of panelists would consider more stringent LCT restriction; among those considering more stringent restriction the most popular recommendation was to provide approximately half of fat calories from LCT and half from MCT (consensus score 2.1, 75% consensus). Additional data are required to investigate the effects of LCT restriction/MCT supplementation on the prevention or treatment of myopathic symptoms.

Management during intercurrent illnesses (Recommendation Grade D, case report and expert opinion based)—The panel endorsed the recommendations of the New England Consortium of Metabolic Programs for the prevention and treatment of metabolic crisis in affected patients (available at http://www.childrenshospital.org/newenglandconsortium/NBS/VLCADD.html [23]. To these we offer additional recommendations that all intravenous glucose fluids contain appropriate electrolytes (isotonic for bolus fluids and one-quarter to one-half normal saline for maintenance fluids) (consensus score 1.1, 100% consensus). Additional recommendations for the management of metabolic crisis include increasing glucose infusion if the patient fails to improve (adding insulin by drip if necessary) (consensus score 1.1, 100% consensus), and maximizing enteral MCT intake as tolerated (consensus score 1.5, 100% consensus).

When an affected child is ill or otherwise at risk for a metabolic crisis (but is not yet in crisis) the following laboratory evaluation was recommended: glucose, electrolytes, liver function tests, creatine kinase, and if child is affected or at risk for the VLCAD-C phenotype, troponin and cardiology evaluation/echocardiogram (consensus core 1.4–2.5, 75–92% consensus). Assay of plasma carnitine also reached consensus (consensus score 2.4, 69% consensus). When the child is in or nearing a metabolic crisis, the panel recommended adding a plasma ammonia (consensus score 1.8, 75% consensus).

Pharmacotherapy (Recommendation Grade D, case report and expert opinion based)—The use of carnitine is controversial in VLCAD deficiency. Among two case series of infants ascertained through newborn screening, plasma carnitine was in the normal range in 18 infants and low (9) in one [10,15]. VLCAD deficient mice experience a decrease in free carnitine and increase in long chain acylcarnitines in muscle during stress, as well as a decrease in acetyl-carnitine suggestive of decreased acetyl-CoA [24]. The accumulation of long chain acylcarnitine esters has been implicated in muscle pathology in VLCAD deficiency, particularly in the heart [25]. However, there is also evidence that ischemic changes in heart might be due to impaired energy production rather than from long chain acylcarnitine accumulation, emphasizing the importance of available free carnitine to recycle CoA [21,26]. In the VLCAD deficient mouse, carnitine supplementation further increased the baseline increase in long chain acylcarnitines but failed to replenish low carnitine in the heart or other tissues [27]. Plasma and tissue carnitine levels were poorly correlated in VLCAD deficient mice; the decrease in muscle free carnitine with stress was compensated by an increase in free carnitine synthesis in the liver that might be sufficient to recycle acetyl-CoA and replenish muscle carnitine after exercise [28].

At this time it is not known if the administration of carnitine is safe in patients with VLCAD, nor is it known if the benefit of preventing carnitine deficiency outweighs the potential cardiac risk of accumulating long chain acylcarnitines. Until human studies are available, the panel recommended administering oral carnitine only when needed to prevent carnitine deficiency in plasma (consensus score 2.2, 69% consensus). There was no consensus regarding the use of carnitine during acute illness. A plurality recommended waiting to administer carnitine until anabolism was restored to prevent accumulation of long chain carnitine esters from fatty acid oxidation in catabolism, but no recommendation reached consensus (consensus score 2.8, 46% consensus). Until additional data are available, carnitine administration should not be undertaken without awareness of potential underlying risks.

Benzafibrate has been demonstrated to increase palmitate oxidation in VLCAD deficient cells [29,30] in cells of patients with the myopathic form of VLCAD (but not more severe forms). Early data suggest genotype may predict responsiveness. In vivo human studies are needed to determine if benzafibrate therapy might be an effective treatment.

Discussion

Although evidence-based protocols are preferable for clinical management, the clinical data are not yet sufficient to create evidence based protocols for VLCAD deficiency. In order to assist clinicians in dealing with screen-positive and diagnosed patients with this disorder, the Delphi consensus process was used to create consensus protocols. These protocols are not intended to replace physician judgment, and should be replaced by evidence-based protocols as clinical studies are conducted. The evidence grade for these recommendations is generally Grade D, based on case reports or expert opinion.

With regard to dietary management, there was consensus on the importance of preventing catabolic stress, and generally consensus regarding the dietary management of symptomatic infants (usually advocating for more stringent LCT restriction and MCT supplementation). There was less consensus regarding the recommended fat composition of the diet for asymptomatic infants and children and outcomes studies are greatly needed. It is not yet clear whether symptomatic VLCAD deficiency is relatively common but under-diagnosed, or whether a significant portion of infants detected by newborn screening might never become symptomatic unless experiencing significant catabolic stress. Data are critically needed regarding predicting which infants are at risk for the severe cardiac form (VLCAD-C), and how much LCT restriction/MCT supplementation is required to prevent symptoms in these patients. Further, in patients with fasting onset forms of the disorder (VLCAD-H), it is not known whether restriction of dietary intake of LCT/MCT supplementation is beneficial, or whether highly restricted LCT diets could result in essential fatty acid deficiencies potentially impacting neurocognitive development or possibly be sufficiently unpalatable to increase risk for catabolic stress.

Delphi has come into increasing use in the medical literature in the development of clinical protocols. Delphi is commonly criticized for its tendency to converge toward a group “mean”, which in the absence of true medical evidence may not necessarily represent a scientific truth. In some cases this convergence toward the mean is preferable to convergence toward the panelist with the strongest personality, but it must always be accepted that accumulating medical evidence may require significant changes in these recommendations when such evidence is available. Compared to less formal methods of consensus, Delphi offers an advantage of actually measuring consensus as a score or percentage such that the reader can determine the relative strength of the recommendations.

With respect to VLCAD deficiency, it is clear that additional clinical outcomes studies and metabolite–genotype–phenotype correlations are needed. It would be particularly helpful to investigate any possible predictive value in the newborn screen acylcarnitines to determine which infants might be a risk for significant neonatal consequences while awaiting confirmatory testing. Outcomes studies are indicated to determine the optimal management of affected infants, including the role of diet, carnitine and benzafibrate in treatment.

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Table 1

Feeding recommendations for patients at risk for severe infantile cardiomyopathy phenotype.

Phenotype	Age Range	Feeding	Status	Recommendation	Consensus	
					Score	Percent
Severe infantile cardiomyopathy	<12 months	Breast-fed	Asymptomatic	(Continue breast-feeding)	(3.46)	(54)
				(Maximally MCT-enriched formula)	(3.07)	(30)
			Symptomatic	Maximally MCT-enriched formula	1.8	85
		Bottle-fed	Asymptomatic	Change from standard formula	1.8	77
				(Maximally MCT-enriched formula)	(2.3)	(64)
			Symptomatic	Maximally MCT-enriched formula	1.6	86
	>12 months		Asymptomatic	LCT restriction, MCT supplementation	1.7	100
				(10% calories LCT, 20% MCT)	(2.2)	(57)
			Symptomatic	10% calories LCT, 20% MCT	2.1	69

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Table 2

Feeding recommendations for patients at risk for fasting intolerance or myopathic phenotype.

Phenotype	Age Range	Feeding	Status	Recommendation	Consensus	
					Score	Percent
Fasting Intolerance or Myopathy	<12 months	Breast-fed	Asymptomatic	Continue breast-feeding	1.7	93
				(Add MCT supplements)	(3.2)	(36)
			Symptomatic	Supplement with MCT	2.5	71
				(Change to maximally MCT-enriched formula)	(3.5)	(21)
		Bottle-fed	Asymptomatic	(Change to higher MCT formula)	(2.6)	(64)
			Symptomatic	(Change to higher MCT formula)	(2.6)	(64)
	>12 months		Asymptomatic	Dietary modification recommended	1.1	93
				“Heart-healthy” diet plus MCT	2.5	75
Fasting Intolerance	>12 months		Symptomatic	Dietary modification recommended	1.1	93
				“Heart-healthy” diet plus MCT	2.3	71
Myopathy	>12 months		Symptomatic	Dietary modification recommended	1.1	93
				“Heart-healthy” diet plus MCT	2.2	78

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