Complete Summary

GUIDELINE TITLE

Task force guidelines handbook: EFNS guidelines on diagnosis and management of fatty acid mitochondrial disorders.

BIBLIOGRAPHIC SOURCE(S)

Angelini C, Federico A, Reichmann H, Lombes A, Chinnery P, Turnbull D. Task force guidelines handbook: EFNS guidelines on diagnosis and management of fatty acid mitochondrial disorders. Eur J Neurol 2006 Sep;13(9):923-9. [23 references] PubMed

GUIDELINE STATUS

This is the current release of the guideline.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Lipid storage myopathies (LSMs), including:

- Carnitine palmitoyltransferase II deficiency
- Primary systemic carnitine deficiency
- Primary muscle carnitine deficiency
- Very long acyl-CoA-dehydrogenase deficiency
- Trifunctional enzyme deficiency
- Medium-chain acyl-CoA-dehydrogenase deficiency
- Short-chain acyl-CoA-dehydrogenase deficiency
- Riboflavin-responsive multiple acyl-CoA dehydrogenase deficiency

GUIDELINE CATEGORY

Diagnosis
Management
Prevention
Treatment

CLINICAL SPECIALTY

Endocrinology
Family Practice
Internal Medicine
Medical Genetics
Neurology
Nutrition
Pediatrics

INTENDED USERS

Dietitians
Pharmacists
Physicians

GUIDELINE OBJECTIVE(S)

To provide guidelines for diagnosis and management of fatty acid mitochondrial disorders

TARGET POPULATION

Adults and children with fatty acid mitochondrial disorders

INTERVENTIONS AND PRACTICES CONSIDERED

Diagnosis

1. Assessment of signs and symptoms
2. Laboratory tests

Management/Prevention/Treatment

General Interventions

1. Avoidance of fasting
2. High carbohydrate, low fat diet with medium-chain triglycerides and reduced long-chain fats

Carnitine Palmitoyltransferase II Deficiency

1. Prevention of myoglobinuric episodes (avoidance of strenuous exercise during fasting or cold)
2. Intravenous infusion of glucose solution

Muscle and Systemic Carnitine Deficiencies

1. L-carnitine supplementation
2. Medium-chain triglyceride (MCT) diet

Long and Medium-chain Acyl-CoA-dehydrogenase Deficiencies

1. L-carnitine supplementation
2. Newborn screening

Riboflavin-responsive multiple Acyl-CoA Dehydrogenase Defects

Riboflavin supplementation

MAJOR OUTCOMES CONSIDERED

- Effectiveness of treatment
- Complications of fatty acid mitochondrial disorders

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

The task force for metabolic disorders systematically searched the MEDLINE database using key words, and examined textbooks and existing guidelines. According to the guidance for the preparation of neurological management by European Federation of Neurological Societies (EFNS) Task Force, articles were included if they contained data, which could be rated according to grades of recommendation for treatment classified in terms of evidence-based medicine (see the "Availability of Companion Documents" field in this summary).

NUMBER OF SOURCE DOCUMENTS

30 papers

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Evidence Classification Scheme for a Diagnostic Measure

Class I: A prospective study in a broad spectrum of persons with the suspected condition, using a "gold standard" for case definition, where the test is applied in a blinded evaluation, and enabling the assessment of appropriate tests of diagnostic accuracy

Class II: A prospective study of a narrow spectrum of persons with the suspected condition, or a well-designed retrospective study of a broad spectrum of persons with an established condition (by "gold standard") compared to a broad spectrum of controls, where test is applied in a blinded evaluation, and enabling the assessment of appropriate tests of diagnostic accuracy

Class III: Evidence provided by a retrospective study where either persons with the established condition or controls are of a narrow spectrum, and where test is applied in a blinded evaluation

Class IV: Any design where test is not applied in blinded evaluation OR evidence provided by expert opinion alone or in descriptive case series (without controls)

Evidence Classification Scheme for a Therapeutic Intervention

Class I: An adequately powered prospective, randomized, controlled clinical trial with masked outcome assessment in a representative population or an adequately powered systematic review of prospective randomized controlled clinical trials with masked outcome assessment in representative populations. The following are required:

a. Randomization concealment
b. Primary outcome(s) is/are clearly defined
c. Exclusion/inclusion criteria are clearly defined
d. Adequate accounting for dropouts and crossovers with numbers sufficiently low to have minimal potential for bias
e. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences

Class II: Prospective matched-group cohort study in a representative population with masked outcome assessment that meets a–e above or a randomized, controlled trial in a representative population that lacks one criteria a–e

Class III: All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome assessment is independent of patient treatment

Class IV: Evidence from uncontrolled studies, case series, case reports, or expert opinion

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Review of patient data and published cases

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Most guideline recommendations derived in this document are from case reports (class IV evidence), as no large trials have been conducted in fatty acid disorders. These guidelines reflect consensus opinions of experts in the field (good practice points). The consensus was reached analysing series of treated patients and in discussing pre-existing guidelines.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Rating of Recommendations for a Diagnostic Measure

Level A rating (established as useful/predictive or not useful/predictive) requires at least one convincing class I study or at least two consistent, convincing class II studies.

Level B rating (established as probably useful/predictive or not useful/predictive) requires at least one convincing class II study or overwhelming class III evidence.

Level C rating (established as possibly useful/predictive or not useful/predictive) requires at least two convincing class III studies.

Rating of Recommendations for a Therapeutic Intervention

Level A rating (established as effective, ineffective, or harmful) requires at least one convincing class I study or at least two consistent, convincing class II studies.

Level B rating (probably effective, ineffective, or harmful) requires at least one convincing class II study or overwhelming class III evidence.

Level C rating (possibly effective, ineffective, or harmful) requires at least two convincing class III studies.

Good Practice Points When only class IV evidence was available but consensus could be reached the Task Force gives recommendations as good practice points.

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

The guidelines were validated according to the European Federation of Neurological Societies (EFNS) criteria (see "Availability of Companion Documents" field in this summary).

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

The levels of evidence (class I-IV) supporting the recommendations and ratings of recommendations (A-C, Good Practice Points) are defined at the end of the "Major Recommendations" field.

Carnitine Palmitoyltransferase (CPT) II Deficiency

In the most typical presentations CPT II deficiency is seen in young adults (see Table 1 below) experiencing episodes of muscle pain and rhabdomyolysis triggered by prolonged exercise and cold.

Table 1. Carnitine Palmitoyltransferase II (CPT II) Deficiency

Young adults Paroxysmal myoglobinuria Residual: malonyl-CoA insensitive CPT activity CPT gene is located in chromosome 1 Serine 113 to leucine is the most common missense mutation 60% cases (429C > T)

Preventing myoglobinuric episodes is important and this can be achieved by avoiding strenuous exercise during fasting or cold. During an attack 5% of glucose solution is used as an alternative metabolic fuel. According to published guidelines a standard treatment protocol for myoglobinuria is intravenous infusion of hypotonic sodium chloride and sodium bicarbonate (sodium chloride 110 mmol/l and bicarbonate 40 mmol/l) in 5% of glucose solution to which 10 g of mannitol per litre is added in a 20% of solution. The solution should be infused into a young adult of 75 kg weight at the rate of 12 l/day in order to obtain a diuresis of 8 l/day and keep pH above 6.5. This therapeutic regimen will control both hyperkalemia and acidosis and therefore might prevent acute renal failure.

Carnitine Transport Defects

Primary L-carnitine deficiency syndromes are rare biochemical disorders and can be classified on the basis of clinical and biochemical criteria into muscle carnitine deficiency and systemic carnitine deficiency.

Systemic Carnitine Deficiency

Primary systemic carnitine deficiency is a well-recognized treatable entity of childhood (see Table 2 below) characterized by progressive cardiomyopathy, lipid storage myopathy (LSM) and attacks of hypoglycaemia, hepatomegaly with Reye-like syndrome that may lead to permanent brain damage.

Table 2. Primary Systemic Carnitine Deficiency

Inheritance: autosomal recessive
Gene: OCTN2 organic cation transporter
Clinical presentation
Progressive cardiomyopathy
Muscle weakness
Fasting hypoglycaemia
Urine: normal organic acid pattern
Low total carnitine in plasma, urine and muscle
Normal ratio carnitine/acyl-carnitines
Molecular biology: several point mutations reported

OCTN2, organic cation transporter 2

Diagnosis

In several cases a defect of carnitine high-affinity transport organic cation transporter 2 (OCTN2) gene has been demonstrated in cultured fibroblasts and genomic DNA can be screened for mutations.

Guidelines for Therapy

Carnitine supplementation corrects cardiomyopathy and other clinical signs. In some cases this treatment might avoid cardiac transplant. The L-carnitine dose may vary from 100 to 600 mg/kg/day on the basis of the calculated carnitine depletion from muscle, liver, heart and kidney. Individually adjusted dosing may require plasma level measurement. No side-effects are noted for L-carnitine supplementation except occasional diarrhoea or fishy body odour. In some cases a medium chain triglyceride (MCT) diet may be added (**class IV evidence**).

Muscle Carnitine Deficiency

In primary muscle carnitine deficiency the clinical syndrome is confined to skeletal muscle; the clinical features are episodes of fluctuating muscle weakness, affecting mostly limb and neck muscles and severe myalgia.

Diagnostic Guidelines and Therapy

The patients show appropriate ketogenesis on fasting and on a high fat diet. Biochemical features are low muscle carnitine (below 15%) and absence of organic aciduria. Carnitine concentrations in the plasma and liver are normal. There is *'in vitro'* stimulation by L-carnitine of labelled palmitate and oleate oxidation.

Although much is known about mechanisms of carnitine transport, data on muscle specific transport (low affinity) in human muscle carnitine deficiency cases are still scanty. In a childhood case, an abnormal low affinity carnitine transport was found in cultured muscle. This could be due to either a delayed maturation or an abnormal carnitine carrier protein. The available evidence indicates that low muscle content is the result of a genetic defect of the sarcolemmal carnitine transporter. Therefore, muscle carnitine deficiency could be caused by an abnormal low-affinity carrier or by a low amount of sarcolemmal carnitine carrier. It is distinguished from carnitine insufficiency by the absence of acyl-carnitine elevation in plasma or urine.

Treatment with L-carnitine replacement and MCT diet has been successful in a number of cases (**class IV evidence**).

Defects of Beta-Oxidation

Defects of fatty acids oxidation may affect muscle alone or in conjunction with signs in other tissues (i.e. liver and heart [see Table 3 in the original guideline document]). For most of the different enzyme deficiencies the clinical features are similar. In some patients this is reflected by exercise-induced muscle pain and rhabdomyolysis. The diagnosis is often suggested by characteristic patterns of organic acids excreted in the urine, which are specific for various enzymatic blocks.

Enzymatic and immunochemical analysis performed in fibroblasts and/or in muscle and liver mitochondria will confirm the diagnosis. (See also "Guidelines for laboratory diagnosis of fatty acid oxidation defects" in the original guideline document.)

Inborn errors of beta-oxidation are:

1. Very long-chain acyl-CoA deficiency (VLCAD)
2. Trifunctional enzyme deficiency
3. Medium-chain acyl-CoA deficiency (MCAD)
4. Short-chain acyl-CoA deficiency (SCAD)
5. Riboflavin-responsive disorders of beta-oxidation

Very Long-Chain Acyl-CoA-Dehydrogenase Deficiency

Very long-chain acyl-CoA deficiency has mostly been described in children. The patients reported so far can be grouped according to their clinical course: the first group has onset in the first few months of life and shows a high mortality; the second group is characterized by recurrent episodes of coma after fasting, but presents no cardiomyopathy; the third group presents with late-onset rhabdomyolysis and myalgia after muscle exercise.

Trifunctional Enzyme Deficiency

The disease is inherited as an autosomal recessive trait. Onset of symptoms is in the first year of life, characterized by intermittent hypoglycaemia, lethargy, and coma. The typical presentation is a progressive lethargy, evolving into coma

during a fasting or during a febrile episode associated with vomiting and diarrhoea that induces a catabolic state. Hepatomegaly, cardiomyopathy and muscle weakness are usually observed.

Medium-Chain Acyl-CoA-Dehydrogenase Deficiency

Medium-chain acyl-CoA deficiency is the most common error of fatty oxidation found in the US, UK, and Northern Europe. It is manifested by a recurrent syndrome of somnolence, vomiting, coma, hypoglycaemia, fatty infiltration of the liver, and dicarboxylic aciduria. The crises are often precipitated by intercurrent infections. Patients cannot oxidize the medium-chain fatty acids (C12 to C6). The disorder becomes life threatening during episodes of stress or fasting (see Table 4 below), which result in decreased caloric intake or increased catabolism.

Table 4. Medium-chain Acyl-CoA-dehydrogenase Deficiency

Children
Reye-like syndrome
Fasting hypoglycaemia, non-ketotic
Episodes of coma
Low total plasma carnitine
Decreased tissue carnitine
Decreased octanoic oxidation in fibroblasts
Medium-chain dicarboxylic aciduria
Chromosome lp3l
Common mutation 329 lysine to glutamic acid 90% of cases (986 A > G, K304E)

Treatment Recommendation

The treatment is similar in long-chain beta-hydroxy acyl-CoA-dehydrogenase (LCHAD) and medium-chain acyl-CoA-dehydrogenase (MCAD) deficiency: fasting and long intervals between meals should be avoided; a high-carbohydrate, low-fat diet should be administered and L-carnitine supplementation can be useful in preventing secondary carnitine insufficiency (**class IV evidence**). Prevention is important, considering the high incidence of the disease (1/8930 in a newborn screening programme in Pennsylvania) and the good prognosis in patients under adequate dietary control. The best prevention is the identification of the patients during the asymptomatic period, possibly at birth. Screening of all newborns can be achieved by searching for the typical metabolites in the urine.

Short- Chain Acyl-CoA-Dehydrogenase Deficiency (SCAD)

Few patients with SCAD deficiency have been described. SCAD deficiency is associated with different clinical phenotypes: a severe infantile form and a late-onset myopathic picture.

Riboflavin-Responsive Multiple Acyl-CoA-Dehydrogenase Defects (RR-MAD)

RR-MAD is a relatively common LSM presenting in adult life with fluctuating episodes of profound weakness, associated with carnitine insufficiency and glutaric

aciduria and usually underdiagnosed, that responds dramatically to riboflavin (see Table 5 below).

Table 5. Riboflavin-responsive Multiple Acyl-CoA-dehydrogenase Deficiency

Myopathic form
Adult onset
Lipid storage myopathy
Low SCAD, MCAD
Low free carnitine, increased acyl-carnitines, glutaric aciduria type 2
Riboflavin responsive

SCAD, short-chain acyl-CoA deficiency; MCAD, medium-chain acyl-CoA deficiency

Treatment Recommendations

It is important to recognize these patients as they improve after riboflavin treatment (100–200 mg/day). Several cases of LSM-associated beta-oxidation defects have been reported, because of multiple acyl-CoA-dehydrogenase deficiency that was riboflavin responsive (**class IV evidence**).

Evidence that a biochemical defect involving the oxidation of short-chain fatty acids causes a deficiency of both short-chain acyl-CoA dehydrogenase (SCAD), MCAD and flavin adenine nucleotide (FAD) and flavin mononucleotide (FMN) cofactor depletion in biopsied muscle mitochondria should be sought in most cases, especially in those who are riboflavin responsive.

Good Practice Points for Treatment of Fatty Acid Disorders

The main caution in defects of mitochondrial beta-oxidation is the avoidance of fasting (**class IV evidence**). By not allowing patients in such disorders to become dependent for energy needs on beta-oxidation, the accumulation of toxic intermediate metabolites is avoided and development of most critical symptoms is minimized. Fat consumption should be restricted to 25% of total calories and have reduced amount of long-chain fatty acid (LCFA) (**class IV evidence**). Increased caloric intake from carbohydrates may be necessary during intercurrent illness because of increased metabolic demands on the body. A low-fat/high-carbohydrate diet is beneficial in reducing rhabdomyolytic episodes in several disorders of fatty acid metabolism including CPT II deficiency and trifunctional enzyme deficiency. The current dietary treatment of LCFAs defects (high carbohydrate with medium-even-chain triglyceride and reduced long-chain fats) is based on evidence provided by expert opinion alone or by descriptive case series without controls. It is difficult to perform double-blind studies to prevent cardiomyopathy, rhabdomyolysis and muscle weakness. A possible alternative diet has been proposed by replacing dietary medium-even-chain fatty acids by medium-odd-chain fatty acids, or by precursors of acetyl-CoA such as by the anaplerotic effect of propionyl- CoA* to restore energy production and improve cardiac and skeletal muscle function.

*The anaplerotic capacity of propionyl-CoA refers to its capacity to provide the formation of methylmalonyl-CoA and energy to the Krebs cycle, because it is a precursor of succinyl-CoA, a citric acid cycle intermediate.

Definitions:

Evidence Classification Scheme for a Diagnostic Measure

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Class II: A prospective study of a narrow spectrum of persons with the suspected condition, or a well-designed retrospective study of a broad spectrum of persons with an established condition (by "gold standard") compared to a broad spectrum of controls, where test is applied in a blinded evaluation, and enabling the assessment of appropriate tests of diagnostic accuracy

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e. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences

Class II: Prospective matched-group cohort study in a representative population with masked outcome assessment that meets a–e above or a randomized, controlled trial in a representative population that lacks one criteria a–e

Class III: All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome assessment is independent of patient treatment

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Rating of Recommendations for a Diagnostic Measure

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Rating of Recommendations for a Therapeutic Intervention

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Level C rating (possibly effective, ineffective, or harmful) requires at least two convincing class III studies.

Good Practice Points When only class IV evidence was available but consensus could be reached the Task Force gives recommendations as good practice points.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is identified and graded for elected recommendations (see "Major Recommendations" field).

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Appropriate diagnosis and management of fatty acid mitochondrial disorders

POTENTIAL HARMS

No side-effects are noted for L-carnitine supplementation except occasional diarrhea or fishy body odour.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

This guideline provides the view of an expert task force appointed by the Scientific Committee of the European Federation of Neurological Societies (EFNS). It represents a peer-reviewed statement of minimum desirable standards for the guidance of practice based on the best available evidence. It is not intended to have legally binding implications in individual cases.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

The European Federation of Neurological Societies has a mailing list and all guideline papers go to national societies, national ministries of health, World Health Organisation, European Union, and a number of other destinations. Corporate support is recruited to buy large numbers of reprints of the guideline papers and permission is given to sponsoring companies to distribute the guideline papers from their commercial channels, provided there is no advertising attached.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness
Staying Healthy

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Angelini C, Federico A, Reichmann H, Lombes A, Chinnery P, Turnbull D. Task force guidelines handbook: EFNS guidelines on diagnosis and management of fatty acid mitochondrial disorders. Eur J Neurol 2006 Sep;13(9):923-9. [23 references] PubMed

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2006 Sep

GUIDELINE DEVELOPER(S)

European Federation of Neurological Societies - Medical Specialty Society

SOURCE(S) OF FUNDING

European Federation of Neurological Societies

GUIDELINE COMMITTEE

European Federation of Neurological Societies Task Force on Diagnosis and Management of Fatty Acid Mitochondrial Disorders

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Task Force Members: C. Angelini, Department of Neurology, University of Padova, Padova, Italy; A. Federico, Department of Neurological and Behavioural Sciences, University of Siena, Siena, Italy; H. Reichmann, Neurologischen Universitaetsklinik Universitaetsklinikum Carl Gustav Carus der Technischen Universität Dresden, Dresden, Germany; A. Lombes, Unite de Recherche INSERM 153, Hôpital de la Salpétrière, Paris, France; P. Chinnery, Department of Neurology, The University of Newcastle upon Tyne, Newcastle upon Tyne, UK; D. Turnbull, Department of Neurology, The University of Newcastle upon Tyne, Newcastle upon Tyne, UK

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

This paper was done as a part of a European Biobank Network. The authors have no conflict of interests with guideline recommendations.

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: Available to registered users from the European Federation of Neurological Societies Web site.

Print copies: Available from Dr Corrado Angelini, Department of Neurology, University of Padova, Padova, Italy; Phone: +39 049 821 3625; Fax: +39 049 875 1770; E-mail: corrado.angelini@unipd.it

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Brainin M, Barnes M, Baron JC, Gilhus NE, Hughes R, Selmaj K, Waldemar G; Guideline Standards Subcommittee of the EFNS Scientific Committee. Guidance for the preparation of neurological management guidelines by EFNS scientific task forces – revised recommendations 2004. Eur J Neurol. 2004 Sep;11(9):577-81. Electronic copies: Available in Portable Document Format (PDF) from the European Federation of Neurological Societies Web site.
- Guideline papers. European Federation of Neurological Societies. Electronic copies: Available from the European Federation of Neurological Societies Web site.

PATIENT RESOURCES

None available

NGC STATUS

This NGC summary was completed by ECRI on April 10, 2007. The information was verified by the guideline developer on May 18, 2007.

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