

MITO 101 – Illness

Juan M. Pascual, MD, PhD

Division of Pediatric Neurology
Departments of Neurology, Physiology and Pediatrics
The University of Texas Southwestern Medical Center

Neurometabolic Clinic
Children's Medical Center and
UT Southwestern Medical Center Hospitals and Clinics

5323 Harry Hines Blvd.
Dallas, TX 75390-8813
Juan.Pascual@UTSouthwestern.edu

Illness in mitochondrial patients

Key points

- Every time a patient afflicted by a mitochondrial disease becomes ill, several systematic considerations and investigations are in order for two main reasons. First, to understand the precise nature of the illness: is the illness caused by an infection or precipitated by malnutrition or is it yet another manifestation of the original mitochondrial disease? Second, to minimize its impact on various essential organ systems.
- Often times, unnecessary delays towards the instauration of effective treatment for the many common illnesses that afflict mitochondrial patients arise from the misconception that any new illness in these subjects must somehow stem from their underlying mitochondrial dysfunction and that, consequently, treatment will be ineffective.
- Although mitochondrial diseases do indeed debilitate multiple body systems and increase the incidence of complications, most of these are treatable and even preventable (Table 1).

The importance of information

- Because of global health care inadequacies, an acutely ill mitochondrial patient will only rarely be assessed by a mitochondrial expert. It is therefore important that patients or caretakers carry a summary of key medical, diagnostic and analytical reports with them so as to facilitate their emergent assessment.
- Most care providers will supply their patients with a one-page summary containing the essential features of their illness upon request.
- Table 2 lists a minimum set of generic interventions helpful in triaging an ill mitochondrial patient. These guidelines can be modified if the patient's illness can be immediately recognized, or expanded if the patient is new to a particular care facility or afflicted by a life-threatening illness.

A systematic approach to the ill mitochondrial patient

- After the initial patient assessment, a series of questions should be reviewed and additional investigations and interventions considered (Table 3).
- When it cannot be ascertained that the patient has a confirmed mitochondrial disease, or when the underlying disease is still under investigation by other specialists, collection of additional samples during the current illness may ultimately help to reach a diagnosis. Samples should be submitted for the measurement of blood amino acids, acylcarnitines, lactate, pyruvate, ammonia, and urinary organic acids and amino acids, for the performance of a Supplemental Newborn Screening (feasible at any age using a dried blood paper card) and, in the case of cerebrospinal fluid, for frozen storage until expert consultation can be obtained.
- Next, it is crucial to establish whether the current illness is part of the underlying syndrome or it is an unrelated coincidental event. Table 4 lists common manifestations of mitochondrial diseases. However, extreme caution should be exercised before attributing any of these manifestations to the underlying mitochondrial disease, until and unless a coincidental illness can be ruled out. This is of paramount importance in the case of infection, which can cause most of the manifestations listed in Table 4.

Special treatment considerations

- While an intercurrent illness is confirmed and specific treatment started, a series of supportive interventions must also be initiated to counterbalance the extra demands that are placed on virtually every organ and system.

- Maintenance of prior medications is of paramount importance, particularly anticonvulsants, gastrointestinal and cardiovascular agents, and psychotropic drugs.
- When gastrointestinal access or tolerance is limited, intravenous or rectal formulations are available for some commonly prescribed agents. For example, patients who receive multiple anticonvulsants may benefit from intravenous benzodiazepines while unable to utilize the oral route.
- Vitamins, cofactors and other supplements should be maintained and can even be doubled or tripled during an intercurrent illness.
- Because caloric and total nutritional needs increase during any illness, total intake can be supplemented by an extra 25-50%. Lipid infusions, however, may be contraindicated in fatty acid oxidation defects, although specific chain length lipids and precursors are available as dietary supplements for select disorders.
- Parenteral hydration can be increased to 150% maintenance levels or titrated to obtain a brisk urinary output, if the cardiovascular system is not affected by the mitochondrial disease.
- Extra oxygen can be administered for both anemia and cardiopathy.
- Special care should be applied to prevent nosocomial infections, e.g. from indwelling urinary bladder catheters or central venous lines, and periodic surveillance cultures may also be obtained. Lastly, immobility can cause loss of muscle, pressure-related ulcers and contractures, and it can predispose to deep venous thrombosis. Thus, use of low molecular weight heparinoids, compressive leg devices and rehabilitative interventions should be considered early.

Fulminant illnesses

- A special situation arises when an illness triggers a catastrophic decompensation of mitochondrial function. Table 5 lists the cardinal manifestations of severe mitochondrial impairment that can follow even a seemingly minor or coincidental disease.
- Care must be taken to distinguish lactic acidosis or liver failure due to aggravated mitochondrial dysfunction from that due to circulatory failure and shock.
- In addition to the life-supporting treatments described in Table 5, specific mitochondrial diseases render the patient prone to acute encephalopathy, seizures, or heart failure that can be responsive to emergent cofactor administration. For example, L-carnitine (infused at 100-400 mg/kg/day) can drastically ameliorate carnitine transport defects and MCAD deficiency, biotin (10-50 mg/day) can be used to treat certain forms of lactic acidosis, riboflavin (vitamin B2, 100-300 mg/day) is used to treat forms of multiple acyl-CoA dehydrogenation deficiency and thiamine (vitamin B1, 50-500 mg/day) can be efficacious in cases of pyruvate dehydrogenase deficiency.

Table 1.

Risks and vulnerabilities of mitochondrial patients.

<u>Adverse outcomes</u>	<u>Causes and associations amenable to intervention</u>
Aspiration pneumonia	Impaired swallow, inadequate diet consistency
Malnutrition	Oral incoordination, recurrent infections
Dehydration	Inadequate intake, insensible respiratory losses
Dental infections	Poor hygiene
Joint contractures	Immobility, insufficient rehabilitative intervention
Limb injuries and falls	Neuropathy, visual loss, epilepsy or ataxia
Skin breakdown	Poor hygiene, inactivity, inadequacy of assistive devices
Depression	Fragmentation of care, uncertain life expectancy

Peer and societal neglect Poverty, mental retardation

Table 1 footnote: Ill mitochondrial patients are at risk for a variety of iatrogenic complications, particularly when less desirable pharmacological agents are used. For a description of drug-related risks, please refer to the appropriate section of this monograph.

Table 2.

Emergent patient assessment

1. Recording of vital signs
2. Bedside determination of pulse oxymetry, hydration status, blood glucose and urinary ketones
3. History and physical examination
4. Collection of samples for
 - Complete blood count
 - Electrolytes
 - BUN and creatinine
 - Transaminases (AST, ALT, GGT)
 - Creatine kinase (CK)
 - Lactic acid
 - Venous blood gas
 - Troponin (if cardiopathy is suspected)
5. Electrocardiogram and chest X ray
6. Inspection of past medical records for diagnosis (or lack thereof) and baseline analytic values
7. Review, when needed, of disease-specific online professional resources (GeneReviews, OMIM, PubMed)
8. Expert telephone consultation where available

Table 3.

Practical approach to the ill mitochondrial patient.

1. Has the patient's mitochondrial disease been confirmed?
2. Is the current illness a manifestation of the underlying mitochondrial disease?
3. What caused the illness and can a future occurrence be prevented?
4. How can the illness' impact be reduced?
 - Continuing prior medications
 - Maintaining prior supplements
 - Additional supplementation
 - Nutrition
 - Hydration
 - Respiration
 - Infection prevention
 - Mobilization
 - Avoidance of drugs that may impact mitochondria

Table 4.

Mitochondrial disease symptoms that resemble other illnesses.

Fatigue
 Irregular heartbeat
 Lethargy and coma

Delirium
 Renal failure and renal tubular acidosis
 Diabetes
 Pancreatitis
 Vomiting
 Intestinal pseudo-obstruction
 Depression and other psychiatric disorders

Table 5.
Management of life-threatening metabolic dysfunction.

<u>Indicator</u>	<u>Intervention</u>
Hypoglycemia	Administration of intravenous glucose dissolved in balanced electrolyte solution at up to 10 mg/kg/min
Ketoacidosis	Administration of glucose as above and, when plasma bicarbonate < 10 mmol/l, infusion of sodium bicarbonate sufficient to correct initially one half of the calculated base deficit
Lactic acidosis	Infusion of sodium bicarbonate as above followed by adjusted infusion to maintain plasma bicarbonate > 10 mmol/l. Furosemide at 1 mg/kg per dose may be used to treat hypernatremia resulting from excess sodium bicarbonate, whereas potassium can also be added to prevent furosemide-induced hypokalemia. In some instances, intravenous dichloroacetate at 15-200 mg/kg followed by constant infusion may be used to increase clearance of lactic acid
Fulminant liver failure	Replacement of liver-synthesized proteins (albumin, coagulation factors). Organ transplantation

References

GeneReviews at GeneTests: Medical Genetics Information Resource (database online). Copyright, University of Washington, Seattle. 1997-2007. Available at <http://www.genetests.org>. Accessed September 10, 2007.

Online Mendelian Inheritance in Man, OMIM (TM). McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University (Baltimore, MD) and National Center for Biotechnology Information, National Library of Medicine (Bethesda, MD). Available at: <http://www.ncbi.nlm.nih.gov/omim/>. Accessed September 10, 2007.

Mitochondrial Medicine, S. DiMauro, M. Hirano, E. Schon, eds. Informa Healthcare, 2006.

Physician's Guide to the Treatment and Follow-Up of Metabolic Diseases, N. Blau, G. Hoffmann, J. Leonard, J. Clarke, eds. Springer, 2005.