Predisposition to infection and SIRS in primary mitochondrial disorders: 8 years' experience in an academic center

Target Audience: *patients and families affected by primary mitochondrial disorders, primary care providers*

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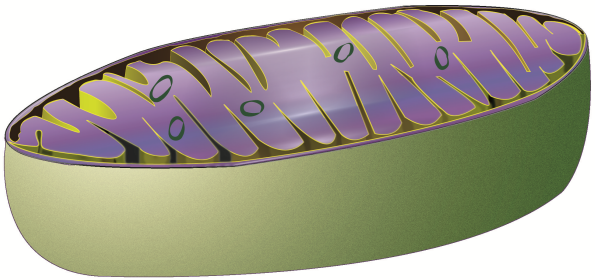
Infection and Immune Function in Primary Mitochondrial Disorders

- Introduction
  - Primary mitochondrial disorders
  - The immune system
- Review of MGH mitochondrial patient registry (8 years' experience)
  - Patients & diagnoses
  - Experience with
    - Infections
    - System immune response syndrome (SIRS)
    - Immunodysfunction
- Clinical implications & future directions

Primary Mitochondrial Disorders

- Cause: dysfunction of the mitochondrion, the "powerhouse" organelle of the cell

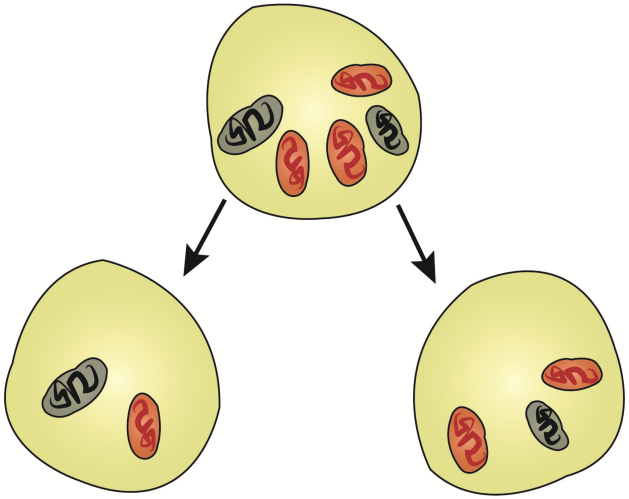
- Mitochondrial functions
  - Oxidative-phosphorylation (energy production)
  - Fatty acid oxidation (energy metabolism)
  - Apoptosis (controlled cell death)
  - Calcium regulation



- Epidemiology
  - Estimated ~1:4000 individuals affected

Diagnosis of Primary Mitochondrial Disorders

Goal: determine the probability and possible cause of primary mitochondrial disease



- Problems:
  - No single way to diagnose
    - Can affect multiple organ systems
    - No definitive *biomarker* (blood test)
    - Not all genes known
    - Phenotypic variation (same gene, different symptoms)
    - **Heteroplasmy** (unequal distribution of mitochondria & their DNA in cells) & **maternal inheritance**
  - Secondary mitochondrial dysfunction can mimic primary mitochondrial disorders

Diagnosis of Primary Mitochondrial Disorders

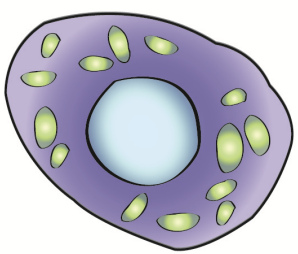
- Clinical criteria (signs and symptoms)
  - Determine the likelihood of a mitochondrial disorder
    - Bernier criteria (*Bernier et al. Neurology 2002; 59: 1406-11*)
    - Morava criteria (*Morava et al. Neurology. 2006;67:1823-6*)

- Genetic analysis
  - **Mitochondrial** DNA-encoded genes
    - Maternal inheritance
    - Heteroplasmy
  - **Nuclear** DNA-encoded genes

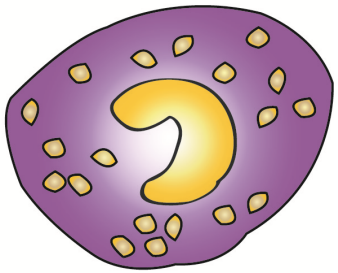
- Biochemical studies
  - "Blood test": peripheral biochemical screening
  - "Tissue test": muscle or other tissue biopsy: microscopy (LM, EM) for morphology, immuno-histochemistry (COX, SDH), biochemistry, polarography, ATP production (requires freshly isolated tissue/ mitochondria)
  - "Tissue test function" Physiology: CPET, MRI/MRS

The Immune System

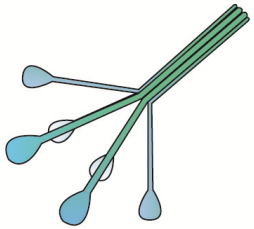
- Major defense system against infections
- Immune cells are found in multiple tissues *(e.g. blood, skin, gut, lung, muscle…)*
- Proteins, other molecules
- Immune dysfunction can lead to:
  - **Infections**
  - Systemic immune response syndrome (**SIRS**)
  - Autoimmunity
  - Malignancy (cancer)
  - Severe allergies



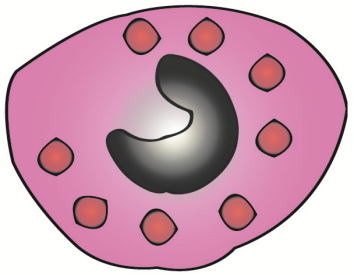
mast cell



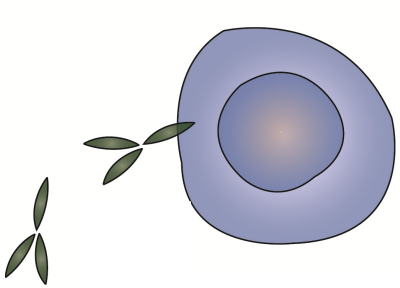
basophil



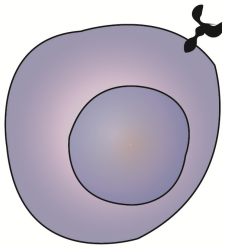
complement



eosinophil



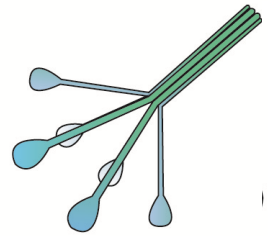
B-cell



T-cell

Subsets of the Primary Immune System

- **Innate immune system**
  - Inborn
  - Nonspecific
  - Does not require previous exposure
  - Involves complement, immune cells (including phagocytes, macrophages, eosinophils, basophils, innate T cells)
- **Adaptive**
  - Diversifies with age and exposure
  - Pathogen specific
  - Occurs in response to previous exposure
  - Involves B-cells, T-cells, and antibody production



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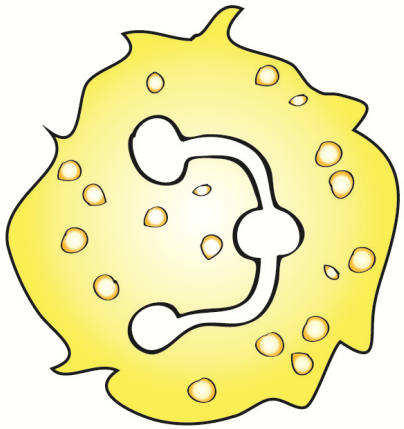
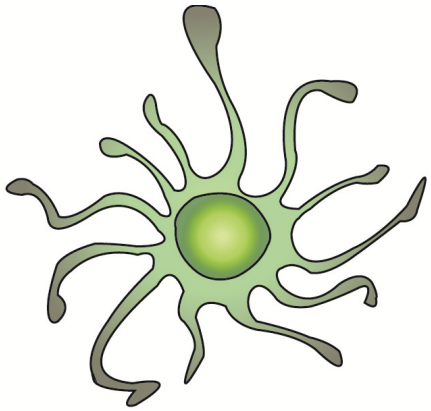
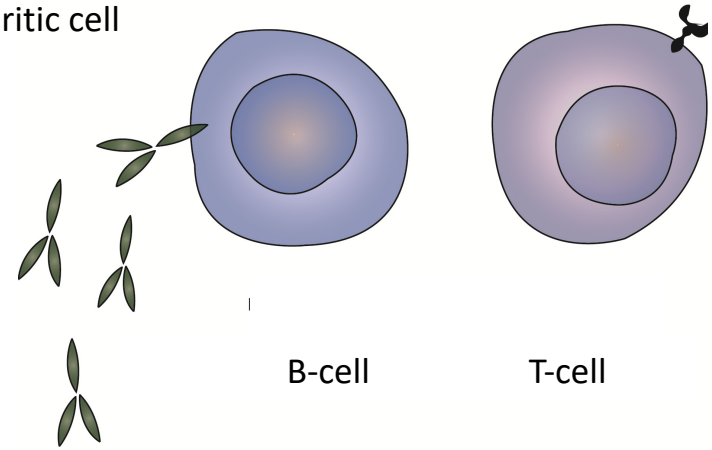


neutrophil



dendritic cell



B-cell T-cell

Examples that link Mitochondrial Functions and the Immune System

Innate

- Viral immunity requires link between the mitochondria and effectors from pattern recognition receptor (PRR) signaling

- Bacterial immunity may require production of reactive oxygen species (ROS) produced by mitochondria to kill bacteria

  (*Cloonan, Choi. Curr Opin Immunol 2012; 24: 32-40*)

Adaptive

- T-cell memory generation requires mitochondrial oxidative metabolism

  (*Nature. 2009; 460:103-107*)

- T-cell subtypes performing different roles in the immune system have distinct metabolic signatures, implying different states of energy metabolism & mitochondrial function

  (*Dang et al. Cell.2011;146:772-784*)

Mitochondrial Genes that are known to cause Dysfunction of the Immune System

Syndrome	Gene	Phenotype/ Immunologic Phenotype	Bernier Criteria Classification
Barth Syndrome	*Taz*	3-methylglutaconic aciduria, cardioskeletal myopathies, neutropenia (*Jefferies. Am J Med Genet Part C Semin Med Genet 163C:198–205*)	*Likely affected*
Omenn Sydnrome	*Adenylate kinase (AK) 2*	Inflammatory variant leaky severe combined immunodeficiency (SCID) (*Henderson et al. J Allergy Clin Immunol. 2013 Apr;131:1227-30*)	*Unlikely affected*
Cartilage Hair Hypoplasia	*Mitochondrial RNA Processing Endoribonuclease (RMRP)*	Dwarfism, predisposition to infections, variable immune deficiency with T cell dysfunction (*de la Fuente et al. J Allergy Clin Immunol. 2011;128:139-46*)	*Possible*

Walker et al. Powering the Immune System: Mitochondria in Immune Function & Deficiency. 2014; manuscript submitted for publication.

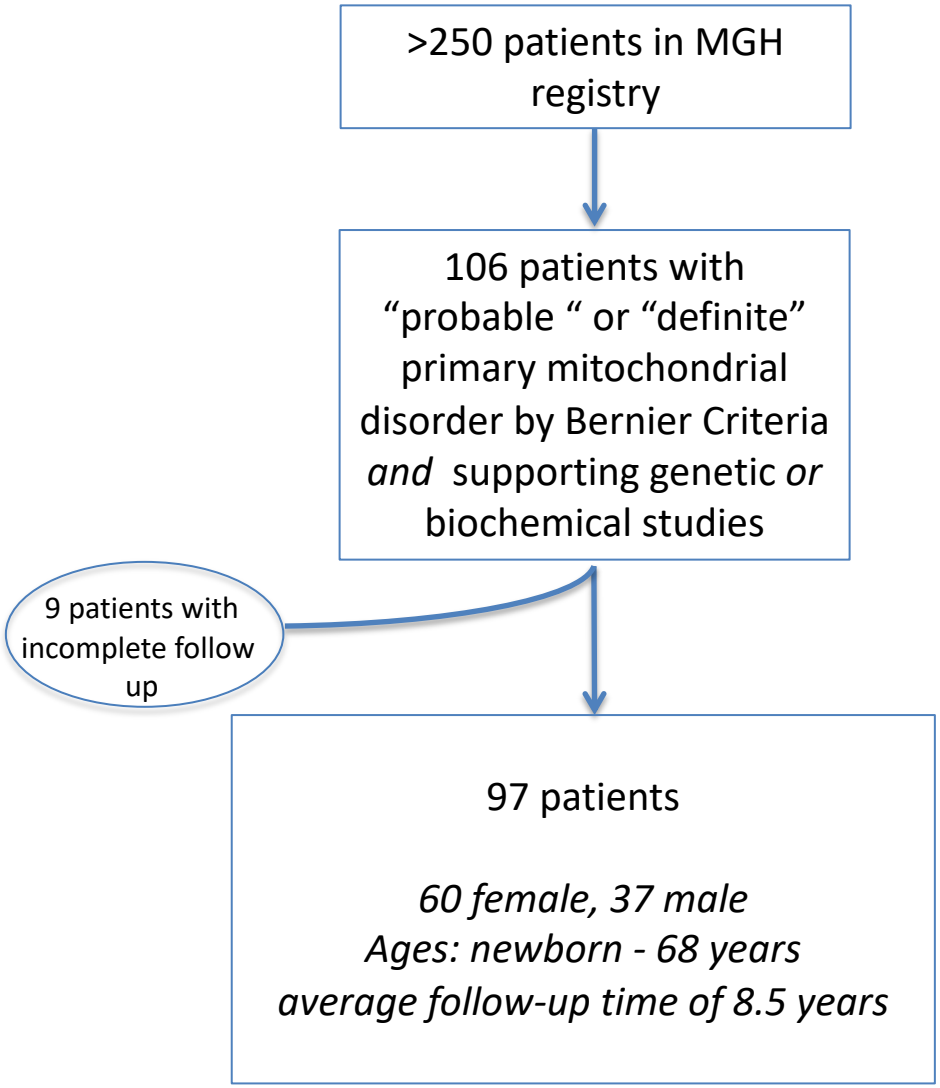
Review of 8 years' clinic experience with patients with primary mitochondrial disorders in an academic center

Predisposition to infection and SIRS in mitochondrial disorders: 8 years' experience in an academic center

Walker MA, Slate N, Alejos A, Volpi S, Iyengar RS, Sweetser D, Sims KB, Walter JE

J Allergy Clin Immunol Pract. 2014 Jul-Aug;2(4):465-468.e1. Epub 2014 Apr 13.

Cohort of patients with mitochondrial disease



Patient cohort: Genetic findings (32, 32%)

Figure E1.

Molecular diagnosis	Published clinical syndrome	No. affected	No. with biochemical testing (no. with positive biochemical findings)
mtDNA defects			
$tRNA^{Leu}$, m.3243A>G	MELAS	7	0 (0)
$tRNA^{Lys}$, m.8344A>G	MERRF	5	0 (0)
ATP synthase *MT*-ATP6 subunit, m.8993T>C	NARP	2	0 (0)
ETC I subunit ND6, m.14484T>C	1 with, 1 without clinical LHON phenotype	2	1 (1)
$tRNA^{Leu}$ m.12280A>G (homoplasmic); ETC I subunit ND1, m.42167T>C (heteroplasmic); ETC I subunit ND2, m.4917A>G (heteroplasmic)	None	1	1 (1)
$tRNA^{Phe}$, m.606A>G; mtDNA depletion	None	1	1 (1)
mtDNA deletion	Kearne-Sayre syndrome	1	1 (1)
large mtDNA deletion	MIDD	1	1 (1)
mtDNA depletion with multiple ETC deficiencies	None	2	2 (2)
nDNA defects			
WF1 point mutation (exact mutation not available)	DIDMOAD/Wolfram syndrome	1	0 (0)
POLG, p.G848S, p.A467T, p.G737R	1 SANDO, 1 MIRAS, 5 none	7	4 (3)
ETC I NDUFAB subunit, exon 4, c.394G>T	None	1	1 (1)
ETC I *NDUFV1* subunit, c.499del and c.365C->T	None	1	1 (1)

Walker et al, J Allergy Clin Immunol Pract. 2014 Apr 14: 2:1-4.

Patient cohort: Biochemical studies (75, 75%)

Figure E1.

Biochemical assay or pathology-based diagnoses without genetic data	No. of patients
Oxidative phosphorylation defect	70
Pyruvate dehydrogenase deficiency	1
Progressive external ophthalmoplegia with ragged red fibers	1
Short/branched-chain acyl-CoA dehydrogenase deficiency	1
Short-chain hydroxyl acyl-CoA dehydrogenase deficiency	1
Short-chain 3-ketothiolase deficiency	1

Walker et al, J Allergy Clin Immunol Pract. 2014 Apr 14: 2:1-4.

Our question:

What is the frequency of infection and systemic immune response syndrome (SIRS) in primary mitochondrial disorders?

Criteria for “Serious or Recurrent” Infection

Inclusion criteria

- Infection requiring hospitalization
- Infection requiring surgical intervention (Tympanoplasty, incision & drainage, etc.)
- Infection meeting Systemic Immune Response (SIRS) criteria
  - Inflammatory state
  - Defined by vital sign changes, clinical and laboratory findings

    (*Goldstein et al. Pediatr Crit Care Med 2005;6:2-8*)

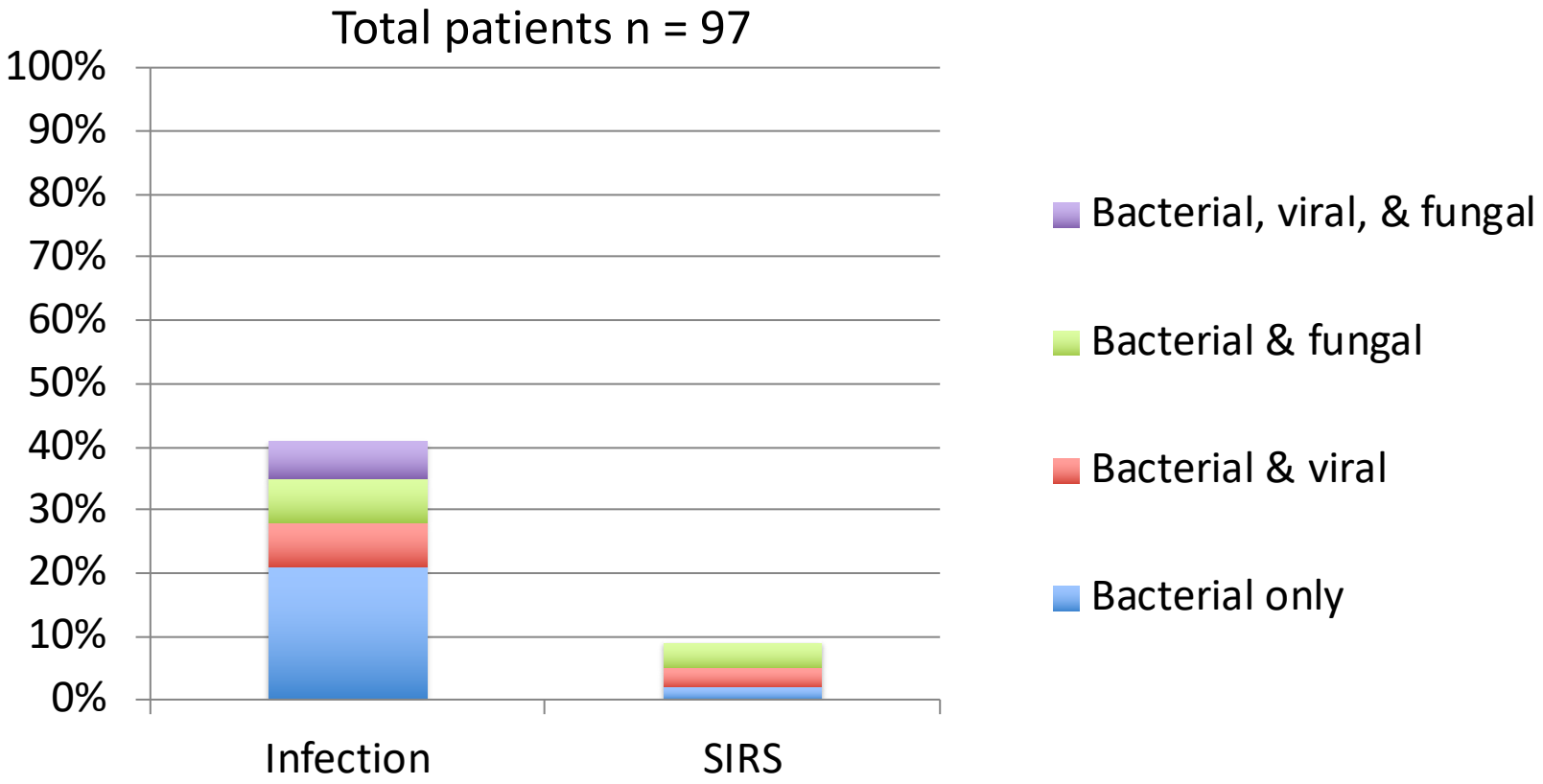
Exclusion Criteria

- Urinary tract infections – due to high rate of neurogenic bladder in primary mitochondrial disorders
- Pneumonia with respiratory insufficiency-- unless occurring at a higher rate than in patients with other neuromuscular disorders with respiratory insufficiency

  (*Bach et al. Am J Phys Med Rehabil 1998;77:8-19*)
- Bloodstream infections with central venous lines-- unless occurring at a higher rate than in all pediatric patients with CVLs

  (*Wagner et al. Arch Dis Child 2011;96:827-31*)

Experience with Infection & SIRS



- A significant fraction of patients **(~40%)** experienced serious or recurrent infections, primarily bacterial
- A number of patients **(~10%) experienced one or more episodes of SIRS**, which occurs at a rate of 0.0017% nationally (*MMWR Morb Mortal Wkly Rep 1990;39:31-4*)

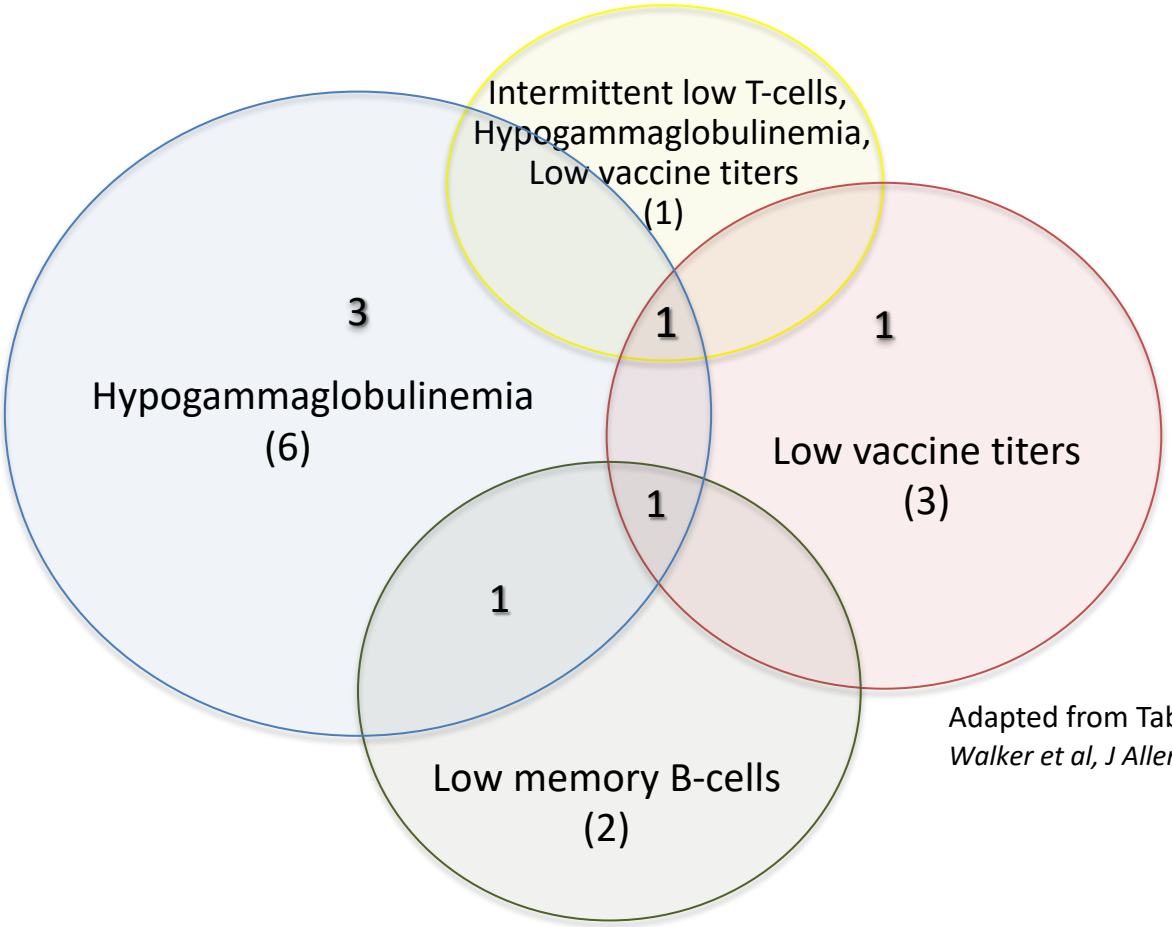
Experience with Infection & SIRS

Pathogen	No. affected	Sites
Staphlococcus aureus	15	MSSA bacteremia with sepsis (4), MSSA bacteremia (2), MRSA bacteremia (1), meningitis (1, also with bacteremia), peritonitis and tracheitis (1), MSSA cellulitis (1), recurrent MRSA skin abscesses (1), pneumonia (2, 1 also with bacteremia), foot ulcer (1), abdominal wound (1)
Candida albicans	8	Fungemia (3, 2 with sepsis), esophagitis (1), nonhealing foot ulcer (1), abdominal wound (1), chronic vagnitis (1)
Clostridium dificile	6	Colitis with sepsis (2), colitis (4)
Enterococcus	5	Bacteremia with sepsis (2), urosepsis (1), pneumonia with sepsis (1), pneumonia (1)
Escherichia coli	5	Bacteremia with sepsis (2), bacteremia (1), urosepsis (1), acute otitis media (1)
Pseudomonas aeruginosa	5	Bacteremia with sepsis (1), bacteremia (1), pneumonia (1), acute otitis media (2)
Respiratory synctial virus	5	Pneumonia with sepsis (1), bronchiolitis with sepsis (2), pneumonia (1), bronchiolitis (1)

Adapted from Table I,

Walker et al, J Allergy Clin Immunol Pract. 2014 Apr 14: 2:1-4.

Summary of Immune Phenotypes
Nine patients (10%)



One patient had low binding antibodies
One patient with low IgA, alone

Adapted from Table II,
Walker et al, J Allergy Clin Immunol Pract. 2014 ;14: 2:1-4

Outcome after Immunoglobulin Treatment

In 5 affected patients treated with subcutaneous immunoglobulin replacement therapy we observed:

- decreased frequency and severity of infections
- prevention of developmental regression
- improved quality of life

In mitochondrial patient subcutaneous immunolgobulin (scIg) treatment (weekly) is preferred over intravenous (monthly)

- Better tolerated: less side effects (headaches, chills)
- More compatible with autonomic dysfunction

Study Limitations

- Retrospective design
  - Potential for selection bias
  - Potential for information bias
  - Potential for incomplete or inaccurate records
- Preponderance of oxidative phosphorylation defects

  (may reflect relative distribution of mitochondrial disorders in the general population)
- Testing for immunodeficiency for only a subset of patients

Clinical Implications

- Patients with primary mitochondrial disorders may benefit from baseline screening for immune deficiency and autoimmune disease.
- Patients with otherwise unexplained multisystem disorders including immune deficiencies warrant screening for primary mitochondrial disorders.
- Providers caring for patients with primary mitochondrial disorders should maintain high clinical suspicion for infection and SIRS.
- Patients with primary mitochondrial disorders and recurrent infection may benefit from aggressive hydration during illness, prophylactic antibiotics and/or intravenous immunoglobulin therapy, in consultation with appropriate specialists.

Future Directions

- We are extending clinical immunologic screening of patients with primary mitochondrial disorders at MGH*f*C
- Further prospective clinical studies and laboratory investigations are required to better understand the connection between primary mitochondrial disorders and immunodysfuntion
- Further study and improved assays for autoimmune dysfunction (including atopy, autonomic dysfunction, small fiber neuropathy) are needed.
- Guidelines for infection prophylaxis and treatment in primary mitochondrial disorders are needed.
- Complex, multidisciplinary teams are required for optimal management of the immune and autoimmune features of primary mitochondrial disorders (allergy and immunology, cardiology, specialized neurology)

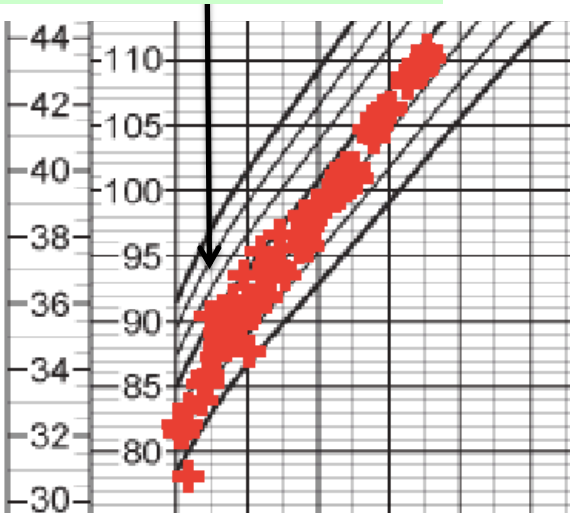
A case of combination therapy: scIg + CoQ10

- 2 year-old child with low weight and recurrent infections
- Presented to Immunology: Poor vaccine response, abnormal T cell function
- Infections resulted in declining skills and frequent hospitalization
- Metabolic evaluation revealed low CoQ10 levels in muscle biopsy

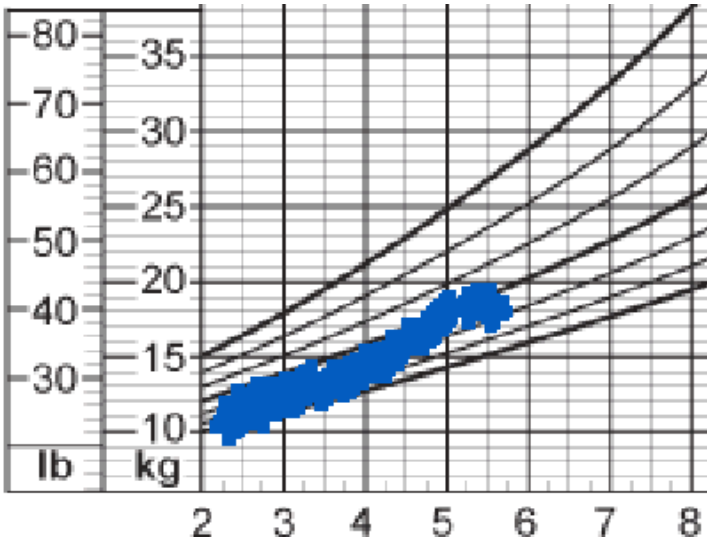
  Final diagnosis: CoQ10 deficiency + selective antibody deficiency
- Treatment: CoQ10 replacement + scIg
- Treatment resulted in proper weight gain, improved development

Farough. Et al. Coenzyme Q10 and Immunity: A case report and new implications for treatment of recurrent infections – under review

Initiation of treatment



Height



Weight

The MGH & MGH*f*C Team

Neurogenetics clinic

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Metabolic Program

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Primary Immunodeficiency Program

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Experience with infection & SIRS

Pathogen	No. affected	Sites
Acinetobacter calcoaceticus	1	Bacteremia with sepsis
Acinetobacter lwoffii	2	Bacteremia with sepsis (1), bacteremia (1)
β-Hemolytic *Streptococcus*	2	Recurrent pharyngitis and ear infection (1, surgical culture), recurrent pharyngitis
Borrelia burgdorferi	1	Systemic
Citrobacter braaki	1	Bacteremia with sepsis
Clostridium difficile	6	Colitis with sepsis (2), colitis (4)
Enterobacter	4	Bacteremia with sepsis (1), bacteremia (2), pneumonia (1)
Enterococcus	5	Bacteremia with sepsis (2), urosepsis (1), pneumonia with sepsis (1), pneumonia (1)
Escherichia coli	5	Bacteremia with sepsis (2), bacteremia (1), urosepsis (1), acute otitis media (1)
Flavimonas oryzihabitans	1	Pneumonia
Flavobacterium	1	Pneumonia
Fusarium species	1	Colitis
Klebsiella	3	Bacteremia with sepsis (1), urosepsis (1), pneumonia (1)
Moraxella	2	Bacteremia (1), pneumonia (1)
Pseudomonas aeruginosa	5	Bacteremia with sepsis (1), bacteremia (1), pneumonia (1), acute otitis media (2)
Serratia marcescens	3	Bacteremia with sepsis (2), pneumonia (1)
Shigella species	2	Colitis
Staphylococcus aureus	15	MSSA bacteremia with sepsis (4), MSSA bacteremia (2), MRSA bacteremia (1), meningitis (1, also with bacteremia), peritonitis and tracheitis (1), MSSA cellulitis (1), recurrent MRSA skin abscesses (1), pneumonia (2, 1 also with bacteremia), foot ulcer (1), abdominal wound (1)
Staphylococcus epidermis	2	Bacteremia with sepsis (1), foot ulcer (1)
Stenotrophomonas	3	Pneumonia (3)
Streptococcus salivarius	1	Bacteremia with sepsis
Streptococcus pyogenes	2	Recurrent pharyngitis
Cytomegalovirus	2	Systemic illness (2)
Herpes simplex virus	1	Encephalitis
Influenza A	1	Systemic illness with sepsis
Influenza B	1	Systemic illness with sepsis
Respiratory syncytial virus	5	Pneumonia with sepsis (1), bronchiolitis with sepsis (2), pneumonia (1), bronchiolitis (1)
Rotavirus	3	Colitis (all born prior to institution of routine immunization)
Varicella	1	Chickenpox and recurrent shingles
Candida albicans	8	Fungemia (3, 2 with sepsis), esophagitis (1), nonhealing foot ulcer (1), abdominal wound (1), chronic vaginitis (1)
Candida guilliermondii	1	Fungemia with sepsis
Candida parapsilosis	3	Fungemia with sepsis (1), fungemia (1), acute otitis media (1)

MRSA, Methicillin-resistant *Staphlococcus aureus; MSSA*, methicillin-sensitive *Staphylococcus aureus*.
*Although some infections were likely opportunistic infections, no clear pattern exists that were suggestive of a single underlying mechanism of immune deficiency. Data in parenthesis indicates the number of patients.

Experience with immunodeficiency

Patient no.	Deficiency	Age, y	WBC/ALC (10^3/cells cm^3)	Lymphocyte subsets	Antibody deficiency	Vaccine response	T-cell proliferation	IgE and eosinophil	Serious and/or recurrent infections	Antibiotic prophylaxis	Immunoglobulin therapy	Response to Ivig	Clinical history of other immune dysfunction
1	SCHADD	5	6.3/2.3	Intermittent T- cell lymphopenia	Low IgG	Low Hib and pneumococcal, normal tetanus	NA	Normal	Bacterial, fungal	Yes	Yes, since 2 y old	Yes	Atopy (AR, asthma, food intolerance and medication allergy)
2	ETC I with POLG1 mutation	10	8.0/3.4	NA	Low IgG, IgA	NA	NA	Normal	Bacterial	NA	Yes, since 2.5 y old	Yes	Atopy (asthma, food intolerance)
3	ETC I, II, III mtDNA depletion	13	4.8/1.48 (low)	Low switched memory B cells (2.9%)	Low IgG	NA	Mildly decreased with mitogen (PHA) and absent with antigen (tetanus), normal with interleukins	Transient high and low IgE	Bacterial, fungal, viral	No	Yes, since 2 y old	Yes	Atopy (AD, AR, asthma, food and medication allergy)
4	ETC I, III	21	6.4/1.7	NA	Low IgG	Normal	NA	Normal	Bacterial	No	Yes, since 18 y old	Yes	Transient atopy (AR, asthma)
5	ETC I	29	4.5/2.4	NA	Elevated IgG	Normal titers but low pneumococcal avidity, normal tetanus and Hib	Low T-cell proliferation to mitogen and antigen	Transient high IgE	Bacterial, fungal, viral	Yes	Yes, since 28 y old	Yes	Atopy (asthma, food, medication allergies), autonomic dysfunction
6	ETC I, III	10	9.5/5.6	Low switched memory B cells (1.9%)	Transient low IgG and IgA	Low pneumococcal, normal tetanus	NA	Transient high IgE	Bacterial, viral (warts)	Yes	No		Atopy (AD, FA, EoE), AI (Hashimoto thyroiditis)
7	ETC III	30	4.6/1.3	NA	Low IgG	NA	NA	Normal	Bacterial, fungal	No	No		Atopy (AR, asthma)
8	ETC I, II	10	5.7/3.5	NA	Low IgA	NA	NA	Normal	Bacterial, viral	No	No		Autonomic dysfunction with small fiber neuropathy
9	ETC I	12	4.2/2.8	NA	None	Low antipneumococcal titers	NA	Normal	Bacterial, fungal	No	No		Allergic rhinitis