

Vulnerability of pediatric patients with mitochondrial disease to vaccine-preventable diseases

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Clinical Implications

- Patients with mitochondrial disease experience significant morbidity and mortality due to infection.
- The rise in outbreaks of vaccine-preventable diseases places this vulnerable population at risk, necessitating an understanding of their protective titer status to these infectious diseases.

TO THE EDITOR:

Mitochondrial diseases (MD) are the most common inborn errors of metabolism, with a minimum prevalence of 1 in 5000.¹ Mutations in nDNA and mtDNA genes involved in mitochondrial function lead to disorders of oxidative phosphorylation and mitochondrial maintenance. The phenotype of MD is multisystemic, involving organs systems with large energy requirements (eg, central nervous system). Recently, it has been demonstrated that mitochondria play a critical role in immunity, and the phenotype of immune dysfunction in patients with MD is becoming evident,² raising concerns regarding the risk of infection. Infection is a major cause of morbidity in patients with MD, precipitating acidosis and organ dysfunction/failure with a rapidly fatal course.^{3,4} More than 80% of patients with MD may experience recurrent or severe infections,⁵ and sepsis (55%) and pneumonia (29%) are the 2 most common causes of death.⁶ Therefore, assessing and managing risk factors for infection in patients with MD is critical to maintaining their health and well-being.

Adherence to the childhood immunization schedule is recommended for patients with MD to prevent the sequelae of infection. Unfortunately, outbreaks of vaccine-preventable diseases are on the rise due to nonadherence in the general population. Because infection can be catastrophic for patients with MD, the current study was undertaken to assess the serum antibody titers of vaccine-preventable diseases in a cohort of pediatric patients with MD. Patients were enrolled in a natural history study of infection and immune function in patients with MD (NCT01780168).

Pediatric patients (N = 26) from the natural history study cohort with “probable” or “definite” MD by revised Walker criteria⁷ were selected for study (see Table E1 in this article’s Online Repository at www.jaci-inpractice.org): 18 males and 8 females with an average age of 10.8 ± 3.6 years. All patients had multisystem disease, and the mitochondrial phenotypes were

identified as Kearns Sayre syndrome (N = 3), Leigh syndrome (N = 5), and MD, not otherwise specified (N = 18). Molecular testing data (whole exome, mitochondrial sequencing) were available for most patients (N = 24), and revealed pathogenic and suspect variants in genes involved in mitochondrial function. In addition, most patients (N = 25) had supporting pathologic, enzymatic, and radiologic evidence of MD. A medical record review showed that 73% of our pediatric cohort was identified with immune abnormalities, most of which included recurrent or delayed recovery from infection (58%) and hypogammaglobulinemia (19%).

To capture a history of infection and immune dysfunction in our cohort, a directed questionnaire was administered to parents or caregivers of affected patients to formally assess for a history of (1) recurrent infection and (2) evaluation and treatment for immune deficiency (N = 25) (Figure 1; see Table E2 in this article’s Online Repository at www.jaci-inpractice.org). Regarding a history of infection, the most frequent complaints were 2+ sinus infections/y (42%) and recurrent fungal infection (42%). Forty-six percent of patients received intravenous antibiotics, and 29% were admitted to the intensive care unit for infection. The most common symptom reported by our cohort was delayed recovery from infection (79%). Remarkably, we found that patients oftentimes had been evaluated for or had a diagnosis of immune deficiency (75% and 46%, respectively). Concerning ongoing treatment, immunoglobulin therapy (17%) was prescribed because of recurrent infections or documented immune dysfunction.

Adherence to childhood vaccination recommendations was assessed from vaccine records provided by the caretakers (Figure 2, A). All patients in the cohort were eligible for the current recommended vaccination schedule. Adherence to the recommended schedule was greater than or equal to 80% for most of the vaccines studied, with the exception of hepatitis A (HAV) and varicella. For HAV, 27% of the patients surveyed were “unknown,” whereas 4% were nonadherent. These data likely reflect issues surrounding the initial implementation of HAV. For varicella, 77% of patients were adherent with the recommended schedule, whereas 8% were nonadherent, 4% were “incomplete for age,” and 12% were “unknown.”

Serum titer data are presented in Figure 2, B. All serum titers were performed by the clinical laboratory of the National Institutes of Health Clinical Center, or Mayo Medical Laboratories. Less than 15% of patients were seronegative for polio, diphtheria, tetanus, HAV, mumps, and rubella. Up to 33% of the patients were seronegative for *Haemophilus influenzae b* (Hib). Although all our patients were outside the window of risk for meningitis due to Hib infection (ie, age <5 years), this pathogen is also associated with pneumonia and sepsis, common causes of death in children with MD.⁶ These infections combined with a recent rise in antibiotic resistance of Hib⁸ present a risk for metabolic decompensation to children with MD. Fifty-five percent of the patients were seronegative for hepatitis B (HepB). Studies of HepB immunity have shown that the antibody titers decline with age, and booster studies

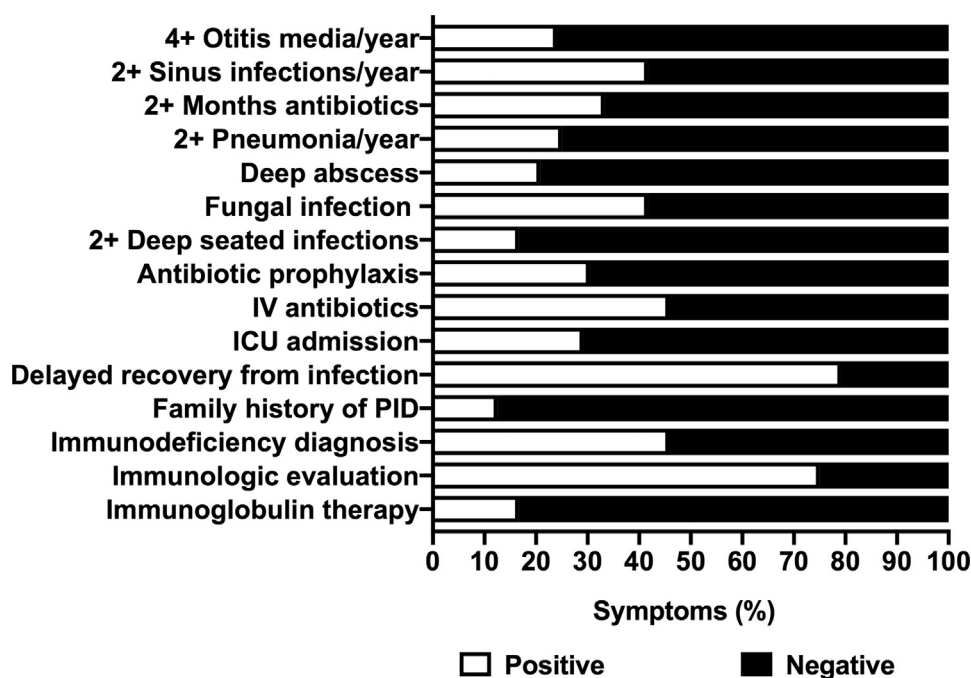


FIGURE 1. Immune symptoms in patients with MD. *ICU*, Intensive care unit; *IV*, intravenous; *PID*, primary immunodeficiency. Table of immune symptoms derived from primary immunodeficiency questionnaire and additional questions. See [Table E2](#) for the question list.

are necessary to determine protection status.⁹ Approximately 20% of patients with MD were seronegative for measles, while 60% were seronegative for varicella, microbial pathogens experiencing recent outbreaks. As per the performing laboratory (Mayo Medical Laboratories), sensitivity and specificity of the assay for varicella titers was reported to be 92.2% and 100%, respectively. Interestingly, patient 19 in the cohort ([Table E1](#)) experienced 2 separate episodes of varicella infection despite being vaccinated. Considering all titers, 56% of our cohort was seronegative for 2+ vaccine-preventable diseases. We next stratified our analysis of serum titers to include individuals who were adherent to the recommended schedule for that vaccine ([Figure 2, C](#)). Overall, the data remained fundamentally the same: Hib (35% seronegative), HepB (56% seronegative), measles ($\approx 20\%$ seronegative), and varicella (65% seronegative).

On the basis of previous work from our group⁵ and our results herein, approximately 17% to 20% of patients with MD have received immunoglobulin therapy at some point in their medical history ([Figure 1](#)). Because of the pooled nature of immunoglobulin preparations, all 3 of our patients on immunoglobulin therapy had positive titers to all the vaccines surveyed, as expected. Given the protection presumably offered by immunoglobulin therapy, we next asked whether low serum IgG levels were related to titer status. After excluding patients on immunoglobulin therapy, we found that patients who were vaccinated and seronegative for 3 or more titers tended to have lower serum IgG levels ($P < .05$; [Figure 2, D](#)).

Overall, our study raises an important clinical issue regarding infection risk in patients with MD. Although the

underlying mechanisms are not yet known, the clinical significance of these findings are of major relevance for the care of patients with MD for whom infections are associated with high degree of morbidity and mortality. Monitoring of serum titers in patients with MD may be indicated, especially in areas with increased risk of exposure, and requires further evaluation. Furthermore, booster vaccinations should be considered in children who are seronegative despite having received a complete series. For those patients with MD who cannot be vaccinated, or do not respond to booster vaccination, information regarding their immune status is important for mitigating infection risk. Although we did observe an association between immunoglobulin therapy, serum IgG levels, and titer status, we are not at the point of issuing treatment recommendations. Although some patients with MD do currently receive immunoglobulin therapy, more extensive investigation is needed to evaluate the utility and risk profile of this therapy.

Although our study is limited by the cross-sectional design, it nonetheless conveys an important message regarding the vulnerability of patients with MD to vaccine-preventable diseases. To better understand this risk, we would propose (1) a prospective analysis of vaccination to define whether patients fail to develop or lose titers, and (2) an analysis of the efficacy of revaccination. While awaiting the results of these proposed studies, we would encourage clinicians to be attentive to the risk of infection in patients with MD. Although there are many factors that contribute to the risk of infection in patients with MD, the risk of vaccine-preventable diseases is potentially modifiable via vaccination, screening, revaccination, and knowledge of immune status.

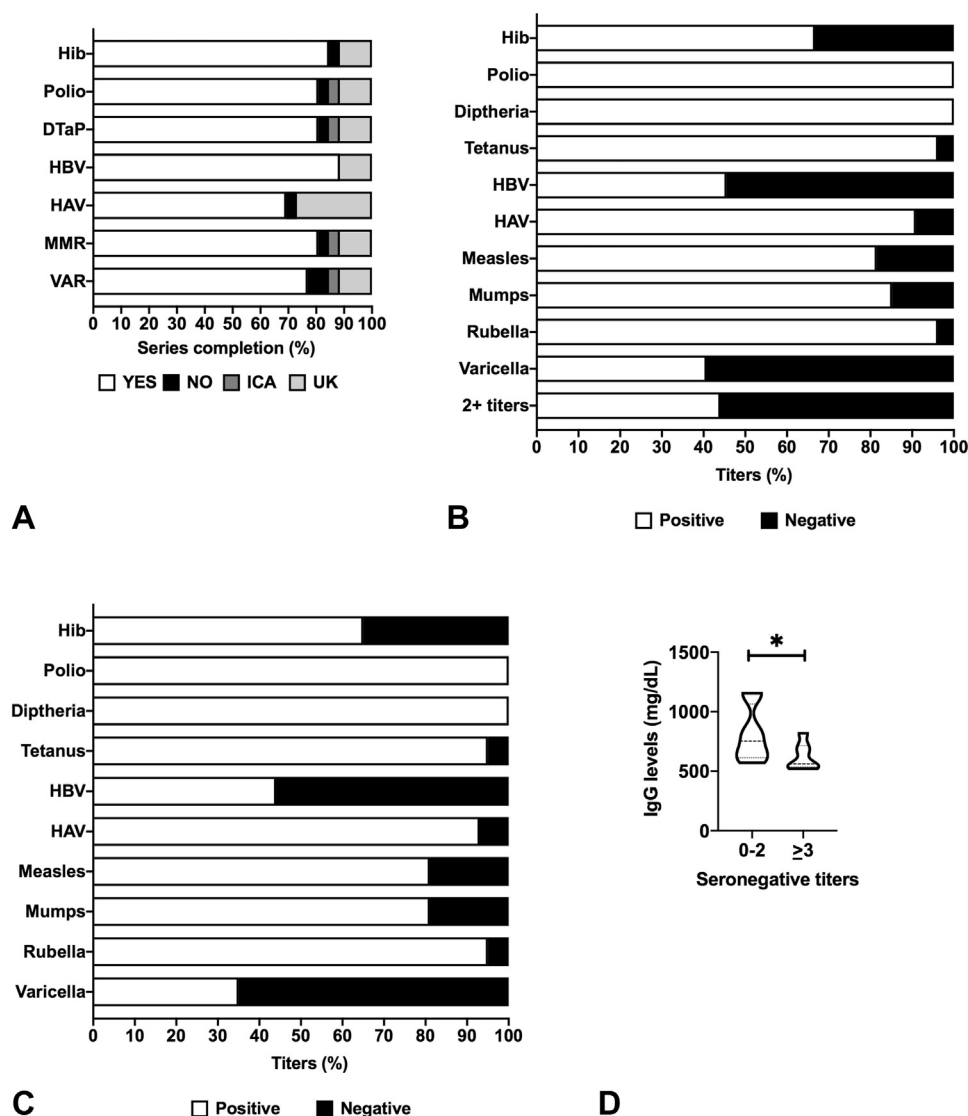


FIGURE 2. Vaccination status in patients with MD. **A**, Adherence to vaccination recommendations. **B**, Vaccine titers. **C**, Subgroup analysis of patients who were adherent to the vaccination schedule. **D**, Serum IgG levels and titer status in vaccinated individuals. *DTaP*, Diphtheria, tetanus, pertussis; *HBV*, hepatitis B virus; *MMR*, measles, mumps, rubella; *VAR*, varicella. 0 to 2 titers (N = 12), 3 or more titers (N = 7), Student *t* test **P* < .05.

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ONLINE REPOSITORY

TABLE E1. Clinical details of patients with MD

Patient	Mitochondrial phenotype	Molecular findings	Variant (% heteroplasmy [blood])	Variant class	Pathologic/radiologic findings	Immunologic findings
1	KSS	5-kb mtDNA del.	m.8483_13459del4977	PV	Muscle: RRF+, RB+, COX-fibers MRI: white matter changes in subcortical U fibers, midbrain, pons	
2	KSS	5-kb mtDNA del.	m.8468_13444del4977	PV	Muscle: increased mtDNA content	
3	KSS	3.8-kb mtDNA del.	m.8404_12385del10337	PV	MRI: signal abnormalities in globus pallidus and white matter adjacent to dentate nuclei	Delayed recovery from infection
4	LS	SURF1	c.312_321del110insAT	PV	MRI: necrotization of brainstem, midbrain, cerebellum, bilateral basal ganglia disease, elevated cerebellar lactate	Recurrent infections
5	LS	SURF1 ATP6	c.312_321del110insAT m.G8689A (100%)	PV PV	Muscle: decreased CI, mild type II atrophy, pleomorphic mitochondria MRI: hyperintensities in basal ganglia	Recurrent infections
6	LS	TK2 COX10	NA NA	VUS VUS	Muscle: decreased CI, CII, CIV activity MRI: white matter volume loss and abnormal signal in thalami and pons	Recurrent infections
7	LS	SCO1 SERAC1 SERAC1	NA c.227_228dupAT c.G548A	VUS PV VUS	MRI: hyperintense lesions c/w Leigh syndrome	
8	LS	NDUFS2 NDUFS2	c. T875C c.455_457del CTC	LPV VUS	Muscle: increased citrate synthase activity MRI: symmetrical lesions in the pons and medulla, midbrain lesions	Delayed recovery from infection
9	MD	MT-RNR2 MT-ND5	m.G2120A (100%) m. A12634G (100%)	VUS VUS	Muscle: decreased CI + CIII, CII + CIII activity Liver: abnormal mitochondrial morphology MRI: signal abnormalities in periautrial white matter	Hypogammaglobulinemia, recurrent infections, Klebsiella sepsis
10	MD	MT-TV MT-ND4	m.C1617T (100%) m.C12135A (100%)	VUS VUS	Muscle: mitochondrial proliferation	Hypogammaglobulinemia, IgA deficiency
11	MD				Muscle: decreased CI activity, decreased CII, CIII subunits on immunoblot	Hypogammaglobulinemia, recurrent infections
12	MD	MT-CYB	m.A14879T (100%)	PV	Muscle: decreased CI/III, increased number of mitochondria MRI: delayed myelination/gliososis occipital horn	
13	MD	NDUFA9 NDUFS2 MT-ND1 MT-ND5	c.C253T c.G1359A m.T4126C (100%) m.G13708A (100%)	VUS VUS Secondary PV Secondary PV	Muscle: decreased CI, CIII, CIV activity	Impaired vaccination response, recurrent infection
14	MD				Muscle: decreased CI/CIII activity	

(continued)

TABLE E1. (Continued)

Patient	Mitochondrial phenotype	Molecular findings	Variant (% heteroplasmy [blood])	Variant class	Pathologic/radiologic findings	Immunologic findings
15	MD	WARS2	NA	VUS	Muscle: increased mtDNA content MRI: Cerebral, cerebellar atrophy	Hypogammaglobulinemia, recurrent infections
16	MD				Muscle: mtDNA depletion	Recurrent infections, decreased NK-cell function
17	MD	MT-COII	m.G7754A (100%)	VUS	Buccal: decreased CIV activity Liver: abnormal mitochondrial morphology, steatosis	Hyperinflammation
18	MD	NUBPL NUBPL	c.G693+1A c.T815-27C c.G166A	PV LPV LPV	MRI: cerebellar abnormalities	
19	MD				Muscle: decreased mtDNA content	Varicella infection × 2, delayed recovery from infection
20	MD	PMPCB MT-CYB	5-kb deletion m.A1552G (3%)	PV PV	Muscle: decreased CIII activity PBMC: decreased CIII activity LCL: decreased CIII activity	Recurrent infection, Hypogammaglobulinemia
21	MD	MGME1	c.C17968871T	VUS	Muscle: decreased ETC	Recurrent infections, neutropenia
22	MD				Muscle: increased mitochondrial content, abnormal morphology MRI: multiple small foci in cerebral white matter c/w gliosis	Pertussis infection
23	MD	ATP6 NDUFA9	m.T0988C (NA) c.C881T	VUS VUS	Muscle: decreased CI/CIII Fibroblasts: diminished ETC activity and reserve	Recurrent infections
24	MD	MT-TV	m.C1617T (100%)	VUS		Recurrent infection
25	MD	ATP6	m.G9157A (59%)	LPV	Muscle: normal	Salmonella sepsis, mast cell activation disorder
26	MD	NDUFS1	c.C1333G	VUS	Muscle: decreased CI, CIII activity	

CI, Complex I; CII, complex II; CIII, complex III; CIV, complex IV; CV, complex V; ETC, electron transport chain; KSS, Kearns Sayre syndrome; LC, Leigh syndrome; LCL, lymphoblastoid cell line; LPV, likely pathogenic variant; MD, mitochondrial disease not otherwise specified; MRI, magnetic resonance imaging; NA, not available; NK, natural killer; PV, pathogenic variant; VUS, variant of unknown significance.

TABLE E2. Questionnaire to assess history of infections and evaluation and treatment for immunodeficiency

1. 4+ ear infections in 1 y
2. 2+ severe sinus infections in 1 y
3. 2+ mo treatment of antibiotics with little effect
4. 2+ pneumonias per year
5. Recurrent deep-skin or organ abscesses (eg, liver and lungs)
6. Persistent thrush in mouth or fungal infection on skin
7. ≥ 2 deep-seated infections (eg, septicemia and meningitis)
8. History of antibiotic prophylaxis for infections
9. Need for intravenous antibiotics to clear infections
10. History of admission to the intensive care unit for infection
11. History of delayed recovery from infection
12. Family history of a primary immunodeficiency
13. History of an immunological evaluation
14. Patient history of primary immunodeficiency
15. History of intravenous immunoglobulin therapy

Questions 1-7, 9, and 12 were taken from the Jeffrey Modell Foundation (<http://www.info4pi.org/library/educational-materials/10-warning-signs>). Additional items include questions 8, 10-11, and 13-15.

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