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Hospitalizations for mitochondrial disease across the lifespan in the U.S.

Shana E. McCormack [a,b,*], Rui Xiao [c], Todd J. Kilbaugh [d], Michael Karlsson [d,e], Rebecca D. Ganetzky [f], Zarazuela Zolkipli Cunningham [g], Amy Goldstein [h], Marni J. Falk [b,f], Scott M. Damrauer [i]

[a] Division of Endocrinology and Diabetes, Children's Hospital of Philadelphia, Philadelphia, PA, United States
[b] Department of Pediatrics, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, United States
[c] Department of Biostatistics and Epidemiology, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, United States
[d] Department of Anesthesiology and Critical Care Medicine, Children's Hospital of Philadelphia, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, United States
[e] Mitochondrial Medicine, Department of Clinical Sciences, Lund University, Lund, Sweden
[f] Division of Human Genetics, Children's Hospital of Philadelphia, Philadelphia, PA, United States
[g] Division of Neurology, Children's Hospital of Philadelphia, Philadelphia, PA, United States
[h] Division of Neurology, Children's Hospital of Pittsburgh, Pittsburgh, PA, United States
[i] Division of Vascular Surgery, Hospital of the University of Pennsylvania, Perelman School of Medicine at the University of Pennsylvania, Philadelphia PA & Department of Surgery, Corporal Michael Crescenz VA, Philadelphia, PA, United States

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ABSTRACT

Importance: Mitochondrial disease is being diagnosed with increasing frequency. Although children with mitochondrial disease often have severe, life-limiting illnesses, many survive into adulthood. There is, however, limited information about the impact of mitochondrial disease on healthcare utilization in the U.S. across the lifespan.
Objectives: To describe the characteristics of inpatient hospitalizations related to mitochondrial disease in the U.S., to identify patient-level clinical factors associated with in-hospital mortality, and to estimate the burden of hospitalizations on individual patients.
Design: Cross-sectional and longitudinal observational studies.
Setting: U.S. hospitals.
Participants: Individuals with hospital discharges included in the triennial Healthcare Cost and Utilization Project (HCUP) Kids Inpatient Database (KID) and the National Inpatient Sample (NIS) in 2012 (cross-sectional analysis); individuals with hospital discharges included in the HCUP California State Inpatient Database from 2007 to 2011, inclusive (longitudinal analysis).
Exposure: Hospital discharge associated with a diagnosis of mitochondrial disease.
Main outcome measures: Total number and rate of hospitalizations for individuals with mitochondrial disease (*International Classification of Diseases, 9th revision, Clinical Modification* code 277.87, disorder of mitochondrial metabolism); in-hospital mortality.
Results: In the 2012, there were approximately 3200 inpatient pediatric hospitalizations (1.9 per 100,000 population) and 2000 inpatient adult hospitalizations (0.8 per 100,000 population) for mitochondrial disease in the U.S., with associated direct medical costs of $113 million. In-hospital mortality rates were 2.4% for children and 3.0% for adults, far exceeding population averages. Higher socioeconomic status was associated with both having a diagnosis of mitochondrial disease and with higher in-hospital mortality. From 2007 to 2011 in California, 495 individuals had at least one admission with a diagnosis of mitochondrial disease. Patients had a median of 1.1 hospitalizations (IQI, 0.6–2.2) per calendar year of follow-up; infants under 2y were hospitalized more frequently than other age groups. Over up to five years of follow up, 9.9% of participants with any hospitalization for mitochondrial disease were noted to have an in-hospital death.
Conclusions and relevance: Hospitalizations for pediatric and adult mitochondrial diseases are associated with serious illnesses, substantial costs, and significant patient time. Identification of opportunities to prevent or shorten such hospitalizations should be the focus of future studies.

Abbreviations: HCUP-NIS, Healthcare Cost and Utilization Project – Nationwide Inpatient Sample; HCUP-KID, Healthcare Cost and Utilization Project – Kids' Inpatient Sample.

* Corresponding author at: Children's Hospital of Philadelphia, Division of Endocrinology and Diabetes, 3401 Civic Center Boulevard, Suite 11NW, Philadelphia, PA 19104, United States.
E-mail address: mccormacks1@email.chop.edu (S.E. McCormack).

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1. Introduction

Mitochondria are sub-cellular organelles that serve many critical functions, including production of energy. "Primary mitochondrial respiratory chain disease" refers to the class of disorders caused by pathogenic mutations in mitochondrial and/or nuclear DNA affecting function of the mitochondrial respiratory chain complexes. Despite substantial clinical heterogeneity, many patients with severe forms of mitochondrial disease present in infancy and childhood, thus pediatricians are often the first practitioners to encounter patients with suspected mitochondrial disease [1]. Although previously considered a rare class of disorders, recent estimates suggest that pathogenic mitochondrial and nuclear gene mutations are present in at least 1 in 4300 adults [2].

Efforts are ongoing to improve standardization of care for patients with mitochondrial disease, including the development of expert consensus guidelines [3]. Many of the treatment recommendations center around the care of acutely ill patients. Despite anecdotal and survey evidence of substantial healthcare utilization in individuals with mitochondrial disease, there are few systematic investigations of their hospitalization patterns and costs. Families have indicated that this lack of information adds to their difficulty in planning care [4].

Therefore, the objective of the present study was to investigate the impact of hospitalizations for mitochondrial disease across the lifespan in the U.S.

2. Methods

2.1. Study design and setting

i) Cross-sectional observational study. Analyses were performed using the Kids´ Inpatient Database (KID, pediatric) and the National Inpatient Survey (NIS, adult) from the Healthcare Cost and Utilization Project (HCUP), Agency for Healthcare Research and Quality (AHRQ) for the year 2012 [5]. Sample weights are used to generate national estimates.

ii) Longitudinal observational study. This analysis used the California State Inpatient Database (SID-HCUP/AHRQ), for the years 2007–2011, inclusive [6]. This database includes all admissions for patients of all ages to civilian hospitals in California; admissions for the same individual can be tracked over time.

2.2. Human subjects considerations

These analyses of de-identified data from a national sample were determined by the Children's Hospital of Philadelphia (CHOP) Institutional Review Board (IRB) not to meet the criteria for human subjects research, and therefore, ongoing IRB oversight was not required (FWA0000459).

2.3. Sample identification

Hospitalizations were classified as either including ("mitochondrial disease") or not including ("not mitochondrial disease") a specific diagnosis of mitochondrial disease as designated by ICD9-CM code 277.87 (disorder of mitochondrial metabolism). In addition, individuals with Leigh syndrome, a neurodegenerative condition in which many identified mutations affect the mitochondrial respiratory chain and/or pyruvate dehydrogenase complex [7], may receive the non-specific ICD9 code 330.8 ("other specified cerebral degenerations of childhood"). We sought to capture details of hospitalizations for individuals with possible Leigh syndrome. In addition, we sought to compare hospitalizations with diagnostic code of 277.87 to those with other chronic neurologic or neuromuscular conditions that are separately coded. Therefore, we performed sensitivity analyses on hospitalizations including ICD9 330.8, ICD9 334.0 (Friedreich's Ataxia, whose pathogenesis includes mitochondrial dysfunction [8]), and ICD9 359.1 (muscular dystrophy). Hospitalizations flagged as "neonatal" or "maternal", i.e., pertaining to childbirth, were excluded from all analyses because our focus was on hospitalizations related to illness.

2.4. Demographics

Patient age and sex at admission were noted. Since the majority of individuals with mitochondrial disease were white, population ancestry was classified as white versus non-white. As a proxy for socioeconomic status (SES), quartile classification of the estimated median income for residents in the patient's zip code was included. This value ranges from 1 to 4, going from poorest to wealthiest households.

2.5. Chronic conditions

The number of chronic conditions for each participant was included [9].

2.6. Hospital characteristics

These included: census region, teaching status, and whether the hospital was a free-standing children's hospital (pediatric analysis only).

2.7. Hospitalizations

Outcomes examined included: whether emergency room use occurred, number of in-hospital diagnoses, principal admitting diagnoses, whether a major operation occurred, length of stay, in-hospital mortality, and total hospital costs. Total hospital costs represent costs incurred (wages, supplies, utility costs), versus charges, that reflect the amount billed. Hospital-specific cost-to-charge ratios were used to generate estimated hospital costs from the charges.

2.8. Statistical analyses

For the cross-sectional analyses of HCUP-KIDS and HCUP-NIS hospitalizations, descriptive statistics were generated. Appropriate tests for survey data implemented in SAS (v 9.4) (surveyreg, surveyfreq) were used to compare characteristics of hospitalizations where mitochondrial disease was versus was not included. U.S. census data [10] were used to generate estimates per 100,000 population [11]. To enrich the description of hospitalizations, frequency plots were generated with in-hospital diagnoses mapped hierarchically onto phenotypes for purposes of visualization [12]. Bivariate logistic regression for survey data was performed to identify clinical characteristics associated with in-hospital mortality. Characteristics noted to be statistically significantly associated with in-hospital mortality in bivariate analyses were then included in multivariable logistic regression analyses to determine the independence of effects. For longitudinal analysis of hospitalizations related to mitochondrial disease in California between 2007 and 2011, descriptive statistics were generated. For each individual, number of hospitalizations in each calendar year of follow up was calculated. Analyses were performed in R (v.3.2.2).

3. Results

3.1. Cross-sectional analysis

Results of the pediatric cross-sectional analysis are shown in Table 1A (details in Supplemental Table 1A). In 2012, an estimated 3200 inpatient pediatric hospitalizations in the U.S. included the ICD9 code for mitochondrial disease. Children and adolescents hospitalized with a mitochondrial disease diagnosis were more likely to be of white, non-Hispanic ancestry, to reside in geographic areas with higher median income, and to be privately insured. Substantially more chronic conditions were noted in hospitalizations for children with mitochondrial

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