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Incidence and prevalence of mtDNA-related adult mitochondrial disease in Southwest Finland, 2009–2022: an observational, population-based study

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ABSTRACT

Background Mitochondrial diseases are common inherited metabolic disorders. Due to improved case ascertainment and diagnosis methods, the detection of new diagnoses of mitochondrial disease can be expected to increase. In December 2009, the prevalence of mitochondrial DNA (mtDNA)-related mitochondrial disease was 4.6/100 000 (95% CI, 2.7 to 7.2) in the adult population of Southwest Finland. We investigated the number of new diagnoses and the incidence of mitochondrial disease in Southwest Finland between December 2009 and December 2022.

Methods We collected data on all adult patients from Southwest Finland diagnosed with mitochondrial disease on 31 December 2009 and 31 December 2022. Most patients had been diagnosed at the Turku University Hospital (TUH) neurology outpatient clinic. Patients were also identified by searching the TUH electronic patient database for relevant International Classification of Diseases, Tenth Revision codes and conducted mtDNA analyses.

Results 42 new patients were diagnosed giving a mean annual rate of 3.2 new diagnoses. In 2022, the minimum prevalence estimate of adult mtDNA-related mitochondrial disease was 9.2/100 000 (95% CI, 6.5 to 12.7). The prevalence of adult mtDNA disease associated with m.3243A>G was 4.2/100 000 (95% CI, 2.5 to 6.7), and that with large-scale mtDNA deletions was 1.3/100 000 (95% CI, 0.4 to 2.9). During the 13-year period, the annual incidence of adult mtDNA disease was 0.6/100 000 and that of adult m.3243A>G-related disease 0.3/100 000.

Conclusion Our results suggest that improved means of diagnostics and dedicated effort increase the detection of mitochondrial disease.

INTRODUCTION

Mitochondrial disease conventionally refers to inherited disorders affecting mitochondrial respiratory chain function, leading to deficient aerobic energetics and consequently impaired ATP production.[1] Understanding the prevalence and incidence of mitochondrial disease is of importance for care delivery planning and healthcare resource allocation. Population-based studies have revealed that mitochondrial disease is a common form of inherited metabolic disease. In Europe, comprehensive studies on the prevalence of mitochondrial DNA (mtDNA)-related mitochondrial disease have been previously carried out in the province of North Ostrobothnia in Finland and in North East England.[2–5]

Improved case ascertainment and diagnosis methods may affect the incidence of new diagnoses of mitochondrial disease. At the University of Turku and Turku University Hospital (TUH; Turku, Finland), we have conducted research on the clinical features and epidemiology of adult mitochondrial disease since 2009. During this period, we have also strived to improve the clinical diagnostics and care of patients with mitochondrial disease. We decided to investigate the number of new diagnoses at TUH and the incidence of mitochondrial disease in Southwest Finland during this ongoing effort.

PATIENTS AND METHODS

In Finland, diagnostics of mitochondrial disease has been concentrated in publicly funded university hospitals. TUH (Turku, Finland) serves the population of the province of Southwest Finland. We reviewed all adult patients (age ≥18 years) diagnosed with mtDNA-related mitochondrial disease at TUH.

Most patients with mitochondrial disease were diagnosed at the neurology clinic. Some patients were referred for consultation because of a mitochondrial disease diagnosed elsewhere at TUH. We searched the electronic patient database to detect subjects with International Classification of Diseases, Tenth Revision (ICD-10) diagnoses of mitochondrial myopathy (G71.3) and optic atrophy (H47.2) and a text search of medical charts for terms ‘mitochondrial myopathy’, ‘mitochondrial disease’ and ‘Leber’s disease’. The electronic database included data on mtDNA genetic analyses conducted at TUH during 2003–2021. These comprised an analysis of whole mtDNA, as well as a targeted analysis

of mtDNA deletions and the disease-associated mtDNA variants m.1555A>G, m.3243A>G, m.3460G>A, m.8344A>G, m.8993T>C/G, m.11778G>A and m.14484T>C. Genetic analyses were performed at TUH. Next-generation sequencing (NGS) was used for whole mtDNA. PCR with restriction enzyme digestion was used to investigate single mtDNA variants. Multiplex ligation-dependent probe amplification analysis was used for the detection of large mtDNA deletions. Some patients had been identified during previous research on mitochondrial disease epidemiology at the University of Turku.[6–8] Only diagnoses of established pathogenic variants were included.

We collected data on all adult patients from Southwest Finland diagnosed with mitochondrial disease on 31 December 2009 and 31 December 2022. The latter date was also used to estimate the current prevalence of mitochondrial disease (prevalence date). We also looked in detail all those patients who were diagnosed with mitochondrial disease at TUH between 1 January 2010 and 31 December 2022 and were at least 18 years of age on 31 December 2022. The date of genetic diagnosis of mitochondrial disease was determined from the medical charts. For the population prevalence estimate, we determined the number of living adult patients with clinically manifest mitochondrial disease at the prevalence date. The adult population of Southwest Finland was 372 972 on 31 December 2009 and 401 346 on 31 December 2022. Population data were obtained from Statistics Finland (https://pxdata.stat.fi/PxWeb/pxweb/en/StatFin/StatFin__vaerak/statfin_vaerak_pxt_11re.px/; search criteria in the StatFin database: 11re – Population according to age (1 year) and sex by area, 1972–2022; MK02 Southwest Finland, age 18 and over; accessed 9 Jan 2024).

Statistical methods

The 95% CIs for prevalence were calculated with Microsoft Excel using the Poisson distribution. The ranges shown are the two-sided Clopper-Pearson binomial CIs for the frequency.

RESULTS

At the end of 2009, there were 17 adult patients diagnosed with mtDNA-related mitochondrial disease who were alive and lived in the province of Southwest Finland (table 1). Hence, the minimum prevalence estimate of adult mtDNA-related mitochondrial disease was 4.6/100 000 (95% CI, 2.7 to 7.2), and the prevalence of adult mtDNA disease related to m.3243A>G was 0.8/100 000 (95% CI, 0.2 to 2.4).

42 new patients (23 women, 19 men) were diagnosed with mtDNA disease at TUH between 2010 and 2022 (online supplemental table S1), giving a mean of 3.2 new diagnoses per year (median 3; range 0–9). There were 12 new diagnoses (mean 2, range 0–6 per year) during the years 2010–2015 and 30 new diagnoses during the years 2016–2022 (mean 4, range 1–9 per year). The mean age at diagnosis of the 42 new patients was 48 years (median 51 years) (online supplemental table S1). The most common molecular diagnoses were m.3243A>G (n=22, 52%) and m.11778G>A (n=6, 14%). Family history was suggestive of maternal inheritance in 25 patients (60%).

In December 2022, there were 37 adult patients with mitochondrial disease who lived in Southwest Finland, giving a minimum prevalence estimate of 9.2/100 000 (95% CI, 6.5 to 12.7) for adult mtDNA-related mitochondrial disease (table 1). The prevalence of adult mtDNA disease related to m.3243A>G was 4.2/100 000 (95% CI, 2.5 to 6.7), and that of m.11778G>A was 1.7/100 000 (95% CI, 0.7 to 3.6). The prevalence of adult Leber hereditary optic neuropathy (LHON) with a molecular diagnosis of m.11778G>A or m.3460G>A was 2.2/100 000 (95% CI, 1.0 to 4.2). The prevalence of large-scale mtDNA deletions was 1.3/100 000 (95% CI, 0.4 to 2.9). Since January 2010, 30 adult residents of Southwest Finland were diagnosed with mtDNA disease (table 1), so the annual incidence of adult mtDNA disease during the 13 year period was 0.6/100 000 and that of adult m.3243A>G-related disease was 0.3/100 000.

DISCUSSION

Since 2009, we have had an ongoing effort to improve the diagnostics of adult mitochondrial diseases at the University of Turku and TUH. We found a considerable increase in the number of patients diagnosed with mitochondrial disease in Southwest Finland between 2009 and 2022, resulting in increased population prevalence

Table 1 Adult patients resident in Southwest Finland, diagnosed with mtDNA disease at Turku University Hospital, 2010–2022

	Diagnosed patients alive in 12/2009 (N)	Patients diagnosed since 1/2010 (N)	Diagnosed patients alive in 12/2022 (N)
Genetic diagnosis			
m.3243A>G	3	16	17
m.11778G>A	6	4	7
Deletions	2	3	5
m.8344A>G	2	2	3
Other	4	5	5
All	17	30	37

mtDNA, mitochondrial DNA.

estimates. We suggest that this increase is related to heightened awareness of mitochondrial disease and their clinical features and possibly also to improved availability of genetic investigations. The Finnish healthcare system is publicly funded. Diagnostics of mitochondrial disease takes place in tertiary-level specialist care (university hospitals). Most importantly, sufficient experience and knowledge to suspect mitochondrial disease are needed. Second, the increased availability and reduced costs both of complete mtDNA sequencing and whole exome sequencing have increased the yield of molecular diagnoses of mitochondrial disease.

The prevalence of mitochondrial disease has been evaluated in previous studies. In the population-based study from the province of North Ostrobothnia in Finland, m.3243A>G was found in 14 patients from 10 pedigrees.[2] The frequency of m.3243A>G was calculated to be ≥16.3/100 000 in the adult population, while the prevalence of clinically affected individuals with m.3243A>G was estimated to be 5.7/100 000. In the same province, the prevalence of large-scale mtDNA deletions was 1.6/100 000 in the adult population.[3] A comparison of these figures with the prevalence estimates in the present study suggests that these forms of mtDNA-related mitochondrial disease may be somewhat more common in North Ostrobothnia than in Southwest Finland.

In this study, ascertainment bias might take place if the likelihood of looking for mitochondrial disease would differ between various phenotypes, or the likelihood of detection would vary between different genetic causes. With the retrospective method used here, we can only speculate. It would however seem plausible that patients with common genetic causes such as large-scale mtDNA deletions or the m.3243A>G or patients with more severe phenotypes would receive a diagnosis. Large-scale mtDNA deletions can remain undetected in NGS analysis of mtDNA from white blood cells. In our data, muscle mtDNA was available from many patients, but a complete analysis of mtDNA from a non-mitotic tissue was not performed on all patients. Rare mtDNA variants and patients with uncommon or oligosymptomatic phenotypes are still likely to be under-represented in this study. However, as our results are fairly well in line with the data presented by others, we suggest that unique causes of ascertainment bias are not likely.

As another limitation, even more text search terms and ICD-10 items could have been added. The ICD-10 diagnoses H49.4 and H49.8 include also other diagnoses than those (progressive external ophthalmoplegia and Kearns-Sayre syndrome) related to mitochondrial disease. The use of abbreviations of mitochondrial syndromes such as MELAS, MERRF and NARP in the patient notes is variable, but we suggest that it is unlikely that the notion of a 'mitochondrial disease' would have been completely absent from the patient notes of the affected individuals. This is why we also searched the mtDNA genetic tests so that all individuals with genetically confirmed mtDNA disease would be included as completely as possible. The database query was performed at the end of 2021. However, we also included individuals we diagnosed in 2022. As one of the authors (MHM) was at the time responsible for the neurological diagnostic service for mitochondrial disease at TUH and thus well informed of patients newly diagnosed with mitochondrial disease, it is unlikely that the overall results are affected in the sense that other new diagnoses would have been missed.

Several studies have addressed the prevalence of adult mtDNA disease in North East England. The prevalence of clinically manifest mtDNA disease was estimated to be 9.2/100 000 and that of m.3243A>G to be 3.65/100 000.[4] A continuation study by the same group suggested a minimum prevalence of 20/100 000 for mtDNA mutations. The overall minimum point prevalence of clinically affected adults was 9.6/100 000, and that of m.3243A>G was 3.5/100 000.[5] These figures are like those in our study suggesting that the population prevalence of adult mtDNA-related mitochondrial disease is similar in these two North European populations. Recent studies[9 10] suggest that the most common mtDNA haplogroups in the general healthy Finnish population are H (41%–46%) and U (25%–28%). Mitochondrial haplogroups were, however, not routinely investigated in the patients described in this study.

Despite increased immigration to Finland during the past three decades, the population in Finland remains comparatively homogenous, consisting mostly of Finns speaking either Finnish or Swedish as their first language. According to the official statistics (Statistics Finland 2022: Population 31.12.2022 by region, background country, sex, age, origin, year and information and by region, language, age, sex, year and information; https://pxdata.stat.fi/PxWeb/pxweb/en/StatFin/StatFin__vaerak/statfin_vaerak_pxt_11rt.px/), 91% of the population in Southwest Finland are of Finnish origin and 9% are classified as having some foreign background. Similarly, in Southwest Finland, the first language is Finnish for 85 %, Swedish for 5.7 % and some foreign language for ~9%. Among the many foreign languages, the most common is Russian (1.2 %), closely followed by Estonian and Arabic.

The epidemiology of LHON has previously been studied in several countries. The prevalence of LHON was reported to be 2.1/100 000 in Finland[6] and 3.7/100 000 in North East England.[11] In Denmark, LHON prevalence has been reported as 1.85/100 000.[12] However, a study from the Finnish province of North Ostrobothnia has suggested a prevalence lower than 1.36/100 000 for the three common LHON variants (m.3460G>A, m.11778G>A and m.14484 T>C) being lower than that elsewhere in Western Europe or elsewhere in Finland.[13] Similarly, the prevalence of the three common LHON variants has recently been reported to be only 0.3/100 000 in New Zealand, where the population is mostly of European origin.[14] We found a LHON prevalence estimate at 2.2/100 000 in the adult population that was close to the previous estimate in the general Finnish population.

The prevalence figures in our study were based on clinically affected patients with genetically definite

mitochondrial disease, that is, patients who have clinical features compatible with mitochondrial disease and who harbour a known pathogenic mtDNA variant that can explain the symptoms. The analysis of mtDNA in maternal relatives would result in a considerably higher number of individuals harbouring the mutation. Indeed, studies on population samples where most individuals are healthy and do not present any features suggestive of mitochondrial disease have revealed that the frequency of pathogenic mtDNA variants may be as high as 1/200–1/250.[5 15 16] It is very difficult to speculate on the number of undiagnosed individuals. In 2010–2022, we observed a constant accumulation of patients with mtDNA disease. However, based on our experience in Southwest Finland, it is likely that adult mitochondrial disease is still under-recognized in Finland. Moreover, this most probably applies to other countries with highly developed healthcare systems as well. Dedicated effort and interest in the clinical diagnostics of mitochondrial disease make a considerable difference. From a global perspective, we still know little about mitochondrial disease in many developing countries and in underrepresented populations. Further studies in these areas are needed.[17]

Our results suggest that the most common cause of mtDNA-related disease in the adult population is m.3243A>G followed by m.11778G>A and sporadic large-scale mtDNA deletions. The spectrum is identical to that in North East England (online supplemental table S2). However, a marked proportion of patients carry other pathogenic mtDNA variants that in our patients accounted for 24% (n=9), and the corresponding proportion was 27% in the UK data.[5] If the clinical features suggest a mitochondrial disease, it is important to pursue the diagnosis further, even when the most common variants have been ruled out.

A definite diagnosis clarifies the underlying cause of symptoms to the patient and their close ones and often brings a long diagnostic journey to an end. In addition, diagnosis of a mitochondrial disease has specific implications for medical treatment and follow-up and also warrants genetic counselling. Our results, along with previous experience elsewhere in Finland and in North East England, suggest that a dedicated clinical and research effort across medical specialities in mitochondrial disease diagnostics is associated with a considerable increase in the number of patients receiving correct diagnosis.

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