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Review

The epidemiology of mitochondrial disorders—past, present and future

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Abstract

A number of epidemiological studies of mitochondrial disease have been carried out over the last decade, clearly demonstrating that mitochondrial disorders are far more common than was previously accepted. This review summarizes current knowledge of the prevalence of human mitochondrial disorders—data that has important implications for the provision of health care and adequate resources for research into the pathogenesis and treatment of these disorders.

Keywords: Mitochondria; Mitochondrial disease; mtDNA; Epidemiology; Mitochondrial encephalomyopathy

1. Introduction

Until relatively recently, mitochondrial disorders were considered to be obscure, exceptionally rare diseases affecting perhaps one or two per million of the population. Only a limited number of centers throughout the world had clinical and laboratory expertise in mitochondrial medicine, and a general lack of awareness of mitochondrial disease by non-specialist physicians left many patients undiagnosed. However, the complete sequencing of the human mitochondrial genome (mtDNA) [1], followed by the identification of pathogenic mtDNA mutations [2,3], led to a huge surge in interest in human mitochondrial disease in the early 1990s. These advances paved the way for future epidemiological studies which clearly demonstrate that mitochondrial disorders are amongst the most common inherited human diseases. This review will focus on monogenic mitochondrial disorders due to a well-defined pathogenic mutation of mtDNA of nuclear DNA, or associated with a clear-cut respiratory chain disorder with a presumed monogenic basis. It has also been suggested that mtDNA may contribute to the pathogenesis of a number of common multi-factorial disorders such as diabetes mellitus [4] and neurodegenerative disease [5]. The role of mtDNA in complex traits is controversial, and not the topic of this article.

2. The challenge of mitochondrial disease epidemiology

Epidemiological studies of human disease are difficult, time-consuming and expensive. Mitochondrial disorders pose additional problems for the epidemiologist. A large, stable and yet accessible study population is essential to minimize variability through sampling effects and ultimately yield accurate figures. Population genetic bottlenecks and founder effects can lead to the under- or overrepresentation of specific mtDNA [6] and recessive nuclear [7] disorders. As in other areas of human genetics, mitochondrial diagnostic services have largely evolved from a research setting, leading to poorly defined and overlapping referral patterns making accurate epidemiology difficult to achieve.

Identifying a cohort of patients with suspected mitochondrial disorders is also not straightforward. Many patients with mitochondrial disease share features with other inherited conditions, and common sporadic disorders, such as diabetes mellitus, stroke and cardiomyopathy, are

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common features of mitochondrial disease. It can be difficult to decide which patients to investigate in detail, but some form of selection is essential because subsequent investigations may be invasive and costly. The second problem is the expanding clinical phenotype. Within the last 5 years, mitochondrial disorders have been linked to novel clinical phenotypes not previously thought to be relevant. Exercise intolerance is a good example of a phenotype that was probably under-recognized in the past.

The problems continue even when a clinically defined cohort has been identified. Invasive clinical tests, such as a muscle biopsy, may be required to make an accurate assessment of individual cases. Although this is acceptable from a clinical diagnostic stance, it poses particular ethical issues when tracing the disorder through unaffected family members. Assuming it is possible to perform all necessary invasive tests, interpreting the results of the laboratory investigations can be difficult. For example, muscle histochemistry and respiratory chain complex analysis may be normal in patients with the 3243A>G mtDNA tRNA Leu$^{(UUR)}$ gene mutation [8], and mtDNA deletions are not always present in limb muscle from patients with autosomal dominant progressive external ophthalmoplegia (ad-PEO) [9]. There may also be disagreement between different centers on the precise methods and interpretation of biochemical studies.

In addition to the difficulties of performing invasive tests on asymptomatic relatives, epidemiological studies of mitochondrial disease pose further ethical dilemmas. Is it acceptable to contact distant relatives and enrol them in a study which, by its definition, implies that they are at risk of a disorder? How do we interpret the results of the laboratory tests? For example, what are the long-term implications of a certain percentage level of mutated mtDNA in a particular tissue, and how can we assess the risks of recurrence amongst offspring? One approach is to carry out the study on a pure research basis, insisting that the results of any investigations remain confidential. In our experience this strategy is often not acceptable to the study subjects, particularly if they agree to a potentially harmful biopsy procedure, and the only approach is to be explicit about our knowledge, and lack of knowledge, from the outset, enabling each subject to make informed consent.

It is important to bear these difficulties in mind when interpreting different epidemiological studies of mitochondrial disease. No one study is perfect, but as the data continue to accumulate, the figures from different studies start to coalesce, suggesting that we are approaching a final figure for the minimum prevalence of mitochondrial disease—at least by current definitions.

3. Phenotype-specific studies

The first epidemiological surveys followed the identification of specific mtDNA mutations in patients with specific clinical phenotypes. Studies of the 3243A>G mutation in patients with diabetes mellitus are a good example, although similar work has been carried out in cohorts of deaf patients [10], in patients with young stroke [11], or other disorders. The reported frequency of 3243A>G in diabetes mellitus ranges from 0.13% [12] to 60% [13], depending upon the specific population under study and the study design. No one study is comparable, and the reported values only reflect the precise cohort under study, making it difficult to draw more general conclusions about mtDNA mutations in the general population. These studies have been reviewed in a number of articles [14].

4. Population based studies—adults

The first population-based study of a single pathogenic mtDNA mutation was carried out in northern Ostrobothnia in Finland [15]. Majamaa and colleagues took advantage of the structured health care system in Finland to examine the medical records and identify a cohort of adults with clinical features suggestive of mitochondrial disease from a population of 245,201. Molecular genetic testing of the probands followed by careful family tracing allowed them to estimate the frequency of the 3243A>G mutation in the general population giving a minimum point prevalence of 16.3/100,000 (95% CI=11.3–21.4/100,000) or 1 in 6135 [15]. The frequency of the 3243A>G mutation was particularly high in certain disease groups including those with deafness and a family history of hearing loss (7.4%), occipital stroke (6.9%), ophthalmoplegia (13%) and hypertrophic cardiomyopathy (14%).

The first population-based study of all mitochondrial disorders was carried out in northeast England [16]. This study had a different design and was based upon the referral of adults with suspected mitochondrial disease to a single referral center in Newcastle upon Tyne which serves a population of 2,122,290. Thorough clinical, biochemical and genetic studies were carried out on patients referred over a 15-year period. Family members were studied and affected relatives living within the study region were included in a minimum point-prevalence figure of 6.57/100,000 (95% CI=5.30–7.83) or 1 in 15,220 for the mid-year period in 1997. Further family tracing in unaffected individuals enabled an estimation of the unaffected carrier rate on the same prevalence date. When these figures were combined, it was estimated that 12.48/100,000 or 1 in 8013 individuals within the region either had mitochondrial disease or were at risk of developing mitochondrial disease, based upon the strict diagnostic criteria used at the time [16]. Being an adult population, the vast majority of affected individuals were found to harbor pathogenic mtDNA defects, including point mutations that cause Leber hereditary optic neuropathy (LHON, 50%), mtDNA rearrangements (predominantly single deletion disorders, 20%) and other mtDNA point mutations (30%). A more detailed

clinical and genetic study of the LHON refined the prevalence figures for this disorder on June 30th 1998 to 11.82/100,000 (95% CI=10.38–13.27/100,000) [17], confirming the established predominance of the 11778G>A *ND4* mutation as a cause of LHON (56%), followed by the 3460G>A *ND4* mutation (31%), and the 14484T>C *ND6* mutation (6.3%). Rare primary LHON mutations appear to account for ~5% of families [18]. This work established LHON as a major cause of visual failure affecting young adults, affecting 1 in 14,067 males, and showed that ~1/3 of LHON families have at least one individual who is heteroplasmic for the causative mtDNA mutation [17].

There were clear discrepancies between the results of these two studies. In northeast England the prevalence of the 3243A>G (1.41/100,000, 95% CI=0.83–1.20) appeared to be 10-fold less than the prevalence in Finland (see above, and Table 1). Although tempting to suggest that the mutation rate of 3243A>G was particularly high in the Finnish population, obvious differences in the study design precluded any firm conclusions. These issues are only just being resolved with ongoing disease surveillance in northeast England. The expanding clinical and molecular spectrum of mitochondrial disease, coupled with the development of new molecular techniques to aid the diagnosis of multiple deletion disorders [19] and the noninvasive testing for mtDNA point mutations [20], confirms that the original prevalence figures were an underestimate. Preliminary data suggest that the 3243A>G mutation is present in at least 1 in 13,000 of the population in northeast England, and the overall prevalence of mitochondrial disorders in adults is substantially greater than was originally thought (Schaefer et al., unpublished observations).

5. Population based studies—children

The first published study of pediatric mitochondrial disease was based upon a population of 358,616 children in western Sweden studied intensively in Gothenburg over a

Table 1
Population-based studies of mitochondrial disease

Age group	Study population	Mutation or disease	Disease prevalence/ 100,000 (95% CI)	Mutation prevalence/ 100,000 (95% CI)
Adults	Northern England	All mtDNA deletions	1.33[a] (0.76–1.89)	0.98[b] (0.50–1.48)
	Point prevalence August 1997	All mtDNA point mutations	5.24[a] (4.12–6.37)	11.50[b] (9.83–13.17)
	Males <65 years	LHON mutations	3.29[a] (2.39–4.18)	8.86[b] (7.39–10.32)
	Females <60 years	3243A>G	0.95[a] (0.47–1.43)	1.41[b] (0.83–1.20)
	Population size=2,122,290	8344A>G	0.25[a] (0.01–0.5)	0.28[b] (0.02–0.54)
	[16]	All mtDNA mutations	6.57[a] (5.30–7.83)	12.48[b] (10.75–14.23)
	Northern England	LHON 11778G>A 3460G>A 14484T>C	3.22 (1.47–3.97)	11.82 (10.38–13.27)
	Point prevalence August 1997			
	Males <65 years			
	Females <60 years			
	Population size=2,122,290			
	[17]			
	Northern Finland	A3243G	5.71 (4.53–6.89)	16.3 (11.3–21.4)
	Adult point prevalence			
	Population size=245,201			
	[15]			
	Northern Finland	A8344G		0 (0–1.5)
	Adult point prevalence			
	Population size=245,201			
	[23]			
Children	Western Sweden	Mitochondrial disorders	4.7[c] (2.8–7.6)	
	Point prevalence January 1999			
	<16 years of age			
	Population size=358,616			
	[21]			
	Victoria, Australia	Mitochondrial disorders	5.0[d] (4.0–6.2)	–
	Birth incidence from 1,706,694			
	Births between 1987–1996			
	[22]			

CI=confidence interval; LHON=Leber hereditary optic neuropathy.

[a] The prevalence of mtDNA disease is based upon affected adults (>16–<65 years for males, >16–<60 years for females).

[b] The prevalence of mtDNA mutations is based upon all individuals below retirement age (<65 years for males, <60 years for females). The figure for the mutation prevalence of deletions is less than the disease prevalence because all of the deletions in this study were sporadic, so the total number of cases remains the same but the denominator is greater for the population prevalence of mutations.

[c] Point prevalence based upon patients diagnosed between 1984 and 1998.

[d] Birth prevalence measured between 1987 and 1996.

15-year period [21]. Affected individuals were defined on clinical, biochemical and molecular genetic grounds, with a strong emphasis on respiratory chain complex assays given the predominance of nuclear genetic disorders in childhood mitochondrial disease. This approached identified 32 affected children under 16 years of age giving a minimum point prevalence of 4.7/100,000 (95% CI=2.8–7.6/100,000) or 1 in 21,277 on January 1, 1999. In preschool children (born between 1884 and 1992), the incidence of mitochondrial encephalomyopathies was 8.9/100,000 (95% CI=5.3–14.0/100,000), or 1 in 11,000, reflecting the median age of onset in this group of 3 months (range, birth to nine years), and the median survival to 12 years of age [21].

A similar study was carried out at the same time in south Australia, based upon referrals to the Melbourne children's hospital over a 10-year period [22]. Using clinical, biochemical and molecular genetic criteria, this study determined the minimum birth prevalence of child respiratory disease in 1,706,694 births as 5.0/100,000 (95% CI=4.0–6.2/100,000) or 1 in 20,000. Autosomal recessive respiratory chain disorders were more common in Australian children of Lebanese origin, affecting 58.6/100,000 (95% CI=34.7–92.6/100,000) [22].

It is remarkable that these two studies, carried out at opposite ends of the globe, produced an almost identical result. A similar proportion of children had a pathogenic mtDNA mutation in both studies, averaging at ~15% of the total. These two concordant studies suggest that the figure of 1 in 20,000 is probably accurate, making respiratory chain disorders amongst the most common inherited metabolic diseases.

6. Prospects for the future

The published data raise a number of additional intriguing questions. Does the prevalence of mitochondrial disease vary though out the world, and if so, what is the reason for this variation?

Anecdotal evidence suggests that the prevalence of mtDNA disorders does vary. For example, in northeast England, three primary LHON mtDNA mutations (11778G>A, 14484T>C and 3460G>A) account for ~50% of all mitochondrial disease in adults, causing blindness in ~1 in 14,000 adult males [17], but these mutations have not been found in a population of >250,000 in northern Finland (Kari Majamaa, personal communication). Likewise, the 3243A>G mutation appears to be rare in the African-American population (Salvatore DiMauro, personal communication). There is limited data comparing the prevalence of different mtDNA mutations in different populations. The 8344A>G mtDNA mutation was found in 0.28/100,000 (95% CI=0.02–0.54/100,000) in northeast England [16], but not in a population of 353,895 in northern Finland (95% CI=0–1.5/100,000) [23]. However, even with studies of this size, the 95% confidence intervals for these observations comfortably overlap, and it is not possible to draw any firm conclusions. Much larger studies will be required to address these issues. Even when studies are based upon millions of people, population history can have a profound effect on regional prevalence rates. Population genetic bottlenecks, usually due to migration or population admixture, can lead to striking differences in the prevalence of different mitochondrial disorders or different genetic defects. This probably explains the unusually high prevalence of autosomal recessive childhood respiratory chain disease in Australian children of Lebanese origin [22], and why the 14484T>C mtDNA mutation is the most common cause of LHON in eastern Canada [24].

There is therefore clear evidence that population demographics can influence the prevalence of mtDNA mutations and disease, but additional genetic factors may also play a part. There is a well-recognized association between the polymorphisms that define mtDNA haplogroup J and the 14484T>C and 11778G>A mtDNA mutations that cause LHON—but no such association exists for 3460G>A (recently reviewed in Ref. [25]). The reason for this association is not clear. The mtDNA genetic background may influence the penetrance and clinical presentation of 14484T>C and 11778G>A [26]—but if this were the case, one would expect to find multigenerational families transmitting these mutations on a different haplogroup background without visual failure. These families have never been seen despite extensive mtDNA sequencing of control individuals by a number of groups over recent years. An alternative hypothesis is that haplogroup J predisposes to the actual mutation event, or its propagation from low levels of heteroplasmy. Again, formal studies have not been carried out to address this issue, but would be extremely revealing. Recent work implicated another polymorphic change influencing the clinical presentation of the 3243A>G mutation. The 12308A>G polymorphism was associated with stroke-like episodes in patients also harboring 3243A>G [27], but subsequent work failed to confirm the association [28]. Moreover, unlike LHON, there does not appear to be a link between 3243A>G and mtDNA haplotype [29]. Epistatic genetic effects from nuclear genes may also prove important, as has been suggested for LHON [30] and maternally inherited deafness due to the 1555A>G mutation [31]. Defining the nuclear genetic influence poses additional challenges, requiring a major tour de force in defining large study groups and extensive genotyping, but there is hope that this will provide crucial insight into the pathophysiology of mitochondrial disorders and the variable clinical phenotype which presents a major clinical challenge.

7. Conclusions

Combing the results of the epidemiological data on childhood and adult mitochondrial disease suggests that the

minimum prevalence is at least 1 in 5000, and could be much higher. A detailed study of both pediatric and adult respiratory chain disease in the same population is needed to substantiate this conclusion—but the goalposts are already moving, as the phenotypic spectrum of mitochondrial disorders continues to broaden. It is clear that mitochondrial pathology places a major burden on the community. These disorders are a major health issue, and appropriate resources are required to pursue research into the pathophysiology and treatment, along with adequate supportive care for patients and their families.

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