

Commentary

Health care professionals, for long accustomed to thinking in terms of pathological entities rather than functional significance, have had difficulty in grasping the full implications of the distinctions between impairment, disability and handicap, as defined by the WHO. Even now, nearly 20 years after this classification was introduced, the terms are still frequently misused. It could be argued that we should aim for better understanding and more appropriate usage of the existing terms, rather than redefining them; but there are several reasons why change is needed.

Firstly, the international disability movements have generally rejected the WHO definitions in favour of two basic concepts related to the social model of disability: 'impairment' meaning the loss or abnormality plus the effect on function; and 'disability/handicap', the disadvantage or restriction of activity caused by social factors which take little or no account of people who have impairments and thus exclude them from the mainstream of social activities.¹ This simpler classification has the additional advantage of being easier to translate for non-English speakers, as few other languages recognise the subtle distinction between disability and handicap. Furthermore, we should refer to 'disabled people', not to 'the disabled', or 'the handicapped'. The latter terms are offensive because they classify people on the basis of a single characteristic and do not acknowledge their individuality.

Is this another example of 'political correctness'? Perhaps – but being PC is no bad thing. By adopting PC terminology we not only acknowledge that there may be some justification for the new terms, we also help to bring about change. Phrases which our generation regards as 'PC' and uses tongue in cheek could become the accepted language and attitude of the next generation.

Articulate people with physical disabilities rightly point out that they are disadvantaged by the attitudes of society more than by their loss of function – a view elegantly presented in the advertising campaigns of the Spastics Society, now known as Scope ('our biggest handicap is

poor communication – yours'). The weaknesses of this 'social model' of disability are all too obvious to the parent or carer whose life is devoted to providing the total care needed by their profoundly multiply disabled adult offspring. Hutchison is right to try and bridge the gap between these differing perspectives.

Secondly, better classification, definition, and registration of impairments would have many scientific and practical benefits. Although the terminology used in the OPCS survey probably came closer to the ideal than any other attempt so far, its application in routine service has proved difficult. Ways of measuring quality of life would be helpful² and might make registration more acceptable. At present, some people actively avoid being registered, because they do not feel disabled and do not wish to be defined as such – whatever the professionals might think.

Thirdly, a change in terminology might facilitate provision of services for people with disabilities, without having to apply the dreadful 1948 definitions of disability. The dilemma is a real one. A person has an impairment which, without equipment and resources for better living conditions, will render him disabled. In order to minimise his disability, he must first submit to being classified as disabled. Surely we can do better than this.

We should accept the challenge to re-think our attitudes and our terminology, but we must learn the lessons of the past 20 years and make sure the new terms are acceptable and understandable. Change must be driven by the real needs of disabled people. Complex human problems must not be forced into the crude and often arbitrary categories demanded by our still primitive computer software.

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- 2 Lindström B. Quality of life for children and disabled children based on health as a resource concept. *J Epidemiol Community Health* 1994; 48: 529–30.

Investigation of mitochondrial disease

Mitochondrial diseases are now recognised as a significant group of neurometabolic disorders in childhood¹ and may be caused by mutations in mitochondrial DNA (mtDNA). The major energy generating reactions in a cell are concentrated in the mitochondrion where the pathways of carbohydrate, fatty acid, and amino acid oxidation converge and feed into the tricarboxylic acid cycle and thence the electron transport chain. This review will use the term 'mitochondrial disorder' to refer to diseases of the electron transport chain and associated central pathways, many of which are associated with lactic acidosis and/or caused by mtDNA mutations.

Diagnosis of mitochondrial diseases is frequently difficult because of the wide variety of clinical presentations which are possible particularly in the paediatric age range. While there have been major advances in recent years, a molecular diagnosis is considerably less likely in paediatric than in adult practice. In this review we will first discuss the general investigation of these patients. We will then introduce the basic biology of mtDNA in order to classify mtDNA diseases by mode of inheritance (table 1) and the specific investigation of some of the commoner clinical syndromes (table 2).

Which patients warrant investigation?

Patients may present with a recognised clinical syndrome or a suggestive constellation of symptoms. Mitochondrial studies are clearly indicated in patients with Leber's hereditary optic neuropathy (LHON) (in which patients present in adolescence with acute loss of vision),^{2–4} Kearns-Sayre syndrome (in which patients present with proximal myopathy, chronic progressive external ophthalmoplegia, and retinopathy), mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS)^{5,6} and myoclonic epilepsy and ragged red fibres (MERRF)⁷ (table 2). Because mtDNA diseases

Table 1 Mode of inheritance of mtDNA disease

1. Sporadic	Major rearrangements (Kearns-Sayre syndrome, CPEO, Pearson's)
2. Mitochondrial	Point mutations (MELAS, MERRF, NARP, LHON, aminoglycoside induced deafness)
3. Autosomal dominant	Familial duplications
4. Autosomal recessive	Variable deletions
	Depletion
	Chaperonin deficiency
5. X linked	?Susceptibility in LHON

CPEO=chronic progressive external ophthalmoplegia.

may mimic so many unrelated disorders, the pickup rate is much lower in patients with multisystem disease. Suggestive features include primary lactic acidosis, muscle weakness particularly with progressive external ophthalmoplegia and cytochrome oxidase deficiency, cardiomyopathy, etc, as in table 3.

A raised blood lactate concentration may be due to poor sampling or be secondary to a wide variety of conditions including hypoperfusion, liver dysfunction, sepsis, and other genetic metabolic diseases.⁸ Lactic acidemia is present as a primary biochemical abnormality in patients with defects in pyruvate metabolism, the tricarboxylic acid cycle, gluconeogenesis, and glycogen metabolism. A normal blood lactate does not exclude a mitochondrial disorder, and some patients have episodes of severe lactic acidosis punctuated by periods when blood lactate is within the normal range.⁸ A raised cerebrospinal fluid lactate is a more sensitive and specific finding, but even this is not always helpful in the early stages of MELAS or Leigh's syndrome. Furthermore, cerebrospinal fluid lactate may remain above the normal range for several days after an episode of meningitis or prolonged seizures.

Muscle biopsy is extremely helpful in many mitochondrial disorders as both cytochrome oxidase deficiency and ragged red fibres are commonly seen. However, a normal biopsy is the rule in conditions such as LHON where there are no clinical features of muscle disease. Studies of electron transport chain function are less useful than histochemistry as an initial screen, particularly in paediatric practice, where needle biopsy is preferable to open biopsy. However, electron transport chain activities in fibroblasts and/or muscle may be diagnostic in infantile cytochrome oxidase deficiency.

Mitochondrial genetics

Mitochondria are unique among mammalian cytoplasmic organelles in having their own genome. This mtDNA is maternally inherited, presumably because the sperm contributes almost no cytoplasm to the zygote. mtDNA codes for 13 proteins which are all subunits of the respiratory chain.⁹ However, the majority of components of this

complex array of multimeric proteins are encoded in the nucleus and have to be imported into the mitochondrion, as are many other essential mitochondrial proteins (such as chaperonins for protein assembly). Thus while mtDNA diseases might be maternally inherited, they can also have a mendelian pattern of inheritance or be sporadic. mtDNA also has genes for 22 transfer RNAs and two ribosomal RNAs because the mitochondrion has its own genetic code and protein assembly system. Unlike nuclear DNA where there are usually only two copies of each gene per cell, mtDNA is a multicopy gene. In normal individuals all of the thousands of mtDNAs are identical (that is homoplasmy). In disease, there may be more than one distinct population of mtDNA in each cell (heteroplasmy), one being normal and the other(s) mutant. The proportion of mutant mtDNA in any cell or tissue may vary from 0–100% and this may change with time^{10 11} and have profound effects on respiratory function.

Heteroplasmy probably explains some of the variation in phenotype found in patients with the same mutation and makes it essential to choose an appropriate tissue such as muscle for mtDNA analysis (table 4). Varying levels of heteroplasmy may also make antenatal diagnosis difficult.

Specific investigations in mitochondrial diseases

REARRANGEMENTS OF mtDNA

mtDNA rearrangements are usually sporadic (table 1).¹² A single large deletion of mtDNA is a common finding in all tissues including blood in patients with Pearson's syndrome (sideroblastic anaemia with liver and pancreatic dysfunction).¹³ Identical deletions may be detected in patients with Kearns-Sayre syndrome and Pearson's syndrome. Furthermore Pearson's syndrome may progress to Kearns-Sayre syndrome, presumably because of postnatal changes in the distribution of mutant mtDNA.¹⁴ As this occurs, deleted mtDNA becomes less readily detectable in blood. Some but not all patients with Kearns-Sayre syndrome have in addition a related mtDNA duplication.¹⁵ This is important because duplications are often detectable in blood and may be present in rare familial cases.

POINT MUTATIONS IN mtDNA

Point mutations (single base changes) of mtDNA are associated with a maternal inheritance pattern. The first

Table 2 Some presentations of mtDNA disease in childhood

Clinical presentation	Possible molecular abnormality
1. Infancy	
(A) Leigh's syndrome	PHD deficiency, generalised cytochrome oxidase deficiency, mtDNA point mutations, 8993, 9344
(B) Encephalopathy Hypotonia Seizures Respiratory failure	mtDNA depletion, generalised cytochrome oxidase deficiency, mtDNA point mutations 8993, 8344, 3243
(C) Multisystem disease	mtDNA depletion, mtDNA point mutations 8993, 8344, 3243
(D) Pearson's syndrome Sideroblastic anaemia Pancytopenia Exocrine pancreatic dysfunction Liver failure	Major rearrangements, deletions, and duplications
2. Later childhood	
(A) Ocular myopathy Kearns-Sayre syndrome CPEO	Major rearrangements, deletions, and duplications Variable deletions, mtDNA point mutation 3243
(B) Proximal myopathy	mtDNA point mutations 8344, 3243
(C) Encephalopathy Kearns-Sayre syndrome MELAS MERRF	Major rearrangements, deletions, and duplications mtDNA point mutation 3243 mtDNA point mutation 8344
(D) NARP	mtDNA point mutation 8993
(E) Pearson's syndrome	Variable deletions
(F) Cardiomyopathy	mtDNA point mutations 3260, 3243, 8993, 8344, major rearrangements

CPEO=chronic progressive external ophthalmoplegia; PHD=pyruvate dehydrogenase.

Table 3 Features of multisystem disease which may suggest a mitochondrial cause

Combinations of the following features may be suggestive of a mitochondrial disease. Very few are specific.

Very suggestive

Muscle: ragged red fibres, cytochrome oxidase deficiency, progressive external ophthalmoplegia, ptosis
Metabolic: cerebrospinal fluid lactic acidosis, primary blood lactic acidosis.
Brain: areas of low attenuation in basal ganglia on computed tomography (or prolonged T1 or T2 on MRI), infarcts especially in parieto-occipital region. Calcification of basal ganglia on computed tomography. Transient hemiparesis and/or hemianopia
Eye: pigmentary retinopathy
Heart: unexplained cardiomyopathy, heart block
Kidney: tubular defects including Fanconi's syndrome
Haematological: sideroblastic anaemia with vacuolated red and white cell precursors

Associated features

Brain: dementia, myoclonus, ataxia, focal seizures, headache
Eye: cataracts. Optic atrophy
Ear: nerve deafness
Pancreas: exocrine pancreatic dysfunction
Gut: villous atrophy, episodic vomiting
Endocrine: diabetes (both types I and II), hypoparathyroidism, short stature, growth hormone deficiency, diabetes insipidus
Bone marrow: sideroblastic anaemia, vacuolisation, pancytopenia
Liver: unexplained hepatocellular dysfunction

MRI=magnetic resonance imaging.

Table 4 Tissues for investigation of specific mitochondrial disorders

Tissue available for DNA analysis	Major rearrangements	Variable deletions	Point mutations	Depletion	Infantile cytochrome oxidase deficiency	PDH deficiency
Blood	3	4	1-3	4	4	3
Cultured cells						
Lymphoblasts	3	4	2	4	4	2
Fibroblasts	3	4	2	4	1	1
Myoblasts	2	3	2	3	1	2
Frozen muscle	1	1	1	1	1	2
Frozen other tissue	2	2	2	3	1	2
Fixed tissue*	4	4	2-3	4	4	4

*Including minute quantities of stained tissue on slides. Key: 1=ideal tissue; 2=suitable for diagnosis; 3=may be useful; 4=unlikely to be helpful. PDH=pyruvate dehydrogenase.

description was in LHON,²⁻⁴ which is unlike most other mtDNA diseases in several ways. Firstly, there is a male predominance which might be explained by interaction with a hypothetical X linked factor. Secondly, patients are frequently homoplasmic for mutant mtDNA so blood is the ideal tissue for analysis. Thirdly, these patients have few if any additional neurological features and rarely a raised lactate. These last two points are also features of the 1555 mutation, which is associated with both rare cases of sporadic nerve deafness and a familial predisposition to aminoglycoside induced deafness.^{16 17}

There are now at least 14 mtDNA point mutations associated with various other mitochondrial diseases which may present as myopathies, cardiomyopathies, or multisystem disease.¹⁸ In almost all cases the level of mutant is lower in blood than in muscle and may fall with age.¹¹ While blood is adequate for diagnosis of the majority, muscle is better if it is available (except in neurogenic weakness, ataxia, and retinitis pigmentosa (NARP) where blood concentrations remain high).

AUTOSOMAL DOMINANT VARIABLE DELETIONS

In families with variable deletions, each affected individual is heteroplasmic for several different mtDNA deletions, and most of the deletions are only found in a single family member.¹⁹ In this condition, the inheritance pattern is autosomal dominant, and the deletions arise de novo within each individual. Patients usually present with chronic progressive external ophthalmoplegia or occasionally Pearson's syndrome,²⁰ in adulthood or adolescence. Muscle is the ideal tissue for analysis as the deletions are rarely detectable in blood.

DEPLETION OF mtDNA IN INFANTILE CYTOCHROME OXIDASE DEFICIENCY

Moraes *et al* have recently identified a group of patients with low cytochrome oxidase in whom muscle is depleted of mtDNA.²¹ As the remaining mtDNA appears to be structurally normal this appears to be a quantitative rather than a qualitative change in mtDNA.^{21 22} Patients with multisystem disease (for example, affecting the central nervous system, liver and/or kidney in addition to muscle) appear to have depletion in the affected tissue.²¹ As the diagnosis is made by quantitating the level of mtDNA relative to nuclear DNA in the appropriate tissue it is not possible to use blood and rarely fibroblasts for diagnosis.

LEIGH'S SYNDROME

Leigh's syndrome is a heterogeneous group of disorders and inheritance may be autosomal recessive, mitochondrial, or X linked. Nuclear mutations in genes such those encoding subunits of pyruvate dehydrogenase are a significant cause of Leigh's syndrome.²³ In this group, the phenotype is severe in males and very variable in females

probably because of variation in the degree of X inactivation. Another important group of Leigh's syndrome is autosomal recessive cytochrome oxidase deficiency, and in both conditions the enzyme defect can be demonstrated in fibroblasts.

Several different mtDNA mutations have now been implicated as a cause of Leigh's disease.²⁴⁻²⁶ All of these are readily detected in blood of affected individuals and their families.

Conclusion

While there have been major advances in the detection and understanding of mitochondrial diseases, there are still large numbers of patients with suspected mitochondrial disease without a clear diagnosis. This could improve with more appropriate samples and/or analysis, but further scientific advances are also needed.

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Genetic testing of children

Presymptomatic diagnosis of some individuals at risk of genetic disease is possible by clinical examination or by simple investigations (for example, sweat test for cystic fibrosis, haemoglobin electrophoresis for haemoglobinopathies, creatine phosphokinase levels for Duchenne and Becker muscular dystrophy, ultrasound screening for adult polycystic kidney disease). Similarly, carriers of recessive disorders (for example, haemoglobinopathies) and balanced chromosomal rearrangements can be identified. In the assessment of carrier status in girls from Duchenne muscular dystrophy families, it has been traditional to leave testing until teenage. For other disorders, testing has been performed earlier – sometimes inadvertently (for example, with prenatal diagnosis, carriers of balanced chromosome rearrangements are detected in utero).

Recently, the mapping and cloning of a number of medically important genes has greatly increased both the number of disorders for which tests are possible and the accuracy of those tests. In some situations, it is important that the carrier state is identified even in fetal life (for example, female carriers of the X linked condition ornithine transcarbamylase deficiency can frequently be symptomatic and require close postnatal observation) – but what about all the other plethora of situations? Is it in the child's interests for this information to be known? Harper and Clarke raised these concerns in a *Lancet* article after their experience of requests for presymptomatic testing for Huntington's disease.¹ Their protocol only allowed testing of adults upon their own request and testing of children was refused, including requests from adoption agencies. As a result of this concern, the Clinical Genetics Society (UK) convened a working party to consider the issues and their report has recently been published.²

The remit of the working party was to examine current attitudes and practice with regard to this issue, focus attention on any difficulties raised by the genetic testing of children, and make appropriate recommendations about future practice. The working party included representatives from clinical and laboratory genetics, paediatrics, law, and psychiatry. They sent an initial questionnaire to approximately 3000-4000 health professionals (512 replied), which included 990 consultant paediatricians of whom 337 (34%) replied. Some months later, a supplementary questionnaire was sent to the same 990 consultants of whom 260 responded.

Current practice and attitudes

The predominant view expressed in the survey was that requests for testing should only be considered if initiated by the child's parents or medical advisers, although 50% of the paediatricians felt that adoption agencies had the right to request testing (even if the result would have no direct health benefit for the child) as opposed to 28% of geneticists. Attitudes varied from disorder to disorder. Where some intervention might be indicated in childhood, either therapeutic or via surveillance for complications, most geneticists and paediatricians were in favour of testing (for example, Marfan's syndrome, hyperlipidaemias, polyposis coli, von Hippel-Lindau syndrome). For some disorders where onset could occur in childhood, a small majority of geneticists and a larger majority of paediatricians would perform a test (for example, adult polycystic kidney disease, Becker muscular dystrophy). There was another group of conditions where the majority of paediatricians but a minority of geneticists would test (for example, myotonic dystrophy, facioscapulohumeral muscular dystrophy).

The most striking difference in attitude is apparent when respondents were asked if they would test a 5 year old child at the parents' request for Huntington's disease and prion dementia. Only two out of 49 geneticists who responded would test for Huntington's disease compared with 100 out of 189 paediatricians and none of the geneticists would test for prion dementia but 66 out of 114 paediatricians would. The views of those paediatricians and geneticists who would test are at variance with the working party's conclusion that predictive testing for an adult onset disorder should generally *not* be undertaken if the child is healthy and there are no useful medical interventions if the test proved positive. This is particularly important as the legal view expressed in the document is that it may be regarded as negligent to test a child for Huntington's disease (except in very particular circumstances) given the general consensus that it is unwise to do so.

There was a wide range of views about testing children for carrier status for cystic fibrosis and balanced chromosomal translocations and certainly it appeared to be common practice among paediatricians to test the healthy siblings of their affected patients. Geneticists as a group were less likely to view parental wishes alone as sufficient to justify testing.