RESPIRATORY FAILURE IN A NEWBORN INFANT

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Mrs Jones was a 20-year-old primiparous woman, blood group A, rhesus negative and rubella immune. She had normal antenatal ultrasound scans at 16, 20 and 34 weeks' gestation. The risk of her fetus having Down's syndrome was 1:3810. She reported good fetal movements throughout the pregnancy and there was no family history of note. She was admitted to hospital in labour at full-term with intact membranes. The fetal heart rate was normal.

CASE STUDY

A male infant, John, was born by vaginal delivery at 41 weeks' gestation. Thick meconium was present in the liquor at delivery but none was seen below the vocal cords. At birth, he had poor respiratory effort and a heart rate of 60/minute. He was treated with bag and mask ventilation and his respiratory effort improved. The APGAR scores were 5 at 1 minute and 9 at 5 minutes of age. Cord blood gas analysis was not performed.

At 1 h of age, he was noted to be pale, with poor respiratory efforts and an oxygen saturation of 80% in air. He also had decreased movements. He was sedated, intubated, ventilated and transferred to the neonatal unit. At 75 minutes of age an arterial blood gas in air was: pH 7.01, pCO_2 8.0 kPa, pO_2 7.7 kPa, HCO_3 15 mmol/l and base excess −17 mmol/l. The ventilation was adjusted (FiO_2 40%, maximum pressure 26/5 cmH_2O) and at 120 minutes of age an arterial blood gas was: pH 7.23 pCO_2 4.0 kPa, pO_2 20 kPa, HCO_3 12 mmol/l and base excess −13 mmol/l.

INITIAL DIAGNOSIS

The history of meconium in the liquor, the need for resuscitation at birth, and the metabolic acidosis led the admitting senior house officer to make a working diagnosis of perinatal asphyxia. Since oxygenation was relatively easy, he thought that meconium aspiration, respiratory distress syndrome and persistent pulmonary hypertension of the newborn were unlikely.

During the next 48 h ventilation requirements were minimal. A chest *x* ray was normal. Blood gases showed a normal pCO_2 and pO_2 but a persistent metabolic acidosis. Sedation was discontinued and he was extubated. He was noted to have decreased movements but no convulsions. Because of his poor respiratory effort he was re-intubated and ventilated and further investigations were performed:

- an EEG was normal
- brain MRI showed normal cranial anatomy and no evidence of ischaemia
- chest *x* rays remained normal
- an ECG was normal. There was no evidence of pulmonary hypertension.

Further discussions with the family did not reveal a family history of a muscle disorder and the mother was sure that she had felt fetal movements during her pregnancy. Polyhydramnios had not been noted during pregnancy. Mrs Jones did not have clinical features of myotonic dystrophy.

FURTHER INVESTIGATIONS

Many muscle disorders can present in the newborn period. The more common disorders include myotonic dystrophy, spinal muscular atrophy, mitochondrial myopathy, fatty acid oxidation abnormalities and congenital myasthenia gravis. In the absence of a specific lead, additional investigations indicated in a newborn suspected of having a muscle disorder are shown in table 1.

John had a persistent metabolic acidosis (pH 7.29 and base excess >−10 mmol/l). His arterial pO_2 and pCO_2 remained normal while he was ventilated. The plasma lactate was 6.1 mmol/l (reference range: 0.6–2.4 mmol/l) and CSF lactate was 5.0 mmol/l (reference range: 1.2–2.1 mmol/l). The creatinine phosphokinase, ammonia, thyroid function, liver function and very long chain fatty acids were normal. The EMG and nerve conduction studies (technically difficult to perform) were normal.

In view of the metabolic acidosis and lactic acidosis, the most likely diagnosis was a mitochondrial respiratory chain disorder or (less likely) a fatty acid oxidation disorder. A mitochondrial respiratory

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Table 1 Suggested investigations for mitochondrial myopathies

Blood	Blood gas	Glucose	Ammonia
	Electrolytes & anion gap	Thyroid function	Liver function test
	Amino acids	Acylcarnitine	Creatinine kinase
	Chromosomes	Lactate	Pyruvate
	White cell enzymes	Very long chain fatty acids	
CSF	Glucose	Lactate	Pyruvate Glycine
Urine	Organic acids	Sugar	Ketones
Muscle	Biopsy	EMG/NCS	Mitochondrial enzyme assay

EMG, electromyogram; CSF, cerebrospinal fluid; NCS, nerve conduction studies.

chain disorder is most readily diagnosed by light and electron microscopy of a muscle biopsy and mitochondrial enzyme assay of a frozen muscle biopsy. The muscle biopsy should be handled rapidly in conjunction with the local laboratory to ensure enzymatic activity is not adversely affected. Liaison with both local and national experts in congenital muscle disorders is clearly essential from an early stage. Fatty acid oxidation disorders require an assay of blood carnitine and very long chain fatty acids.

John remained ventilator dependent. He had frequent episodes of right or left upper lobe collapse of the lung. A trial of neostigmine did not improve muscle movement. On light and electron microscopy, the muscle biopsy showed markedly increased lysosomal glycogen, marked vacuolation and abnormal mitochondria. Staining of the muscle biopsy showed increased succinate dehydrogenase activity and decreased cytochrome C oxidase activity (fig 1). The mitochondrial enzymes on the muscle biopsy were as follows:

- complex 1 0.078 (reference range 0.104–0.268)
- complex 2/3 0.018 (reference range 0.04–0.204)
- complex 4 0.002 (reference range 0.014–0.034).

The results of other investigations were as follows:

- very long chain fatty acids: normal
- anti-acetylcholine receptor antibodies: absent
- acylcarnitine: normal
- white cell enzymes: normal
- genetic screening test for Prader-Willi syndrome: negative
- genetic screening test spinal muscular atrophy: negative.

OUTCOME

An increased succinate hydrogenase activity and decreased cytochrome c activity are typical of mitochondrial chain disorders. John also had complete depletion of mitochondrial enzyme complexes, which is uniformly associated with a poor prognosis if present in the neonatal period. Following discussion with his parents, local staff and national experts in paediatric neurology, metabolic medicine and mitochondrial respiratory chain disorders, John was extubated and died within a few hours.

The parents were seen by the geneticists who had a difficult task of informing the parents of the hereditary nature of the disease but with rather complex inheritance. They gave the parents a 1 in 4 chance of future pregnancies being affected but awaited additional genetic analyses of samples collected perimortem.

DISCUSSION

A newborn infant presenting with decreased movement and who failed extubation from mechanical ventilation several times clearly needed further investigation. Although there are many causes of muscle disorders in this group of patients, mitochondrial DNA defects (mtDNA) warranted consideration, exclusion and systematic investigation because they are associated with adverse outcome and might have implications for future pregnancies by virtue of their genetic basis. Other causes of lactic acidosis were considered during the course of John's illness but, as he was otherwise well, causes including impaired cardiac function, sepsis, etc were unlikely to explain his clinical condition—namely poor movement.

Mitochondrial disease presents in a heterogeneous manner. There are a number of characteristic syndromes such as Kearns–Sayre (ataxia, pigmented retina, cardiac conduction defects), MELAS (myoclonic epilepsy with lactic acidosis and stroke-like episodes), MERFF (myoclonic epilepsy with ragged red fibres), Leigh's syndrome (neurogenic weakness, ataxia, retinitis pigmentosa and brain stem defects), chronic progressive external ophthalmoplegia (CPEO), Leber's hereditary optic neuropathy (LHON) and Pearson's syndrome (transfusion dependent sideroblastic anaemia or pancytopaenia with exocrine pancreas failure).[1] However these syndromes most commonly present after the second or third decade.

In the newborn infant, establishing the clinical diagnosis is difficult. mtDNA disease has an incidence of 1/10 000 live births.[2] The presence of persistent lactic acidosis, hypotonia, cardiomyopathy, deafness, endocrine disturbance or seizures should be regarded as ''red flags'' that raise the possibility of an underlying mtDNA disease in this age group.[3] Scalglia reported the clinical features of 113 cases of mtDNA in children aged from 2 weeks to 18 years.[2] This cohort most commonly presented with a combination of cardiomyopathy and myopathy (39.8%) or non-specific encephalopathy (38.9%). The cardiac group had hypertrophic cardiomyopathy (58%), dilated cardiomyopathy (29%), arrhythmia (11%) and mild cognitive deficit (20%). In those who presented with no cardiac manifestations, 100% had moderate to severe developmental delay, 79% were hypotonic, 50% had seizures, 32% had ophthalmologic abnormalities, 21% had sensorineural deafness, 20% had hypertonia, 12% had movement disorders and 6% had ataxia. In the whole cohort 60% had an elevated plasma lactate on at least one occasion.

The principal function of mitochondria is to produce an energy substrate for DNA replication and protein synthesis. Mitochondria are dependent upon several intracellular metabolic pathways to guarantee a supply of ATP in a variety of cellular conditions.[1 4] Glycolysis and fatty acid oxidation are two of these pathways on which the mitochondria depend in nutritionally replete and fasting states respectively. Nicotinamide adenine dinucleotide (NADH) from glycolysis and flavin adenine dinucleotide ($FADH_2$) from fatty acid oxidation are used in the mitochondrial pathway to produce ATP. The mitochondrial pathway is a process of oxidative phosphorylation and consists of five multisubunit complexes (I–V) that are located on the inner mitochondrial membrane (fig 2).

NADH from glycolysis is a substrate for complex I and $FADH_2$ is the substrate for complex II. Electrons are transferred in

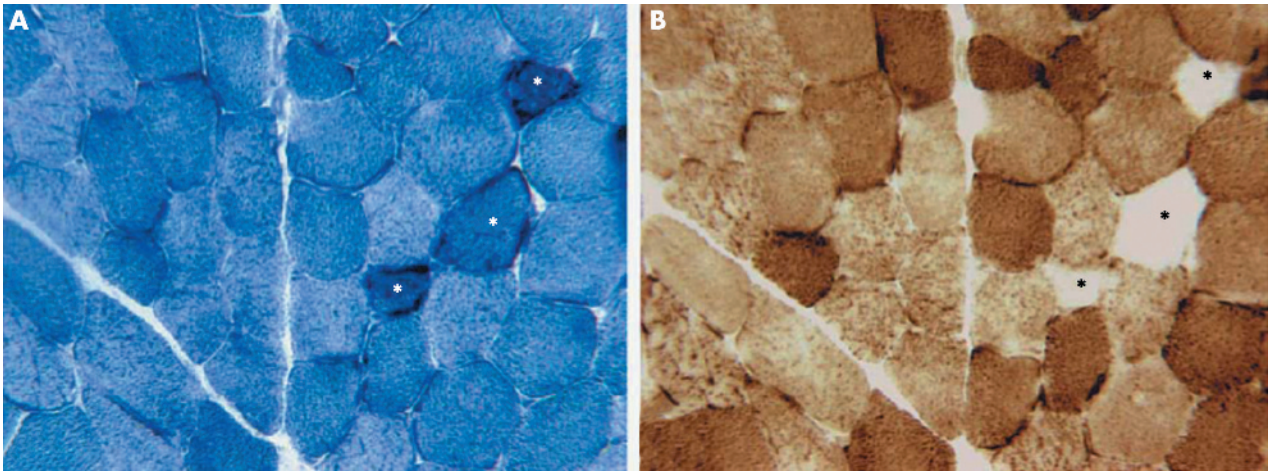

Figure 1 Muscle biopsy stained with succinate dehydrogenase (asterix in A) and absence of activity on staining with cytochrome c oxidase (asterix in B). Reproduced with permission from Di Mauro.[1]

succession from either complex I or II to complex III and then IV. The resulting electrochemical gradient of about 150 mV drives the generation of ATP via complex V.

Mitochondrial disease can result from mutations or deletions of the DNA that encodes any of the proteins involved in glycolysis, fatty acid oxidation or oxidative phosphorylation. Mitochondrial DNA is inherited from the mother and in the normal state all of the mtDNA is identical (homoplasmy).[1] However, human mtDNA has a mutation rate that is 10–20 times higher than that of nuclear DNA and thus there is the potential for a dual population of mutant or wild type mtDNA (or heteroplasmy). The clinical expression of pathogenic mtDNA depends upon the proportion of mutant to wild type mtDNA and the organ in which this mutant mtDNA is expressed. Organs with a high metabolic rate such as the heart, brain and skeletal muscle have a lower threshold at which a proportion of mutant mtDNA will cause their dysfunction.

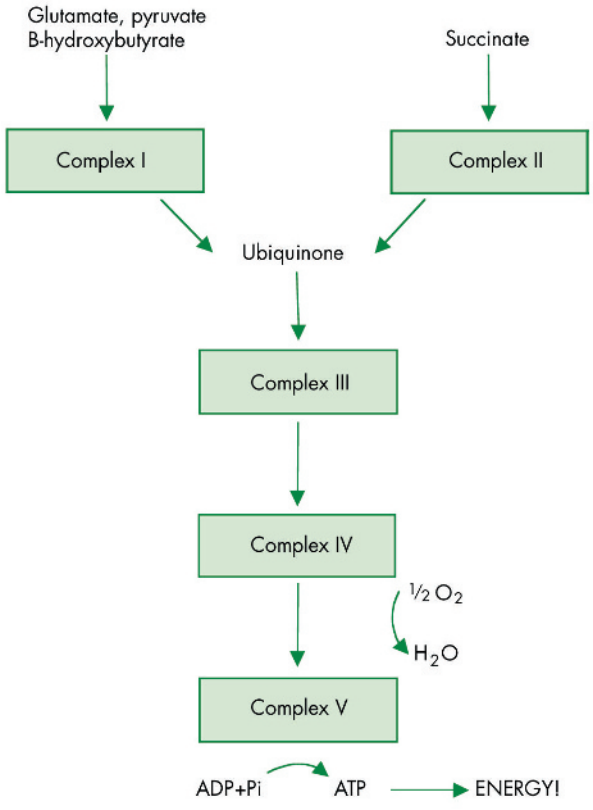

Figure 2 Graphical representation of how the different mitochondrial enzyme complexes interact to generate energy via electron transfer and use of oxygen.

The investigations in a suspected case should be performed in a systematic manner and are assisted by the early discussion with a specialist centre (fig 2 and table 1). The investigations outlined in table 1 classically show an increased lactate and lactate:pyruvate ratio, a normal or mildly elevated creatinine phosphorkinase and a normal EMG.[3] An MRI is useful to exclude features of MELAS and Leigh's or other cerebral abnormalities. The muscle biopsy is diagnostic and demonstrates the presence of ragged red fibres on Gomori staining. These ragged red fibres stain strongly for succinate dehydrogenase (complex II) and for cytochrome oxidase (complex IV), stain positively in MELAS and negatively in CPEO, Kearn–Sayre and MERRF.[3] In addition the homogenised muscle can be used to assay the quantity of complexes present. A significant deficit in the complex concentration was found in 71% of Scalgia's cohort with complex I (32%) and combined complex I, III, IV (26%) being the most common.[2] Forty per cent of those with complex deficit had cardiomyopathy.

The issue of molecular genetics is of interest. Although specific point mutations have been identified (Kearns–Sayre nt 3243; MELAS nt 3243, 3271; MERFF nt 8344, 8356; Leigh's nt 8993, 8344), their identification assists in genetic counseling but does not predict how the point mutation might manifest in the offspring. Scalglia's cohort demonstrated pathogenic and nuclear mtDNA mutations in respectively 13 (11.5%) and 3 (2.6%) of cases.[2] In this cohort the mean age of presentation

was significantly later in those with a pathogenic mtDNA mutation (110 months vs 32 months). Lamont described a series of 190 children whose mtDNA had been analysed between 1992 and 1996.[5] Mutations were identified in 15 cases (7.9%) with a point mutation in eight cases and a large scale rearrangement in seven. The median age of onset of symptoms in the mtDNA mutation and non-mutation groups was respectively 6 years and 1 year of age. The most common features in the mtDNA mutation group were myopathy, ataxia, progressive external ophthalmoplegia and stroke-like episodes. In the non-mtDNA mutation groups the commonest symptoms were developmental delay, seizures, ataxia and myopathy. Only progressive external ophthalmoplegia, myopathy and pigmentary retinopathy were significantly associated with an mtDNA mutation. An increased serum lactate was identified more frequently in the mtDNA mutation group (78% compared with 44%). Where a muscle biopsy had been performed ragged red and cytochrome oxidase negative fibres were found in 89% of the mtDNA mutation group compared with 17% in the alternative group. There were general between-group differences in the MRI findings but none was specific or diagnostic.

There is no treatment that alters the clinical course of mtDNA disease and management is largely supportive. Dichloroacetate has been shown to reduce cerebral lactate.[6] Coenzyme Q10, the antioxidant vitamins C and E, and replacement of L-carnitine in secondary carnitine deficiency are all rational therapeutic strategies but none has an effect on the functional outcome in adults. The study of homoplasmic mtDNA mutations in the mouse model might lead to tissue-specific therapeutic interventions that could have a role in the heteroplasmic mtDNA mutation disease in the future.[7]

AUTHORS' NOTE

We are pleased to report that Mrs Jones gave birth to a healthy boy in 2005.

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REFERENCES

1 **DiMauro S**, Schon EA. Mitochondrial Respiratory-Chain Disorders. *New Engl J Med* 2003;**348**:2656–68.
2 **Scaglia F**, *et al.* Clinical spectrum, morbidity, and mortality in 113 pediatric patients with mitochondrial disease. *Pediatrics* 2004;**114**:925–31.
3 **Clay AS**, Behnia M, Brown KK. Mitochondrial disease: a pulmonary and critical-care medicine perspective. *Chest* 2001;**120**:634–48.
4 **Leonard JV**, Schapira AH. Mitochondrial respiratory chain disorders I: mitochondrial DNA defects. *Lancet* 2000;**355**:299–304.
5 **Lamont PJ**, *et al.* Clinical and laboratory findings in referrals for mitochondrial DNA analysis. *Arch Dis Child* 1998;**79**:22–7.
6 **Chinnery PF**, Turnbull DM. Clinical features, investigation, and management of patients with defects of mitochondrial DNA. *J Neurol, Neurosurg & Psych* 1997;**63**:559–63.
7 **Johnson KR**, *et al.* A nuclear-mitochondrial DNA interaction affecting hearing impairment in mice. *Nat Genet* 2001;**27**:191–4.

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Infant size and growth and adult disease

Small size and slow growth in infancy have been linked to increased risk of coronary disease in adult life. This has led to suggestions that strategies to promote greater intrauterine or postnatal growth might lead to better adult health. Now a systematic review (David Fisher and colleagues. *International Journal of Epidemiology* 2006;**35**:1196–1210) has shown little evidence to support these suggestions.

The review included 19 studies relating to 10 leading causes of adult disease taken from the Global Burden of Disease Study published in *The Lancet* in 1997. Larger infants had an increased risk of type 1 diabetes as adults. Larger infant boys, but not girls, had a reduced risk of later coronary disease. There was insufficient evidence to relate infant size or growth to other important adult diseases such as cancer, mental illness, stroke, chronic obstructive pulmonary disease or type 2 diabetes. It is concluded that present evidence does not support the use of strategies to alter infant growth in order to prevent adult disease.

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