

CASE REPORTS

Mitochondrial encephalomyopathy with corticosteroid dependence

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ABSTRACT A 12-year-old boy with corticosteroid-responsive mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS) is described. His mother proved to have an asymptomatic mitochondrial myopathy on examination of a muscle biopsy specimen. Three weeks after the onset of vomiting, headache, ataxia and visual and speech impairment, he presented with a background of somatic growth retardation, deafness and school failure. Examination revealed disorientation, dysphasia, dyspraxia, optic atrophy, hemianopia, hemiparesis and sensory inattention. A cranial computed tomographic scan disclosed a large, low-density area, which was consistent with infarction, in the left posterior hemisphere and marked calcification of the basal ganglia bilaterally. Within two weeks of the commencement of corticosteroid treatment, the neurological dysfunction resolved. Attempts to decrease the dosage of dexamethasone caused an exacerbation of symptoms repeatedly. Two weeks after ceasing corticosteroid therapy, the patient developed a serious neurological relapse and a new, large, low-density area, which resembled an infarction, in the right posterior hemisphere on a computed tomographic scan. The reintroduction of corticosteroid therapy again resulted in the rapid resolution of all symptoms. It became evident that the patient had an exquisitely sensitive corticosteroid dependency, whereby a reduction in the dexamethasone dosage of even 0.25 mg a day caused confusion, headaches and increasing lactic acidemia. Although it is difficult to assess the impact of various therapies in MELAS because of the episodic nature of the disease, this remarkable corticosteroid responsiveness also has been noted in four previously reported patients with MELAS syndrome; therefore, it would seem reasonable to suggest that corticosteroid therapy now should be considered as standard treatment for this condition. However, corticosteroid therapy in other forms of mitochondrial disorders still awaits careful evaluation.

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Mitochondrial diseases are a heterogeneous group of disorders in which mitochondrial dysfunction produces clinical disease. Mitochondrial myopathies are mitochondrial diseases in which the clinical presentation and course are determined by the pathological involvement of extraocular and/or other skeletal muscles. Frequently, they are hereditary disorders that are characterized by ptosis, external ophthalmoplegia, proximal weakness and lactic acidemia. With evolution of the disease process, multisystem (for example, retinal, peripheral-nerve, cardiac) involvement may become manifest but, in other cases, the disease appears to remain restricted to one tissue.¹

Mitochondrial encephalomyopathy (or cytopathy) is a multisystem mitochondrial disease in which both muscles and the central nervous system are involved but, in contrast to the mitochondrial myopathies, central-nervous-system dysfunction dominates the clinical picture.² Morphologically, skeletal-muscle mitochondria are non-specifically abnormal. Histochemical examination of muscle biopsy specimens usually shows subsarcolemmal accumulations of abnormal mitochondria as a characteristic abnormality that is termed "ragged, red fibres". Biochemically, defects of substrate utilization, oxidation-phosphorylation coupling or the respiratory chain are present within the affected tissues.³

The respiratory chain is responsible for the transfer of reducing equivalents from oxidized nicotinamide adenine dinucleotide (NADH) and succinate, which are generated by the oxidation of metabolites by way of the tricarboxylic-acid cycle, to molecular oxygen. It consists of four multienzyme complexes that are termed

complex I (NADH-coenzyme Q oxidoreductase), complex II (succinate-coenzyme Q oxidoreductase), complex III (coenzyme Q-cytochrome c oxidoreductase), and complex IV (cytochrome c oxidase), which are embedded in the inner mitochondrial membrane, and two molecular-weight redox carriers, coenzyme Q and cytochrome c.⁴

The energy that is generated by the oxidation-reduction reactions of the respiratory chain is stored in an electrochemical proton gradient (energy pool), which can be coupled to the synthesis of adenosine triphosphate from adenosine diphosphate and inorganic phosphorus by adenosine triphosphate synthetase (complex V).⁵ This process is called respiratory chain-linked oxidative phosphorylation or, merely, oxidative phosphorylation. Respiratory-chain dysfunction produces symptoms and signs of disease that primarily are a result of energy insufficiency. The specific clinical picture most likely depends on the degree of enzyme deficiency and the specific tissue(s) that is affected.

Mitochondria contain their own DNA and a complete system for its replication, transcription and translation. However, the majority of the mitochondrial proteins are coded by nuclear DNA; only 10% are coded by mitochondrial DNA (mtDNA).⁴ To date, 13 polypeptides (seven subunits of complex I, one subunit of complex III, three subunits of complex IV and two subunits of complex V) have been identified as being coded by mtDNA.⁶

Mitochondrial DNA is inherited primarily from the mother because sperms have few mitochondria and almost all the mitochondria of the zygote are derived from the ovum.⁴ Therefore, genetic information from the mitochondrial genome is transmitted only from women to either male or female offspring, hence the term "maternal inheritance". A disorder that is transmitted through the mitochondrial genome should show a maternal inheritance pattern and cannot be transmitted by affected men.

Most human mitochondrial disorders have occurred sporadically but several large sibships have been reported where cytoplasmic (maternal) inheritance appeared likely,⁷ and there have been other reports in which inheritance patterns were more consistent with an autosomal pattern, which would implicate the nuclear genome as at fault.⁸ Twenty per cent of patients with mitochondrial myopathies have similarly affected relatives, and the rate of maternal-to-paternal transmission is approximately nine to one.⁷

The increased incidence of maternal, as opposed to paternal, transmission in familial mitochondrial myopathies suggests that these disorders may be caused by mutations of mtDNA.⁷ Human mtDNA has been estimated to have a mutation rate of approximately 10-times that of nuclear DNA.⁹ Holt et al. recently have demonstrated that mtDNA heteroplasmy can occur in humans and that human disease may be associated with defects of the mitochondrial genome.¹⁰

Symptoms that are referable to the central nervous system in mitochondrial encephalomyopathy vary widely. This apparent heterogeneity may not only possibly reflect mitochondrial inheritance but also variations in the degree of deficiency of each of the five enzyme complexes, or the varying metabolic consequences that may be seen with the same degree of deficiency of each of the enzyme complexes. Nevertheless, three distinct syndromes of mitochondrial encephalomyopathy are distinguishable on clinical grounds: the Kearns-Sayre syndrome;^{11,12} myoclonus epilepsy with ragged, red fibres (MERRF);^{13,14} and mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS).¹⁵ Hybrid forms which sometimes bear the features of two-or-more subtypes such as MERRF and MELAS do occur.¹⁶

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TUESDAY, AUGUST 1, 1989

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As from today the Hoechst said that the re-listing of original research products their products comes after LASIX and DAONIL will be many months of continuing negotiations with The Department of Community Services and Health.

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Back on P.B.S. August 1

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Daonil® N.H.S. 5mg tablets 100 plus 5 Repeats
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Daonil®

active ingredient: glibenclamide

Abridged Product Information

Indications: Initial and change over therapy for maturity onset diabetes. **Actions:** The pharmacological effects of glibenclamide on carbohydrate, protein and fat metabolism are those of insulin, whose secretion it stimulates. **Precautions:** Because of its high efficacy dosage, adjustment is particularly important to avoid hypoglycaemia. Excessive alcohol intake. Also, see interactions. **Contraindications:** Type 1 diabetes, serious impairment of renal function, diabetic coma and pre-coma. **Use in Pregnancy & Lactation:** (Category C) Oral hypoglycaemics are not recommended during pregnancy and lactation. **Adverse Reactions:** Mild gastrointestinal disturbances are rarely encountered. Hypoglycaemia due to dietary habits and dose. Allergy, very rarely haemopoietic reactions. **Interactions:** Combination with the following may cause hypoglycaemia: long acting sulphonamides, tuberculostatics (ethionamide), phenylbutazone, salicylates, chloramphenicol, tetracycline, compounds, cyclophosphamide, MAO inhibitors, B-receptor blockers or coumarin derivatives. Long term treatment with corticosteroids and thiazides may cause some deterioration in control. **Adult Dosage:** Commencing at 2.5mg per day, the dosage range is: 2.5mg-20mg per day. Up to 10mg taken as a single daily dosage. **Presentation:** 5mg white oblong tablets, PBS 100/5 repeats. Further information available on request.

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Abridged Product Information

Composition: Frusemide. **Indications:** Cardiac, renal and pulmonary oedema, hypertension of mild or moderate degree. **Precautions:** Before diuretic therapy is started, hypovolaemia, hypotension or greatly reduced serum electrolytes should be corrected. Although Lasix seldom causes hypokalaemia, a high-potassium diet is an advantage. During long-term treatment, serum electrolytes, creatinine, non-protein nitrogen, serum urea, etc should be checked regularly. Appropriate surveillance and replacement therapy are essential. Administer with caution during pregnancy and lactation. **Contraindications:** Renal failure due to poisoning with nephrotoxic or hepatotoxic substances or when accompanied by hepatic coma. Severe hypokalaemia, hyponatraemia, hypovolaemia and subsequent hypotension. **Use in Pregnancy:** (Category C); **Use in Lactation:** Frusemide passes into the breast milk. **Adverse reactions:** Disturbances of water and electrolyte balance may arise particularly with high doses. Possible complications include thrombosis and embolism. Allergic reactions, such as rashes or thrombocytopenia, are encountered only occasionally. Extremely rare, a few instances of leukopenia, acute pancreatitis, anaphylactic reactions or impairment of hearing have occurred. Great caution should be exercised in administering curare or its derivatives to patients undergoing Lasix therapy. **Dosage, Adults:** Lasix has a wide therapeutic range. Oedema: 20-400mg, with 20-40mg once daily sufficing in most cases. Hypertension: 40-80mg is recommended. **Children:** 1-3mg/kg day up to 40mg max. **Presentation:** Tablets 40mg; 50's: tablets 20mg; 50's, 10mg/mL oral solution; 30mL; Ampoules, 20mg/2mL; 5's. **Poison schedule:** S4. Further information available on request.

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The MELAS syndrome was not recognized as a discrete entity until 1984, when Pavlakis et al. gathered nine cases from the medical literature and added two of their own.¹⁵ All cases shared the features of ragged, red fibres on examination of a muscle biopsy specimen, normal early development, short stature, seizures and hemiparesis, hemianopia or cortical blindness. Lactic acidemia was a common finding.

Four familial cases of MELAS have been reported — two sibling pairs,^{17,18} one mother-and-son pair¹⁹ and a family with four normal sons and an affected mother, son and daughter.²⁰ MELAS appears to be familial but the mode of inheritance is uncertain. Transmission may be either by mendelian or maternal inheritance with defects of either a nuclear or mitochondrial genome.²¹ The coordinated actions of both the nuclear and mitochondrial genomes are required for the biosynthesis of a normal respiratory-enzyme complex. If either is dysfunctional, the system fails.

Many cases of MELAS now have been reported and in-vitro studies of muscle mitochondrial metabolism in these patients have identified a variety of functional biochemical defects in the mitochondrial respiratory chain.^{1,3,22} The defects that have been reported most commonly have involved respiratory-chain complex I²³⁻²⁸ or complex IV,²⁹ both of which contain polypeptide subunits that are encoded by mitochondrial genes.²⁷ As specific biochemical defects in mitochondrial function are being identified, future efforts also will be directed at molecular studies in mitochondriopathies to define the underlying mutations and the products of mutated genes (defective respiratory-enzyme polypeptides) and to uncover the biochemical mechanisms which determine and/or modulate the clinical manifestations of the genetic disorders.

Therapeutic experience in MELAS is limited but corticosteroid-responsiveness has been reported in four cases of presumed MELAS.^{2,30-32} We report here a boy with MELAS syndrome who repeatedly has shown a substantial clinical response to treatment with corticosteroid agents. Several attempts at corticosteroid withdrawal have resulted in a relapse of the disorder.

Clinical record

A 12-year-old boy presented on July 1, 1983 after the onset of intermittent morning vomiting that was associated with headache, gait ataxia, word-finding difficulty and blurred vision in the right visual field.

After a normal birth and early infancy, he had walked at 14 months of age and his speech had developed normally. Since the age of three years he suffered from gradually progressive left-sided deafness and his academic record was poor.

Examination revealed a physically underdeveloped right-handed boy who weighed 20 kg. He was disorientated, mildly dysphasic and dyspraxic bimanually with slow mentation. Mild

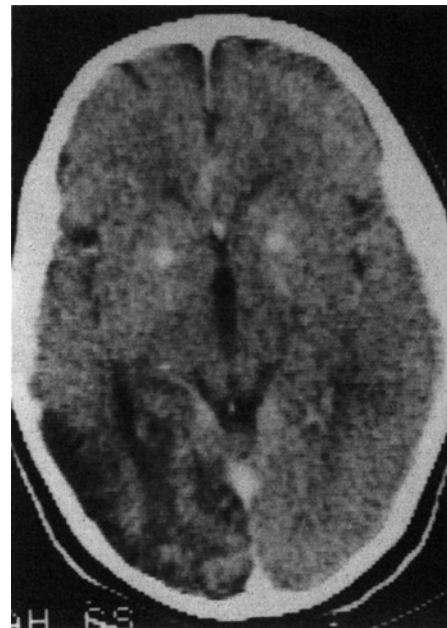


FIGURE 1: Plain cranial computed tomographic scan showing a low-density area in the left temporo-occipital region and calcification of the basal ganglia bilaterally.

bilateral optic atrophy, an incongruous right homonymous hemianopia and right sensory inattention were present.

A cranial computed tomographic scan showed heavy calcification of the basal ganglia bilaterally, and a large area of low density in the periphery of the left temporal, parietal and occipital lobes (Figure 1). Electroencephalography revealed low-to-moderate amplitude θ and δ activity on the left side, which was more prominent posteriorly. Cerebrospinal-fluid examination was normal, apart from a mildly elevated protein level of 0.60 g/L (normal, 0.15-0.45 g/L).

On Day 5, he developed a right hemiparesis and right hemianaesthesia. A cerebral glioma was suspected and, therefore, dexamethasone therapy (5 mg twice a day) was instituted. The patient's vomiting subsided the following day and over the next two weeks his hemiparesis, aphasia and apraxia resolved.

On Day 11, he suffered two right-sided partial motor seizures that prompted treatment with phenytoin (200 mg a day). Left temporal epileptiform activity and bilateral slow-wave activity were present on a repeat electroencephalogram (subsequent electroencephalograms five and 11 months later gave normal results). The daily dose of dexamethasone was reduced gradually to 2 mg by Day 19, when the patient was discharged home.

Subsequent investigations

An electrocardiogram showed non-specific T-wave inversion in the anterior chest leads and ST-segment depression in the lateral chest leads. Echocardiography gave normal results. Audiometry revealed severe bilateral hearing loss of 70-80 db. Visual evoked potentials were of low amplitude but of normal latencies bilaterally.

The resting plasma lactate level was elevated significantly (2.2-5.3 mmol/L; normal, 0.3-1.3 mmol/L) throughout his illness. Blood leukocyte and plasma lysosyme enzyme levels were normal, as were plasma long-chain fatty-acid and carnitine levels.

Nerve conduction studies were normal but

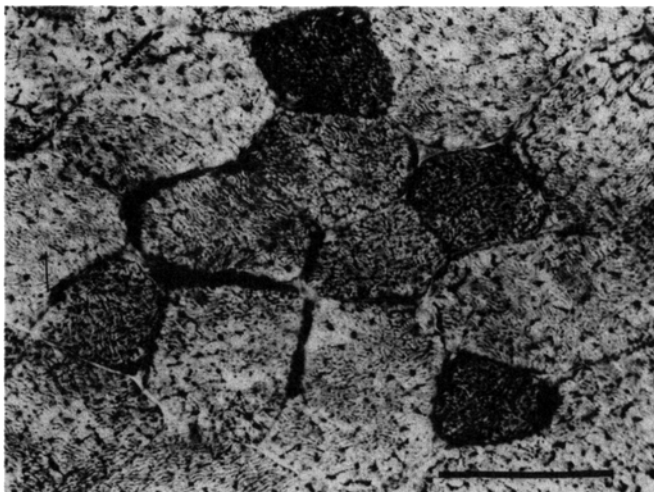


FIGURE 2: Cryostat section. Succinate dehydrogenase preparation showing positively stained crescents at the periphery (bar = 100 μ m).

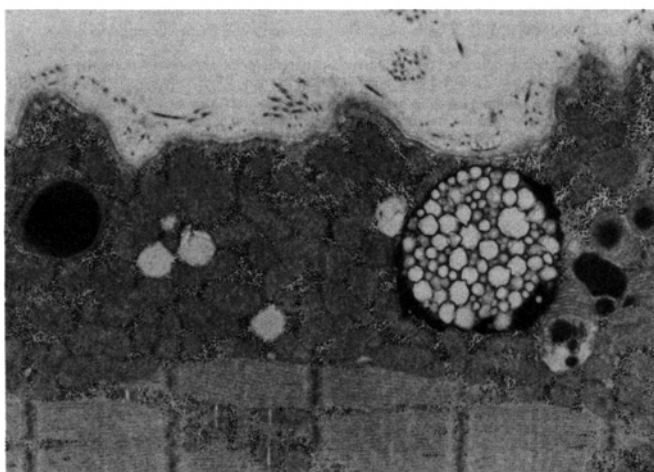


FIGURE 3: Electronmicrograph showing mitochondrial inclusion and circular arrangement of cristae. (Magnification \times 54 900, reduced to 55%.)

needle electromyography showed patchy myopathic changes in the right biceps brachii muscle. A biopsy of the left vastus lateralis muscle revealed increased variation in muscle-fibre diameter (20–80 μ m) and ragged, red fibres on examination of a Gomori's trichrome-stained preparation. Dark fibres in the NADH and succinate dehydrogenase preparations were suggestive of a mitochondrial abnormality (Figure 2). Electronmicroscopy disclosed large accumulations of mitochondria in the subsarcolemmal region. Abnormal variations were present in the structure of the cristae with electron-dense inclusions within some mitochondria (Figure 3).

Biochemical analysis was performed on the muscle. The muscle carnitine concentration was 0.92 nmol/mg wet weight (normal, 0.6–4.0 nmol/mg wet weight) and 38.0 nmol/mg non-collagen protein (normal, 10–50 nmol/mg non-collagen protein). The muscle cytochrome oxidase duplicate concentrations were 1.28 and 1.34 nmol/min-mg⁻¹ wet weight (normal, 1.33–2.17 nmol/min-mg⁻¹ wet weight) and the concentration of muscle carnitine palmitoyl transferase, by means of the exchange method, was 17.9 nmol/min-mg⁻¹ wet weight (normal, 12–28.5 nmol/min-mg⁻¹ wet weight). The fibroblast cytochrome oxidase concentration was 24.6 nmol/min-mg⁻¹ protein (normal, 21.5–25.7 nmol/min-mg⁻¹ protein) and the rolenone-insensitive NADH cytochrome c reductase concentration was 25 nmol/min-mg⁻¹ protein (control, 20 nmol/min-mg⁻¹ protein). Studies of pyruvate and malate oxidation did not reveal any decreases in C¹⁴-pyruvate and uniform-C¹⁴ malate

under all the conditions that were tested. No obvious defect was apparent in the fibroblast respiratory chain.

A biopsy specimen of the left vastus lateralis muscle from the patient's mother showed an increase in the variability of muscle-fibre diameters (30–90 μ m) but no ragged, red fibres were identified. Electron-dense inclusions, which were similar to those that had been seen in the patient's muscle, were seen infrequently in mitochondria on electronmicroscopy. His mother's serum lactate level was normal.

Progress

On September 15, 1983, the patient developed a headache which responded immediately to an increase in dexamethasone therapy from 2.0 to 2.5 mg a day. The dose then was reduced very gradually and the drug finally was ceased by mid July 1984. However, two weeks later, the patient experienced the acute onset of headache, ataxia, vomiting and confusion. He was drowsy and manifested left sensory inattention and a dense, incongruous left homonymous hemianopia. A cranial computed tomographic scan showed a new area of diminished attenuation in the right temporo-occipital region in addition to the old left temporoparietal-occipital lesion (Figure 4). Dexamethasone therapy was reintroduced and a rapid improvement in the patient's mental state was apparent within hours. Two weeks later (mid August 1984), his neurological examination was normal apart from bilateral optic-disc pallor.

By January, 1985, it had become obvious that the patient had an exquisitely sensitive



FIGURE 4: Plain cranial computed tomographic scan showing a new low-density area in the right temporo-occipital region, and the older area of low density in the left temporo-occipital lobes with dilatation of the posterior horn of the left lateral ventricle. Calcification of the basal ganglia is present bilaterally.

corticosteroid dependency. A dosage of dexamethasone of 1.0 mg a day proved to be a satisfactory maintenance dosage, whereas 0.75 mg a day of dexamethasone resulted in confusional episodes, sometimes with headache and nausea.

On October 11, 1987, the patient presented with diabetic ketoacidosis. His arterial pH was 6.97 and his plasma level of glucose was 72 mmol/L (normal, 3.3–5.5 mmol/L), of bicarbonate was 6 mmol/L (normal, 22–30 mmol/L), of lactate was 5.3 mmol/L (normal, 0.3–1.3 mmol/L) and of ketones was 1.5 mmol/L. The hyperglycaemia responded promptly to an insulin-and-dextrose infusion but the ketoacidosis persisted for four days. Upon his regaining awareness, a new left homonymous hemianopia was detected. Therefore, the dose of dexamethasone was increased temporarily to 3 mg a day and then gradually was reduced to his maintenance dosage of 1 mg a day after two weeks, by which time the hemianopia had resolved.

Discussion

This patient manifested somatic growth retardation, deafness, encephalopathy with borderline mental deficiency, stroke-like incidents and seizures together with lactic acidosis, "ragged, red fibres" in skeletal muscle and multiple low-density areas and bilateral calcification of the basal ganglia on cranial computed tomographic scan. The clinicopathological findings meet the criteria for the MELAS syndrome.¹⁵ Non-specific calcification in the basal ganglia, especially the globus pallidus, often is described in cases of mitochondrial encephalomyopathy;^{2,11,16} its significance is not clear.

The treatment of mitochondrial encephalomyopathy aims to minimize the energy demands on dysfunctional mitochondria and to manipulate the mitochondrial milieu

Prescribing Information

COMPOSITION Cefotaxime sodium

Description. Claforan is a semisynthetic cephalosporin for use by injection only. It is a white to pale yellow crystalline powder, soluble in water (greater than 20%) and produces a pale yellow solution. The pKa value is 3.35. The pH of the formulated material is 4.5 to 6.5. Raising the pH (as by addition of strong base) will result in an intense yellow colour and possible degradation. The sodium content of the formulated material is approximately 2.09 mmol (48 mg) per g of Claforan.

Pharmacology pharmacokinetics. Claforan is very poorly absorbed after oral ingestion and therefore is administered by intramuscular and intravenous injection. Following intramuscular administration of a 1g dose of Claforan to normal volunteers, the mean peak plasma concentration at 30 minutes post administration was approximately 20 mcg/mL.

After intravenous dosage, administered over a 2-5 minute period, a peak plasma level of approximately 102 mcg/mL was obtained. For intravenous infusion administered over a 30 minute period, a mean concentration of approximately 40 mcg/mL was obtained. The respective concentration declined as follows:

(1g)	1 hour	2 hours	3 hours
IV	20 mcg/mL	8	1.8
IV infusion	14	4	1.5
IM	15	10	4.0

Repetitive dosing showed no significant evidence of accumulation. The mean elimination half-life after intramuscular administration was 1.45 hour, 1.06 hour after rapid intravenous injection, and 1.13 hour after 30 minute intravenous infusion. Claforan is desacetylated in the body, with concentrations of the desacetyl metabolite appearing both in the blood and urine. The process is rapid with measurable levels detectable in the plasma within 5 minutes after administration. The desacetyl metabolite is microbiologically active against a similar spectrum of bacteria, but is less active by a factor of 2 to 3. The desacetyl metabolite has also been shown to be degraded to an open lactone form. This metabolite is not microbiologically active and only very low levels can be detected in the plasma after administration of normal therapeutic doses. Studies in human volunteers measuring radioactive recovery in the urine have indicated that 20 - 36% of administered drug is excreted as unchanged drug, 15 - 25% as the desacetyl metabolite and 20 - 25% as the opened lactone derivative of the desacetyl metabolite.

Claforan is 32 - 44% bound to plasma protein, while the desacetyl derivative is only bound by half of this value. The affinity for plasma proteins is low, as evidenced by the high urinary clearance, 85 - 90% of the administered dose is recovered in the urine, while the faeces accounted for 7 - 9.5% of the recovery total. 70 - 80% of the administered dose is recovered in the first 4 hours after administration. The elimination half-life of Claforan is 0.7 - 1.3 hours, while that of the metabolites is approximately 2 hours.

Mean peak urinary concentrations obtained after 1g administration of Claforan intravenously, intramuscularly and by intravenous infusion at 4 hours were 1309 mcg/mL, 903 mcg/mL, and 599 mcg/mL, respectively.

Following IV administration of 1g Claforan mean peak concentrations of 35 mcg/mL were recorded in the bile after 30 minutes and declined to 3.30 mcg/mL after 4 hours. Concentrations of Claforan in the CSF are considerably lower than in the plasma.

Following 1g intramuscular dosage the mean plasma clearance is 318 mL/min/1.73m². Studies have shown that concomitant use of 0.5% lignocaine solution does not affect the pharmacokinetics or bioavailability of Claforan form intramuscular administration.

Interaction studies between parenterally administered Claforan and orally ingested probenecid, showed that probenecid increased the retention of Claforan by 14 - 40%, and decreased the renal clearance by 11 - 32%.

Microbiology. At plasma concentrations achieved with the recommended therapeutic doses Claforan is usually active against the following micro-organisms in vitro:

Gram-positive: staphylococci, including penicillinase producing strains, *Streptococcus pyogenes*, *Diplococcus pneumoniae*, (*Streptococcus faecalis* are mostly resistant).

Gram-negative: *Escherichia coli*, *Klebsiella pneumoniae*, *Haemophilus influenzae*, *Neisseria sp.*, gonococcus (including penicillin resistant gonococcus), *Proteus mirabilis*, *Proteus morgani*, *Proteus vulgaris*, *Proteus rettgeri*, *Serratia marcescens*.

Approximately 25% of *Pseudomonas aeruginosa* strains and 43% of bacteroides strains have an in vitro MIC of less than or equal to 16 mcg/mL.

There is in vitro evidence of synergy between Claforan and aminoglycoside antibiotics such as gentamicin against some species of Gram-negative bacteria including some strains of *Pseudomonas*. Claforan is resistant to many B lactamases (penicillinases and cephalosporinases). Claforan's bactericidal effect is due to inhibition of cell wall synthesis.

Susceptibility tests. Quantitative methods that require measurement of zone diameters give the most precise estimates of antibiotic susceptibility. Interpretation involves correlation of the diameters obtained in the disc test with minimum inhibitory concentration (MIC) values for Claforan.

Reports from the laboratory giving results of the standardised single disc susceptibility test using a 30 mcg Claforan disc should be interpreted according to the following criteria:

Susceptible organisms produce zones of inhibition 23 mm or greater indicating sensitivity and that the tested organism is likely to respond to therapy. Organisms of intermediate susceptibility produce zones of inhibition 15 to 22 mm, indicating that the tested organism would be susceptible if high dosage is used or if the infection is confined to tissues and fluids (eg. urine) in which high antibiotic levels are attained. Resistant organisms produce zones of 14 mm or less, indicating that other therapy should be selected. A bacterial isolate may be considered susceptible if the MIC value for Claforan is less than 16 mcg/mL. Organisms are considered resistant if the MIC value is greater than 32 mcg/mL.

INDICATIONS Treatment of infections caused by susceptible microorganisms. Efficacy has been demonstrated in the following: infections of the respiratory tract (upper and lower); infections of the urinary tract; septicaemia (cefotaxime has been administered with gentamicin for septicaemia, and such therapy may be instituted prior to isolation of causative organism); intra-abdominal infections; gonorrhoea (including gonorrhoea caused by B lactamase producing strains of *N. gonorrhoeae*); ENT infections; soft tissue infections; bone and joint infections; meningitis (Claforan should be combined with chloramphenicol in the initial treatment of meningitis in adults and children pending the availability of culture and sensitivity results, appropriate therapy should then be instituted, it should not be used either as a single drug in initial therapy or in infants and neonates). In serious cases Claforan may be used before the results of sensitivity tests become available. Claforan may be used for the prevention of postoperative infection in obstetrical surgery, vaginal hysterectomy and abdominal hysterectomy (see Dosage and Administration).

CONTRAINDICATIONS Claforan should not be used in patients with known hypersensitivity to cephalosporins. Caution should be exercised in penicillin allergic patients, as the possibility of cross sensitivity exists.

Lignocaine hydrochloride should not be used as a diluent for intramuscular injection in patients who are sensitive to lignocaine.

WARNINGS Claforan is physically incompatible with aminoglycosides. Where an aminoglycoside antibiotic is administered at the same time as Claforan they should be administered separately and not mixed together as a single preparation.

As with other broad spectrum antibiotics, colitis including rare instances of pseudomembranous colitis, has been reported with Claforan.

PRECAUTIONS Claforan should be used with caution in patients with known hypersensitivity to penicillin or other B lactam antibiotics. The possibility of severe or fatal anaphylactic reactions should be borne in mind and appropriate treatment kept available.

Use in pregnancy. The safety of Claforan in pregnancy has not been established. Claforan has not been

shown to cause any embryotoxic or teratogenic effects in animals. However, Claforan crosses the placenta and it should be administered during known or suspected pregnancy only if in the judgement of the treating clinician such use is deemed essential to the patient's welfare and the expected benefits outweigh any potential risks.

Use in lactation. Claforan is excreted in the milk. Peak concentrations, measured 2 or 3 hours after IV administration of 1g doses, ranged from 0.25 to 0.52 mcg/mL (mean 0.32 ± 0.09). These concentrations in breast milk could affect the oropharyngeal flora of the suckling infant. Therefore, Claforan is not recommended for nursing mothers unless the expected benefits outweigh any potential risk or if alternative arrangements for feeding the infant can be made.

Liver and renal disease. Transient rises in hepatic enzymes, urea and creatinine have been seen in some patients given Claforan, so careful monitoring of hepatic and renal function is advised where any dysfunction exists. For dosage adjustment in moderate and severe renal impairment see Dosage and Administration.

Repeated use of lignocaine hydrochloride should be avoided in patients with severe liver disease or decreased hepatic blood flow due to the possibility of lignocaine toxicity (resulting from decreased metabolism and accumulation).

Superinfection with nonsusceptible organisms, including fungi, may occur and requires appropriate therapy.

Cephalosporin antibiotics in high doses should be given with caution to patients receiving aminoglycoside antibiotics or potent diuretics such as frusemide.

ADVERSE REACTIONS Hypersensitivity. Skin rashes eg. maculopapular rash or urticaria, pruritus, eosinophilia, fever and rarely other allergic reactions have been reported.

Blood. Leucopenia and granulocytopenia have been reported rarely. Some patients have developed positive direct Coombs tests during treatment with Claforan.

Liver. Increases in serum transaminases and alkaline phosphatase levels have been noted.

Local reactions. Pain, phlebitis and tenderness have been reported in approximately 4.8% of cases.

Gastrointestinal. Nausea, diarrhoea. As with other broad spectrum antibiotics colitis including rare instances of pseudomembranous colitis, has been reported with Claforan.

Kidneys. Elevations in serum creatinine and blood urea have been reported infrequently.

DOSAGE AND ADMINISTRATION Claforan should be administered only by the intramuscular or intravenous routes.

The dosage, route of administration and dosage interval will depend on the site and severity of the infection, sensitivity of the pathogens and condition of the patient.

Dosage in adults. For urinary tract infections the recommended dose is 2g daily in divided doses. For other infections the minimum recommended dosage is 2g daily in divided doses. This dosage may be increased to 3, 4 or 6g daily according to the severity of the infection, sensitivity of causative organisms and condition of patient.

For prevention of postoperative infection. In vaginal or abdominal hysterectomy: 1g should be administered intramuscularly 30 to 60 minutes before incision and repeated thereafter on completion of surgery and at 8 hourly intervals for a total duration of 24 hours.

In obstetrical surgery (Caesarian section): 1g should be administered intravenously after the cord has been clamped and thereafter at 6 and 12 hours.

For the treatment of gonorrhoea. Uncomplicated gonorrhoea due to non B lactamase producing organisms: one single intramuscular dose of 1g.

Uncomplicated gonorrhoea due to B lactamase producing organisms: one single intramuscular dose of 0.5g of Claforan plus probenecid, 1g orally, given 1 hour earlier.

Paediatric dosage. Children: The usual dosage range is 100 to 150 mg/kg/day in 3 to 4 divided doses. However in very severe infections doses of up to 200 mg/kg/day may be required.

Neonates: There is insufficient data to recommend the use of Claforan in neonates.

Mode and duration of administration. Intravenous injection: For intravenous injection the contents of one vial of Claforan 1g are dissolved in at least 4mL Water for Injection and then injected over a period of 3 to 5 minutes either into a vein or into the distal part of a clamped off infusion tube.

Intravenous infusion: For short infusion, 2 vials Claforan 1g are dissolved in 40mL Water for Injection or an infusion solution (eg. Dextrose Solution, Haemacel, Macrodex, Rheomacrodex) and then infused over 20 to 30 minutes. For continuous intravenous infusion, 2 vials Claforan 1g are dissolved in 100mL of an isotonic saline or dextrose solution and infused over 4 hours. Sodium bicarbonate solutions must not be mixed with Claforan.

Intramuscular administration: For intramuscular injection the contents of one vial of Claforan 1g are dissolved in 4mL Water for Injection and then injected laterally deep into the gluteus muscle. It is not advisable to inject more than 4mL into either buttock. The pain of injection can be avoided by dissolving Claforan 1g in 4mL of 0.5% lignocaine solution, (see Precautions and Contraindications). Intravascular injection of this solution must be strictly avoided.

If the daily dose exceeds 2g, or if Claforan 2g is administered more than twice daily, intravenous injection is to be preferred.

In administering the 500mg dose, half the amount of any one of the solutions mentioned above may be used.

The duration of treatment depends on the patient's response. It should be continued for at least three days after normalisation of the body temperature.

Use in patients with impaired renal function. From the limited data available in this patient population the biological half-life of the desacetyl metabolite of cefotaxime increases significantly and progressively below creatinine clearance of 20mL/minute.

Furthermore, when the creatinine clearance is less than 5mL/minute the half-life of the parent compound is also increased. Because of these changes in the pharmacokinetics of the drug it is recommended that dosage adjustments should be made in patients with creatinine clearances of less than 20mL/minute in order to achieve approximately equal peak serum levels during repeated dosage.

As a guide it is suggested that the dose be reduced by half in patients with creatinine clearances less than 20mL/minute with further reductions in patients with a clearance of less than 5mL/minute.

DRUG INTERACTIONS Claforan exhibits an additive microbiological effect with gentamicin. However, because of physical incompatibility Claforan should not be mixed with an aminoglycoside antibiotic into a single preparation.

Administration of oral probenecid decreases renal clearance slightly and increases total body concentrations. (See Pharmacokinetics).

Compatibility. Claforan is compatible with the following commonly used intravenous infusion fluids which do not contain sodium bicarbonate and in which it retains satisfactory potency for up to 24 hours at 25 degrees C: Sodium Chloride Injection BP, 5% Dextrose Injection BP, Dextrose and Sodium Lactate Injection BP, Compound Sodium Lactate Injection BP (Ringer-Lactate Injection).

Claforan is also compatible with 0.5% lignocaine. Freshly prepared solutions should be used. Caution: These solutions for i.m. injections only.

Provided the recommended storage conditions are observed, there is no change in potency or safety. After the period mentioned above any unused solution should be discarded.

OVERDOSAGE No cases of Claforan overdose have been reported. Animal evidence suggests that Claforan has a very low toxic potential. The LD50 studies in rats and mice administered Claforan intravenously have shown no mortality nor associated symptoms of intoxication up to doses of 2000 mg/kg and 716 mg/kg respectively.

Serum levels of cefotaxime may be reduced by haemodialysis.

PRESENTATION Injection, vials 500mg, 1g, 2g; 1s.

Storage. The vial containing the powder should be stored in a cool area (below 25 degrees C) and away from heat and light. The shelf life of the powder, when stored under these conditions, is 2 years. Reconstituted solution: 1g of Claforan reconstituted with 4mL of Water for Injection is stable for up to 24 hours under refrigeration.

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Don't be misled by minimum dosage comparisons

Antibiotic cost calculations based on the minimum recommended dose can be misleading. When the minimum and maximum recommended dosage levels are considered, the results are surprising.



	Claforan	ceftriaxone	ceftazidime*
List price ex-manufacturer	1g vial \$8.93 2g vial \$17.00	\$24.17 \$45.65	\$15.92 \$32.67
(Derived from April 1989 PBS)	Minimum dose† Maximum dose†	2g/day 6g/day	1g/day 6g/day

Claforan

cefotaxime

THE COST EFFECTIVE CEPHALOSPORIN

† Adult i. v. dosage from prescribing information MIMS Annual 1989
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biochemically so as to permit optimal function. Conditions that increase the body's energy demands are known to exacerbate mitochondrial encephalomyopathy.⁴ Therefore, general measures in patient management should include the avoidance of extremes of temperature (that is, exercise, fever) and/or treatment with antipyretic agents; the avoidance of severe lactic acidosis and of glucose intolerance; the maintenance of adequate hydration; and the ingestion of small, frequent meals, rather than permitting prolonged periods between meals. Drugs that inhibit the function of the respiratory chain (phenytoin, barbiturate agents) and inhibit mitochondrial protein synthesis (chloramphenicol, tetracycline) should be avoided if possible.

Specific therapeutic modalities which have been tried for the various mitochondrial disorders include compounds that can act as artificial electron acceptors, such as vitamins C and K₃,³³ riboflavin (vitamin B₂),³⁴ a long-chain, fatty-acid-free diet;³⁵ L-5-hydroxytryptophan and carbidopa;³⁶ coenzyme Q;³⁷ and corticosteroid agents.^{38,39} Therapeutic successes have been sporadic but at times dramatic. As there is a tendency to report successful results only, therapies with detrimental effects need to be reviewed carefully. Indeed, major deterioration occurred in two cases with the Kearns-Sayre syndrome after corticosteroid therapy.⁴⁰

The response to corticosteroid therapy in this case of MELAS was striking. Total neurological resolution occurred within two months of the commencement of dexamethasone at the first presentation and repeated attempts to decrease the dose of dexamethasone resulted in an exacerbation of the symptoms. Two weeks after corticosteroid therapy initially was ceased, the patient developed headache, drowsiness, ataxia, vomiting, a left homonymous hemianopia, left sensory inattention and a left hemiparesis. A new large area, which resembled an infarction, was present in the right cerebral hemisphere posteriorly on computed tomographic scan. The reintroduction of corticosteroid therapy again resulted in a rapid resolution of all symptoms. It subsequently became evident that the patient had an extremely sensitive corticosteroid dependency, whereby a reduction in the dosage of dexamethasone of even 0.25 mg a day resulted in the recurrence of symptoms.

As the natural history of MELAS is quite erratic and episodic, there is a potential hazard in interpreting the efficacy of various therapies in isolated cases overzealously, particularly if their institution may have coincided with the natural resolution of symptoms and signs. Nevertheless, the consistently rapid and dramatic clinical improvement which followed the institution of dexamethasone in this case was most impressive and, it seemed, beyond coincidence.

There have been four instances where the treatment of MELAS with dexamethasone,² methylprednisolone³⁰ or prednisolone^{31,32} has resulted in a clinical improvement; two of these cases were corticosteroid-dependent to the point where attempts at the withdrawal of medication resulted in an exacerbation of symptoms.^{2,31} Shapira et al. have postulated that instability of the mitochondrial membrane may have caused an uncoupling of oxidative phosphorylation and that the improvement that was associated with corticosteroid therapy might have been the result of a membrane-stabilizing effect, thus permitting more efficient oxidative phosphorylation and lowering the demands on glycolysis for energy.² It also is possible that corticosteroid agents exert their effects by the induction of antiphospholipase compounds.

The efficacy of corticosteroid therapy in our case, both in the prevention of encephalopathic events and the enhancement of recovery from stroke-like episodes, together with the similar experience of others,^{2,30-32} would suggest that corticosteroid treatment is of value in patients with MELAS and should be considered at this time to be standard therapy for this disorder. As the number of similar cases is small and the natural history of MELAS is episodic, caution must be exercised in the interpretation of therapeutic interventions, and more-substantial evidence will be derived from randomized, prospective multicentric therapeutic trials. The role of corticosteroid therapy in other mitochondrial disorders still is unclear and awaits careful evaluation.

References

- Morgan-Hughes J. The mitochondrial myopathies. In: Engel AG, Banker BQ, eds. *Myology*. New York: McGraw-Hill, 1986: 1709-1743.
- Shapira Y, Harel S, Russell A. Mitochondrial encephalomyopathies: a group of neuromuscular disorders with defects in oxidative metabolism. *Isr J Med Sci* 1977; 13: 161-164.
- DiMauro S, Bonilla E, Zeviani M, et al. Mitochondrial myopathies. *Ann Neurol* 1985; 17: 521-538.
- Peterson PL, Martens ME, Lee CP. Mitochondrial encephalomyopathies. *Neurol Clin* 1988; 6: 529-544.
- Lee CP, Martens M. Mitochondrial respiration and energy metabolism in muscle. In: Engel AG, Banker BQ, eds. *Myology*. New York: McGraw Hill, 1986: 643.
- Kroon AM, Van den Bogert C. Biogenesis of mitochondria and genetics of mitochondrial defects. *J Inher Metab Dis* 1987; 10 (suppl 1): 54-61.
- Egger J, Wilson J. Mitochondrial inheritance in a mitochondrially mediated disease. *N Engl J Med* 1983; 309: 142-146.
- Schnitzler ER, Robertson WC. Familial Kearns-Sayre syndrome. *Neurology* 1979; 29: 1172-1174.
- Brown WM, George M Jr, Wilson AC. Rapid evolution of animal mitochondrial DNA. *Proc Natl Acad Sci USA* 1979; 76: 1967-1971.
- Holt IJ, Harding AE, Morgan-Hughes JA. Deletions of muscle mitochondrial DNA in patients with mitochondrial myopathies. *Nature* 1988; 331: 717-719.
- Kearns TP, Sayre GP. Retinitis pigmentosa, external ophthalmoplegia and complete heart block: an unusual syndrome with histologic study in one of two cases. *Arch Ophthalmol* 1958; 60: 280-289.
- Berenberg RA, Pellock JM, DiMauro S, et al. Lumping or splitting? "Ophthalmoplegia-plus" or Kearns-Sayre syndrome? *Ann Neurol* 1977; 1: 37-54.
- Fukuhara N, Tokiguchi S, Shirakawa S, Tsubaki T. Myoclonus epilepsy associated with ragged red fibres (mitochondrial abnormalities): disease entity or syndrome? Light and electron microscopic studies of two cases and review of the literature. *J Neurol Sci* 1980; 4: 117-133.
- Fitzsimons RB, Clifton-Bligh P, Wolfenden WH. Mitochondrial myopathy and lactic acidemia myoclonic epilepsy, ataxia and hypothalamic infertility: a variant of Ramsay-Hunt syndrome? *J Neurol Neurosurg Psychiatry* 1981; 44: 79-82.

CORDILOX® PATIENTS GET ON WITH LIFE.

(Verapamil hydrochloride)

Abridged Prescribing Information

Generic name:

Verapamil hydrochloride.

Chemical name:

α -isopropyl- α -[(N-methyl-N-homoveratryl)- γ -aminopropyl]-3,4-dimethylhexyloxyphenyl-acetonitrile hydrochloride.

Chemical Characteristics:

Verapamil hydrochloride is a white, or almost white, odourless powder. M.P. about 146°C. Solubility: Water 1 in 20. Ethanol 1 in 25. Chloroform 1 in 1.5. Ether practically insoluble. A 5% aqueous solution has a pH of 4.5 to 6.5.

INDICATIONS:

- Hypertension
- Angina of effort
- Angina at rest
- Vasospastic angina (including Prinzmetal's variant angina)
- Tachyarrhythmias, including paroxysmal supra-ventricular tachycardia
- Atrial fibrillation with rapid ventricular response
- Atrial flutter with rapid ventricular response

Use in pregnancy:

Only limited information is available on the use of Cordilox in pregnancy. The drug should therefore not be used in pregnant women, or those likely to become pregnant, unless the expected benefits outweigh any potential risks.

Use in lactation:

The use of Cordilox during lactation should be avoided unless expected benefits outweigh any potential risk. However, preliminary results indicate that verapamil may reach concentrations of 10-65 ng/ml in the milk of nursing mothers. Such concentrations are unlikely to produce clinical effects in the infant.

CONTRAINDICATIONS:

- Cardiogenic shock.
- Recent myocardial infarction.
- Known hypersensitivity to verapamil hydrochloride; or to aspirin or azo dyes, since the 120 mg oral formulation contains tartrazine.

WARNING:

Use verapamil hydrochloride with caution in conjunction with beta adrenergic blocking drugs as the myocardial depressant effects of each drug may be additive.

Precautions:

In sick-sinus syndrome and second and third degree heart block, Cordilox may further impair SA or AV nodal function respectively.

In the presence of cardiac failure full compensation with cardiac glycosides should be ensured prior to administration of Cordilox. Caution is necessary in initiating treatment, or increasing dosage of Cordilox in patients with cerebrovascular accidents, sinus bradycardia, heart block and hypotension.

Interactions:

Both Cordilox and beta blocking drugs may slow AV conduction and depress myocardial contractility by different mechanisms. Cardiac function, heart rate and rhythm, and blood pressure should be closely monitored during simultaneous oral administration.

Other anti-arrhythmic, anti-hypertensive and cardiodepressant drug therapy should be reviewed prior to introduction of Cordilox.

Cordilox has been reported to increase plasma levels of digoxin. Physicians should be alert for symptoms of possible digitalis intoxication, and may wish to measure digoxin levels in plasma. However extensive experience indicates that this possible interaction is of only slight clinical relevance.

DOSAGE AND ADMINISTRATION:

In mild and moderate hypertension:

The usual starting dose is one 80 mg tablet two or three times a day. The maintenance dose may be adjusted to one 160 mg tablet two or three times a day.

Usual maintenance dose 160 mg twice daily:

The individual dose, and frequency of dosing, should be determined in accordance with the indication and individual patient response.

Paediatric: Dose range 40-360 mg per day in 2 or 3 divided daily doses according to age and response.

Geriatric/renal failure: The recommended daily dosage is usually well tolerated.

Hepatic failure: Caution should be exercised when initiating therapy since the pharmacological action of Cordilox may be increased or prolonged by hepatic insufficiency.

ADVERSE REACTIONS:

Cordilox is usually well tolerated.

More common reactions include constipation, flush, headache and dizziness.

Hypotension, bradycardia, development or worsening of symptoms of cardiac failure and rhythm disturbances have been reported.

Rarely non-specific immunological reactions such as skin rashes may occur.

Individual hypersensitivity to verapamil in the absence of accumulation or overdose, has been described.

OVERDOSAGE:

Symptoms:

Bradycardia, cardiac arrest, second and third degree AV block, hypotension and myocardial insufficiency.

Treatment:

Serious oral overdoses should be treated by induced emesis, or gastric lavage and aspiration, prior to admission to intensive care.

Repeated intravenous calcium gluconate (10 ml, 10% solution) and sodium bicarbonate if metabolic acidosis develops represent logical therapy.

Intravenous fluids and cardiorespiratory support may be necessary. Dialysis would not seem potentially useful.

Other treatment, selected in accordance with the presenting symptoms, may include atropine, isoprenaline (isoprotenerol), dopamine, cardiac glycosides and noradrenaline (norepinephrine). Recorded overdoses

survived include a 14 year old girl who ingested 2.4 g and a 28 year old woman who took 5.6 g.

PRESENTATION:

Cordilox 40 mg (100 tablets) NHS General Benefit - 100 tablets, 5 repeats.

Cordilox 80 mg (100 tablets) NHS General Benefit - 100 tablets, 5 repeats.

Cordilox 120 mg (100 tablets) NHS General Benefit - 100 tablets, 5 repeats.

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15. Pavlakis SG, Phillips PC, DiMauro S, et al. Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes: a distinctive clinical syndrome. *Ann Neurol* 1984; 16: 481-488.
16. Kuriyama M, Umezaki H, Fukuda Y, et al. Mitochondrial encephalomyopathy with lactate-pyruvate elevations and brain infarctions. *Neurology* 1984; 34: 72-77.
17. Hart ZH, Chang CH, Perrin EV, et al. Familial poliodystrophy, mitochondrial myopathy, and lactic acidemia. *Arch Neurol* 1977; 34: 180-185.
18. Shapira Y, Cederbaum SD, Cancilla PA, et al. Familial poliodystrophy, mitochondrial myopathy and lactic acidemia. *Neurology* 1975; 25: 614-621.
19. Yamamoto T, Beppu H, Tsubaki T. Mitochondrial encephalomyopathy: fluctuating symptoms and CT. *Neurology* 1984; 34: 1456-1460.
20. Driscoll P, Larsen PD, Gruber AB. MELAS syndrome involving a mother and two children. *Arch Neurol* 1987; 44: 971-973.
21. Rosing HS, Hopkins LC, Wallace DC, et al. Maternally inherited mitochondrial myopathy and myoclonic epilepsy. *Ann Neurol* 1985; 17: 228-237.
22. DiMauro S, Bonilla E, Zeviani M, et al. Mitochondrial myopathies. *J Inher Metab Dis* 1987; 10 (suppl 1): 113-128.
23. Kobayashi M, Morishita H, Sugiyama N, et al. Mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes syndrome and NADH-CoQ reductase deficiency. *J Inher Metab Dis* 1986; 9: 301-304.
24. Kobayashi M, Morishita H, Sugiyama N, et al. Two cases of NADH-coenzyme-Q reductase deficiency — relationship to MELAS syndrome. *J Pediatr* 1987; 110: 223-227.
25. Nishizawa M, Tanaka K, Shinozawa K, et al. A mitochondrial encephalomyopathy with cardiomyopathy. A case revealing a defect of complex I in the respiratory chain. *J Neurol Sci* 1987; 78: 189-201.
26. Byrne E, Trounce I, Dennett X, et al. Progression from MERRF to MELAS phenotype in a patient with combined respiratory complex I and IV deficiencies. *J Neurol Sci* 1988; 88: 327-337.
27. Schapira AHV, Cooper JM, Morgan-Hughes JA, et al. Molecular basis of mitochondrial myopathies: polypeptide analysis in complex-I deficiency. *Lancet* 1988; 1: 500-503.
28. Ichiki T, Tanaka M, Nishikimi M, et al. Deficiency of subunits of complex I and mitochondrial encephalomyopathy. *Ann Neurol* 1988; 23: 287-294.
29. DiMauro S, Zeviani M, Bonilla E, et al. Cytochrome c oxidase deficiency. *Biochem Soc Trans* 1985; 13: 651-653.
30. Peterson P, Martens M, Lee CP, et al. MELAS: a disorder of mitochondrial metabolism. *Neurology* 1986; 36(suppl): 94.
31. Skoglund RR. Reversible alexia, mitochondrial myopathy and lactic acidemia. *Neurology* 1979; 29: 717-720.
32. Montagna P, Gallassi R, Medori R, et al. MELAS syndrome: characteristic migrainous and epileptic features and maternal transmission. *Neurology* 1988; 38: 751-754.
33. Eleff S, Kenneway NG, Buist NR, et al. 31P NMR study of improvement in oxidative phosphorylation by vitamins K3 and C in a patient with a defect in electron transport at complex III in skeletal muscle. *Proc Natl Acad Sci USA* 1984; 81: 3529-3533.
34. Arts WFM, Scholte HR, Bogaard JM, et al. NADH-CoQ reductase deficient myopathy: successful treatment with riboflavin. *Lancet* 1983; 2: 581-582.
35. Askanas V, Engel WK, Kwan HH, et al. Autosomal dominant syndrome of lipid neuromyopathy with normal carnitine: successful treatment with long-chain fatty-acid-free diet. *Neurology* 1985; 35: 66-72.
36. Feit H, Kirkpatrick J, Van Woert MH, Pandian G. Myoclonus, ataxia, and hypoventilation: response to L-5-hydroxytryptophan. *Neurology* 1983; 33: 109-112.
37. Bresolin N, Bet L, Binda A. Clinical and biochemical correlations in mitochondrial myopathies treated with coenzyme Q10. *Neurology* 1988; 38: 892-899.
38. Mastaglia FL, Thompson PL, Papadimitriou JM. Mitochondrial myopathy with cardiomyopathy, lactic acidosis and response to prednisone and thiamine. *Aust NZ J Med* 1980; 10: 660-664.
39. Przyemmel H. Therapy of mitochondrial disorders. *J Inher Metab Dis* 1987; 10: 129.
40. Curless RG, Flynn J, Bachynski B, et al. Fatal metabolic acidosis, hyperglycemia, and coma after steroid therapy for Kearns-Sayre syndrome. *Neurology* 1986; 36: 872-873.

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Familial Mediterranean fever in six Australian children

Patrick J. Moore, Albert Mansour, John D. McDonald, Andrew Kemp, K. Ramanand Kamath and Stuart F.A. Dorney

ABSTRACT Six Australian children fulfilled the diagnostic criteria for familial Mediterranean fever. None had a family history of the disease, but five children came from ethnic groups that typically were associated with the disease. The symptoms commenced before five years of age in all the children, and three children underwent unnecessary operations because of the symptoms of recurrent fever and abdominal pain. All six children benefited from colchicine prophylaxis by mouth. More cases can be expected to be recognized in Australia because of the large number of Australian children with a Mediterranean heritage.

(Med J Aust 1989; 151: 108-110)

Familial Mediterranean fever, or familial paroxysmal polyserositis, is a rare autosomal recessive disease of unknown aetiology which mainly affects persons from countries that border the eastern Mediterranean sea.¹ It is characterized by repeated, self-limited attacks of fever and serositis (peritonitis, pleuritis and/or synovitis). Less-common manifestations involve the skin, eyes and pericardium. Attacks occur unpredictably and may be associated with significant morbidity, but mortality is increased only in those patients who develop amyloidosis.

Many series of patients with familial Mediterranean fever have been reported from the Mediterranean countries and the United States,²⁻⁶ and two cases of familial Mediterranean fever have been reported in Australian adults.^{7,8} However, we are unaware of any previous reports that have involved Australian children.

We have diagnosed familial Mediterranean fever in six Australian children during the last 10 years. We have reported them to bring this disorder to the attention of Australian medical practitioners who care for children because, for many of the children, the diagnosis was delayed for years, during which time many unnecessary investigations and operations were performed. As it is a treatable disorder, early diagnosis can prevent much suffering.

Clinical records

The clinical features of our six patients are summarized in the Table. There were four boys and two girls; no two children were from the same family. None of the families had a history of familial Mediterranean fever, but five children came from ethnic groups that commonly are associated with the disorder: four children were of Mediterranean origin and one child was of

Armenian origin. The other child had one Dutch parent and one English parent. The age of onset of the symptoms ranged from 1.25 to five years (mean, three years of age) and the time between onset and diagnosis varied from one to eight years (mean, 4.75 years).

All the children suffered typical recurrent attacks of fever and abdominal pain, with four children having pleuritic symptoms and three children having joint involvement as well. The interval between the attacks ranged from one to two weeks, to two to three months. One child's joint symptoms were dominant and for some time he was thought to have juvenile rheumatoid arthritis. Four patients were labelled as having various other disorders that were associated with recurrent abdominal pain before familial Mediterranean fever was suspected. Three patients underwent a total of four unnecessary operations: one child underwent a tonsillectomy, one child underwent an appendectomy and one girl underwent both a tonsillectomy and a laparotomy for suspected intestinal malrotation. Extensive investigations were performed to exclude other disorders that were capable of explaining the episodes.

All six children showed dramatic responses to prophylactic colchicine therapy by mouth, with the disappearance of the attacks of fever and serositis. Two children, who became non-compliant, suffered subsequent relapses, but their symptoms declined again after the reinstitution of the colchicine therapy. No serious side-effects have occurred so far.

One of the patients, Case 4, suffered hypertension during his attacks. Estimations were made of his 24-hour urinary catecholamine levels which were found to be elevated. This patient, and one other, had a mildly raised urinary protein excretion rate.

Discussion

Familial Mediterranean fever first was recognized as an entity in 1958,⁹ although reports that described similar disorders under various names had appeared from as early as 1908.¹⁰⁻¹⁵

The diagnosis of familial Mediterranean fever is based on six clinical criteria: short attacks of fever which occur at varying intervals; painful manifestations in the abdomen, chest, joints or skin which accompany the fever; the absence of any other causative factor or pathological finding *in vivo* or at post-mortem examination that is capable of explaining the condition; amyloidosis, clinically of the nephropathic type, and pathologically of the perireticulin type; features of autosomal recessive inheritance; and a prevalence in persons of Mediterranean stock, especially Sephardic Jews and Armenians.¹ The first three criteria must be met for a diagnosis to be made. All our patients fulfilled these criteria, and five patients also were of Mediterranean stock. A syndrome that is similar to familial Mediterranean fever has been reported in the Dutch,¹⁶ and our other patient had one Dutch parent. The fact that all our patients showed dramatic responses to colchicine prophylaxis lends support

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