“Mitochondrial myopathy” or mitochondrial disease? EEG, ERG, VEP studies in 13 children

ANN HARDEN, G PAMPIGLIONE, A BATTAGLIA*

From the Department of Clinical Neurophysiology, The Hospital for Sick Children, Great Ormond Street, London, UK

SUMMARY Neurophysiological investigations (EEG, ERG, VEP) were carried out in 13 patients with proven “mitochondrial myopathy”. There were nine girls and four boys. Varied abnormalities were seen in the EEGs of all cases, and in one patient unusual repetitive bursts of irregular slow waves and spikes were observed. The ERG was abnormal in five of the 12 cases tested, while the VEP (flash) was definitely abnormal in six out of these 12 cases. These neurophysiological findings suggest some involvement of both the brain and the visual system. It seems therefore appropriate that this condition be considered a “mitochondrial disease” affecting many systems rather than only muscles.

Mitochondrial abnormalities in the muscle were first reported by Luft and co-workers¹ in a patient with a “hypermetabolic disorder” of non-thyroid origin. Although several years elapsed before the description of a second case,^{2,3} an extensive literature has since accumulated on mitochondrial abnormalities associated with a great variety of neuromuscular disorders.⁴⁻¹¹ The term “mitochondrial myopathy” is now used to describe a condition with short stature, low weight, mono or bilateral ptosis, ophthalmoplegia, pigmentary retinopathy, weakness of neck flexors and girdle muscles in particular, fatigability, ataxia and deafness.¹² Diagnosis is confirmed by muscle biopsy which shows “ragged red” fibres on Gomori trichome staining and striking changes with oxidative enzyme reactions. At electron microscopic level, grossly enlarged, distorted and bizarre mitochondria are seen.^{4,12}

Clinical and pathological aspects of “mitochondrial myopathy” have been extensively reported in the literature but electroencephalographic (EEG), electroretinographic (ERG) and visual evoked potentials (VEP) investigations were only men-

tioned on few occasions and as a minor detail. In the present study, neurophysiological investigations including EEG, ERG, and VEP are described in 13 children with proven “mitochondrial myopathy”. Details of the clinical and muscle biopsy aspects in these cases have been reported elsewhere as “mitochondrial cytopathy”.¹³

Material and Method

Thirteen patients aged 6 to 14 years were admitted to The Hospital for Sick Children over the period 1969-81. All of them were proved to have “mitochondrial myopathy” or “cytopathy” on both clinical and muscle biopsy findings. There were nine girls and four boys. EEG, ERG and VEP studies were performed with a total of 25 EEGs and 18 ERG plus VEPs. Nine patients had only one EEG while the others had two to six records. ERG and VEP studies were carried out in 12 of the patients (10 had a single test). A standard technique was used to record the EEG using silver/silver chloride electrodes attached to the scalp with collodion, according to measurements from bony landmarks.¹⁴ The EEGs were taken with either Offner type T or Grass 8-10 channel EEG apparatus, using respectively a time constant of 0.3 or 0.4 seconds, HF response linear to 70 c/s and a paper speed of 60, 30 or 15 mm/second. ERG and VEP studies were carried out with techniques already described elsewhere.^{15,16}

Results

EEG FINDINGS

The timing of the neurophysiological investigations in relation to the clinical events is given in fig 1. The age of onset of symptomatology varied from birth to ten years. The EEGs were taken from 1 to 13 years

Address for reprint requests: Dr G Pampiglione, Department of Clinical Neurophysiology, The Hospital for Sick Children, Great Ormond Street, London WC1N 3JH.

*Present address: Dr A Battaglia, Istituto di Neuropsichiatria Infantile, Università degli Studi di Pisa, Via dei Giacinti 2, 56018 Calambrone (Pisa), Italy.

Received 4 September 1981 and in revised form 24 February 1982.
Accepted 7 March 1982

Fig 1 Timing of neurophysiological investigations (EEG, ERG, VEP) in relation to clinical events in 13 cases of mitochondrial myopathy.

after the appearance of the first symptoms. In two cases follow-up studies extended over a period of several years. Seizures occurred in only two patients (cases 2 and 7) and were of both focal and grand mal type. The majority of patients were referred for neurophysiological investigations because of pigmentary retinopathy of variable degree, but other referral problems were retardation, seizures, anorexia, episodic vomiting and failure to thrive.

All EEGs showed abnormalities with a variable excess of irregular slow activity (2–7 Hz up to 200 microvolts) with patchy distribution. In addition, seven of the patients showed more specific abnormalities, such as multifocal sharp elements (cases 4 and 12), abnormal sensitivity to photic stimulation

(cases 1, 2, 7, and 10), or absence of normal rhythmic activities (cases 2, 5, 7, and 8). On eye closure the alpha rhythm was absent in four out of the 13 cases at the time of the first EEG. The mu rhythm was recognisable and well formed in eight of the 13 cases. Overbreathing was carried out in 11 patients and usually elicited a moderate increase in the amount and amplitude of the slow components over both hemispheres. During spontaneous sleep, occurring only in case 4, 14–6 positive spikes were frequently seen and on one occasion a generalised brief burst of high amplitude irregular slow waves mixed with spikes occurred. In four patients (cases 1, 2, 7, and 10) paroxysmal features were seen during photic stimulation (fig 2) at 12–20 flashes per second, accompanied by minimal clinical changes (whole body jerk) in only one patient (case 7).

In one patient (case 7) serial EEGs showed rather unusual features with multifocal abnormalities and an excess of slow activity more marked posteriorly than anteriorly. At times larger amplitude, isolated slow waves each lasting 0.5 second, reaching 200 to nearly 400 microvolts, appeared in the posterior temporal regions, more obvious on the left than on the right side and independent of eye closure. These waves reappeared at intervals of 1 to 10 seconds, without however constant periodicity (fig 3, top). In addition, sharp elements or spikes or both were seen particularly in the occipital region, facilitated by eye closure and markedly increased by photic stimulation, particularly at high rates of flickering. In the second EEG, taken 4 months after the first one, when the patient was 12 years old, the record

Fig 2 Left: Case 10 showing paroxysmal features during photic stimulation at 12–20 flashes per second. No obvious clinical changes were seen. Right: In case 7 paroxysmal features already seen in the resting record were facilitated by photic stimulation, and on this occasion were accompanied by a single body jerk.

Fig 3 Case 7 (top): This EEG shows slow activity more marked posteriorly than anteriorly and larger amplitude, isolated slow waves in the posterior temporal regions, more obvious on the left than on the right side. (bottom): On this occasion the EEG shows periodic bursts of large amplitude slow waves mixed at times with small sharp waves and/or spikes persisting in four EEGs taken over a period of 18 months.

Fig 4 ERG (recorded from a surface electrode on the bridge of the nose) and flash VEP (recorded from the mid-occipital region) in three patients. Top (Case 12): The ERG and VEP are both normal. Middle (Case 11): No ERG is present but the VEP is well defined, suggesting preservation of function of visual pathways from the macular region. Bottom (Case 13): The ERG is within normal limits but the usual earlier components (within first 100 ms) of the VEP are only poorly defined, in keeping with some loss of function of visual pathways or cerebral cortex. Stimulus at arrow. Both eyes stimulated simultaneously.

showed repetitive bursts of irregular large amplitude slow waves, reaching up to over 500 microvolts, mixed at times with sharp waves or spikes or both. These bursts lasting 1 to 3 seconds and recurring at intervals of 2 to 20 seconds showed either generalised or variable anterior-posterior predominance, but were not accompanied by any obvious clinical change. Such phenomena persisted in the subsequent three EEGs taken over an 18 month period (fig 3, bottom). A definite improvement however was seen in the sixth EEG, taken when the patient was almost 15 years old; there was a diminution in slow activity and of paroxysmal features with disappearance of the repetitive phenomena.

ERG AND VEP FINDINGS

The ERG was present and of usual amplitude and waveform in seven out of the 12 cases investigated. In three patients, no ERG was recognisable (cases 3, 8, and 11) while in the remaining two (cases 4 and 5) only a low amplitude ERG could be detected (fig 4). The VEP was present with well defined early components in six out of the 12 cases investigated. The usual early components were either absent or ill defined in five patients (cases 2, 3, 8, 9, and 13), while in the remaining patient (case 7) the VEP, although present, was of unusual configuration with enlarged components (fig 4). All the patients with abnormal ERG and VEP features had variable degrees of pigmentary retinopathy, but failing vision (such as night blindness or decreased visual acuity) occurred in only three patients.

Discussion

Height and weight below the third centile, muscular weakness particularly involving neck and girdle muscles, fatiguability, deafness, pigmentary retinopathy, ptosis, ophthalmoplegia and ataxia were the salient clinical features of these cases. They all showed abnormal mitochondria in skeletal muscle. Other cases have been reported in the literature with similar features, although classified in many different ways and with a very wide age range (from childhood to advanced adult age). The cases with mitochondrial myopathy and myoclonic phenomena described by Fukuhara *et al*¹⁷ and Fitzsimons *et al*¹⁸ with extensive bibliography are probably a different disorder.

Although various metabolic derangements have been demonstrated¹⁹⁻²² nothing is known about the underlying cause of "mitochondrial myopathy".²³ In previous reports of the literature, it has been suggested that the different age of onset of "mitochondrial myopathy", the increase of CSF protein and the spongiosis of the central nervous system found at

necropsy^{23, 24} and by computed tomography²⁵ suggest a slow virus infection in the pathogenesis of this condition. The repetitive phenomena seen in the EEG of one of our cases (case 7) are somewhat reminiscent of subacute sclerosing panencephalitis and therefore suggestive of a slow virus infection, but the evidence is poor. The EEGs of all our patients showed various degrees of abnormality, indicating some cerebral involvement in this disorder. EEG studies were only rarely performed on the cases reported in the literature, the findings being described as either "normal" or showing "diffuse slow activity with or without discharges": such EEG descriptions however were extremely brief and comparison with our findings was not possible.

The abnormal ERG findings in five of our patients are of interest and are in keeping with variable degrees of retinal involvement. The absence of an ERG does not necessarily imply total loss of retinal function and in fact some of our patients with no ERG had a near normal VEP, presumably because the macular region was little affected. With such relatively high incidence of ERG abnormality, it seems likely that the poor VEP and poor vision seen in some of our patients were due to retinal damage, though lesions in the optic pathways or visual cortex cannot be excluded.

"Mitochondrial myopathy" has a variety of clinical features some of which are in common with those of abetalipoproteinaemia, Refsum's disease, myasthenia gravis, myotonic dystrophy, myotubular myopathy, Cockayne's syndrome, Fisher syndrome and some vascular or neoplastic brain stem lesions. Variable amounts of slow activity are reported to occur in the EEG of patients with myasthenia gravis and myotonic dystrophy;²⁷ in the latter, in addition, low frequency alpha rhythm, focal epileptiform activity and low voltage activity have also been reported.²⁸ In the very few cases of Cockayne's syndrome reported so far in the literature, in only one case²⁹ an EEG was taken and said to be normal; ERG and VEP studies were never performed. In the cases of Fisher syndrome (both adults and children) with EEG investigations there were either no abnormalities or variable amounts of slow components.³⁰⁻³² No EEG abnormalities have yet been reported in patients with myotubular myopathy, abetalipoproteinaemia and Refsum's disease. The electroretinogram and visual evoked potentials may be altered in diseases with retinal involvement, such as abetalipoproteinaemia and Refsum's disease, but in the literature there are no studies in childhood.

In conclusion, the EEG, ERG, VEP findings in "mitochondrial myopathy" show a variable involvement of brain and visual system suggesting a

wider distribution of abnormal mitochondria than just in the muscular system. It seems therefore more appropriate that this condition should be considered a "mitochondrial disease" rather than a myopathy. Histochemical and electron microscopic studies of brain, retina and other tissues in such patients would offer additional evidence.

We are indebted to our clinical colleagues particularly to Dr John Wilson and Dr EM Brett for referring the patients and to Dr B Lake for the histopathology.

References

- Luft R, Ikkos D, Palmieri G, Ernster L, Afzelius B. A case of severe hypermetabolism of nonthyroid origin with defect in the maintenance of mitochondrial respiratory control: a correlated clinical, biochemical and morphological study. *J of Clin Inv* 1962;**41**:1776.
- Haydar NA, Conn HL, Affi A, Wakid N, Ballas S, Fawaz K. Severe hypermetabolism with primary abnormality of skeletal muscle mitochondria: functional and therapeutic effects of chloramphenicol treatment. *Ann Intern Med* 1971;**74**:548-58.
- Di Mauro S, Bonilla E, Lee CP, *et al.* Luft's disease: further biochemical and ultrastructural studies of skeletal muscle in the second case. *J Neurol Sci* 1976;**27**:217-32.
- Olson W, Engel WK, Walsh GO, Einaugler R. Oculocraniosomatic neuromuscular disease with "ragged red" fibers. *Arch Neurol* 1972;**26**:193-211.
- Schneck L, Adachi M, Briet P, Wolintz A, Volk BW. Ophthalmoplegia plus with morphological and chemical studies of cerebellar and muscle tissue. *J Neurol Sci* 1973;**19**:37-44.
- Morgan-Hughes JA, Mair WGP. Atypical muscle mitochondria in ocular skeletal myopathy. *Brain* 1973;**96**:215-24.
- Shy GM, Gonatas NK, Perez M. Two childhood myopathies with abnormal mitochondria. I. Megaconial myopathy. II. Pleoconial myopathy. *Brain* 1966;**89**:133.
- Shy GM, Silberberg DH, Appel SH. A generalised disorder of nervous system, skeletal muscle and heart resembling Refsum's disease and Hurler's syndrome: 1-Clinical, pathologic and biochemical characteristic. *Am J Med* 1967;**42**:163-8.
- Price HM, Gordon GB, Munsat TL, Pearson CM. Myopathy with atypical mitochondria in type 1 skeletal muscle fibres: a histochemical and ultrastructural study. *J Neuropathol Exp Neurol* 1967;**26**:475.
- Okamura K, Santa T, Nagae K, Omae T. Congenital ocular skeletal myopathy with abnormal muscle and liver mitochondria. *J Neurol Sci* 1976;**27**:79-91.
- Gonatas NK, Evangelista I, Martin G. A generalised disorder of nervous system, skeletal muscle and heart resembling Refsum's disease and Hurler syndrome: 2-Ultrastructure. *Am J Med* 1967;**42**:169-78.
- Dubowitz V. *Muscle disorders in childhood*. London: WB Sanders, 1978.
- Egger J, Lake BD, Wilson J. Mitochondrial cytopathy. A multisystem disorder with ragged red fibres on muscle biopsy. *Arch Dis Childh* 1981;**56**:741-52.
- Pampiglione G. Some anatomical considerations upon electrode placement in routine EEG. *Proceedings and Journal of the Electrophysiological Technologists Association* 1956;**7**:1-11.
- Harden A. and Pampiglione G. Neurophysiological approach to disorders of vision. *Lancet* 1970;**1**:379-85.
- Harden A, Picton-Robinson N, Bradshaw K, Pampiglione G. Ten years' experience of ERG/VEP/EEG studies on visual disorders in paediatrics. In: Barber C, ed. *Evoked Potentials*, Lancaster: MTP Press Ltd, 1980;**28**:257-66.
- Fukuhara N, Tokiguchi S, Shirakawa K, Tsubaki T. Myoclonic epilepsy associated with ragged-red fibres (mitochondrial abnormalities): disease entity or a syndrome? *J Neurol Sci* 1980;**47**:117-33.
- Fitzsimons RB, Clifton-Bligh P, Wolfenden WH. Mitochondrial myopathy and lactic acidemia with myoclonic epilepsy, ataxia and hypothalamic infertility: a variant of Ramsay-Hunt syndrome? *J Neurol Neurosurg Psychiatry* 1981;**44**:79-82.
- Di Mauro S, Schotland DL, Bonilla E, Lee CP, Gambetti PL, Rowland LP. Progressive ophthalmoplegia, glycogen storage and abnormal mitochondria. *Arch Neurol* 1973;**29**:170-9.
- Di Mauro S, Mendell JR, Sahenc Z, *et al.* Fatal infantile mitochondrial myopathy and renal dysfunction due to cytochrome C oxidase deficiency. *Neurology (Minneapolis)* 1980;**30**:795-804.
- Spiro AJ, Moore CL, Prineas JW, Strasberg PM, Rapin A. A cytochrome related inherited disorder of the nervous system and muscle. *Arch Neurol* 1970;**23**:103-12.
- Hackett TN, Bray PF, Ziter FA, Nyham WL, and Creer KM. A metabolic myopathy associated with chronic lactic acidemia, growth failure and nerve deafness. *J Pediatr* 1973;**83**:426-31.
- Direkze M, Campell G. Further studies on progressive external ophthalmoplegia. *Acta Neurol Scand* 1975;**51**:245-8.
- Castaigne P, Laplane D, Fardeau M. Myopathie avec anomalies mitochondriales localisées aux fibres de type 1: documents cliniques, histochimiques et ultrastructuraux une forme atrophique diffuse à debut oculaire. *Rev Neurol (Paris)* 1972;**126**:81-96.
- Daroff RE, Solitaire GB, Pincus JH. Spongiform encephalopathy with chronic progressive external ophthalmoplegia: central ophthalmoplegia mimicking ocular myopathy. *Neurology (Minneapolis)* 1966;**16**:161-9.
- Bertorini T, Engel WK, Di Chiro G, Dalakas M. Leucoencephalopathy in oculocraniosomatic neuromuscular disease with ragged red fibres: Mitochondrial abnormalities demonstrated by computerised tomography. *Arch Neurol* 1978;**35**:643-7.
- Kiloh LG, McComas AJ, Osselson JW. *Clinical electroencephalography*. 3rd Ed, London, Butterworths, 1972.

- ²⁸ Beijersbergen RSHM, Kemp A, Storm Van Leeve W. EEG observations in dystrophia myotonica (Curschmann-Steinert). *Electroencephalogr Clin Neurophysiol* 1980;**49**:143–51.
- ²⁹ MacDonald WB, Fitch KD, Lewis IC. Cockayne's syndrome: An heredofamilial disorder of growth and development. *Pediatrics* 1960;**25**:997.
- ³⁰ Bell W, Van Allen M, Blackman J. Fisher syndrome in childhood. *Develop Med Child Neurol* 1970;**12**:758–66.
- ³¹ Palmucci L, Brignolio F, Doriguzzi C, Ravetti C, Schiffer D. Fisher syndrome. Presentation of a clinical case. *Acta Neurol (Napoli)* 1978;**33**:270–2.
- ³² Becker WJ, Watters GV, Humphreys P. Fisher syndrome in childhood. *Neurology (NY)* 1981;**31**:555–60.