Forearm P-31 Nuclear Magnetic Resonance Spectroscopy Studies in Oculopharyngeal Muscular Dystrophy

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ABSTRACT: Five siblings with autosomal dominant oculopharyngeal muscular dystrophy (OPMD) underwent P-31 Nuclear Magnetic Resonance Spectroscopy studies of forearm flexor muscles. Mean values of PCr/(PCr + Pi) in the patients were reduced ($p = 0.01$) and pH elevated ($p = 0.02$) in resting muscle when compared to controls. During exercise PCr/(PCr + Pi) fell quickly to values less than controls ($p < 0.0001$) despite submaximal exercise output and developed exercise-induced acidosis which exceeded that of controls ($p = 0.05$). Acidosis recovered slowly despite relatively normal recovery of PCr/(PCr + Pi) following exercise. Within the patient group, however, one member had normal resting, exercise and recovery values. The studies suggest that OPMD is a more widespread disorder of striated muscle than clinically appreciated. The pattern of findings observed in OPMD differs from those identified in denervation, disuse and mitochondrial myopathy.

RÉSUMÉ: Spectroscopie au P-31 par résonance magnétique nucléaire de l'avant-bras dans la dystrophie musculaire oculopharyngée. Cinq membres d'une fratrie atteints de dystrophie musculaire oculopharyngée (DMOP) dont l'hérédité est autosomale dominante, ont subi une étude des muscles fléchisseurs de l'avant-bras au moyen de la spectroscopie par résonance magnétique nucléaire. Les valeurs mayennes de PCr/(PCR + Pi) chez les patients étaient réduites ($p = 0.01$) et le pH élevé ($p = 0.02$) dans les muscles au repos comparés aux contrôles. Pendant l'exercice le PCr/(PCr + Pi) s'est abaissé rapidement à des valeurs inférieures à celles des contrôles ($p < 0.0001$) malgré un niveau d'exercice submaximal et ils développé une acidose induite par l'exercice qui était supérieure à celle des contrôles ($p = 0.05$). L'acidose a régressé lentement malgré une récupération relativement normale du PCr/(PCr + Pi) après l'exercice. Cependant, un individu parmi le groupe des patients avait des valeurs normales au repos, à l'exercice et lors de la récupération. Ces études suggèrent que la DMOP est une affection du muscle strié qui est plus répandue que ne le laisse soupçonner la clinique. Le tableau observé dans la DMOP est différent de ceux indentifiés dans la dénervation, la non-utilisation et la myopathie mitochondriale.

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Oculopharyngeal muscular dystrophy (OPMD) is an autosomal dominant disorder first described in 1915 by Taylor.[1] The characteristic clinical features include 'late' onset ptosis (40s), dysphagia, ophthalmoplegia and variable proximal limb weakness. Most cases reported have an autosomal pattern of inheritance with a large North American pedigree having arisen from a single French Canadian ancestor.[2] An autosomal recessive pattern of inheritance has also been described.[3] Ultrastructural studies have described abnormal mitochondria suggesting mitochondrial dysfunction, perhaps similar to the 'mitochondrial myopathies'.[4-6] To our knowledge, P-31 NMRS studies have not been previously described.

We examined 10 members from two generations within a single family with this disorder. Five siblings were clinically affected. P-31 NMRS studies were obtained in forearm flexor muscles of the 5 affected members prior to, during and following an exercise protocol.

Methods

The methods employed for P-31 NMRS in our laboratory have been described[7] and are similar to those used in other reports.[8-10] The subject inserted a forearm into the 26 cm bore of the 1.89 T superconducting magnet (Oxford Systems; TMR-32) placing the forearm flexor muscle group over a 2.5 cm or 4 cm surface coil (choice governed by forearm size) embedded in a non-metallic arm rest. The magnet was shimmed on the proton signal at 80.3 MHz and P-31 NMRS, using the same doubly

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tuned coil, at 32.5 MHz with pulses applied at 2.256 second intervals. For resting studies, 128 accumulations were averaged. For exercise and recovery studies, 32 accumulations were used except for the first 4 spectra during recovery where 16 accumulations were obtained.

The exercise protocol required the patient to squeeze a rubber bulb connected to a manometer to 100 mmHg every 2 seconds for 5 minutes then to 300 mmHg (or maximum if unable) for a further 2.5 minutes. Recovery spectra were gathered for 15 minutes following the above. The results were compared, using a two-tailed Student's T-test, with a control group of normal volunteers (n = 26). These subjects were able to complete the protocol as required. Mean age was 34 ± 7 years (M16; F10). Work output was not "normalized" to pre-contraction muscle power so that: (i) any inability to satisfy the protocol could be identified by the bulb pressures attained and the consequent decline in PCr/(PCr + Pi); (ii) our results could be compared with published data. The means in the patient group were obtained by using the single or mean (in patients with 2 studies) value for each category in each patient.

Results

Clinical Observations

Figure 1 illustrates the available family information. Table 1 summarizes the clinical information.

Patient 1 (JJ)

This 68-year-old female had longstanding ptosis and difficulty walking. Examination disclosed bilateral ptosis, mild weakness of ocular adduction and abduction with mild trunk and limb weakness. Additional problems included cervical and lumbar degenerative disc disease with lumbar spinal stenosis, carpal tunnel syndrome and hypertension. Concentric needle electrode recording from the right deltoid and supraspinatus muscles disclosed polyphasic, low amplitude and short duration motor units. A deltoid muscle biopsy revealed muscle fibers of variable size, a single necrotic fiber and Type 1 fiber predominance. Under electron microscopy occasional atrophic fibers and one regenerating fiber were observed. Several fibers had myelin figures and lipid bodies. The mitochondria were normal.

Patient 2 (CH)

This 56-year-old male had a twenty year history of ptosis and a ten year history of dysphagia, choking spells and recurrent pneumonia. Examination disclosed nasal speech, bilateral ptosis, and limitation of upgaze. The limb muscles had normal power and bulk. Brachioradialis, biceps and right quadriceps reflexes were reduced but other deep tendon reflexes were intact. Concentric needle EMG of the right deltoid and vastus lateralis muscles was normal. Esophageal manometry revealed low pharyngeal spike pressures and little peristaltic activity in the proximal esophagus.

Patient 3 (IB)

This 67-year-old female had ptosis and leg weakness for 7 years and dysphagia, choking and orthopnea for 15 years. Examination revealed nasal speech, bilateral ptosis, gaze limitation in all directions, weakness of the tongue and palate, and mild trunk and limb weakness. Concentric needle EMG of deltoid and first dorsal interosseous muscles disclosed

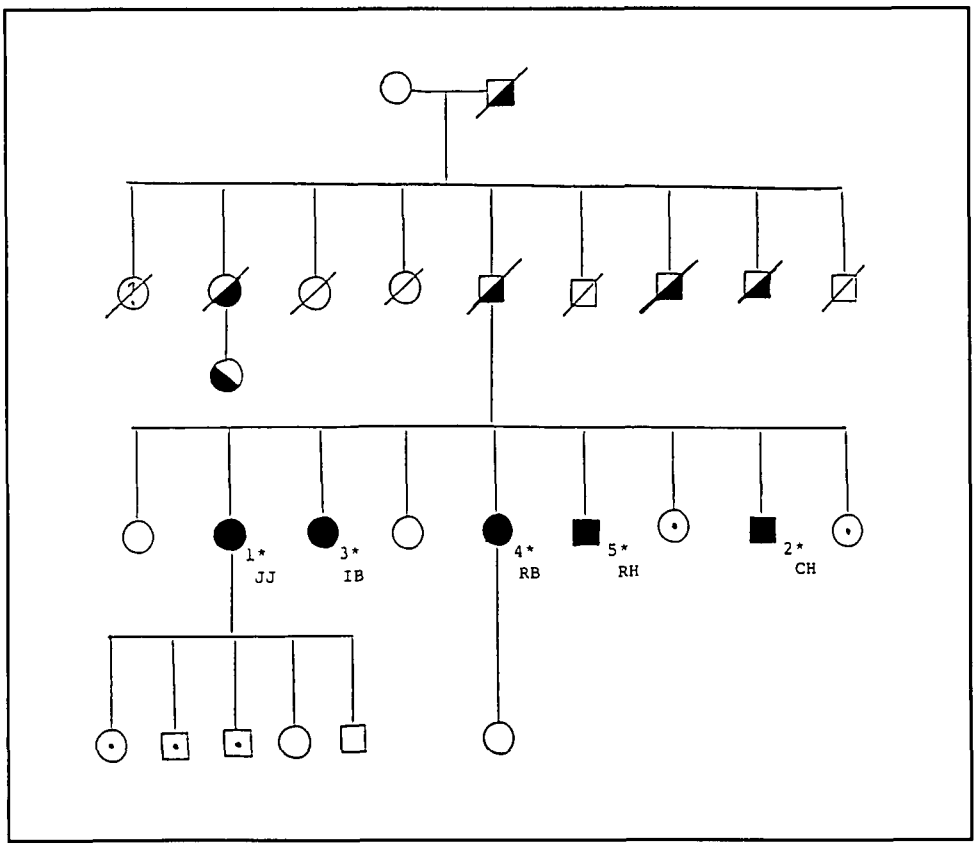

Figure 1 – Family tree. Asterisks and numbers refer to the cases studied in this report. Symbols: square - males; circles - females; filled symbol - examined, affected; open symbols - presumed unaffected by history; symbols with central dot - unaffected and examined; half filled symbol - presumed affected by history; / - dead.

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Table 1: Summary of Findings in Individual Patients

Case	Ptosis	Dysphagia	Weakness	CK	P-31 NMRS** Rest	P-31 NMRS** Exercise	Maximum Pressure*
1. (JJ)	+	–	+	590	↓PCr/SUM	not done	
2. (CH)	+	+	–	254 463		↓PCr/SUM ↓pH	180
3. (IB)	+	+	+	309		↓PCr/SUM ↓pH	60
4. (RB)	+	+	+	195	↓PCr/SUM	↓PCr/SUM	100
5. (RH)	+	–	+	143 155	normal studies		240

+ present; – absent; CK (creatine kinase) values expressed as U/L (normal 35-230; PCr/SUM-PCr/(PCr + Pi); ↓ reduction or increase ↑ exceeded controls
* Maximum bulb pressure achieved with squeezing (see methods). Expected pressure was 300 mmHg
SUM = (PCr + Pi)
** Only changes that differed from controls by 2 standard deviations are listed

scattered fibrillation potentials and positive sharp waves, runs of neuromyotonic discharges and polyphasic short duration motor unit potentials. In vastus lateralis muscle, excessive numbers of polyphasic motor unit potentials were the only abnormality. Esophageal manometry identified low pharyngeal spike pressures, poor coordination between the pharynx and cricopharyngeal sphincter, and an inert proximal esophagus.

Patient 4 (RB)

This 64-year-old female had noted ptosis and dysphagia since age 50 with more recent difficulty climbing stairs and in handgrip. On examination she had bilateral ptosis, upgaze limitation, nasal speech, facial weakness, distal and proximal limb weakness and absent deep tendon reflexes.

Patient 5 (RH)

This 62-year-old male had a two year history of ptosis and proximal limb weakness. Examination disclosed bilateral ptosis, mild facial weakness and mild lower limb proximal weakness. Deep tendon reflexes were absent.

P-31 NMRS Studies

Seven studies included 5 obtained through the rest, exercise and recovery protocol (4 patients) and two studies at rest only. Mean values of PCr/(PCr + Pi) were significantly lower than controls ($p = 0.01$) [Table 2]. In 2 studies (2 patients) this reduction exceeded 2 control standard deviations. PCr/(PCr + Pi) fell significantly below that of controls during early exercise ($p < 0.0001$) despite subnormal exercise output (reduced bulb-manometric pressures). pH of resting muscle exceeded that of controls ($p = 0.02$), but fell to significantly lower values ($p = 0.05$) shortly following maximum exercise and recovered more slowly than in controls. Figures 2 and 3 provide examples of these changes (Patient 2, study #1). Figure 4 illustrates the early excessive decline in PCr/(PCr + Pi) compared to pH with exercise (a) and the inappropriate acidosis post-exercise (b). In Patient 2, two complete studies were obtained 2 years apart with similar findings. One patient (Patient 5) had resting and exercise studies within the normal range, but exercise output was reduced. Findings in individual patients are given in Table 1. The ratio ATP/(PCr + Pi) did not differ from controls at rest.

Table 2: P-31 NMRS Results

Resting	Patients (N = 5)	Controls (N = 26)	Significance* (p value)
PCr/(PCr + Pi)	0.84 ± 0.03	0.87 ± 0.02	0.01
pH	7.11 ± 0.03	7.06 ± 0.04	0.02
MILD EXERCISE			
PCr/(PCr + Pi)	0.47 ± 0.18 (n = 4)	0.74 ± 0.06	< 0.0001
pH	7.08 ± 0.09	7.04 ± 0.05	NS
MAXIMUM EXERCISE			
PCr/(PCr + Pi)	0.39 ± 0.04 (n = 3)	0.48 ± 0.11	NS
pH	6.53 ± 0.32 (n = 4)	6.78 ± 0.22	0.05

Values are means ± SD
* 2-tailed Student's T-test

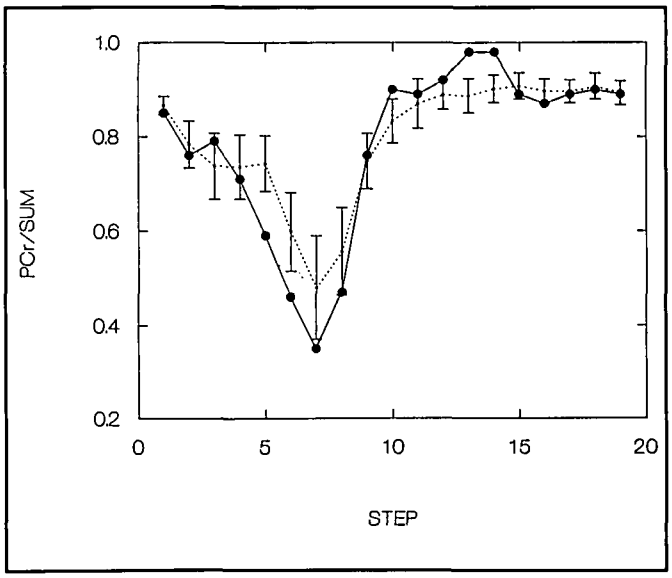

Figure 2 — Patient 2 (Study #1). Plot of PCr/(PCr + Pi) for each step of protocol. Step 1 - rest; steps 2 to 5 - light exercise; steps 6 and 7 - intense exercise; steps 8 to 19 - recovery. Dotted line represents pooled data from 26 normal controls (error is one SD above and below the mean). Note that the patient had an early fall in PCr/(PCr + Pi) exceeding that of controls.

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During exercise the ratio was usually preserved at the expense of PCr/(PCr + Pi), but did decline in 2 patients.

Discussion

Our patients exhibited clinical, electrophysiological and esophageal manometric features of autosomal dominant OPMD as described by Taylor,[1], Victor, Hayes and Adams,[11] Barbeau,[2] Murphy and Drachman,[12] and others.[13-15] It is likely that our family is a pedigree of that reported by Barbeau.[2] As in the above reports, patients had late onset ptosis and dysphagia with variable degrees of ophthalmoplegia, proximal limb involvement, and needle electromyographic findings consistent with a myopathic disorder including the abnormal spontaneous activity observed in one patient. Manometric esophageal recordings identified low pharyngeal spike pressures, incoordination of cricopharyngeal sphincter action and impairment of upper esophageal motility, as previously noted by Duranceau et al.[14] Muscle biopsy in one patient did not identify nuclear filamentous inclusions,[16-18] rimmed vacuoles[19] or mitochondrial abnormalities,[4-6] but the rather nonspecific findings in our case have been described in several previous reported cases with this disorder.[13,19] The P-31 NMRS studies provided three interesting findings: 1) A mild reduction in PCr/(PCr + Pi) and an increased pH in resting muscle. 2) Excessive exercise-induced intracellular muscle acidosis with slow recovery post-exercise. 3) An early and prominent fall in PCr/(PCr + Pi) with exercise. 4) Normal findings in one patient.

The forearm flexor muscles are not within the usual proximal site of clinical limb muscle involvement in OPMD. Four of our patients did have some clinical evidence of proximal weakness, and in Patients 1,3, and 4 there was mild evidence of more generalized limb involvement. In Patient 2, spectroscopy abnormalities were striking despite normal distal and proximal limb strength. The results suggest that OPMD is a widespread disorder of striated muscle. The explanation for variable expressivity is unclear. There are two[20,21] reports of an oculopharyngeal myopathy associated with distal limb involvement but their relationship to OPMD is unknown. Reduced muscle PCr/(PCr + Pi) is nonspecific and has been described in Duchenne muscular dystrophy,[22-25] mitochondrial myopathy,[8,26-28] and denervation,[7,29] but not forearm disuse.[7]

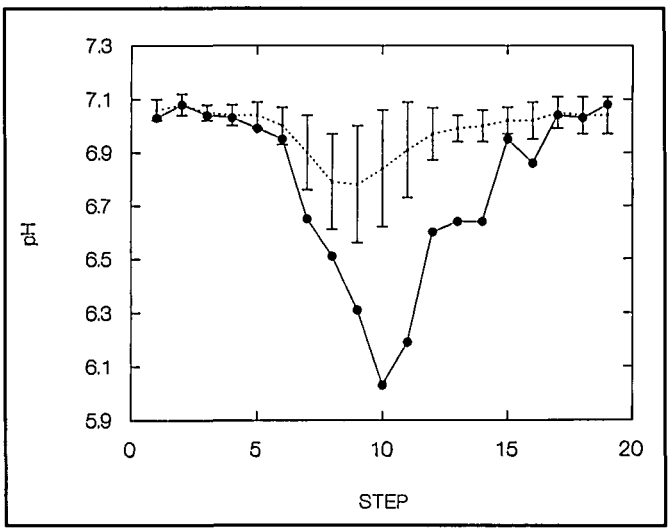
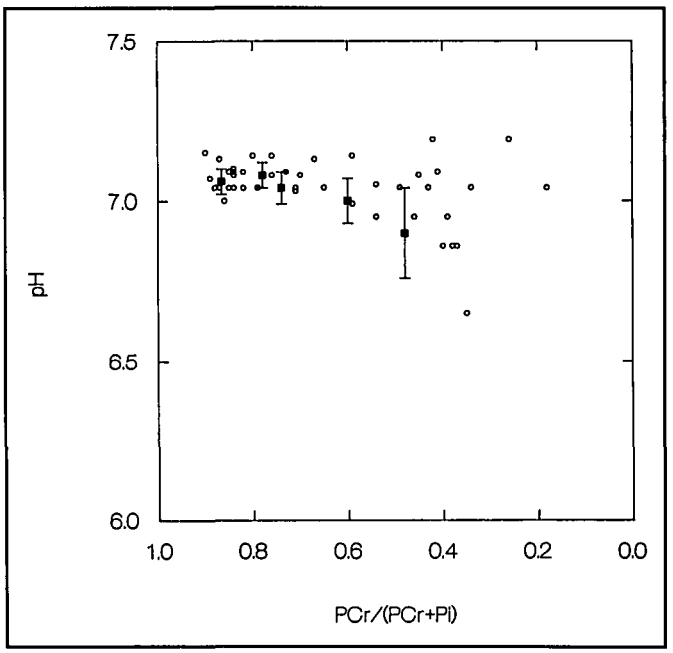
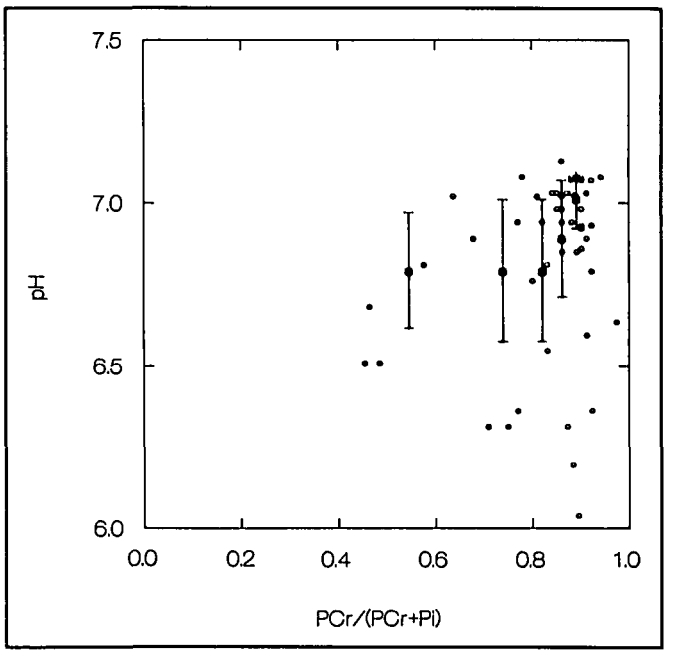


Figure 3 — As in Figure 2, plot of pH for each step of protocol compared with control data. Note the severe exercise-induced acidosis with slow recovery.



A



B

*Figure 4 — Plot of PCr/(PCr + Pi) versus pH during rest and exercise (**A**) and recovery (**B**). The solid squares are means (± SD) from 26 normal controls. Results from OPMD patients are indicated by circles. Note the frequency of low PCr/(PCr + Pi) values during exercise (**A**) and the low pH values during recovery (**B**).*

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There may be several explanations for these findings based on our current knowledge of dystrophic muscle: a reduced number of functioning fibers; a redistribution of muscle fiber types; a population of abnormal but functioning fibers; a combination of the above. Excitation-contraction ATPase requirements of bioenergetic reserves in a depopulated pool of functional muscle fibers may have exceeded normal in even low-level work states, i.e. at 'rest'. Increased PCr flux by activated myofibrillar creatine kinase from increased ADP[30] may have reduced the phosphorylation potential as estimated by PCr/(PCr + Pi).[31] Alternatively, the dystrophic process may have targeted critical enzymatic steps in oxidative phosphorylation or consumed an inordinate share of bioenergetic resources in an attempt to repair damaged muscle fibers. Acceleration of ATPase needs during light exercise would lead to PCr consumption in excess of normal expectations – hence our findings of subnormal exercise output and an early excessive fall in PCr/(PCr + Pi). Our work output was not "normalized" to pre-exercise grip strength so that this inability to meet "normal" work demand could be demonstrated. The early fall in PCr/(PCr + Pi), compared to controls may have been a consequence. We did not observe a reduction in the rate of PCr/(PCr + Pi) recovery following exercise as described in mitochondrial myopathy.[8,26] High energy phosphate content may be lower in Type I fibers,[32] but Type I content in limb muscles is quite variable ranging between 30-80%.[33] In Patient 1, Type I fiber predominance was suggested by deltoid muscle biopsy. It is unknown whether similar findings might have been observed in forearm flexor muscles. Predilection of both fiber types in OPMD has been noted.[34] The absence of prominent forearm weakness and wasting may suggest that abnormal functioning fibers, rather than reduced fiber numbers account for the early fall in PCr/(PCr + Pi).

The magnitude of the exercise-induced lactic acid deficit[35] is a function of muscle work requirements.[36] The work requirements in our patients likely exceeded cellular bioenergetic resources. Although pH during recovery was lower than expected for the PCr/(PCr + Pi) ratio, this may be a result of a lag in pH correction following excessive work demands. On the other hand, all the pH findings, especially the alkalosis at rest, may not be explained entirely on this basis. Resting muscle in Duchenne muscular dystrophy had an elevated pH in two studies reported[25,37] but not in reports by others.[24] Youkin et al.[25] speculated that elevated pH was secondary to creatine depletion rather than increased creatine kinase activity, but the precise explanation remains unclear. Denervated muscle also had an elevated pH, but exercise acidosis was only mild.[29] Recently Hahn et al.[38] have reported similar pH findings in a family with Becker's muscular dystrophy. Our studies also differ from the modest acidosis and its rapid recovery reported in mitochondrial myopathy[8] and thus do not support descriptions of OPMD which suggest mitochondrial myopathy or neurogenic etiology.[39,40] Excessive intracellular acidosis has also been previously described in 'post viral muscle fatigue syndrome'[41] but this entity is controversial.

Although the individual changes observed in P-31 NMRS studies of OPMD may not be unique, their combination may be. Our studies were done on siblings, raising the possibility that the results may not be representative of all patients with OPMD. The potential usefulness of the technique, as in other neuromuscular disorders with abnormal findings, will likely be in the serial evaluation of prospective therapeutic trials – improvement in bioenergetic indices might precede a favourable clinical response. Some trials have already been attempted along these lines.[24]

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