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MITOCHONDRIAL DYSFUNCTION IN MYASTHENIA GRAVIS

REPORT OF A CASE

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SUMMARY — The case of an 11-year-old boy with external ophtalmoparesia, tetraparesia and bilateral eyelid ptosis is reported. He was 7-years-old when first symptoms appeared. Anticholinesterasic drugs were used. He was submitted to muscle biopsy. The results of histochemistry analysis showed storage of granulous material at the subsarcolemmal region of muscle fibers by SDH. Increase in the number of mitochondria with electron dense bodies was found at electron microscopy. Anticholinesterasic drugs administration was interrupted and consequently he got worse, and bouts of dyspnea occurred. Due to this worsening anticholinesterasic agents were reintroduced together with prednisone, and he improved. Due to clinical and histological expressions we think it is possible that morphological mitochondrial alterations may occur also in myasthenia gravis.

Disfunção mitocondrial na miastenia grave: relato de caso.

RESUMO — É relatado o caso de um paciente de 11 anos de idade com oftalmoparesia extrinseca, ptose palpebral bilateral e tetraparesia desde os 7 anos de idade. A concentração de anticorpos contra receptor de acetilcolina por radioimunoensaio foi 0,6 nM/1; a pesquisa de anticorpos contra músculo estriado foi negativa. Exame eletromiográfico revelou decremento de 26,1%. Foi tratado com brometo de piridostigmina na dose de 60 mg/d. Submetido a biópsia de tecido muscular estriado (biceps braquial esquerdo) com avaliações por métodos histoquímicos e microscopia eletrônica, que revelaram: acúmulos de mitocôndrias na região subsarcolemal na coloração pela SDH; aumento da concentração de mitocôndrias e corpúsculos eletrodensos à microscopia eletrônica; esses achados são sugestivos de miopatia mitocondrial. Em conseqüência da interrupção das drogas anticolinesterásicas ocorreu piora das manifestações deficitárias, disfagia e dispnéia. Reintroduzidos os anticolinesterásicos, associados a imunossupressão com corticosteróides, houve melhora e retomada pelo paciente de suas atividades habituais. Destarte, é discutido o caráter inespecífico das alterações morfogenéticas e disfunções de mitocôndrias em outras patologias neuromusculares, incluindo a miastenia grave, como neste caso em particular.

The metabolic machinery of the cell is the basis for life maintenance of aerobic organisms [2]. At mitochondria occur the aerobic metabolic cycle with the main source of the energy [2,3,4]. A higher income of energetic cycle is obtained by redox potential. The importance of mitochondria is verified at the oxidative metabolism [12], and at genetic aspects [4,13] and morphogenesis [11]. The mitochondrial cytopathy shows the involvement of multiple functions of the body [3,5,7]. Nevertheless, the majority of morphologic mitochondrial alterations are nonspecific and occur in several diseases [9,11,12]. An evaluation of the bearing of mitochondria in a patient who presented acquired extrinsic ophthalmoparesia, tetraparesia and bouts of dyspnea owing interruption of anticholinesterasic agents and prednisone, drugs usually used in patients with myasthenia gravis, is presented in this report.

This work was achieved at the Division of Neurology, Hospital das Clinicas (HC), Faculty ef Medicine, University of São Paulo (FMUSP).

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CASE REPORT

DA, a Brazilian boy, 11 years old (Reg. 2470751-B, IIC, FMUSP) four years prior to admission developed ptosis of the left eyelid, and was twice submitted to surgery for correction without results. One year ago he developed ptosis on the right eyelid and presented proximal weakness in the four limbs. A few months later dysphonia and dyspnea crises occurred frequently and he obtained moderate improvement with the use of the pyridostigmine bromide (PB) (60 mg/d). Subsequently he got worse due to interruption of treatment. Because of that we introduced PB and prednisone (10 mg/d). Physical examination revealed bilateral ptosis and proximal tetraparesia. Routine laboratory tests were normal. Serum concentration of antibodies against skeletal muscle was 0.6 nM/1 (normal value 0.6 nM/1 by anti-IgG radioimmunoassay with dissociation constant of 1068 x 10^{-9} M). The electrophysiological study showed a decremental gauge of 26.1% (Fig. 1). Respiratory function was normal; no myasthenic pattern was found at the flow/volume respiratory curve. Muscle biopsy (left biceps braquialis muscle) showed storage of granulous material at the subsarcolemmal region of the muscle fibers by SDH on histochemical evaluation (Fig. 2). The electron microscopy (EM) revealed an increased number of mitochondria with inner electron dense bodies (Fig. 2).

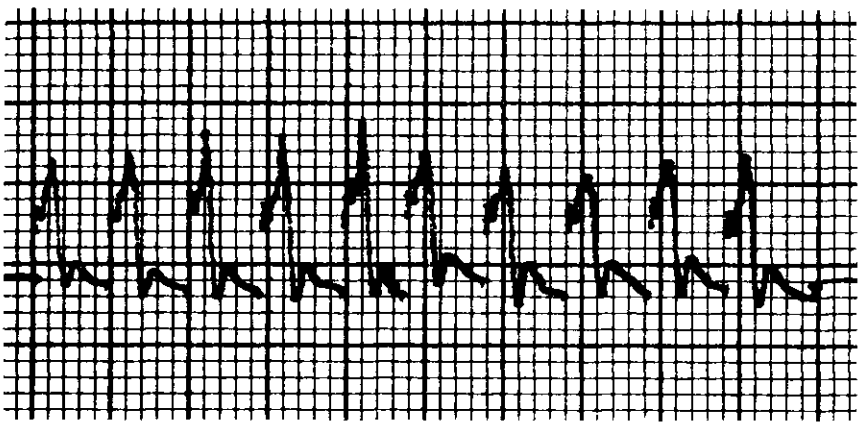

Fig. 1 — Case DA. Electrophysiological evaluation shows decremental gauge of 26.1% (normal value 10%) in the repetitive stimulation test of the superior left eyelid (calibration: 500 uV/20m seg). The motor and sensivity speed conduction and 'F wave' are normal.

COMMENTS

In the case reported we found mitochondrial abnormalities: increase in their number and the presence of granulous subsarcolemmal material specified as electron dense bodies by EM. Those alterations are considered nonspecific abnormalities as long as observed in a number of different primary neuromuscular disorders [6,11,14]. Our patient presented clinical involvement compatible with myasthenia gravis. Several mitochondrial abnormalities are verified in mitochondrial cytopathies and in some muscle diseases [6,12,14]. Oxidative dysfunctions in the respiratory chain occur at several steps, with clinical heterogeneity in their presentation. At the same time, metabolic evaluation of oxidative metabolism in some patients with myasthenia gravis showed a defect of the mechanism that controls the respiration rate of mitochondria to maintain the energy requirement of the cell [8]. This was reported by Meiger in a case of myasthenia gravis which showed decreased phosphorylative efficency indicating low coupling [8].

In our myasthenic patient the microscopic alterations of mitochondria were considered nonspecific abnormalities as found in several neuromuscular dysfunctions.

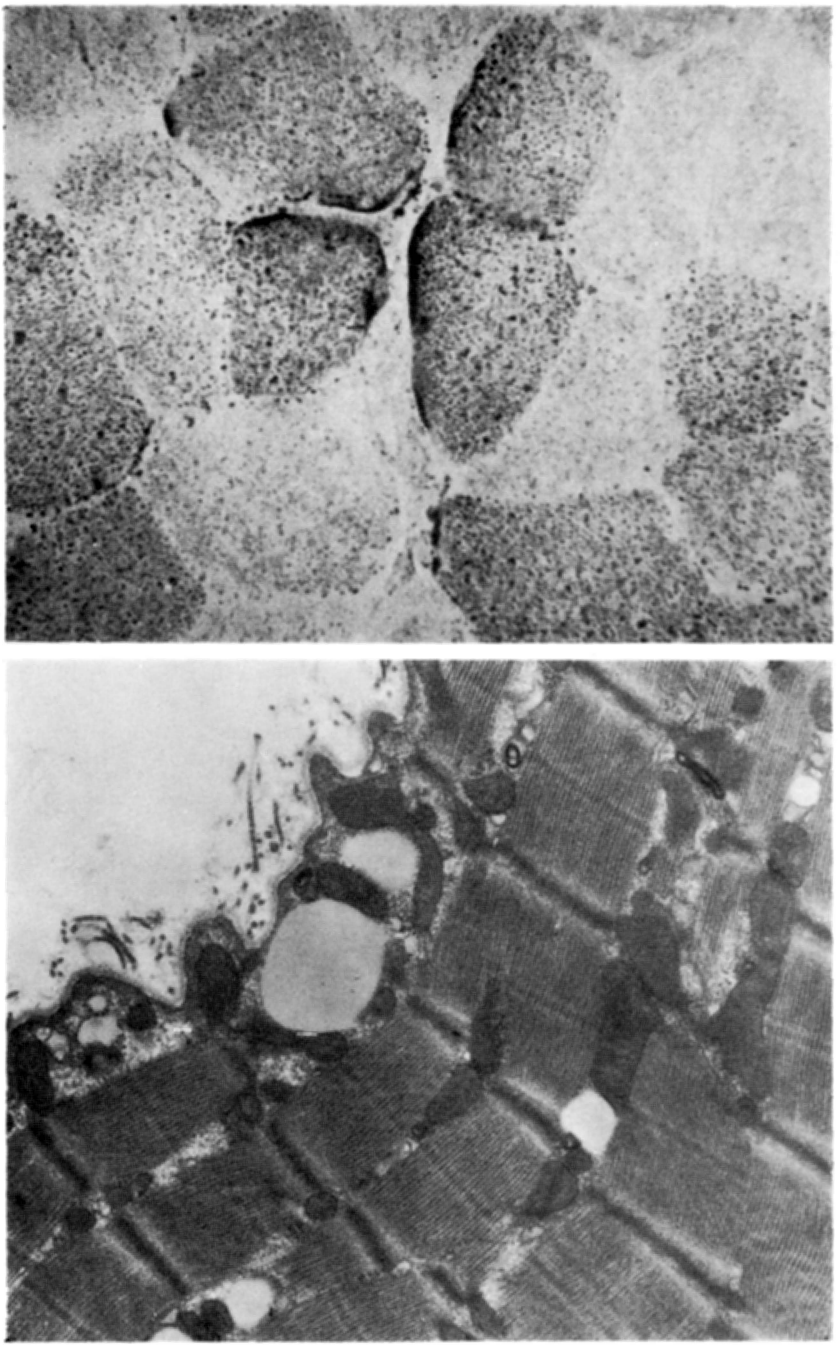

Fig. 2 — Case DA. Above*: muscle biopsy of the left biceps braquialis shows increase of dark granulous material especially in the subsarcolemmal region, suggesting storage of mitochondria (SDH ×350).* Below: *histologic evaluation of muscular biopsy by electron microscopy shows non-specific alterations of muscular fibers: presence of vacuoles of glycogen and fat in the subsarcolemmal region; enlargement of T system and some degenerated cells are also observed.*

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