

Muscular Dystrophy

ABSTRACTS

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- Bottiglieri T., 1994. The clinical potential of ademetionine (S-adenosylmethionine) in neurological disorders.
- Cheliout-Heraut F., 1997. [Visual, auditory and somatosensory potentials in the diagnosis of vitamin B12 deficiency]
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Multiple sclerosis and neurotransmission

Ali Qureshi G.; Halawa A.; Baig S.; Siden A. Clinical Research Center, Dept. Clin. Neuroscience Family Med., Huddinge University Hospital, S-141 57 Stockholm Sweden

Biogenic Amines (Netherlands), 1996, 12/5 (353-376)

In this study, the role of excitatory amino acids (EAA), nitrite (metabolite of nitric oxide), vitamin B12, homocysteine (HC), monoamines, and neuropeptides such as cholecystokinin (CCK) and neuropeptide Y in multiple sclerosis (MS) is defined on the basis of accumulated results obtained in cerebrospinal fluid from 47 MS patients. These results were compared with 25 healthy subjects. These results showed the significant increase of free radical NO, arginine, tryptophan, noradrenaline and HC, and decrease in the levels of Aspartate, glutamate, dopamine, vitamin B12, CCK-4 and CCK-8 in MS patients. From these results, the role of NO, HC and deficiency of vitamin B12 are considered as some of the factors attributing to the degeneration of MS.

The clinical potential of ademetionine (S-adenosylmethionine) in neurological disorders.

Bottiglieri T, Hyland K, Reynolds EH. Metabolic Disease Center, Baylor Research Institute, Dallas, Texas.

Drugs 1994 Aug;48(2):137-152

This review focuses on the biochemical and clinical aspects of methylation in neuropsychiatric disorders and the clinical potential of their treatment with ademetionine (S-adenosylmethionine; S-AMe). S-AMe is required in numerous transmethylation reactions involving nucleic acids, proteins, phospholipids, amines and other neurotransmitters. The synthesis of S-AMe is intimately linked with folate and vitamin B12 (cyanocobalamin) metabolism, and deficiencies of both these vitamins have been found to reduce CNS S-AMe concentrations. Both folate and vitamin B12 deficiency may cause similar neurological and psychiatric disturbances including depression, dementia, myelopathy and peripheral neuropathy. S-AMe has a variety of pharmacological effects in the CNS, especially on monoamine neurotransmitter metabolism and receptor systems. S-AMe has antidepressant properties, and preliminary studies indicate that it may improve cognitive function in patients with dementia. Treatment with methyl donors (betaine, methionine and S-AMe) is associated with remyelination in patients with inborn errors of folate and C-1 (one-carbon) metabolism. These studies support a current theory that impaired methylation may occur by different mechanisms in several neurological and psychiatric disorders.

[Visual, auditory and somatosensory potentials in the diagnosis of vitamin B12 deficiency]. [Article in French]

Cheliout-Heraut F, Durand MC, Desterbecq E, Dizien O, de Lattre J. Service d'explorations fonctionnelles, hopital Raymond Poincare, Garches, France.

Neurophysiol Clin 1997;27(1):59-65

We describe visual, brain stem auditory, and somatosensory evoked (VEP, BAEP, SEP) in a 49-year old male patient presenting with subacute degeneration of the spinal cord due to vitamin B12 deficiency. Neurological signs included tetraplegia with a C4-C5 spinal cord compression that was unchanged after surgical decompression. Before treatment, the duration of the bilateral VEP was slightly increased, though their amplitude and morphology were not modified. BAEP were normal. However, abnormalities of SEP with loss of cortical potentials were noticed. Two months after initiation of the treatment, both VEP and SEP recorded in response to median nerve stimulation had improved, but there was still no cortical response to tibial nerve stimulation. Eighteen months later, VEP were normal and recovery of SEP in response to tibial nerve stimulation was observed; however, alterations of peripheral sensory and motor action potentials were still present. These findings are in good agreement with previously reported pathological changes in patients presenting with subacute combined degeneration. Similar abnormalities have been described in patients with multiple sclerosis. Evoked potentials in this case proved to be useful for the diagnosis and the evaluation of the efficacy of the treatment. These findings also suggest that demyelination of the posterior part of the spinal cord and peripheral axonal degeneration might be the main pathological changes related to vitamin B12 deficiency. The former, but not like the latter, were clearly responsive to the treatment.

Role of intracellular calcium in promoting muscle damage: a strategy for controlling the dystrophic condition.

Duncan CJ.

Experientia 1978 Dec 15;34(12):1531-1535

It is suggested that various muscle diseases and examples of experimentally-induced muscle damage arise because of a high calcium level in the myoplasm. When $[Ca^{2+}]_i$ is raised experimentally in amphibian or mammalian muscle by treatment with A23187 or caffeine, myofilament degradation follows quickly. Such a rapid action suggests the involvement of a sequence of proteolytic activity that is stimulated by a rise in $[Ca^{2+}]_i$. Ca^{2+} might either trigger protease activity directly or indirectly, or promote the release of lysosomal enzymes. A high $[Ca^{2+}]_i$ in dystrophic muscle is believed to be the resultant of a sequence of events that is summarized in the figure. Suggestions are presented for different ways in which the steady-state position of $[Ca^{2+}]_i$ might ultimately be controlled for the clinical amelioration of some dystrophic conditions.

Biochemical rationale and the cardiac response of patients with muscle disease to therapy with coenzyme Q10.

Folkers K, Wolaniuk J, Simonsen R, Morishita M, Vadhanavikit S.

Proc Natl Acad Sci U S A 1985 Jul;82(13):4513-6

Cardiac disease is commonly associated with virtually every form of muscular dystrophy and myopathy. A double-blind and open crossover trial on the oral administration of coenzyme Q10 (CoQ10) to 12 patients with progressive muscular dystrophies and neurogenic atrophies was conducted. These diseases included the Duchenne, Becker, and limb-girdle dystrophies, myotonic dystrophy, Charcot-Marie-Tooth disease, and Welander disease. The impaired cardiac function was noninvasively and extensively monitored by impedance cardiography. Solely by significant change or no change in stroke volume and cardiac output, all 8 patients on blind CoQ10 and all 4 on blind placebo were correctly assigned (P less than 0.003). After the limited 3-month trial, improved physical well-being was observed for 4/8 treated patients and for 0/4 placebo patients; of the latter, 3/4 improved on CoQ10; 2/8 patients resigned before crossover; 5/6 on CoQ10 in crossover maintained improved cardiac function; 1/6 crossed over from CoQ10 to placebo relapsed. The rationale of this trial was based on known mitochondrial myopathies, which involve respiratory enzymes, the known presence of CoQ10 in respiration, and prior clinical data on CoQ10 and dystrophy. These results indicate that the impaired myocardial function of such patients with muscular disease may have some association with impaired function of skeletal muscle, both of which may be improved by CoQ10 therapy. The cardiac improvement was definitely positive. The improvement in well-being was subjective, but probably real. Likely, CoQ10 does not alter genetic defects but can benefit the sequelae of mitochondrial impairment from such defects. CoQ10 is the only known substance that offers a safe and improved quality of life for such patients having muscle disease, and it is based on intrinsic bioenergetics.

Two successful double-blind trials with coenzyme Q10 (vitamin Q10) on muscular dystrophies and neurogenic atrophies.

Folkers K, Simonsen R. Institute for Biomedical Research, University of Texas at Austin 78705, USA.

Biochim Biophys Acta 1995 May 24;1271(1):281-6

Coenzyme Q10 (vitamin Q10) is biosynthesized in the human body and is functional in bioenergetics, anti-oxidation reactions, and in growth control, etc. It is indispensable to health and survival. The first double-blind trial was with twelve patients, ranging from 7-69 years of age, having diseases including the Duchenne, Becker, and the limb-girdle dystrophies, myotonic dystrophy, Charcot-Marie-Tooth disease, and the Welander disease. The control coenzyme Q10 (CoQ10) blood level was low and ranged from 0.5-0.84 microgram/ml. They were treated for three months with 100 mg daily of CoQ10 and a matching placebo. The second double-blind trial was similar with fifteen patients having the same categories of disease. Since cardiac disease is established to be associated with these muscle diseases, cardiac function was blindly monitored, and not one mistake was made in assigning CoQ10 and placebo to the patients in both trials. Definitely improved physical performance was recorded. In retrospect, a dosage of 100 mg was too low although effective and safe. Patients suffering from these muscle dystrophies and the like, should be treated with vitamin Q10 indefinitely.

Free radicals, lipid peroxides and antioxidants in blood of patients with myotonic dystrophy.

Ihara Y, Mori A, Hayabara T, Namba R, Nobukuni K, Sato K, Miyata S, Edamatsu R, Liu J, Kawai M. Clinical Research Institute, National Minamiokayama Hospital, Okayama, Japan.

J Neurol 1995 Feb;242(3):119-122

We studied the levels of free radicals, lipid peroxides and antioxidants, as well as superoxide dismutase (SOD) activity in the blood of six patients with myotonic dystrophy (MyD) (mean age 52.8, SD 5.0 years) and seven controls (mean age 48.8, SD 6.3 years). Electron spin resonance was used to assess the free radicals by the spin-trapping method using 5,5-dimethyl-1-pyrroline-1-oxide. The levels of C centre radical ($P < 0.05$) and H radical ($P < 0.05$) in blood from the six MyD patients were significantly higher than those in the seven controls. The SOD activities in red blood cells and serum from the six MyD patients showed no significant difference from those in the seven controls. The serum lipid peroxide concentration was increased in five of the MyD patients and tended to increase further as the disease progressed. The serum vitamin E level was low in two patients and in the low normal range in three. Serum coenzyme Q10 was decreased in four patients. The serum selenium level was decreased in two patients and that of serum albumin was decreased in three. Therefore we conclude that increased levels of free radicals and lipid peroxides and decreased antioxidant levels play an important role in the pathogenesis of MyD.

Muscular dystrophy and activation of proteinases.

Kar NC, Pearson CM.

Muscle Nerve 1978 Jul;1(4):308-313

Evidence is presented for the existence of many different systems of proteolytic enzymes in human skeletal muscle. These include the lysosomal system of cathepsins as well as proteinases and peptide hydrolases that are optimally active at neutral and alkaline pH ranges. The majority of proteolytic enzymes examined are found to show increased activity in dystrophic human muscle. Moreover, a high initial rise is observed in cathepsin B1, a thiol-dependent endopeptidase of lysosomes, and in dipeptidyl peptidase IV, a membrane-associated peptidase. In addition, a calcium-activated neutral proteinase is found to be significantly elevated in muscle from patients with Duchenne dystrophy. The possible roles of these proteinases in intracellular protein catabolism and muscle wasting are discussed.

Distal myopathy: histochemical and ultrastructural studies.

Kumamoto T, Fukuhara N, Nagashima M, Kanda T, Wakabayashi M.

Arch Neurol 1982 Jun;39(6):367-371

In three familial cases and one sporadic case of late-onset distal myopathy, muscle wasting started in the distal portions of the lower extremities. The most striking change seen by light microscopy was the appearance of rimmed vacuoles. These were presumed to be autophagic, because they were found by electron microscopy to contain membranous lamellar structures and other heterogenous materials enclosed by a limiting membrane. On the other hand, lysosomal activity was markedly increased in skeletal muscle. In 6% to 22% of affected muscle fibers there were acid phosphatase-positive granules deep in the sarcoplasm, whereas control muscles had no such granules. The degenerative process in distal myopathy may be different from that in other muscular dystrophies.

Immunohistochemical study of clathrin in distal myopathy with rimmed vacuoles.

Kumamoto T, Abe T, Nagao S, Ueyama H, Tsuda T. Third Department of Internal Medicine, Oita Medical University, Japan.

Acta Neuropathol (Berl) 1998 Jun;95(6):571-575

Clathrin-coated vesicles are involved in three receptor-mediated intracellular transport pathways: export from the Golgi apparatus, transfer of lysosomal enzymes from the Golgi apparatus to lysosomes, and endocytosis at the plasma membrane. Seeking evidence of transport abnormalities in distal myopathy with rimmed vacuoles (DMRV), we performed immunohistochemistry for clathrin in muscle biopsy specimens from patients with this disorder or other neuromuscular disorders, and also in control muscle samples resected in orthopedic procedures. While most myofibers from control muscle did not stain for clathrin, some fibers revealed finely granular sarcoplasmic staining. In specimens from patients with Duchenne and Becker muscular dystrophy, amyotrophic lateral sclerosis, peripheral neuropathy, and DMRV, numerous clathrin-positive granules were often scattered through the sarcoplasm and seen to a lesser extent in subsarcolemmal regions. Quantitative immunohistochemical assessment showed more reactivity for clathrin in DMRV than in controls and other diseased muscles, particularly in atrophic fibers and type 2 fibers. Not all strongly clathrin-positive muscle fibers contained rimmed vacuoles, although most fibers with vacuoles were clathrin positive. The result suggests that the lysosome system is activated and receptor-mediated intracellular transport pathways function appropriately in the muscles of DMRV patients.

Increased lysosome-related proteins in the skeletal muscles of distal myopathy with rimmed vacuoles.

Kumamoto T, Ito T, Horinouchi H, Ueyama H, Toyoshima I, Tsuda T. Third Department of Internal Medicine, Oita Medical University,

Muscle Nerve 2000 Nov;23(11):1686-1693

Investigators have speculated that the degenerative process in distal myopathy with rimmed vacuoles (DMRV) mainly involves the lysosomal system. To investigate possible protein abnormalities related to intracellular lysosomal proteolytic pathways in DMRV-affected muscles, we performed immunohistochemical analyses of certain proteins in muscle biopsy specimens obtained from patients with various neuromuscular diseases, including DMRV, muscular dystrophy, polymyositis, and amyotrophic lateral sclerosis, and in normal human muscles specimens. Immunohistochemically, most muscle fibers in normal control specimens showed little or no reaction for clathrin and alpha- and gamma-subunits of adaptin-constituted adaptin proteins (AP)-1 and AP-2, respectively. Abnormal increases in these proteins were demonstrated mainly in the cytoplasm of atrophic fibers or in necrotic fibers in all diseased specimens. Particularly in DMRV-affected muscles, alpha- and gamma-adaptins were often observed inside or on the rims of vacuoles and in the cytoplasm of vacuolated fibers. Abnormal increases in Golgi-zone protein were also demonstrated in DMRV muscles. The rims of rimmed vacuoles were negative for kinectin, an endoplasmic reticulum-binding protein. Positive staining for both proteins, however, was sometimes seen inside the vacuoles in DMRV-affected fibers. These results suggest increased endocytosis at the plasma membrane as well as secretion involving transport from the trans-Golgi network of the Golgi apparatus in DMRV. Accumulation of various lysosome-related proteins within the rimmed vacuoles indicates at least some of these vacuoles may be autolysosomes. Copyright 2000 John Wiley & Sons, Inc.

Increased endocytosis with lysosomal activation in skeletal muscle of dystrophic mouse.

Libelius R, Jirmanova I, Lundquist I, Thesleff S.

J Neuropathol Exp Neurol 1978 Jul;37(4):387-400

Endocytosis in dystrophic muscles was studied by a combination of biochemical, radiochemical, and light and electron microscopic techniques. It was observed that the uptake of horseradish peroxidase (HRP) and 3H-Inulin in vitro was increased in leg skeletal muscles from dystrophic mice compared with littermate controls. Endocytosis of HRP in vivo was also increased in dystrophic muscles. When HRP was administered intravenously, light microscopic examination of the muscles showed that the macromolecular tracer was present not only in the extracellular space but also as intracellular deposits in several dystrophic muscle fibers. Ultrastructural examination of these fibers showed HRP to be present in membrane limited bodies of variable size, some of which likely represented secondary lysosomes, located preferentially close to the A-I junction. HRP was also found inside vacuoles which were sometimes in close vicinity to autophagic vacuoles. Primary uptake vesicles containing HRP appeared to originate from the sarcolemma and the transverse tubules. Biochemical determination of lysosomal enzyme activities revealed elevated levels of both cathepsin D and N-acetylglucosaminidase in dystrophic muscles as compared with controls. The results suggest an increased endocytic activity in dystrophic muscles with distribution of exogenous macromolecular tracers into endocytic vesicles and lysosomal structures. The hypothesis is put forward that endocytic activity constitutes an important mechanism of lysosomal activation in dystrophic muscles.

Free radicals: a potential pathogenic mechanism in inherited muscular dystrophy.

Murphy ME, Kehrer JP.

Life Sci 1986 Dec 15;39(24):2271-2278

Despite years of intensive work, the biochemical defect responsible for the pathogenesis of inherited muscular dystrophy has not been identified either in humans or animal models. This review examines evidence in support of the hypothesis that free radicals may be responsible for muscle degeneration in this disorder. A variety of cellular abnormalities noted in dystrophic muscles can be accounted for by free radical mediated damage. In addition, chemical by-products associated with free radical damage are found in dystrophic muscle tissue from humans and animals with this disease. Various enzymatic antioxidant systems can be enhanced as a normal cellular response to oxidative stress, and such changes are seen both in dystrophic muscle cells and certain other tissues of dystrophic animals. An increased level of free radical damage would follow from either: enhanced production of free radical species, or a deficient component of the cellular antioxidant system, such as vitamin E. The free radical hypothesis of muscular dystrophy can account for data supporting several alternative theories of the pathogenesis of this disease, as well as other observations which have not previously been explained.

Myotonic dystrophy treated with selenium and vitamin E.

Orndahl G, Sellden U, Hallin S, Wetterqvist H, Rindby A, Selin E.

Acta Med Scand 1986;219(4):407-14

We have previously reported the successful treatment of a patient with myotonic dystrophy with selenium and vitamin E. This paper deals with the treatment of a further five patients with myotonic dystrophy in different stages. All five patients improved subjectively and objectively in two or more respects. All improved their grip strength according to vigorimeter measurements (Martin), two normalized their gait, another two can now sit down on their heels and stand up, one patient can now walk on his toes, one can now get up from lying on the floor without using a chair and two patients have improved their physical capacity. Patients in early stages of the disease improved faster and more markedly than those in late stages. Electromyographical measurements also showed improvements, in that the myotonic discharges had diminished. The daily dose was 4 mg of Na₂SeO₃ and 600 mg of vitamin E. Serum concentration of selenium increased in all patients at the beginning of the treatment, but stabilized at a level slightly above the normal. No side-effects were observed.

[Duchenne muscular dystrophy. Effects of vitamin E administration on urinary luminescence]. [Article in Spanish]

Pizarro M, Lissi E, Reyes J, Holmgren J. Departamento de Quimica, Facultad de Quimica y Biologia, Universidad de Santiago de Chile.

Rev Med Chil 1998 Oct;126(10):1165-72

BACKGROUND: Urinary luminescence is increased in patients with Duchenne muscular dystrophy, probably due to the higher oxidative stress present in this disease. **AIM:** To assess the effects of vitamin E supplementation on urinary luminescence in children with Duchenne muscular dystrophy.

PATIENTS AND METHODS: Eighteen children with muscular dystrophy aged 12.2 years old and nine control children aged 10 years old, received 400 IU/day of vitamin E during one month. Prior to supplementation and twice a week thereafter, spot urine samples were obtained to measure urinary luminescence in a scintillation counter.

RESULTS: There was a wide variability in urinary luminescence within and between children. Mean values decreased after vitamin E supplementation in six of nine controls and in 12 of 18 children with muscular dystrophy.

CONCLUSIONS: Vitamin E supplementation significantly decreases urinary luminescence in healthy children and in patients with Duchenne muscular dystrophy. Therefore, it could be useful for the treatment of this disease.

The early changes in experimental myopathy induced by chloroquine and chlorphentermine.

Schmalbruch H.

J Neuropathol Exp Neurol 1980 Jan;39(1):65-81

In soleus muscles of rats treated for 2 to 11 days with high doses of chloroquine or chlorphentermine, muscle fibres showed autophagocytosis followed by segmental contracture and necrosis. Vasculature degeneration, "splitting", and internal nuclei were absent. At variance with findings in progressive muscular dystrophy, the incidence of intramembrane particles was unchanged and membrane defects in necrotizing fibres were absent. Autophagic vacuoles were formed by cup-shaped cisternae derived from tubules that often enclosed single mitochondria. Golgi complexes occurred in the centre of the fibres; dilated vesicles of the sarcoplasmic reticulum contained an electron-dense substance, possibly lysosomal enzymes. Exocytosis of autophagic vacuoles and of almost undigested mitochondria was observed. The changes in the plasma membrane were as in other cells: a bulge was formed that was cleared of intramembrane particles; the membrane fused with the limiting membrane of the autophagic vacuole, the content of which was expelled through an orifice. Inside autophagic vacuoles, persisting phospholipids arranged themselves into protein-free lipid bilayers, that formed concentric membranes or single-layered vesicles. Both drugs are known to inhibit degradation of phospholipids; the findings indicate that the rate of autophagocytosis and exocytosis were enhanced as well. Fibre necrosis was probably due to the fact that fibres eventually became unable to maintain their integrity.

Association of demyelination with deficiency of cerebrospinal-fluid S-adenosylmethionine in inborn errors of methyl-transfer pathway.

Surtees R, Leonard J, Austin S. Department of Child Health, Institute of Child Health, London, UK.

Lancet 1991 Dec 21;338(8782-8783):1550-1554

Long-term deficiency of cobalamin or folate causes a demyelinating disease of the brain and spinal cord. A reduced supply of methyl groups has been implicated as its cause. To examine the mechanisms of demyelination in human beings, we have studied three children with sequential inborn errors of the methyl-transfer pathway. One child had abnormal methylfolate metabolism, one abnormal methylcobalamin metabolism, and one hypermethioninaemia probably caused by methionine adenosyltransferase

deficiency. Magnetic resonance imaging of the brain and measurement of cerebrospinal-fluid concentrations of 5-methyltetrahydrofolate, methionine, and S-adenosylmethionine were carried out before and after 6-12 months of appropriate treatment. Each patient had abnormal myelination before treatment; the scans suggested demyelination. The only consistent biochemical abnormality in the cerebrospinal fluid was a low concentration of S-adenosylmethionine. Treatment led to substantial clinical improvement, apparent remyelination, and increases in cerebrospinal-fluid S-adenosylmethionine concentration into the normal range. Cerebrospinal-fluid concentrations of S-adenosylmethionine and methionine were significantly lower in eight other children with errors of the methyl-transfer pathway than in an age-matched reference population (mean [95% confidence interval] standard deviation score -1.81 [0.57], p less than 0.001 for S-adenosyl methionine and -1.82 [0.19], p less than 0.001 for methionine). The concentrations of these metabolites increased to within the reference range on treatment. We have shown that demyelination is associated with cerebrospinal-fluid S-adenosylmethionine deficiency and that restoration of S-adenosylmethionine is associated with remyelination.

Demyelination and inborn errors of the single carbon transfer pathway.

Surtees R. Institute of Child Health (UCLMS), London, UK.

Eur J Pediatr 1998 Apr;157:157-162

Inborn errors of the single-carbon transfer pathway are rare disorders of folate and cobalamin metabolism. They may be complicated by demyelination resembling subacute combined degeneration of the cord and brain. The study of CSF metabolites in children with serial errors affecting the single-carbon transfer pathway has suggested that S-adenosylmethionine deficiency is a cause of the demyelination. This deficiency is corrected by treatment that causes clinical improvement and remyelination. Some treatments can only have an indirect effect on the brain and this is discussed with other evidence that the liver may produce factors that are necessary for the maintenance of central myelin.

Creatine monohydrate in muscular dystrophies: A double-blind, placebo-controlled clinical study.

Walter MC, Lochmuller H, Reilich P, Klopstock T, Huber R, Hartard M, Hennig M, Pongratz D, Muller-Felber W Friedrich-Baur-Institute, Ludwig-Maximilians-University of Munich, Germany. Maggie.Walter@lrz.uni-muenchen.de

Neurology 2000 May 9;54(9):1848-50

The authors assessed the safety and efficacy of creatine monohydrate (Cr) in various types of muscular dystrophies in a double-blind, crossover trial. Thirty-six patients (12 patients with facioscapulohumeral dystrophy, 10 patients with Becker dystrophy, 8 patients with Duchenne dystrophy, and 6 patients with sarcoglycan-deficient limb girdle muscular dystrophy) were randomized to receive Cr or placebo for 8 weeks. There was mild but significant improvement in muscle strength and daily-life activities by Medical Research Council scales and the Neuromuscular Symptom Score. Cr was well tolerated throughout the study period.

Methylcobalamin (methyl-B12) promotes regeneration of motor nerve terminals degenerating in anterior gracile muscle of gracile axonal dystrophy (GAD) mutant mouse.

Yamazaki K, Oda K, Endo C, Kikuchi T, Wakabayashi T. Laboratory Animal Research Center, Tsukuba Research Laboratories, Eisai Co., Ltd., Ibaraki, Japan.

Neurosci Lett 1994 Mar 28;170(1):195-197

We examined the effects of methylcobalamin (methyl-B12, mecobalamin) on degeneration of motor nerve terminals in the anterior gracile muscle of gracile axonal dystrophy (GAD) mutant mice. GAD mice received orally methyl-B12 (1 mg/kg body wt/day) from the 40th day after birth for 25 days. In the distal endplate zone of the muscle, although most terminals were degenerated in both the untreated and methyl-B12-treated GAD mice, sprouts were more frequently observed in the latter. In the proximal endplate zone, where few degenerated terminals were seen in both groups of the mice, the perimeter of the terminals was increased and the area of the terminals was decreased significantly in the methyl-B12-treated GAD mice. These findings indicate that methyl-B12 promotes regeneration of degenerating nerve terminals in GAD mice.

SUGGESTED READING

Experimental progressive muscular dystrophy and its treatment with high doses anabolizing agents.

Bardelli M, Simonetti E.

Ital J Orthop Traumatol 1978 Apr;4(1):115-127

We are still a long way from discovering an unequivocal pathogenetic interpretation of progressive muscular dystrophy in man. Noteworthy efforts have been made in the experimental field; a recessive autosomic form found in the mouse seems to bear the closest resemblance to the human form from the genetic point of view. Myopathy due to lack of vitamin E and myopathy induced by certain viruses have much in common anatomically and pathologically with the human form. The authors induced myodystrophy in the rat by giving it a diet lacking in vitamin E. The pharmacological characteristics of vitamin E and the degenerative changes brought about by its deficiency, especially in the muscles, are illustrated. It is thus confirmed that the histological characteristics of myopathic rat muscle induced experimentally are extraordinarily similar to those of human myopathy as confirmed during biopsies performed at the Orthopaedic Traumatological Centre, Florence. The encouraging results obtained in various authoritative departments in myopathic patients by using anabolizing steroids have encouraged the authors to investigate the beneficial effects of one anabolizing agent (Dianabol, CIBA) at high doses in rats rendered myopathic by a diet deficient in vitamin E. In this way they obtained appreciable changes in body weight (increased from 50 to 70 g after forty days at a dose of 5 mg per day of anabolizing agent), but most of all they found histological changes due to "regenerative" changes in the muscle tissue, which however maintained its myopathic characteristics in the control animals that were not treated with the anabolizing agent. The authors conclude by affirming the undoubted efficacy of the anabolizing steroids in experimental myopathic disease, but they have reservations as to the transfer of the results into the human field, where high dosage cannot be carried out continuously because of the effects of the drug on virility; because the tissue injury too often occurs at an irreversible stage vis-a-vis the "regeneration" of the muscle tissue; and finally because the dystrophic injurious agent is certainly not the lack of vitamin E but something as yet unknown.

[Surgery of the spine in Duchenne's muscular dystrophy]

Chataigner H; Grelet V; Onimus M Service de Chirurgie des Scolioses et Orthopedie Infantile, Hopital Saint-Jacques, Besancon.

Rev Chir Orthop Reparatrice Appar Mot (France) May 1998, 84 (3) p224-30

PURPOSE OF THE STUDY: The authors present a retrospective review of 27 patients presenting a Duchenne muscular dystrophy and who were operated for spinal deformity, with special reference to functional result and postoperative evolution of vital capacity.

MATERIAL AND METHODS: Age at surgery averaged 14. Mean scoliotic angulation was 42 degrees. A thoraco-lumbar kyphosis was present in 15 cases (kyphotic index less than 10 degrees). A pelvic obliquity averaging 17 degrees was associated in 19 cases. Mean pre-operative vital capacity was 56 per cent. Preoperative evolution of vital capacity was documented in 18 cases: annual rate of decrease was 4.3 per cent. Heart ejection fraction averaged 63 per cent in 23 cases, and was normal in 4 cases. Instrumentation was extended from D3, D4 or D5 to L5 (5 cases) or S1 (22 cases). Spinal fixation was done in all patients by sublimar wiring with Luque rods (5 cases) or Hartshill rectangle (22 cases). Sacral fixation was done with ilio-sacral screws linked to the rectangle by Cotrel Dubousset rods and dominos (15 cases).

RESULTS: Mean blood loss was 1750 cc. Postoperatively, 25 patients were extubated on the operative day, 1 patient at D + 1, and one patient underwent a tracheostomy after one month. Scoliosis was reduced to 10 degrees after surgery and 13 degrees after 30 months follow-up. Pelvic obliquity was reduced to 4 degrees after surgery and 7 degrees after 30 months. A good spinal balance was present after surgery in 20 patients; at follow-up, a coronal or sagittal imbalance averaging 40 mm was observed in 22 patients. Postoperative evolution of vital capacity was documented in 21 cases. The annual decrease rate was 6.4 per cent. Rate was higher in patients presenting a good preoperative vital capacity (over 70 per cent) and very low in patients presenting a preoperative vital capacity under 40 per cent. 10 patients were deceased at review after a mean 53 months survival, at a mean age of 19. 17 patients were alive with a 50 months follow-up.

DISCUSSION: Spinal surgery in Duchenne muscular dystrophy has a low morbidity. It allows to keep sitting position to the child and to preserve quality of life. Surgery should be considered as soon as frontal or sagittal collapse of the spine is observed. However surgery does not result in respiratory improvement nor in life duration lengthening.

Role of dystrophin isoforms and associated proteins in muscular dystrophy (review).

Culligan KG; Mackey AJ; Finn DM; Maguire PB; Ohlendieck K Department of Pharmacology, National University of Ireland, University College Dublin, Belfield, Dublin, Ireland.

Int J Mol Med (Greece) Dec 1998, 2 (6) p639-48

The membrane cytoskeletal component dystrophin and its associated glycoproteins play a central role in the molecular pathogenesis of several muscular dystrophies, i.e. Duchenne/Becker muscular dystrophy, congenital muscular dystrophy and various forms of limb-girdle muscular dystrophy. Although the most frequent of these disorders, Duchenne muscular dystrophy, is mainly recognized as a disease of skeletal muscle fibers, pathophysiological changes also involve the heart and diaphragm, as well as the peripheral and central nervous system. Thus current research efforts into the elucidation of the molecular mechanisms

underlying these genetic diseases are not only directed towards studying skeletal muscle necrosis but also investigate abnormalities of heart and brain dystrophin-glycoprotein complexes in cardiomyopathy and brain deficiencies associated with muscular dystrophy. Furthermore, many isoforms of dystrophin and dystrophin-associated components have been identified in various non-muscle tissues and their function(s) are mostly unknown. With respect to skeletal muscle fibers, the characterization of new dystrophin-associated proteins, such as dystrobrevin, sarcospan and the syntrophins, led to a modified model of the spatial configuration of the dystrophin-glycoprotein complex. However, it is generally accepted now that beta-dystroglycan forms the plasmalemma-spanning linkage between dystrophin and the laminin-binding protein alpha-dystroglycan and that this complex is associated with the sarcoglycan subcomplex of sarcolemmal glycoproteins. (120 Refs.)

Social adjustment in adult males affected with progressive muscular dystrophy.

Eggers S; Zatz M Centro de Miopatias, Departamento de Biologia, Universidade de Sao Paulo, Brazil saeggers@usp.br

Am J Med Genet (United States) Feb 7 1998, 81 (1) p4-12

Adult male patients affected with Becker (BMD, N = 22), limb girdle (LGMD, N = 22) and facioscapulohumeral (FSHMD, N = 18) muscular dystrophy were interviewed to assess for the first time how the disease's severity and recurrence risk (RR) magnitude alter their social adjustment. BMD (X-linked recessive) is the severest form and confers an intermediate RR because all daughters will be carriers, LGMD (autosomal-recessive) is moderately severe with a low RR in the absence of consanguineous marriage, and FSHMD (autosomal-dominant) is clinically the mildest of these three forms of MD but with the highest RR, of 50%. Results of the semistructured questionnaire [WHO (1988): Psychiatric Disability Assessment Schedule] showed no significant difference between the three clinical groups, but more severely handicapped patients as well as patients belonging to lower socioeconomic levels from all clinical groups showed poorer social adjustment. Taken together, myopathic patients displayed intermediate social dysfunction compared to controls and schizophrenics studied by Jablensky [1988: WHO Psychiatric Disability Assessment Schedule]. Since the items of major dysfunction proportion among myopathic patients concern intimate relationships (70%), interest in working among those unemployed (67%), and social isolation (53%), emotional support and social and legal assistance should concentrate on these aspects. Interestingly, the results of this study also suggest that high RRs do not affect relationships to the opposite sex.

Spinal instrumentation for Duchenne's muscular dystrophy: experience of hypotensive anaesthesia to minimise blood loss

Fox HJ; Thomas CH; Thompson AG Birmingham Orthopaedic Spinal Service, England.

J Pediatr Orthop (United States) Nov-Dec 1997, 17 (6) p750-3

Nineteen patients with Duchenne's muscular dystrophy underwent segmental spinal instrumentation and posterior fusion between 1989 and 1994. The indication for surgery was loss of the ability to walk and development of scoliosis with sitting discomfort. Preoperative assessment included evaluation of pulmonary function. Average age at operation was 12.5 years. Instrumentation and fusion extended from upper thoracic levels to L-5 or the sacrum. A Hartshill rectangle was used in all cases, with banked allograft bone. Severe intraoperative blood loss was avoided by use of hypotensive anaesthesia. Perioperatively, systolic blood pressure was maintained between 75 and 85 mm Hg. Average blood loss was 1,246 ml (range, 400-3,100) or 30% of estimated total blood volume. Average transfusion requirements were 3 units of packed cells. Postoperative analgesia was provided by infusion via an epidural catheter. There were no postoperative wound or chest infections. Three patients required catheterisation for urinary retention. Postoperatively patients were fitted with a Neofract jacket to allow early mobilisation and discharge. Mean postoperative length of stay was 16 days. Posterior spinal fusion by using the Hartshill rectangle provided good correction and fixation. Hypotensive anaesthesia permitted surgery to be performed rapidly in a relatively dry field and avoided the complications of severe intraoperative blood loss and massive transfusion.

Limb-girdle muscular dystrophy (LGMD-1C) mutants of caveolin-3 undergo ubiquitination and proteasomal degradation. Treatment with proteasomal inhibitors blocks the dominant negative effect of LGMD-1C mutants and rescues wild-type caveolin-3.

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J Biol Chem 2000 Dec 1;275(48):37702-37711

Caveolin-3 is the principal structural protein of caveolae in striated muscle. Autosomal dominant limb-girdle muscular dystrophy (LGMD-1C) in humans is due to mutations (DeltaTFT and Pro --> Leu) within the CAV3 gene. We have shown that LGMD-1C mutations lead to formation of unstable aggregates of caveolin-3 that are retained intracellularly and are rapidly degraded. The mechanism by which LGMD-1C mutants of caveolin-3 are degraded remains unknown. Here, we show that LGMD-1C mutants of caveolin-3 undergo ubiquitination-proteasomal degradation. Treatment with proteasomal inhibitors (MG-132, MG-115, lactacystin, or

proteasome inhibitor I), but not lysosomal inhibitors, prevented degradation of LGMD-1C caveolin-3 mutants. In the presence of MG-132, LGMD-1C caveolin-3 mutants accumulated within the endoplasmic reticulum and did not reach the plasma membrane. LGMD-1C mutants of caveolin-3 behave in a dominant negative fashion, causing intracellular retention and degradation of wild-type caveolin-3. Interestingly, in cells co-expressing wild-type and mutant forms of caveolin-3, MG-132 treatment rescued wild-type caveolin-3; wild-type caveolin-3 was not degraded and reached the plasma membrane. These results may have clinical implications for treatment of patients with LGMD-1C.

Duchenne muscular dystrophy: a model for studying the contribution of muscle to energy and protein metabolism.

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Reprod Nutr Dev (France) Mar-Apr 1998, 38 (2) p181-6

Duchenne muscular dystrophy (DMD) is associated with a dramatic muscle mass loss. We hypothesized that DMD would be associated with significant changes in both energy and protein metabolism. We studied the resting energy expenditure (REE) in DMD and control children using indirect calorimetry, and their protein metabolism using an intravenous infusion of leucine and glutamine labeled with stable isotopes. In spite of a 75% muscle mass loss in the DMD children, the REE only decreased by 10%. DMD was associated with increased leucine oxidation but neither protein degradation nor protein synthesis were different from that of the controls. In contrast, whole body turnover of glutamine, an amino acid mainly synthesized in the muscle, was significantly decreased. These studies emphasized the quantitatively poor contribution of muscle to energy and protein metabolism in children. The qualitative impact of muscle mass loss on amino acid metabolism (glutamine) offers a fascinating field of research for the next few years and has therapeutic potential. (24 Refs.)

Deletion analysis & calpain status for carrier detection in a family with Duchenne muscular dystrophy.

Hussain T; Devi NG; Kumari CK; Anandaraj MP Institute of Genetics & Hospital for Genetic Diseases, Osmania University, Hyderabad.

Indian J Med Res (India) Sep 1998, 108 p93-7

Eight females with a family history of Duchenne muscular dystrophy (DMD) were analysed for their carrier status by m-calpain test, which monitors the m-calpain (milli-calpain), a proteolytic enzyme in the platelets, using an ELISA technique. Four of the eight females were identified as carriers by virtue of their elevated enzyme levels as compared to control. DNA samples of these members were analysed to ascertain the carrier status, by PCR followed by dosage analysis by densitometry. DNA analysis confirmed the findings by calpain test, which underlines the reliability of this phenotypic test for carrier detection in DMD. Calpain test has been informative in a large group of patients and carriers tested so far. Since the calpain test is cost and labour effective, it is suited for routine and widespread screening purposes.

Clinical, pathological, and genetic features of limb-girdle muscular dystrophy type 2A with new calpain 3 gene mutations in seven patients from three Japanese families.

Kawai H; Akaike M; Kunishige M; Inui T; Adachi K; Kimura C; Kawajiri M; Nishida Y; Endo I; Kashiwagi S; Nishino H; Fujiwara T; Okuno S; Roudaut C; Richard I; Beckmann JS; Miyoshi K; Matsumoto T First Department of Internal Medicine, School of Medicine, The University of Tokushima, Japan.

Muscle Nerve (United States) Nov 1998, 21 (11) p1493-501

We report on the clinical, pathological, and genetic features of 7 patients with limb-girdle muscular dystrophy type 2A (LGMD2A) from three Japanese families. The mean age of onset was 9.7+/-3.1 years (mean+/-SD), and loss of ambulence occurred at 38.5+/-2.1 years. Muscle atrophy was predominant in the pelvic and shoulder girdles, and proximal limb muscles. Muscle pathology revealed dystrophic changes. In two families, an identical G to C mutation at position 1080 in the calpain 3 gene was identified, and a frameshift mutation (1796insA) was found in the third family. The former mutation results in a W360R substitution in the proteolytic site of calpain 3, and the latter in a deletion of the Ca²⁺-binding domain.

Pilot study of myoblast transfer in the treatment of Becker muscular dystrophy.

Neumeyer AM; Cros D; McKenna-Yasek D; Zawadzka A; Hoffman EP; Pegoraro E; Hunter RG; Munsat TL; Brown RH Jr Department of Neurology, Massachusetts General Hospital, Boston 02129, USA.

Neurology (United States) Aug 1998, 51 (2) p589-92

We evaluated myoblast implantation therapy in three subjects with Becker muscular dystrophy who received 60 million myoblasts in one tibialis anterior (TA) muscle 2 months after beginning cyclosporine immunosuppression (5 to 10 mg/kg) that continued for 1 year. Strength of the implanted and control TA muscles was measured before and after treatment using a gauge to record TA contraction force. Our protocol controlled for the effects of cyclosporine and myoblast injections. In this pilot study, myoblast implantation did not improve strength of the implanted TA muscles.

The molecular basis of activity-induced muscle injury in Duchenne muscular dystrophy.

Petrof BJ Department of Medicine, Royal Victoria Hospital, McGill University, Montreal, Quebec, Canada.

Mol Cell Biochem (Netherlands) Feb 1998, 179 (1-2) p111-23

Duchenne muscular dystrophy (DMD) is the most common of the human muscular dystrophies, affecting approximately 1 in 3500 boys. Most DMD patients die in their late teens or early twenties due to involvement of the diaphragm and other respiratory muscles by the disease. The primary abnormality in DMD is an absence of dystrophin, a 427 kd protein normally found at the cytoplasmic face of the muscle cell surface membrane. Based upon the predicted structure and location of the protein, it has been proposed that dystrophin plays an important role in providing mechanical reinforcement to the sarcolemmal membrane of muscle fibers. Therefore, dystrophin could help to protect muscle fibers from potentially damaging tissue stresses developed during muscle contraction. In the present paper, the nature of mechanical stresses placed upon myofibers during various forms of muscle contraction are reviewed, along with current lines of evidence supporting a critical role for dystrophin as a subsarcolemmal membrane-stabilizing protein in this setting. In addition, the implications of these findings for exercise programs and other potential forms of therapy in DMD are discussed. (93 Refs.)

[Myocardial involvement in carrier states for Duchenne muscular dystrophy. A rare cause of supraventricular arrhythmia]

Ruchardt A; Eisenlohr H; Lydtin H Medizinische Klinik, Krankenhauses des Landkreises Starnberg.

Dtsch Med Wochenschr (Germany) Jul 31 1998, 123 (31-32) p930-5

HISTORY AND CLINICAL FINDINGS: Two women, both aged 54 years, were admitted because of supraventricular arrhythmias of recent onset. Patient 2 was also in heart failure. Male family members of both patients were known to have Duchenne's muscular dystrophy, of which one had died.

INVESTIGATIONS: The electrocardiogram of patient 1 demonstrated atrial fibrillation. Patient 2 had a raised serum creatine kinase concentration and increased pulmonary marking in the chest radiogram. Patient 1 had normal findings on left heart catheterization, but immunohistochemical analysis of a myocardial biopsy revealed dystrophin mosaic with 20% dystrophin-negative fibres. Patient 2 had a reduced ejection fraction and 80% dystrophin-negative fibres.

DIAGNOSIS, TREATMENT AND COURSE: Myocardial involvement in the carrier state for Duchenne's muscular dystrophy having been demonstrated in both women, patient 1 received antihypertensive treatment while patient 2, who was in cardiac failure, was given diuretics, ACE-inhibitor and beta-receptor blockers.

CONCLUSION: Cardiomyopathy in carriers of Duchenne's muscular dystrophy is a rare cause of supraventricular arrhythmias. The cause can be confirmed by immunochemical analysis of an endomyocardial biopsy.

[Genetic diagnosis of Duchenne/Becker muscular dystrophy; clinical application and problems]

Takeshima Y Department of Pediatrics, Kobe University School of Medicine.

No To Hattatsu (Japan) Mar 1998, 30 (2) p141-7

Duchenne/Becker muscular dystrophies (DMD/BMD) are the most common inherited muscular disease and caused by mutations in the dystrophin gene. A half to two-thirds of DMD and BMD patients carry deletions (usually of several kilobases of genomic DNA). The clinical progression in DMD and BMD patients with deletions can be predicted in 92% of cases based on whether the deletion maintains or disrupts the translational reading frame (frame-shift hypothesis). However, some exceptional cases have been reported in which some posttranscriptional modifications were suggested, such as alternative splicing and reinitiation of translation. Splicing mutation is one kind of mutations of dystrophin gene, and usually induced by a small mutation of exon-intron boundary sequence. However, intraexonal small mutation also induces exon skipping, due to disruption of an exon recognition sequence, which is an intraexonal sequence and necessary for splicing of the upstream intron. Carrier diagnosis is one of the important clinical application of genetic diagnosis. In the case of DMD/BMD with deletions of the dystrophin gene, carrier diagnosis is difficult because of the

existence of normal X chromosome. In these cases a linkage analysis is useful, and in some cases non-carriers can be directly diagnosed on the basis of microsattelite polymorphism detected in deleted region of patient. For the molecular diagnosis of DMD/BMD it is important to analyze not only at the genomic DNA level, but also at the mRNA, protein, and clinical levels. And the relationship between the molecular abnormality and clinical phenotype should be examined, especially extramuscular symptoms such as heart failure and mental retardation.

Early onset, autosomal recessive muscular dystrophy with Emery-Dreifuss phenotype and normal emerin expression.

Taylor J; Sewry CA; Dubowitz V; Muntoni F Department of Paediatrics and Neonatal Medicine, MRC Clinical Sciences Centre, Imperial College School of Medicine, Hammersmith Hospital, London, UK.

Neurology (United States) Oct 1998, 51 (4) p1116-20

OBJECTIVE: To describe the clinical and histopathologic picture of a childhood-onset, severe variant of scapuloperoneal MD with rigidity of the spine.

BACKGROUND: Rigidity of the spine is a feature of numerous syndromes, including X-linked Emery-Dreifuss MD, Bethlem myopathy, and the rigid spine syndrome. These are, however, relatively static or very slowly progressive neuromuscular disorders, usually associated with preserved ambulation into adult life.

PATIENTS AND METHODS: Five unrelated children (three boys and two girls) presented in the first 2 years of life with poor neck control, waddling gait, and frequent falls. Early wasting of the distal leg muscles, biceps, triceps, and neck muscles was noted in all patients, and all had contractures and severe rigidity of the spine. The condition progressed rapidly, and all patients lost ambulation before the age of 8 years. Cardiac function was normal in all.

RESULTS: Creatine kinase was moderately elevated in all, and muscle biopsy specimens showed nonspecific dystrophic changes with normal expression of dystrophin, the sarcoglycans, and laminin alpha2, alpha5, beta1, and gamma1 chains. Emerin expression was normal in two of the boys whose tissue was available for study.

CONCLUSIONS: The distribution of weakness, wasting, and contractures of the patients described resembled Emery-Dreifuss MD, but the rapid progression of weakness and contractures and the involvement of both sexes together with normal emerin expression suggest that this form is not X-linked Emery-Dreifuss MD. We suggest that these patients represent a severe MD characterized by early onset distal wasting and severe rigidity of the spine, with probable autosomal recessive inheritance.

Congenital muscular dystrophy with complete laminin-alpha2-deficiency, cortical dysplasia, and cerebral white-matter changes in children.

Tsao CY; Mendell JR; Rusin J; Luquette M Department of Pediatrics, The Ohio State University, Columbus, USA.

J Child Neurol (United States) Jun 1998, 13 (6) p253-6

Congenital muscular dystrophy consists of Fukuyama congenital muscular dystrophy, Walker-Warburg syndrome, muscle-eye-brain disease, and occidental congenital muscular dystrophy, which is further divided into laminin-alpha2-positive and laminin-alpha2-negative subgroups. These forms of congenital muscular dystrophy are frequently associated with abnormal white-matter changes, whereas the Fukuyama form, Walker-Warburg syndrome, and muscle-eye-brain disease are also frequently found to have polymicrogyria. We now report two infants with complete laminin-alpha2-deficiency who have not only abnormal cerebral white-matter lesions, but also bioccipital polymicrogyria. There are significant similarities in the clinical and cerebral manifestations among the various types of congenital muscular dystrophy. The diagnosis of the Fukuyama form, laminin-alpha2-deficiency, Walker-Warburg syndrome, and muscle-eye-brain disease cannot always be established on radiological studies alone.

Nine-year follow-up study of heart rate variability in patients with Duchenne-type progressive muscular dystrophy.

Yotsukura M; Fujii K; Katayama A; Tomono Y; Ando H; Sakata K; Ishihara T; Ishikawa K The Second Department of Internal Medicine, Kyorin University School of Medicine, Tokyo, Japan.

Am Heart J (United States) Aug 1998, 136 (2) p289-96

OBJECTIVES: The purpose of this study was to investigate the progression of autonomic dysfunction in patients with Duchenne-type progressive muscular dystrophy (DMD) over time by using heart rate variability.

BACKGROUND: Although previous studies suggest the presence of autonomic dysfunction in patients with DMD, the precise cause

is not known. On the other hand, it is well known that analysis of heart rate variability provides a useful, noninvasive means of quantifying autonomic activity. High frequency power is determined predominantly by the parasympathetic nervous system, whereas low frequency power is determined by both the parasympathetic and sympathetic nervous systems.

METHODS AND RESULTS: Frequency and time domain analyses of heart rate variability during ambulatory electrocardiographic monitoring were performed in 17 patients with DMD over a 9-year period. At the time of entry, the mean patient age was 11 years and the mean Swinyard-Deaver stage was 4. In the first year, high frequency power was significantly lower and the ratio of low frequency to high frequency was significantly higher in patients with DMD than in the normal control subjects. These differences become significantly greater as the disease progressed. At the time of entry, low and high frequency powers increased at night in both groups. However, over time, high and low frequency powers at night tended to decrease. All of the time domain parameters were significantly lower in the patients with DMD at all time points compared with the normal control subjects.

CONCLUSIONS: We concluded that DMD patients have either a decrease in parasympathetic activity, an increase in sympathetic activity, or both as their disease progresses.

MUSCULAR DYSTROPHY

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Duchenne muscular dystrophy: a model for studying the contribution of muscle to energy and protein metabolism.

Hankard R

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Social adjustment in adult males affected with progressive muscular dystrophy.

Eggers S; Zatz M

Centro de Miopatias, Departamento de Biologia, Universidade de Sao Paulo, Brazil

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Am J Med Genet (United States) Feb 7 1998, 81 (1) p4-12

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Department of Pediatrics, Kobe University School of Medicine.

No To Hattatsu (Japan) Mar 1998, 30 (2) p141-7

Duchenne/Becker muscular dystrophies (DMD/BMD) are the most common inherited muscular disease and caused by mutations in the dystrophin gene. A half to two-thirds of DMD and BMD patients carry deletions (usually of several kilobases of genomic DNA). The clinical progression in DMD and BMD patients with deletions can be predicted in 92% of cases based on whether the deletion maintains or disrupts the translational reading frame (frame-shift hypothesis). However, some exceptional cases have been reported in which some posttranscriptional modifications were suggested, such as alternative splicing and reinitiation of translation. Splicing mutation is one kind of mutations of dystrophin gene, and usually induced by a small mutation of exon-intron boundary sequence. However, intraexonal small mutation also induces exon skipping, due to disruption of an exon recognition sequence, which is an intraexonal sequence and necessary for splicing of the upstream intron. Carrier diagnosis is one of the important clinical application of genetic diagnosis. In the case of DMD/BMD with deletions of the dystrophin gene, carrier diagnosis is difficult because of the existence of normal X chromosome. In these cases a linkage analysis is useful, and in some cases non-carriers can be directly diagnosed on the basis of microsatellite polymorphism detected in deleted region of patient. For the molecular diagnosis of DMD/BMD it is important to analyze not only at the genomic DNA level, but also at the mRNA, protein, and clinical levels. And the relationship between the molecular abnormality and clinical phenotype should be examined, especially extramuscular symptoms such as heart failure and mental retardation.

[Detection of mutation in dystrophin gene in Duchenne muscular dystrophy--multiplex PCR and Southern blot analysis]

Kawamura J

Department of Internal Medicine, National Higasisaitama Hospital.

Nippon Rinsho (Japan) Dec 1997, 55 (12) p3126-30

The genetic defect responsible for Duchenne muscular dystrophy (DMD) can be identified as a partial deletion of the dystrophin gene in 50% of cases, or as a partial duplication in a further 10%. Multiplex PCR has been applied to screening of mutations in dystrophin gene, and it can identify 98% of deletions detected by Southern blot analysis. However, PCR cannot be available for quantifying DNA, so that detection of carrier status or duplication cannot be identified by multiplex PCR. Quantitative analysis of Southern blot hybridization is the most widely used and reliable method for detection of carrier and duplication mutation in dystrophin gene, but this method is a technically demanding procedure. (10 Refs.)

Scoliosis in Duchenne muscular dystrophy : aspects of orthotic treatment.

Heller KD; Forst R; Forst J; Hengstler K

Orthopaedic Department, University Clinic RWTH Aachen, Germany.

Prosthet Orthot Int (Denmark) Dec 1997, 21 (3) p202-9

The x-linked Duchenne muscular dystrophy (DMD) is the most frequent generalized muscle disorder arising from a lack of the sarcolemmic protein "dystrophin". Patients with DMD develop in the majority a progressive scoliosis when they cease walking and/or standing at the age of 10 years and become confined to a wheelchair. Increasing muscle weakness leads to a progression of the curvature, the pelvic tilt and problems in sitting. Together with the simultaneous progressive weakness of the respiratory muscles a restrictive pulmonary insufficiency will occur. Surgical stabilization of the spine (> 20 degrees Cobb, forced vital capacity > 35%) by an adequate multisegmental instrumentation enabling early mobilization is now the treatment of choice. However, orthotic treatment may offer an acceptable compromise in exceptional cases, if the patient rejects surgical intervention or

is in the late (inoperable) stages of the disease. Such a treatment is superior to a primary sitting support provision with insufficient possibilities of correction. The authors' experiences with 48 scoliosis orthoses made for 28 patients with DMD are reported. A "double plaster" cast has emerged as the best method to optimize adaption, especially in severe curvatures and the time taken for manufacturing the orthosis. A great deal of experience, patience and the consideration of the patients' individual demands are inevitable for a successful orthotic treatment.

Challenges in Duchenne muscular dystrophy.

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Neuromuscul Disord (England) Dec 1997, 7 (8) p482-6

The last seven years has witnessed an explosion in our understanding of the muscular dystrophies. In the early 1980s, prenatal diagnosis of Duchenne muscular dystrophy was developed. The cloning of the gene, in 1996, resulted in a better understanding of the disease process and led to the identification of a novel complex at the membrane. This information led to the cloning of other genes responsible for the autosomally inherited dystrophies. As we approach the millenium, the challenge is shifting to the development of therapy of these diseases. This review, in honour of Professor Alan Emery, explains how these advances have an impact in the clinical management of patients and head the promise the progress holds for the future. (47 Refs.)

Problems and potential for gene therapy in Duchenne muscular dystrophy.

Kakulas BA

Australian Neuromuscular Research Institute, Perth, Australia.

Neuromuscul Disord (England) Jul 1997, 7 (5) p319-24

Hopes ran high that a cure for Duchenne muscular dystrophy (DMD) would quickly follow the discovery of dystrophin by Lou Kunkel and his group in the 1980's. Myoblast transplantation, the favoured method of gene 'complementation', unfortunately did not progress beyond the experimental stage. A more sober approach to gene therapy followed using a variety of transfection or direct methods to introduce the normal gene. In view of these advances it is timely for the potential of gene therapy for DMD to be considered in the light of the disease process. It may be assumed that if dystrophin is replaced muscle fibre necrosis will cease. For this purpose expression of the gene should be continuous and expressed throughout the body well before there are irreversible changes. It would seem that gene therapy would not be particularly helpful if this occurs when the muscle lesions are near the end stage. If our objective is to retain ambulation dystrophin must be replaced well before the end stage. It should be kept in mind that even when the disorder first becomes clinically apparent at the age of about 5 years, muscle lesions are very advanced in the limb girdle groups. Therefore, the best that may be hoped to achieve by gene therapy at the age of 5 years would be to arrest the process at that stage of involvement with the patient having permanent but static weakness. Cardiac lesions are probably minimal at this time. To improve life expectancy, the respiratory muscles would need to be preserved. The enormous size of the gene is another difficulty so that some thought has been given to the introduction of a 'minigene' converting the clinical phenotype from DMD to the more benign Becker phenotype with improved life expectancy.

Improved adenoviral vectors for gene therapy of Duchenne muscular dystrophy.

Hauser MA; Amalfitano A; Kumar-Singh R; Hauschka SD; Chamberlain JS

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Neuromuscul Disord (England) Jul 1997, 7 (5) p277-83

We have been exploring the feasibility of gene therapy for Duchenne muscular dystrophy by characterizing parameters important for the design of therapeutic protocols. These studies have used transgenic mice to analyze expression patterns of multiple dystrophin vectors, and have been accompanied by the development of viral vectors for gene transfer to dystrophic mdx mouse muscle. Analysis of transgenic mdx mice indicates that greater than 50% of the fibers in a muscle group must express dystrophin to prevent development of a significant dystrophy, and that low-level expression of truncated dystrophins can function very well. These results suggest that gene therapy of DMD will require methods to transduce the majority of fibers in critical muscle groups with vectors that express moderate levels of dystrophin proteins. Strategies for the development of viral vectors able to deliver dystrophin genes to muscle include the use of muscle specific regulatory sequences coupled with deletion of viral gene sequences

to limit virus-induced immune rejection of transduced tissues. These strategies should enable production of adenoviral vectors expressing full-length dystrophin proteins in muscle.

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Selenium in health and disease: a review.

Foster LH; Sumar S
Nutrition Research Centre, South Bank University, London, UK.
Crit Rev Food Sci Nutr (United States) Apr 1997, 37 (3) p211-28

Selenium (Se) was discovered 180 years ago. The toxicological properties of Se in livestock were recognized first; its essential

nutritional role for animals was discovered in the 1950s and for humans in 1973. Only one reductive metabolic pathway of Se is well characterized in biological systems, although several naturally occurring inorganic and organic forms of the element exist. The amount of Se available for assimilation by the tissues is dependent on the form and concentration of the element. Se is incorporated into a number of functionally active selenoproteins, including the enzyme glutathione peroxidase, which acts as a cellular protector against free radical oxidative damage and type 1 iodothyronine 5'-deiodinase which interacts with iodine to prevent abnormal hormone metabolism. Se deficiency has been linked with numerous diseases, including endemic cardiomyopathy in Se-deficient regions of China; cancer, muscular dystrophy, malaria, and cardiovascular disease have also been implicated, but evidence for the association is often tenuous. Information on Se levels in foods and dietary intake is limited, and an average requirement for Se in the U.K. has not been established. Available data suggest that intake in the U.K. is adequate for all, except for a few risk groups such as patients on total parenteral nutrition or restrictive diets. (122 Refs.)

Assessment of selenium and vitamin E deficiencies in dairy herds and clinical disease in calves.

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Institute for Hygiene and Pathology of Animal Nutrition, Veterinary Faculty Ljubljana, Slovenia.

Vet Rec (England) Oct 19 1996, 139 (16) p391-4

Because of the very low concentrations of selenium in the dry matter of grass, grass silage, hay and maize silage Slovenian dairy herds need to be supplemented with selenium. Selenium in the form of mineral and feed mixtures maintained adequate mean (sd) blood serum selenium concentrations of 43.9 (27.6) to 65.3 (18.5) micrograms/litre in lactating cows, but in late lactation and in the dry period when only mineral mixtures were used, about 60 per cent of the cows had marginal serum selenium concentrations, mainly because of the low intake of the mineral supplement. In 18 herds which were either unsupplemented or irregularly supplemented with selenium, the mean (sd) concentrations in blood serum were 13.7 (5.5) micrograms/litre and 17.4 (9.2) micrograms/litre, respectively, for selenium and 2.98 (2.72) mg/litre and 1.62 (1.73) mg/litre for vitamin E, indicating that under extensive farming conditions in Slovenia the lack of both micronutrients may be responsible for nutritional muscular dystrophy in calves. Among 37 clinical cases, cardiorespiratory signs predominated in 25 of the calves and skeletal myopathy was dominant in 12. A very low mean serum selenium concentration [9.7 (7.2) micrograms/litre] and typically high activities of aspartate aminotransferase (AST) [1125 (373) U/litre] and creatine kinase (CK) [9169 (3681) U/litre] were observed for the myocardial form of the disease, and 2797 (550) U/litre and 22,650 (13,500) U/litre were observed for the skeletal form of the disease. A highly significant ($P < 0.0001$) difference in the selenium concentration of liver dry matter between the regularly supplemented [402 (207) micrograms/kg] and irregularly supplemented [173 (69) micrograms/kg] herds was observed. If a minimum value of 300 micrograms/kg of liver dry matter is accepted as the criterion for the determination of adequate selenium status, 93 per cent of the samples from the irregularly supplemented herds were selenium deficient. A similar proportion was estimated to be selenium deficient when the criterion was taken to be 30 micrograms selenium/litre of blood serum.

Wheat kernel ingestion protects from progression of muscle weakness in mdx mice, an animal model of Duchenne muscular dystrophy.

Hubner C; Lehr HA; Bodlaj R; Finckh B; Oexle K; Marklund SL; Freudenberg K; Kontush A; Speer A; Terwolbeck K; Voit T; Kohlschutter A

Department of Neuropediatrics, Virchow Medical Center, Humboldt University, Berlin, Germany.

Pediatr Res (United States) Sep 1996, 40 (3) p444-9

A simple, reproducible test was used to quantify muscle weakness in mdx mice, an animal model of Duchenne muscular dystrophy. The effect of bedding on wheat kernels and of dietary supplementation of alpha-tocopherol on the progression of muscle weakness was investigated in mdx mice. When measured during the first 200 d of life, mdx mice developed muscle weakness, irrespective of bedding and diet. When kept on wood shavings and fed a conventional rodent diet, mdx mice showed progressive muscle weakness over the consecutive 200 d, and eventually showed a significant weight loss during the next 200-d observation period. Progression of muscle weakness and weight loss were almost completely prevented in mdx mice that were kept on wheat kernel bedding. In contrast, only incomplete maintenance of muscle strength and body weight was observed in mdx mice kept on wood shavings and fed the alpha-tocopherol-supplemented diet. It is concluded from these experiments that a component of wheat kernels other than alpha-tocopherol is essential to prevent the progression of muscle weakness in mdx mice.

Extraocular, limb and diaphragm muscle group-specific antioxidant enzyme activity patterns in control and mdx mice.

Ragusa RJ; Chow CK; St. Clair DK; Porter JD

The mechanisms primarily responsible for the degenerative processes occurring in dystrophic skeletal muscle remain unresolved. The identification of the mechanisms that lead to the complete sparing of extraocular muscle in dystrophinopathies is of particular interest. A number of studies have provided evidence to suggest that the muscle pathology that characterizes muscular dystrophy may be, in part, free radical mediated. In the present study, we examined the antioxidant enzyme status of extraocular, diaphragm and gastrocnemius muscles in control strain and mdx mice. Our results revealed that in the control strain, both extraocular and diaphragm muscles had higher copper/zinc superoxide dismutase, manganese superoxide dismutase and selenium dependent glutathione peroxidase activities as compared to the gastrocnemius. Furthermore, the diaphragm had higher glutathione reductase activity as compared to the gastrocnemius. These findings indicate that the highly aerobic extraocular and diaphragm muscles have higher antioxidant enzyme capacity than the gastrocnemius, a muscle more dependent on anaerobic energy metabolism. Changes in the antioxidant enzyme status of the mdx mouse correlated, in part, with the degree of histopathological involvement of the three muscle groups assessed.

Aortic and iliac artery thrombosis in calves: nine cases (1974-1993).

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Department of Veterinary Internal Medicine, Western College of Veterinary Medicine, University of Saskatchewan, Saskatoon, Canada.

J Am Vet Med Assoc (United States) Jul 1 1996, 209 (1) p130-6

OBJECTIVE--To identify common clinical and diagnostic features of calves with aortic or iliac artery thrombosis that might aid in antemortem diagnosis of this condition. **DESIGN**--Retrospective case series.

ANIMALS--9 calves < or = 6 months old in which aortic or iliac artery thrombosis was confirmed at necropsy.

RESULTS--All calves had an acute onset of paresis or flaccid paralysis of 1 or both hind limbs. Affected limbs were hypothermic and had diminished spinal reflexes and diminished pulse pressures. Diagnosis was definitively established in 2 calves by use of angiography. All 9 calves died or were euthanized.

CLINICAL IMPLICATIONS--This condition is rare and could be mistaken for more common diseases of young cattle, such as traumatic injury of the axial or appendicular skeleton, vertebral osteomyelitis, nutritional muscular dystrophy associated with vitamin E or selenium deficiency, injury to the sciatic or femoral nerves, or clostridial myositis.

[Selenium concentration in blood and Duchenne-type progressive muscular dystrophy]

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Department of Hygiene, Miyazaki Medical College.

Nippon Rinsho (Japan) Jan 1996, 54 (1) p134-40

The concentration of selenium (Se) and the activity of glutathione peroxidase (GSH-Px) in plasma and erythrocytes were measured in healthy men and in patients with Duchenne-type progressive muscular dystrophy (DMD). In healthy men, the Se concentration in erythrocytes showed a steep rise with aging and ascended gradually in plasma. The GSH-Px activity in both plasma and erythrocytes clearly increased with aging. The relationship between the Se concentration and the GSH-Px activity in healthy men showed a parallel rise with aging, but the coefficients of correlation were not very high ($r = 0.44$ and 0.56 in plasma and erythrocytes, respectively). In DMD patients, on the other hand, the Se concentration in erythrocytes decreased steeply with aging, and it decreased gradually in plasma. The GSH-Px activity in both plasma and erythrocytes apparently increased as in healthy men with aging, but the level was about 80% of that of healthy men. When selenite (Se+4) is added to the whole blood in vitro at 25 degrees C, it is rapidly taken up by erythrocytes (within several minutes) and is then released into plasma (a period of 30 min), then subsequent reuptake by erythrocytes is proceeded slowly. Our attention was attracted to the pattern of selenite release from erythrocytes of DMD patients.

Two successful double-blind trials with coenzyme Q10 (vitamin Q10) on muscular dystrophies and neurogenic atrophies.

Coenzyme Q10 (vitamin Q10) is biosynthesized in the human body and is functional in bioenergetics, anti-oxidation reactions, and in growth control, etc. It is indispensable to health and survival. The first double-blind trial was with twelve patients, ranging from 7-69 years of age, having diseases including the Duchenne, Becker, and the limb-girdle dystrophies, myotonic dystrophy, Charcot-Marie-Tooth disease, and the Welander disease. The control coenzyme Q10 (CoQ10) blood level was low and ranged from 0.5-0.84 microgram/ml. They were treated for three months with 100 mg daily of CoQ10 and a matching placebo. The second double-blind trial was similar with fifteen patients having the same categories of disease. Since cardiac disease is established to be associated with these muscle diseases, cardiac function was blindly monitored, and not one mistake was made in assigning CoQ10 and placebo to the patients in both trials. Definitely improved physical performance was recorded. In retrospect, a dosage of 100 mg was too low although effective and safe. Patients suffering from these muscle dystrophies and the like, should be treated with vitamin Q10 indefinitely.

Biochemical rationale and the cardiac response of patients with muscle disease to therapy with coenzyme Q10.

Folkers K, Wolaniuk J, Simonsen R, Morishita M, Vadhanavikit S
Proc Natl Acad Sci U S A 1985 Jul;82(13):4513-6

Cardiac disease is commonly associated with virtually every form of muscular dystrophy and myopathy. A double-blind and open crossover trial on the oral administration of coenzyme Q10 (CoQ10) to 12 patients with progressive muscular dystrophies and neurogenic atrophies was conducted. These diseases included the Duchenne, Becker, and limb-girdle dystrophies, myotonic dystrophy, Charcot-Marie-Tooth disease, and Welander disease. The impaired cardiac function was noninvasively and extensively monitored by impedance cardiography. Solely by significant change or no change in stroke volume and cardiac output, all 8 patients on blind CoQ10 and all 4 on blind placebo were correctly assigned (P less than 0.003). After the limited 3-month trial, improved physical well-being was observed for 4/8 treated patients and for 0/4 placebo patients; of the latter, 3/4 improved on CoQ10; 2/8 patients resigned before crossover; 5/6 on CoQ10 in crossover maintained improved cardiac function; 1/6 crossed over from CoQ10 to placebo relapsed. The rationale of this trial was based on known mitochondrial myopathies, which involve respiratory enzymes, the known presence of CoQ10 in respiration, and prior clinical data on CoQ10 and dystrophy. These results indicate that the impaired myocardial function of such patients with muscular disease may have some association with impaired function of skeletal muscle, both of which may be improved by CoQ10 therapy. The cardiac improvement was definitely positive. The improvement in well-being was subjective, but probably real. Likely, CoQ10 does not alter genetic defects but can benefit the sequelae of mitochondrial impairment from such defects. CoQ10 is the only known substance that offers a safe and improved quality of life for such patients having muscle disease, and it is based on intrinsic bioenergetics.

[Efficiency of ubiquinone and p-oxybenzoic acid in prevention of E-hypovitaminosis-induced development of muscular dystrophy]

Kuz'menko IV, Donchenko GV, Kovalenko VN, Gololobov AD, Tarasova NV
Ukr Biokhim Zh (USSR) Sep-Oct 1981, 53 (5) p73-9

It is shown that E-hypovitaminosis-induced muscular dystrophy in rabbits is accompanied by a sharp decrease in the body mass, an increase in the urine creatine-index, a decrease in the vitamin E and ubiquinone contents in the liver and skeletal muscle tissues. In the myocardium mitochondria a decrease in the vitamin E content and an increase in the ubiquinone content are observed. The activity of NADH-cytochrome c-, NADH-ubiquinone- and succinate-ubiquinone-reductase also varies in mitochondria of the studied tissues. In myocardium organellas a direct dependence is found between the content of ubiquinone, NADH- and succinate-ubiquinone-reductase activity and an inverse one-between its content and the activity of the NADH-cytochrome c-reductase system. It is established that p-oxybenzoic acid as well as vitamin E prevents development of muscular dystrophy and causes changes analogous in direction in the activity of the ubiquinone-dependent enzymic systems of mitochondria. Ubiquinone-9 is less efficient in preventing the development of muscular dystrophy.

Effect of coenzyme Q on serum levels of creatine phosphokinase in preclinical muscular dystrophy.

Folkers K; Nakamura R; Littarru GP; Zellweger H; Brunkhorst JB; Williams CW Jr; Langston JH
Proc Natl Acad Sci U S A 1974 May;71(5):2098-102

No abstract.

[Some indices of energy metabolism in the tissues of mice with progressive muscular dystrophy under the action of ubiquinone]

Monakhov NK, Obol'nikova EA, Igdal LG, Torosian ZhK, Antelava NA
Vopr Med Khim (USSR) May 1974, 20 (3) p276-84

Coenzyme Q10 (vitamin Q10) is biosynthesized in the human body and is functional in bioenergetics, anti-oxidation reactions, and in growth control, etc. It is indispensable to health and survival. The first double-blind trial was with twelve patients, ranging from 7-69 years of age, having diseases including the Duchenne, Becker, and the limb-girdle dystrophies, myotonic dystrophy, Charcot-Marie-Tooth disease, and the Welander disease. The control coenzyme Q10 (CoQ10) blood level was low and ranged from 0.5-0.84 microgram/ml. They were treated for three months with 100 mg daily of CoQ10 and a matching placebo. The second double-blind trial was similar with fifteen patients having the same categories of disease. Since cardiac disease is established to be associated with these muscle diseases, cardiac function was blindly monitored, and not one mistake was made in assigning CoQ10 and placebo to the patients in both trials. Definitely improved physical performance was recorded. In retrospect, a dosage of 100 mg was too low although effective and safe. Patients suffering from these muscle dystrophies and the like, should be treated with vitamin Q10 indefinitely.

Free radicals, lipid peroxides and antioxidants in blood of patients with myotonic dystrophy.

Ihara Y, Mori A, Hayabara T, Namba R, Nobukuni K, Sato K, Miyata S, Edamatsu R, Liu J, Kawai M
Clinical Research Institute, National Minamiokayama Hospital, Okayama, Japan.
J Neurol. 1995 Feb. 242(3). P 119-22

We studied the levels of free radicals, lipid peroxides and antioxidants, as well as superoxide dismutase (SOD) activity in the blood of six patients with myotonic dystrophy (MyD) (mean age 52.8, SD 5.0 years) and seven controls (mean age 48.8, SD 6.3 years). Electron spin resonance was used to assess the free radicals by the spin-trapping method using 5,5-dimethyl-1-pyrroline-1-oxide. The levels of C centre radical ($P < 0.05$) and H radical ($P < 0.05$) in blood from the six MyD patients were significantly higher than those in the seven controls. The SOD activities in red blood cells and serum from the six MyD patients showed no significant difference from those in the seven controls. The serum lipid peroxide concentration was increased in five of the MyD patients and tended to increase further as the disease progressed. The serum vitamin E level was low in two patients and in the low normal range in three. Serum coenzyme Q10 was decreased in four patients. The serum selenium level was decreased in two patients and that of serum albumin was decreased in three. Therefore we conclude that increased levels of free radicals and lipid peroxides and decreased antioxidant levels play an important role in the pathogenesis of MyD.

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