Open Journal of Nutrition and Food Sciences

ISSN 2690-2478

Review Article

Semmola-Meryon-Duchenne Syndrome: Possible Therapeutic Role of Nutritional Supplements

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Abstract

Aim: There is no satisfactory therapy for progressive disabling genetic neuromuscular disorders such as Semmola-Meryon-Duchenne syndrome. It is hoped that the emerging research evidence can contribute to improving treatment of such diseases. Therefore, reviewing the relevant literature for the recent research evidence is recommended in an attempt to improve the therapeutic services for patients with such conditions.

Materials and methods: There is no satisfactory therapy for Semmola-Meryon-Duchenne syndrome. Two Iraqi brothers with Semmola-Meryon-Duchenne syndrome are described, and the literatures suggesting a possible therapeutic role of nutritional supplements are examined.

Results: Review of the relevant literature suggested a possible therapeutic role of nutritional supplements in Semmola-Meryon-Duchenne syndrome. The use of Coenzyme Q10 in the treatment of Semmola-Meryon-Duchenne syndrome can lower the elevated serum creatine phosphokinase which results from deteriorating muscle. The muscles of patients with muscular dystrophy may be deficient in a Coenzyme Q10. L-Arginine is a potential treatment for Semmola-Meryon-Duchenne as it may increase utrophin levels in muscles. Utrophin is another cytoskeleton protein with over 80% homology with dystrophin and may compensate for the lack of dystrophin in muscles. Glutamine therapy in Semmola-Meryon-Duchenne syndrome may have beneficial protein-sparing effect as it reduce whole body protein degradation and glutamine de novo synthesis leading to sparing of nitrogen precursors. Ten days of oral glutamine and amino acid supplementation can equally inhibit whole-body protein degradation in children with Semmola-Meryon- Duchenne syndrome. The use of creatine monohydrate 5 grams daily in the treatment of Semmola-Meryon-Duchenne syndrome can preserve muscle strength in the short term.

Two brothers with Semmola-Meryon-Duchenne syndrome were treated with supplementation of amino acids, coenzyme Q10, glutamine, and creatine monohydrate. Within six weeks, the parents noticed some improvement in muscular strength with lessening of the difficulties in squatting and climbing stairs.

Conclusion: Nutritional supplements including coenzyme Q10, L-Arginine, glutamine, and creatine may have some beneficial effects when used in the treatment of Semmola-Meryon-Duchenne syndrome.

Keywords: Semmola-Meryon-Duchenne syndrome; Nutritional supplements; Glutamine therapy

Introduction

Semmola-Meryon-Duchenne syndrome is a severe X-linked recessive muscular dystrophy with progressive muscle weakness generally begins at about the age of four years, affecting first the upper legs and pelvis followed by involvement of the upper arms. The Neapolitan physician Giovanni Semmola (1793-1866) was probably the first to describe this severe type of early muscular dystrophy in 1834. Giovanni Semmola described two boys with muscular dystrophy associated with obvious muscular hypertrophy. Giovanni Semmola gave a clinical description of muscle dystrophy in a lecture to Academia Pontaniana in Naples [1].

In 1852, Dr. Edward Meryon (Figure 1) reported a familial disorder affecting males causing significant muscle disease without central nervous system abnormalities. The disorder was associated with early degeneration of muscles with fatty infiltration. Edward Meryon suggested that the disorder was caused by a sarcolemmal defect and the disorder was genetically transmitted through females and affected males only. In a communication to the Royal Medical and Chirurgical Society in December, 1851, Edward Meryon described in detail eight boys in three families with Semmola-Meryon-Duchenne syndrome. This communication was published in the Transactions of the Society in 1852. In the same paper published in the Transactions of the Medical and Chirurgical Society in 1852, Edward Meryon described two more families afflicted by the disorder. Edward Meryon also published in 1864 a long chapter entitled paralysis from granular degeneration of the voluntary muscles in a book (Figure 2) entitled practical and pathological researches on the various forms of paralysis published. In this chapter, Meryon included two families from his earlier publication [1].

Figure 1: A sketch of Dr. Edward Meryon, an English physician.

Citation: Aamir Jalal Al Mosawi. Semmola-Meryon-Duchenne Syndrome: Possible Therapeutic Role of Nutritional Supplements. Open J Nutr Food Sci. 2019; 1(1): 1005.

Publisher Name: Medtext Publications LLC

Manuscript compiled: Dec 13th, 2019

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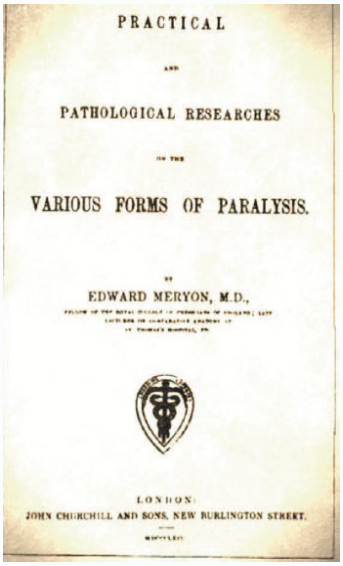
PRACTICAL

AND

PATHOLOGICAL RESEARCHES

ON THE

VARIOUS FORMS OF PARALYSIS.

BY

EDWARD MERYON, M.D.,

LONDON:
JOHN CHURCHILL AND SONS, NEW BURLINGTON STREET.

Figure 2: The book entitled practical and pathological researches on the various forms of paralysis published by Edward Meryon.

In 1861, the French physician Guillaume-Benjamin-Amand Duchenne provided a detailed description of the disorder and pictures of an affected patient. Duchenne called the disorder progressive muscular atrophy, and in 1868 he performed the first muscle biopsy on a patient affected by this condition. The 1861 edition of Duchenne's book entitled "Paraplegia hypertrophique de l'enfance de cause cerebrale" included a detailed account of a boy who had the disorder. In 1862, Duchenne published an Atlas entitled Album de photographies pathologiques, the Atlas included photos of Duchenne s patient with this disorder. In 1868, Duchenne described another thirteen children affected by the disorder. Duchenne was the first to examine a tissue biopsy from a living patient with a microscope [1].

Materials and Methods

There is no satisfactory therapy for Semmola-Meryon-Duchenne syndrome. Two Iraqi brothers with Semmola-Meryon-Duchenne syndrome are described, and the literatures suggesting a possible therapeutic role of nutritional supplements are examined.

Two brothers were seen at the Children Teaching Hospital of Baghdad Medical City on the second of June, 2018 because progressive weakness of the lower limbs resulting in awkward walking, and difficulty with running and standing up. Their difficulty was more obvious during climbing stairs as they needed to hold the bar of the stairs. The parents and a sister were healthy.

The younger brother aged five years, and had difficulty in squatting, standing from sitting, climbing stairs, and Gower sign (A sign associated with weakness of the proximal muscles of the lower limb. The sign is positive when a patient has to use their hands and arms to "walk" up their body from a squatting position because of weakness of hip and thighs). Was positive (Figure 3). At the clinic the boy was rather hyperactive and difficult to control.

Nerve conduction study was performed by surface and needle electrode on right median nerve, right ulnar nerve, right and left common peroneal nerves. The nerve conduction study (Table 1) showed, reduced amplitude of the compound action potentials, normal sensory parameters, normal distal motor latencies, motor conduction velocities, and normal F-wave latencies.

Figure 3: The younger brother with Semmola-Meryon-Duchenne syndrome had difficulty in squatting, standing from sitting, and Gower sign.

Needle Electromyography (EMG) study was performed on right deltoid, right biceps, right brachial-radials, right vastus medialis, right and left tibialis anterior, and gastrocnemious muscle. Needle Electromyography (EMG) study (Table 1) showed increased resistance to needle insertion, spontaneous activity grade 2 to 3, in the form of fibrillation and positive sharp waves, and no myotonic discharges. The average duration of 20 MUAP: Right deltoid=5.1 msec (n=8.1 msec), right biceps=5.1 msec (n=8.S msec). Right vastus medialis=5.4 msec (n=8.1 msec), right tibialis anterior=7.1 msec (n=10 msec), left tibialis anterior=7.7 msec (n=10 msec).

Polyphasia of short duration low amplitude was observed in 20% to 30%. Early full recruitment pattern of low amplitude.

The findings of the nerve conduction and Electromyography (EMG) study supported the clinical diagnosis as they were consistent with chronic diffuse dystrophic myopathic process of moderate to severe degree. The proximal lower limb muscles were maximally involved. The findings of the nerve conduction and Electromyography (EMG) study showed no evidence of peripheral polyneuropathy or anterior horn cell diseases.

The older brother aged seven years, and had less difficulty in squatting than his younger brother , but he also had difficulty standing from sitting and in climbing stairs, and Gower sign was positive (Figure 4).

Nerve conduction study was performed by surface and needle electrode on right median nerve, right ulnar nerve, right and left common peroneal nerves. The nerve conduction study (Table 2) showed reduced amplitude of the compound action potentials, normal sensory parameters, normal distal motor latencies, motor conduction velocities, and normal F-wave latencies. Needle Electromyography

Figure 4: The older brother difficulty in squatting, difficulty standing from sitting, and Gower sign was positive.

Table 1: Nerve conduction and needle Electromyography (EMG) studies of the younger brother.

	Sensory				Motor		
Nerve	Latency msec/cm	Amplitude-μV	SNCV m/sec	Muscle	DML Msec/cm	WNCV msec/cm	F-wave Latency
Right median	2.1	20.3	66.3	APB	3	51.5	20.3
Right ulnar	2	22.2	68.2	FDI	2.9	66.6	21.2
Right common peroneal				Tibialis Ant.	3.5		
				EDB	4.2	42.5	42.5
Left common peroneal				Tibialis Ant.	3.6		
				EDB	4.3	43.2	44.2
Left sural	2.2	14.2	41.2				

Table 2: Nerve conduction and needle Electromyography (EMG) studies of the older brother.

	Sensory				Motor		
Nerve	Latency msec/cm	Amplitude-μV	SNCV m/sec	Muscle	DML Msec/cm	WNCV msec/cm	F-wave Latency
Right median	2.2	20.3	56.3	APB	3.2	56.5	22.3
Right ulnar	2	22.2	58.2	FDI	3	55.6	23.2
Right common peroneal				Tibialis Ant.	3.5		
				EDB	4.2	42.5	45.5
Left common peroneal				Tibialis Ant.	3.6		
				EDB	4.3	43.2	46.2
Left sural	2.2	15.2	44.2				

(EMG) study was performed on right deltoid, right biceps, and right brachio-radials. Right vastus medialis, right and left tibialis anterior, and gastrocnemious muscle.

Needle Electromyography (EMG) study (Table 2) showed increased resistance to needle insertion, spontaneous activity grade 2 to 3, in the form of fibrillation and positive sharp waves and no myotonic discharges. The average duration of 20 MUAP: Right deltoid = 4.1 msec (n = 9 msec), right biceps = 5.1 msec (n = 8.8 msec), right vastus medialis = 3.3 msec (n = 9 msec), right tibialis anterior = 5.6 msec (n = 11 msec) m, left tibialis anterior = 5.1 msec (n = 11 msec). Polyphasia of short duration low amplitude was observed in 20%-30%. Early full recruitment pattern of low amplitude.

The findings of the nerve conduction and Electromyography (EMG) study supported the clinical diagnosis as they were consistent with chronic diffuse dystrophic myopathic process of moderate to severe degree. The proximal lower limb muscles were maximally involved. The findings of the nerve conduction and Electromyography (EMG) study showed no evidence of peripheral polyneuropathy or anterior horn cell diseases.

The two brothers developed obvious hypertrophy of the calf muscles during the course of their illness.

Review of the relevant literature suggested a possible therapeutic role of nutritional supplements in Semmola-Meryon-Duchenne syndrome. The use of Coenzyme Q10 in the treatment of Semmola-Meryon-Duchenne syndrome can lower the elevated serum creatine phosphokinase which results from deteriorating muscle. The muscles of patients with muscular dystrophy may be deficient in a Coenzyme Q10. L-Arginine is a potential treatment for Semmola-Meryon-Duchenne as it may increase utrophin levels in muscles. Utrophin is another cytoskeleton protein with over 80% homology with dystrophin and may compensate for the lack of dystrophin in muscles. Glutamine therapy in Semmola-Meryon-Duchenne syndrome may have beneficial protein-sparing effect as it reduce whole body protein degradation and glutamine de novo synthesis leading to sparing of nitrogen precursors. Ten days of oral glutamine and amino acid supplementation can equally inhibit whole-body protein degradation in children with Semmola-Meryon-Duchenne syndrome. The use of creatine monohydrate 5 grams daily in the treatment of Semmola-Meryon-Duchenne syndrome can preserve muscle strength in the short term [3-14].

The two patients were treated with supplementation of amino acids, coenzyme Q10, glutamine, and creatine monohydrate. Within six weeks, the parents noticed some improvement in muscular strength with lessening of the difficulties in squatting and climbing stairs.

Discussion

There is no satisfactory therapy for many of the disabling genetic disorders such as Semmola-Meryon-Duchenne syndrome. However, it is hoped that emerging research evidence can contribute to improving treatment of such conditions. Therefore, reviewing the relevant literature for the recent research evidence is recommended to improve the therapeutic services for patients with such disorders.

Several therapies have been tried for the treatment of muscular dystrophy during the 1950s and 1960s. However, treatment was not associated with convincing therapeutic effect. Some clinical improvement in uncontrolled studies has been reported with treatment with anabolic steroids (De Toni, 1959; Bekeny and colleagues, 1959; Hantschmann, et al. 1962; Dowben, 1960S). However, in one controlled trial, Barwick and colleagues (1963) found that two anabolic steroids didn't give better response than a placebo [1].`

Laevadosin (a nucleotide-nucleoside mixture preparation) was tried by Beckmann (1959, 1964). Treatment was not associated with functional improvement in patients with rapidly progressive muscular dystrophy and irreversible muscle damage. However, benefit occurred in some patients treated with Laevadosin. Thomson and Guest (1963) used Laevadosin in six patients with Semmola- Meryon-Duchenne syndrome and in one patient with the limb-girdle muscular dystrophy. The patients were used as their own controls. Parenteral Laevadosin was given for forty days.

Thomson and Guest noticed some amelioration of the dystrophic process as there was an increase in muscle power and reduced activity of serum aldolase and transaminases. In another study Guest and McLay (1964) also used patients as their own control. They found improvement in nineteen patients treated with Laevadosin for 5 and 28 months. In a controlled trial, Pearce et al. [2] treated patients with the Semmola-Meryon-Duchenne syndrome with Laevadosin for six weeks. They assessed response to treatment by objective assessment of changes in muscle power and the level of serum creatine kinase. They did not observe any benefit associated with treatment compared with placebo group.

Folkers et al. [3] emphasized that the serum elevation of creatine phosphokinase results from deteriorating muscle. They thought that there could be a Coenzyme Q10 deficiency in muscles of patients with muscular dystrophy. They suggested that restoration of Coenzyme Q10 activity in muscles by treatment could possibly increases the use of creatine phosphokinase in muscles to form phosphocreatine from creatine and ATP resulting in lowering serum creatine phosphokinase. They treated children with preclinical muscular dystrophy with Coenzyme Q10. They found the followings:

A 40-week treatment of an infant (1 year to 2 years of age) lowered serum creatine phosphokinase (P<0.001; total creatine phosphokinase assays, 76).

A 40-week treatment of a boy (3.5 years of age) lowered serum creatine phosphokinase (P<0.01), whereas treatment for 80 weeks lowed creatine phosphokinase (P<0.001; total creatine phosphokinase assays, 118).

Folkers et al thought that the response of preclinical dystrophy to Coenzyme Q10 suggests deficiency of Coenzyme Q10 in skeletal muscle [3].

Folkers et al. [4] emphasized that heart disease is commonly associated with almost all muscular dystrophies and myopathies. In a double-blind and open crossover trial, they enrolled twelve patients with progressive muscular dystrophies and neurogenic atrophies. Disorders included Semmola-Meryon-Duchenne syndrome, Becker muscular dystrophy, and limb-girdle dystrophies, myotonic dystrophy, Charcot-Marie-Tooth disease, and Welander disease.

Folkers et al monitored the impaired cardiac function non-invasively by impedance cardiography. Eight patients were treated with Coenzyme Q10 and four patients were treated with placebo, and all were correctly assigned (P less than 0.003). After three months, four patients in the treatment group experienced improved physical well-being, while none of the placebo patients experienced such improvement. The four patients in the placebo group were treated later with Coenzyme Q10 and three of them showed improvement. Six of the eight patients in the Coenzyme Q10 group were treated with placebo; five of the six maintained improved cardiac function while one of the patients whom crossed over from Coenzyme Q10 group to placebo relapsed.

Folkers et al. thought that the impaired myocardial function of patients with muscle disease has an association with impaired function of skeletal muscle, and thus both may benefit from Coenzyme Q10 therapy. Folkers et al. [4] hypothesized that Coenzyme Q10 therapy could have improved some underlying mitochondrial impairment.

Chaubourt et al. [5] from Laboratoire de Neurobiologie Cellulaire et Moléculaire in France emphasized that progressive muscle degeneration in Semmola-Meryon-Duchenne syndrome results from a lack of dystrophin, a membrane cytoskeleton protein. Chaubourt, et al. suggested that treatment of Semmola-Meryon-Duchenne syndrome can be based theoretically on compensation of dystrophin loss with utrophin which is another cytoskeleton protein with over 80% homology with dystrophin. Utrophin is expressed, at the neuromuscular junction, in normal and Semmola-Meryon-Duchenne syndrome muscles and possibly can perform the cellular functions of dystrophin. Thus, finding a therapeutic agent which can up-regulate utrophin is a very logic goal for therapy.

In normal adult mice and in an animal (mice) model of Semmola-Meryon- Duchenne dystrophy, treatment with L-Arginine, the substrate of nitric oxide synthase led to:

- The appearance of a pool of utrophin localized at the membrane which increased.
- L-Arginine (or nitric oxide, and hydroxyurea) increased utrophin levels and enhanced its membrane localization in cultured myotubes.

This effect did not occur with D-Arginine suggesting involvement of nitric oxide synthase in this process. Chaubourt et al. [5] thought that L-Arginine is a potential treatment for Semmola-Meryon-Duchenne and Becker dystrophies.

Folkers and Simonsen [6] from the Institute for Biomedical Research, University of Texas conducted two successful double-blind trials with coenzyme Q10 (vitamin Q10). The first double-blind trial included twelve patients (age: 7 years to 69 years) who had Semmola-Meryon-Duchenne and Becker dystrophies, limb-girdle dystrophies, myotonic dystrophy, Charcot-Marie-Tooth disease, and Welander disease.

The control coenzyme Q10 (CoQ10) blood level was low and ranged from 0.5 microgram/ml to 0.84 microgram/ml. They patients were treated for three months with 100 mg coenzyme Q10 daily and a matching placebo. The second double-blind trial included fifteen patients who had the same disorders. A definite improvement in physical performance was observed.

Hankard et al. [7] from Nemours Children's Clinic in Florida studied protein anabolic effect of glutamine in six boys with Semmola-Meryon- Duchenne syndrome. The patient s age ranged from 8years to 13 years. The study suggested that acute oral glutamine may have protein-sparing effect in children with Semmola-Meryon-Duchenne syndrome by reducing whole body protein degradation and glutamine de novo synthesis leading to sparing of nitrogen precursors.

Hankard et al. [8] from Nemours Children's Clinic in Florida treated six children with Semmola-Meryon-Duchenne syndrome received intravenous infusion of L-[1-(13) C] leucine and L-[2-(15) N] glutamine in the post- absorptive state. Five weight and height matched controls received the same. Glutamine rate of appearance was about 24% lower boys with Semmola- Meryon-Duchenne syndrome than in controls. Hankard et al [8]. suggested that dramatic muscle mass loss in boys with Semmola-Meryon-Duchenne syndrome is associated with a significant protein wasting. The increased leucine oxidation reflects a more negative whole body leucine balance, and a significant decrease in glutamine availability in the post-absorptive state. Hankard et al. thought that glutamine could be a conditionally essential amino-acid in Semmola-Meryon-Duchenne syndrome.

A study conducted by Mok et al. [9] from Paris found that ten days of oral glutamine and amino acid supplementation equally inhibited whole-body protein degradation in children with Semmola-Meryon-Duchenne syndrome.

Evangeliou et al. [10] from Aristotle University in Greece reviewed the literature to assess the clinical applications of creatine supplementation in pediatrics. They found data suggesting short and long-term therapeutic benefit of creatine supplementation in children with muscular dystrophies including facioscapulohumeral dystrophy, Becker dystrophy, Semmola-Meryon- Duchenne syndrome and sarcoglycan deficient limb girdle muscular.

Banerjee et al. [11] from All India Institute of Medical Sciences in New Delhi conducted a randomized, placebo-controlled single blinded study to evaluate the effect of oral creatine supplementation in thirty three steroid- naive, ambulatory boys with Semmola-Meryon-Duchenne syndrome. Eighteen patients received creatine monohydrate 5 grams daily for eight weeks, while 15 received placebo (500 mg of vitamin C). Parents of the patients reported subjective improvement on creatine supplementation versus worsening in placebo (P=.02). Banerjee et al found that creatine monohydrate was well tolerated and oral creatine monohydrate significantly improved the muscle phosphocreatine /inorganic phosphate ratio and preserved the muscle strength in short term.

Tarnopolsky from McMaster University in Ontario, Canada suggested that creatine supplementation can enhance function in myopathies patients by

- Improving muscle mass and strength
- Improve endurance
- Lowering calcium levels
- Providing anti-oxidant effects
- Reducing apoptosis

Patients with muscular dystrophy respond to several months of creatine monohydrate supplementation (0.075 g/kg/day to 0.1 g/kg/day) with greater strength (9%) and fat-free mass (0.63 kg). Patients with myotonic dystrophy do not show as consistent effect, possibly due to creatine transport issues. Creatine monohydrate supplementation shows modest benefits only at lower doses and possibly negative effects (cramping) at higher doses in McArdle's disease patients. The side effects of creatine supplementation in all groups of myopathies were negligible in comparison to the very substantial and well-known side effects from the use of corticosteroids in myopathies [12].

Letellier from France emphasized that glutamine is a potent gluconeogenic precursor and stimulates insulin secretion. In a randomized crossover trial on thirty pre-pubertal boys with Semmola-Meryon-Duchenne syndrome, they found that acute glutamine transiently stimulates insulin secretion boys with this condition [13].

Felber et al. [14] from Salzburg, Austria thought that the decrease in intracellular creatine concentration in Semmola-Meryon-Duchenne syndrome results in deterioration of intracellular energy homeostasis and cause aggravation of muscle weakness and degeneration. They treated a 9-year-old patient with Semmola-Meryon-Duchenne syndrome with oral creatine supplementation for 155 days. They suggested a potential role for creatine supplementation in the symptomatic therapy of patients with muscle disease.

Conclusion

Nutritional supplements including coenzyme Q10, L-Arginine, glutamine, and creatine may have some beneficial effects when used in the treatment of Semmola-Meryon-Duchenne syndrome.

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