Mediterranean Journal of Nutrition and Metabolism 7 (2014) 173–179
DOI:10.3233/MNM-140017
IOS Press

Nutritional treatment in a patient affected by Mithochondrial Neuro-Gastrointestinal Encephalomyopathy (MNGIE)

Barbara Paolini[a,*], Irene Del Ciondolo[a], Elisa Lapini[a], Elisa Pasquini[a], Katia Gennai[a], Lucia Ceccarelli[a] and Fabio Ferretti[b]

[a] *UOSA Dietetica Medica, Azienda Ospedaliera Universitaria Senese Policlinico Santa Maria alle Scotte, Siena*
[b] *U.O.C. di Soddisfazione dell'Utenza e Sociologia Sanitaria*

Abstract. MNGIE is an uncommon, autosomal recessive multisystem disorder, caused by loss of function of mutations in the TYMP/ECGF1 encoding for thymidine phosphorilase (TP). MNGIE phenotype is characterized by gastrointestinal disorders, peripheral neuropathy, ophtalmoplegia and leukoencephalopathy. We report a clinical case of a 23 year old female, affected by MNGIE and submitted to allogeneic hematopoietic stem cells transplantation (HSCT). At the first nutritional status examination, weight was 36 Kg, BMI was 15 Kg/m^2 and bioimpedance showed a protein-caloric malnutrition. The clinical history revealed asthenia, abdominal pain, headache and amenorrhea. Her diet was unbalanced and insufficient. We elaborated a balanced and hyper caloric diet with a protein supplementation (10 g/day) with a concentrate of isolated whey proteins with high soluble cysteine content and a plant-based superoxide dismutase (SOD). Follows up were planned monthly, then after 3 months and the prescribed calorie intake was finally reached with a gradual improvement of her nutritional status. After one year and a half, weight was 40,5 Kg, BMI was 16,9 with an improvement of blood tests, BIA and muscle strength. Clinically the patient reported a significant improvement of asthenia, fatigue and of abdominal pain but amenorrhea persisted. Patients affected by MNGIE and submitted to HSCT improve their clinical status but malnutrition often persists. Nutritional counselling can positively affect clinical course of this disease, considerably improving body composition and symptoms.

Keywords: Malnutrition, MNGIE, nutritional treatment

1. Introduction

Mitochondrial Neuro-Gastrointestinal Encephalomyopathy (MNGIE) is an uncommon, autosomal recessive multisystem disorder, caused by loss of function mutations in the TYMP/ECGF1, the gene encoding thymidine phosphorilase (TP). TP deficiency leads to a general increase in its substrates, deoxythymidine (dThd) and deoxyuridine (dUrd) in urine and serum and to an impairment in mitochondrial DNA replication and repair [1, 2].

It is classified as an uncommon disease but its exact prevalence is unknown [3], we have identified 138 patients till now, both genders are equally affected [4]. This disease is spread in whole the world even if we notice a moderately high prevalence in Europe. A study conducted in 2011 in a group of 102 patients showed that 53% were from Europe, 13,7% from America, 13,7% from Asia, 3% from Oceania [5]. One third of the affected patients has consanguineous parents [6] and one half of these patients has brothers or sisters or other relatives who are affected by MNGIE.

However we report differences in their clinical presentation of the disease even in patients with the identical mutation of Thymidine phosphorilase (TYMP) gene, and in the same family, so that we can assume that environmental factors or other genetic factors can affect the phenotype [7].

*Corresponding author: Barbara Paolini, UOSA Dietetica Medica, Azienda Ospedaliera Universitaria Senese Policlinico Santa Maria alle Scotte, Siena. E-mail: barbara-paolini@libero.it.

ISSN 1973-798X/14/$27.50

Table 1
Variations of blood tests during nutritional treatment

	1° visit	1° month	2° month	3° month	4° month	5° month	9° month	12° month	15° month
Total protein (g/dl)	6,4	6,6	6,8	6,6	7	7	5,8	5,8	6,4
Normal range 6,0-8,0									
Albumin (g/dl)	3,9	4,06	3,93	3,96	3,85	4,13	3,2	3	3,4
Normal range 3,5 e 5,0									
Transferrin (mg/dl)	323	304	347	370	380	432	300	298	370
Normal range 200–400									
Prealbumin (mg/dl)	20	22	39,5	39,8	40	40	25	19,7	22,6
Normal range 20–40									

MNGIE phenotype is characterized by severe gastrointestinal dismotility, peripheral neuropathy, ophtalmoplegia and leukoencephalopathy. The typical patient is thin and short. The gastrointestinal disorders (vomiting, diarrhea, cramps, dysphagia, intestinal pseudo-obstruction, gastro paresis) slowly lead to intestinal obstruction that evolves in cachexia. We report a clinical case of a 23 year old Italian female who came for a nutritional evaluation in March 2011, sent by the department of "Malattie Neurometaboliche", affected by MNGIE (diagnosed in May 2009 when she was 21 year old-date of birth: 04/03/1987) and submitted to allogeneic hematopoietic stem cells transplantation (HSCT) in April 2010 [8].

We carried out a descriptive statistical analysis of these values to describe their variations in time (between the beginning of the therapy, after 9 months and after 15 months).

The aim of our nutritional treatment was to improve body composition, nutritional status, clinical symptoms and the global health condition. The dietetic therapy intended to supply a balanced intake of energy and nutrients with an eventual supplementation of protein.

2. Case report

Diagnosis was made when she reported cervicobrachialgia and paresthesia arisen after a car accident. The patient's clinical history disclosed repeated episodes of abdominal pain, recurrent vomiting and diarrhoea severe asthenia, less resistance to fatigue, headache, amenorrhea since the age of 15. Physical examination revealed short stature (155 cm) and thinness (weight 37 Kg) with a Body Mass Index (BMI = weight/height Kg/ m^2) of 15,4 Kg/m^2.

Neurological examination showed a moderate limbs weakness, absence of deep reflex, a moderate eyelid ptosis but unimpaired perception. Serum lactic acid levels were increased (2,3 mmol/l, normal range: 0,3-1,3 mmol/l). The analysis on peripheral nerve conduction showed a sensitive-motoric neuropathy, so that we suspected the diagnosis of MNGIE. Leucocitary TP activity was absent (normal range 75–850 nmol/h/mg) and plasma levels of thymidine and deoxyuridine were increased (respectively 9,0 and 16,0 μmol/L). Brain RM showed bilateral alterations in the periventricular white matter [9]. These results allowed us to make the final diagnosis of MNGIE.

The diet was divided into 7 meals with regard to the need of assuming medical therapy and because of the difficulty of the patient to assume large meals.

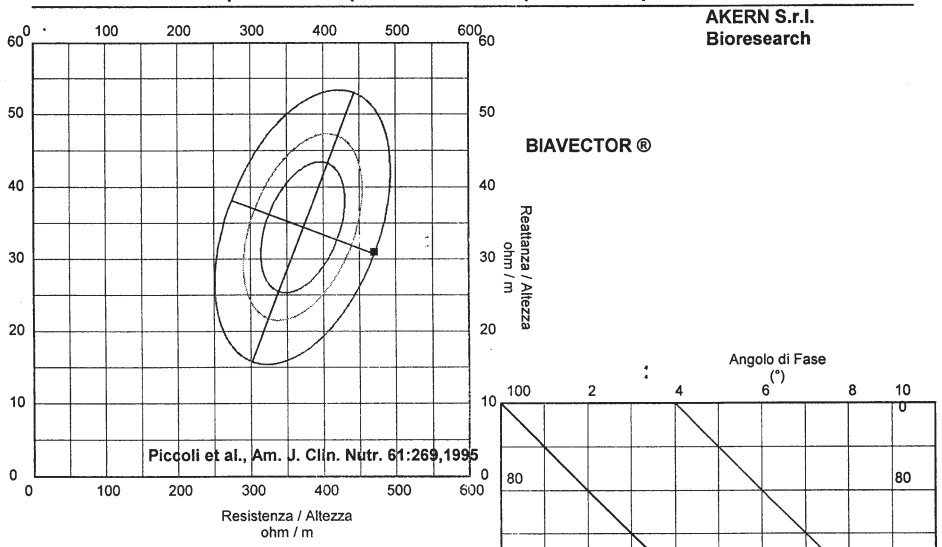
In April 2010 she was submitted to HSCT from a consanguineous donor (her brother), one month after HSCT gastrointestinal symptoms and asthenia disappeared. One year after HSCT we noticed a significant improvement in muscle strength measured by Medical Research Council (MRC) score. Ptosis and areflexia were still present and the sensitive-motoric neuropathy still persisted. Since the first month after HSCT, leucocitary TP activity had normalized together with plasma levels of thymidine and deoxyuridine, lactic acid had reached levels of 1,5 mmol/l [10, 11]. At the first nutritional status examination, weight was 36 Kg and BMI was 15 Kg/m^2 (severely underweight).

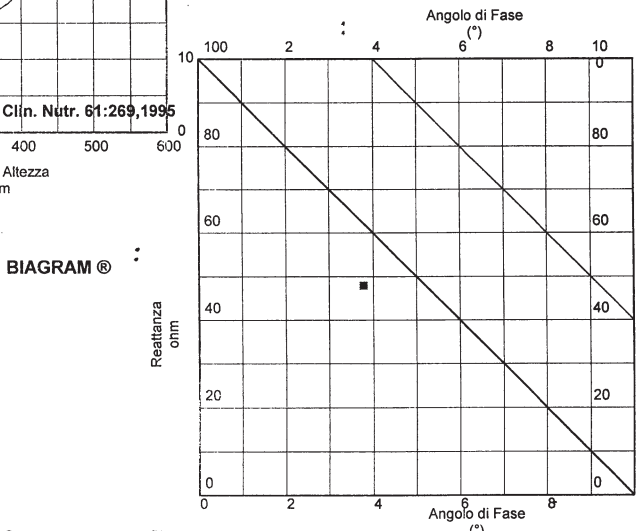
Triceps and subscapular skin measured with Holtain plicometer were respectively 6,5 mm and 5,2 mm; these values showed an extreme reduction of the adipose panniculo and confirmed the condition of malnutrition. Muscle strength measured by Hand Dynamometer JAMAR showed very low values (right 16 Kg, left 15 Kg).

Table 2
Results of bioimpedance at the first visit

BODYGRAM - Analisi quantitativa e qualitativa della composizione corporea

AKERN S.r.l.
Bioresearch





Soggetto S

Sesso :	F
Eta' :	**23**
Altezza :	**155 cm**
Peso :	**36 kg**
Resistenza :	**731 ohm**
Reattanza :	**48 ohm**
Angolo di Fase :	**3,8°**

giorno esame
Ora esame
■ Primo Esame
XC/H = 30,97 ohm/m
RZ/H = 471,61 ohm/m
● Esame Corrente
XC/H = 30,97 ohm/m
RZ/H = 471,61 ohm/m

giorno esame
Ora esame
■ Primo Esame
XC = 48 ohm
PA = 3,8°
● Esame Corrente
XC = 48 ohm
PA = 3,8°

Risultati

Na/K Scambiabile	**= 1,7**	Peso Massa Magra	**= 33,0 kg (91,6%)**
Massa Cellulare	**= 11,4 kg (34,6%)**	Massa Muscolare	**= 15,1 kg (41,9%)**
Acqua Totale	**= 24,1 lt (67,0%)**	Metabolismo Basale	**= 626,7 kcal**
Acqua Extracellulare	**= 14,2 lt (59,0%)**	BMI	**= 15,0**
Acqua Intracellulare	**= 9,9 lt (41,0%)**	BCMI	**= 4,7**
Peso Massa Grassa	**= 3,0 kg (8,4%)**		

Table 3
Variations of weight, BMI, PA, BCM/weight and BCMI during nutritional treatment

	1° visit	1° month	2° month	3° month	4° month	5° month	9° month	12° month	15° month
Weight (kg)	36	35,8	36,6	36	36	35,9	38,1	39	40,5
BMI (Kg/m^2)	15	14,9	15,2	15	15	14,9	15,9	16,2	16,9
PA°	3,8	4	4,4	5	5,5	5,4	5,6	4,8*	6,2 (+39%)
BCM/Weight (%)	34,6	36,3	41,4	46,5	49,7	49,2	53,1	45,4	57,2% 50% (38%)
BCMI	4,7	4,9	5,9	6,4	6,7	6,6	7,8	6,6	8,5 (+45%)

At the first nutritional examination we evaluated the following blood tests: glycemia, uric acid, cholesterol, LDL, HDL, triglyceride, total, conjugated ad un conjugated bilirubin, SGOTT, SGPT, GAMMA GT, TSH, fT3, fT4, creatinine, blood urea, sodium, potassium, blood count, blood iron, serum ferritin, transferring, total protein, albumin, prealbumine, alkaline phosphatases, cholinesterase. For the evaluation of the nutritional status we noticed in particular total protein and other protein with different half life:

- Albumin, with a slow turnover: 3,9 g/dl
- Transferrin, with a medium turnover: 323 mg/dl
- Prealbumin, with a fast turnover: 20 mg/dl

Bioimpedance showed a protein and caloric malnutrition, with a phase angle of 3,8°, BIAGRAM graphic showed and impairment in hydration (water retention) with an increase in extracellular water.

Even if all the blood tests related to nutritional status (total protein, transferrin, prealbumin) were within the normal limits, anthropometric measurements and bioimpedance showed a state of protein-caloric malnutrition.

According to the nutritional history her diet appeared unbalanced, her mean daily caloric intake of 1800 Kcal, protein 11% (53 g = 0,9/Kg of ideal weight of 55 Kg), lipid 49%, carbohydrates 40% and fiber 12 g, which was insufficient for her needs. We noticed an excessive lipid assumption (mainly saturated fats because of the meal seasoning and too elaborate cooking methods) and a poor fiber intake (fruit and vegetables). To accurately determine her caloric intake we used a photographic Atlas: Atlante Fotografico delle porzione degli Alimenti dell'Istituto Scotti Bassani.

We elaborated a balanced and hyper caloric diet above all 2650 Kcal, with 10 g of protein supplementation with this distribution of nutrients: protein 16%, lipids 29%, carbohydrates 55%. With the protein supplementation we reached 97 g of protein which was 1,76 g/Kg of ideal weight, seeing that she had not renal or liver failure.

We added the protein supplement because the patient found it difficult to eat large sizes of meat and fish, so the supplementation granted a minimum protein intake. This supplementation is a concentrate of isolated whey proteins with high soluble cysteine content and a plant-based superoxide dismutase (SOD). This product is recommended in malnutrition in patients with an increased need of glutathione and antioxidants and it is used in the dietetic therapy in patients with a severe lack of protein and endogenous antioxidants. It helps to stimulate immune response and it improves the asthenia typical of these patients.

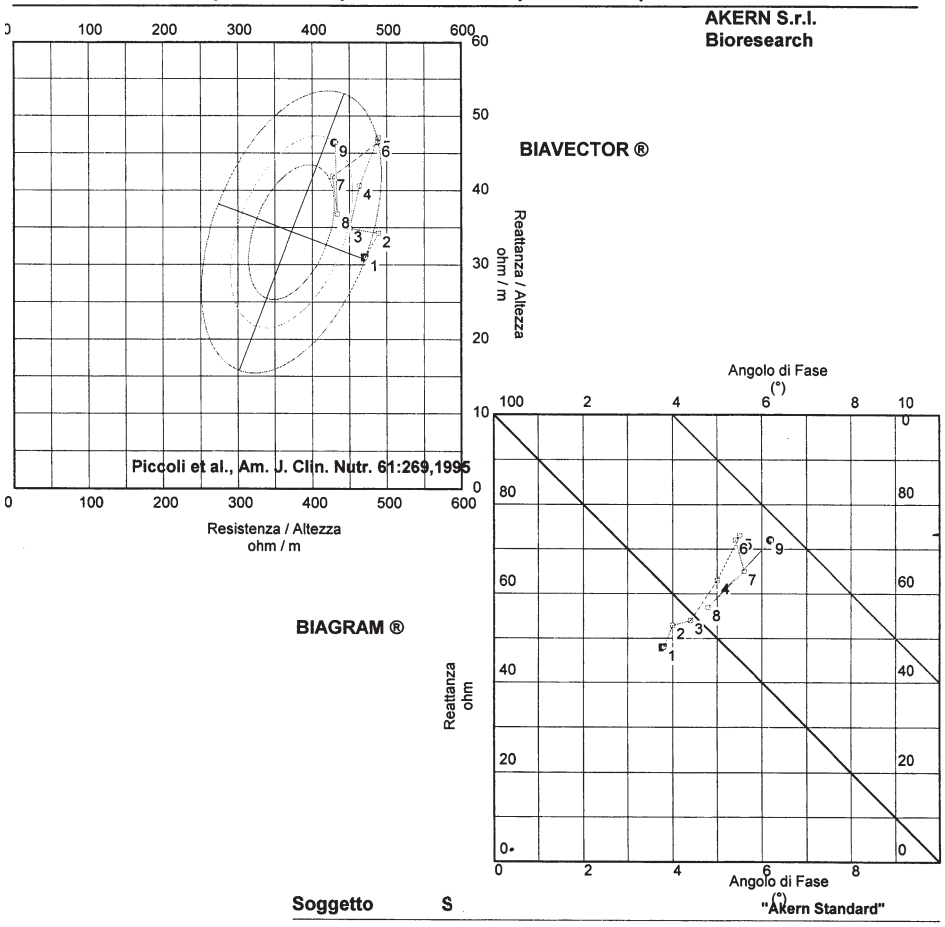
We asked her to fulfill a 24 hour recall to evaluate her compliance to the nutritional therapy from a quantitative and qualitative point of view.

Follows up were planned monthly for the first 5 months then every 3 months. The prescribed calorie intake was gradually reached thanks to the care and the goodwill of the patient, who at the beginning wasn't able to finish her meals because of early satiety and lack of appetite. During the period of observation, we noticed a gradual improvement of her nutritional status, except from an attack of gastroenteritis (after 5 months) and in particular a transplant rejection (after 9 months), when the patient found difficult to maintain a suitable calorie intake because of nausea and recurrent vomiting for which she had to assume probiotic and prokinetic agents. After 9 months we also noticed a worsening of blood tests with:

- Total protein 5,8 g/dl
- albumin 3 g/dl
- transferrin 298 mg/dl
- prealbumin 19,7 mg/dl

Table 4
Results of bioimpedance at the first visit

BODYGRAM - Analisi quantitativa e qualitativa della composizione corporea



Soggetto **S**

Sesso :	F
Eta' :	**25**
Altezza :	**155 cm**
Peso :	**40,5 kg**
Resistenza :	**668 ohm**
Reattanza :	**72 ohm**
Angolo di Fase :	**6,2°**

giorno esame
Ora esame
■ Primo Esame
XC/H = 30,97 ohm/m
RZ/H = 471,61 ohm/m
● Esame Corrente
XC/H = 46,45 ohm/m
RZ/H = 430,97 ohm/m

giorno esame
Ora esame
■ Primo Esame
XC = 48 ohm
PA = 3,8°
● Esame Corrente
XC = 72 ohm
PA = 6,2°

Risultati

Na/K Scambiabile	**= 1,1**		
Massa Cellulare	**= 20,3 kg (57,2%)**	Peso Massa Magra	**= 35,5 kg (87,8%)**
Acqua Totale	**= 26,0 lt (64,2%)**	Massa Muscolare	**= 24,8 kg (61,3%)**
Acqua Extracellulare	**= 11,7 lt (45,0%)**	Metabolismo Basale	**= 1117,5 kcal**
Acqua Intracellulare	**= 14,3 lt (55,0%)**	BMI	**= 16,9**
Peso Massa Grassa	**= 5,0 kg (12,2%)**	BCMI	**= 8,5**

At the 9th month bioimpedance showed a reduction of PA (4,8°) probably because of edema due to the lack of protein, in this period protein supplementation was 20 g/daily.

At the first nutritional examination blood test resulted within the normal limits one year after HSCT, and bioimpedance showed a protein caloric malnutrition, as from the value of PA and hydration. Clinically our first examination showed a persistence of her symptoms (less resistance to fatigue, asthenia, abdominal discomfort). Weight had gradually augmented, even in conjunction with the transplant rejection because of corticosteroids therapy that she had assumed since February 2012 (11th month since the beginning of nutritional treatment) to June 2012 (14th month), with a starting dose of 25 mg/day, with a gradual reduction of the dose and which she had definitely suspended in July 2012 (15th month).

In the 5th month weight was unvaried, while PA and hydration had almost normalized.

After one year and a half, weight was 40,5 Kg (increase of 4,5 Kg), BMI was 16,9 Kg/m^2, with an evident improvement of the nutritional status, confirmed by blood tests, bioimpedance and muscle strength measured by hand grip (right 25 Kg, left 22 Kg). The patient reported a significant reduction of asthenia, fatigue and abdominal pain but amenorrhea still persisted.

Bioimpedance after 15 months showed an improvement in the body composition (BIAVECTOR from point 1 that represents the initial condition and point 9 at the end of nutritional treatment). Hydration and nutritional status had improved and PA reached normal values (6,2°) [12].

3. Conclusions

It's interesting to note that our patient has well tolerated the high caloric intake prescribed: this result has been possible because, even before our nutritional intervention, she already assumed a hyper lipid and caloric diet and getting up very early in the morning, she could have 2 breakfasts and 3-4 snacks during the day.

As regards BIA and BIVA we must say that these exams have limitations in their results in patients who are affected by severe malnutrition or who have body fluids alterations.

Today, 4 years after HSCT, the patient is still in a good clinical condition with resolution of gastrointestinal symptoms and of asthenia, but amenorrhea still persists and her weight remains unvaried.

HSCT is a treatment recently proposed for this disease and we have no available data about long terms follow ups of these patients. However many studies have demonstrated that HSCT is effective in almost all the cases to treat the biochemical features of MNGIE: it normalizes the TP levels in blood and deoxythymidine and deoxyuridine concentrations in urine. Its clinical efficiency hasn't been demonstrated yet, indeed in many patients neurological symptoms still persist and we have noticed only a partial resolution of gastrointestinal disorders, at last we haven't got any data about long term survival.

Another feature which needs to be clarified is the best time to submit MNGIE patients to HSCT, since transplant related morbidity and mortality increase with the progression of the disease and number of comorbidities. Therefore it is advantageous submitting MNGIE patients to HSCT, when they are relatively healthy, in order to minimize the complications of the procedure [13–15].

Patients affected by MNGIE and submitted to HSCT improve their clinical status but malnutrition often persists. A severe condition of cachexia can induce patients to follow an unbalanced and hyper lipid diet in order to increase their weight, however without any change in their nutritional status. In conclusion we can underline how nutritional counseling can positively affect the clinical course of this disease, considerably improving body composition and symptoms.

References

[1] Teitelbaum JE, Berde CB, Nurko S, Buionomo C, Perez-Atayde AR, Fox VL. Diagnosis and management of MNGIE syndrome in children: Case report and review of literature. Journal of Pediatric Gastroenterology and Nutrition 2012;35:377-83.

[2] Hirano M, Nishigaki Y, Martí R. Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE): A disease of two genomes. Neurologist. 2004;10(1):8-17.

[3] Shoffner JM. Mitochondrial Neurogastrointestinal Encephalopathy Disease. In: Pagon RA, Adam MP, Bird TD, Dolan CR, Fong CT, Stephens K, editors. updated 2010 May 11.

[4] Hirano M, Garone C, Quinzii CM. CoQ(10) deficiencies and MNGIE: Two treatable mitochondrial disorders. Biochim Biofis Acta. 2012;1820(5):625-31.

[5] Garone G, Tadesse S, Hirano M. Clinical and genetic spectrum of mitochondrial neurogastrointestinal encephalomyopathy. BRAIN. 2011;134:3326-32.

[6] Nishino I, Spinazzola A, Papadimitriou A, Hammans S, Steiner I, Hahn CD, Connolly AM, Verloes A, Guimarães J, Maillard I, Hamano H, Donati MA, Semrad CE, Russell JA, Andreu AL, Hadjigeorgiou GM, Vu TH, Tadesse S, Nygaard TG, Nonaka I, Hirano I, Bonilla E, Rowland LP, DiMauro S, Hirano M. Mitochondrial neurogastrointestinal encephalomyopathy: An autosomal recessive disorder due to thymidine phosphorylase mutations. Ann Neurol. 2000;47(6):792-800.

[7] Lara MC, Valentino ML, Torres-Torronteras J, Hirano M, Martí R. Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE): Biochemical features and therapeutic approaches. Biosci Rep. 2007;27:151-163.

[8] Cardaioli E, Da Pozzo P, Malfatti E, Battisti C, Gallus GN, Gaudiano C, Macucci M, Malandrini A, Margollicci M, Rubegni A, Dotti MT, Federico A. A second MNGIE patient without typical mitochondrial skeletal muscle involvement. Neurol Sci. 2010;31(4):491-4.

[9] Cardaioli E, Sicurelli F, Carluccio MA, Gallus GN, Da Pozzo P, Mondelli M, Margollicci MA, Micheli V, Federico A, Dotti MT. A new thymidine phosphorylase mutation causing elongation of the protein underlies mitochondrial neurogastrointestinal encephalomyopathy. J Neurol. 2012;259(1):172-4.

[10] Sicurelli F, Carluccio MA, Toraldo F, Tozzi M, Bucalossi A, Lenoci M, Jacomelli G, Micheli V, Cardaioli E, Mondelli M, Federico A, Marotta G, Dotti MT. Clinical and biochemical improvement following HSCT in a patient with MNGIE: 1-year follow-up. J Neurol. 2012;259(9):1985-7.

[11] Filosto M, Scarpelli M, Tonin P, Lucchini G, Pavan F, Santus F, Parini R, Donati MA, Cotelli MS, Vielmi V, Todeschini A, Canonico F, Tomelleri G, Padovani A, Rovelli A. Course and management of allogeneic stem cell transplantation in patients with mitochondrial neurogastrointestinal encephalomyopathy. J Neurol. 2012;259(12):2699-706.

[12] Kyle UG, Genton L, Pichard C. Low phase angle determined by bioelectrical impedance analysis is associated with malnutrition and nutritional risk at hospital admission. Clinical Nutrition. 2013;32(2):294-9. doi:10.1016/j.clnu.2012.08.001.

[13] Hirano M, Martí R, Casali C, Tadesse S, Uldrick T, Fine B, Escolar DM, Valentino ML, Nishino I, Hesdorffer C, Schwartz J, Hawks RG, Martone DL, Cairo MS, DiMauro S, Stanzoni M, Garvin JH Jr, Savage DG. Allogeneic stem cell transplantation corrects biochemical derangements in MNGIE. Neurology. 2006;67(8):1458-60. Epub 2006 Sep 13.

[14] Filosto M, Scarpelli M, Tonin P, Lucchini G, Pavan F, Santus F, Parini R, Donati MA, Cotelli MS, Vielmi V, Todeschini A, Canonico F, Tomelleri G, Padovani A, Rovelli A. Course and management of allogeneic stem cell transplantation in patients with mitochondrial neurogastrointestinal encephalomyopathy. J Neurol. 2012;259(12):2699-706 doi: 10.1007/s00415-012-6572-9. Epub 2012 Jun 19

[15] Lara MC, Valentino ML, Torres-Torronteras J, Hirano M, Martí R. Mithocondrial neurogastrointestinal encephalomyopathy (MNGIE): Biochemical features and therapeutic approaches. Biosci Rep. 2007;27(1-3):151-63.