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Parenteral nutrition improves nutritional status, autonomic symptoms and quality of life in transthyretin amyloid polyneuropathy

Massimo Russo [a], Gian Luca Vita [a], Claudia Stancanelli [b,c], Anna Mazzeo [b], Giuseppe Vita [a,b,*], Sonia Messina [a,b]

[a] *Nemo Sud Clinical Centre, AOU Policlinico, Messina, Italy*
[b] *Unit of Neurology, Department of Clinical and Experimental Medicine, University of Messina, Messina, Italy*
[c] *Biomedical Department of Internal and Specialistic Medicine, University of Palermo, Palermo, Italy*

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Abstract

Transthyretin familial amyloid polyneuropathy (TTR-FAP) is an inherited amyloidosis, leading to death in about ten years in most cases due to cardiac failure or wasting syndrome. Previous studies showed that modified body mass index was related to time before death, duration of gastrointestinal disturbances, malabsorption and functional capacity. We report two patients in whom nutritional status worsened despite diet modification, hypercaloric supplement and two relevant therapeutic approaches such as liver transplant and tafamidis meglumine, respectively. The first patient, a 52-year-old lady carrying Thr49Ala mutation, had a disease duration of twelve years and had lost weight up to 35 kg because of daily diarrhea. The second patient, a 63-year-old man with Glu89Gln mutation and a disease duration of fifteen years, was in the New York Heart Association (NYHA) Functional Classification class III and his weight was 39 kg. In both cases, a peripherally inserted central catheter was placed for parenteral nutrition. It allowed to improve their nutritional status and clinical conditions, with body weight gains of 11 and 8 kg in a one year follow-up, respectively. Moreover, reduction of autonomic symptoms including postural hypotension, nausea and diarrhoea was recorded with ameliorated quality of life. Our experience suggests that parenteral nutrition may be useful in reducing complications and disabilities in TTR-FAP patients, even when all dietary adjustments have been ineffective. Reasonably, the improvement in nutritional status may prolong survival in TTR-FAP patients.

Keywords: TTR-FAP; Familial amyloid polyneuropathy; Nutritional status; Parenteral nutrition; modified body mass index (mBMI)

1. Introduction

Familial amyloid polyneuropathy (FAP) is an autosomal dominant inherited form of amyloidosis, mostly associated with mutations of the transthyretin (TTR) gene. More than 100 point mutations in TTR gene have been identified so far, the most common being the Val30Met. Several phenotypes of TTR-FAP, including the polyneuropathic, oculoleptomeningeal, and cardiac types, have been reported, and heterogeneity of clinical features is described even for the same mutation [1]. Typically, the first symptoms occur in the fourth decade but very late onset, up to the 70s, has been reported [2]. Symptoms start with discomfort over the feet, including numbness and spontaneous pains. Later the syndrome is characterized by progressive sensorimotor and autonomic involvement with impotence, gastrointestinal symptoms, postural hypotension, and bladder dysfunction. Liver transplantation (LT) has a higher effectiveness in Val30Met versus non-Val30Met patients, being influenced by nutritional status, age, severity of neuropathy and cardiac involvement [1]. Tafamidis meglumine, a selective TTR kinetic stabilizer that inhibits the amyloid cascade, has been approved by European Medicines Agency in 2011, and promising new disease-modifying RNA therapies are on the horizon [3]. Death generally occurs in about 10 years, in most cases due to cardiac failure or wasting syndrome [4,5].

In a prospective study performed in 27 patients with TTR-FAP, modified body mass index (mBMI) was closely related to time before death, duration of gastrointestinal disturbances, malabsorption and functional capacity [6]. Furthermore, even the outcome after LT was different in patients with a mBMI greater than 600 at the time of LT [7–9].

We report our experience in two patients with TTR-FAP in whom the placement of a peripherally inserted central catheter (PICC) allowed to ameliorate nutritional status, autonomic function and quality of life (QOL).

* Corresponding author. Unit of Neurology and Neuromuscular Diseases, AOU Policlinico "G. Martino", Via Consolare Valeria 1, Messina 98125, Italy. Tel.: +39 090 221 2793; fax: +39 090 221 2789.
E-mail address: giuseppe.vita@unime.it (G. Vita).

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2. Case reports

2.1. Case 1

Patient 1 was a female carrying a Thr49Ala TTR mutation. She had a positive family history: her father and her uncle were affected. The patient started to complain of diarrhea, nausea and delayed gastric emptying sensation at the age of 40. Her weight before the onset of the disease was 55 kg (BMI 23.2). At the age of 44 she underwent LT. When she was 48 years old, she started a regular follow-up at our Neuromuscular Center, including Compound Autonomic Dysfunction Test (CADT) [10] and Norfolk Quality of Life-Diabetic Neuropathy (Norfolk QOL-DN) questionnaire [11]. At that time, her body weight was 50 kg (BMI 21.1, mBMI 796). For the presence of symptomatic orthostatic hypotension, she started treatment with midodrine. Neurological examination showed distal muscular weakness, weak/absent tendon reflexes, and mild distal reduction of pinprick and temperature sensation in lower limbs. Pallesthesia was normal. Nerve conduction studies showed a sensory-motor axonal polyneuropathy.

Two years later, she developed a sensory ataxic gait and for this reason the use of a stick became necessary; renal failure in conservative treatment was present. She continued to lose weight, up to 46 kg (BMI 19.4, mBMI 737). Symptoms of orthostatic hypotension became severe, with frequent syncopal episodes. Fludrocortisone 0.1 mg and compression of legs and abdomen were started. CADT score was 7.

At the age of 51, her body weight was 42 kg (BMI 17.7, mBMI 630), CADT was 4. 24-hour blood pressure monitoring showed a mean value of 95/64 mmHg with a reversed circadian blood pressure rhythm. She had clinical and echocardiographic signs of cardiac amyloidosis (NYHA II). A specific low fiber and hypercaloric diet, with integration of products formulated for optimal digestion and absorption, was prescribed. However, 1 year after, her body weight was 35 kg (BMI 14.8, mBMI 525). Diarrhea was present daily and a considerable worsening of CADT and Norfolk QOL-DN scores was recorded (Fig. 1).

We decided to add a stable parenteral nutrition and to decrease oral nutrition. For this purpose a PICC was placed. The patient added 1 liter/day of Oliclinomel N4-550e (BAXTER). Further intravenous hydration was administered occasionally by the general practitioner.

After six months, we recorded an important gain of weight, up to 45 kg (BMI 19, mBMI 750) with a clinical improvement documented by increased blood pressure. CADT score rose from 1 to 8 and Norfolk QOL-DN score decreased from 106 to 88 with marked reduction of diarrhea, occasional lipothymia, disappearance of vomiting and improved QOL. Midodrine and fludrocortisone were stopped. The benefit was maintained after twelve months (Fig. 1). No complications have been reported.

2.2. Case 2

Patient 2 was a male with Glu89Gln mutation. He belonged to a family with a three generation history of TTR-FAP. He had a 15-year follow-up at our clinic since he was 48. At that time the patient was still asymptomatic and his weight was 58 kg (BMI 22.1). At the age of 51, he started to complain of burning

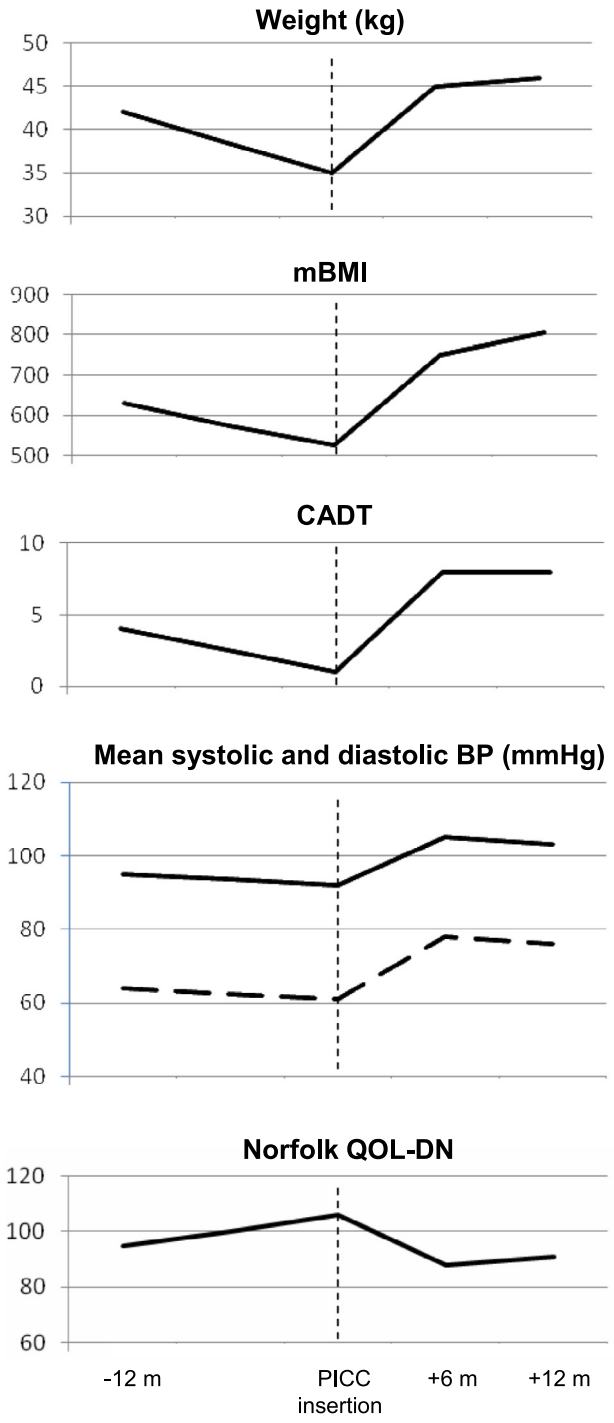

Fig. 1. Body weight, mBMI, CADT score, mean systolic and diastolic blood pressure on 24-hour monitoring, and Norfolk QOL-DN score 12 months before, at the time of PICC insertion, and after 6 and 12 months in Case 1. Vertical discontinued line indicates PICC insertion.

paraesthesia distally in lower limbs. Nerve conduction studies showed a sensory axonal polyneuropathy.

At the age of 55, cardiac amyloidosis deposits were detected with Technetium-99m-diphosphonate (99mTc-DPD) whole body scan. He became cardiologically symptomatic two years later (NYHA I). Neurological examination revealed a normal muscular strength with absent tendon reflexes and distal hypoesthesia including pinprick and temperature sensation.

Symptoms of autonomic failure appeared when he was 60, with diarrhea and erectile dysfunction. His weight was 52 kg (BMI 19.8). He started tafamidis meglumine 20 mg/day. After two years, tafamidis was suspended for poor compliance to the treatment and progression of the disease.

After two years, the gait was possible only with deambulator for the presence of ataxic gait and distal weakness at lower limbs. Shortness of breath was present even in minor activity (NYHA III). CADT score was 9 with daily diarrhea. Body weight was 44 kg (BMI 16.8; mBMI 653). A specific low fiber and hypercaloric diet was started.

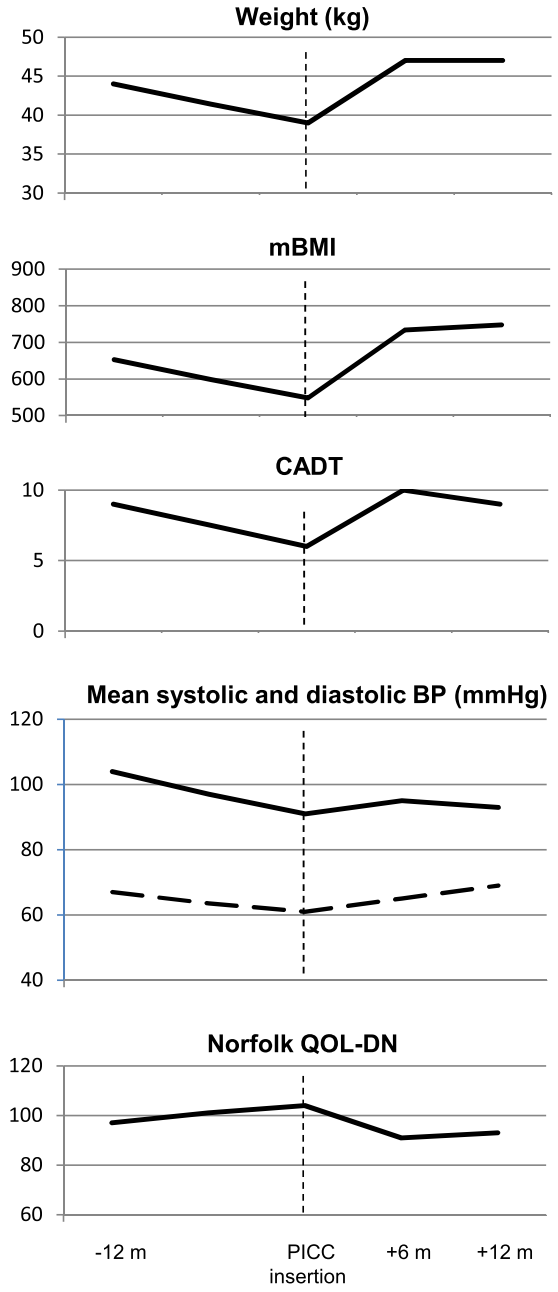

Fig. 2. Body weight, mBMI, CADT score, mean systolic and diastolic blood pressure on 24-hour monitoring, and Norfolk QOL-DN score 12 months before, at the time of PICC insertion, and after 6 and 12 months in Case 2. Vertical discontinued line indicates PICC insertion.

At the age of 63, his weight was 39 kg (BMI 14.9; mBMI 548). Therefore a PICC was placed and parenteral nutrition started, adding 1 liter/day of Oliclinomel N4-550e to a diminished oral nutrition. After six months, his weight raise up to 47 kg (BMI 17.9; mBMI 734). CADT score increased from 6 to 10 and Norfolk QOL-DN score improved with only occasional episodes of diarrhea, disappearance of vomiting and enhanced QOL. The clinical improvement was maintained after twelve months without complications (Fig. 2).

3. Discussion

Several studies have demonstrated that mBMI is a useful biological marker and correlates well with prognosis, functional capacity and post-liver transplant survival in TTR-FAP [7–9]. Tafamidis meglumine and diflunisal, two molecules that stabilize and inhibit the dissociation of circulating TTR tetramers, thus preventing the deposition and formation of amyloidogenic abnormal TTR fibrils, are able to produce a stabilization of mBMI values and a mBMI > 960 was associated with a 7-fold higher probability of stability of NIS-LL after 12 months of tafamidis compared with subjects with lower mBMI [12–14]. Unfortunately, the preservation of the nutritional status is still a big challenge in TTR-FAP management, especially in cases with prevalent and severe autonomic involvement. In this report, we described two patients in whom nutritional status worsened despite diet modification, hypercaloric supplement and two relevant therapeutic approaches such as LT in case 1, and tafamidis meglumine in case 2.

The two TTR mutations carried by our patients have been recently reported in a phenotype-to-genotype correlation survey [5]. Thr49Ala mutation is characterized by an early onset in the 5th decade, autonomic disturbances as inaugural symptoms which may remain isolated for many years, moderate polyneuropathy, dysautonomia and cachexia as major causes of mortality followed by cardiomyopathy. Glu89Gln mutation is marked by onset in the 5th–6th decade, prevalent distal paraesthesias/carpal tunnel syndrome as presenting symptoms, early heart dysfunction but with fatigue, palpitation, dyspnea appearing later, heart failure and sudden death as major cause of mortality followed by dysautonomia and cachexia.

This study reports the documented effects of parenteral nutrition on different outcome measures in TTR-FAP patients. PICC is inserted in a peripheral vein in the arm and then advanced proximally toward the heart through increasingly larger veins until the tip rests in the distal superior vena cava or cavoatrial junction. It can remain in situ for extended periods of time, up to 6–12 months. Its insertion is easy and safe due to placement into peripheral veins of the arm and the advantage of a central location of catheter tip suitable for all osmolarity and pH solutions. Its cost is less expensive than centrally inserted central catheters. Despite a widespread use of PICC in critical care settings, clinicians must know recommendations to prevent related adverse events such as venous thrombosis and bloodstream infections [15]. Our experience suggests that parenteral nutrition administered by PICC may be a symptomatic treatment, useful to increase body weight and mBMI of TTR-FAP patients, even

when all dietary adjustments have been ineffective. Together with a concomitant reduction of oral amount of food and a good hydration status, PICC use was followed by reduction of invalidating symptoms as diarrhea, nausea, vomiting and orthostatic hypotension, improving quality of life. In our patients, PICC was placed when mBMI were 525 and 548 with a good response. Considering that a significant difference in survival was observed between transplant recipients with an mBMI greater than 600 at the time of LT compared with those with an mBMI less than 600 [7,8], we can extrapolate that PICC insertion is recommended when mBMI is in the range 500–600. Being a symptomatic therapy of late stages of a neurodegenerative disease, parenteral nutrition must be continued indefinitely. Reasonably, as documented in previous studies [6,7], the improvement in nutritional status may prolong survival in TTR-FAP patients, but a study of a larger cohort of patients is necessary to confirm this statement.

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