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6MWT performance correlates with peripheral neuropathy but not with cardiac involvement in patients with hereditary transthyretin amyloidosis (hATTR)

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Abstract

Hereditary transthyretin amyloidosis (hATTR) is a life-threatening multisystemic disease with sensory-motor peripheral neuropathy, cardiomyopathy and dysautonomia. Although the six-minute walk test (6MWT) is one of the most popular clinical tests to assess functional exercise capacity in cardiopulmonary and neuromuscular diseases, little is known about 6MWT in evaluating hATTR patients. A prospective single-center pilot study was performed in twenty hATTR patients, comparing 6MWT with widely used outcome measures. After 18 months, fourteen patients were re-evaluated. 6MWT performance was highly related with familial amyloidotic polyneuropathy stage and polyneuropathy disability score, and with CMT examination score, neuropathy impairment score-lower limbs and Kumamoto score. There was no correlation with compound autonomic dysfunction test, modified body mass index and numerous indices of heart dysfunction. After 18 months, familial amyloidotic polyneuropathy stage and polyneuropathy disability score systems were not able to reveal any significant change, whereas all other outcome measures significantly worsened. Among the outcome measures monitoring the neuropathic disturbances, neuropathy impairment score-lower limbs showed the highest responsiveness to change (adjusted effect size: 0.79), followed by CMT examination score (0.67), Kumamoto scale (0.65), 6MWT (0.62). 10MWT showed a very small value (0.21). Compound autonomic dysfunction test had a large value (0.91) whereas modified body mass index a small/moderate value (0.49). 6MWT is a simple and sensitive tool to monitor neuropathic involvement but not cardiac dysfunction in hATTR course.

Keywords: Hereditary transthyretin amyloidosis; Six-minute walk test; Peripheral neuropathy; Cardiomyopathy.

1. Introduction

Hereditary transthyretin (TTR) amyloidosis (hATTR) is a progressive multisystemic disease transmitted as an autosomal dominant trait, characterized by axonal sensory-motor neuropathy associated with autonomic and cardiac involvement [1,2]. If untreated, fatal outcome occurs within ten years since the onset. Liver transplantation remained the only available treatment for twenty years [3], until tafamidis became in 2011 the first specific drug approved by the Regulatory Agencies [4,5]. Very recently, two randomized, double-blind, controlled trials testing the therapeutic efficacy of two different chemically modified oligonucleotides to treat hATTR, represent a revolution, showing that the rate of disease progression can be slowed, and perhaps ameliorated [6,7]. In the last few years there has been a considerable effort to harmonize standards of care and outcome measures (OM) in hATTR, with the aim to know the natural history and to find sensitive tools for revealing the effects of the available treatments on multiple faces of the disease [8–11].

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The six-minute walk test (6MWT) is one of the most popular clinical tests used for assessment of functional capacity. It evaluates the global and integrated responses of all the systems involved in walking, including the pulmonary and cardiovascular systems and neuromuscular units. Because the 6MWT accurately reflects patients' activities of daily living, it has been applied widely for evaluation of functional exercise capacity in neuromuscular disorders such as myotonic dystrophy [12], Pompe disease [13], Duchenne muscular dystrophy [14], diabetic neuropathies [15] and Charcot-Marie-Tooth disease [16].

6MWT has been recently found a valuable tool to assess functional capacity and monitor changes following chemotherapy in patients with AL cardiac amyloidosis [17–19]. Only very few papers report the use of 6MWT in hATTR. Apart from a case report illustrating increased walked meters on 6MWT after 6-month exercise training program in a liver transplanted patient [20], 6MWT distance has been found reduced in liver transplanted patients versus normal controls [21], and increased in patients with TTR amyloid cardiomyopathy (both hereditary and wild type forms) after 12-month treatment with an IONIS antisense oligonucleotide [22].

The aim of our study was to evaluate the validity of the 6MWT as clinical tool reflecting patients' neuropathic and cardiac involvement in a cohort of hATTR patients.

2. Patients and methods

Twenty consecutive patients with hATTR, who came for clinical evaluation at Messina University Hospital Amyloidosis Centre, were recruited to participate in this study. Inclusion criteria were: (i) presence of peripheral neuropathy, (ii) unaided or aided ambulation at 6MWT for any distance. They were 14 men and 6 women, aged 49–78 years (mean ± SD; 61.3 ± 9.7). They carried the following TTR mutations: Glu89Gln (n. 11), Phe64Leu (n. 7), Thr49Ala (n. 2). Duration of the disease ranged from 2 to 20 years (mean ± SD; 7.6 ± 4.9). Thirteen patients were on treatment with tafamidis and one had received liver transplantation. They belonged to FAP stage 1 (n. 14) and stage 2 (n. 6) [23]. Polyneuropathy Disability (PND) score [24] was as follows: PND I (n. 6), II (n. 8), IIIa (n. 4), IIIb (n. 2). Local ethics committee approval was obtained and all patients gave written informed consent.

The 6MWT was performed according to the guidelines provided by the American Thoracic Society [25]. The evaluator instructed patient to walk at his/her own pace while attempting to cover as much distance as possible during the allotted time. During the test, patients were allowed to rest or stop and then continue as soon as they could resume the walk. At the completion of six minutes, the patient was told to "stop" and the distance covered was recorded. If needed, patient could use any ambulation support (cane, stick, crutches). The 6MWT was performed along a long, flat, straight, enclosed corridor with turnaround points at an interval of 25 m.

The 6MWT distance was compared with already validated OMs previously used in hATTR patients, specifically:

- Timed 10-meter walk test (10MWT) assesses functional mobility and walking speed in meters per second over a short duration. It sets a total distance of 14 m, marked at the beginning and end 2 m with tape, and the subject makes a 14-m distance from the sign "start". Time is measured except beginning and end 2 m for acceleration and deceleration. A lower value indicates a slower gait speed [6].
- CMT Examination Score (CMTES), version 2 (range 0–28, 0 is normal), is a 7-item composite impairment and disability scale, which comprises motor and sensory symptoms and signs [26].
- Neuropathy Impairment Score-Lower Limbs (NIS-LL) (0–88 points, 0 is normal) has been developed by Mayo Clinic: the scale captures clinically meaningful changes in neurological function including muscle weakness, reflexes, sensation [27].
- Kumamoto scale is a 14-item composite score, ranging from 0 (normal) to 96 points, which entails sensory disturbances, motor weakness, autonomic dysfunction and visceral organ impairment [28].
- Compound Autonomic Dysfunction Test (CADT) is a questionnaire developed to evaluate the main symptoms of autonomic dysfunction observed in hATTR. The test includes five items, each ranging from 0 (severe dysfunction) to 4 (normal). Normal score is 16 in women and 20 in men [29].
- Modified Body Mass Index (mBMI), calculated by multiplying BMI (kg/m^2) by serum albumin concentration (g/L) to compensate for possible oedema [30].

Cardiac involvement was evaluated by a cardiologist with expertise in amyloidosis, by using a combination of consensus criteria and diagnostic tools including New York Heart Association (NYHA) class, electrocardiography, Doppler-echocardiography with measurement of left inter-ventricular septal (IVS) thickness and diastolic function by E/A and E/E′ ratio. IVS thickness >12 mm is considered diagnostic of amyloid heart involvement and an increase of IVS ≥ 2 mm defines the presence of cardiac disease progression, as indexed by International Society of Amyloidosis criteria [31,32]. In normal individuals the E/E′ ratio is ≤8 and increases in the presence of diastolic dysfunction. An E/E′ ratio ≥15 is highly suggestive of elevated filling pressures [33]. Serum brain natriuretic peptide (BNP) and N-terminal pro-hormone BNP (NT-proBNP) were also used as biomarkers of cardiac dysfunction.

After 18 (range 15–21) months since the baseline examination, fourteen patients were re-evaluated (three patients had deceased and three had lost the ability to walk).

Statistical analysis was performed by GraphPad Prism, version 7.00 (GraphPad Software, La Jolla, CA, USA). The relationship between variables was studied using non-parametric Spearman correlation test. Graphs indicate mean and error with 95% confidence interval. Comparison between groups was performed by Mann–Whitney test for unpaired data

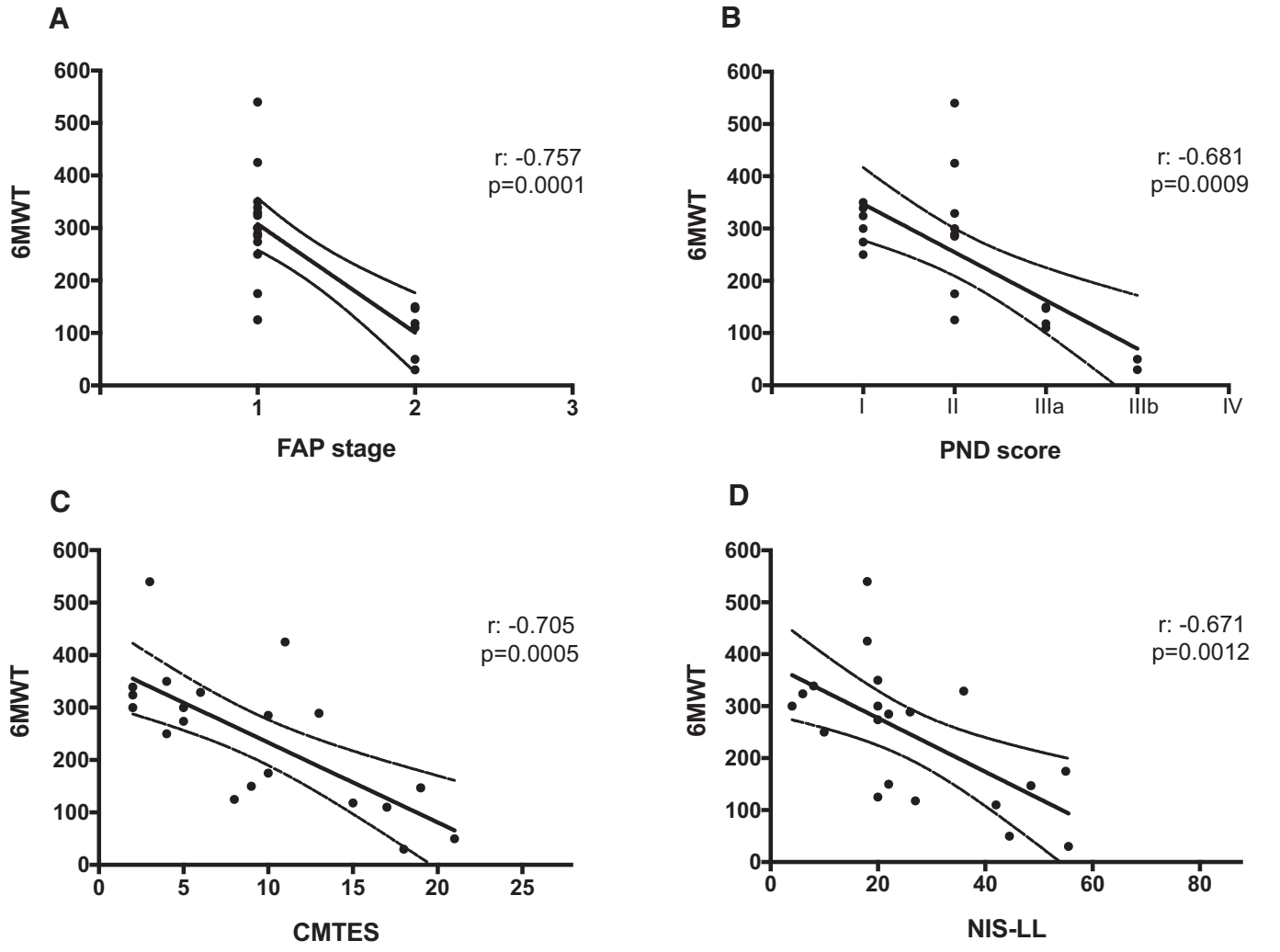

Fig. 1. Spearman correlation of 6MWT distance in meters versus FAP stage (A), PND score (B), CMTES (C) and NIS-LL (D). Graphs indicate mean and error with 95% confidence interval.

and by Wilcoxon matched-pairs signed rank test. Results are expressed as mean ± standard deviation (SD). A level of significance of $p < 0.05$ was considered. Responsiveness of 6MWT and other OMs was assessed by calculating the standardized response mean (SRM) as the mean baseline-to-18-month change in score divided by the SD of the individual's score change. The SRM threshold levels were defined as follows: 'trivial' (<0.20), 'small' (≥0.20<0.50), 'moderate' (≥0.50<0.80), or 'large' (≥0.80) [34]. To avoid over- or underestimation of magnitude of the change over time, adjusted effect size (ES) was calculated with the formula: SRM $^{*}\sqrt{2}\,^{*}\sqrt{(1-r)}$, where r = the correlation between the measure at baseline and after 18 months [35,36].

3. Results

At baseline, distance covered at 6MWT ranged between 30 and 540 m (mean ± SD; 245.5 ± 129.7). 6MWT showed a significant inverse correlation with FAP stage (r: −0.757, $p = 0.0001$), PND score (r: −0.681, $p = 0.0009$), CMTES (r: −0.705, $p = 0.0005$) and NIS-LL (r: −0.671, $p = 0.0012$) (Fig. 1). Distance in meters covered on 6MWT also correlated with gait speed on 10MWT expressed in m/sec (r: 0.737, $p = 0.0002$) and in an inverse direction with Kumamoto score (r: −0.778, $p < 0.0001$), but neither CADT nor mBMI showed any statistically significant correlation (Fig. 2).

15/20 patients were classified as NYHA class II and 5/20 as NYHA class III. 18/20 patients presented an IVS thickness >12 mm, and 12/20 ≥ 15 mm. 11/20 patients had an E/E′ ratio > 8, 10/20 > 12, and 6/20 ≥ 15. No correlation was found between 6MWT and measures of cardiac involvement, including NYHA class, IVS thickness, E/A and E/E′ ratios, serum BNP and NT-proBNP. Moreover, 6MWT differed between patients divided in two subgroups neither according to NYHA class II and III, IVS thickness ≤ and > 12 mm or in the range 13–14 mm and ≥ 15 mm, nor according to E/E′ ratio ≤ and > 8, 12 or 15.

When 14 patients were re-evaluated after 18 months, FAP stage, PND score and 10MWT were not able to reveal any significant change (Fig. 3). Individually, FAP stage remained

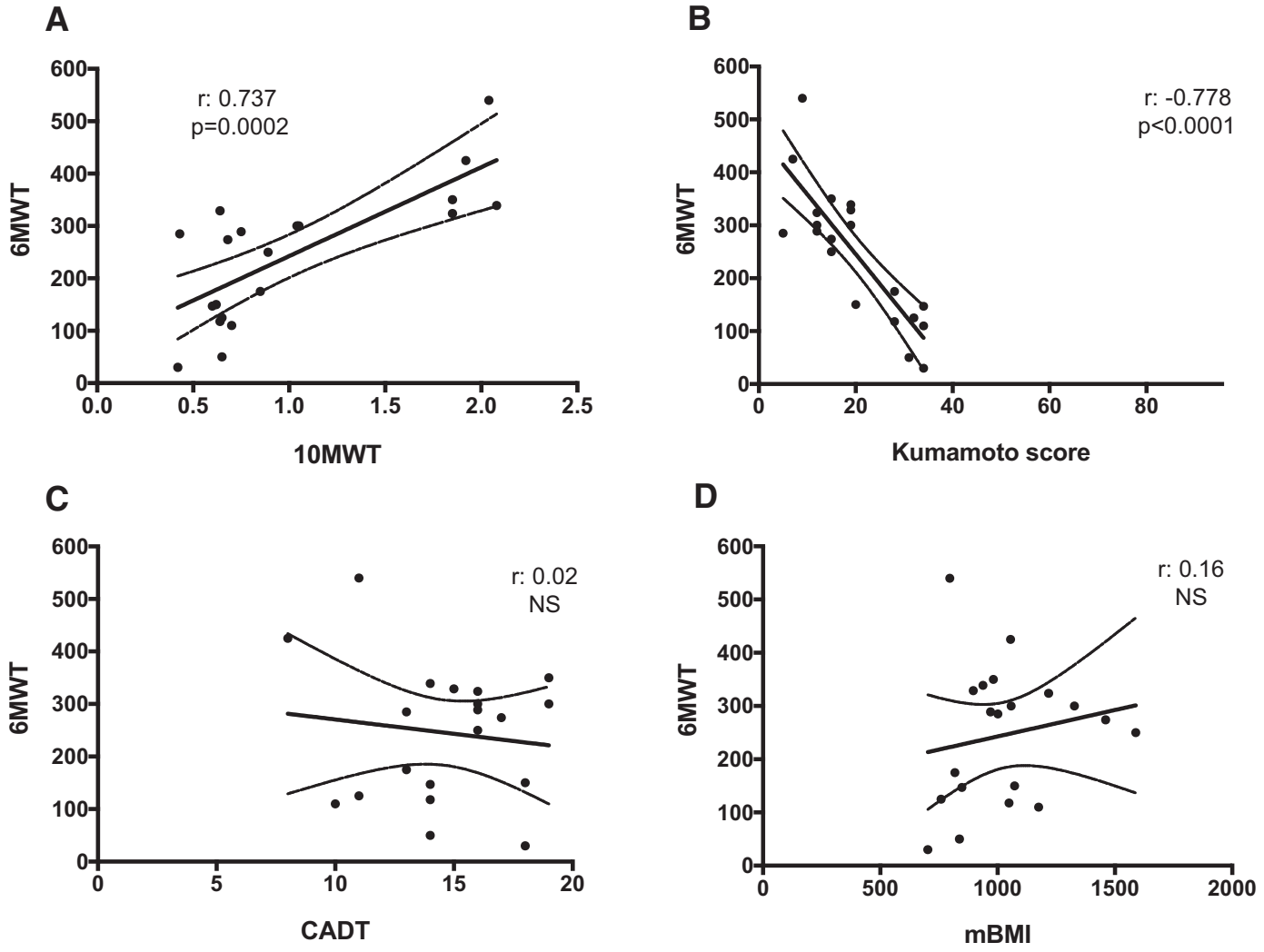

Fig. 2. Spearman correlation of 6MWT distance in meters versus 10MWT (m/sec) (A), Kumamoto score (B), CADT (C) and mBMI (D). Graphs indicate mean and error with 95% confidence interval.

stable in all patients except one who showed a shift from 1 to 2. The same patient had a shift of PND score from I to IIIa and three other patients shifted from IIIa to IIIb. Distance in meters covered on 6MWT significantly reduced (229.7 ± 101 vs 171.8 ± 120; $p = 0.0081$), with a parallel significant increase of CMTES (8.6 ± 6.7 vs 13.1 ± 7.4; $p = 0.0002$), NIS-LL (25.9 ± 16.7 vs 34.7 ± 19.2; $p = 0.0347$) and Kumamoto score (21.5 ± 7.9 vs 29.4 ± 14.6; $p = 0.0115$), confirming an augmented disability (Fig. 4A–D). Interestingly, relying on the previous studies [37,38], five patients on tafamidis could be defined as responders to treatment as ΔNIS-LL ≤ 2 between baseline and reassessment after 18 months. All five responders showed a Δwalked distance at 6MWT $\pm$ 15 m, confirming the disease course stabilization also with the new test. As a mean, CADT significantly reduced (15.4 ± 2.5 vs 13.1 ± 3.6; $p = 0.0059$), proving a worsening of autonomic dysfunction (Fig. 4E). mBMI also significantly decreased (1090.5 ± 238.2 vs 1024.7 ± 276.1; $p = 0.0067$) (Fig. 4F). Table 1 shows correlation between Δ6MWT and the delta of the other OMs. A statistical significance was found with ΔCMTES, ΔNIS-LL, ΔKumamoto score and ΔCADT.

Among the OMs monitoring the neuropathic disturbances, NIS-LL showed the highest responsiveness to change (adjusted ES = 0.79), followed by CMTES (0.67), Kumamoto scale (0.65), 6MWT (0.62), all in the 'moderate effect' range. 10MWT showed a very small value (0.21). CADT had a 'large effect' value (0.91), whereas mBMI was in the 'small effect' range (0.49). FAP stage showed a 'trivial effect' value (0.14), and PND score a value just over the 'trivial-small' cut-off (0.28) (Table 2).

4. Discussion

The 6MWT is a widely used measure of functional exercise capacity in patients with cardiopulmonary diseases, and also considered a surrogate endpoint in many systolic heart failure drug trials for a long time [39]. In both AL

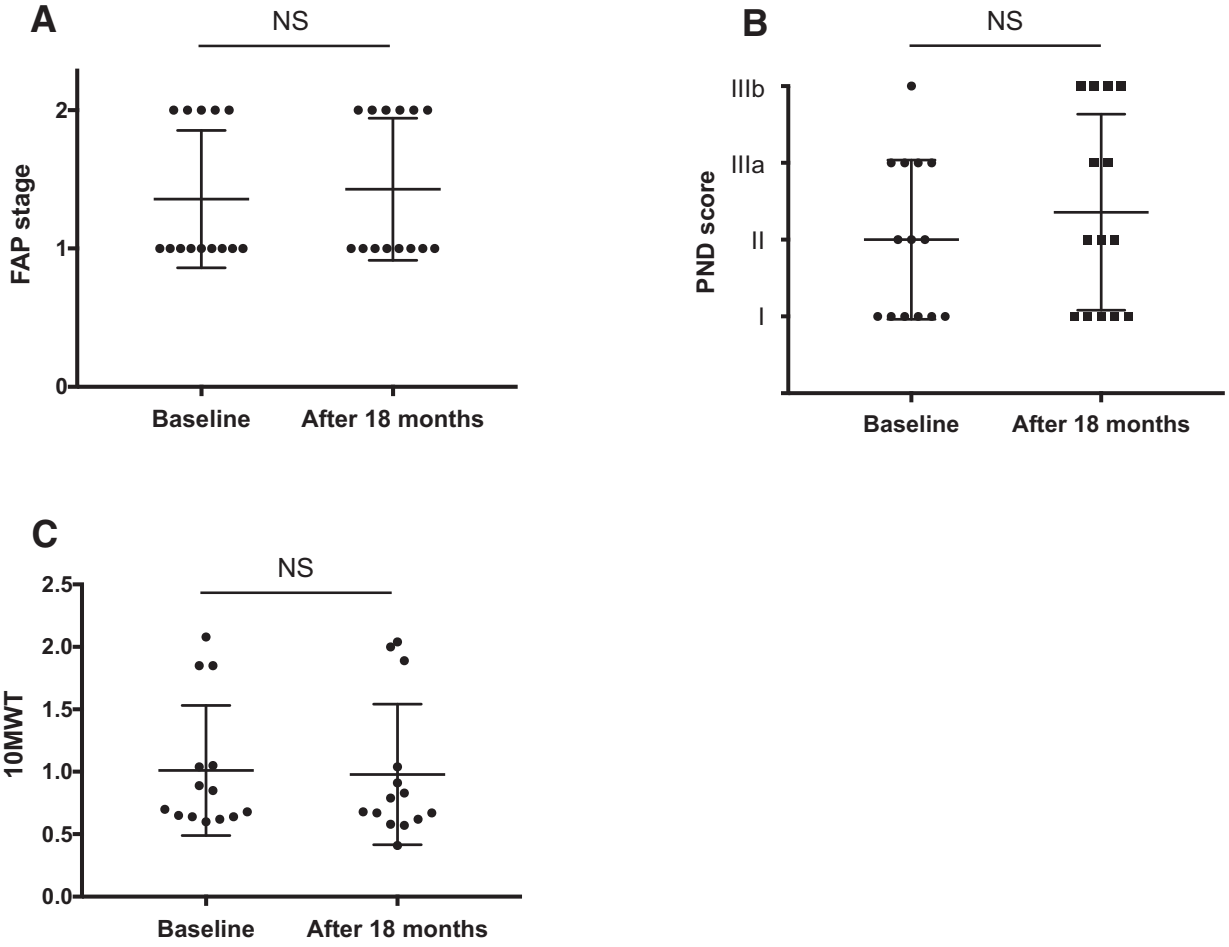

Fig. 3. Scatter plot of FAP stage (A), PND score (B) and 10MWT (m/sec) (C) at baseline and after 18 months (n. 14; mean ± SD). There is no statistical difference between the two timepoints.

and TTR amyloid cardiomyopathy, 6MWT has been implemented very recently to investigate presence and degree of heart dysfunction but with no detailed analysis on the neuropathic involvement [17–19,22]. So, our study is the first to explore the correlation between 6MWT and the multiple organ dysfunction in hATTR patients. First of all, 6MWT resulted highly correlated with both FAP stage and PND score which are functional, albeit gross, measures of disease severity. The 6MWT showed also an excellent correlation with composite scales capturing neuropathic dysfunction such as CMTES and NIS-LL but no correlation with 10MWT. We chose the two former OMs, excluding the corresponding CMT Neuropathy Score and NIS + 7 which include instrumental neurophysiological data, with the aim to have tools entirely depending on clinical symptoms and signs. Indeed, better functional capacity corresponds with less disability and impairment and higher motor performance [11]. Our results show that the 6MWT may have great utility in assessing the functional neuropathic status of hATTR patients although we must admit that it captures only a short amount of time in the clinic and it does not directly measure everyday activity.

Regarding dysautonomia, 6MWT correlated with Kumamoto score but not with CADT. The explanation is that the former includes autonomic dysfunction but also sensory and motor disturbances, whereas the latter is a pure autonomic test. hATTR is a multi-organ and multi-symptom disease that may present with sensory-motor peripheral neuropathy, autonomic neuropathy with impotence and orthostatic hypotension, cardiomyopathy, gastrointestinal impairment, and other less frequent disturbances. More than one hundred twenty mutations have been identified and, whereas the symptoms described may be present in patients with different mutations, phenotypes are not always uniform, and the same mutation may have varied phenotypes even within the same family [2]. The three mutations carried by our patients have heterogeneous phenotypes: (i) Glu89Gln mutation, the most frequent in our cohort, is characterized by severe heart involvement and moderate peripheral neuropathy and dysautonomia; (ii) Phe64Leu mutation is marked by severe peripheral neuropathy, moderate dysautonomia and mild cardiomyopathy; (iii) Thr49Ala is distinguished by severe autonomic disturbances, moderate polyneuropathy and cardiomyopathy [40,41]. So,

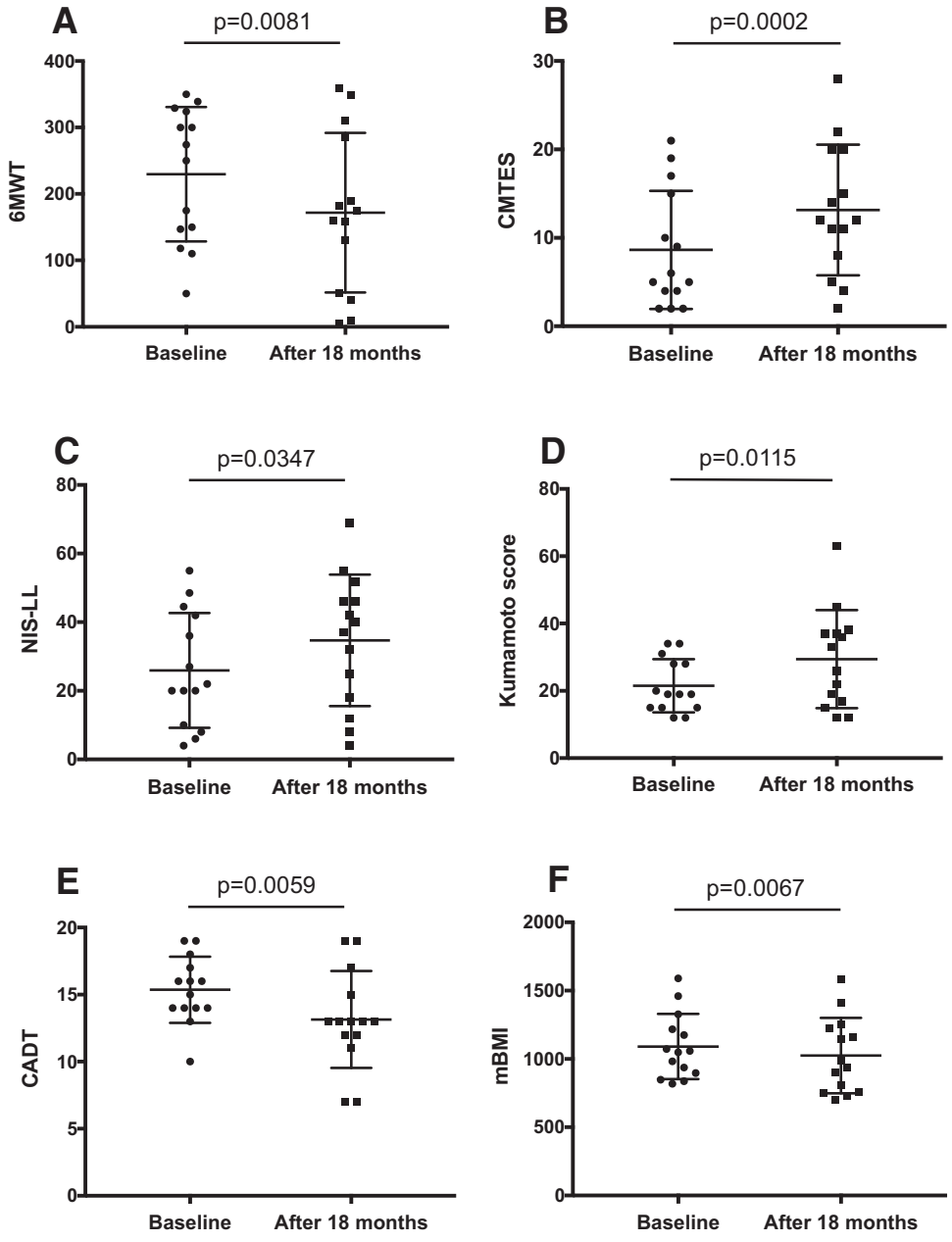

Fig. 4. Scatter plot of 6MWT distance (A), CMTES (B), NIS-LL (C), Kumamoto score (D), CADT (E) and mBMI (F) at baseline and after 18 months (n. 14; mean ± SD). Statistical difference is respectively indicated between the two timepoints.

the lack of correlation at baseline between 6MWT and CADT is not surprising at all, since neuropathy and dysautonomia may vary in occurrence and degree in individual patients.

When 14 out of 20 patients at baseline were re-assessed after 18 months, the aim was to document neither the disease natural history nor the changes after treatment, since thirteen subjects were on tafamidis whereas one transplanted and six in FAP stage 2 had no access to the drug according to Italian Drug Regulatory Agency, but to verify the sensibility to change of 6MWT and other OMs widely used in hATTR. 6MWT performed well and its delta correlated with changes in CMTES, NIS-LL and Kumamoto score. A parallel decrease was also found between walked distance at 6MWT and CADT score indicating augmented dysautonomia. The use of 6MWT is simple and easy, it may be recommended to longitudinally monitor the neuropathic involvement in hATTR patients. The test resulted effective in revealing worsening as well as stabilization of the neuropathic course of the disease. The availability of different treatments from tafamidis to the innovative drugs, inotersen and patisiran [6,7] recently approved by the Committee for Medicinal Products for Human Use of European Medicines Agency, makes it necessary to have now sensitive and easy-to-perform tools reflecting the

Table 1
Correlation between Δ6MWT and the delta of other OMs (baseline versus reassessment after 18 months).

	Spearman correlation *r*	Significance (*p* value)
ΔFAP stage	−0.3784	NS
ΔPND score	−0.4934	NS
Δ10MWT	0.1545	NS
ΔCMTES	−0.6467	0.0146
ΔNIS-LL	−0.6674	0.0110
ΔKumamoto score	−0.8	0.0009
ΔCADT	0.6861	0.0083
ΔmBMI	−0.0197	NS
ΔNYHA class	0	NS
ΔIVS thickness	0.2109	NS
ΔE/A ratio	0.4851	NS
ΔE/E′ ratio	−0.137	NS

Table 2
Sensitivity to change of OMs between baseline and after 18 months.

	Spearman correlation *r*	Mean change	SD_{change}	SRM	Adjusted ES
FAP stage	0.8607	0.07	0.27	0.27	0.14
PND score*	0.8803	0.36	0.63	0.56	0.28
10MWT	0.9746	0.07	0.08	0.93	0.21
6MWT	0.8647	64.64	54.34	1.19	0.62
CMTES	0.899	4.50	3.01	1.50	0.67
NIS-LL	0.7646	12.84	11.01	1.17	0.79
Kumamoto score	0.8049	9.64	9.27	1.04	0.65
CADT	0.5035	2.36	2.59	0.91	0.91
mBMI	0.9121	77.18	66.02	1.17	0.49

SRM: standardized response mean; ES: Effect size.
* For calculation, PND score was converted as follows: I = 1; II = 2; IIIa = 3; IIIb = 4.

daily life activity to monitor the disease course, identify responders and non-responders and accordingly modify treatment program.

On the contrary, 6MWT did not appear a good test to follow the cardiac involvement in our patients. Although it is widely use in cardiological diseases and recently also in AL and TTR amyloid cardiomyopathy [17–19,22], lack of correlation between 6MWT and hATTR heart dysfunction may be explained by concomitant peripheral nerve and heart involvements with a prevalent role of neuromuscular system in influencing the walked distance during six minutes. This hypothesis is also supported by the much lower distance covered at 6MWT by our patients (245.5 ± 129.7 at baseline in n. 20; 172.3 ± 120.1 at re-assessment in n. 14) in comparison to that reported in hATTR cardiomyopathy (442.56 ± 77.22) [22] and in AL amyloidosis (368 ± 105 in subjects with cardiac involvement and 420 ± 116 without cardiac involvement) [18].

In conclusion, our pilot study revealed that 6MWT is sensitive to detect worsening as well as stabilization in the hATTR course regarding neuropathic involvement but not cardiac dysfunction, when both are present in the clinical phenotype. Such information may lead to improve the design of future clinical trials. Further multicentre study on larger cohort including different TTR mutations and phenotypes are needed to confirm its efficacy in monitoring multiorgan course and changes after treatments.

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