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Prospective study of clinical, neurophysiological and urodynamic findings in multiple sclerosis patients undergoing percutaneous transluminal venous angioplasty

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HIGHLIGHTS

- Percutaneous transluminal angioplasty (PTA) had been under scrutiny as multiple sclerosis treatment.
- We prospectively quantified eventual neurophysiological and urodynamic changes occurring post PTA.
- Central neural conduction properties remained overall unchanged despite transient subjective well-being improvement.

ABSTRACT

Objective: Verify whether Percutaneous Transluminal Angioplasty (PTA) may affect neural conduction properties in Multiple Sclerosis (MS) patients, thereby modifying patients' disability, with prospective neurophysiological, urodynamic, clinical and subjective well-being evaluations.
Methods: In 55 out of 72 consecutively screened MS patients, the following procedures were carried out before (T0), at 2–6 months (T1) and at 6–15 months (T2) after a diagnostic phlebography, eventually followed by the PTA intervention if chronic cerebrospinal venous insufficiency (CCSVI) was diagnosed: clinical/objective evaluation (Expanded Disability Status Scale, EDSS), ratings of subjective well-being, evaluation of urodynamic functions and multimodal EPs (visual, acoustic, upper and lower limbs somatosensory and motor evoked potentials).
Results: The number of dropouts was relatively high, and a complete set of neurophysiological and clinical data remained available for 37 patients (19 for urological investigations). The subjective well-being score significantly increased at T1 and returned close to basal values at T2, but their degree of objective disability did not change. Nevertheless, global EP-scores (indexing the impairment in conductivity of central pathways in multiple functional domains) significantly increased from T0 (7.9 ± 6.0) to T1 (9.2 ± 6.3) and from T0 to T2 (9.8 ± 6.3), but not from T1 and T2 ($p > 0.05$). Neurogenic urological lower tract dysfunctions slightly increased throughout the study.
Conclusions: The PTA intervention did not induce significant changes in disability in the present cohort of MS patients, in line with recent evidence of clinical inefficacy of this procedure.
Significance: Absence of multimodal neurophysiological and functional testing changes in the first 15 months following PTA suggests that conduction properties of neural pathways are unaffected by PTA. Current findings suggest that the short-lived (2–6 months), post-PTA, beneficial effect on subjective well-being measures experienced by MS patients is likely related to a placebo effect.
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1. Introduction

Multiple Sclerosis (MS) is a multifactorial disease (Lucchinetti et al., 2000; Compston and Cole, 2008): perivenular inflammation in the white matter followed by demyelination of central nervous fibers, together with axonal loss and neurodegeneration, contribute to affect sensory (somatic, visual, auditory) motor, cognitive and urinary system functions, leading to increase of disability over time. In animal models, demyelination slows down conduction properties of neural pathways and reduces the ability to transmit neural impulses at high frequency; when combined with axonal degeneration, partial or complete conduction blocks may also occur (McDonald and Sears, 1970), leading to functional impairment in virtually all sensory and motor domains.

While Magnetic Resonance Imaging (MRI) is the gold standard to detect and to monitor MS lesions (Compston and Cole, 2008), neurophysiological techniques as multimodal Evoked Potentials (EPs) still represent the unique opportunity to evaluate *in vivo* the conductivity of fast-propagating nervous conduction fibers of the central and peripheral nervous system. Moreover, there is an established correlation between disability in MS as assessed by the Expanded Disability Status Scale (EDSS) (Kurtzke, 1983) and EPs abnormalities, if the central neural conduction of several perceptive modalities (visual, acoustic, upper and lower limbs somatosensory) and corticospinal pathways (upper and lower limbs) is extensively evaluated (Facchetti et al., 1997; O'Connor et al., 1998; Fuhr et al., 2001; Leocani et al., 2006; Kallman et al., 2006; Invernizzi et al., 2011; Kiylioglu et al., 2015). Therefore, multimodal EPs may be regarded as an appropriate tool to monitor (O'Connor et al., 1998; Invernizzi et al., 2011; Schlaeger et al., 2012, 2016) and predict (Fuhr et al., 2001; Leocani et al., 2006; Kallman et al., 2006; Jung et al., 2008; Schlaeger et al., 2014b; Magnano et al., 2014; Giffroy et al., 2016) the disease evolution in terms of disability, especially when performed during relapse-free periods (Schlaeger et al., 2014a).

A recently debated line of thinking postulated that demyelination may occur as a consequence of an altered brain venous outflow due to restriction of the azygous or internal jugular veins, leading to putative chronic cerebrospinal venous insufficiency (CCSVI): following this debated concept (Zivadinov and Weinstock-Guttman, 2018), white matter inflammation was postulated to be "a consequence of a breakdown of the blood–brain barrier due to elevated transmural pressure, followed by erythrocyte, plasma and iron extravasation, thus resulting in damage to the immune tolerance and setting off a cascade of inflammatory events and immune responses that can persist over time" (Singh and Zamboni, 2009). A ten-year living debate on the role of CCSVI in the pathogenesis of MS and in determining the severity of clinical manifestation (Patti et al., 2012) has been under way, as the incidence of CCSVI varied from 0 to 100% in people with MS and from 0-23% in controls (Ghezzi et al., 2011; Zivadinov et al., 2011). In spite of this, percutaneous transluminal angioplasty (PTA) –aimed to restore the altered venous flow in the neck veins- has been performed worldwide in about 20.000 MS patients (Zivadinov and Weinstock-Guttman, 2018), both in public and private centers, often in uncontrolled trials but even in some randomized controlled trials (cfr. Zivadinov and Weinstock-Guttman, 2018). However, Cochrane evidence to support or refuse the efficacy of this procedure is still lacking (van Zuuren et al., 2014).

A still uninvestigated way to verify whether PTA may affect neural conduction properties in MS patients, thereby modifying patients' disability, is a prospective study looking at neurophysiological changes in parallel with clinical variables and subjective well-being scales. As neurogenic lower urinary tract (NLUT) dysfunctions contribute to global disability and deeply affect the quality of life, and they are frequently (from 50% to 90%) found in MS patients (de Sèze et al., 2007; Del Popolo et al., 2008), we additionally evaluated urodynamic functions in these patients.

We prospectively studied MS patients referred for diagnostic phlebography, eventually followed by PTA. In all patients, clinical/objective evaluation, ratings of subjective well-being, evaluation of urodynamic functions and a vast neurophysiological battery including multimodal EPs (visual, acoustic, upper and lower limbs somatosensory and motor evoked potentials), were carried out before (T0), at 2–6 months (T1) and at 6–15 months (T2) after the diagnostic phlebography, eventually followed by the PTA intervention.

2. Methods

Seventy-two consecutive outpatients with a diagnosis of MS made by their own treating neurologist were referred to the Unit of Neuroimaging and Neurointervention of our Institute, where two neuroradiologists, unaware of patients' neurological clinical condition, recommended diagnostic phlebography and intravenous pressure measurement, above and below the internal jugular vein stenosis, to evaluate indications for PTA intervention. PTA was performed only when morphologic stenosis and pressure gradient >1 mm Hg were demonstrated and associated. The morphologic stenosis was evaluated by two different neuroradiologists, who also obtained the written informed consent to the interventional procedure from patients. The entire study protocol was approved by the Local Ethic Committee. The personnel of the Neurology and Neurophysiology Section performed and analyzed clinical and neurophysiological examinations. The personnel of the Urology Section performed and analyzed urological investigations. Both neurologists and urologists were blind regarding the interventional neuroradiological procedures performed.

2.1. Interventional neuroradiological procedures

Of the 72 MS patients referred, 4 refused to undergo any investigation, 55 underwent diagnostic phlebography followed by PTA, while in the remaining 13 patients only diagnostic phlebography was performed. An angiographic catheter was introduced through the femoral veins and driven up to azygous veins, internal jugular veins and vertebral veins and phlebography was executed. The intravein pressures were measured inside of right atrium of heart, in the proximal tract of azygous vein, vertebral vein plexus, subclavian veins and intrajugular veins. The intra atrium pressure was considered as the reference pressure for the other sampling sites. In case of morphologic stenosis, only the pressure gradient higher than 1 mmHg suggested the PTA. A catheter with a balloon attached was inserted and driven up to the narrowed portion of the vessel. There, the balloon was inflated no more than 2 times for 20 s with the aim to stretch the vessel to a larger diameter and to reduce the intravenous pressure gradient. A bolus of heparin therapy was administrated if the PTA was performed.

2.2. Neurophysiological investigations

The neurophysiological evaluation consisted in the execution of multimodal evoked potentials, carried out according to standard guidelines as recommended by the International Federation of Clinical Neurophysiology: upper limbs (UL) and lower limbs (LL) somatosensory evoked potentials (SEPs) (Cruccu et al., 2008), UL and LL motor evoked potentials (MEPs) (Groppa et al., 2012), visual evoked potentials (VEPs) (Deuschl and Eisen, 1999), brainstem auditory evoked potentials (BAEPs) (Nuwer et al., 1994, Deuschl and Eisen, 1999).

UL-SEPs were obtained by surface electrical stimulation of the median nerve, whilst LL-SEPs of the tibial nerve at the ankle. Peak

latencies of the main peripheral, spinal and cortical components were measured, and the central conduction times (CCTs) were calculated as the difference between cortical and spinal latencies.

VEPs were obtained by pattern-reversal achromatic checks (subtending 15 min/arc and 64′ min/arc of visual angle) and recorded over Oz of the 10–20 international EEG system, with Cz as the reference. Peak latency and peak-to-peak amplitude of the main cortical P100 component were measured.

BAEPs to clicks at 85 dB normal hearing level were recorded at the Cz electrode referred to the ipsilateral and contralateral ear. The peak latency of the main waves I, III and V was measured and inter-peak latencies were calculated.

MEPs were obtained by Transcranial Magnetic Stimulation (TMS) of the motor cortex, by recording evoked responses bilaterally from upper and lower limbs muscles (opponens pollicis muscle and flexor hallucis brevis muscle, fespectively). Monophasic magnetic single pulse stimuli were delivered by a Magstim magnetic stimulator connected with a 9 cm circular coil. Suprathreshold (120%) intensities of stimulation were applied around the vertex, during aslight tonic voluntary contraction (about 20% of maximal isometric tension) of each target muscle. At least four reproducible MEPs were obtained from each muscle via a pair of surface electrodes placed on the target muscles in a belly tendon montage. According to Groppa et al. (2012), the central motor conduction time (CMCT) was calculated by the F-wave method and following radicular stimulation to subtract the peripheral transit time from the corticospinal muscular response.

2.3. EPs analysis

Two independent neurologists calculated off-line peak latencies and peak-to-peak amplitudes, blindly regarding the performed interventional procedure. EPs abnormalities were quantified for each stimulated side according to a conventional 4-point graded ordinal score, slightly modified from Leocani et al. (2006): the 0 value indicated normal central conduction time (SEP, MEP, BAEP) or latency of the main cortical component (VEPs) and normal amplitude; 1 indicated increased CCT or latency, more than 2.5 SD (standard deviation) of normative data set of the lab.; 2 indicated increased CCT or latency with additional definite morphological abnormality of a major cortical component; 3 indicated absence of a major cortical component. Findings were verified in at least two reproducible sets of responses. Improvement or worsening of a single EP modality (T1 vs T0 and T2 vs T1) was defined as a change of at least 10%, based on judgment concordance of at least two experimenters (Leocani and Comi, 2008). The "global EP score" (gEP-score) was a single 0–36 value, resulting from the sum of left + right side scores for each modality of stimulation (SEP-UL, SEP-LL, VEP, BAEP, MEP-UL, MEP-LL).

2.4. Urodynamic investigations

Of the 55 patients who underwent to PTA, 36 were evaluated with urodynamic investigations at enrollment. However, a full set of evaluations at T0, T1 and T2 remained available only in 19 patients (5 males).

Neurogenic Lower Urinary Tract Dysfunction (NLUTD) was evaluated according to the latest NLUT dysfunctions guidelines (Pannek et al., 2009). These included non-invasive (uroflowmetry) and invasive (filling cystometry and pressure-flow study of voiding) tests. In this way, the most significant urological parameters in determining both the NLUTD and the quality of life of patients could be evaluated: presence/absence of urinary incontinence (UI), presence/absence of detrusor overactivity (DO), overactivity volume (OV) (i.e., bladder volume at first occurrence of DO) and detrusor pressure (PDO).

Negative prognostic values are represented by the presence of UI and DO, every positive value of OV, high PDO values, and consequently every increase of these parameters, as elevated storage pressure (Gerridzen et al., 1992) and high pressure DO (HPDO) (Nosseir et al., 2007) are the most important risk factors for renal damage.

Each patient underwent to cystometry and then to uroflowmetry. All investigations were carried out according to the International Continent Society (ICS) standards. For cystometry, a 6-Fr double lumen intravesical and rectal catheter was used; the infusion rate during cystometry was 30 mL/min, with the patient in a supine position. Maximum urine flow rate and presence/absence of post-voiding residual volume were evaluated during uroflowmetry.

Dichotomous data (UI and DO) were analysed by McNemar test, while for OV and HPDO comparisons the Wilcoxon test was used. The level of significance was set at $p < 0.05$.

2.5. Time-table of the study

Both groups of patients underwent a basal neurological and neurophysiological/urological evaluation the day before the phlebography (T0) and the degree of disability was also calculated by EDSS. The same clinical/neurophysiological evaluation was again performed in all patients at T1 (range: 2 months – 6 months) and at T2 (range: 6 months – 15 months). At T1 and T2, patients were requested to compile a Visual-Analogue-Scale (VAS) rating their current subjective well-being status in comparison with the previous sampling time. VAS scores ranged from -5 (indicating the worst possible change) to 5 (indicating the best possible change), while the 0 value indicated no change versus T0. Each sampling time lasted one or two consecutive days for each patient. EDSS and VAS scores were compared by Wilcoxon test, with a level of significance of $p < 0.05$.

3. Results

Of the 68 patients enrolled, 26 (7 in the no-PTA group, and 19 in the PTA) performed only clinical and neurophysiological baseline examinations at T0. Therefore, a complete set of data at T0, T1 and T2 remained available for 37 patients who underwent PTA and 5 patients who underwent only diagnostic phlebography. Hence, due to the residual small sample size of the latter group, these data are reported only descriptively. Table 1 summarizes demographic and clinical characteristics of the patients who completed the study.

Of the 37 patients who underwent PTA (and continued unaltered their treatment regimen throughout the study), 13 had a Relapsing

Table 1
Clinical characteristics of the 37 patients who underwent PTA and completed the trial.

Age at enrolment	Mean, SD = 47.8 ± 2.8; range 18–67
Female/male ratio	25/12
Disease duration (months)	Mean, SD: 193 ± 113.5
MS form	RR: 13 (35.1%)
	SP: 17 (45.9%)
	PP: 2 (5.4%)
	Undefined: 5 (13.5%)
Therapy	None: 14 (37.8%)
	INF: 12 (32.4%)
	AZA: 3 (8.1%)
	COP: 2 (5,4%)
	MTX: 1 (2.7%)
	NAT: 5 (13.5%)
Basal EDSS	Mean, SD = 5 ± 1.7, range 2–7
Basal VAS (instantaneous well being)	Mean, SD = 0.9 ± 1.1, range 0–2

Legend to the table: RR = Relapsing-Remitting; SP = Secondary Progressive; PP = Primary Progressive; Undefined = lack of information from the referring physician; INF: Interferon at various dosages; AZA = Azathioprine; COP = Copolymer; MTX = Mitoxantrone; NAT = Natalizumab.

Remitting (RR) MS form and 17 a Secondary Progressive (SP) MS form (see Table 1). No significant differences between these two groups of MS patients were found for all of the outcome variables considered in the following paragraphs; therefore, clinical, subjective, neurophysiological and urological data were analyzed pooling all patients together, according to the stratification of Table 1.

3.1. Disability and subjective well-being status

In the 37 PTA patients, the degree of disability as assessed by the EDSS was unchanged (p always > 0.05) from T0 (5 ± 1.7, range 2–7) to T1 (4.8 ± 1.5, range 2–7) to T2 (4.9 ± 1.6, range 2–7).

The rating of subjective well-being significantly ($p < 0.01$) increased at T1 (2.2 ± 0.9) versus T0, while at T2 (1.3 ± 1.3) it significantly decreased versus T1 ($p < 0.05$) and was overlapping ($p > 0.05$) to the rating of instantaneous well-being at T0 (0.9 ± 1.1).

In the five patients who underwent only diagnostic phlebography, both EDSS and the rating of subjective well-being were unchanged from at T1 to T2; at T0, they were comparable to those of patients undergone to PTA (EDSS 4.9 ± 1.5; well-being 1 ± 0.9).

3.2. Neurophysiological findings

In this group of patients, the frequency of CCTs abnormalities among the different EPs modalities (Table 2) slightly increased from T0 to T1 and T2. This was paralleled by significantly ($p < 0.05$) increased gEP-scores from T0 (7.9 ± 6.0) to T1 (9.2 ± 6.3) and from T0 to T2 (9.8 ± 6.3), but not from T1 and T2 ($p > 0.05$).

Also in the five patients who underwent only diagnostic phlebography not followed by PTA, the gEP-score increased at T1 (9.6 ± 5.8) versus T0 (7.7 ± 5.7) and at T2 (10.1 ± 6.8) versus T0.

Looking at the distribution of central conductivity changes at T1 and T2 for each of the explored functional systems (i.e., upper and lower somatosensory pathways, visual, auditory, upper and lower motor pathways) (Fig. 1), most of CCTs (SEPs, MEPs, VEPs, BAEPs) remained unchanged versus T0 (normal or still in pathological range); about 10% of SEPs, MEPs and VEPs worsened versus the previous sampling time, while less than 10% of them improved: among these 22 improved "sides" (4 bilateral), 18 (81.8%) remained in pathological range at T1 and T2. Only 4 "sides" previously abnormal (2.8%) recovered a pattern of normal central conduction.

3.3. Urological findings

None of the investigated parameters changed significantly over time in the 19 MS patients who underwent PTA (see Table 3 for a descriptive summary).

Table 2
Frequency by "side" of CCTs abnormalities among the different EPs (74 sides for each system investigated) in the 37 patients undergone to PTA.

	T0	T1	T2
SEPs-upper limbs	50.0% (37; 12 bil.)	52.7% (39; 14 bil.)	55.4% (41; 15 bil.)
SEPs-lower limbs	74.3% (55; 25 bil.)	79.7% (59; 29 bil.)	83.8% (62; 31 bil.)
VEPs	48.6% (36; 15 bil.)	55.4% (41; 18 bil.)	54.1% (40; 17 bil.)
BAEPs	9.5% (7; 2 bil.)	10.8% (8; 2 bil.)	10.8% (8; 2 bil.)
MEPs-upper limbs	36.5% (27; 10 bil.)	41.9% (31; 13 bil.)	47.3% (35; 14 bil.)
MEPs-lower limbs	43.2% (32; 9 bil.)	50% (37; 12 bil.)	50% (37; 13 bil.)

Legend: bil. = number of patients with bilateral CCT abnormality.

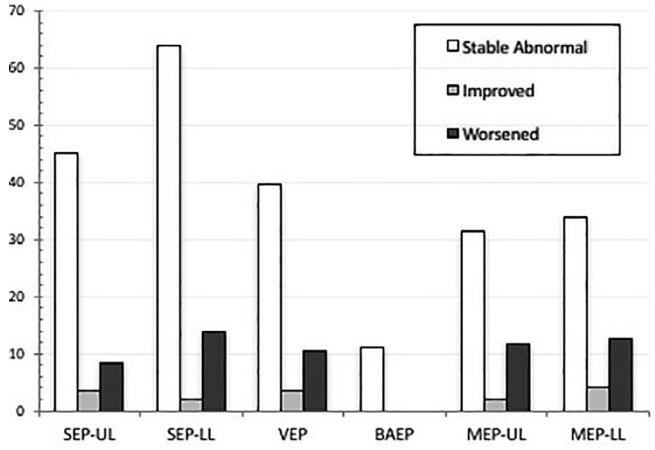

Fig. 1. Number of CCTs by side at T1 + T2 (n = 148, 37 patients) for each EP modality. The number of sides with normal central conductivity at T0, that remained stable throughout the study, was: 65 (43.9%) for upper limbs SEPs, 31 (20.9%) for lower limbs SEPs, 69 (46.6%) for VEPs, 132 (89.2%) for BAEPs, 81 (54.7%) for upper limbs MEPs and 74 (50%) for lower limbs MEPs.

Table 3
Frequency of alterations of urodynamic variables in the 19 patients undergone to PTA.

	T0	T1	T2
Incontinence (UI)	3 (15,8%)	3 (15,8%)	4 (21,1%)
Detrusor overactivity (DO)	9 (47,3%)	7 (36,8%)	10 (52,6%)
Overactivity Volume (OV)	8 (42,1%)	7 (36,8%)	10 (52,6%)
Detrusor Pressure (Pdet)	8 (42,1%)	7 (36,8%)	10 (52,6%)
High pressure DO (HPDO)	4 (21,1%)	5 (26,3%)	5 (26,3%)

At a descriptive level: UI was unchanged from T0 to T1 in all patients, while at T2 incontinence was found in an additional patient, that also showed residual voiding urine. DO was overall unchanged from T0 to T1 to T2 in all cases. In one patient at T1, DO disappeared, while one patient developed it. In the 9 patients with DO at T0, OV was reduced in 3, absent in 1, and increased in 5 at T1.

HPDO remained >40 cm H2O from T0 to T1 in 4 patients and in 5 patients at T2; in one case it decreased from 52 cm H2O at T0 to 5 cm H2O in T1; in 2 patients it remained <40 cm cm H2O from T0 to T1; in the patient who developed DO in T1, HPDO was 26 cm H2O. In 1 patient, DO was not present from T0 to T1 and HPDO was 0 cm H2O.

4. Discussion

Despite the long standing debate about the relevance of PTA interventions in treating MS has been definitely moved towards the demonstration of its clinical inefficacy (Zamboni et al., 2018; Zivadinov and Weinstock-Guttman, 2018), the current one is to date the only prospective study investigating neurophysiological and urodynamic follow up, in parallel with clinical objective and subjective findings, in MS patients undergoing endovascular treatment with PTA. Previously, only a single case report showed an improvement of central motor conduction time following PTA intervention in a MS patient (Plasmati et al., 2010), but no other neurophysiological studies are still available to quantitatively monitor functional changes related to central neural conduction properties in these patients. This precludes statements regarding a possible myelination repair, accompanying (or not) an eventual improvement of disability, following PTA procedures.

Results of the current study confirm that the PTA did not modify patients' disability, as assessed by the EDSS, throughout

the following 15 months, in line with recent evidences in a randomized-controlled trial (Zamboni et al., 2018). This was functionally paralleled by a lack of improvement of gEP-score and urodynamic indexes, which instead worsened or remained pathologically stable over time. Indeed, the gEP-score significantly deteriorated from T0 to T1 and remained stable at T2, paralleling the small number of CCTs improvements throughout the study (Fig. 1). Similar worsening of gEP-scores were seen in the five patients who underwent diagnostic phelobography but not PTA; however, such a small sample size does not allow to draw any conclusion. Interestingly, of the 22 CCTs improved at T1 + T2 taking into consideration all the explored functional domains, 8 (36.4%) were found in the five patients treated with Natalizumab. However, no further comment can be made for this aspect, although it seems in line with a dedicated study (Meuth et al., 2011).

Despite these findings, the subjective well-being of most of the treated patients significantly improved in the first six months following the PTA, and returned close to baseline values at the second sampling time (up to 15 months), in line with previous observations of a dichotomy between subjective improvement and objective decline following PTA (Zagaglia et al., 2013). The most conservative interpretation accounting for this dissociation, as well as for the transient subjective beneficial effect, would suggest that a placebo effect following the interventional procedure has taken place. This is plausible, taking into consideration the high patients' expectations, hyped by mass media in recent years (Chafe et al., 2011). To this purpose, an emerging literature is demonstrating that cognitive and emotional processes linked with placebo administration are able to activate internal mechanisms that somewhat modify physiology (Zubieta and Stohler, 2009), to an extent that they might constitute resiliency mechanisms with a potential to aid in the recovery processes of the organism. We cannot exclude a priori that PTA intervention might have affected cognitive and emotional processes, whose functionality has been not explored in the current study. However, this seems unlikely as no association between cognitive impairment and depression with presence and severity of CCSVI has been observed (Benedict et al., 2013).

The degree of improvements observed in different EP modalities during the follow-up period (Fig. 1) is in line with the recovery rate seen in other longitudinal studies in patients with MS (Meuth et al., 2011), and possibly suggests that conduction properties of central nervous pathways in MS patients maintain a margin of spontaneous recovery that can be detected at a functional level with conventional neurophysiological investigations. Due to their correlation with disability as assessed by EDSS (Facchetti et al., 1997; O'Connor et al., 1998; Leocani et al., 2000; Leocani et al., 2006; Kallman et al., 2006; Jung et al., 2008; Kiylioglu et al., 2015), cumulative abnormalities of multimodal EPs have been proven to be a useful tool to quantify beneficial effects of treatment with natalizumab at a functional level (Meuth et al., 2011). As in previous studies, also in the current one, conduction abnormalities along longest nervous pathways (i.e., SEPs and MEPs from lower limbs) were the ones showing the best association with EDSS during follow-up, while BAEPs were the less affected ones (Leocani et al., 2006). This because the weight of walking impairment and spinal cord dysfunction is the main factor determining the disability level, as measured through the EDSS score. It is known that TMS variables may improve following interferon (White and Petayan, 2004; Feuillet et al., 2007) or fingolimod therapies (Iodice et al., 2016), but this was not the case after PTA intervention in our sample of patients.

The function of the lower urinary tract (LUT) is mainly storage and voiding of urine and is regulated by a neural control system in the brain and in the spinal cord that coordinates the activity of the urinary bladder and bladder outlet. Therefore, any disturbance of the nervous system that controls the LUT can result in neurogenic LUT dysfunction. NLUT dysfunctions can cause a variety of long-term complications and the most dangerous one is the damage of renal function. Because MS symptoms and long-term complications do not correlate (Nosseir et al., 2007), implying that asymptomatic patients can present abnormal urodynamic findings (Del Popolo et al., 2008), it is important to identify patients with NLUT dysfunctions: elevated storage pressure in the bladder, either alone or combined with vesicoureteric reflux (VUR), is the most important risk factor for renal damage. Sustained elevated storage pressure in the bladder is mainly due to a combination of increased detrusor activity during the storage phase (detrusor overactivity or low compliance), combined with detrusor-sphincter-dyssynergia (DSD). In our sample of patients, NLUT dysfunctions was not consistently modified throughout the study in the 19 patients who underwent PTA and completed the trial. However, a global -not significant- worsening tendency (Table 3) was noted for all the considered functional parameters, the most pronounced being DO, OV and HDOP (all +10%). These findings indirectly suggest that PTA did not modify conduction properties of supraspinal pathways controlling the LUT, similarly to what directly observed neurophysiologically for somatosensory, motor, auditory and visual functions. Also the number of patients with overt Incontinence, the most disabling of the considered variables, slightly increased at T2 versus T1 and T0 (Table 3). These results are in keeping with those of a recent randomized controlled trial in which a higher proportion of patients in the PTA group than in the sham group worsened for post-void residual urine volume and balance (Zamboni et al., 2018).

4.1. Limitations of the study

While the group of patients undergone to PTA represents the largest sample to date prospectively followed up by neurophysiological and urological investigations, the number of patients undergone to diagnostic phlebography only is small, likely reflecting a "cumulative decisional bias" of patients, referring and treating physicians towards the PTA.

Moreover, the number of dropouts, either for neurophysiological evaluations (25/68; 36.7%) or NLUT investigations (17/37; 45.9%) is overall high. This makes the sample of patients evaluated by urological investigations small: however, no previous studies have yet followed up PTA effects on this crucial issue for quality of everyday life in patients with MS.

The reduced adherence to the study protocol might rely on several, mutually additive, factors including: patients' (often coming from far places) burden in terms of time (two consecutive days for each sampling time); dissatisfaction to see unimproved EPs and urodynamic evaluations at T1 or T2 (patients were provided with copies of all examinations results); stability or worsening of the clinical picture despite the angiographic procedure.

We did not perform imaging investigations to evaluate the correlation with the lesion load in the brain and spinal cord at MRI. Therefore, we could not verify whether abnormalities of multimodal EPs, which are known to correlate with EDSS (Fuhr et al., 2001; Leocani et al., 2006; Kallman et al., 2006; Jung et al., 2008; Schlaeger et al., 2014a), also correlated with lesion load. The decision to not perform correlation with lesion load at MRI investigations, i.e. the most extensively used surrogate biomarker in MS pharmacological trials (Barkhof and Filippi, 2009), was based on i) practical reasons of protocol burden tolerability, and ii) previous findings of a poor correlation between conventional MRI indices of lesion load and disability (Nijeholt and van Walderveen, 1998; Charil et al., 2003; Li et al., 2006), i.e. the well-known clinico-radiological paradox of MS (Barkhof, 2002). Moreover, we aimed to evaluate clinical, neurophysiological and urological findings at a maximum follow up of 15 months, while MRI findings (central

atrophy and lesion volume change) are known to correlate with EDSS evolution not earlier than at 10 years (Popescu et al., 2013).

5. Conclusions

Current findings confirm that the relatively short-lived, subjective, beneficial effect experienced by MS patients undergoing PTA intervention is not paralleled by any objectively measurable change in disability (as assessed by EDSS) (Zamboni et al., 2018; Zivadinov and Weinstock-Guttman, 2018) or, as an original finding, by functional testing as multimodal EPs and LUT investigations, in the first 15 months following the procedure. This raises the likely possibility of a placebo effect. Nevertheless, the function of the tested somatosensory, motor, visual, auditory and urinary central pathways was unaffected by the PTA intervention. Results provide the neurophysiological ground (i.e., absence of neural conduction improvement in central multimodal pathways, including function of urinary tracts) underlying the clinical inefficacy of PTA in MS (Zivadinov and Weinstock-Guttman, 2018).

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Conflict of interest

None.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinph.2018.10.015.

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