ORIGINAL ARTICLE

The effects of antimuscarinic treatment on the cognition of spinal cord injured individuals with neurogenic lower urinary tract dysfunction: a prospective controlled before-and-after study

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Study design: Prospective controlled before-and-after study.

Objectives: To investigate the effects of antimuscarinic treatment of neurogenic lower urinary tract dysfunction on the cognition of individuals with spinal cord injury (SCI) during the early post-acute phase.

Setting: Single SCI rehabilitation center.

Methods: Patients with acute traumatic SCI admitted for primary rehabilitation from 2011 to 2015 were screened for study enrollment. Study participants underwent baseline neuropsychological assessments prior to their first urodynamic evaluation (6–8 weeks after SCI). Individuals suffering from neurogenic detrusor overactivity received antimuscarinic treatment, and those not requiring antimuscarinic treatment constituted the control group. The neuropsychological follow-up assessment was carried out 3 months after the baseline assessment. The effects of group and time on the neuropsychological parameters were investigated.

Results: The data of 29 individuals were evaluated (control group 19, antimuscarinic group 10). The group had a significant ($P \leq 0.033$) effect on immediate recall, attention ability and perseveration. In the control group, individuals performed significantly ($P \leq 0.05$) better in immediate recall both at baseline (percentile rank 40, 95% CI 21–86 versus 17, 95% CI 4–74) and follow-up (percentile rank 40, 95% CI 27–74 versus 16, 95% CI 2–74). The time had a significant ($P \leq 0.04$) effect on attention ability, processing speed, word fluency and visuospatial performance. The individuals in both groups performed better at the follow-up compared to the baseline assessment.

Conclusion: Even though, we did not observe cognitive deterioration in the investigated, cognitively intact SCI individuals during the first 3 treatment months, the concerns regarding deleterious effects of antimuscarinics on cognition remain.

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INTRODUCTION

The majority of individuals with spinal cord injury (SCI) suffer from neurogenic lower urinary tract dysfunction (NLUTD). Individuals with suprasacral SCI may incur neurogenic detrusor overactivity and detrusor-sphincter dyssynergia.¹ These alterations may lead to incontinence, urinary retention and elevated bladder pressure during urine storage and voiding. Subsequently, increased intravesical pressure and/or vesicoureteral reflux may threaten the upper urinary tract. The focus of bladder management is therefore on achieving adequate drainage (for example, intermittent catheterization) as well as low bladder pressure during urine storage and voiding using antimuscarinic drugs.^{1–3} The efficacy of antimuscarinic drugs for the long-term treatment of NLUTD is well established.¹ However, SCI individuals often require higher doses of antimuscarinic drugs than those with idiopathic detrusor overactivity, which may lead to more or more severe adverse effects.⁴

Muscarinic receptors are widespread throughout the body, and thus, antimuscarinic treatment may give rise to a variety of adverse effects. Peripheral effects include constipation, dry mouth, dry eyes

and tachycardia, whereas central effects include agitation, confusion, delirium and cognitive dysfunction.^{5–8} Particularly older individuals have an increased risk of cognitive deterioration with antimuscarinic treatment.^{7,8} The antimuscarinic treatment for NLUTD in SCI individuals starts at a relatively young age and commonly lasts life-long. Thus, cognitive deterioration in SCI individuals with antimuscarinic treatment is a concern. However, the data on the effects of antimuscarinic treatment on cognitive function in individuals with NLUTD are very limited.^{9,10}

The aim of the present study was thus to investigate the effects of antimuscarinic treatment of NLUTD on the cognition of individuals with SCI during the early post-acute phase. The following hypothesis was tested: the neuropsychological performance of SCI individuals with NLUTD decreases significantly under antimuscarinic treatment during the early post-acute phase (until 3 months after injury).

MATERIALS AND METHODS

This prospective cohort study had been approved by the competent ethics committee (KEK LU 11060) and registered with ClinicalTrials.gov (NCT01600404). All applicable institutional and governmental regulations

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were followed. All study participants gave written informed consent, and all data were encrypted and kept confidential. No financial or other support had been received for this study.

Study participants and protocol

The admission list of a single SCI rehabilitation center (150 in-patients) was screened weekly from 01 November 2011 to 30 June 2015 for patients with acute traumatic SCI being admitted for primary rehabilitation within 8 weeks after SCI. In order to exclude other factors affecting the results of the neuropsychological assessments, the following exclusion criteria were applied: age younger than 18 or older than 65 years, diagnosed head or brain injury, dementia or impaired cognitive function, psychological disorders, abuse of substances with central nervous effect and antimuscarinic treatment. In order to ensure the fitness of the investigated individuals to undergo the neuropsychological assessments, the following exclusion criteria were applied: neurological lesion level above C5 (5th cervical level according to the International Standards for Neurological Classification of Spinal Cord Injury), severe comorbidities, color blindness or impaired vision and insufficient German language skills. Furthermore, upon receipt of written consent, study participant completed the Beck Depression Inventory II (BDI-II) and a pain questionnaire (modified International Spinal Cord Injury Pain Basic Data Set) (secondary outcome measures). Study participants suffering from moderate to severe depression (BDI-II score > 19) or pain (average pain during last 7 days > 5/10) were excluded.

Enrolled study participants underwent the baseline neuropsychological assessment prior to their first urodynamic evaluation, which usually takes place 6–8 weeks after SCI. Study participants suffering from neurogenic detrusor overactivity or detrusor-sphincter dyssynergia were started on antimuscarinic treatment according to the guidelines of the European Association of Urology.¹ Individuals not requiring antimuscarinic treatment constituted the control group. The neuropsychological follow-up assessment was carried out 3 months after the baseline assessment.

Patient characteristics, the type of NLUTD, the current bladder evacuation method and the administration of drugs with antimuscarinic properties were collected from the medical records (secondary outcome measures). Using the composite reference rating scale (low, moderate, high) collated by Salahudeen *et al.*,¹¹ the antimuscarinic effect of concomitant medication (indications other than NLUTD) during the course of the study was assessed (antimuscarinic burden) (secondary outcome measure).

Table 1 List of exclusion criteria

Exclusion criteria	Count/percentage
Head or brain injury	62/20.9%
Age > 65 years	56/18.9%
Lesion level above C5	37/12.5%
Informed consent denied	27/9.1%
Insufficient German language skills	27/9.1%
Psychological disorders	26/8.8%
Substance abuse	13/4.4%
Admission > 8 weeks after SCI	12/4.0%
Severe comorbidities	9/3.0%
Impaired cognitive function	8/2.7%
Age < 18 years	6/2.0%
Duration of rehabilitation < 3 months	5/1.7%
Pain (NRS > 5/10)	5/1.7%
Treatment with AM	2/0.7%
Major surgery planned	1/0.3%
Non-traumatic SCI	1/0.3%

Abbreviations: AM, antimuscarinics; NRS, numeric rating scale; SCI, spinal cord injury. The total count and the sum of the percentages exceed the number of excluded patients and 100% because some patients presented with more than one exclusion criterion. C5-5th cervical level.

Neuropsychological assessment

The neuropsychological assessments were performed using the following tests (primary outcome measures): California verbal learning test, d2 test of attention, stroop test, thurstone word fluency test, visuospatial performance subtests from the Hamburg-Wechsler-Adult-Intelligence-Test and the Gestalt closure test from the Kaufmann Assessment Battery as well as the divided attention subtest from the test battery of Zimmermann and Fimm. The divided attention test was performed on a computer. The assessors were blinded regarding the group allocation of the study participants. If available, parallel test versions were used for the follow-up assessments. All used tests were validated German versions. The percentile rank cutoff value for normal performance in the neuropsychological assessments was set at 16.¹²

Statistical analyses

A sample size of 20 in each group was determined to be sufficient to detect a difference of > 1 s.d. in the neuropsychological test parameters between the two groups in the presence of a 50% variance with a power of 80% and a significance level of 5%. A change of > 1 s.d. is considered a clinically relevant change in neuropsychological testing.^{12,13}

According to international recommendations, injury level and severity were classified into four groups: (1) American Spinal Injury Association Impairment Scale (AIS) D, (2) AIS A-C paraplegia, (3) AIS A-C low-level tetraplegia (C8-C5) and (4) AIS A-C high-level tetraplegia (C4-C1).¹⁴ Based on their education level, the study participants were categorized into three groups using the International Standard Classification of Education (ISCED): (1) ISCED level 2 (lower secondary education), (2) ISCED level 3 (upper secondary education) and (3) ISCED level 4–8 (tertiary education). The antimuscarinic burden of concomitant medication was determined for each study participant by calculating the sum of the composite rating scales (low = 1, moderate = 2, high = 3).¹¹

The group assignment was also blinded for the statistical analyses. The median and 95% confidence intervals or proportions were calculated. The differences in the proportions between the groups were tested using Fisher's exact test. The effects of group assignment (antimuscarinics/control) and time (baseline/follow-up 3 months) on the neuropsychological parameters were investigated using the method described by Brunner *et al.*¹⁵ for the nonparametric (rank-based) analysis of longitudinal data in factorial designs. The Wilcoxon rank-sum test was used to investigate the differences between the groups at the specific time points. The statistical analyses were performed using the R software environment (version 3.3.0, Copyright 2016, The R Foundation for Statistical Computing) and the package *nparrLD*.¹⁶ A *P*-value of ≤ 0.05 was considered significant.

RESULTS

A total of 250 patients with acute traumatic SCI who were admitted for primary rehabilitation were screened for study enrollment. In 191 patients, at least one exclusion criterion was present (Table 1). Written informed consent was denied by 27 patients, and thus, 32 patients were enrolled in the study. The recruitment of study participants was stopped before the full number was enrolled, because of the low recruitment rate. One study participant did not complete the neuropsychological follow-up assessment because of severe pain (control group), and one participant in each group was excluded as a result of mild traumatic brain injury, which had been diagnosed after study enrollment. Thus, the data of 29 individuals were evaluated (control group 19, antimuscarinic group 10). Their characteristics are presented in Table 2. There was no significant ($P \geq 0.09$) difference between the groups regarding gender distribution, age, SCI severity, education level, antimuscarinic burden, BDI-II score, pain and evaluation time points.

The individuals in the antimuscarinic group were treated with solifenacin (10 mg once daily, $n = 7$), fesoterodine (8 mg once daily, $n = 2$) or darifenacin (15 mg once daily, $n = 1$) as a result of neurogenic detrusor overactivity ($n = 10$). The type and dose of

Table 2 The characteristics of the evaluated individuals

	Control	AM	P-value
Gender (n/%)			
Women	5/26%	1/10%	0.6
Men	14/74%	9/90%	
Age (years)	31 (20–60)	25 (18–60)	0.1
SCI (n/%)			
Tetraplegia	6/32%	4/40%	0.7
Paraplegia	13/68%	6/60%	
Severity SCI (n/%)			
Tetraplegia AIS A-C	4/21%	4/40%	0.1
Paraplegia AIS A-C	9/47%	6/60%	
AIS D	6/32%	0/0%	
Education (n/%)			
ISCED level 2	8/42%	5/50%	0.5
ISCED level 3	5/26%	4/40%	
ISCED level 4–8	6/32%	1/10%	
AM medication* (n/%)			
No AM drug	6/32%	2/20%	0.8
One AM drugs	10/53%	5/50%	
Two AM drugs	3/16%	3/30%	
AM burden*	1.0 (95% CI 0–2)	1.5 (95% CI 0–4)	0.27
BDI-II			
Baseline	6 (95% CI 4–8)	7 (95% CI 4–11)	0.3
Follow-up 3 months	5 (95% CI 4–9)	12 (95% CI 3–15)	0.09
Pain (NRS)			
Baseline	2 (95% CI 1–3)	2 (95% CI 0–4)	0.6
Follow-up 3 months	2 (95% CI 0–3)	2 (95% CI 0–5)	0.9
Evaluation time point (weeks)			
Baseline	7.3 (4.4–10.3)	6.6 (5.0–9.3)	0.2
Follow-up 3 months	12.9 (10.0–19.0)	14.0 (12.3–17.6)	0.1

Abbreviations: AIS, American Spinal Injury Association Impairment Score; AM, group treated with antimuscarinics; AM medication/AM burden, concomitant medication with antimuscarinic effects (*indications other than neurogenic lower urinary tract dysfunction); baseline, weeks after injury; BDI-II, Beck depression inventory II; follow-up 3 months, weeks after baseline neuropsychological investigation; ISCED, International Standard Classification of Education; NRS, numeric rating scale; pain, average pain during last 7 days (NRS 0–10); SCI, spinal cord injury.

The data are presented as the median and the range or the 95% confidence interval (CI) where appropriate. control —control group.

antimuscarinic medication did not change during the course of the study. The concomitant medication with antimuscarinic effects is presented in Table 3. All individuals in the antimuscarinic group used intermittent catheterization for bladder evacuation; whereas in the control group, 11 individuals emptied the bladder with intermittent catheterization and 8 spontaneously.

The median percentile ranks of the assessed neuropsychological parameters were all higher than or equal to 16 (cutoff value for normal performance) in both groups and at both assessment time points (Table 4). The group assignment (antimuscarinics/control) had a significant ($P \leq 0.033$) effect on immediate recall during verbal learning testing, attention ability and perseveration during word fluency testing (non-parametric variance analysis). *Post hoc* analyses revealed that the individuals in the control group performed significantly ($P \leq 0.05$) better in the immediate recall testing compared to

those in the antimuscarinic group both at baseline and follow-up (Table 4). There were no other significant differences in the neuropsychological parameters between the two groups.

The individuals in both groups performed better at the follow-up compared to the baseline assessment. The time (baseline/follow-up 3 months) had a significant ($P \leq 0.04$) effect on attention ability, processing speed, word fluency and visuospatial performance (non-parametric variance analysis) (Table 4).

DISCUSSION

We have investigated the effects of antimuscarinic treatment of NLUTD on the cognition of individuals with SCI during the early post-acute phase. The hypothesis, that the neuropsychological test results of the investigated SCI individuals with NLUTD decrease significantly under antimuscarinic treatment, was rejected. The median percentile ranks of the assessed neuropsychological parameters were all higher than or equal to the cutoff value (that is, 16) for normal performance. The individuals in both groups performed better at the follow-up compared to the baseline assessment.

Non-parametric variance analysis revealed that the group assignment had a significant effect on immediate recall during verbal learning testing, attention ability and perseveration during word fluency testing. However, only immediate recall performance was significantly different between the two groups. The individuals in the control group performed better in immediate recall both at baseline and follow-up. In the antimuscarinic group, the poor performance of one individual had a great effect on the California verbal learning test results due to the small sample size ($n=10$). Sakakibara *et al.*⁹ investigated the effect of imidafenacin on cognitive function in patients with a mean age of 70 years, suffering from neurogenic overactive bladder. They did not observe any changes in cognitive function 3 months after the administration of imidafenacin. Similarly, Veenboer *et al.*¹⁰ did not detect differences between the behavior of children with neurogenic bladder and long-term antimuscarinic treatment and that of children without antimuscarinic medication. However, in older individuals with non-neurogenic overactive bladder, oxybutynin was reported to cause cognitive deterioration.^{17–19} The memory deterioration caused by oxybutynin was comparable to brain aging of 10 years,¹⁸ whereas darifenacin, solifenacin and fesoterodine showed no effect on cognitive function.^{18–21} In the present study, solifenacin, fesoterodine or darifenacin were used to treat neurogenic detrusor overactivity. The differences in cognitive function seem to be due to differences in the binding affinity to muscarinic receptors between the antimuscarinic drugs and the ability to cross the blood-brain barrier.^{5,22,23} The M_3 and M_2 receptors are involved in bladder contraction and relaxation, respectively, whereas M_1 receptors in the brain play an important role in cognition.²³ In general though, cognitive deterioration does not seem to be characteristic for antimuscarinic drugs used to treat NLUTD. However, in older individuals with a great antimuscarinic burden due to poly-medication, the detrimental effect of antimuscarinic treatment on cognitive function is well documented.^{7,8} In the present study, the antimuscarinic burden of the evaluated individuals was low to moderate.

The evaluated individuals generally performed better in the follow-up tests compared to the baseline assessment. This was observed in both the control and the antimuscarinic group. The time interval between the two assessments was 3 months, and parallel test versions were used, if available. However, practice effects are not completely avoidable in longitudinal neuropsychological assessments.²⁴ After 3 months, study participants most likely did not remember the

Table 3 The concomitant medication with antimuscarinic effects of the evaluated individuals

Medication	Rating scale	Control (n = 19)	AM (n = 10)
Amitriptyline	High	0	2/20%
Tizanidine	High	1/5%	1/10%
Trimipramine	High	0	1/10%
Baclofen	Moderate	4/21%	0
Tramadol	Moderate	1/5%	1/10%
Morphine	Low	0	2/20%
Oxycodone	Low	5/26%	2/20%
Quetiapine	Low	4/21%	0
Venlafaxine	Low	1/5%	2/20%

The total count and the sum of the percentages exceed the number of evaluated individuals and 100% because some individuals were treated with more than one concomitant drug with antimuscarinic effects. Rating scale—composite rating scale of AM effect. Control—control group. AM—group treated with antimuscarinics for neurogenic lower urinary tract dysfunction.

questions or specific tasks and their original answers, however they were familiar with the tests at the follow-up assessment. Even if the neuropsychological tests are completely different between two assessment time points, individuals acquire knowledge of how to respond to tests and thus, perform better during the subsequent assessment (test sophistication).²⁵

Even modest cognitive impairment has a negative effect on rehabilitation outcomes.^{26,27} Cognitive impairment interferes with a patient's ability to compensate for restrictions or to acquire new skills and thus, rehabilitation strategies and measures need to be adjusted or intensified accordingly. In SCI patients during primary rehabilitation, cognitive impairment may result from brain injury, psychological stress or disorders, pain or neurodegenerative processes in the brain.^{28–31} Furthermore, poly-medication due to pain, depression, spasticity and NLUTD, which is common in SCI patients, may increase the antimuscarinic burden and lead to cognitive impairment,

Table 4 The neuropsychological test results of the evaluated individuals

Test	Value	Time point	Control	AM	P-value
			Median (95% CI)	Median (95% CI)	
California verbal learning test					
Total recall	Raw	Baseline	56 (49–65)	46.5 (42–61)	n.s.
		Follow-up	57 (50–66)	51 (46–56)	n.s.
	PR	Baseline	51 (21–86)	16 (8–72)	n.s.
		Follow-up	55 (24–89)	30.5 (15–51)	n.s.
Immediate recall	Raw	Baseline	12 (10–14)	9 (7–14)	n.s.
		Follow-up	12 (10–14)	9 (5–14)	n.s.
	PR	Baseline	40 (21–86)	17 (4–74)	0.05
		Follow-up	40 (27–74)	16 (2–74)	0.04
Delayed recall	raw	Baseline	12 (9–14)	9 (6–14)	n.s.
		Follow-up	12 (9–15)	10 (8–12)	n.s.
	PR	Baseline	44 (10–65)	24 (2–65)	n.s.
		Follow-up	44 (14–79)	18 (10–60)	n.s.
d2 Test of attention					
Total number	Raw	Baseline	149 (132–161)	165 (125–187)	0.14
		Follow-up	172 (131–180)	169 (104–222)	0.8
	PR	Baseline	21 (12–34)	42 (8–69)	0.3
		Follow-up	46 (12–58)	44 (2–95)	0.3
Total errors	Raw	Baseline	8.0 (3–16.4)	9.1 (0–19.4)	n.s.
		Follow-up	8.3 (2.9–11.8)	10.3 (0.4–19)	n.s.
	PR	Baseline	58 (24–76)	35 (4–99)	n.s.
		Follow-up	66 (38–82)	42.5 (3–99)	n.s.
Stroop test					
Test time	Raw	Baseline	39 (32–45)	42 (32–49)	n.s.
		Follow-up	38 (30–42)	32.5 (25–43)	n.s.
	PR	Baseline	35 (17–57)	20.5 (10–35)	n.s.
		Follow-up	35 (22–65)	38.5 (31–69)	n.s.
Test errors	Raw	Baseline	0 (0–1)	0 (0–3)	n.s.
		Follow-up	0 (0–2)	0 (0–0)	n.s.
	PR	Baseline	77 (41–77)	77 (10–77)	n.s.
		Follow-up	77 (20–77)	77 (77–77)	n.s.
Thurstone word fluency test					
Fluency	Raw	Baseline	27 (19–31)	25 (21–27)	n.s.
		Follow-up	32 (24–36)	27 (21–33)	n.s.
	PR	Baseline	35 (12–53)	27 (17–35)	n.s.
		Follow-up	69 (22–76)	41 (22–69)	n.s.

Table 4 (Continued)

Test	Value	Time point	Control	AM	P-value
			Median (95% CI)	Median (95% CI)	
Perseveration	Raw	Baseline	0 (0–1)	0 (0–2)	n.s.
		Follow-up	0 (0–1)	0.5 (0–2)	n.s.
	PR	Baseline	83 (53–83)	53 (32–83)	
		Follow-up	83 (53–83)	53 (19–83)	
Visuospatial performance					
Block design	Raw	Baseline	30.5 (27–41)	35.5 (29–42)	n.s.
		Follow-up	35.5 (33–44)	38.5 (29–44)	n.s.
	PR	Baseline	37 (25–84)	56.5 (37–84)	n.s.
		Follow-up	56.5 (50–91)	75 (37–91)	n.s.
Picture completion	Raw	Baseline	16 (14–16)	14.5 (12–16)	n.s.
		Follow-up	16 (14–17)	15 (14–16)	n.s.
	PR	Baseline	95 (50–95)	62.5 (25–95)	n.s.
		Follow-up	95 (50–99)	75 (50–95)	n.s.
Gestalt closure	Raw	Baseline	21 (19–23)	20 (18–22)	n.s.
		Follow-up	22 (20–24)	21 (20–23)	n.s.
	PR	Baseline	63 (37–91)	50 (25–84)	n.s.
		Follow-up	84 (50–95)	63 (50–91)	n.s.
Divided attention					
Auditory	Median	Baseline	603 (481–691)	539 (412–652)	n.s.
		Follow-up	623.5 (563–649)	562.5 (406–623)	n.s.
	PR	Baseline	21 (5–69)	46 (12–92)	n.s.
		Follow-up	17.5 (12–34)	36.5 (16–88)	n.s.
Visual	Median	Baseline	757 (678–823)	798.5 (707–940)	n.s.
		Follow-up	752 (712–798)	735.5 (668–823)	n.s.
	PR	Baseline	66 (31–79)	29 (8–69)	n.s.
		Follow-up	60 (46–69)	60 (21–79)	n.s.
Total errors	Raw	Baseline	2 (0–3)	1 (0–5)	n.s.
		Follow-up	0.5 (0–1)	1 (1–2)	n.s.
	PR	Baseline	21 (12–62)	36 (7–83)	n.s.
		Follow-up	54 (34–73)	36 (18–79)	n.s.
Total omissions	Raw	Baseline	1 (0–2)	2 (0–4)	n.s.
		Follow-up	1 (1–2)	0.5 (0–2)	n.s.
	PR	Baseline	50 (24–73)	29 (7–69)	n.s.
		Follow-up	42 (27–54)	42 (21–76)	n.s.

Abbreviations: n.s., not significant; pr, percentile rank values of applied tests.

Bold P-values signify values ≤ 0.05 . control—control group. AM—group treated with antimuscarinics. raw—raw values of applied tests. *Post hoc* analyses have not been performed based on the results of the variance analysis.

especially in older patients.^{7,8} Older individuals are more vulnerable to cognitive deterioration due to antimuscarinic bladder treatment, because of the decrease in cholinergic activity in the brain with increasing age.²³ In previous investigations, the effects of antimuscarinic bladder treatment on cognition have been investigated mainly in older individuals.^{9,22,23} However, no age-stratified analyses have been performed. Based on the present results, cognitive deterioration does not seem to be an issue in the treatment of NLUTD in younger patients with currently used antimuscarinic drugs during primary rehabilitation,⁴ if the antimuscarinic burden of the concomitant medication is low. Nevertheless, the possibility of cognitive deterioration in the wake of antimuscarinic medication in SCI individuals should not be excluded from consideration. The antimuscarinic treatment of NLUTD in affected SCI individuals lasts life-long, and thus, the long-term effect of antimuscarinic treatment of NLUTD on cognition needs to be investigated in future studies.

The non-randomized treatment assignment pertains to the limitations of the present study and may have resulted in a selection bias. However, the baseline patient characteristics showed no relevant differences between the two evaluated groups. We decided to stop the recruitment of study participants before the full number was enrolled, because of the low recruitment rate. The low recruitment rate was the result of the stringent exclusion criteria, which had been applied to exclude other relevant factors affecting the results of the neuropsychological assessments apart from the AM treatment of NLUTD. Thus, the statistical power was too low for some differences in the neuropsychological assessments between groups or time points to reach significance. However, the outcome parameters demonstrated a general trend of improvement over time, and our concern was cognitive impairment as a result of the antimuscarinic treatment of NLUTD. Furthermore, differences in the baseline characteristics between the two groups may have not been statistically significant as

a result of the small sample size. However, the results showed no relevant differences between the groups. The *post hoc* tests were not corrected for type 1 errors, which may have resulted in false positive results. However, our concern was cognitive impairment, and there was a general trend of cognitive improvement at follow-up. A further limitation of the present study is that the majority of study participants in both groups were treated with concomitant medication with antimuscarinic effects. However, there was no difference in the number of concomitant drugs with antimuscarinic effects or the antimuscarinic burden between the two investigated groups. The concomitant medication with antimuscarinic effects as well as the antimuscarinic treatment of NLUTD did not have a negative effect on the cognitive abilities of the evaluated individuals. Furthermore, we have investigated the effects of antimuscarinic treatment of NLUTD on the cognition of individuals with SCI during the first 3 months of treatment. Thus, we cannot draw any conclusions regarding the long-term effect of antimuscarinic treatment of NLUTD on cognition. However in previous studies, negative effects of antimuscarinic medication on cognition were observed within 3 weeks of treatment.^{17–20}

CONCLUSIONS

Even though, we did not observe cognitive deterioration in the investigated, cognitively intact SCI individuals with antimuscarinic treatment of NLUTD during the first 3 months of treatment, the concerns regarding deleterious effects of antimuscarinics on cognition remain and need to be investigated in future studies.

DATA ARCHIVING

There were no data to deposit.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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