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Cognitive functions in individuals with spinal cord injury: Do symptoms of autonomic dysreflexia or orthostatic hypotension have an effect?

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Abstract

Aim: This study aimed to compare the cognitive functions of individuals with spinal cord injury (SCI) and age- and education level-matched healthy controls, and to compare the cognitive functions between individuals with T6 or rostral and T6 caudal injuries.

Materials and Methods: This prospective and cross sectional study included 50 individuals with SCI and 47 age- and education level-matched healthy controls. The SCI individuals were divided into two groups as those with T6 or rostral (n = 20) and T6 caudal (n = 30) injuries. All participants underwent the Addenbrook Cognitive Examination-Revised (ACE-R) test to assess memory, attention and orientation, language, and verbal fluency.

Results: The memory, verbal fluency, and language subgroups of the ACE-R were significantly higher in the control group than in the SCI group. Compared with the control group, memory, verbal fluency, and language subscores were significantly reduced in individuals with T6 or rostral injury, and memory and verbal fluency were in individuals with T6 caudal injury. However, there was no significant difference in any of the ACE-R subscores between individuals with T6 or rostral and T6 caudal injuries.

Conclusion: Significant differences in certain parts of cognitive functioning were found in individuals with SCI compared with age- and education level-matched controls. However, no significant differences were noted in any parts of cognitive functioning between individuals with T6 or rostral and T6 caudal injuries. Although cognitive impairment is an important sequelae following SCI, autonomic dysfunctions appear to have no effect on cognitive impairments in this population.

Introduction

Spinal cord injury (SCI) can cause significant permanent changes in an individual's life. Studies have often focused on the physical consequences of SCI due to the motor and sensory loss below the lesion level. However, it has been demonstrated that cognitive consequences including limited attention, poor concentration and reduced memory up to 60% may be present [1]. Cognitive impairments negatively affect the rehabilitation success, self-perception, and social integration in individuals with SCI [2]. Despite these results, there is uncertainty about the cause of cognitive impairments. Concomitant traumatic brain injury is mostly blamed as the cause of cognitive impairments [3, 4]. In addition, premorbid neuropsychological status, chronic pain, and sleep apnea are other possible contributors for the cognitive impairments [1, 4, 5]. More recently, it has been suggested that autonomic cardiovascular disorders such as orthostatic hypotension and autonomic dysreflexia may affect cognitive functions [6, 7].

Cognitive impairments have been shown in association with increased blood pressure and hypotension in non-SCI population [8-10]. SCI individuals with injury level at T6 (6th thoracic segment) or rostral commonly experience orthostatic hypotension and autonomic dysreflexia leading to extreme fluctuations in blood pressure in these popu-

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lation [11]. In the preliminary data of a study conducted with a small number of participants, Jegede et al. reported that hypotensive individuals with SCI had impairment in cognitive functions compared to normotensives, as in non-SCIs [12]. Despite some studies reporting cognitive impairment caused by hypertension in healthy individuals, the available evidence linking recurrent episodes of autonomic dysreflexia with cognitive decline after SCI is still preliminary [10].

We hypothesized that the cognitive functions of individuals with SCI with T6 or rostral injury, who have the potential to experience frequent blood pressure fluctuations with episodes of orthostatic hypotension and autonomic dysreflexia, and those with T6 caudal injury may be different. Therefore, in this study, it was aimed 1) to compare the cognitive functions of individuals with SCI and age- and education level-matched healthy controls, and 2) to compare the cognitive functions between individuals with T6 or rostral injury and those with T6 caudal injury.

Materials and Methods

Study design

This investigation was designed as a prospective and cross-sectional study conducted in a tertiary rehabilitation hospital. The clinical research ethics committee of a medical centre approved the study (Ankara City Hospital, E2-22-1320). All participants were informed about the study procedures and their written consent was obtained. The study was conducted in accordance with the Declaration of Helsinki.

Participants

This study involved 50 consecutive individuals with SCI who admitted to a tertiary rehabilitation hospital for three months between March 2022 and May 2022, met the study criteria and agreed to participate in the study, and 47 age- and education level-matched healthy controls. Inclusion criteria were as follows: (1) traumatic SCI, (2) aged 18-65 years, (3) A, B, C and D according to the American Spinal Injury Association Impairment Scale (AIS), (4) at least 6 months have passed since SCI, and (5) cooperation can be established. Exclusion criteria as follows: (1) psychiatric diseases (for example, bipolar disorder, schizophrenia), (2) neurological diseases (for example, Alzheimer's, dementia, epilepsy, Parkinson's, stroke), (3) cardiovascular diseases, (4) history of traumatic brain injury, (5) hearing and language problems, and (6) chronic pain and sleep apne.

Based on the study conducted by Nightingale et al. [6] and using the G*Power 3.1.9.4 software, the memory measurement values of the Rey Auditory Verbal Learning Test were taken as the primary outcome measurement in sample size calculation. In the analysis, performed by taking the scores 51.8 ± 9.8 and 46.9 ± 8.2, the minimum number of patients was found to be at least 39 for each group and a total of 78 with 95% power and 5% type I error probability.

Age, gender, education level, neurological injury level (T6 or rostral / T6 caudal), injury severity (complete / incomplet), and time since injury of all individuals with SCI included in the study were recorded. The completeness and level of injury of SCI individuals were determined with AIS according to the International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI) [13] by a physiatrist. Individuals with T6 or rostral injury were included if they had a history of blood pressure fluctuations. Experiencing three or more symptoms of autonomic dysreflexia (headache, sweating, flushing, goosebumps) or orthostatic hypotension (dizziness, fainting, blurred vision, fatigue, and nausea) was considered a history of blood pressure fluctations.

Forty-seven healthy individuals without neurological or psychiatric diseases matched for age and education level were included as the control group. Healthy-controls enrolled from the hospital staff and local community.

Cognitive assessment

All participants underwent the Addenbrook Cognitive Examination-Revised (ACE-R). This instrument consists of five parts examining the cognitive functions with different subscores: memory [26 points], attention and orientation [18 points], language [26 points], verbal fluency [14 points], and visuospatial skills [16 points]. The maximum score is 100, which is the sum of the points of the all parts [14]. Turkish validity of ACE-R was examined by Mihci et al [15].

Hand motor functions were required to complete the visuospatial skills part, and some tetraplegic patients were unable to perform this part. Therefore, the visuospatial skills part was not used in our study and the participants were evaluated with four parts (memory, attention and orientation, language and verbal fluency). Cognitive assessment of all participants was performed by a single experienced psychologist.

Statistical analysis

Study data were analyzed using IBM SPSS Statistics for Windows, version 24.0 (Released 2016. Armonk, NY: IBM Corp.). Quantitative data in the study are age, education, time since injury and ACE-R subscores parameters, while qualitative data are gender, level of injury and severity of injury. The Kolmogorov-Smirnov test was performed to determine whether the variables were normally distributed. Continuous variables were presented in median and minimum-maximum values or mean and standard deviation for abnormally or normally distributed data, respectively. The Chi-squared test was used to compare categorical variables, results expressed as frequency (%). Mann-Whitney U test or Student's t-test were used for group comparisons for abnormally or normally distributed data, respectively. A p value of < 0.05 was regarded as statistically significant.

Results

Demographic parameters and ACE-R subscores of SCI and healty control groups and injury parameters of SCI group were demonstrated in Table 1. There was no significant difference between the SCI and control groups in terms of age ($p = 0.746$), gender ($p = 0.457$), and education level ($p = 0.120$). The memory, verbal fluency, and language subgroups of the ACE-R were significantly higher in the

Table 1. Demographics and ACE-R subscores of individuals with SCI and controls and injury parameters of SCI.

		SCI (n = 50) n (%), Mean ± SD	Control (n = 47) n (%), Mean ± SD	p value
Demographics				
Age (years)		36.26 ± 12.91	35.46 ± 10.91	0.746
Gender	Male	39 (78.0)	29 (72.5)	0.457
	Female	11 (22.0)	18 (27.5)	
Education (years)		10.38 ± 3.14	10.57 ± 3.94	0.120
Injury parameters				
Time since injury (months)		33.94 ± 42.98		
Level of injury	T6 or rostral	20 (40.0)		
	T6 caudal	30 (60.0)		
Severity of injury	Complete	23 (46.0)		
	Incomplete	27 (54.0)		
ACE-R subscores				
Attention and orientation		17.48 ± 1.38	17.51 ± 0.90	0.895
Memory		17.32 ± 3.64	20.36 ± 4.37	<0.001*
Verbal fluency		8.90 ± 2.01	10.40 ± 1.67	<0.001*
Language		22.72 ± 4.05	24.21 ± 2.46	0.032*

SCI: Spinal cord injury, ACE-R: Addenbrook Cognitive Examination-Revised, SD: Standard deviation
*: Significant difference between groups p < 0.05.

Table 2. Comparison of demographic and injury parameters of SCI individuals with T6 or rostral and T6 caudal injuries.

		T6 or rostral (n = 20) n (%), Mean ± SD	T6 caudal (n = 30) n (%), Mean ± SD	p value
Demographics				
Age (years)		36.05 ± 15.30	36.40 ± 11.31	0.926
Gender	Male	18 (90.0)	21 (64.3)	0.094
	Female	2 (10.0)	9 (35.7)	
Education (years)		10.20 ± 3.07	10.50 ± 3.24	0.745
Injury parameters				
Time since injury (months)		34.25 ± 28.98	33.73 ± 50.71	0.967
Severity of injury	Complete	10 (50.0)	13 (43.3)	0.643
	Incomplete	10 (50.0)	17 (56.6)	

SCI: Spinal cord injury, SD: Standard deviation.

control group than in the SCI group ($p < 0.001$, $p < 0.001$, and $p = 0.032$, respectively) (Table 1).

The SCI group was divided into two groups as T6 or rostral and T6 caudal injury. Twenty (40%) individuals with SCI had T6 or rostral injury and 30 (60%) had T6 caudal injury. There was no significant difference in demographic and injury characteristics between the two groups with SCI (Table 2).

Compared with the healthy control group, individuals with SCI with T6 or rostral injury had significantly reduced memory, verbal fluency, and language ACE-R subscores ($p = 0.012$, $p < 0.001$, and $p = 0.004$, respectively). Similarly, individuals with SCI with T6 caudal injury had significantly reduced memory and verbal fluency ACE-R subscores compared with the healthy control group (both $p = 0.002$). However, there was no significant difference in any of the ACE-R subscores between individuals with T6 or rostral and T6 caudal injury (all $p > 0.05$). Table 3 summarizes the comparison of ACE-R sub-score results between the groups.

Discussion

This study reported several considerable differences in specific parts of cognitive functioning in individuals with SCI as compared with age- and education level-matched healthy controls. Considerable differences from the control group were found in memory, verbal fluency, and lan-

Table 3. Comparison of Addenbrook Cognitive Examination-Revised subscore results between the groups.

	T6 or rostral (n = 20)	Control (n = 47)	p value
Attention and orientation	17.90 ± 0.44	17.51 ± 0.90	0.073
Memory	17.50 ±3.44	20.36 ± 4.37	0.012*
Verbal fluency	8.70 ± 1.86	10.40 ± 1.67	<0.001*
Language	21.45 ± 5.21	24.21 ± 2.46	0.004*
	T6 caudal (n = 30)	Control (n = 47)	p value
Attention and orientation	17.20 ± 1.62	17.51 ± 0.90	0.286
Memory	17.20 ± 3.82	22.36 ± 4.37	0.002*
Verbal fluency	9.03 ± 2.12	10.40 ± 1.67	0.002*
Language	23.56 ± 2.84	24.21 ± 2.46	0.295
	T6 or rostral (n = 20)	T6 caudal (n = 30)	p value
Attention and orientation	17.90 ± 0.44	17.20 ± 1.62	0.067
Memory	17.50 ± 3.44	17.20 ± 3.82	0.779
Verbal fluency	8.70 ± 1.86	9.03 ± 2.12	0.572
Language	21.45 ± 5.21	23.56 ± 2.84	0.070

All values are given as mean ± standard deviation

*: Significant difference between groups $p < 0.05$.

guage. However, no significant differences were noted in any parts of cognitive functioning between individuals with T6 or rostral and T6 caudal injuries.

The current study, one of the aims of which was to compare the cognitive functions of individuals with SCI and age- and education level-matched healthy controls, showed that there was a decrease in various parts of cognitive functions in individuals with SCI, consistent with the literature. Previous studies have presented lots of evidence about cognitive impairment following SCI. For example, Craig et al. examined cognitive functions in individuals with SCI and compared to controls using the neuropsychiatry unit cognitive assessment tool. They noted individuals with SCI had weaker cognitive function than the controls in some parts including memory, language, visoconstructional skills, executive functioning, and attention [16]. Nightingale et al. reported cognitive dysfunctions in individulas with SCI compared to age and sex-matched noninjured controls [6]. A recent review by Distel et al. emphasized a strong association between cognitive dysfunction and chronic SCI [5]. Although cognitive dysfunction has been strongly reported in this population, the reasons for this impairment are still less clear.

It has been suggested that potential contributors to the cognitive impairment following SCI include concomitant brain injury, premorbid neuropsychological status, chronic pain, and sleep apnea [1, 5]. In this study, the other aim of which was to compare the cognitive functions of individuals with T6 or rostral and T6 caudal injuries, those with concomitant brain injury, neurological and psychological diseases, chronic pain, and sleep apnea were not included. Thus, the relationship between blood pressure fluctuations and cognitive functions was tried to be revealed.

Due to segmentally specialized autonomic innervation of the vascular system and heart, neurological level of SCI assigns degree of subsequent cardiovascular dysfunction. The majority of individuals with T6 or rostral injury experience blood pressure fluctations as a result of deterioration of supraspinal sympatho-excitatory drive to spinal sympathetic preganglionic neurons [10]. These blood pressure fluctuations occur as the hypertensive and hypotensive crises called autonomic dysreflexia and orthostatic hypotension, and generally appear more than once a day in the same individual [17]. It has been reported that hypotension may cause ischemic damage due to cerebral hypoperfusion [18, 19], and hypertension may impair arterial structure and function due to reasons such as increased blood-brain barrier permeability, impaired vascular tone, and deep structural remodeling in able-bodied individuals [20]. In addition, several animal studies have shown that cerebrovascular functional and structural maladaptations occur as a result of cardiovascular disorders in rats with high thoracic level SCI [21, 22]. Increasing evidence supporting relationships between adverse cardiovascular changes and cognitive impairments in the non-SCI literature has been stated to be predictable to the SCI population [7]. Therefore, cardiovascular dysfunctions following cervical and upper thoracic SCI have begun to be considered as a contributing factor for vascular cognitive impairments [5, 10]. However, there are limited number of studies containing preliminary data on this subject. A study noted that SCI individuals with hypotension had significantly worse cognitive functions than SCI individuals without hypotension [12]. A more recent study reported significant relationships between cognitive test performance and orthostatic hypotension for individuals with T6 and rostral injuries and a history of blood pressure fluctuations [6]. Another study stated that the wide fluctuations in blood pressure seen in autonomic dysreflexia may lead to the formation of chronic silent cerebral infarction, which is presumed to cause cognitive impairment [7]. However, there is no clear aggrement on the relationship between SCI level and cognitive impairment in the literature [1]. While most of the studies on this subject reported that the level of injury had no effect on cognitive impairment [16, 23], other studies found some cognitive differences between paraplegic and tetraplegic patients [24]. In this study, the cognitive functions of individuals with T6 or rostral injuries with symptoms of orthostatic hypotension and autonomic dysreflexia and those with T6 caudal injuries without blood pressure fluctuations were compared. However, there was no difference in any cognitive measure between the SCI groups. The difference of the results on the relationship between SCI level and cognitive disorders is possibly attributed to the heterogeneity in the study design, sample size, types of tests used to evaluate cognitive functions, time since SCI, and statistics. Furthermore, the lack of cognitive difference between those with and without blood pressure fluctations in this study may be due to the transient nature of blood pressure fluctuations in SCI that may act with a different mechanism on cerebrovascular structure and function from that of chronic hypotension and hypertension [10]. Because, the studies supporting that cognitive impairment may occur with blood pressure changes were generally based on evidence in able-bodied individuals without injury [18, 25]. Also, the mean time since SCI in this study was close to 3 years. Perhaps, the effect of blood pressure fluctuations on cognitive functions could be demonstrated in individuals with a longer duration of SCI.

This study has some limitations that should be mentioned. First, one of the five parts of the cognitive assessment test, could not be used because it was not motor-free. As a result the visuospatial skills part was not evaluated. Second, we excluded individuals with a history of traumatic brain injury from the study, but brain imaging at the time of SCI was not available. Therefore, it cannot be entirely certain that mild traumatic brain injury has been excluded. Despite these limitations, the presence of a control group matched for age and education level and the fact that cognitive tests were administered to all participants face-to-face by an experienced psychologist are the strengths of the study.

Conclusion

Significant differences in certain parts of cognitive functioning were found in individuals with SCI compared with age- and education level-matched healthy controls. Memory, verbal fluency, and language functions appeared to be lower in individuals with SCI than in the control group. Impairment of cognitive functions following SCI appears to be an important sequelae. Cognitive assessment may be useful for individuals with SCI, especially if they have difficulties with the rehabilitation process and integration into society. However, no significant differences were noted in any parts of cognitive functioning between individuals with T6 or rostral and T6 caudal injuries. In this population, autonomic dysfunctions do not seem to have any effect on the etiology of cognitive impairments.

Ethics approval

The study was approved by The Clinical Research Ethics Committee of Ankara City Hospital (E2-22-1320).

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