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Original Article

Cognitive impairments in patients with spinocerebellar ataxia types 1, 2 and 3 are positively correlated to the clinical severity of ataxia symptoms

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Abstract: Aims: This study is to assess cognitive function in patients with spinocerebellar ataxia types 1, 2 and 3 (SCA1, SCA2 and SCA3). Methods: We performed neuropsychological examinations on 8 SCA1 patients, 2 SCA2 patients, and 8 SCA3 patients, as well as 32 healthy subjects matching these patients in age, gender, nationality, and years of education. The neuropsychological examinations were focused on testing executive functions, visuo-spatial perception and verbal memory, attention, immediate and delayed recall, logical thinking function and orientation function. Results: SCA1 patients had significantly impaired executive function, visuo-spatial perception, and attention compared to healthy subjects. Cognitive disorders such as immediate and delayed recall, executive function and verbal memory were observed in SCA2 and SCA3 patients, while attention and visuo-spatial function were not affected. The severity of motor impairment was determined using the international cooperative ataxia rating scale, the scores of which ranged from 11 to 78. The number of patients with mild ataxia, moderate ataxia and severe ataxia was 3, 11, and 3, respectively, with the most severe ataxia occurring on a patient with SCA1. The scores of activities of daily living scale ranged from 20 to 66. Conclusions: Our results showed that mild executive dysfunction occurred in patients with SCA1, SCA2 and SCA3, and verbal fluency and word memory dysfunctions were detected in patients with SCA2 and SCA3. In addition, we found that the decreased logical thinking function and orientation function were observed in patients with SCA1, SCA2 and SCA3. The cognitive status was correlated with the clinical severity of ataxia symptoms rather than age, age of onset, years of education and the duration of disease.

Keywords: Spinocerebellar ataxia, cognitive impairment, executive function, attention

Introduction

The common feature of spinocerebellar ataxia (SCA) is middle-age-onset, progressive ataxia and autosomal dominant inheritance. More than 30 different subtypes of SCA have been discovered, among which SCA types 1, 2 and 3 (SCA1, SCA2 and SCA3) are the most common types [1]. SCA includes both sporadic and hereditary forms, and the majority of patients with SCA1, SCA2 and SCA3 are attributed to the latter. In most cases of SCA, the main parts of pathological damage were in the spinal cord, cerebellum and brain stem. The pathogenesis of SCA1, SCA2 and SCA3 is the unstable cytosine-adenine-guanine (CAG) trinucleotide expansion that produces poly glutamine [2].

Possible subtype-specific cognitive impairments in SCA patients are still controversial [3, 4]. Patients with SCA1, SCA2 and SCA3 present mainly attention and executive dysfunctions [5]. Executive dysfunction is prominent in SCA1 compared with controls and all other SCA types, and mild deficits of verbal memory are present in all of SCA1, SCA2 and SCA3 [2]. Arja et al. demonstrated that deficits in SCA8 patients primarily exist in attention and information processing, as well as in concept formation, reasoning, executive functions and verbal production [6]. Suenaga et al. discovered that verbal fluency and immediate visual memory task were markedly impaired in patients with SCA6 [7]. Based on these findings, we hypothesize that different subtypes of SCA have varied degrees and different locations of cognitive dysfunction.

There are a few studies on cognitive impairment in SCA1, SCA2 and SCA3, but patients

with SCA1 in Kazakh minority population are never investigated. The present study investigates whether patients with SCA1, SCA2 or SCA3 have cognitive impairments on attention, verbal fluency, immediate word recall, delayed word recall, visuo-spatial perception, executive function, logical thinking or orientation function. In addition, we study whether cognitive dysfunctions are correlated with age, age at onset, disease duration, international cooperative ataxia rating scale (ICARS) scores, activities of daily living (ADL) scores or years of education.

Materials and methods

Subjects

The study comprised 18 patients with SCA1, SCA2 or SCA3, who were selected from the SCA outpatient clinic at the Department of Neurology. SCA was clinically diagnosed for these patients by Harding diagnosis standard [8]. Then, the patients were genetically examined to determine which haplotype should be carried out on them. The patients of SCA2 and SCA3 were selected from 6 families of Han, while SCA1 patients were chosen from 1 family of Kazakh minority.

A total of 32 healthy subjects with matched nationality, age, sex, and years of education, mostly spouses of the patients, served as the control. Among them, 16 ethnic Kazakh subjects served as the control for SCA1 (control 1), and the other 16 ethnic Han subjects served as the control for SCA2 and SCA3 (control 2).

Exclusion criteria were as follows: i) Alzheimer's disease, ii) cerebral trauma and cerebrovascular disease, iii) lead poisoning, iv) use of alcohol or psychotropic drugs, and v) psychiatric disorders. Patients with at least one of the above-mentioned history were excluded.

The study was approved by the Ethics Committee of the First Affiliated Hospital of Xinjiang Medical University, and performed following the declaration of Helsinki. We did not use any pharmacological treatment for either patients or controls in this study. All subjects underwent standard cognitive status assessments and signed the written informed consents. For Kazakh subjects who did not understand Chinese, the observers translated test instructions into Kazakh verbally. All of the neuropsychological tests were performed on the same day and in a peaceful and spacious room by the same observer who had received professional training.

Ataxia severity rating

The severity of ataxia in each patient was rated on according to ICARS [9]. Daily activities of each subject were evaluated according to ADL.

Neuropsychological battery

All subjects were examined by mini-mental state examination (MMSE) [10] to appraise general cognitive impairments. To evaluate attention and working memory, Digit Span (DS) that was used in the Wechsler batteries (intelligence and memory) was employed, including two tests (digit forward and digit backward). Repeating numbers forward was related mostly to attention while backward task was likely to involve working memory and mental tracking [11]. In addition, we used Rapid Verbal Retrieve to examine verbal fluency [12]. Immediate memory was examined using word recall from the Alzheimer's Disease Assessment Scale-cognitive. The observer would read ten words twice, and the subjects would remember word quantity that was averaged and used as the result of immediate word recall. We assessed delayed memory of the Alzheimer's Disease Assessment Scale-cognitive 10 item word list after a delay of 5 min as part of memory testing [7]. We also assessed executive function by means of the Alzheimer's Disease Assessment Scale-cognitive executive command and Stroop Test (ST-Chinese Version) [13] as part of executive function. To evaluate visuo-spatial perception, we used Clock Drawing Test [14]. To assess logical thinking function, we used Comprehensive Functional Evaluation-Solving Question Function-Logical Thinking Function. Moreover, we used Alzheimer's Disease Assessment Scale-cognitive-Orientation to examine everyone's orientation function including time and place orientation.

Statistical analysis

Statistical comparisons were performed using the Mann-Whitney test and Fisher's exact test by SPSS 17.0 statistical software (SPSS Inc., Chicago, IL, USA). We used one-way ANOVA to

Table 1. Clinical data of controls and SCA1, SCA2 and SCA3 patients

Tests	SCA1 (n = 8)	Control 1 (n = 16)	P1	SCA2 (n = 2)	SCA3 (n = 8)	Control 2 (n = 16)	P2	P3
Gender (m/f)	4/4	7/9	0.556	1/1	7/1	9/7	0.706	0.142
Age (yrs)	47.0 ± 9.6	40.3 ± 10.2	0.136	46.5 ± 16.3	44.1 ± 8.1	44.6 ± 8.5	1.00	1.00
Age of onset (yrs)	39.1 ± 7.7	-	-	38.0 ± 14.1	36.8 ± 6.3	-	-	-
Disease duration (yrs)	10.0 ± 4.9	-	-	8.5 ± 2.1	7.4 ± 3.7	-	-	-
Years of education (yrs)	7.7 ± 5.2	10.6 ± 3.4	0.834	7.5 ± 2.1	11.0 ± 3.3	10.3 ± 3.8	0.261	0.742
ADL	38.1 ± 15.8***	20.0 ± 0.00	0.001	46.0 ± 28.3*	45.6 ± 16.7***	20.0 ± 0.0	0.013	0.001
ICARS	34.5 ± 23.4	-	-	41.0 ± 25.5	36.8 ± 16.6	-	-	-

Note: ADL, activities of daily living; ICARS, international cooperative ataxia rating scale. Data are means ± SD. *, P < 0.05; **, P < 0.01; ***, P < 0.001. P1, statistical difference between patients of SCA1 and control 1; P2, statistical difference between patients with SCA2 and control 2; P3, statistical difference between patients with SCA3 and control 2.

compare the significance among patients with SCA1, SCA2 and SCA3. Post-hoc group comparisons were made using least significant difference (LSD) test. The results were presented as means ± standard deviation. Differences with $P < 0.05$ or $P < 0.01$ were considered statistically significant. For correlation studies, we used Spearman correlation coefficient.

Results

SCA subtypes are not correlated with age, age at onset, disease duration, years of education, ADL scores or ICARS scores

To evaluate the correlation between different SCA types and clinical data of patients, Mann-Whitney test and ANOVA analysis were performed. Mann-Whitney test showed no significant difference between patients and controls in age, age of onset, disease duration, or years of education (**Table 1**). The scores of ICARS ranged from 11 to 78, with the number of patients with mild ataxia being 3 (SCA1, n = 2; SCA3, n = 1), the number of patients with moderate ataxia being 11 (SCA1, n = 4; SCA2, n = 1; SCA3, n = 6), and the number of patients with severe ataxia being 3 (SCA1, n = 1; SCA2, n = 1; SCA3, n = 1). Of note, the most severe ataxia occurred on a patient with SCA1. Four of the patients must rely on wheelchairs to move. Furthermore, the scores of Activities of Daily Living Scale ranged from 20 to 66, with higher degrees of disease corresponding to higher scores of ADL. ANOVA analysis revealed that no significant difference existed among patients of different SCA types in age, age at onset, disease duration, years of education, ADL scores or ICARS scores (**Table 1**). These data suggested that SCA1, SCA2 and SCA3 were not correlated with age, age of onset, disease duration, years of education, ADL scores or ICARS scores.

Some parameters of neuropsychological performance of SCA patients are dependent on different types of SCA

To determine the neuropsychological performance of controls and SCA1, SCA2 and SCA3 patients, we examined MMSE, attention and working memory, verbal fluency, memory, visuospatial and executive function, and logical thinking function. The mean performance on the MMSE of patients with SCA1, SCA2 or SCA3 differed significantly from controls, while no significant difference was observed among patients of different SCA types according to ANOVA analysis. The data showed that patients with SCA1, SCA2 and SCA3 had different degrees of impairments in all cognitive tests, but the impairments were mild. SCA1 patients had cognitive decline in 3 out of 9 cognitive test scores (33%), SCA2 had decline in 5 out of 9 test parameters (56%), and SCA3 had decline in 6 out of 9 test parameters (66.7%) (**Table 2**).

Regarding attention and working memory, SCA1 patients and control 1 evidenced significant differences on attention (DS forward, $P = 0.023$), but patients of SCA2 ($P = 0.157$) and SCA3 ($P = 0.192$) were significantly different from control 2 according to Mann-Whitney test. By means of one-way ANOVA, patient groups (SCA1, SCA2 and SCA3) manifested significant difference in DS forward ($F = 3.854$, $P = 0.045$). In addition, post-hoc LSD test discovered that SCA1 performance was significantly worse than that of SCA3 ($P = 0.015$), while SCA3 had dysfunction of working memory ($P = 0.023$). Regarding verbal fluency and memory, SCA2 and SCA3 patients showed significant deviation compared with control 2 on verbal fluency (RVR test) and memory (immediate recall and delayed recall). However, there was no difference among patient groups according to

Table 2. Neuropsychological performance of controls and SCA1, SCA2 and SCA3 patients

Tests	SCA1 (n = 8)	Control 1 (n = 16)	P1	SCA2 (n = 2)	SCA3 (n = 8)	Control 2 (n = 16)	P2	P3
MMSE	24.1 ± 2.7*	27.3 ± 2.6	0.016	20.5 ± 7.8*	25.3 ± 3.9*	29.2 ± 1.2	0.013	0.014
Attention and working memory								
DS (forward)	5.5 ± 1.2*	7.0 ± 1.6	0.023	7.0 ± 1.4	7.5 ± 1.7	8.4 ± 1.0	0.157	0.192
DS (backward)	3.5 ± 0.5	3.5 ± 1.0	0.742	1.5 ± 2.1	3.0 ± 1.0*	4.4 ± 1.3	0.078	0.023
Verbal fluency								
RVR (total number)	32.3 ± 6.7	37.3 ± 7.8	0.172	27.0 ± 4.2***	30.5 ± 11.5*	51.4 ± 9.3	0.013	0.001
RVR (correct number)	28.7 ± 5.7	28.8 ± 15.8	0.32	23.5 ± 0.7***	28.5 ± 10.0*	50.4 ± 9.5	0.013	0.001
Memory								
Immediate recall	5.0 ± 2.2	4.8 ± 1.6	0.653	2.2 ± 1.0*	5.5 ± 1.7**	6.2 ± 1.5	0.013	0.005
Delayed recall	3.1 ± 3.5	4.1 ± 2.8	0.417	2.5 ± 0.7***	1.6 ± 1.8***	5.6 ± 1.7	0.001	0.001
Visuo-spatial and executive function								
Executive command	0.1 ± 0.4	0.0 ± 0.0	0.653	1.5 ± 0.7*	0.3 ± 0.7	0.0 ± 0.0	0.013	0.653
Stroop test A	30.0 ± 9.8*	21.2 ± 6.7	0.045	37.6 ± 19.3*	33.7 ± 19.7*	14.9 ± 4.3	0.026	0.005
Stroop test B	35.7 ± 13.7**	23.8 ± 5.5	0.004	39.8 ± 14.1*	36.1 ± 16.0*	18.0 ± 6.5	0.013	0.001
Stroop test C	40.5 ± 16.7	27.1 ± 5.1	0.052	59.7 ± 2.3*	61.3 ± 19.5***	24.0 ± 6.2	0.013	0.001
CDT	1.37 ± 1.3*	2.7 ± 1.3	0.045	2.0 ± 2.8	1.9 ± 1.4*	3.1 ± 1.1	0.549	0.038
Logical thinking function								
LTT	15.0 ± 7.6	19.4 ± 2.5	0.214	15.0 ± 7.1	16.2 ± 7.4	19.4 ± 2.5	0.392	0.452
Orientation function	0.5 ± 0.76	0.13 ± 0.42	0.321	1.0 ± 1.41	0.25 ± 0.71	0.0 ± 0.00	0.327	0.653

Note: MMSE, mini-mental state examination; DS, Digit Span; RVR, Rapid Verbal Retrieve; CDT, Clock Drawing Test; LTT, logical thinking test. Data are means ± SD. *, P < 0.05; **, P < 0.01; ***, P < 0.001. P1, statistical difference between patients of SCA1 and control 1; P2, statistical difference between patients with SCA2 and control 2; P3, statistical difference between patients with SCA3 and control 2.

Table 3. Correlation study in 18 patients with SCA1, SCA2 or SCA3

Tests	Age	Age of onset	Disease duration	Years of education	ICARS	ADL
MMSE	NS	NS	NS	NS	-0.478*	-0.558*
DS (forward)	NS	NS	NS	0.577*	-0.577*	-0.703**
DS (backward)	NS	NS	NS	NS	NS	NS
RVR (total number)	NS	NS	NS	NS	NS	NS
RVR (Correct number)	NS	NS	NS	NS	NS	NS
Immediate word recall	NS	NS	NS	NS	NS	NS
Delayed word recall	NS	-0.470*	NS	NS	NS	NS
Executive command	NS	NS	NS	NS	NS	NS
Stroop test A	NS	NS	NS	NS	0.596**	0.728**
Stroop test B	0.609**	0.494*	NS	-0.479*	0.610**	0.676**
Stroop test C	NS	NS	NS	NS	0.584*	0.669**
CDT	-0.670*	-0.668**	NS	NS	-0.528*	-0.628**
CFE	-0.512*	NS	-0.558*	NS	-0.504*	-0.491*
Orientation function	0.779**	0.747**	0.498*	NS	0.651**	0.663**

Note: ADL, activities of daily living; ICARS, international cooperative ataxia rating scale. MMSE, mini-mental state examination; DS, Digit Span; RVR, Rapid Verbal Retrieve; CDT, Clock Drawing Test; CFE, Comprehensive Functional Evaluation. Data are means ± SD. *, P < 0.05; **, P < 0.01; ***, P < 0.001. P1, statistical difference between patients of SCA1 and control 1; P2, statistical difference between patients with SCA2 and control 2; P3, statistical difference between patients with SCA3 and control 2.

ANOVA. For visuo-spatial and executive function, SCA1, SCA2 and SCA3 patients showed significantly worse performance than controls as evaluated by Mann-Whitney test (**Table 2**). Especially, significant differences in executive command test were found among patients (F = 4.808, P = 0.024) according to ANOVA. In addition, the percentage of correct commands for SCA2 patients was worse than those of SCA1 (P = 0.008) and SCA3 (P = 0.014) patients according to LSD test. However, in Stroop tests, SCA3 patients (P = 0.031) spend longer time than SCA1 patients according to LSD test. Though the performance of SCA2 patients was worse

than that of SCA1 patients, there was no statistically significant difference between SCA1 and SCA2. In visuo-spatial function test, SCA1 and SCA3 patients procured worse clocks than controls, respectively. Moreover, there was no significant difference on logical thinking function and orientation function between patients and controls according to Mann-Whitney test (**Table 2**). These data suggested that some parameters of neuropsychological performance of SCA patients were dependent on different types of SCA.

Visuo-spatial perception and executive function are related to the severity of disease, while logical thinking function and orientation function are correlated to relevant factors

To investigate the correlation between relevant influence factors and cognitive tests, correlation analysis was performed on all 18 patients with SCA1, SCA2 and SCA3. Our study showed that working memory, visuo-spatial perception and executive function were related with the severity of ataxia on DS (Forward), Stroop test and Clock Drawing Test (all $P < 0.05$). There was correlation between working memory and years of education ($r = 0.557$, $P = 0.012$), ICARS ($r = -0.557$, $P = 0.012$) and ADL ($r = -0.703$, $P = 0.001$). All visuo-spatial perception and executive function tests were negatively correlated with ADL scores and ICARS (**Table 3**). Furthermore, logical thinking function and orientation function did not show statistically significant difference in patients with SCA1, SCA2 and SCA3, but were correlated with relevant factors. Comprehensive Functional Evaluation scores were negatively correlated with age ($r = -0.512$, $P = 0.03$), disease duration ($r = -0.558$, $P = 0.016$), ADL score ($r = -0.491$, $P = 0.039$) and severity of ataxia ($r = -0.504$, $P = 0.033$). Orientation function scores were correlated with age ($r = 0.779$, $P = 0.000$), age of onset ($r = 0.747$, $P = 0.000$), disease duration ($r = 0.498$, $P = 0.036$), ADL score ($r = -0.663$, $P = 0.003$) and severity of ataxia ($r = 0.651$, $P = 0.003$) (**Table 3**). These data indicated that the cognitive status was correlated with the clinical severity of ataxia symptoms rather than age, age of onset, years of education and the duration of disease.

Discussion

SCA1, SCA2 and SCA3 have their individual characteristics. For example, SCA1 mainly presents ophthalmoplegia, which means difficulty in looking upwards. The characteristics of SCA2 are upper limb hyporeflexia and obviously slow eye glance. The main characteristics of SCA3 are myoclonus and amyotrophy, as well as eyelid retraction responsible for exorbitism. Our results are consistent with previous reports. Nevertheless, SCA1 patients do not always have ophthalmoplegia, probably because Kazakh population with SCA1 is minority or the duration of their disease is too short to produce this symptom. Ataxia is a predominant clinical manifestation in patients with SCA2 [2]. In our study, ICARS scores was ranged from 11 to 78 (SCA1, 14-78; SCA2, 23-59; SCA3, 11-55). They mainly had dysfunction of posture, gait and motor coordination. Among them, one of SCA2 patients had severe ataxia, and one of SCA3 patients had the most severe ataxia. Some of the patients relied on wheelchairs to move, and were not able to live all by themselves. Klinke I et al. [4] found that problems in gross motor coordination (proximal) of SCA1 and SCA6 patients were evident, showing the most severe ataxia. SCA pathological lesions are principally in cerebellum, brain stem, spinal cord, and basal ganglia to various degrees.

In this study, mild cognitive defects of various degrees were mainly performed on attention, visuo-spatial perception and executive function, verbal fluency, immediate and delayed memory in SCA1, SCA2 and SCA3. Especially, executive function was impaired in all SCA1, SCA2 and SCA3. Our major results are consistent with previous results [3, 4, 15-17], but slight differences exist. Klinke I [5] reported that verbal memory was not impaired in SCA1 and SCA3 patients, while Bürk K et al. [2] reported that mild deficits in verbal memory were present in SCA1, SCA2 and SCA3 patients. Impairments on executive function were different among SCA1, SCA2 and SCA3. In addition, SCA2 and SCA3 had memory dysfunction that included immediate recall (in SCA2) and delayed recall (in SCA3). In our study, verbal memory of SCA3 patients was clearly impaired, but the data for SCA2 patients were not enough to allow reliable conclusions. SCA1 patients had no impairment.

However, our study still showed distinct verbal memory impairment in SCA1 patients. This might be due to the fact that we used different neuropsychological batteries to detect the cog-

nitive function of patients. Furthermore, another possible explanation might be that the patients with SCA1 are Kazakh national minority who have different cultural background and customs that may lead to different scores of cognitive tests. On the other hand, they might never say or hear the words used in the questions in immediate and delayed recall tests in their daily life, so the scores were inversely more than SCA2 and SCA3.

It was reported that executive dysfunction was presented in SCA1, SCA2 and SCA3 patients, and SCA1 patients had more severe impairments compared with SCA2 and SCA3. However, in our study, SCA1 patients only had similar impairments compared with other groups. The reasons may be that we asked subjects to read the color as quickly as possible no matter what Chinese characters were in the color dot in Stroop test to examine subjects' executive function. SCA1 patients were Kazakh national minority, most of who didn't understand Chinese, so they could not read them quickly.

It has been shown that frontal lobe related with executive functions are present in SCA1 [15], SCA2 [18], SCA3 [17], and SCA6 [19] patients who have significant cognitive defects. Nevertheless, it has been disputed whether cerebellum is involved in the cognition of cerebral cortex, particularly the frontal and parietal lobes [20-22]. Cerebellum contributes to cognitive tasks, including executive and language functions [23-27]. In SCA15 patients, cognitive decline suggested that the spreading of damage was beyond the cerebellum, while the cognitive defects in SCA6 patients might be related to cortico-cerebellar circuits [6]. We found that our patients had atrophy of cerebellum, brainstem and cortical areas according to MRI. In the present study, our patients had prominent defects in attention, execution and verbal fluency. However, it was not sure whether the executive function, verbal fluency and memory impairments were resulted from damages to the cerebellum alone.

Kawai et al. [17] found that impairments were not correlated with disease duration in SCA3. Francesco et al. [28] reported the dissociation between motor and cognitive impairments in SCA2 patients. The severity of cognitive impairments was related to age of onset of the disease ($P = 0.002$), but not to the duration or the overall brief ataxia rating scale score brief ataxia rating scale score in SCA2 [29]. Fancellu et al. [30] reported the dissociation in the progression of motor disability and cognitive impairments, suggesting that motor and cognitive functions might be related to different progression rates in SCA1 and SCA2. In our study, cognitive impairments in SCA1, SCA2 and SCA3 were correlated with the severity of ataxia. Although some of the tests were related to age, age of onset, years of education and disease duration, and the number of our subjects was not large enough for us to make this conclusion.

In conclusion, SCA1, SCA2 and SCA3 caused mild impairment on executive function. SCA2 and SCA3 led to dysfunctions in verbal fluency and word memory. In addition, logical thinking function and orientation function were decreased in SCA1, SCA2 and SCA3. The cognitive defects were correlated with clinical severity of ataxia symptoms rather than age, age of onset, years of education and disease duration.

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Disclosure of conflict of interest

None.

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