Cognitive Impairments in Patients with Spinocerebellar Ataxia Type 3 (SCA3) in China

Ruihao Wang[1], Song Tan[1], Bo Song[1], Jingtao Wang[1], Fang Ge[2], Shilei Sun[1], Wang Miao[1], Jun Wu[1], Limei Wang[1], Rui Zhang[1], Yuan Gao[1], Changhe Shi[1], Huixia Niu[1], Hui Fang[1], Avinash Chandra[1], Yuming Xu[1]*

[1] Department of Neurology, the First Affiliated Hospital of Zhengzhou University, Zhengzhou, 450052, China
[2] Department of Neurology, Peking Union Medical College Hospital, Beijing, 100730, China
* Corresponding author: Prof. Yuming Xu, xuyuming@zzu.edu.cn

Abstract: To date there is very few clinical studies published on the cognitive characteristics in patients with SCA3 in China, we sought to evaluate the cognitive function in a cohort of clinically diagnosed and molecularly confirmed patients with SCA3 in China. The neuropsychological tests that were used to evaluate the cognitive function consisted of the Mini-Mental State Examination (MMSE), Clock Drawing Test (CDT), Digit Cancellation Test (DC), Digit Symbol Substitution Test (DSST), Stroop Color-Word Test (SCWT), Trial-Making Test (TMT), Verbal Fluency Test (VFT), and Wechsler Intelligence Scale-Digit Span Test (WISC-DST). The psychiatric symptoms were assessed by the Hamilton Anxiety Scale (HAMA) and Hamilton Depression Scale (HAMD). The severity of motor symptoms was evaluated by the Scale for the Assessment and Rating of Ataxia (SARA). 15 patients with genetically confirmed SCA3 and 15 normal control subjects were enrolled in the study. There was no significant difference in age, gender or educational level among these 2 groups. CDT, DC, DSST, SCWT, TMT, VFT were significantly more impaired in patients with SCA3 than those in the control group. There was no significant difference in the MMSE, DST, HAMA and HAMD between SCA3 patients and controls. In conclusion, our study demonstrates that patients with SCA3 in China present cogintive impairments, manifesting mainly as executive and visuospatial dysfunction. [Ruihao Wang, Song Tan, Bo Song, Jingtao Wang, Fang Ge, Shilei Sun, Wang Miao, Jun Wu, Limei Wang, Rui Zhang, Yuan Gao, Huixia Niu, Changhe Shi, Hui Fang, Avinash Chandra, Yuming Xu. **Cognitive Impairments in Patients with Spinocerebellar Ataxia Type 3 (SCA3) in China.** *Life Sci J.* 2013;10(1):1655-1659] (ISSN:1097-8135). http://www.lifesciencesite.com. 243

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1. Introduction

Spinocerebellar ataxia type 3 (SCA3) is the most common type of autosomal dominant cerebellar ataxias (ADCA) in the world and China (Tang et al. 2000), it is caused by an expansion of CAG trinucleotide repeats in a gene located at chromosome 14q32.1 (Kawaguchi et al. 1994). It belongs to rare diseases with an estimated prevalence of about 3/100 000 worldwide (Schöls et al., 2004). The main clinical features include cerebellar ataxia, pyramidal signs, progressive external ophthalmoplegia, exophthalmos, dystonia, and peripheral neuropathy (Schöls et al., 2004). The disease is slowly progressive and unremitting, patients usually will become confined to a wheelchair and later be bedridden in the end stage of the disease (Jacobi et al., 2011).

Apart from motor control, the cerebellum has been implicated in higher cortical functions such as memory, executive functions, visuoconstructive skills and emotion (Bürk, 2007). However, although the motor symptoms of SCA3 have now been thoroughly studied, only several clinical studies have been published on the cognitive impairment in SCA3 (Maruff et al., 1996; Zawacki et al., 2002; Bürk, 2003; Kawai et al., 2004; Braga-Neto et al., 2012). One recent study conducted in Japan studied 16 patient with SCA3 and 20 normal controls, and the study revealed verbal and visual memory deficits, visuospatial and constructional dysfunction, and verbal fluency deficits in patients with SCA3 (Kawai et al., 2004). Another up-to-date study performed in Brazil enrolled 38 patients with SCA3 and 31 normal controls, the authors found that executive and visuospatial function were impaired in patients with SCA3 (Braga-Neto et al., 2012). To date, no clinical report has been published on the cognitive characteristics in patients with SCA3 in China.

In this present study, we sought to investigate the cognitive manifestations in a cohort of Chinese patients with SCA3 in an attempt to replicate and further characterize the cardinal cognitive features of SCA3 in our patient population. We evaluated a wide range of cognitive functions in patients with SCA3 and normal control subjects, the neuropsychological scales we used have all been clinically validated in China.

2. Subjects and Methods

2.1 Subjects

A total of 15 patients with clinically and molecularly confirmed SCA3 seen in our Department

of Neurology of the First Affiliated Hospital of Zhengzhou University, China, from October 2011 to January 2013, were evaluated. 15 healthy volunteers with no history of neuropsychological diseases were recruited as normal control subjects. All of them were native Chinese speakers and met the inclusion criteria, i.e., age under 60 years (to avoid any age-related cognitive phenomena), MMSE score greater than 24, and at least 6 years of education. The local research ethics committee approved this study. All participants provided written informed consent for the clinical investigation and subsequent analysis.

2.2 Neuropsychological Tests

The subjects were given neuropsychological tests including MMSE, CDT, DC, DSST, SCWT, TMT, VFT and DST. MMSE measured the global cognitive function. CDT measured the visuospatial and constructional function. DC, DSST, SCWT, and TMT reflected the core elements of executive function respectively. VFT tested the language and executive function. DST assessed attention and working memory. All the tests had been proven to have a good reliability and validity when used under a Chinese cultural background.

2.2.1 Mini-Mental State Examination (MMSE)

The MMSE (Folstein et al., 1975) was used for general screening of the intellectual abilities.

2.2.2 Clock-Drawing Test (CDT)

All participants were asked to draw the face of a clock pointing ten past eleven. The Sunderland scoring method (Sunderland et al., 1989) was applied, with a maximum score of 10. CDT was used to assess the visuospatial and constructional abilities.

2.2.3 Digit Cancellation Test (DC)

In this task (Franklin et al., 1988), digits 1 to 9 were randomly listed in rows on a paper, the subject was asked cross out the 2 targeted digits (e.g., 2 and 8) within 45 seconds, the number of correct symbols is recorded. It tested the sustained attention and psychomotor speed.

2.2.4 Digit Symbol Substitution Test (DSST)

DSST (Smith, 1982) comprised nine digit-symbol pairs followed by a list of digits. Under each digit the subject should write down the corresponding symbol as fast as possible. The number of correct symbols within the allowed time (90 sec) is recorded. It measures psychomotor speed, sustained attention, visualspatial skills and set shifting.

2.2.5 Stroop Color-Word Test (SCWT)

SCWT was used to measure selective attention, cognitive flexibility and inhibitory control, it comprised 3 parts (Guo et al., 2005). In part A, the test was made up of cards on which the names of colors were written in black inks, the participant was asked to name the words. In part B, the test was made up of cards on which circles were written in various color inks, the participant was asked to name the color. In part C, the test was made up of cards on which the names of colors were written in various color inks. The participant was asked to name the ink color while ignoring the word. The examiner pointed out errors as and when they took place to enable all patients to complete the test. Therefore, time alone in seconds was the base score.

2.2.6 Trail-Making Test (TMT)

There were 2 parts in TMT (Lv et al., 2006). In TMT-A, the participant connects the Arabic numbers (1–25) in the proper numerical sequence. In the Chinese version of TMT-B, an Arabic digit (1–25) was surrounded by either a square or a circle and the participant was asked to connect the digits in sequence with the surroundings of the digits alternating between squares and circles. The time taken was recorded. Scoring was based on the time required to complete the task, and errors were corrected during the test. They assessed speed of visual search, but they also assess mental flexibility, attentional resources, and motor abilities.

2.2.7 Verbal Fluency Test (VFT)

To assess the semantic fluency, the participant was asked to name as many animals or fruit or vegetable as possible in 1 min consecutively, the sum number was recorded. To assess phonemic fluency, the participant was asked to name as many words containing the Chinese character “shui”, “kai”, or “fa” one by one in 1 min, the sum number of unique responses was recorded.

2.2.8 Digit Span Test (DST)

The Digit Span test came from the Chinese version of the Wechsler Adult Intelligence Scale-Revised (WAIS-RC) (Gong, 1992), it was used to evaluate verbal attention (forward) and working memory (backward). The number of correctly reproduced items was recorded respectively.

2.3 Neurological and Psychiatric Evaluation

Clinical assessment and neurological physical examinations were performed. The ataxia clinical assessment was conducted in all subjects using the Chinese validated scale for the assessment and rating of ataxia (SARA) (Schmitz-Hübsch et al., 2006). Subjects were also evaluated by the Hamilton Anxiety Scale (HAMA) (Hamilton, 1953) and Hamilton Depression Scale (HAMD) (Hamilton, 1960).

2.4 Statistical Analysis

Comparisons of the neuropsychological tests between SCA3 patients and normal controls were made using the Mann-Whitney test, Spearman rank correlative analysis was applied to determine the association between the neuropsychological performances and neurologic findings of age at onset, age at examination, disease duration, education,

ataxia (SARA), depression, anxiety in SCA3 patients. Differences were considered significant at $P<0.05$. The entire analysis was calculated using the statistical software Statistical Package for the Social Science (SPSS) 17.0 for Windows.

3 Results

Of the 15 patients with SCA3, 1 patient was wheelchair bound, the remaining 14 patients could ambulate without assistance. The mean age of disease onset was 35.07±7.32 years, mean disease duration was 4.60±3.46 years, the mean SARA score was 8.43±4.43. There were no differences between normal controls and SCA3 patients in age, gender or level of education (Table 1).

Table 1. Clinical Characteristics of Patients with SCA3 and Normal Controls[a]

Characteristic	Control (n=15)	SCA3 (n=15)	P^b
Male-female ratio	7:8	7:8	1
Age of onset	NA	35.07±7.32 (21-44)	NA
Disease duration	NA	4.60±3.46 (1-16)	NA
SARA Score	NA	8.43±4.43 (2.5-21)	NA
Age at examination, y	45.33±6.85 (23-58)	39.53±9.13 (22-56)	0.105
Education level, y	9.73±2.99 (6-15)	8.67±3.12 (6-16)	0.266

SCA3 = Spinocerebellar Ataxia Type 3, SARA = Scale of Assessment and Rating of Ataxia

a. Data were given as mean ± SD followed by the range in the bracket.
b. Mann-Whitney test. Statistical significance was set at $P < 0.05$.

According to Table 2, SCA3 patients did not differ significantly from normal controls with regard to MMSE, DST, HAMD or HAMA. CDT, DC, DSST, SCWT, TMT and VFT tests were significantly more impaired in SCA3 patients than in normal controls.

The relationships between the cognitive dysfunction results and neurologic findings of age at onset, age at examination, disease duration, education, ataxia (SARA), depression, anxiety were statistically analyzed using the Spearman rank correlation analysis, as shown in Table 3. The MMSE score, CDT, SCWT, VFT and DSF showed no significant correlation with age at onset, age at examination, disease duration, education level, SARA, HAMA or HAMD. The DC, DSST, and TMT were significantly correlated with the SARA score, which reflected the severity of ataxia. Between DC and age of onset, DSB and HAMD, there appeared weak correlations.

Table 2. Results of Neuropsychological Tests in Patients with SCA3 and Controls[a]

Test	Control	SCA3	P^b
MMSE	29.00±1.60	28.27±1.67	0.057
CDT	9.40±0.99	8.07±2.09	0.027
DC	28.93±4.73	21.27±7.95	0.003
DSST	40.93±12.43	26.20±10.41	0.002
SCWT-A	23.46±4.85	34.55±9.83	0.001
SCWT-B	35.38±11.57	54.47±18.80	0.000
SCWT-C	65.50±22.54	105.69±44.18	0.001
TMT-A	53.60±11.87	85.63±39.63	0.003
TMT-B	139.57±46.47	192.33±106.45	0.065
VFT-S	47.60±17.03	32.33±7.33	0.013
VFT-P	26.53±9.13	15.27±6.81	0.001
DST-F	7.470±1.13	6.67±1.23	0.084
DST-B	4.60±1.72	3.60±1.50	0.120
HAMA	4.93±3.59	6.93±6.13	0.616
HAMD	3.27±3.35	6.15±5.90	0.095

MMSE = Mini-Mental State Examination, CDT = Clock Drawing Test, DC = Digit Cancellation Test, DSST = Digit Symbol Substitution Test, SCWT = Stroop Color-Word Test, TMT = Trial-Making Test, VFT = Verbal Fluency Test (S = Semantic, P = Phonemic), DST = Wechsler Intelligence Scale-Digit Span Test (F = Forward, B = Backward), HAMA = Hamilton Anxiety Scale), HAMD = Hamilton Depression Scale

a. Data were given as mean ± SD.
b. Mann-Whitney test. Statistical significance was set at $P < 0.05$.

Table 3. Correlation Study between the Neuropsychological Performances and Neurologic Findings in SCA3[a]

Test	Age at Onset	Age at Examination	Disease Duration	Education Level	SARA	HAMA	HAMD
MMSE	-0.184(0.510)	-0.254(0.362)	-0.302(0.274)	-0.105(0.274)	-0.377(0.166)	-0.087(0.758)	0.236(0.398)
CDT	-4.7(0.077)	-0.495(0.061)	-0.126(0.653)	0.122(0.664)	-0.456(0.087)	-0.081(0.775)	-0.043(0.878)
DC	-0.482(0.069)	-0.535(0.040)	-0.380(0.163)	0.021(0.941)	-0.798(0.000)	-0.508(0.053)	-0.380(0.163)
DSST	-0.393(0.147)	-0.517(0.049)	-0.690(0.004)	0.313(0.256)	-0.765(0.001)	-0.328(0.233)	-0.276(0.320)
SCWT-A	-0.271(0.329)	-0.127(0.652)	0.018(0.948)	0.358(0.190)	0.371(0.174)	-0.11(0.97)	0.036(0.899)
SCWT-B	-0.181(0.518)	-0.055(0.844)	0.135(0.631)	0.159(0.572)	0.394(0.146)	0.221(0.429)	0.294(0.288)
SCWT-C	0.118(0.674)	0.206(0.462)	0.419(0.120)	-0.234(0.402)	0.421(0.118)	0.467(0.079)	0.449(0.093)
TMT-A	0.549(0.034)	0.597(0.019)	0.261(0.346)	-0.208(0.457)	0.648(0.009)	0.470(0.077)	0.389(0.152)
TMT-B	0.396(0.144)	0.494(0.061)	0.536(0.040)	-0.356(0.193)	0.723(0.002)	0.501(0.057)	0.489(0.064)
VFT-S	-0.114(0.687)	-0.194(0.488)	-0.313(0.256)	-0.123(0.663)	-0.573(0.026)	-0.018(0.949)	-0.094(0.74)
VFT-P	-0.214(0.443)	-0.218(0.434)	-0.216(0.440)	-0.247(0.376)	-0.388(0.153)	-0.138(0.624)	0.222(0.426)

DST-F	0.087(0.757)	0.053(0.851)	0.171(0.543)	0.048(0.866)	-0.195(0.487)	0.036(0.899)	-0.276(0.320)
DST-B	-0.159(0.571)	-0.233(0.404)	-0.014(0.960)	-0.065(0.818)	-0.219(0.433)	-0.298(0.281)	-0.550(0.034)

SCA3 = Spinocerebellar Ataxia Type 3, SARA = Scale of Assessment and Rating of Ataxia, MMSE = Mini-Mental State Examination, CDT = Clock Drawing Test, DC = Digit Cancellation Test, DSST = Digit Symbol Substitution Test, SCWT = Stroop Color-Word Test, TMT = Trial-Making Test, VFT = Verbal Fluency Test (S = Semantic, P = Phonemic), DST = Wechsler Intelligence Scale-Digit Span Test (F = Forward, B = Backward), HAMA = Hamilton Anxiety Scale), HAMD = Hamilton Depression Scale.

a. Data were given as Spearman rho value followed by *P* value in the bracket. Statistical significance was set at $P < 0.05$.

4 Discussion

As far as we know, this is the first systematic study to evaluate the cognitive function in patients with SCA3 in China. Our results indicated SCA3 patients have visuospatial and executive dysfunction.

In consistent with previous studies, there was no significant difference between SCA3 patient and normal controls with regards to MMSE, which represented global cognitive function. Also there was no significant difference in the Digit Span Test, this implied that SCA3 patients behave normally in verbal attention or working memory. The clock drawing test was significantly affected in SCA3 patients, this proved visuospatial and constructional dysfunction. DC, DSST, SCWT, TMT and VFT all reflect the different core elements of executive function, which had been described previously, and they were all significantly impaired in SCA3 patients. This provided strong evidence that could prove SCA3 patients have executive impairments. Of these, DD, DSST and TMT were significantly correlated with the SARA score, while SCWT and VFT were not, this reasons for discrepancy were not very clear. Although previous literature indicated that depression and anxiety were common in SCA3 patients (Schmitz-Hübsch et al., 2011), our study failed to replicate this phenomena, the short disease duration (4.60±3.46 years) in our patient population was the most likely reason.

There are two explanations that can interpret these outcomes. To begin with, the cerebellum is no longer considered a purely motor control device. In recent years, there is a growing body of evidence which include anatomical (Frank & Peter, 1994) and functional imaging data (Allen et al., 1997) that suggest the cerebellum is involved in cognitive function. Anatomical studies have revealed that the cerebellum has connections with prefrontal and posterior parietal cortex via the pons, well it has been proven that the prefrontal cortex is responsible for the executive function, and the posterior parietal cortex is in charge of visuospatial and constructional function. In addition, functional MRI research also has found the activation during a series of cognitive task.

Another possible reason for cognitive impairment in SCA3 patients is the widespread extracerebellar lesions of the cerebral cortex, including the frontal lobe, parietal lobe and occipital lobe, this has been proven by a series of studies. Although classical studies consider the widespread neuropathologic involvement in SCA3 patients spare the cerebral cortex, an immunohistochemical study using a specific antibody against expanded polyglutamine (polyQ) has demonstrated nuclear accumulation of intranuclear inclusion bodies in neurons of the cerebral cortex (Yamada et al. 2001). Another recent neuroimaging study also has confirmed the cortical involvement at frontal, parietal, temporal and occipital lobes in SCA3 patients (D'Abreu et al., 2012).

Our study has strength. To the best of our knowledge, it is the first study that addresses the cognitive dysfunction in SCA3 patients in China, and a series of neuropsychological tests have been used. But it also has some limitations, which mainly include the small sample number, no information in the CAG repeat length in SCA3 patients, and without functional MRI tests. And further study is needed.

In conclusion, our study demonstrates that patients with SCA3 in China have cognitive impairment, manifesting mainly as executive and visuospatial dysfunction, this may be due to the lesions in the cerebellum itself or widespread lesions in the cerebral cortex, or both. Longitudinal studies with functional neuroimaging and pathoanatomy are needed to further explore the underlying pathogenesis and assess its initiation and progression.

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Corresponding Author:
Prof. Yuming Xu
Department of Neurology
First Affiliated Hospital of Zhengzhou University
Zhengzhou, 450052, China
E-mail: xuyuming@zzu.edu.cn

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