Abstract: Background: There is a general consensus that degeneration due to spinal and bulbar muscular atrophy (SBMA) is restricted to lower motor neurons and androgen insensitivity. However, recent studies suggest that SBMA patients also suffer from cognitive dysfunction. To date, no systematic study evaluating cognitive function of SBMA patients has been published in China. Furthermore, SBMA patients’ visuospatial and constructional functioning is still unclear. Methods: Cognitive function was assessed with a battery of neuropsychological tests, which consisted of the Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), Clock Drawing Test (CDT), Digit Cancellation Test (DCT), Digit Symbol Substitution Test (DSST), Stroop Color-Word Test (SCWT), Trail-Making Test (TMT), Verbal Fluency Test (VFT), and Wechsler’s Intelligence Scale-Digit Span Test (DST). Ten patients with genetically confirmed SBMA and 12 normal controls were enrolled in this study and underwent a clinical, genetic and neuropsychological evaluation. Results: The SBMA patients presented with significant symptoms related to frontal dysfunction as determined by difficulty with completing the DCT, DSST, SCWT, TMT, SCWT, and TMT. However, patients displayed normal performance on the CDT, which indicated that the temporoparietal lobe was likely functionally intact. Furthermore, we found that DCT and DSST scores were correlated with disease duration. Conclusions: Our study demonstrates that Chinese patients with SBMA present with cognitive impairments, which mainly manifest as problems with executive function, attention, and working memory.

Key words: Kennedy’s Disease; Cognitive impairment; Frontal function

INTRODUCTION

Kennedy's disease, also known as spinal bulbar muscular atrophy (SBMA), is a rare, male, adult-onset, X-linked recessive neural degenerative disease. The main clinical features include slowly progressive lower motor neurons, bulbous involvement (such as dysphagia, proximally accentuated weakness of limbs, atrophy, and fasciculation), and signs of androgen insensitivity (Kennedy et al. 1998) (such as gynecomastia, testicular oligospermia, and sexual dysfunction). Recent studies have also found that SBMA patients present with postural tremor (Hanajima et al. 2009; Dias et al. 2011) and sensory system damage (Antonini et al. 2000; Buecking & Pfister 2000). The genetic basis of SBMA was identified in 1991 when La Spada et al. mapped the gene proximal long arm of X-chromosome (Xq11-12). The molecular basis of SBMA is the expansions of a polymorphic tandem CAG repeat, which encodes the polyglutamine tract in the first exon of the androgen receptor (AR) gene. The region is polymorphic within the normal population, numbering between 11–36. Conversely, the repeat region expands to number between 38–62 in Kennedy’s disease (La Spada et al. 1991; Perutz et al. 1994). Classically, degeneration in SBMA was believed to be restricted to the areas mentioned above. However, several clinical, imaging, and neuropsychological findings have challenged this simplified view. A minority of patients suffering from SBMA present with cognitive dysfunction, indicating some form of frontal lobe dementia (Guidetti et al. 1996; Kessler et al. 2005; Soukop et al. 2009). Furthermore, evidence from voxel based morphometry (VBM) MRI studies show large frontal white matter and brainstem atrophy, as well as metabolic abnormalities, in SBMA patients (Kassubek et al. 2007). In addition, pathological investigations have shown frontobasal white matter abnormalities through histopathology (Adachi et al. 2005). Evidence from neuropsychological studies support fronto-temporal lobe involvement leading to significant impairments in executive function, attention, and memory (Guidetti et al. 1996; Soukop et al. 2009). However, visuospatial and constructional function among patients with SBMA is still unclear. To date, no study has been published assessing the cognitive impairments displayed by SBMA patients in China.

In the present study, we investigated cognitive function in a cohort of Chinese patients with SBMA. This was done as an attempt to evaluate and further characterize the key cognitive features of SBMA.

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in a Chinese sample. We evaluated an extensive range of cognitive functions both in a group of SBMA patients and normal control subjects. Associations between neuropsychological measures and clinical reports were also addressed to determine predictors of cognitive impairment in SBMA. The neuropsychological scales used have all been clinically validated in China.

SUBJECTS AND METHODS

1. Subjects:
A total of 10 patients with clinically and genetically confirmed SBMA were enrolled in the study from the Department of Neurology of the First Affiliated Hospital of Zhengzhou University, China, from April 2012 to April 2013. Twelve healthy volunteers with no history of neuropsychological disease were recruited as control subjects. All control participants were native Chinese speakers and met the following inclusion criteria: over 40 years old and educational level consistent with the patient sample. This was done to avoid the effects of age and education on group differences in cognitive performance. The local research and ethics committee both approved this study protocol. Informed consent, clinical information and subsequent cognitive performance data were obtained from all participants.

2. Methods:
Every participant was administered the Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), Clock Drawing Test (CDT), Digit Cancellation Test (DCT), Digit Symbol Substitution Test (DSST), Stroop Color-Word Test (SCWT), Trail-Making Test (TMT), Verbal Fluency Test (VFT), and Wechsler’s Intelligence Scale-Digit Span Test (DST). The MMSE and MoCA measured global cognitive function. The DC, DSST, SCWT, and TWT assessed core elements of executive function. The CDT measured visuo-spatial and constructional function. The VFT examined both language and executive function. The DST assessed attention and working memory. As chronic physical and functional illnesses could lead to a higher risk for developing depression (Unutzer 2007), the Hamilton Anxiety Scale (Hamilton 1959) and Hamilton Depression Scale (Hamilton 1960) were administered. All and of their results were below 7, indicating that no participant was suffering from symptoms of anxiety or depression. All tests showed good reliability and validity when used with Chinese samples.

2.1.1 The Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA) (Folstein et al. 1975)

The MMSE and MoCA are used to screen general intellectual abilities.

2.1.2 Clock-Drawing Test (CDT) (Sunderland et al. 1989)

All participants were asked to draw the face of a clock pointing ten past eleven. The maximum score for this task is three. The CDT is used to assess visuospatial and constructional abilities.

2.1.3 Digit Cancellation Test (DCT) (Franklin et al. 1988)

In this task, the digits 1 to 9 were randomly listed in rows on a sheet of paper. The participant was asked to cross out 2 target digits within 45 seconds. The number of correct targets was recorded. The DCT tests sustained attention and psychomotor speed.

2.1.4 Digit Symbol Substitution Test (DSST) (Morrow 2010)

The DSST is comprised of nine digit-symbol pairs followed by a list of digits. Under each digit, the participants were to write down the corresponding symbol as fast as possible. The number of correct symbols within the allotted time (90 sec) was recorded. The DSST measures psychomotor speed, sustained attention, visuospatial skills, and set shifting.

2.1.5 Stroop Color-Word Test (SCWT) (Guo et al. 2005)

The SCWT is used to measure selective attention, mental flexibility, and inhibitory control. This task had three parts. In part A, the test was made up of cards where the names of colors were written in black ink; the participants were asked to name the words. In part B, the test was made up of cards in which dots were written in various colors; the participants were asked to name the color. In part C, the test was made up of cards in which the names of colors were written in various colors. The participants were asked to name the ink color while ignoring the word. The examiner pointed out errors and enabled all subjects to complete the test. Therefore, response time (in seconds) was the calculated score.

2.1.6 Trail-Making Test (TMT) (Lu et al. 2006)

There were two parts to the TMT. In TMT-A, participants connect Arabic numbers (1–25) in proper numerical sequence. In TMT-B, each Arabic number was surrounded with either a square or a circle. Participants had to connect the numbers in sequence with surroundings of the digits alternating between circles and squares. Response time was the calculated score, and errors were corrected. This test assesses not only visual search speed, but also mental flexibility, attentional resources, and motor abilities.

2.1.7 Verbal Fluency Test (VFT) (Abrahams et al. 2000)

To assess semantic fluency, participants were asked to name as many animals, fruits, and vegetables (1 min allotted for each category). The sum total of the items named was recorded. To assess phonemic fluency, participants were asked to name words containing the Chinese character “shui,” “kai,” and “fa,” one-by-one, for 1 min. The sum total of unique responses was recorded. This test evaluates language and executive
function.

2.1.8 Digit Span Test (DST) (Dai et al. 1990)

The DST was used to evaluate verbal attention (forward) and working memory (backward). The number of correctly reproduced items was recorded, respectively.

2.2 Molecular genetic testing and CAG repeats count (La Spada et al. 1991)

Genomic DNA was extracted from each patient’s fresh venous blood. The CAG repeat region in the first exon of the androgen receptor gene was amplified by the PCR, and ABI 3730 DNA performed the DNA sequencing.

2.3 Statistical Analysis

The clinical data of age, set age, duration, CAG repeats, and educational level was computed and analyzed via t-tests. With respect to the small sample size, comparisons among the neuropsychological tests between SBMA patients and normal controls were conducted using the Mann-Whitney test. The Spearman’s rank order correlation was calculated to determine the associations between neuropsychological performance and age at onset, age at examination, disease duration, education, and CAG repeats. Differences were considered significant at P < 0.05. All analyses were conducted using the Statistical Software Package for the Social Science (SPSS19.0) for Windows.

3. RESULTS

3.1 Clinical data

Clinical characteristics of SBMA patients and controls are presented in Table 1. Of the 10 patients with SBMA, the mean age of disease onset was 36.7 ± 2.62 years; mean disease duration was 19.2 ± 2.64 years. The mean CAG repeats was 45.30 ± 5.91. There was no significant difference between patients with SBMA and normal controls in terms of age and education level.

3.2 Cognitive evaluation

According to Table 2, the MMSE, MoCA, SCWT, TMT, DSST, DCT scores were significantly lower in the SBMA patients than normal controls. The SBMA patients did not differ significantly from normal controls with regard to the CDT or DST-B scores. The VFT scores failed to yield significant differences between the test groups, but the collected data already reflected a noticeable tendency to poor performance of SBMA patients.

3.3 Correlations

The relationships between the cognitive evaluation variables and age at onset, age at examination, disease duration, education, and CAG repeats were also analyzed (see Table 3). The CDT, SCWT, VFT, DST scores, and CAG repeats were not significantly correlated with age at onset, age at examination, disease duration, or education level. The DCT (r = -0.811) and DSST (r = -0.884) scores were significantly correlated with disease duration. Additionally, the correlations between the MMSE and MoCA scores and educational level were significant.

DISCUSSION

To our knowledge, this is the first systematic study to evaluate cognitive function among patients with SBMA in China. The main findings in terms of cognitive impairment can be summarized as follows. Firstly, the SBMA patients showed significant decrements on accomplishing the SCWT, TMT, DSST, and DCT tests. These tests are used to assess key components of executive function and attention, such as mental flexibility, attention, sustained attention, and psychomotor speed. In addition, the patients also exhibited lower performance than normal controls on the DST-F but comparable performance on the DST-B, suggesting that SBMA patients displayed working memory and attention impairments. Secondly, the SBMA patients did not differ from normal controls on the CDT (P = 0.138). A lack of a decrement in CDT performance suggests maintained intact visual-spatial and constructional function that involves temporoparieto-occipital function, especially parietal lobe. Furthermore, there were no significant group differences in VFT performance. The VFT is also an assessment of executive function. Although there was no difference in S-VFT (P = 0.064) and F-VFT (P = 0.051) scores, SBMA patients present a noticeable tendency to lower performance than the control subjects. Thirdly, the DCT and DSST scores reflecting attention and executive function appear to be independent from several clinical parameters, but these measures did significantly correlate with disease duration.

Some imaging studies for frontal, parietal and the brainstem involvements in SBMA patients Cerebral involvement in spinal and bulbar muscular atrophy (Kennedy's disease): A pilot study of PET(Kessler et al. 2005; Lai et al. 2013). In our study, frontal lobe dysfunction was observed among SBMA patients based on the SCWT, TMT, DSST, DCT, and DST scores. Our results conform to those from previous studies (Guidetti et al. 1996; Shaw et al. 1998; Kessler et al. 2005) where SBMA patients display executive function, working memory, and attention deficits that indicate frontal lobe dysfunction.

Executive function impairment was associated with disease duration in the current sample. In other words, along with the duration prolonging, SBMA patients performed more poorly on measures of sustained attention, psychomotor speed, and mental flexibility. Other possible correlates of cognitive impairment, including age, educational level, and CAG repeats, were not predictive of impairment.
There are several possible explanations for these disease outcomes. Firstly, there has been evidence (Fletcher & Henson 2001; Funahashi 2006) supporting frontal lobe cognitive impairment among SBMA patients. This includes evidence from pathological investigations showing frontobasal white matter abnormalities through histopathology (Adachi et al. 2005). Neuropsychological studies have also suggested significant impairments to executive function, attention, and memory (Guidetti et al. 1996). One previous report showed frontal atrophy in a SBMA patient with clinical signs of frontal-type dementia (Kessler et al. 2005). Finally, voxel-based, three-dimensional MRI studies have revealed widespread white matter changes, including changes to the brainstem and cerebellum, which have not been observed in ALS(Kassubek et al. 2005). However, the frontal cognitive impairment observed in SBMA is very similar to that observed in ALS.

Secondly, there is evidence from anatomical (Middleton & Strick 1994) and imaging (Allen et al. 1997; Gottwald et al. 2004) studies suggesting that the cerebellum is involved in cognitive function. Anatomical studies have revealed that the cerebellum has connections with the prefrontal cortex via the pons, and the prefrontal cortex is responsible for executive function. As described in a previous study, if the cerebellum is impaired in SBMA, this could be another reason for why SBMA patients have frontal type dementia.

Thirdly, the detection of bulbar involvement associated with frontal lobe impairment is interesting in light of recent findings (Abrahams et al. 1997). Animal models of ALS strongly suggest that the degeneration process is also directed against interneurons (Munte et al. 1998), which might be a mediator of cognitive pathology in ALS. The subcortex and brainstem might deprive afferents of ascending meso-limbic and meso-thalamo-cortical pathways, causing secondary prefrontal dysfunction. Additionally, subcortical neural pathways are disrupted (Schreiber et al. 2005). Furthermore, it has been suggested that the frontal lobe and bulbus could be considered as a single underlying process based on the absence of calcium-binding proteins in ALS (Alexianu et al. 1994; Silani et al. 1999), which is also named central-peripheral distal axonopathy. Bulbar impairment among SBMA patients might contribute to the disconnection of bulbar-frontal pathways.

In conclusion, the characterization of SBMA as a disease entirely confined to the lower motor neuron system, sensory system, and endocrine system has long been seen as an oversimplification. Although damage to other portions of the CNS and resulting functional impairment may be minor in comparison to the devastating effects on motor function, this incidental damage should not be overlooked when considering either patient care or disease etiology.

Our study demonstrates that Chinese SBMA patients suffer from cognitive impairment, manifesting mainly as problems with executive function, attention, and working memory. This might be due to subcortical/prefrontal/cerebellum lesions, lesions to meso-limbic and meso-thalamo-cortical pathways, or all of the above. Longitudinal studies using functional neuroimaging, pathology analysis, and assessments of neuroanatomy are needed to further assess the initiation and progression of SBMA.

Although cognitive impairment was only measured in a small sample of patients, we observed significant cognitive dysfunction. However, sample size limitations should be considered, as well as our lack of estimating limb functioning, and the lack of functional MRI data to confirm the brain regions involved with the tasks performed. Further studies will be needed to address these limitations.

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Table 1 Clinical Characteristics of Patients with SBMA and Normal Controls a.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>SBMA (n = 10)</th>
<th>Control (n = 12)</th>
<th>P^a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>55.70 ± 5.62</td>
<td>52.17 ± 6.39</td>
<td>0.188</td>
</tr>
<tr>
<td>Set age</td>
<td>36.70 ± 8.29</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Duration</td>
<td>19.20 ± 8.35</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>CAG repeats</td>
<td>45.30 ± 5.91</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Education</td>
<td>6.00 ± 3.27</td>
<td>7.42 ± 2.58</td>
<td>0.268</td>
</tr>
</tbody>
</table>

SBMA = spinal bulbar muscular atrophy.

a. Data are shown as mean ± SD in the table.
b. Independent samples t-tests were used, and Statistical significance was set at P < 0.05.

Table 2 Neuropsychological Test Results for the SBMA Patients and Controls a

<table>
<thead>
<tr>
<th>Test</th>
<th>SBMA (Mean ± SD)</th>
<th>Control (Mean ± SD)</th>
<th>P^a</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMSE</td>
<td>25.70 ± 3.43</td>
<td>28.67 ± 1.72</td>
<td>0.007</td>
</tr>
<tr>
<td>MOCA</td>
<td>17.10 ± 6.12</td>
<td>23.00 ± 3.28</td>
<td>0.012</td>
</tr>
<tr>
<td>DCT</td>
<td>21.40 ± 11.70</td>
<td>31.75 ± 5.43</td>
<td>0.044</td>
</tr>
<tr>
<td>DSST</td>
<td>23.50 ± 16.14</td>
<td>37.58 ± 11.49</td>
<td>0.041</td>
</tr>
<tr>
<td>CDT</td>
<td>2.10 ± 0.99</td>
<td>2.67 ± 0.49</td>
<td>0.138</td>
</tr>
<tr>
<td>SCWT-A</td>
<td>38.785 ± 10.20</td>
<td>23.63 ± 5.11</td>
<td>0.000</td>
</tr>
<tr>
<td>SCWT-B</td>
<td>50.516 ± 12.75</td>
<td>33.42 ± 8.62</td>
<td>0.001</td>
</tr>
<tr>
<td>SCWT-C</td>
<td>81.26 ± 21.69</td>
<td>59.72 ± 15.14</td>
<td>0.008</td>
</tr>
<tr>
<td>TMT-A</td>
<td>102.93 ± 69.69</td>
<td>53.63 ± 10.74</td>
<td>0.001</td>
</tr>
<tr>
<td>TMT-B</td>
<td>254.44 ± 146.18</td>
<td>138.91 ± 49.79</td>
<td>0.008</td>
</tr>
<tr>
<td>S-VFT</td>
<td>30.73 ± 8.21</td>
<td>45.46 ± 20.59</td>
<td>0.064</td>
</tr>
<tr>
<td>P-VFT</td>
<td>19.10 ± 5.32</td>
<td>27.17 ± 10.08</td>
<td>0.051</td>
</tr>
<tr>
<td>DST-F</td>
<td>5.40 ± 0.70</td>
<td>7.33 ± 1.16</td>
<td>0.001</td>
</tr>
<tr>
<td>DST-B</td>
<td>3.50 ± 0.85</td>
<td>4.42 ± 1.62</td>
<td>0.143</td>
</tr>
</tbody>
</table>

MMSE = Mini-Mental State Examination, MoCA = Montreal Cognitive Assessment, BD = Block Design Task, DC = Digit Cancellation Test, DSST = Digit Symbol Substitution Test, CDT = Clock Drawing Test, SCWT = Stroop Color-Word Test, TMT = Trail-Making Test, VFT = Verbal Fluency Test, and DST = Wechsler Intelligence Scale-Digit Span Test.

a. Data are shown as mean ± SD;
b. Mann-Whitney tests were performed, and statistical significance was set at P < 0.05.

Table 3 Correlations between Neurological Tests and Clinical Date in the SBMA Group a

<table>
<thead>
<tr>
<th>Test</th>
<th>Age</th>
<th>Set</th>
<th>Duration</th>
<th>Education</th>
<th>CAG</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMSE</td>
<td>-0.407 (0.242)</td>
<td>-0.189 (0.600)</td>
<td>-0.347 (0.326)</td>
<td><strong>0.803</strong> (0.005)</td>
<td>-0.059 (0.872)</td>
</tr>
<tr>
<td>MOCA</td>
<td>-0.529 (0.116)</td>
<td>-0.349 (0.324)</td>
<td>-0.311 (0.382)</td>
<td><strong>0.817</strong> (0.004)</td>
<td>0.201 (0.577)</td>
</tr>
<tr>
<td>DCT</td>
<td>-0.340 (0.336)</td>
<td>0.468 (0.173)</td>
<td><strong>-0.811</strong> (0.004)</td>
<td>0.025 (0.944)</td>
<td>-0.204 (0.571)</td>
</tr>
<tr>
<td>DSST</td>
<td>-0.523 (0.121)</td>
<td>0.358 (0.310)</td>
<td><strong>-0.884</strong> (0.001)</td>
<td>0.407 (0.243)</td>
<td>-0.162 (0.656)</td>
</tr>
<tr>
<td>CDT</td>
<td>-0.485 (0.155)</td>
<td>-0.345 (0.329)</td>
<td>-0.104 (0.775)</td>
<td>0.169 (0.641)</td>
<td>0.551 (0.099)</td>
</tr>
<tr>
<td>SCWT-A</td>
<td>0.576 (0.082)</td>
<td>0.116 (0.750)</td>
<td>0.456 (0.185)</td>
<td>-0.513 (0.129)</td>
<td>-0.152 (0.675)</td>
</tr>
<tr>
<td>SCWT-B</td>
<td>0.442 (0.200)</td>
<td>-0.079 (0.826)</td>
<td>0.547 (0.102)</td>
<td>-0.494 (0.147)</td>
<td>-0.182 (0.614)</td>
</tr>
<tr>
<td>SCWT-C</td>
<td>-0.012 (0.973)</td>
<td>-0.119 (0.743)</td>
<td>-0.104 (0.776)</td>
<td>0.241 (0.502)</td>
<td>-0.384 (0.273)</td>
</tr>
<tr>
<td>TMTA</td>
<td>0.345 (0.328)</td>
<td>-0.463 (0.177)</td>
<td><strong>0.699</strong> (0.024)</td>
<td>0.285 (0.425)</td>
<td>0.091 (0.802)</td>
</tr>
<tr>
<td>TAMBA</td>
<td><strong>0.782</strong> (0.008)</td>
<td>0.354 (0.316)</td>
<td>0.322 (0.364)</td>
<td>-0.253 (0.480)</td>
<td>-0.122 (0.738)</td>
</tr>
<tr>
<td>SF</td>
<td>-0.146 (0.688)</td>
<td>-0.554 (0.097)</td>
<td>0.558 (0.094)</td>
<td>0.019 (0.958)</td>
<td>-0.220 (0.542)</td>
</tr>
<tr>
<td>PF</td>
<td>-0.257 (0.474)</td>
<td>-0.172 (0.634)</td>
<td>0.003 (0.993)</td>
<td>0.121 (0.738)</td>
<td>0.218 (0.546)</td>
</tr>
<tr>
<td>DSF</td>
<td>-0.268 (0.454)</td>
<td>-0.320 (0.367)</td>
<td>-0.027 (0.941)</td>
<td>0.210 (0.560)</td>
<td>-0.161 (0.656)</td>
</tr>
<tr>
<td>DSB</td>
<td>-0.543 (0.105)</td>
<td>-0.524 (0.120)</td>
<td>0.130 (0.721)</td>
<td>0.145 (0.689)</td>
<td>0.084 (0.817)</td>
</tr>
<tr>
<td>CAG</td>
<td>-0.340 (0.336)</td>
<td>-0.505 (0.137)</td>
<td>0.238 (0.508)</td>
<td>0.226 (0.531)</td>
<td>1.000 (0.000)</td>
</tr>
</tbody>
</table>

MMSE = Mini-Mental State Examination, MOCA = Montreal Cognitive Assessment, DCT = Digit Cancellation Test, DSST = Digit Symbol Substitution Test, CDT = Clock Drawing Test, SCWT = Stroop Color-Word Test, TMT = Trail-Making Test, VFT = Verbal Fluency Test, and DST = Wechsler Intelligence Scale-Digit Span Test.

a. The Spearman’s rho values are provided, followed by the P value in parentheses.
b. Statistical significance was set at P < 0.05.
REFERENCES


