ORIGINAL ARTICLE

# Cognitive changes in spinocerebellar ataxia type 2

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## Abstract

**OBJECTIVES:** Cognitive disorders and dementia occur in 19 to 42% of patients with spinocerebellar ataxia type 2 (SCA2). Neuropsychological tests can reveal executive dysfunction, impaired visual and verbal memory, tongue and speech impairment, attention disorders and impaired verbal fluency.

**METHODS:** We performed psychiatric and neuropsychological examinations in 12 patients diagnosed with genetically confirmed SCA2 and 12 healthy volunteers matching the patients in age, gender, and length of education. The level of motor impairment was determined using the brief ataxia rating scale (BARS). The neuropsychological examination focused on testing executive functions, short-term visual and verbal memory, attention, psychomotor tempo, visual motor coordination, learning ability and comprehension ability. The tests were divided into two subgroups according to the difficulty of motor tasks. The cognitive abilities composite score (CACS) was determined by calculating the arithmetic mean of T scores of the respective tests.

**RESULTS:** Patients with SCA2 had significantly lower CACSs ($p$=0.00005) compared to the healthy volunteers. Patients exhibited impaired performance in both difficult and simple motor tests. The severity of cognitive impairment was related to the age at the onset of the disease ($p$=0.002) but not to the duration or to the overall BARS score.

**CONCLUSIONS:** Compared to healthy volunteers, patients with SCA2 exhibited significantly worse cognitive performance in all areas tested, including the tests of simple motor tasks. Moreover, the cognitive performance of patients worsened as the difficulty of the motor tasks increased.

## INTRODUCTION

Progressive cerebellar syndrome is a common sign of spinocerebellar ataxia. The respective disorders differ in sporadic or familiar occurrence, age of clinical manifestation and the presence of underlying symptoms. Neurodegeneration of various extents and severities affects the cerebellum, brainstem, medulla oblongata and basal ganglia. With the application of molecular genetic diagnosis, we currently know over 30 types of autosomal dominant SCA with different SCA loci (Bird 2009; Manto & Marmolino 2009). The most frequently diagnosed type in the Czech Republic is SCA2, which was detected in 36 patients from 12 families.

The role of cerebellum in non-motor functions has been discussed since the publication of the theoretical paper by Leiner *et al.* (1986). Previously, cognitive functions and emotional regulation were excluded from the function of this brain area. Schmahmann and Sherman (1998) summarised cognitive and emotional symptoms into the category of the cerebellar cognitive affective syndrome based on monitoring information from patients with cerebellum disorders. The psychopathology involved in this syndrome, along with ataxia, was used as a basis of the "dysmetria of thought" hypothesis (Schmahmann 2004). This concept assumes that the cerebellum plays a role in automatic behaviour modulation.

The potential subtype-specific disorder of cognitive functions in patients with SCA (Bürk 2007) is discussed herein. A certain level of cognitive impairment and dementia occurred in 19 to 42% of patients with SCA2 (Dürr *et al.* 1995; Geschwind *et al.* 1997). Bürk *et al.* (1999) observed the presence of dementia in 25% of SCA2 patients. Verbal memory and verbal fluency were affected in non-dementia patients. Other studies reported executive dysfunction, visual memory impairment, tongue and speech disorders and attention disorders (LePira *et al.* 2002; Bürk *et al.* 2003; Klinke *et al.* 2010). The subsequent question is what is the relationship between the severity of cognitive impairment and the duration of the disease or the number of CAG repeats (Zumrová 2005).

The objective of this study was to determine the type and extent of cognitive impairment in patients with SCA2, to compare the results from these patients to those from matched healthy volunteers, and to determine to what extent their motor disorders affect the results of the neuropsychological tests. We also examined the relationship between the level of cognitive impairment and the age at the onset or the duration of the disease.

## PATIENTS AND METHODS

We enrolled 12 patients with SCA2 and confirmed the diagnosis by molecular genetic testing. All patients signed the informed consent form approved by the local ethics committee. Patients underwent psychiatric, neurological and neuropsychological examinations. The results were compared to those from a group of healthy volunteers matching the patients in age, gender and length of education. The patients differed statistically from the healthy volunteers in the length of education. However, regarding the impact on cognitive performance, the absolute difference of one year was not considered clinically relevant. The group characteristics and basic clinical data are summarised in Tables 1 and 2.

We recorded the age at the onset and the duration of the disease. The level of motor impairment was determined using the BARS. The presence of clinically relevant depression, which could bias the results of neuropsychological tests, was used as an exclusion criterion.

Neuropsychological tests focused on executive functions, short-term visual and verbal memory, attention, psychomotor tempo, visual motor coordination, learning ability and comprehension ability. The test battery included the following tests: the Wechsler Adult Intelligence Scale-Revised (WAIS-R), the Rey-Osterrieth Complex Figure Test (RCFT), the Logical Memory Test (subtest z Wechsler Memory Scale III, LM), the Wisconsin Card Sorting Test (WCST), the Numeric Square (NSQ), the Trail Making Test (TMT) and the Phonemic Verbal Fluency Test (VF). The tests were divided into two groups, according to the difficulty of motors tasks. For difficult motor tasks (the subtests of Block Design, Object Assembly, and Symbols from WAIS-R, RCFT, NSQ, and TMT), we expected a higher contribution of motor skills, particularly the motor skills of the upper extremities, to successfully complete the tests. Performance in simple motor tasks (the subtests of Information, Digit Span, Dictionary, Comprehension, Details, Picture Completion, and Picture Arrangement from WAIS-R, VF, LM and WCST) was not directly influenced by the impaired motor skills or such influence was eliminated (WCST).

The performance results of the tests were evaluated with respect to age or age and education (WCST) and were converted to a common score (T score). We determined the cognitive ability composite score (CACS) as the arithmetic mean of the T scores of the respective tests. To compare the performance variability, we calculated the standard deviation of the CACS (CACS SD) as the standard deviation of the T scores of the respective tests. Similarly, we calculated the CACS and CACS SD of difficult and simple motor tasks.

We calculated basic statistical parameters (mean, standard deviation, median, minimum and maximum) for all variables. We used both parametric and non-parametric methods for the calculation, considering the achieved requirements of the statistical tests. The Mann-Whitney U-Test was used to compare the age, the length of education, CACS, CACS SD and the variables of the respective tests between the patients

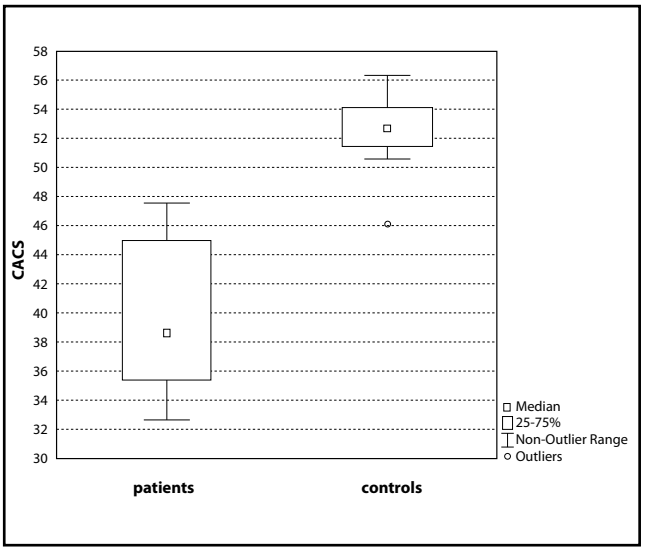


**Fig. 1.** Median CACS in the groups of SCA2 patients and healthy volunteers. CACS - Cognitive Abilities Composite Score

and the healthy volunteers. The comparison between simple and difficult motor tasks was performed using the t-test for dependent samples. Pearson Correlation was used to determine the statistical power of the relationship between the onset and duration of the disease and CACS, and Spearman Rank Order Correlation was used for the BARS and the CACS. Statistical evaluation was performed using the STATISTICA 8 software.

## RESULTS

Patients exhibited significantly worse performance than healthy volunteers in all neuropsychological tests conducted (Table 3). The CACS in the patient group was significantly lower than that in the control group ($p$=0.00005, Figure 1). Patients with SCA2 exhibited worse performance in both difficult and simple motor tasks compared to the control group (Table 4). Moreover, compared to the performance in simple

**Tab. 1.** Basic demographic data on the patient population.

| | Gender | Age (years) | Onset (age) | Duration (years) | Psychiatric diagnosis |
|---|---|---|---|---|---|
| 1 | F | 62 | 42 | 20 | F 06.7 Mild cognitive disorder |
| 2 | F | 55 | 41 | 14 | F 06.6 Organic emotionally labile disorder |
| 3 | M | 46 | 44 | 2 | -- |
| 4 | F | 41 | 34 | 7 | F 06.7 Mild cognitive disorder<br>F 06.3 Organic mood (affective) disorder |
| 5 | M | 38 | 33 | 5 | F 02.8 Dementia in SCA2 |
| 6 | M | 35 | 23 | 12 | F 02.8 Dementia in SCA2 |
| 7 | F | 45 | 32 | 13 | F 06.7 Mild cognitive disorder |
| 8 | F | 45 | 40 | 5 | F 06.3 Organic mood (affective) disorders |
| 9 | M | 23 | - | - | -- |
| 10 | M | 56 | 51 | 5 | F 06.6 Organic emotionally labile disorder |
| 11 | M | 58 | 53 | 5 | F 06.6 Organic emotionally labile disorder |
| 12 | M | 59 | 58 | 1 | -- |

**Tab. 2.** Characteristics of the patient population and the control group.

| Variable | Patients (n=12, females n=5) | | | Controls (n=12, females n=5) | | |
|---|---|---|---|---|---|---|
| | Mean ± SD | Range | Median | Mean ± SD | Range | Median |
| Age (years) † | 49.8 ± 9.1 | 35.0-62.0 | 50.5 | 50.5 ± 10.1 | 37.0-69.0 | 49.0 |
| Education (years) †† | 12.1 ± 2.3 | 8.0-18.0 | 12.0 | 13.4 ± 1.1 | 12.0-16.0 | 13.0 |
| Age at the onset of disease (years) | 41.1 ± 9.7 | 23.0-57.0 | 41.5 | -- | -- | -- |
| Duration of disease (years) | 8.7 ± 5.7 | 2.0-20.0 | 6.0 | -- | -- | -- |
| Length of CAG repeats* | 40.5 ± 1.8 | 38.0-44.0 | 40.5 | -- | -- | -- |
| BARS | 11.6 ± 4.4 | 7.0-19.0 | 9.5 | -- | -- | -- |

* analysis of only a part of the group (n=8); † NS; †† $p$=0.007 (Mann-Whitney U-Test); BARS - Brief Ataxia Rating Scale

**Tab. 3.** Results of the respective neuropsychological tests.

| Test | Patients (n=12, females n=5) | | | | Controls (n=12, females n=5) | | | | *p*-value* |
|---|---|---|---|---|---|---|---|---|---|
| | Mean ± SD | Range | Median | Number | Mean ± SD | Range | Median | Number | |
| Verbal IQ | 44.3±7.3 | 33.3–56.7 | 42.0 | 12 | 58.5±5.7 | 46.7–66.0 | 59.3 | 12 | 0.0003 |
| Performance IQ | 41.2±6.5 | 34.0–52.0 | 39.0 | 12 | 55.9±5.6 | 46.0–64.0 | 56.0 | 12 | 0.0002 |
| Total IQ | 42.5±7.0 | 34.0–55.3 | 39.7 | 12 | 57.8±5.7 | 46.7–66.0 | 58.7 | 12 | 0.0001 |
| Information | 4.8±10.0 | 30.0–56.7 | 41.7 | 12 | 55.8±8.7 | 40.0–73.3 | 56.7 | 12 | 0.006 |
| Digit span | 40.0±9.7 | 30.0–63.3 | 40.0 | 12 | 53.3±12.0 | 33.3–76.7 | 50.0 | 12 | 0.004 |
| Vocabulary | 46.9±10.0 | 33.3–63.3 | 46.9 | 12 | 58.9±3.6 | 53.3–66.7 | 58.3 | 12 | 0.001 |
| Arithmetic | 46.1±9.3 | 30.0–60.0 | 45.0 | 12 | 58.1±5.9 | 53.3–70.0 | 55.0 | 12 | 0.005 |
| Comprehension | 50.0±7.0 | 40.0–60.0 | 50.0 | 12 | 59.4±7.5 | 50.0–73.3 | 60.0 | 12 | 0.007 |
| Similarities | 48.1±8.3 | 36.7–60.0 | 48.3 | 12 | 57.2±4.2 | 50.0–63.3 | 56.7 | 12 | 0.007 |
| Picture completion | 51.9±6.9 | 40.0–60.0 | 53.3 | 12 | 55.3±5.9 | 50.0–70.0 | 53.3 | 12 | NS |
| Picture arrangement | 47.5±8.1 | 33.3–60.0 | 46.7 | 12 | 55.6±5.2 | 43.3–63.3 | 56.7 | 12 | 0.02 |
| Block design | 45.6±8.2 | 33.3–56.7 | 45.0 | 12 | 54.2±9.3 | 40.0–70.0 | 53.3 | 12 | 0.04 |
| Object assembly | 41.7±11.8 | 23.3–60.0 | 38.3 | 12 | 51.1±8.4 | 40.0–70.0 | 51.7 | 12 | 0.05 |
| Digit symbols | 35.8±7.7 | 20.0–46.7 | 36.7 | 12 | 59.2±8.5 | 46.7–76.7 | 56.7 | 12 | 0.00004 |
| M mean time I-X | 40.0±15.5 | 20.0–63.9 | 42.6 | 12 | 59.7±5.8 | 49.4–72.0 | 58.5 | 12 | 0.001 |
| Time A | 22.3±5.9 | 20.0–39.0 | 20.0 | 12 | 49.8±7.5 | 40.0–61.0 | 49.0 | 12 | 0.00003 |
| Time B | 22.3±5.5 | 20.0–35.0 | 20.0 | 12 | 49.7±9.7 | 31.0–63.0 | 52.5 | 12 | 0.00007 |
| NKP | 31.8±8.5 | 21.0–48.0 | 30.0 | 12 | 49.4±10.5 | 25.0–63.0 | 52.5 | 12 | 0.0009 |
| Total errors | 34.2± 4.2 | 27.0– 42.0 | 34.5 | 10 | 48.6± 5.6 | 39.0–57.0 | 49.0 | 12 | 0.0001 |
| % Errors | 34.2± 4.2 | 27.0–42.0 | 34.5 | 10 | 48.3± 5.4 | 38.0–57.0 | 49.0 | 12 | 0.0002 |
| Perseverative responses | 40.9± 3.5 | 37.0–45.0 | 40.0 | 10 | 48.7± 4.5 | 43.0–56.0 | 48.0 | 12 | 0.002 |
| % Perseverative responses | 42.6± 4.0 | 37.0–47.0 | 42.5 | 10 | 48.7± 4.4 | 43.0–55.0 | 47.5 | 12 | 0.01 |
| Perseverative errors | 39.2± 3.6 | 34.0–44.0 | 38.5 | 10 | 48.8± 4.7 | 43.0–57.0 | 47.5 | 12 | 0.0002 |
| % Perseverative errors | 40.7± 4.2 | 34.0–46.0 | 40.0 | 10 | 48.4± 4.3 | 43.0–55.0 | 47.0 | 12 | 0.002 |
| Nonperseverative errors | 31.0± 5.1 | 21.0–39.0 | 32.5 | 10 | 47.5± 7.4 | 35.0–60.0 | 48.5 | 12 | 0.0002 |
| % Nonperseverative errors | 33.0± 5.2 | 23.0–41.0 | 34.0 | 10 | 47.7± 7.0 | 35.0–61.0 | 49.0 | 12 | 0.0003 |
| % Conceptual level responses | 34.5± 5.1 | 29.0–44.0 | 34.5 | 10 | 48.8± 5.3 | 39.0–58.0 | 49.0 | 12 | 0.0002 |

***** Mann-Whitney U-Test

**Table 4. Cognitive performance composite score of (mean T scores) and CACS according to the motor task difficulty of the neuropsychological tests.**

| Variable | Patients (n=12, females n=5) | | | Controls (n=12, females n=5) | | |
|---|---|---|---|---|---|---|
| | Mean ± SD | Range | Median | Mean ± SD | Range | Median |
| CACS† | 39.8 ± 5.5 | 32.7–47.6 | 38.6 | 52.5 ± 2.6 | 46.1–56.3 | 52.7 |
| Difficult motor tasks†† | 34.7 ± 7.9 | 25.0–47.6 | 34.0 | 53.3 ± 4.4 | 47.0–61.5 | 52.4 |
| Simple motor tasks††† | 42.2 ± 5.8 | 34.7–53.2 | 41.2 | 52.2 ± 3.0 | 45.1–56.6 | 52.7 |

CACS - Cognitive Abilities Composite Score; SD - standard deviation
† $p$=0.00005 (Mann-Whitney U-Test) - comparison between the groups
†† CACS patients: $p$=0.00005 (T-test for Dependent Samples), healthy volunteers: $p$=N.S.; CACS SD patients: $p$=0.006 (T-test for Dependent Samples), healthy volunteers: $p$=N.S.; CACS patients vs. healthy volunteers: $p$=0.00004 (Mann-Whitney U-Test); CACS SD patients vs. healthy volunteers: $p$=0.02 (Mann-Whitney U-Test)
††† CACS patients vs. healthy volunteers: $p$=0.0004 (Mann-Whitney U-Test); CACS SD patients vs. healthy volunteers: $p$=N.S. (Mann-Whitney U-Test)

**Tab. 5.** Cognitive performance composite score – standard deviation (SD) and CACS SD according to motor task difficulty of the neuropsychological tests.

| Variable | Patients (n=12, females n=5) | | | Control group (n=12, females n=5) | | |
|---|---|---|---|---|---|---|
| | Mean ± SD | Range | Median | Mean ± SD | Range | Median |
| CACS SD | 9.9 ± 1.9 | 7.4–14.3 | 9.7 | 8.0 ± 1.5 | 5.1–10.5 | 7.9 |
| Difficult motor tasks (SD) | 11.1 ± 3.8 | 5.8–18.5 | 10.4 | 7.9 ± 2.4 | 2.4–10.7 | 8.8 |
| Simple motor tasks (SD) | 8.0 ± 1.7 | 5.3–11.3 | 8.2 | 7.4 ± 1.9 | 3.0–10.7 | 7.8 |

CACS - Cognitive Abilities Composite Score; SD - standard deviation

**Tab. 6.** Correlation analysis of CACS, age of onset, duration of the disease, and level of motor impairment.

| Variables | R (X,Y) | t | *p*-value | n |
|---|---|---|---|---|
| CACS onset of disease* | 0.8 | 4.3 | 0.002 | 12 |
| CACS duration of disease* | –0.2 | –0.5 | NS | 12 |
| CACS BARS** | –0.4 | –1.4 | NS | 12 |

CACS - Cognitive Abilities Composite Score; BARS - Brief Ataxia Rating Scale; *Pearson Correlation; ** Spearman Rank Order Correlation; n - number

motor tasks, patients exhibited markedly worse and more variable performance in difficult motor tasks (Tables 4 and 5), whereas the control group exhibited balanced and less variable performance in these tasks. The severity of cognitive impairment was related to the age at the onset of the disease ($p$=0.002) but not to the duration of the disease or to the overall score of the BARS (Table 6).

## DISCUSSION

Unlike healthy controls, patients with SCA2 exhibited cognitive deficits in all areas tested (with the exception of the subtest of Picture Completion in the IQ test). Our results were in agreement with previously published studies in this population (Kawai *et al.* 2009).

In contrast to the findings of Bürk *et al.* (1999) and Cancel *et al.* (1997), the level of cognitive impairment in our group was not related to the duration of the disease but to the age at the onset of cerebellar symptoms. In agreement with their results, we found no correlation between cognitive impairment and the level of objective motor impairment.

The overall IQ of the patients was significantly lower than that of the healthy volunteers, suggesting that the disease may have weakened not only the knowledge and skills obtained during the life of the patients but also their adequate and accurate use of the knowledge and skills to accomplish comprehensive mental tasks.

Our results suggest that a certain level of cognitive dysfunction is present in patients with SCA2, even in the case that the mental task requires only the minimal use of motor skills. On one hand, the performance of the patients in the phonemic verbal fluency test was the worst, and they failed significantly in the WCST. On the other hand, it was quite clear that the difficulty of the motor tasks and related requirements for attention was negatively correlated with their cognitive performance. We observed that the cognitive performance of the patients worsened with the increasing difficulty of the motor tasks and that the performance was significantly more variable among the tests compared to that of the control group, especially in difficult motor tasks. These findings suggest a role of organic impairment and only partial influence of the impaired motor skills in the cognitive dysfunction of patients with SCA2. Hence, cognitive dysfunction may be an important and independent part of the SCA2 phenotype, rather than a secondary effect of the progressive motor impairment.

In SCA2 patients, we observed clinical manifestations of a dysfunction in the frontal areas (impaired executive functions), even in the cases where no atrophy was confirmed by morphological imaging of the brain. The results of neuropsychological tests were in agreement with the findings of mild frontal hypoperfusion in the majority of the patients. Severe hypoperfusion was observed in the cerebellar region.

Our study was limited by the low patient number. We examined 1/3 of the patients diagnosed with SCA2 in the Czech Republic, and the diagnosis was confirmed by molecular genetic testing. The remaining patients either refused the examinations or were unable to participate due to the advanced stage of the disease or immobility.

A statistically significant difference was found between the groups in the length of education (median 12 vs. 13 years). In practical terms, however, this difference is unimportant and can be partially explained by the school system reform in the Czech Republic (prolongation of the elementary school education by one year).

The mechanism of cognitive impairment in SCA2 patients remains unclear. Several studies using functional imaging of the brain demonstrated the involve-

ment of the functional dopaminergic nervous system. A decrease in the number of striatal dopamine transporters is similar to that observed in Parkinson's disease. Similarly, reduced striatal fluorodopa uptake and the normal density of D2/D3 receptors have also been reported (Furtado *et al.* 2002). Using voxel-based morphometry, reduced brain volume was noted in patients with SCA2, not only in the infratentorial compartment but also in the right orbitofrontal and mesial temporal cortex and in sensorimotor cortex bilaterally (Brenneis *et al.* 2003). Pathological studies have suggested that cerebellar structures, substantia nigra and pons may also be affected. Neuropathological findings have shown that the disease can gradually progress into and affect the neocortex during the later stages of the disease, resulting in cognitive impairment and/or dementia.

Cognitive dysfunction is probably related to the damage to the corticostriatal-thalamocortical circuit and frontal lobes. Currently, the mechanism causing prefrontal dysfunction is not fully understood. The damage at the level of striatum or thalamus leading to a dysfunction of the frontal lobe without morphological correlations is expected to play a role, which is consistent with the findings of basal ganglia impairment due to a degenerative process in SCA2 patients. Another explanation of the cognitive deficits could involve damage to the cerebro-cerebellar connections. This hypothesis has been confirmed by a study using functional imaging of the brain that showed activation of the cerebellum during the tests of executive abilities, suggesting a functional relationship between the cerebellum and the frontal cortex. In theory, the connections between the cerebellum and the parietal lobe suggest that the cerebellum may play a role in visual-spatial orientation.

A psychiatric diagnosis (Table 1) was determined in the majority (9 of 12) of the patients enrolled in our study. These results suggest that spinocerebellar ataxia may be a neuropsychiatric disease and that psychiatric and psychological care might be beneficial for the patients and their families.

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