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Cognitive impairment in SCA-19

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Abstract

The autosomal dominant cerebellar ataxias (ADCAs) are a heterogeneous group of neurodegenerative disorders characterised by progressive cerebellar dysfunction in combination with various associated features. Since 1993, ADCAs have been increasingly characterised in terms of their genetic mutation and are currently referred to as spinocerebellar ataxias (SCAs). The discovery of genetic abnormalities offers the opportunity to study the possible interaction between the identified gene mutation and cognitive function. In this study, we focus on the neuropsychological abnormalities in a Dutch ADCA family, in which a new locus was recently identified (SCA-19). The family members showed frontal-executive dysfunction, with global cognitive impairment occurring in some of the more severely affected patients. Interestingly, the neuropsychological profile of this new family seems to overlap that of individuals with various other SCAs. Apparently, similar pattern of neuronal degeneration in various SCA subtypes accounts for the neuropsychological dysfunction, which is thus not genotype specific.

Key words : ADCA ; SCA ; SCA-19 ; WCST ; Dementia.

Introduction

Autosomal dominant cerebellar ataxias (ADCAs) are a heterogeneous group of neurodegenerative disorders characterised by progressive cerebellar dysfunction in combination with various associated features. Harding (1984) found cognitive impairment in more than 25% of ADCA patients. Kish *et al.* (1994) documented a relationship between ataxia severity and neuropsychological test performance and stated that ADCAs are a heterogeneous group with respect to cognitive status. We now know that genetic heterogeneity partly underlies the variable spectrum of clinical features. ADCAs are currently classified in terms of the genetic mutation involved and are referred to, and numbered, as spinocerebellar ataxias (SCA 1-8, 10-14, 16-19, 21-23). Mutations have been identified for SCA 1, 2, 3, 6, 7, 8, 10, 12, 14 and 17 whereas the genes for SCA 4, 5, 11,13, 16, 19, 21, 22, and 23 remain to be isolated (http://www.gene.ucl.ac.uk/cgi-bin/nomenclature). The identification of the genetic abnormalities has provided the opportunity to study the possible interaction between the identified SCA mutation and cognitive function. Recently, we described a unique SCA-19 linked Dutch ADCA family with a phenotype that was characterised by relatively mild cerebellar ataxia, slow progression, myoclonus, postural tremor, and cognitive impairment (Schelhaas *et al.*, 2001). Age at onset and severity of cerebellar symptoms suggest anticipation. In this report, we focus on the neuropsychological test performance of members of this family and correlate their performance with that of patients with other specific SCA mutations.

Patients and Methods

PATIENTS

Only those patients and their non-affected siblings who had been examined in our out-patient clinic were asked to participate in this neuropsychological study. Of the twelve affected members of a this four-generation family, six patients and two controls were willing to participate, including two patients (II-2 and II-6) and one control subject (II-4) of the second generation, three patients of the third generation (III-1, III-8, III-9), and one patient and his unaffected brother (IV-9 and IV-10) of the fourth generation (Fig. 1). Unfortunately, we were not able to include a control subject of the second generation because one of the two appropriate unaffected candidates was not willing to participate and the other suffered from leukaemia. The clinical features and the results of neuroimaging, evoked potentials, and EEG studies of the six patients are listed in table 1.

Global cognitive functions were assessed with the Mini Mental State Examination (Folstein,

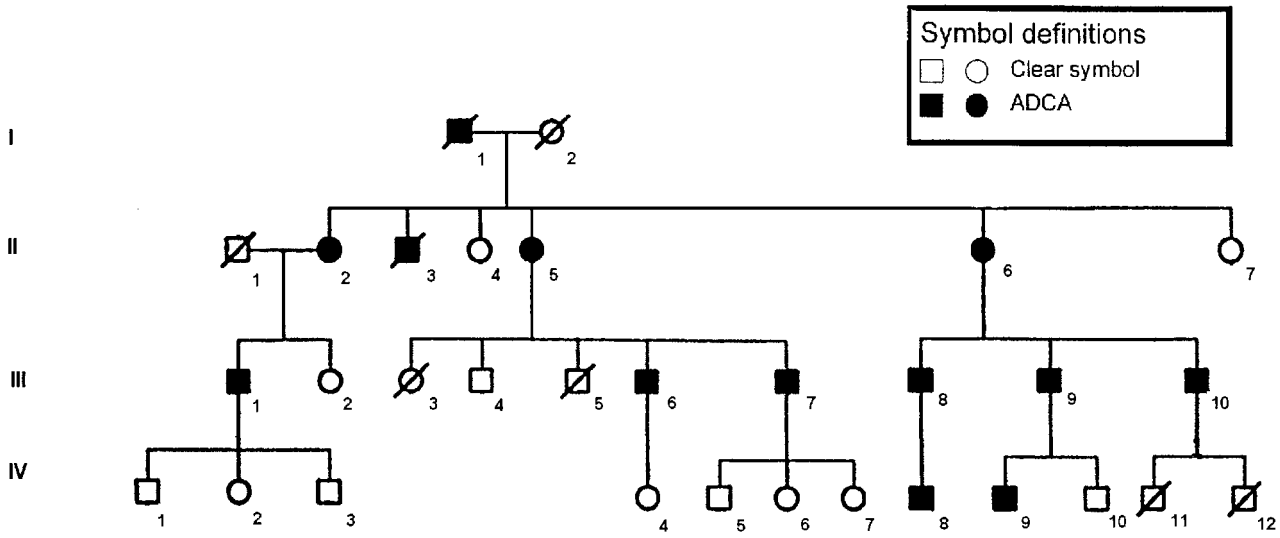

FIG. 1. — SCA-19 pedigree

Table 1

Clinical features, neuroimaging, evoked potentials and EEG studies in 6 patients of a SCA-19 linked Dutch ADCA family

	Second (eldest) generation		Third generation			Sixth (youngest) generation
	II-2	II-6	III-1	III-8	III-9	IV-9
Clinical features						
Age (years)	87	80	55	55	51	11
Age at onset (years)	30	45	45	27	27	n.d.
Oculomotor disturbance	+	+	+	+	+	+
Total ataxia score	79/100	42/100	18/100	26/100	18/100	6/100
Upper limb reflexes	decreased	decreased	decreased	decreased	decreased	decreased
Knee reflexes	decreased	decreased	decreased	decreased	increased	decreased
Ankle reflexes	decreased	decreased	decreased	decreased	increased	decreased
Vibration sense	decreased	decreased	decreased	decreased	normal	decreased
Myoclonus	–	+	–	–	–	–
Neuroimaging (atrophy)						
Frontal cortex	+	–	–	–	–	–
White matter lesions	–	+	–	–	–	–
Pons	–	–	–	–	–	–
Cerebellar hemispheres	+	+++	+	+	+	+
Vermis	–	++	–	–	+	–
Evoked potentials						
TMS (CMCT)* *	n.d.	9.1	9.5	9.6	n.d.	10.2
EEG studies						
Background	Alpha rhytm (9-11Hz.)	n.d.	Alpha rhytm (8-9 Hz.)	Alpha Rhytm (9.5-10 Hz.)	Alpha rhytm (8-9 Hz.)	n.d.
Paroxysmal activity	Paroxysmal rhythmic theta activity (temporal/parietal lobe)	Paroxysmal rhythmic theta activity (temporal/ parietal lobe)	No paroxysmal activity	Paroxysmal theta activity (fronto/temporal lobe)	No paroxysmal activity	

TMS (CMCT), Transcranial magnetic stimulation (Central motor conduction time) **CMCT reference value (mean, SD) 12.3 ± 1.9 ; n.d. no reliable data ; N, normal performance ; F, patient failed to perform the test ; + present, - absent.

Folstein and McHugh, 1975). Premorbid IQ was estimated on the basis of socioeconomic background and education (Luteyn and Van der Ploeg, 1983). Verbal and non-verbal intelligence were assessed with the Wechsler Adult Intelligence Scale-revised (WAIS-R ; Wechsler, 1981), Wechsler Intelligence Scale for Children-Revised (WISC-R ; Wechsler, 1974), Raven Standard Progressive Matrices (RSPM ; Raven, 1960), and Raven Coloured Progressive Matrices (RCPM ; Raven, 1965). Memory performance was tested with the WMS (MQ) (Wechsler, 1945) and the WAIS-Digit Span for immediate memory ; the 15-Word Test (a Dutch version of the Rey auditory Verbal Learning Test) for immediate recall, delayed recall and recognition in the auditory domain

(Heslinga *et al.*, 1983) ; and with the Recognition Memory Test for Faces for memory in the visual domain (Warrington, 1984). The Wisconsin Card Sorting Test (WCST ; Grant and Berg, 1948) was used to evaluate executive functioning. Visuospatial function was measured with the Hooper Visual Organization Test (Hooper, 1958), Recognition Memory Test for Faces (Warrington, 1984), Rey Complex Figure test (Rey, 1941), and the Benton visual retention test (Benton, 1974). Cortical language functions were assessed with the SAN (Deelman *et al.*, 1983). Depression was rated with the Beck Depression Inventory (Beck *et al.*, 1961).

Design and analysis

There were too few affected individuals in this family to allow statistical analysis. This study was therefore designed as a descriptive study. All of the tests administered have been standardised and normative data have been published. As the subjects ranged in age from 7 to 87 years, the test battery had to be adapted for the eldest and youngest subject (Table 1). The three subjects of the eldest generation were tested in the nursery home they were living in, while the others were tested at the Department for Medical Psychology.

Results

Table 2 summarises the test performance of the individuals investigated, namely, two patients and the control subject of the eldest (second) generation, all patients of the middle (third) generation, and the affected patient and his unaffected (control) brother of the youngest (fourth) generation.

The members of the eldest generation were not able to complete the entire test battery. The estimated premorbid IQ was lower than 105 (education not completed) in affected and unaffected individuals of this generation but, in the past, had not affected activities of daily living. The MMSE score was higher than the usual cut-off of 24 in all subjects examined. One patient of this generation suffered from moderate depression. The test performance of the eldest patient (II-2) was very poor in nearly all modalities. The performance of the control subject II-4 on tests of non-verbal intelligence, visual spatial perception, and verbal fluency was worse, but that on the WCST was better, than that of patient II-6. In the middle (third) generation, again, estimated premorbid IQ was lower than 105, the MMSE score was higher than the usual cut-off of 24, and two patients suffered from depression. Patient III-1 performed better than his cousins (III-8 and III-9) on all tests, with the exception of the SAN test. The neuropsychological test performance of patients III-28 and III-34 revealed global cognitive impairment, depression, and poor performance on the WCST. The individuals of this generation also displayed impulsive behaviour.

The neuropsychological test performance of the two brothers of the youngest (fourth) generation was markedly different. Whereas the unaffected brother (IV-10) had a normal performance on nearly all tests with the exception of verbal IQ, patient IV-9 showed general cognitive impairment, with a verbal and non-verbal IQ of 55 and 79, respectively. He also performed poorly on the WCST.

Discussion

The current neuropsychological study is unique in that it involved both affected and unaffected family members of the only SCA-19 linked ADCA family reported so far. Although the methodological design of the study made it possible to correct for family background and for “non-SCA related” cognitive performance, the interpretation of results was complicated by the limited number of affected and non-affected individuals, by the low estimated premorbid IQ of all family members, and by the finding that three patients suffered from depression.

The test performance of the eldest patient in the family was very poor in nearly all modalities. Compared with the unaffected subject, the other affected patient of the eldest generation had a poor performance on the WCST and suffered from moderate depression. Non-verbal intelligence, visual spatial perception, and language were fairly well preserved.

Although depression might be a complicating factor, Leroi *et al.* detected psychopathological (non-cognitive) disorders, mainly mood disorders and personality changes, in 77% of patients with degenerative cerebellar diseases. Furthermore, in a study comparing depressed patients with and without cognitive impairment, Dolan *et al.* reported that cognitively impaired patients had a significantly reduced resting cerebral blood flow (rCBF) in the medial prefrontal cortex and an increased rCBF in the cerebellar vermis. These changes, together with evidence from neuroimaging studies of atrophic (Shah *et al.*) and structural damage in this region (Schmahmann and Sherman, 1998), suggest that the cerebellum, and the vermis in particular, are involved in these disturbances of mood. Thus the depression seen in patients with SCA-19 may be attributable to the disease process. Interestingly, atrophy of the vermis was seen on MRI in the affected individual of this generation.

The differences in performance on the WCST but not on other neuropsychological tests may indicate that executive dysfunction is an important feature in this family. This suggestion is supported by the poor performance on the WCST and the impulsive behaviour, both of which are suggestive of a deficit in response suppression, seen in all patients

Table 2

Neuropsychological tests

	II-2	II-4*	II-6	III-1	III-8	III-9	IV-9	IV-10*
Age (years)	87	84	80	55	57	51	11	7
Duration (years)	56	-	34	34	31	25	2	-
MMSE	25/30	27/30	26/30	27/30	26/30	26/30		
Maximal educational degree	No education completed	No education completed	No education completed	Lower secondary education	Primary school	Primary school	Special education	Primary school
GIT	<105	<105	<105	<105	<105	<105		
Verbal IQ (WAIS/WISC-R)				103	**83**	**80**	**55**	**76**
Non-verbal (Raven SPM/CPM)	**12**/36	19/36	24/36	48/60	25/60	35/60	**16**/36 *IQ :***79**	26/36 IQ :110
MQ (WMS)	**89** (1/23)	101(1.5/23)	100 (0/23)	101 (9/23)	**73** (2.5/23)	**84** (1.5/23)		
Reasoning and abstraction (WAIS/WISC-R)								
Similarities	**F**	**F**	**F**	14	11	7	5**	5**
Comprehension	**F**	**F**	**F**	15	5	12	4**	7**
Arithmetic	**F**	**F**	**F**	7	*1*	*2*	**3****	8**
Digit span (forward/backward)	**4/2**	5/5	5/4	5/**3**	**4/2**	4/**3**	**3/2**	4/3
15-Words/8-Words test (8 if >70)								
Learning curve	**2-4-2-3-4**	**2-3-4-3-5**	3-4-5-6-5	2-4-6-5-7	**3-5-4-6-4**	**2-2-5-5-5**	3-5-5-10-11	8-8-10-10-12
Delayed recall	**0**/8	**3**/8	**3**/8	4/15	**2***/15*	**3***/15*	**7***/15*	11/15
Recognition	**13**/16	15/16	14/16	28/30	**21**/30	**21**/30		
hits	7	7	6	8	8	6		
false alarm (false negative)	3	0	0	**7**	**7**	**9**		
Visualspatial/visual construction								
Hooper VOT	**9**	**9.5**	**18**	23.5	19.5	**21**		
WAIS-R (block design)				13	10	15	**3**	8
WAIS-R (object assembly)				19	12	24	**4**	9
Benton-VRT							N	N
RMT-F				38	38	39		
R-CFT (copy)							**27**	33
R-CFT (recall)							**18**	19.5
WCST								
Categories	**F**	**2**	**0**	4	**2**	**2**	**3**	4
Correct	**F**	76	**16**	73	52	30	**29**	41
Perseverative errors	**F**	32	**68**	29	**80**	**95**	14	17
PN/TE 100%		25%	**98,5***%*	22,7%	**62,5***%*	**74,2***%*		
Language								
WAIS/WISC-R (vocabulary)				41	**20**	**21**	**1**	5
SAN (naming)	18/18	18/18	18/18	18/18	18/18	18/18		
SAN (formulate sentences)	**4**/10	7/10	8/10	**6**/10	8/10	8/10		
BDI (degree of depression)	**18**	8	**17**	9	**31**	**17**		

* ADCA-negative family member ; Scores are raw scores, when not indicated otherwise. ; **Scaled score ; MMSE, Mini Mental State Examination ; GIT, Groninger Intelligence test ; WAIS, Wechsler Adult Intelligence Scale ; Raven SPM/CPM, Raven standard progressive matrices/coloured progressive matrices ; WMS, Wechsler memory scale ; RMT-F, Recognition Memory Test for Faces ; Benton-VRT, Benton visual retention test ; R-CFT, Rey Complex Figure text ; WCST, Wisconsin Card Sorting Test ; PN/TE 100%, percentage of errors that are perseverative ; SAN, Test of the Dutch Aphasia Foundation ; BDI, Beck Depression Inventory ; N, normal performance ; F, patient failed to perform the test. **Bold** numbers *:* abnormal result. If a space is left blank there are now reliable data (or the test is not suitable (age).

Table 3

Summary of literature on neuropsychological testing in specific spinocerebellar ataxia (SCA) genotypes

Entity	Locus	Cognitive impairment	reference
SCA-1	6p	Frontal executive dysfunction with general cognitive decline in the more severely affected patients	Kish, 1994 ; Burk, 2003
SCA-2	12q	Frontal executive dysfunction with general cognitive decline in the more severely affected patients	Storey, 1999 ;Gambardella, 1998, Burk, 2003
SCA-3	14q	Frontal executive dysfunction with general cognitive decline in the more severely affected patients	Maruff, 1996 ; Burk, 2003
SCA-4	16q	Cognitive impairment has not been reported. No extensive neuropsychological study performed.	
SCA-5	11cen	Cognitive impairment has not been reported. No extensive neuropsychological study performed.	
SCA-6	19p	Pure cerebellar syndrome, cognitive impairment has not been reported, no extensive neuropsychological study performed.	
SCA-7	3p	Cognitive impairment as a rare feature. Most patient remain responsive to their environment even at old age.	Enevoldson, 1994 ; Gouw, 1994 : Jobsis,1997
SCA-8	13q	Cognitive impairment in 6 out of 15 individuals in a Finnish population.	Juvonen, 2000
SCA-10	22q	“Pure cerebellar syndrome with epilepsy” Cortical involvement suggested, cognitive impairment not reported.	
SCA-11	15q	“Pure cerebellar syndrome with mild hyperreflexia” Cognitive impairment is not a clinical feature.	
SCA-12	5q	Poor anterograde memory formation, disorientation, apraxia and hemi-inattention in 2 different families	O’Hearn, 2001 ; Fujigasaki, 2001
SCA-13	19q	Childhood onset cerebellar ataxia with moderate mental retardation and delay in motor skill acquisition. Intellectual impairment was global with IQ’s of 62-76.	Herman-Bert, 2000
SCA-14	19q	Cognitive impairment has not been reported. No extensive neuropsychological study performed.	
SCA-16	8q	“Pure cerebellar ataxia and head tremor”. Cognitive impairment has not been reported.	
SCA-17	TBP gen	Signs of dementia in four members of a Belgian family	Fujigasaki, 2001
SCA-19		Frontal executive dysfunction with general cognitive decline in the more severely affected patients	Schelhaas, this study
SCA-21		Moderate cognitive impairment in 2 patients and severe cognitive impairment in 2 young children	Vuillaume, 2002
SCA-22		SCA-19 and SCA-22 share the same locus. In the Chinese family neuropsychological examination disclosed a normal cognitive function.	Chung M-y. 2003
SCA-23		Clinical features have not (yet) been described (http ://www.gene.ucl.ac.uk/cgi-bin/nomenclature)	
FGF-14		Impairment in memory function, abstract thinking, and word fluency, as well as depression and aggressive outbursts in members of one family	Van Swieten, 2003

of the middle (third) generation. In this generation, one patient suffered from depression and, as in the oldest generation, cerebral MRI showed atrophy of the vermis.

There were profound differences in the neuropsychological test performance of both brothers of the youngest (fourth) generation. Whereas the unaffected sibling performed poorly only on verbal IQ, his brother showed general cognitive impairment, with a verbal and non-verbal IQ of 55 and 79, respectively. Again the performance on the WCST was very poor.

Table 2 summarises the literature on neuropsychological testing in all currently classified SCA genotypes. Although various reports failed to mention cognitive impairment as a feature of a specific SCA type, frontal executive dysfunction with generalised cognitive impairment in some severely affected patients has been described in neuropsychological studies of SCA-1, SCA-2, and SCA-3 (Burk *et al.* 2003, Kish *et al.*, 1994 ; Geschwind DH, 1999 ; Bürk *et al.*, 1999 ; Gambardella *et al.*, 1998 ; Storey *et al.*, 1999 ; Maruff *et al.*, 1996). Indeed, our study of SCA-19 suggests that the cognitive deficits of SCA patients do not seem to be genotype specific but rather reflect the pattern of neuronal degeneration, emphasising the importance of intact cerebellar pathways to cognition.

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