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Cognitive impairment in families with pure autosomal dominant hereditary spastic paraparesis

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Summary

In the course of a study of a large family with pure autosomal dominant hereditary spastic paraparesis (AD-HSP), mild cognitive impairment was found in older family members. In order to determine if cognitive impairment occurred more frequently in families with pure AD-HSP than normally expected, a case control study of cognitive function in HSP was undertaken. Thirty-one patients, from 12 kindreds with pure AD-HSP, matched with 31 healthy control subjects for age, sex and years of education, were assessed for evidence of cognitive impairment using the Cambridge Cognitive Examination (CAMCOG). Twenty unaffected siblings matched with twenty healthy control subjects were similarly assessed. The total CAMCOG score in the affected group (mean 89.26/107, SD 11.08, 95% confidence interval 85.2–94.49) compared with the control group (mean 96.52/107, SD 5.52, 95% confidence interval 94.49–98.54) was significantly reduced ($P = 0.0003$). There were also significant abnormalities in three out of the nine subsets including memory ($P = 0.0002$), language comprehension ($P = 0.0166$) and language expression ($P = 0.0025$). The differences between the groups were due to cognitive impairment appearing after the age of 50 years in patients with AD-HSP; CAMCOG scores before this age were similiar to control scores. There was also a minor non-significant difference in total CAMCOG score for the unaffected siblings (mean 93.7/107, SD 8.54, 95% confidence interval 89.70–97.70) compared with the control group (mean 97.9/107, SD 4.61, 95% confidence interval 95.7–100.1) ($P < 0.02$). This study demonstrates that mild cognitive impairment develops after the age of 50 years in patients with pure AD-HSP and is further evidence of degeneration in other systems in this disorder.

Keywords: hereditary spastic paraparesis; cognitive impairment; Cambridge Cognitive Examination

Abbreviations: AD = autosomal dominant (HSP); CAMCOG = Cambridge Cognitive Examination; CAMDEX = Cambridge Mental Disorders of the Elderly Examination; HSP = hereditary spastic paraparesis; MMSE = Mini-Mental State Examination

Introduction

Hereditary spastic paraparesis (HSP) has traditionally been divided into pure and complicated forms based on clinical and pathological observations. In pure HSP progressive spastic paraparesis is the most prominent clinical feature. However, bladder impairment, minor sensory disturbance in the legs, muscle wasting and cerebellar signs are accepted as mild, late and variable characteristics supported by pathological findings (Harding, 1981; Bruyn, 1992). In complicated HSP, spastic paraparesis is associated with other marked clinical features including retinal pigmentation, epilepsy, mental retardation and rarely dementia (Sutherland, 1975; Bruyn and Scheltens,1995).

This division of HSP into pure and complicated forms may be artificial. There is evidence, from neurophysiological studies, of more widespread but subclinical involvement of the nervous system in both forms (Dimitrijevic *et al*., 1982; Tedeschi *et al*., 1991; Durr *et al*., 1994). Tedeschi *et al*. (1991) studied four families with pure autosomal dominant and recessive HSP and demonstrated cognitive impairment in five out of seven members on neuropsychological testing (aged 27–53 years). Neuropathological studies of pure autosomal dominant HSP (AD-HSP) have demonstrated degeneration of the corticospinal and spinocerebellar tracts, and dorsal columns, but less common changes may include degeneration of the anterior horn cells, cerebellum and basal ganglia (Schwarz, 1952; Schwarz and Liu, 1956).

We have reported a family linked to the locus for pure HSP on chromosome 2p (SPG4) in which older affected members showed evidence of mild, late-onset cognitive impairment on neuropsychological testing. It was concluded that the association of AD-HSP and cognitive impairment in this family was not coincidental and that the phenotype consisted of spastic paraparesis and/or a late-onset cognitive impairment which, although usually mild, might occasionally

become symptomatic. The presence of cognitive impairment appeared to be related to age and not to the severity of the paraplegia (Webb *et al*., 1996).

In order to determine if cognitive impairment occurred more frequently in families with 'pure' AD-HSP than usually expected, a case control study was undertaken, using the CAMCOG, the cognitive part of the Cambridge Mental Disorders of the Elderly Examination (CAMDEX) (Roth *et al*., 1986).

Methods

Subjects

This study was approved by the ethics committee of St Vincent's Hospital. Informed consent was obtained from all participating members before inclusion in the study. Families with pure AD-HSP were identified as part of a clinical and epidemiological study of HSP in Ireland. The hospital records of all index cases were reviewed, and as many first and second degree relatives as possible had a neurological examination performed at home or at the hospital by two examiners. Consenting family members of >20 years of age had an additional assessment of cognitive function using the CAMCOG. Both affected and unaffected family members were matched for age, sex and years of education with a healthy control population without neurological disease. Spouses of HSP patients and relatives of out-patient attendees, were used as control subjects and were asked about present complaints and past medical history. A CAMCOG assessment was performed on all control subjects who were healthy and could be matched with an affected or unaffected family member for age, sex and years in education.

Method of clinical assessment

We used the diagnostic criteria for HSP as proposed by Fink *et al*. (1996). Subjects were considered definitely affected with HSP if they satisfied all the following: (i) a progressive gait disturbance; (ii) a family history to support an inherited disorder; (iii) all other causes were excluded; and (iv) their examination showed frank corticospinal tract deficit in the lower limbs, including Grade 4 hyperreflexia and extensor plantar responses. Subjects were considered probably affected if they were asymptomatic but had lower limb hyperreflexia and extensor plantar responses. Unaffected members with an affected parent and an affected child were considered obligate carriers of the abnormal gene.

Method of cognitive assessment

The CAMCOG is the cognitive part of the CAMDEX test and has been shown to have good inter-observer reliability with a median phi (ϕ) coefficient of 0.9. The test also has a high sensitivity and specificity in the differentiation between organic and non-organic cases of cognitive impairment, and is highly correlated with the Blessed Dementia Scale and the psychiatrist's clinical rating of severity. The CAMCOG is normally used to identify dementia in an older population. However, in a previous study we examined a large family with pure HSP and, using extensive neuropsychological tests, identified mild late-onset cognitive impairment. The CAMCOG, which was used as a screening test, accurately identified those with cognitive impairment in that study. The CAMCOG, which is also a relatively short and easy test to administer, is an extension of the Mini-Mental State Examination (MMSE) (Folstein, 1975) with 14 of the 19 items from the MMSE. There are another 43 items covering additional aspects of cognitive function including eight major subclasses assessing orientation, language, memory, praxis, attention, abstract thinking, perception and calculation. When compared with the MMSE, the CAMCOG provides a more extensive and detailed assessment of cognitive functions, it detects milder degrees of cognitive impairment and avoids a ceiling effect, allowing discrimination between individuals, even at the high end of the ability range (Roth *et al*., 1986). However socio-demographic variables (age, sex and education) have a significant and independent effect upon performance of the CAMCOG total score and its subsets (Huppert *et al*., 1995). The score is also influenced by hearing and visual deficits but not by depression (Blessed *et al*., 1991). The maximum total score for the CAMCOG is 107. A score >80 is considered normal, 60–80 mild dementia, 35–59 moderate dementia and <35 severe dementia.

Statistical methods

The comparison of variables between the two groups was statistically analysed using the non-parametric Wilcoxon signed-rank test for matched pairs. Exact *P*-values and 95% confidence intervals are given where appropriate.

Results

Family members and control subjects

Fifteen families were identified with pure AD-HSP. Another previously described family with 12 affected members over two generations, shown to have a late-onset global cognitive impairment on neuropsychological tests, has not been included in this study. Two families were excluded because the affected members were too young for cognitive assessment, and one family refused assessment of cognitive function. Of the 12 remaining families, 31 affected members (including 26 definite and four probable cases and one 40-year-old obligate carrier) and 20 unaffected family members, were assessed for cognitive impairment. The 31 affected members (18 women and 13 men) had no complaint of cognitive impairment. They had a mean age at examination of 49.39 years (range 24–83 years, SD 15.06 years) and an average of 15.94 years in education (range 14–20 years, SD 1.57 years). The average age of HSP onset was 29.53 years

Table 1 *Mean total CAMCOG and subset scores for HSP affected members and matched controls*

	HSP affected (n = 31)	Matched controls (n = 31)	Difference	95% confidence interval	P-value
Mean age (years)	49.38	49.38	0.0	–	n.s.
CAMCOG total score	89.26	96.52	–7.26	–10.81 to –3.70	0.0003
CAMCOG subsets					
Memory	20.0	23.26	–3.26	–4.76 to –1.76	0.0002
Language expression	17.29	18.81	–1.52	–2.46 to –0.57	0.0025
Calculation	1.81	1.94	–0.13	–	n.s.
Orientation	9.71	10.0	–0.29	–	n.s.
Attention	5.74	6.13	–0.39	–	n.s.
Praxis	10.87	11.45	–0.58	–	n.s.
Language comprehension	8.61	8.94	–0.32	–0.54 to –0.10	0.0166
Abstract	5.68	6.06	–0.39	–	n.s.
Perception	9.55	9.94	–0.39	–	n.s.

n.s. = $P > 0.01$.

(range 2–63 years, SD 17.27 years) and the average duration of illness was 19.66 years (range 2–48 years, SD 13.43 years). This affected group was matched with 18 female and 13 male control subjects, with a mean age at examination of 49.39 years (range 24–76 years, SD 12.98 years) and an average of 17.13 years in education (range 14–25 years, SD 2.87). There were no significant differences between the affected and control groups for mean age at examination and number of years in education. There was no observed difference between these two groups for visual or hearing disturbances.

Twenty unaffected family members (13 women, seven men) were also assessed for cognitive impairment using the CAMCOG. They had a mean age at examination of 48.55 years (range 20–75 years, SD 18.41 years) and an average of 16.65 years in education (range 14–22 years, SD 2.13). This unaffected group was also matched with 13 female and seven male control subjects, with a mean age at examination of 49.1 years (range 24–76 years, SD 16.97 years) and an average of 18.35 years of education (range 14–25 years, SD 2.96). There were no significant differences between the unaffected sibling and control groups for mean age at examination and number of years in education.

Cognitive assessment

The results of the CAMCOG examination for the 31 members with HSP and their 31 matched control subjects are shown in Table 1 and the distribution of scores is illustrated in Fig. 1. The difference between the mean total CAMCOG score of the affected group (89.26/107) and the control group (96.52/107) was significant (P = 0.0003). There were also significant differences between the affected and control groups in three out of the nine subsets, including memory (P = 0.0002), language comprehension (P = 0.0166) and language expression (P = 0.0025). Six of the affected group and one of the control group had a CAMCOG score ⩽80. These six affected cases came from five different families and all six cases were >50 years of age. All six had severe disability and five had HSP for >20 years. Among those 25 affected members with a normal CAMCOG score, 12 had HSP for >20 years and seven were severely affected.

We examined the correlation between the CAMCOG total scores and the patient's ages in both the affected (r^2 = 0.3190) and the control group (r^2 = 0.1863). In both groups there was a decline in CAMCOG total score with increasing age which was more marked in the HSP subjects. In patients of >50 years of age there appeared to be a steeper decline in CAMCOG total score in the affected group (r^2 = 0.1405) compared with the control group (r^2 = 0.2608). To determine if the differences between the affected and control groups were age related, the affected cases were divided according to their age at examination, those ⩾50 years (Group A, 15 matched pairs) and those <50 years (Group B, 16 matched pairs) (Table 2). In group A the significant differences between the affected and control groups for CAMCOG total (Fig. 1) and memory (Fig. 2) and language expression subsets remained. In contrast, there was no significant difference observed in any of the subsets or total CAMCOG score for those subjects with an age of <50 years (Table 2).

The results of the CAMCOG for the unaffected siblings and their matched control subjects are shown in Table 3. Although there was more than a four-point difference between the groups for CAMCOG total score this failed to reach significance ($P < 0.02$), and only language expression showed a significant difference (P = 0.0086). The unaffected siblings were also divided according to their age at examination, those ⩾50 years (Group A, 11 matched pairs) and those <50 years (Group B, nine matched pairs). Although the differences between the unaffected siblings and their matched control subjects failed to reach a significant level in either group, probably because of the small numbers, the differences between the unaffected siblings and their matched control subjects was more marked in group A, especially for CAMCOG total and memory subset (Table 4).

There were five families in which one or more members had cognitive impairment (CAMCOG total < 80). In one family there were seven affected members with HSP, of which six

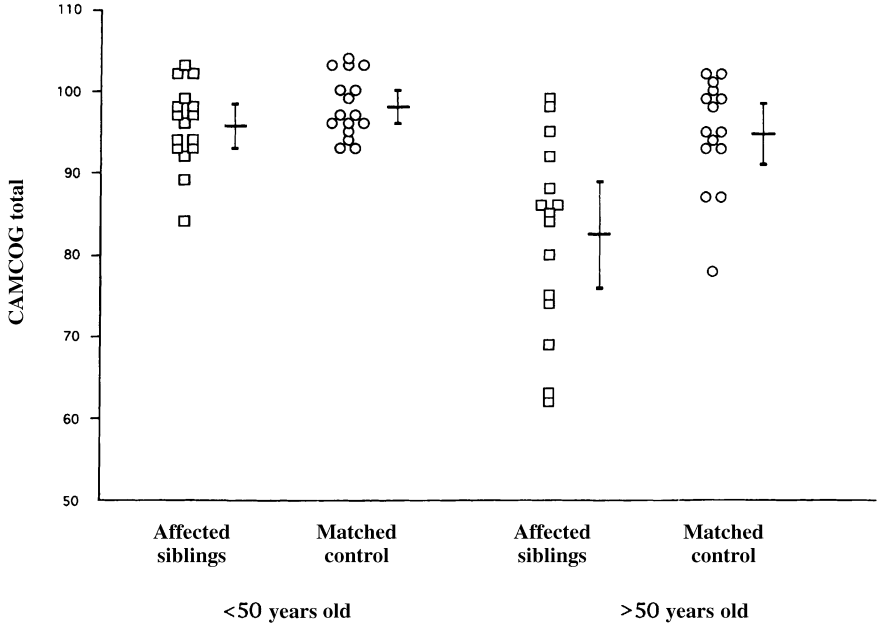

Fig. 1 A scattergram showing total CAMCOG scores for affected AD-HSP members and matched control subjects grouped for age (with mean and 95% confidence interval bars shown to the right of each set of data).

Table 2 *Mean total CAMCOG and subset scores for HSP affected members and matched controls grouped for age*

	Group A (>50 years old at examination)					Group B (<50 years old at examination)			
	Affected cases (n = 15)	Matched controls (n = 15)	Difference	95% confidence interval	P-value	Affected cases (n = 16)	Matched controls (n = 16)	Difference	P-value
Mean age (years)	62.53	60.2	2.33	–	n.s.	37.06	39.25	–2.19	n.s.
CAMCOG total score	82.40	94.87	–12.47	–18.08 to –6.85	0.0002	95.69	98.06	–2.38	n.s.
CAMCOG subsets									
Memory	18.33	23.33	–5.0	–7.60 to –2.40	0.0012	21.56	23.19	–1.63	n.s.
Language expression	16.0	18.60	–2.60	–4.09 to –1.11	0.0029	18.5	19.0	–0.5	n.s.
Calculation	1.73	1.87	–0.13	–	n.s.	1.88	2.0	–0.13	n.s.
Orientation	9.6	10.0	–0.4	–	n.s.	9.81	10.0	–0.2	n.s.
Attention	5.27	6.07	–0.80	–	n.s.	6.19	6.19	0.0	n.s.
Praxis	9.93	11.20	–1.27	–	n.s.	11.75	11.67	+0.06	n.s.
Language comprehension	8.4	8.93	–0.53	–	n.s.	8.81	8.94	–0.13	n.s.
Abstract	4.73	5.87	–1.13	–	n.s.	6.56	6.25	+0.31	n.s.
Perception	8.40	9.0	–0.60	–	n.s.	10.63	10.81	–0.19	n.s.

n.s. = $P > 0.01$.

were >50 years old and two had cognitive impairment. In four families there was only one member affected with cognitive impairment, and in each case that member was >50 years old. Eight members with normal cognitive function were <50 years old. In seven families there was no evidence of cognitive impairment, seven members were <50 years old, and five members were >50 years old.

Discussion

The aim of this study was to determine if cognitive impairment occurred more frequently in family members with pure AD-HSP when compared with normal control subjects matched for age, sex and years in education. Compared with the control group, affected members were shown to have significant impairment on CAMCOG total score and subsets of memory, language expression and comprehension (Table 1). When the affected and control groups were divided according to their age at examination (i.e. <50 years or ⩾50 years), there remained a significant difference between the affected and control groups for cognitive function in the older age group but there was no difference between the younger groups (<50 years old). These findings would suggest that late-onset cognitive impairment is a feature of pure HSP which, although usually mild and asymptomatic, may occasionally become clinically evident.

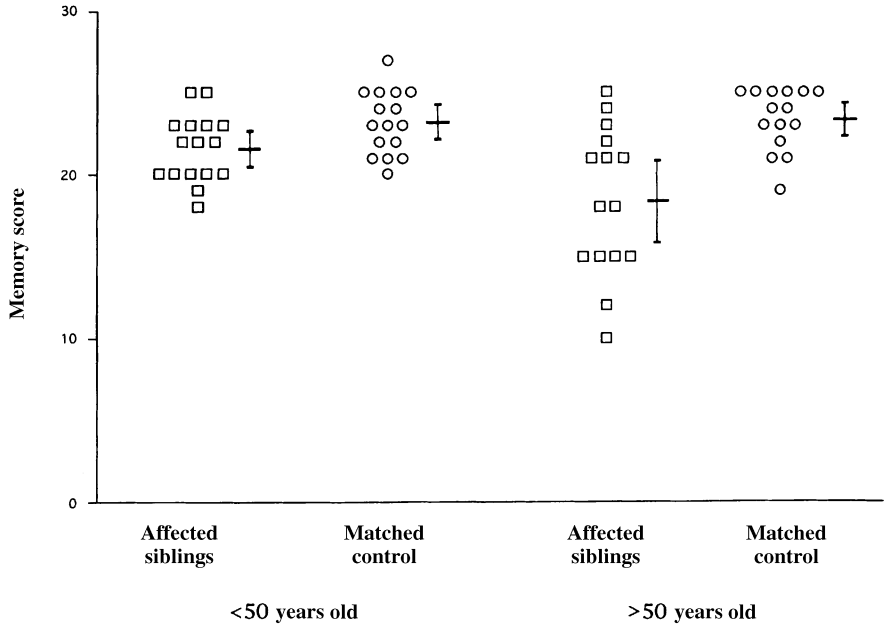

Fig. 2 A scattergram showing memory CAMCOG subset scores for affected AD-HSP members and matched control subjects grouped for age (with mean and 95% confidence interval bars shown to the right of each set of data).

Table 3 *Mean total CAMCOG and subset scores for unaffected HSP siblings and matched controls*

	Unaffected siblings (n = 20)	Matched controls (n = 20)	Difference	95% confidence	P-value
Mean age (years)	48.55	49.10	–0.55	–	n.s.
CAMCOG total score	93.7	97.9	–4.20	–7.72 to –0.68	0.0249
CAMCOG subsets					
Memory	22.70	23.65	–0.95	–	n.s.
Language expression	17.90	19.10	–1.20	–2.00 to –0.40	0.0086
Calculation	1.95	1.95	0.00	–	n.s.
Orientation	9.85	10.00	–0.15	–	n.s.
Attention	6.20	6.10	+0.10	–	n.s.
Praxis	10.9	11.50	–0.60	–	n.s.
Language comprehension	8.70	8.95	–0.25	–	n.s.
Abstract	5.70	6.35	–0.65	–	n.s.
Perception	9.85	10.30	–0.54	–	n.s.

n.s. = $P > 0.01$.

Although the only significant difference between the unaffected siblings and their matched control subjects was in language expression, there was evidence of an age-related decline in the total CAMCOG score in unaffected siblings of patients with AD-HSP (Table 4). There is evidence from haplotype studies that penetrance of the gene for HSP is incomplete, and we suspect that cognitive impairment may be a manifestation of the genotype without evidence of a spastic paraparesis (P. Byrne, S. Webb, F. McSweeney, T. Burke, M. Hutchinson and N. Parfrey, personal communication).

In an earlier study of a large family with pure AD-HSP and late-onset cognitive impairment we identified 13 other families reported with HSP and dementia (Webb *et al*., 1996). These 14 families showed considerable heterogeneity; 11 had autosomal recessive inheritance and three autosomal dominant inheritance. The majority of pedigrees were complicated with other clinical features including ataxia, dysarthria, athetosis, macular pigmentation and optic atrophy. Only four families had HSP and dementia alone, these included two autosomal recessive and two autosomal dominant pedigrees (Rhein, 1916; Arjundas *et al*., 1971; Webb *et al*., 1996; Lizcano-Gil *et al*., 1997). A variant of Gerstmann–Sträussler–Scheinker disease, described in four unrelated Japanese families, and characterized by dementia, spastic paraparesis, ataxia and dysarthria has been linked to a missense mutation of the PrP (prion protein) gene on chromosome 20. Spastic paraparesis and dementia may be the only clinical features of this mutation (Kitamoto *et al*., 1993).

Table 4 *Mean total CAMCOG and subset scores for unaffected HSP siblings and matched controls grouped for age*

	Group A (>50 years old at examination)				Group B (<50 years old at examination)			
	Unaffected siblings (n = 11)	Matched controls (n = 11)	Difference	P-value	Unaffected siblings (n = 9)	Matched controls (n = 9)	Difference	P-value
Mean age (years)	63.18	62.45	+0.73	n.s.	30.97	32.78	–2.11	n.s.
CAMCOG total scores	89.82	96.36	–6.55	n.s.	98.44	99.78	–1.33	n.s.
CAMCOG subsets								
Memory	22.18	23.73	–1.55	n.s.	23.33	23.56	–0.22	n.s.
Language expression	17.18	18.73	–1.55	n.s.	18.78	19.56	–0.78	n.s.
Calculation	1.91	1.91	0.00	n.s.	2.00	2.00	0.0	n.s.
Orientation	9.73	10.0	–0.27	n.s.	10.00	10.00	0.0	n.s.
Attention	6.09	6.00	+0.09	n.s.	6.33	6.22	+0.11	n.s.
Praxis	10.27	11.27	–1.0	n.s.	11.67	11.78	–0.11	n.s.
Language comprehension	8.46	8.91	–0.45	n.s.	9.00	9.00	0.0	n.s.
Abstract	4.91	6.00	–1.09	n.s.	6.67	6.78	–0.11	n.s.
Perception	9.09	9.82	–0.73	n.s.	10.78	10.89	–0.11	n.s.

n.s. = $P > 0.01$.

There are only 13 neuropathological case reports of pure HSP in the literature. Most describe a degenerative process confined to the spinal cord and brainstem. In only two reports was there associated degeneration of the cerebellum and basal ganglia, and in both of these, the changes were clinically silent (Schwarz, 1952; Schwarz and Liu, 1956; Bruyn and Schelten, 1995). The absence of pathological evidence to support the presence of late-onset cognitive impairment in pure AD-HSP may have several explanations. The presence of cognitive impairment in pure AD-HSP occurs after the age of 50 years and the pathological changes associated with this may be absent if death occurred at an earlier age. Because of the predominant motor symptoms of HSP and the perceived lack of cognitive impairment, neuropathological examination may have concentrated on the motor pathways and ignored structures involved in cognition. Lastly, in families with pure AD-HSP there appears to be inter- and intra-familial variation in the expression of late-onset cognitive impairment.

It is perhaps not surprising that we have detected cognitive impairment in AD-HSP; other motor system degenerations including Parkinson's disease, motor neuron disease, spino-cerebellar degeneration and progressive supranuclear palsy are recognised as being complicated by neuropsychological disorder (Cumming, 1986; Neary *et al*., 1990). More extensive neuropsychological studies are required to elucidate the pattern of cognitive impairment in HSP, longitudinal studies are needed to determine the frequency of cognitive impairment within and between families, studies of genotype–phenotype correlation should consider cognitive function in families with 'pure' HSP and neuropathological material from older patients are needed to clarify the underlying pathology.

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