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Neuropsychological profile in myotonic dystrophy

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Summary. Twenty patients with myotonic dystrophy underwent neuropsychological evaluation. Performances were analysed with respect to general cognitive profile, family patterns of cognitive impairment, relation with sex, age, extent of muscular involvement, and sex of affected parent. Results showed severe intellectual deficit in 50% of patients and selective impairment of visuo-spatial and constructional functions. Female patients showed significantly worse global intellectual status than males. No difference in intellectual level was observed in patients with respect to age, extent of muscular involvement and sex of affected parent. No family pattern of cognitive impairment could be identified. Our results show that an extensive neuropsychological battery can reveal the existence of selective mental impairment. It may provide further data on cognitive impairment onset, progression and relation to muscular involvement.

Key words: Myotonic dystrophy – Neuropsychology – Intellectual impairment – Visuo-spatial functions – Constructional functions

Introduction

Intellectual impairment is a well-known feature of myotonic dystrophy (MyD), and is estimated to occur in 24–66% of cases [8, 9, 27, 30, 43]; it seems to be more severe and frequent in the congenital form of the disease [20, 23]. Studies employing formal neuropsychological tests to evaluate the cognitive status of MyD patients are rare and have sometimes yielded conflicting results [4, 24].

Intellectual deficits may precede the appearance of muscular involvement [19], but their mode of onset has never been clarified [21, 38]. A high percentage of cases with mental retardation seem to have been affected since early infancy or childhood [15, 22, 44]. The severity of neuropsychological impairment may be unrelated to the extent of motor disability [26]; its mode of evolution is unclear, although progressive cognitive deterioration has never been documented with formal testing [4, 26].

Even though neuropsychological involvement in MyD has been recently correlated with magnetic resonance imaging (MRI) features [24] evaluations of the functional expression of cerebral lesions detected pathologically and neuroradiologically are not wholly satisfactory [24, 34, 40].

Intellectual impairment in family groups has never been investigated exhaustively to assess whether differences in intellectual involvement are genetically determined.

To define the cognitive profile in MyD, we have administered an extensive neuropsychological battery to a group of patients and have attempted to identify selective functional involvement and its mode of occurrence in family groups. Several functions were investigated, since available data still do not allow the choice of more restricted cognitive areas of investigation.

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Patients and methods

The subjects were 20 patients from ten unrelated families, identified through the files of our Clinic and those of the EMG service for outpatients. Only one was known to have the congenital form of MyD. The clinical and biographical features of patients are reported in Table 1. The group consisted of 10 males and 10 females, with a mean age of 38.8 years (range 20–57) and a mean education of 7.1 years (range 2–13). Disease transmission was maternal in 9 cases, paternal in 7, and of unknown origin in 4 cases. Disease duration could not be ascertained owing to the unreliability of patients and relatives in this respect. In all cases MyD has been diagnosed by a neurologist on the basis of concurrent findings of muscular dystrophy affecting the face and distal segments of the limbs, and EMG patterns of typical myotonic discharges. Muscle involvement was evaluated on a qualitative scale, based on the number of segments involved and the severity of impairment. The deficit was rated "absent" (no clinically evident weakness or atrophy in any segment), "mild" (detectable motor impairment, hindering only the most complex motor activities, i.e. sports), "moderate" (motor impairment slightly interfering with everyday activities), "severe" (marked motor impairment, heavily interfering with everyday activities), and "very severe" (diffuse motor impairment, making the

Table 1. Patients' clinical and biographic features

Patient no.	Family	Sex	Age (years)	Education	Affected parent	Muscular impairment
1	I	F	38	5	Mother	Moderate
2	I	F	34	7	Mother	Moderate
3	I	F	39	4	Mother	Mild
4	II	F	20	8	Mother	Moderate
5	II	M	25	8	Mother	Mild
6	II	F	35	8	Mother	Mild
7	II	M	29	5	Mother	Mild
8	II	F	57	2	Mother	Moderate
9	III	M	25	8	Father	Mild
10	III	M	27	11	Father	Moderate
11	III	M	55	5	Father	Mild
12	IV	F	45	8	?	Severe
13	IV	M	49	11	?	Severe
14	V	M	21	10	Father	Moderate
15	V	M	51	8	Father	Severe
16	VI	M	28	8	?	Severe
17	VII	F	52	4	Father	Moderate
18	VIII	F	50	4	Father	Severe
19	IX	M	47	13	Mother	Severe
20	X	F	49	5	?	Moderate

patient totally dependent). There were 6 patients in the "mild" category, 8 in the "moderate", and 6 in the "severe" one. No patient suffered from diseases unrelated to MyD and capable of producing brain lesions or interfering with test performance, such as symptomatic cerebrovascular disease, previous severe head trauma, thyroid diseases, severe uncorrected disturbances of sight or severe psychiatric diseases.

The control group consisted of 20 healthy subjects, 10 males and 10 females, with a mean age of 39.2 years (range 25–59) and a mean education of 8.05 years (range 3–13), not significantly different from those of the Steinert group (age: $t = 0.1$; NS; education: $t = 1.1$; NS).

Informed consent was obtained from all subjects.

Procedure

The neuropsychological battery included:

1. *Raven's Coloured Progressive Matrices* (RCPM). This test is administered to assess global intellectual abilities. The highest attainable score is 36 [37].

2. *Wechsler Memory Scale* (WMS), with the memory quotient (MQ) used for statistical analysis [47]. The score of the paired associate learning (PAL) subtest of the WMS was considered separately as a measure of learning ability. The highest score in this subtest is 21.

3. *Spatial Span* with Corsi's blocks (SS) tests short-term spatial memory. The score is the maximum number of blocks of which the patient can correctly reproduce two different sequences presented by the examiner. In our battery a maximum of three different sequences of equal length were shown by the examiner [32].

4. *Token Test* (TT), the shortened 36-item version. This is a test of verbal comprehension and is very sensitive to aphasic disturbances [14]. The highest total score is 36.

5. *Copy of Drawings* (CD). This is a task of visuo-spatial and constructional abilities. Patients were asked to copy six drawings, representing a square, a triangle, a circle, a three-dimensional cube, a four-pointed star, and a house in perspective. Scores ranged from 0 to 2 for the first three drawings, and from 0 to 4 for the others, according to quality of reproduction. The total score is the sum of single scores. The highest score is 18. An attempt was made not to count errors due to motor disability.

6. *Kohs' Blocks* (KB). This is a task of visuo-spatial and constructional abilities [18]. The full 17-figure version was employed in this study. Performance was stopped after five consecutive failures. The score is the sum of the points obtained with each picture. Since the performance of KB involves a motor component, the authors were careful to let the patients have extra time to compensate for pure motor deficits, when this was felt necessary.

7. *Wisconsin Card Sorting Test* (WCST). This is a test of set formation and shifting, which is often poorly performed in the presence of frontal lobe lesions [3]. It was employed with rules similar to those of Milner's for the definition of perseverative errors, and with two decks of cards [31]. The test was interrupted after ten criteria had been found, or after all cards had been used up. Both the number of perseverative errors (WCST Err.) and the number of criteria correctly identified (WCST Crit.) were used as scores.

8. *Verbal Fluency* (VF). This is a test of quick lexical access, very sensitive to frontal lobe lesions [28]. Subjects had to generate as many words beginning with A, F, and S as possible, with 1 min for each letter. The score is the total number of words produced, with the exclusion of proper names (i.e. names of people, cities, etc.).

The whole battery was administered in a single session of about 2 h by one of the two examiners involved in data collection.

Data analysis

For the study of individual cognitive profiles "impaired" was defined as each score falling 2 SD below the mean of controls. The Mann-Whitney U test was used for statistical comparisons of test performances. The Kruskal-Wallis test was employed for multiple group comparisons. Since ten tests were employed, the significance threshold for the single cognitive test was set at the 0.005 level, according to Bonferroni's correction.

Results

The statistical comparisons between the two groups are reported in Table 2. The scores of patients with MyD are reported in Table 3. The values marked with an asterisk are those which fall 2 SD below the means of controls. Patients with MyD scored significantly worse than controls on RCPM, KB and CD. Scores on WCST, TT, MQ,

Table 2. Mean test scores and statistical comparisons between patients and controls (for abbreviations, see text)

Test	Steinert	Controls	*P* Mann-Whitney
RCPM	24.2 ± 7.94	31.2 ± 3.43	$P < 0.005$
WCST Crit.	3.7 ± 3.48	6.8 ± 2.89	NS
WCST Err.	28.4 ± 18.57	13.8 ± 10.21	NS
TT	31.7 ± 3.52	34.1 ± 1.99	NS
MQ	94.4 ± 22.98	101.7 ± 14.37	NS
SS	4.1 ± 0.94	4.4 ± 0.84	NS
PAL	14.2 ± 3.59	14.9 ± 2.96	NS
CD	13.6 ± 3.37	16.8 ± 1.68	$P < 0.005$
KB	27.8 ± 34.14	86.1 ± 34.09	$P < 0.001$
VF	22.5 ± 10.35	35.3 ± 13.10	NS

Table 3. Neuropsychological test scores (asterisk marks the scores falling 2 SD below the means of controls; for abbreviations, see text)

Patient no.	Family	RCPM	WCST Crit	WCST Err.	TT	MQ	SS	PAL	CD	KB	VF
1	I	30	2	33	32	94	4	15	*11	* 17	23
2	I	*21	5	16	34	114	4	17	*12	* 8	39
3	I	*11	* 0	*51	*20	* 66		11.5	* 8	* 0	10
4	II	*12	* 0	*51	*28	* 52	3	11	*13	* 7	11
5	II	31	10	2	31	116	4	18	17	28	28
6	II	29	3	24	33	116	4	15.5	17	38	27
7	II	*19	* 2	27	35	* 68	3	9	*13	* 17	15
8	II	*13	* 0	*51	*30		3		*10	* 6	* 7
9	III	*20	2	20	*29	89	6	17	15	* 2	21
10	III	35	7	6	35	140	4	21	17	116	38
11	III	*21	2	*57	33	81	4	9	*11	* 12	* 8
12	IV	*19	3	*37	33	79	3	11	*12	* 13	39
13	IV	32	2	*49	35	97	6	15	*11	* 8	40
14	V	35	10	3	35	108	5	18.5	18	109	18
15	V	*19	* 1	17	33	101	4	17	*10	* 8	21
16	VI	33	9	11	34	108	5	16	18	31	28
17	VII	27	2	*51	31	86	4	15.5	17	18	20
18	VIII	*16	3	29	31	83	5	12.5	* 9	* 11	17
19	IX	31	10	3		86	4	13	16	24	21
20	X	30	2	31	32	87	3	* 8	18	83	20

Table 4. Relationship of Raven's Coloured Progressive Matrices scores to sex of patients, sex of affected parent, and severity of muscular involvement

Groups	RCPM mean + SD	Mann-Whitney	*P*
Males	27.6 ± 6.91		
vs.		$Z = 2.198$	$P < 0.05$
females	20.8 ± 7.71		
Paternal inheritance	24.7 ± 7.76		
vs.		$Z = 0.636$	NS
maternal inheritance	21.9 ± 8.56		
Muscle involvement			
Mild/moderate/severe*		H = 1.222	NS
Mild	21.8 ± 7.28		
vs		T = 42.5	NS
severe	25.0 ± 7.77		

* Kruskal-Wallis test

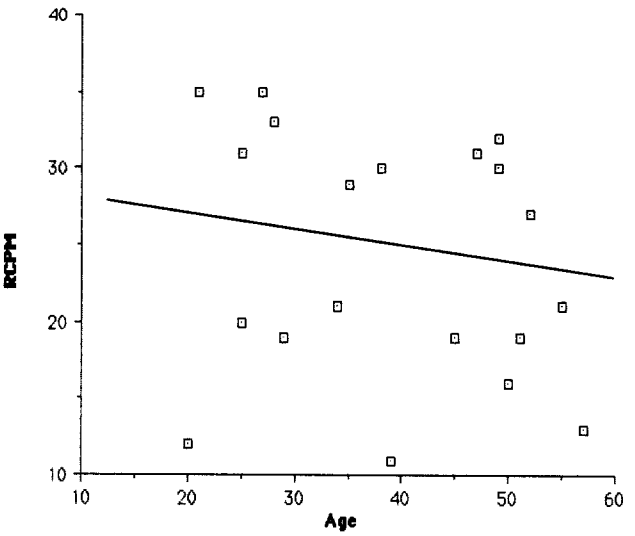

Fig. 1. Raven's Coloured Progressive Matrices score vs age, $r = -0.214$; NS

PAL, SS and VF were not significantly different at the 0.005 level, although differences on WCST, TT and VF were below the 0.05 level (see Table 2).

According to the "impairment" criterion, 10 patients (50%) showed significant global intellectual deficit, as measured by RCPM (Table 3). The highest number of "impaired" scores was on visuo-spatial and constructional tests (KB, 12 patients, 60%; CD, 11 patients, 55%), followed by "frontal" tests (WCST Err., 7 patients, 35%; WCST Crit., 4 patients, 20%), language tests (TT, 4 patients, 20%) and memory tests (MQ, 3 patients, 15%; PAL, 1 patient, 5%) (Table 3).

As can be seen in Table 3 (cases 1 and 13) performance on KB and CD could be "impaired" even when global intellectual level was within the range of normals. On the other hand, "impaired" scores on TT and MQ were often associated with the lowest scores on RCPM and many "impaired" performances on other tests.

In an attempt to check for a possible role of motor disability in the performance of KB and CD, we compared the scores of the patients with a "mild" muscular deficit with those of the patients with a "severe" deficit, by means of the Mann-Whitney U test, without significant differences in either case (KB: T = 39, NS; CD: T = 36.5, NS).

Table 4 shows the comparisons between groups with different degrees of motor impairment. Severity of global

intellectual impairment, as measured by RCPM, was unrelated to extent of muscular involvement ($H = 1.222$, NS), nor was the difference between mildly and severely affected patients significant ($T = 42.5$, NS).

RCPM scores were not correlated with the patients ages ($r = -0.214$, NS) (Fig. 1), and there was no difference between patients with paternal versus maternal inheritance of the disease ($Z = 0.636$, NS) (Table 4).

Female patients scored significantly worse than males on RCPM ($Z = 2.198$; $P < 0.05$) (Table 4); this result may have been influenced by their significantly lower level of education ($Z = 2.596$; $P < 0.01$).

In order to identify possible genetic differences in patterns of cognitive impairment, neuropsychological test scores were analysed both within and between families with three or more affected members. Families I, II and III had the necessary number of patients. Multiple group comparisons showed no significant differences between the three families on any test. As shown in Table 3, no constant cognitive pattern could be identified within families.

Discussion

The present study revealed a fairly constant neuropsychological profile among MyD patients, which appears to be usually characterized by severe impairment of visuo-spatial and constructional abilities, often associated with difficulties in "frontal lobe" tasks and, in the more severe cases, with alterations of language and memory. The fact that severe visuo-spatial deficits were found even in cases without any obvious global intellectual impairment suggests that visuo-spatial involvement should be sought when investigating milder forms of the disease, or when results on other tests are inconclusive.

More severe impairment of spatial orientation and manipulation, as compared with verbal abilities, was observed in MyD by Bird et al. [4] using the WAIS. A dissociation between visuo-spatial and verbal functions was also reported by Huber et al. [24]. Penez [36] and Walker et al. [45] also observed that visuo-spatial and visuo-motor functions are more frequently and characteristically impaired in this disease. Only Woodward et al. [48] apparently found no particular impairment pattern. These features are not common to other muscular dystrophies, since a lower verbal than performance WAIS IQ has been found in Becker and facioscapulohumeral dystrophies [25].

The reasons for such relatively selective cognitive involvement in MyD are not clear. It has been attributed to the thalamic lesions frequently observed [11, 12, 34]. Brumback and Wilson [5], on the other hand, have stressed the importance of right hemisphere involvement in the pathogenesis of both cognitive and psychiatric disturbances in these patients. However, the morphological features and the location of the lesions in the thalamus do not seem to be specific for MyD [35]. Furthermore, similar lesions have been shown to involve diffusely also the whole cerebral cortex in this disease [33], and bilateral white matter abnormalities have been detected using MRI [16]. The extent of this leucoencephalopathy appears to correlate with the severity of intellectual deficit and it does not selectively affect the right hemisphere [24].

The pathogenetic mechanisms of intellectual deficits may, however, be multiple. Disordered brain development [40], hypoxia at birth [7, 15,] and normotensive hydrocephalus [10, 38] have all been associated with cognitive impairment in MyD. More complete neuroradiological and neuropathological data are needed to settle this issue.

The cognitive profile in MyD has been considered suggestive of "subcortical" dementia [1, 13], and this term has in fact been employed by Kissel et al. [26] to characterize the performance of their patients. The term, however, should be used with caution, since it implies that cognitive deficits are acquired in adult age.

While previous studies employed the WAIS to measure intellectual level, RCPM were preferred in this investigation to exclude any motor bias in the evaluation of global performances. In fact, the performance of RCPM requires no motor activity and this test, owing to its sensitivity to brain damage [2, 41], could prove useful for the detection of cognitive impairment in the milder forms of the disease.

Significant intellectual impairment was revealed in at least 50% of our patients. This percentage is higher than might be expected, since this series included only one known congenital case of MyD, and according to Harper [23], the majority of retarded patients belong to this category. This finding may reflect the need for more complete data on the early psychomotor development when assessing the cognitive status of patients with Steinert's disease.

Studies on myotonic dystrophy are often influenced by a recruitment bias, since only the more affected patients tend to come medical attention [29]. Bird et al. [4], for instance, found lower WAIS IQs in probands than in other affected members of their families. Since we did not investigate systematically all members of the patients' families, this bias cannot be fully excluded.

The lack of correspondence observed in this research between severity of intellectual impairment and severity of muscular involvement is in line with the majority of recent studies [26, 48], with the exception of that of Bird et al. [4]. In up to 11% of cases intellectual deficit may be detected without obvious muscular impairment [39]. The awareness of the lack of such a correlation should prompt careful investigations of cognitive functions in all patients suspected of having the disease.

In the present series patients with mild muscular deficit often scored worse on RCPM than subjects with severe impairment, although not significantly, in line with the results of Bundey [6], who considers this a clue to the existence of a genetic heterogeneity of MyD. In our study the difference is so small that no hypothesis seems warranted in this regard.

The lack of correlation between the age of the patients and intellectual deficit may be taken as an indirect suggestion that cognitive impairment is scarcely progressive, if at all. This finding is in accordance with the few

formal evaluations of the progression of mental retardation carried out so far [4, 21].

Global intellectual impairment was not significantly different between patients with paternal and patients with maternal inheritance of the disease, although a trend towards lower RCPM scores could be observed in patients with an affected mother. A correlation between maternal inheritance and severity of intellectual deficits was suggested by Bird et al. [4] and was considered significant by Huber et al. [24]. These findings may in part be due to the frequency of congenital cases of MyD among the offspring of affected mothers, since congenital cases are known to be more frequently and severely mentally retarded [15, 23]. It could also be hypothesized that CNS lesions may be produced in intrauterine life by the same factors responsible for neonatal symptoms [42], even in those patients who do not show the characteristic syndrome at birth. Genetic heterogeneity seems to be a less likely explanation, as shown by the data of Glanz and Fraser [17].

The finding of a significantly lower intellectual level in females that in males with MyD is in accordance with the data of Bird et al. [4]. This difference is not sufficiently explained by assuming genetic heterogeneity, since no familial pattern in the distribution of cognitive deficits was observed in this study. No difference existed between males and females of the control group ($Z = 0.307$, NS). Perhaps the same factors causing the congenital form of MyD among the offspring of affected females are also active on the mother's brain from an early age, compounding the pathogenetic mechanisms which also operate in male patients. Our results may also have been influenced by the significantly lower level of education of female patients.

Regardless of the pathogenetic mechanism of cognitive impairment, no evidence was found that either the global intellectual performance or the cognitive profile have a characteristic family distribution.

Three aspects of the cognitive involvement in MyD require further clarification: the age of onset of mental decline, its eventual progression, and its relationship to muscular symptoms. Except for congenital MyD, clinical onset is often uncertain. A clear demonstration of progression of intellectual deficits has never been obtained with formal tests [4, 21, 46]. Also, available neuropathological studies provide no unequivocal elements with regard to disease onset and progression, since differential patterns of the congenital and acquired involvement of the CNS have not been identified with certainty [12, 40, 49]. It seems justified, therefore, to wonder about the percentage of patients who actually acquire intellectual deficits in adult age. As for the third aspect, a correlation between severity of intellectual impairment and muscle involvement seems unlikely, even though it would be interesting to ascertain whether their rates of progression are correlated.

The answers to these problems also have practical relevance, with regard to the formulation of a prognosis in newly diagnosed cases that appear to have no cognitive deficits. Our results suggest that the systematic and repeated evaluation of MyD patients with an extensive neuropsychological battery stressing visuo-spatial and constructional abilities may prove useful to this end.

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