Correlations between Neuropsychological and Neuroimaging Data in Myotonic Dystrophy

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Abstract

Twentyfour patients with Mytonic Dystrophy (MD) (mean age 42.8 ± 13.4 yrs; range 21-59) of moderate degree underwent neuropsychological and neuroradiological (Magnetic Resonance Imaging - MRI) evaluation.The results show the presence of cognitive impairment, in particular involving visuo-constructive and attentional skills, not related to sex, age at onset or disease duration; subjects with maternal inheritance presented however a poorer performance in respect to those with paternal inheritance. On MRI scans subcortical white matter hyperintense lesions (WMHL) have been found in 18/24 cases, which did not correlated with both the clinical variables and the cognitive impairment. These lesions, in particular those located in the temporal lobes (6/24 subjects), seem to be characteristic of the disease and are probably scarcely progressive.

Key words: Myotonic Dystrophy, neuropsychological evaluation, Magnetic Resonance Imaging.

Basic Appl. Myol. 7(5): 333-337 , 1997

Myotonic Dystrophy (MD) is a dominant inherited disease, which is characterized by muscle atrophy, motor impairment and multisystemic involvement. Mental retardation and cognitive impairment have been reported in MD patients till from the earliest observations [3, 4, 7, 13, 15, 16, 17]. The intellectual disturbances have been correlated with sex, age at onset and mode of inheritance. There is a general agreement that affected females have a poorer cognitive performance than males as well as patients with maternal in respect to subjects with paternal inheritance; these data suggest that inheritance pattern is one important moderating variable in determining the impact of the MD gene on cognitive functioning [4, 6, 11, 14, 17]. Despite the difficulty of identify a specific neuropsychological profile, MD patients seem to be more impaired on visuospatial and constructional tasks and on measures of information-processing speed [4, 13, 19]. Severely impaired subjects have been reported to have psychometric findings compatible with subcortical dementia [8]. Moreover, while motor deficits generally progress with aging, cognitive impairment is relatively stable [3, 12, 17].

As to neuroradiological investigations, the data obtained from CT examinations do not give substantial informations. Indeed, CT scan is able to detect only the presence of atrophy and eventual skull abnormalities [2]. On the contrary, in the recent years studies with Magnetic Resonance Imaging (MRI), which is a highly sensitive instrument for examining *in vivo* brain abnormalities, have been developed. Typical white matter hyperintense lesions (WMHL) have been found, which are similar to those abnormalities revealed by MRI in older individuals [9]; there is a general agreement that these lesions are not related to clinical variables, in particular age, disease duration and motor impairment, but their nature is not yet completely clear. Huber et al. [11] observed that WMHL seem to be more common in patients with severe cognitive dysfunction. Significant differences have been reported between patients with mild WMHL and those with severe WMHL in regard to some measures of frontal functioning [1]; these authors conclude that WMHL could be the cause of cognitive impairment in MD. On the contrary, other studied failed to find significant correlations with cognitive impairment [5, 17]. Anyway, these lesions appear to be an almost constant feature in MD; some of them, typically located in the temporal poles [5, 11], seem to be characteristic of the disease, probably are scarcely progressive and have not been found in other pathological conditions. Damian et al [8] emphasize the significance of both the type of distribution and the total extent of WMHL. WMHL immediately subjacent to cortex in fact are likely to cause significant cognitive deficits, while periventricular demyelination may cause no major dysfunction. These data might be related to disturbance of information-processing and efficiency of transfer from primary to associative cortical areas.

Aim of the present study, which is the continuation of a previous research [17], was to identify correlations between neuropsychological and neuroradiological data.

Table I. Neuropsychological results (M ± SD) of MDpatients and controls.

	MD n. 24	Controls n. 24	p < *
WAIS full-scale I.Q.	87.9 ± 18.2	101.7 ± 18.5	0.05
verbal I.Q.	91.3 ±16.7	103.8 ±15.8	0.05
perfor. I.Q.	84.4 ±19.8	99.6 ± 17.1	0.01
Number cancellation	48.5 ± 5.6	52.3 ± 6.1	0.05
Trail Making Test			
part A	51.9 ±14.0	44.0 ± 12.2	0.05
part B	103.4 ± 23.2	78.5 ± 21.9	0.01
Verbal Fluency (FAS)	24.1 ± 4.2	28.1 ± 6.8	0.05
AVLT			
short-term	37.9 ± 6.7	41.7±6.0	0.05
long-term	7.2 ± 2.6	8.5 + 3.1	n.s.
R-O figure			
copy	27.9 ± 5.2	32.2 + 3.5	**0.01**
retention %	62.1 ± 13.4	72.1 ± 14.2	0.05
PM 47	24.6 ±4.0	27.1 ±4.2	0.05

* Anova one-way

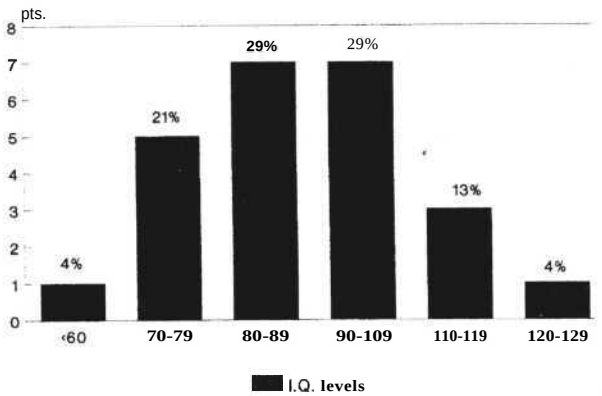

Figure 1. Distribution of WAIS scores in Myotonic Distrophy.

Subjects

Twenty-four patients with MD referring to the Neurological Clinic of the University of Pavia were studied. The mean age was 42.8 ± 13.4 yrs (range 21-59), the mean educational level was 7.5 ± 3.3 yrs (range 4-13). The diagnosis was established on the basis of the clinical picture and of EMG, with or without clinical evidence of other typical organ involvement [10]. The males were 9 (mean age 43.5 ± 14.3 yrs, mean educational level 7.5 ± 3.1), the females were 15 (mean age 42.1 ± 11.9, mean educational level 7.1 ± 3.6). The mean illness duration and the mean age at onset were 12.6 + 8.5 yrs (range 2-30) and 29.7 ± 14.5 yrs (range 4-55). In 10 cases the inheritance of the gene was on paternal side, in 8 on maternal side, in 6 unknown. In only 1 patient the disease has begun in the infancy at the age of 4 yrs.

A clinical disability scale ranging from 0 (mild myotonia) to 7 (inability of walking) was applied in order to subdivide the patients into different handicap groups. Fifteen subjects obtained a score between 1 and 3 (complete autonomy), 9 between 4 and 6. No patient was confined to wheelchair.

None of the subjecs had history of sleep apnea or respiratory insufficiency.

No patient was taking any medication at the time of testing. None of the subjects had history of head trauma, alcoholism or other neurological illness capable to interfere with cognitive functioning.

Twenty-four normal controls, matched for age, sex and educational levels, were also studied. None of them had previous head trauma or other neurological disturbances, or was taking drugs or other substances active on CNS.

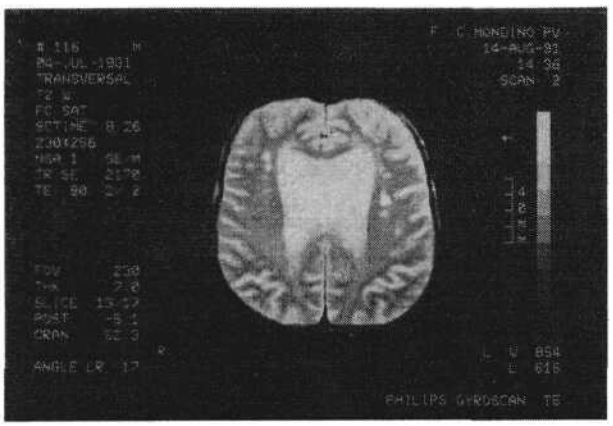

Figure 2. Diffuse supratentorial atrophy in MD patient.

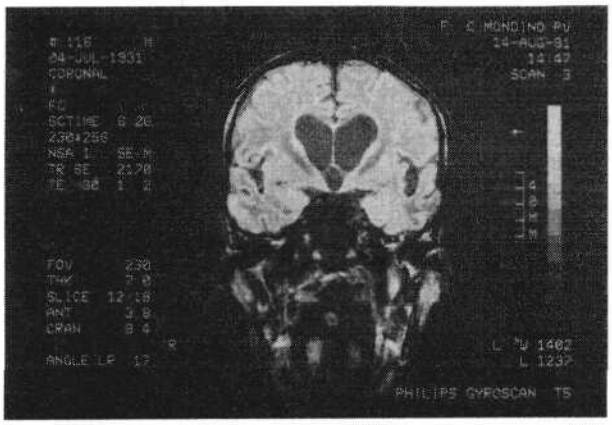

Figure 3. WMHL situated in the periventricular regions.

Table II, Cognitive performance (M ± SD) ofpatients with paternal (pMD) and with maternal inheritance (mMD).

	pMD (n. 10)	n (%) < cut-off	mMD (n. 8)	n (%) < cut-off
WAIS full-scale I.Q.	90.6 ± 14.3	2 (20)	83.4+ 10.7	3 (37)
verbal I.Q.	94.5 ± 13.1	1 (10)	85.9 ±10.9	2 (25)
perfor. I.Q.	86.9 ±12.5	3 (30)	81.9 ± 11.7	3 (37)
Number cancellation	49.2 ± 4.5	1 (10)	45.2 ± 6.0	1 (12)
Trail Making Test				
part A	49.8 ±13.4	3 (30)	52.2 ± 12.9	3 (37)
part B	97.4 ±19.3	4 (40)	109.3 ± 22.1	4 (50)
Verbal Fluency (FAS)	24.7 ± 3.8	1 (10)	23.6 ±3.5	1 (12)
AVLT				
short-term	38.6 ±5.7	1 (10)	36.1 ± 6.0	2 (25)
long-term	7.3 ±2.2	1 (10)	7.1 ±2.5	1 (12)
R-O figure				
copy	28.3 ±4.6	2 (20)	27.2 ±4.9	2 (25)
retention %	64.3 ± 12	1 (10)	61.1 ± 14	1 (12)
PM 47	24.8 ±3.9	2 (20)	22.7 ±3.9	3 (37)

Table III. Neuroradiological findings in MD patients and controls.

	MD (n. 24)	Controls (n.20)	
ATROPHY	12 (50%)	3 (15%)	$p < 0.05$*
WMHL	18 (75%)	3 (15%)	$p < 0.01$*

*χ^2-test

Table IV. Neuroradiological findings in MD patients.

ATROPHY (12/24)			
Degree	mild	moderate	marked
	5	5	2
Localization	diffuse	deep	superf.
	6	4	2
WMHL (18/24)			
Number	1-4	5-10	> 10
	7	6	5
Size	< 10 mm	10-25	> 25
	8	7	3

Methods

Neuropsychological investigation

Patients and controls underwent the following neuropsychological tests, aimed in particular to assess visuo-constructive and attentional functions:

- Wechsler Adult Intelligence scale (WAIS) to evaluate Intelligence Quotient (QI) [21];
- Number Cancellation, to assess selective attention [18];
- Trail Making Test, A and B, which measures divided attention and psychomotor functioning [12];
- Verbal fluency, to evaluate lessical processes; the test requires the subject to produce as many words as he can generate beginning with the following letters: f, a, s [12];
- Rey's 15 words (AVLT) to evaluate short- and long-term verbal memory [12];
- Rey-Osterrieth Complex Figure (R-O) (copy and 3-minute recall), to evaluate visuo-constructive and memory functions. The recall score was calculated as percentage retention [12];
- Raven's Coloured Matrices (PM 47) for the evaluation of non verbal intelligence [12].

Neuroradiological investigation

A RM Philips Gyroscan unit, operating at a field strenght of 0.5 T was used. Sagittal section 7 mm thick, (TR = 522; TW = 25) with "Fast-Field Echo" (FFE) technique was employed, in order to obtain T1 weighted images; then coronal and axial sections (7 mm thick), with Spin Echo (SE) technique was performed (TR = 2500; TE = 40/100).

Two aspects in particular were evaluated: cerebral atrophy and focal white matter lesions. Cerebral atrophy was rated on a 0 to 3 scale (0 = absent; 1 = mild; 2 = moderate; 3 = marked), in relation to age. The WMHL on T2 weighted images were rated according to number (1-4; 5-10; >10) and size (< 10 mm; 10-25 mm; > 25 mm).

Twenty normal subjects, aged between 20 and 60 yrs, have been taken as a control group.

Statistical analysis

The statistical analysis of the results was employed by using ANOVA 1 way, linear regression and χ^2-test.

Results

The results of the neuropsychological evaluation are summarized in table I. MD patients obtained a poorer performance in respect to normal controls on all neuropsychological measures, except AVLT long-term. The fig. 1 shows the distribution of WAIS scores: our patients performed at a low-average level. Only 1 subject obtained a IQ below 60 and higher than 110, respectively. No correlation was found with sex, age at onset, duration of the disease and degree of motor impairment. As to the mode of inheritance, because of the small number of cases, a statistical evaluation could not be applied; however, the percentage of patients who scored below the cut-off (i.e. 2 standard deviations of the means of the control group) was higher in the group with maternal inheritance than in the group with paternal inheritance (table II).

Tables III shows the results of the neuroradiological evaluation. The presence of atrophy and WMHL was significantly higher in MD patients than in controls ($p < 0.05$ and $p < 0.01$, respectively). The qualitative analysis of the neuroradiological data shows (table IV) the presence in most cases of atrophy of mild-moderate degree, mainly diffuse or deep (fig. 2); in no case infratentorial atrophy was found. WMHL were present mainly in the periventricular regions; in some cases these lesions are widely represented (fig. 3). No correlation was found between neuroradiological data and clinical and cognitive variables. In 6 patients (mean age 29.9 ± 9.2 yrs; mean illness duration 6.5 ± 3.2 yrs; mean age at onset 23.1 ± 7.5 yrs) typical WMHL in the temporal lobes have been reported; these cases, however, did not show peculiar clinical or cognitive characteristics.

Conclusions

The neuropsychological results of this study indicate that IQ of our MD patients is at a low-average level. These data are in agreement with the literature and with our previous study [17]; in that research, however, the better performance was probably related to the higher cultural level. As far as the other cognitive measures are concerned, our patients were impaired on all the tests administered, except for long-term verbal memory. On the other hand, the neuropsychological evaluation we employed was aimed to assess in particular visuo-constructive and attentional functions; these data therefore seem to confirm a predominant impairment of these abilities in MD [4, 13, 19].

The neuroradiological findings confirm the presence of diffuse WMHL; in agreement with our previous research [17], in which however only a small number of patients underwent MRI investigation, these lesions do not seem to correlate with clinical and cognitive variables. WMHL are similar to those found in other pathological conditions, such as multiple sclerosis, or in the elderly, but in MD they may be present, in particular those located in the temporal lobes, also in young people with a short illness duration, and are not related to other possible concomitant diseases, cardiovascular in particular, or ventilatory insufficiency. Therefore, these findings, though their nature is still unclear, may be considered characteristic of MD.

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