Neurology®

Reduced cerebral blood flow and impaired visual–spatial function in proximal myotonic myopathy

G. Meola, V. Sansone, D. Perani, et al.

Neurology 1999;53;1042
DOI 10.1212/WNL.53.5.1042

Reduced cerebral blood flow and impaired visual–spatial function in proximal myotonic myopathy

G. Meola, MD; V. Sansone, MD; D. Perani, MD; A. Colleluori, MD; S. Cappa, MD; M. Cotelli, PhD; F. Fazio, MD; C.A. Thornton, MD; and R.T. Moxley, MD

Article abstract—*Objective:* To compare brain involvement in myotonic dystrophy (DM) with that of proximal myotonic myopathy (PROMM). *Background:* PROMM is a multisystem disease with many features in common with DM. *Methods:* Twenty patients with DM ($CTG_{[500-700]}$), 20 patients with PROMM, and 20 normal control subjects were studied. Neuropsychological testing was performed in 12 patients with PROMM and in 18 patients with DM; brain MRI was performed in 17 of 20 PROMM patients and 15 of 20 DM patients. Ten patients with PROMM and 11 patients with DM were subjected to $H_2{}^{15}O$ PET. *Results:* Two-thirds of the patients with PROMM and one-half of those with DM were impaired on visual–spatial recall, whereas one-third of the patients with PROMM and less than half of those with DM showed an impairment in visual–spatial construction. Brain MRI was normal, or showed only nonspecific white matter abnormalities in both PROMM and DM patients. PET studies in PROMM patients showed a bilateral decrease in regional cerebral blood flow (rCBF) of the orbitofrontal and medial frontal cortex, whereas DM patients had more widespread hypoperfusion that extended to the dorsolateral frontal cortex and subcortical regions. *Conclusions:* Impaired visual–spatial function may be present in proximal myotonic myopathy. This correlates best with a reduction in regional cerebral blood flow observed in $H_2{}^{15}O$ PET brain scans rather than with specific structural abnormalities observed on brain MRI.
Key words: Proximal myotonic myopathy—Myotonic dystrophy—PET—MRI—Neuropsychological tests.

NEUROLOGY 1999;53:1042–1050

Proximal myotonic myopathy (PROMM) and myotonic dystrophy (DM) both involve multiple organ systems, including the brain.[1-9] Hypersomnia (10%),[1,3,10] apathy (5%),[3,10] grand mal seizures (5%),[3,10] and mental retardation (5%)[3] have all been noted in PROMM. Hund et al.[10] observed diffuse, confluent lesions in white matter on brain MRI in six patients with PROMM in whom no symptoms or signs of mental disorder were present. Three of six of these patients had strokelike episodes. The changes on MRI resemble those described in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy,[11] and the authors suggested that these abnormalities are a feature of PROMM. In contrast to these findings, Meola et al.[4] reported normal brain MRI findings in four patients with PROMM. Only one patient, a 70-year-old woman with hypertension, had an abnormal MRI, which showed nonspecific white matter lesions.

Common symptoms of mental aberration in DM include apathy, indifference, and lack of motivation even in patients with mild weakness. A suspicious, paranoid, or frankly hostile personality is common. Neuropsychological test results have demonstrated personality disorders,[12] dementia,[13-15] mental retardation,[13-15] and depression[13] in patients with adult-onset DM. Prominent structural changes in the brain are infrequent, but some patients with DM have white matter hyperintense lesions in the anterior portions of the temporal lobes.[16,17] Generalized atrophy has also been observed.[14] The relatively few neuropathologic studies available have shown a diffuse loss of myelin in the deep white matter of the brain corresponding to the white matter hyperintense lesions observed on the brain scans.[15,18] Pathologic tau proteins have been found in the hippocampus, the entorhinal cortex, and in most of the temporal areas, and the amount of tau protein was higher in a more severely affected patient.[19] A possible relationship between the decrease of catecholaminergic neurons in the medullary reticular formation and the presence of alveolar hypoventilation has also been suggested.[20]

From the Department of Neurology (Drs. Meola and Sansone) and Institute of Neuroscience and Bioimaging National Research Council (Drs. Perani, Colleluori, and Fazio), H. San Raffaele, University of Milan, Italy; the Neurological Department, University of Brescia, and Instituto di Ricovero E Cura A Carattere Scientifico, S. Giovanni di Dio (Drs. Cappa and Cotelli), Brescia, Italy; and Department of Neurology (Drs. Thornton and Moxley), University of Rochester, NY.

Supported by the University of Milan, Italy, MURST 40% and 60% (G.M.); the National Council of Research, Italy (D.P.); Muscular Dystrophy Association (C.T., R.T.M.); General Clinical Research Center–NIH 5M01RR0044 (C.T., R.T.M.), R03 AG14502-01 (C.T., R.T.M.), and R01 AR44069-01A1 (C.T., R.T.M.); Paul Beeson Physician, Faculty, Scholars in Aging Research Program (C.T.); the Saunders Foundation (C.T., R.T.M.); and the Wayne C. Gorrell Jr. Molecular Biology Laboratory (C.T., R.T.M.).

Presented in part at the 50th annual meeting of the American Academy of Neurology; Minneapolis, MN; April 1998.

Received July 22, 1998. Accepted in final form April 17, 1999.

Address correspondence and reprint requests to Dr. Giovanni Meola, Department of Neurology, University of Milan, San Donato Hospital, V. Morandi, 30, 20097–San Donato Milanese, Milan, Italy.

Table 1 *Clinical and laboratory data of muscle and brain involvement in our patients with proximal myotonic myopathy*

Family no. and patient no.		Age, y/sex	MRC grade*		Onset of muscle symptoms, decade	Onset of brain symptoms, decade	GCA†	FCA†	WMHL†
			Proximal	Distal					
Family 1	III-1	59/F	4+	5	3	5	1	0	0
	III-7†	73/F	3	4	3	6	0	0	1
	III-8‡	68/M	3	5	—	2	1	2	0
	III-14	65/M	4+	5	4	—	0	0	0
	IV-2	22/F	5	5	1	—	0	0	0
	IV-3	37/F	2	4	2	—	0	0	0
	IV-5	34/F	4+	5	3	2	0	0	0
	IV-7	43/M	5−	5	2	—	0	0	0
	IV-14	44/F	4+	5	3	3	ND	ND	ND
	V-2	18/M	4+	5	—	1	1	0	0
Family 2	Patient 2	45/M	4+	5	4	—	0	0	0
Family 3	II-1	67/F	4	4+	1	3	0	0	1
	III-7	39/F	4	5	1	2	0	0	0
Family 4	II-1	70/M	4	4+	4	5	2	0	1
	III-1	36/F	4	5	2	—	0	0	0
Family 5	I-1	67/M	4	5	2	2	ND	ND	ND
	II-1	47/M	4+	5	2	—	ND	ND	ND
	II-2	52/M	4	5	2	4	0	1	0
Family 6	II-1	55/F	4	5	3	—	0	0	0
	II-3	50/F	4	5	3	—	0	0	1

* Medical Research Council (MRC) grading from 0 to 5 according to the MRC (Aids to the Examination of the Peripheral Nervous System. Memorandum 45—Pendragon House, London, 1976).

† See text for details on grading for general cerebral atrophy (GCA), focal cerebral atrophy (FCA), and white matter hyperintense lesions (WMHL).

‡ Patient not ambulatory.

— = no symptoms; ND = not done.

To determine whether PROMM patients have brain alterations similar to those found in patients with DM we performed neuropsychological testing, brain MRI, and $H_2{}^{15}O$ PET.

Methods. *Selection of patients.* We studied 20 patients with PROMM from 6 unrelated families (2 from Italy and 4 from the United States; age range, 18 to 73 years; mean age, 50 years; 11 women and 9 men). In all families at least one affected person was tested for and did not show an expanded CTG repeat in the DM gene on chromosome 19. In family 1, which has been described previously,[4] linkage to chromosomes 7 and 17 in addition to chromosome 19 was excluded. In this family and in families 3 and 6, linkage to chromosome 3q was also excluded.[21,22] The remaining families were uninformative for linkage, but CTG repeat size in the DM gene was normal in the affected family members. Patient 2 was adopted, so there is no available information on the family pedigree. However, given the presence of proximal weakness, electromyographic myotonia, and early-onset cataracts in the presence of a normal-size CTG repeat in the DM gene, a diagnosis of PROMM was made. Additional supportive findings were the presence of preserved tendon reflexes in the affected limbs and calf hypertrophy. Twenty DM patients ($CTG_{[500-700]}$) (age range, 24 to 68 years; mean age, 43 years; 10 women and 10 men) from 13 unrelated families from northern Italy were also studied. Comparable neuropsychological tests and neuroimaging procedures were performed in both the Italian and the US patients.

Seventeen of the 20 patients with PROMM and 18 of the 20 DM patients were ambulatory. It was possible to perform neuropsychological testing in 12 of 20 patients with PROMM and in 18 of 20 patients with DM. MRI evaluation was possible in 17 of 20 PROMM patients and in 15 of 20 DM patients. $H_2{}^{15}O$ PET scanning of the brain occurred in 10 of 20 PROMM patients and 11 of 20 DM patients. Tables 1 and 2 summarize the clinical and laboratory findings in the patients with PROMM and DM.

Neuropsychological procedures. Neuropsychological testing was administered by an experienced examiner in a quiet environment in the hospital or at the patient's home. Approximately 60 to 90 minutes were needed to administer the battery of tests required. It included a screening test for dementia (Mini-Mental State Examination [MMSE]) and tests of nonverbal reasoning (Raven's colored matrices), conceptual abilities (Weigl's sorting test), auditory language comprehension (Token test), verbal fluency

Table 2 *Clinical and laboratory data of muscle and brain involvement in our patients with myotonic dystrophy*

Patient no.	Age, y/sex/ CTG range	MRC grade*		Onset of muscle symptoms, decade	Onset of brain symptoms, decade	GCA†	FCA†	WMHL†
		Proximal	Distal					
1‡	67/M/E2	2	3	5	6	ND	ND	ND
2‡	68/F/E2	2	2	3	4	2	0	0
3	28/M/E2	5	4	1	—	1	2	0
4	60/F/E2	3	4	1	4	ND	ND	ND
5	53/F/E2	3	4	2	4	0	1	2
6	48/F/E2	4+	4	2	—	0	0	0
7	62/M/E2	4+	4	4	—	2	0	1
8	27/M/E2	5	4	2	—	0	0	0
9	35/M/E2	5	4	2	—	0	0	1
10	24/M/E2	5	4	2	—	0	0	0
11	55/F/E2	5	4	2	—	ND	ND	ND
12	49/F/E2	5	4	3	—	0	1	2
13	38/M/E2	5	4+	2	—	ND	ND	ND
14	27/M/E2	5	4+	1	—	0	0	0
15	51/F/E2	5	4+	3	—	0	0	0
16	40/F/E1	5	4+	2	—	0	0	2
17	31/F/E2	4	3	2	—	1	0	1
18	32/F/E2	4	3	2	2	ND	ND	ND
19	26/M/E2	5	4	2	—	0	0	1
20	33/M/E2	5	4	2	—	1	1	1

* Medical Research Council (MRC) grading from 0 to 5 according to the MRC (Aids to the Examination of the Peripheral Nervous System. Memorandum 45—Pendragon House, London, 1976).

† See text for details on grading for general cerebral atrophy (GCA), focal cerebral atrophy (FCA), and white matter hyperintense lesions (WMHL).

‡ Patient is not ambulatory.

— = no symptoms; ND = not done.

with phonemic and semantic cues, verbal and spatial short-term memory (digit span and Corsi block tapping span), memory for prose (logical memory test), spatial learning (Corsi supraspan learning), constructional abilities and visual spatial recall (Rey's complex figure), and a self-administered depression rating scale (Cognitive Behavioral Assessment 2.0 depression scale [Bertolotti G, Michielin P, Sanavio E, Simonetti G, Vidotto G, Zotti AM; Organizzazioni Speciali, Firenze, 1986]). The tests were administered and scored according to published procedures.[23,24] Data were compared with 20 age-, gender-, and education-matched control subjects. Not all patients were able to perform the full battery of tests. A few refused the testing and a few had severe distal weakness that made holding a pen impossible. The results of the neuropsychological testing in Patient III-8, from family 1 were not included in the statistical analysis because of his history of psychiatric disorders and the long-standing use of neuroleptic drugs. A review of his medical records suggested a diagnosis of schizophrenia, superimposed on delayed mental development, which was further complicated by a probable vascular dementia. The data from Patient V-2 from family 1 was also not included in the overall analysis because of the long-standing use of antiepileptic drugs and the patient's history of delayed mental development. His father refused to permit PET scanning and also refused the procedure for himself.

Neuropsychological performance was analyzed by direct comparison of the raw test scores among the three groups using one-way analysis of variance. Because of the multiple comparisons, the Bonferroni-corrected significance threshold was set at 0.0042. Furthermore, to identify the number of patients who could be considered cognitively impaired, the scores were corrected for age, education, and gender using normative data from a large sample of control subjects (>300). A score in the pathologic range in two or more tests was considered a criterion for cognitive impairment. The number of patients fulfilling this criterion in each group was compared by means of a contingency table (chi-square statistics).

To assess the possible effect of age on neuropsychological performance, the age of the cognitively impaired DM patients was compared with the unimpaired group (the presence of only two impaired subjects among the PROMM patients prevented the possibility of a statistical comparison) using the Mann–Whitney *U* test.

Magnetic resonance imaging. MRI was performed with a scanner operating at a field strength of 1.5 T, and in-

cluded spin-echo pulse sequences in T1-, proton density-, and T2-weighted imaging. For all scans, section thickness was 5 mm. All MRI studies were evaluated by a neuroradiologist without knowledge of the clinical status of the patient. Seventeen patients with PROMM underwent MRI (three patients refused the procedure). MR images were obtained for 15 of 20 patients with DM. The remaining five DM patients were unable to undergo this procedure because of cardiac pacemakers. By mutual agreement between the neuroradiologist and neurologist, our evaluation of the findings on MRI followed the methods of Huber et al.[13] with slight modification. The grading is described in the following paragraphs.

General cerebral atrophy (GCA). GCA was evaluated relative to age rather than on an absolute scale. Atrophy was rated on a scale of 0 to 3, with higher numbers indicative of increasing severity. A score of 0 represented normal-appearing ventricles and cisterns relative to age, and no parenchymal atrophy with widening of sulci. Higher numbers indicated varying degrees of increasing ventricular and cisternal spaces.

Focal cerebral atrophy (FCA). FCA was rated using the same scale as that used for GCA, but the rating was made with respect to a specific region of the brain, such as when a particular lobe (e.g., temporal) was judged to be smaller or more atrophic than expected for the patient's age (sulci more widened and increased in number).

White matter hyperintense lesions (WMHL). Focal white matter disease was judged by both the size and confluency of these lesions: 0, no lesions; 1, a few bilateral hyperintense lacunae; 2, lesions $>$ 2 cm; and 3, bilateral lesions $>$ 2 cm, usually confluent.

MRI results were compared with MR images obtained by members of the neuroradiology department in Italy from 20 individuals who undertook the examination for different diagnostic purposes: 11 for transient tingling in the hands; 4 for persistent headache; 2 for transient, nonspecific speech problems; and 3 for occasional dizziness and gait disturbances. No GCA, FCA, or WMHL were present in these subjects.

Data for each individual patient are presented in table 1 for PROMM and in table 2 for DM.

PET acquisition procedures. Eight patients with PROMM and 11 patients with DM from Italy were studied by $H_2{}^{15}O$ PET in a resting state. Two additional patients with PROMM from the United States had SPECT regional cerebral blood flow (rCBF) studies of the brain. The PET tomograph used was GE-Advance (General Electric Medical System, Milwaukee, WI). The system consists of 18 rings of bismuth germanate, which allows 35 transaxial images with a slice thickness of 4.25 mm covering an axial field of view of 15.2 cm. Transmission data were acquired using a pair of rotating pin sources filled with 68Ge (10 mCi per pin). Image reconstruction was performed with a filtered back-projection algorithm on a 128 $\times$ 128 matrix with a pixel size of 1.9 mm. rCBF was measured by recording the distribution of radioactivity following an IV bolus injection of 7 to 8 mCi $H_2{}^{15}O$ through a forearm cannula. The integrated counts collected for 70 seconds, starting 20 seconds after injection time, were used as an index of rCBF.

PET data analysis. Reconstructed images of $H_2{}^{15}O$ PET were transferred to a dedicated workstation for image processing (SUN-SPARC 2, Sun Microsystems, Palo Alto, CA). The data were analyzed with Statistical Parametric Mapping 1996 (using software from the Wellcome Department of Cognitive Neurology, London, UK) implemented in Matlab version 4.2 (Mathworks Inc., Sherborn, MA).[25]

PET images were transformed into a stereotactic space.[26] This normalizing spatial conformation matches each scan to a reference or template image that already conforms to the standard space.

After specifying the appropriate design matrix, group, subject, and covariate effects were estimated according to the general linear model at each and every voxel.[25] We applied analysis of covariance,[26] in which the design matrix included global activity and age as confounding covariates. To test the hypothesis about regionally specific group-versus-group effects, the estimates were compared using linear contrasts. The resulting set of voxel values for each contrast constitute a statistical parametric map (SPM) of the t statistic SPM. In this particular implementation of the general linear model, the t statistic is, effectively, the rCBF difference between the mean rCBF of the control group and the rCBF of the patient group under investigation, divided by the error estimated with the control group data (after correcting for age and global effect). The SPMs were transformed to the unit normal distribution (SPM Z) and thresholded at 3.09 (or corrected at p = 0.001). The resulting foci were then characterized in terms of spatial extent (k) and peak heights (u).[27]

Results. *Mental status.* The presence of cognitive and behavioral disorders was determined on the basis of a clinical interview with patients and relatives. A diagnosis of depression (family 3, Patients II-1 and III-7) and of dementia (family 1, Patients III-8 and V-2; family 4, Patient II-1; and family 5, Patient II-2) according to criteria in the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV)[28] was made in 6 of 20 patients with PROMM. In Patient III-8 from family 1, clinical signs and symptoms of mental retardation began at 14 years of age. His first admission to a psychiatric hospital was at 27 years of age. He was diagnosed at the time as having paranoid schizophrenia and oligophrenia. At 65 he had a stroke with residual mild left hemiparesis. Within 2 months he was diagnosed as having dementia of uncertain cause. He is currently in a psychiatric hospital. Patient V-2 from family 1 had generalized seizures at 3 years of age, after normal delivery and birth. At 4 years of age, mental delay became apparent and seemed to be related to uncontrolled seizures. Performance at school was poor. At the time of this report, the patient is unemployed. A diagnosis of dementia was made in two other patients. Memory difficulty was the initial symptom in Patient II-1 from family 4 who complained of depression and cognitive impairment. His cognitive deficits had progressed to the point that a diagnosis of an Alzheimer's type of dementia was made. His 36-year-old daughter complains of mood swings and often feels depressed, but she is able to continue her everyday activity. Patient II-2 from family 5 is currently unemployed and is on disability for his disorder. He is currently complaining of problems with memory, language, attention, concentration, and executive functioning. He also reports intermittent difficulty with comprehension of both written and oral material, important word-finding problems. He has difficulty with elevated levels of anxiety, depression, and anger. The patient is currently seeing a

psychiatrist. His 47-year-old brother (Patient II-1) has profound weakness and has much difficulty rising from the floor and he has trouble rising from a chair. He has bilateral cataracts. He complains of attention deficits and memory problems. He is currently taking medication for generalized seizures that began at the age of 30. Neuroimaging scans are unavailable.

The same clinical criteria used to asses the presence of cognitive and behavioral complaints in PROMM patients were used for DM patients. Three patients (15%) had a definite attitude of distrust and suspiciousness (Patients 9, 11, and 19) that fitted the criteria of a paranoid personality disorder, and two patients (Patients 14 and 10) had a borderline personality disorder according to the DSM-IV criteria.[28] Recurrent, brief depressive disorders according to DSM-IV[28] have been found in two patients (Patients 6 and 18). In three patients (Patients 1, 2, and 4) there were multiple cognitive deficits, including memory impairment and difficulty in executive functioning, that were severe enough to cause impairment in occupational and social functioning so that a diagnosis of dementia was made according to the DSM-IV criteria.[28] Excessive daytime sleepiness was a subjective complaint in 16 of 20 patients, but only in threee of these patients was it severe enough to interfere with everyday activity.

Neuropsychological tests. The intergroup comparison (table 3) indicates that patients with DM have generally lower scores than age- and education-matched control subjects. Patients with PROMM performed, in general, at an intermediate level between DM and control subjects. Significant differences were found for four tests: MMSE, story recall, and copy and recall of Rey's figure. A post hoc analysis using Scheffe's method showed that patients with DM performed at a significantly lower level than control subjects ($p < 0.05$) on MMSE, story recall, and Rey copy. In the case of Rey recall, both patients with PROMM and DM were impaired compared with control subjects.

In regard to normative data, approximately two-thirds (64%) of the patients with PROMM and one-half (53%) of those with DM showed an impairment of visual–spatial recall (Rey recall), whereas only one-third of the patients with PROMM (36%) and less than half of the DM patients (47%) showed an impairment in visual–spatial construction (Rey copy). An impairment of verbal short-term and long-term memory was significantly more common in patients with DM than in patients with PROMM (61% of patients with DM versus 18% of patients with PROMM: $\chi^2 = 5.09$; $p > 0.005$ in the story recall test; and 28% of patients with DM failed in the digit span test whereas all patients with PROMM performed correctly on this test: $\chi^2 = 4.0$; $p > 0.005$). Considering the number of scores below the age- and education-corrected cutoff value for each pathologic group (PROMM and DM) on our battery of neuropsychological tests, the overall neuropsychological performance of impaired tests was 16 of 125 in the PROMM group versus 55 of 214 impaired tests in the DM group ($\chi^2 = 7.93$; $p > 0.005$). The incidence of more pronounced neuropsychological impairment, as measured by abnormal performance in more than two tests, was higher in DM patients than in PROMM patients (2 of 12 PROMM patients and 9 of 18 DM patients; approaching statistical significance, $\chi^2 = 3.44$, $p = 0.06$). In the DM group, the average age of the patients showing impairment in testing was significantly higher (Mann–Whitney U test, $z = -2.65$, $p = 0.008$).

Table 3 *Mean demographic variables and neuropsychological test scores for myotonic dystrophy (DM) and proximal myotonic myopathy (PROMM) patients compared with 20 controls*

Variable	Patients		Control subjects	p Value
	PROMM	DM		
Age, y	50.4	38.7	41.3	NS
Education, y	9.2	8.7	9.8	NS
MMSE score	28.8	27.9	29.6	0.003
Raven PMC score	29.6	26.7	30.4	NS
Token test score	34.4	35.4	35.6	NS
Weigl's test score	10.4	9.9	12.7	NS
Controlled association letters, score	33.1	25.8	34.1	NS
Controlled association categories, score	37.4	37.9	41.3	NS
Story recall score	11.9	9.4	14.0	0.004
Digit span score	5.4	4.8	5.3	NS
Corsi span score	4.7	4.8	5.2	NS
Corsi supraspan score	24.0	15.4	21.9	NS
Rey copy score	29.7	25.9	35.2	0.001
Rey recall score	14.0	12.3	21.4	0.002

MMSE = Mini-Mental State Examination; PMC = progressive matrices colored; NS = not significant.

Magnetic resonance imaging. Figures 1 and 2 show the scores of the grading used to assess GCA, FCA, and WMHL for both PROMM (see figure 1) and DM (see figure 2) patients. The results have been compared with 20 control subjects whose brain MR images showed no GCA, FCA, or WMHL (see tables 1 and 2).

Nine of the 17 patients with PROMM who underwent MRI evaluations had normal results (see table 1). There was no correlation between symptoms of brain disease and the alterations observed in neuropsychological testing, or with degree of neuromuscular involvement or age (see table 1).

Of the DM patients undergoing MRI (n = 15), five had normal MRI results (see table 2). Of the remaining patients there was a more widespread distribution of the focal hyperintense lesions compared with the distribution of these lesions in patients with PROMM. However, as in the PROMM patients, our results show no correlation between abnormalities of brain function on neuropsychological testing and the degree of neuromuscular involvement or the age of the patients (see table 2).

Positron emission tomography. In both the PROMM and the DM patients there was a marked decrease in rCBF in the frontal lobes bilaterally. In the PROMM patients reductions in rCBF occurred bilaterally in the orbitofrontal and the medial frontal cortex. The group analysis showed a greater decrease in patients with DM. In the DM patients there was not only a bilateral decrease in rCBF in the orbitofrontal and medial frontal cortex, and in the tempo-

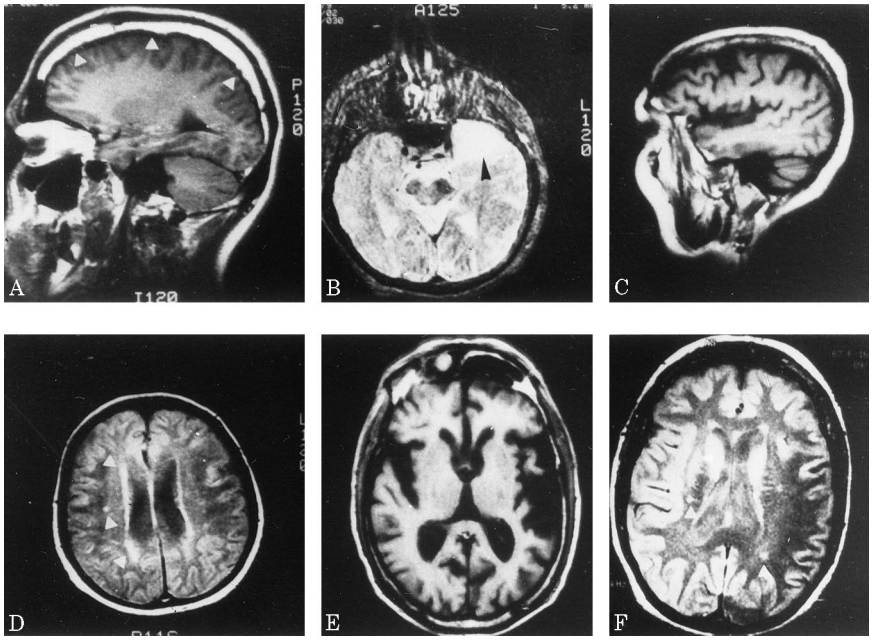

Figure 1. Brain MRI in patients with proximal myotonic myopathy. See table 1 for clinical and laboratory details on each patient. (A) Family 1, Patient V-2. General cerebral atrophy (GCA), 1; focal cerebral atrophy (FCA), 0; white matter hyperintense lesions (WMHL), 0. Note increased thecal thickness (arrows). (B) Family 1, Patient III-8. GCA, 1; FCA, 2; temporal lobe cyst; WMHL, 0. (C) Family 1, Patient III-1. GCA, 1; FCA, 0; WMHL, 0. (D) Family 1, Patient III-7. GCA, 0; FCA, 0; WMHL, 1 (arrows). (E): Family 4, Patient II-1. GCA, 2; FCA, 0; WMHL, 1. (F) Family 3, Patient II-1. GCA, 0; FCA, 0; WMHL, 1 (arrows).

ral pole, but there was also a decrease in the dorsolateral frontal cortex, the hypothalamus, and the left basal ganglia (figures 3 and 4).

Discussion. The results of neuropsychological testing and PET in our patients with PROMM and DM, as well as the findings of dementia and depression in 6 of 20 patients with PROMM, suggest that—like DM—PROMM affects certain regions of the brain. However, the limited number of patients available requires caution in our interpretation of the findings. We may have overestimated the frequency of brain symptoms in PROMM due to a selection bias for patients having dementia and depression. It is also possible that we may have studied a subset of patients with PROMM because PROMM is probably a heterogeneous disorder.[29] However, the patients in the current study from the families with a family tree that permitted linkage analysis showed no linkage to chromosomes 19q or 3q loci.

Although it is true that some neuropsychological tests, like the copying of Rey's figure, require motor speed and coordination for normal performance, it seems unlikely that the deficiencies in performance that we observed in the patients with PROMM and DM have resulted solely from their basic motor deficits. None of the patients we have included in our analysis have impaired motor and coordination abilities sufficient to account for the results observed on the cognitive testing (see tables 1 and 2). We have taken care to disregard minor abnormalities in the drawing pattern that could have resulted from motor defects in our scoring procedure. It is also important

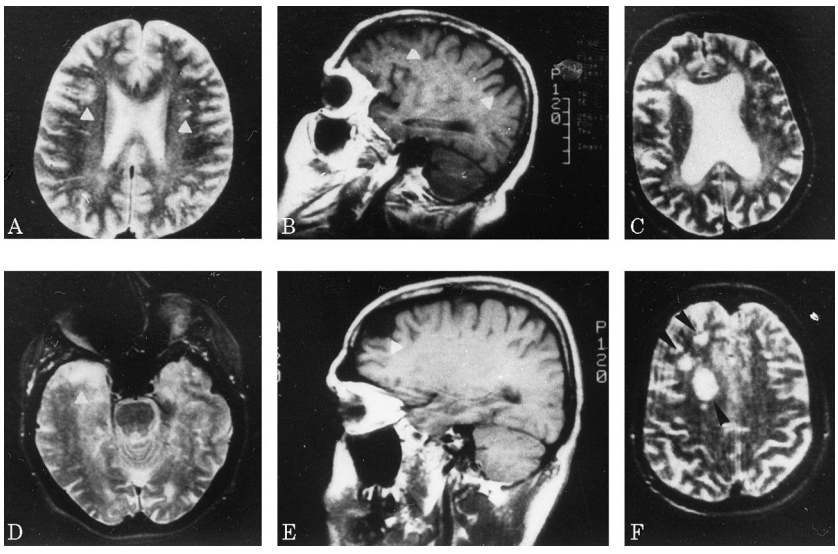

Figure 2. Brain MRI in patients with myotonic dystrophy. Grading is as in figure 1. See table 2 for clinical and laboratory details on each patient. (A) A 35-year-old man. General cerebral atrophy (GCA), 0; focal cerebral atrophy (FCA), 0; white matter hyperintense lesions (WMHL), 1 (arrows). (B) A 68-year-old woman. GCA, 2 (arrows); FCA, 0; WMHL, 0. (C) A 62-year-old man. GCA, 2; FCA, 0; WMHL, 1. (D) A 40-year-old woman. GCA, 0; FCA, 0; WMHL, 2. (E) A 36-year-old man. GCA, 1 (arrow); FCA, 2 (frontal lobe cyst); WMHL, 0. (F) A 53-year-old woman. GCA, 0; FCA, 1; WMHL, 2.

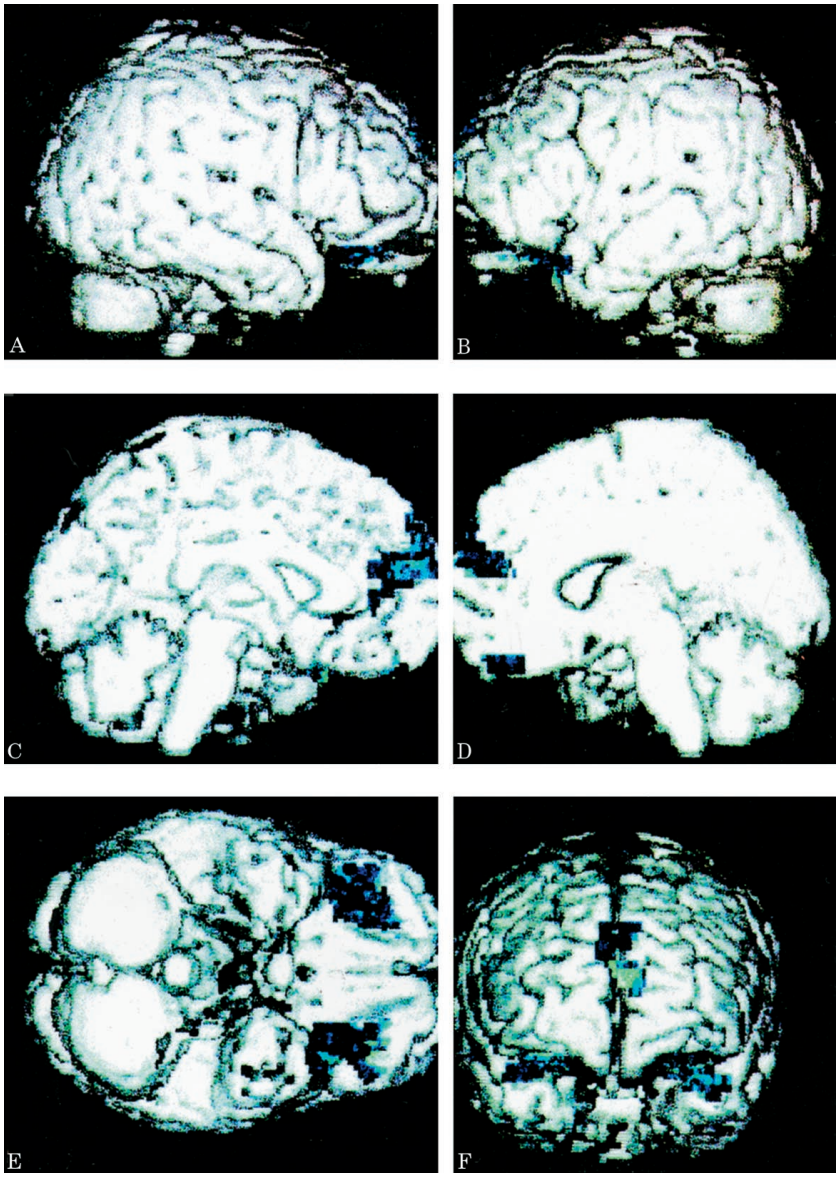

Figure 3. Three-dimensional brain rendering (by statistical parametric mapping [SPM-96]) demonstrating the areas of hypoperfusion in patients with proximal myotonic myopathy compared with the control group ($p < 0.001$; $z = 3.09$, corrected for multiple comparisons).

to emphasize that some of our patients had scores in the normal range on copying and showed impairment only in recall.

The limited total number of PROMM and DM patients with marked impairment has prevented a detailed evaluation of the effects of age. Neuropsychological impairment, in both PROMM and DM, was more frequent in the older age group, suggesting that there may be a gradual decline in certain areas of cognitive function.

The nonspecific structural abnormalities observed on brain MR images performed in both PROMM and DM patients do not correlate clearly with the alterations that we have observed on cognitive testing. Conversely, functional neuroimaging with PET has demonstrated a common pattern of cerebral hypoperfusion in both groups, with rCBF reductions in the ventral and mesial aspects of the frontal lobes (orbitofrontal cortex) and in the temporal poles. Unfortunately our current battery of neuropsychological tests has not included some of the classic measurements of frontal lobe function, such as the Wisconsin Card Sorting Test or the Stroop interference task, so that a correlation between rCBF frontal abnormalities and impaired visual–spatial responses is limited. It is, however, interesting to consider that the orbitofrontal cortex and the temporal poles are interconnected areas of brain, which can constitute a crucial network for the control of emotional behavior.[30,31] Behavioral and affective changes, such as depression, apathy, or anxiety, are present in some of our patients with PROMM and DM. It is conceivable that the alterations in CBF that we have observed in the frontal lobes may contribute in part to producing the disturbance in behavior seen in these patients with PROMM and DM.

Previous PET studies in DM[32,33] have suggested that there may be a primary abnormality of the carrier-mediated transport that accounts for the decline of glucose utilization measured by ^{18}F-labeled

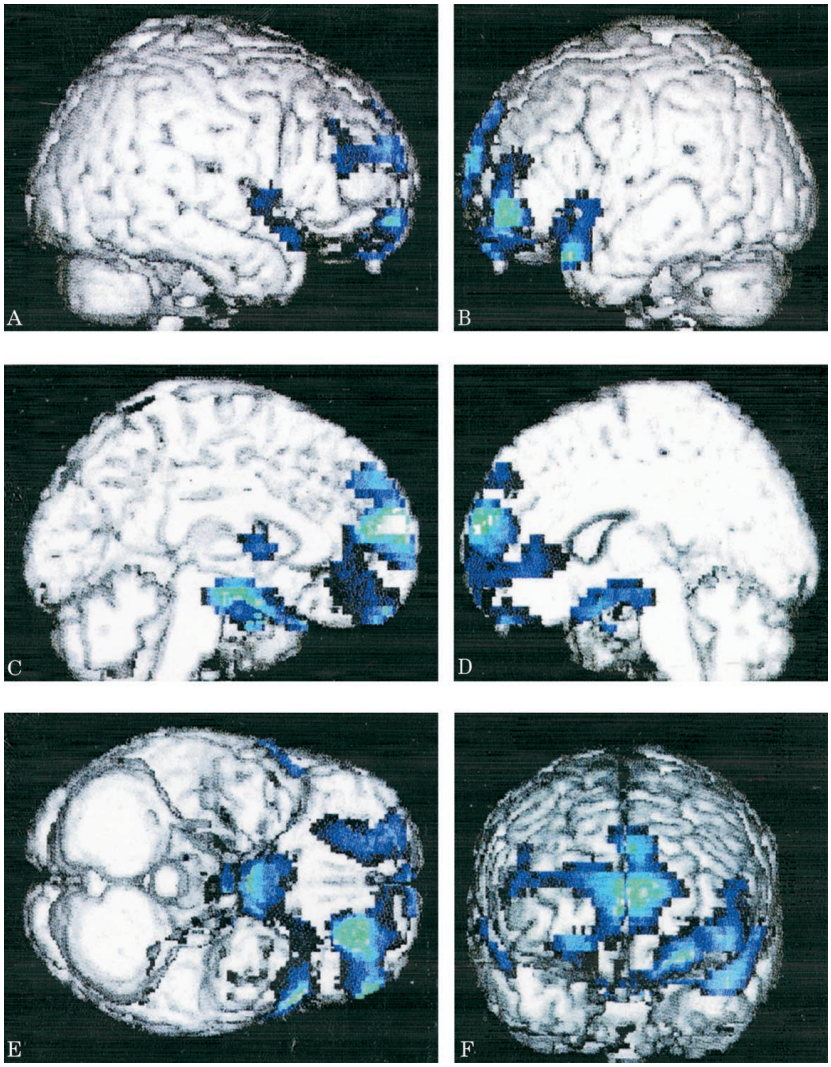

Figure 4. Three-dimensional brain rendering (by statistical parametric mapping [SPM-96]) demonstrating the areas of hypoperfusion in patients with myotonic dystrophy compared with the control group ($p < 0.001$; $z = 3.09$, corrected for multiple comparisons).

2-fluoro-2-deoxy-D-glucose (FDG) PET. These observations raise the possibility that the reduction in cerebral glucose metabolism observed in DM may be due to an alteration, such as a defect in membrane function (carrier-mediated transport). Indeed, both PROMM and DM are multisystem disorders and may have multisystem alterations in membrane function. Common pathophysiology seems likely to exist for PROMM and DM. It is possible that this abnormality may involve the insulin receptor. Preliminary data in PROMM and DM have demonstrated insulin resistance during euglycemic insulin infusion studies (Moxley, unpublished data) and during an intravenous glucose tolerance test.[34] In the future it would be helpful to perform PET/FDG studies on glucose kinetics in patients with PROMM and DM to determine whether there is a relationship between peripheral insulin resistance, which is common in these disorders, and the alterations in brain function and CBF.

Acknowledgment

The authors are grateful to the patients for their collaboration.

References

1. Thornton CA, Griggs RC, Moxley RT. Myotonic dystrophy with no trinucleotide repeat expansion. Ann Neurol 1994;35:269–272.
2. Ricker K, Koch MC, Lehmann–Horn F, et al. Proximal myotonic myopathy: a new dominant disorder with myotonia, muscle weakness, and cataracts. Neurology 1994;44:1448–1452.
3. Ricker K, Koch MC, Lehmann–Horn F, et al. Proximal myotonic myopathy. Clinical features of a multisystem disorder similar to myotonic dystrophy. Arch Neurol 1995;52:25–31.
4. Meola G, Sansone V, Radice S, et al. A family with an unusual myotonic and myopathic phenotype and no CTG expansion (proximal myotonic myopathy syndrome): a challenge for future molecular studies. Neuromuscul Disord 1996;6:143–150.
5. Moxley RT. Proximal myotonic myopathy: mini-review of a recently delineated clinical disorder. Neuromuscul Disord 1996;6:87–93.
6. Moxley RT, Udd B, Ricker K, et al. 54th ENMC International Workshop: PROMM (proximal myotonic myopathies) and other proximal myotonic syndromes—workshop report. Neuromuscul Disord 1998;8:508–518.
7. Udd B, Krahe R, Wallgren–Pettersson C, Falck B, Kalimo H. Proximal myotonic dystrophy—a family with autosomal dominant muscular dystrophy, cataracts, hearing loss, and hypogonadism—heterogeneity of proximal myotonic disorders. Neuromuscul Disord 1997;7:217–228.
8. Phillips MF, Rogers MT, Barnetson R, et al. PROMM: the

expanding phenotype. A family with proximal myopathy, myotonia and deafness. Neuromuscul Disord 1998;8:439–446.
9. Harper PS. Myotonic dystrophy. 2nd ed. London: WB Saunders, 1989.
10. Hund E, Jansen O, Koch MC, et al. Proximal myotonic myopathy with MRI white matter abnormalities of the brain. Neurology 1997;48:33–37.
11. Ruchous MM, Guerouaou D, Vandenhaute B, et al. Systemic vascular smooth muscle cell impairment in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy. Acta Neuropathol 1995;89:500–512.
12. Delaporte C. Personality patterns in patients with myotonic dystrophy. Arch Neurol 1998;55:635–640.
13. Huber SJ, Kissel JT, Shuttleworth EC, et al. Magnetic resonance imaging and clinical correlates of intellectual impairment in myotonic dystrophy. Arch Neurol 1989;46:536–540.
14. Damian MS, Schilling G, Bachmann G, Simon C, Stoppler S, Dorndorf W. White matter lesions and cognitive deficits: relevance of lesion pattern? Acta Neurol Scand 1994;90:430–436.
15. Abe K, Fujimura H, Toyooka K, et al. Involvement of the central nervous system in myotonic dystrophy. J Neurol Sci 1994;127:179–185.
16. Miaux Y, Chiras J, Eymard B, et al. Cranial MRI findings in myotonic dystrophy. Neuroradiology 1997;39:166–170.
17. Chang L, Ernst T, Osborn D, Seltzer W, Leonido–Yee M, Poland RE. Proton spectroscopy in myotonic dystrophy. Correlations with CTG repeats. Arch Neurol 1998;55:305–311.
18. Ogata A, Terae S, Fujita M, Tashiro K. Anterior temporal white matter lesions in myotonic dystrophy with intellectual impairment: an MRI and neuropathological study. Neuroradiology 1998;40:411–415.
19. Vermersch P, Sergeant N, Ruchoux MM, et al. Specific tau variants in the brains of patients with myotonic dystrophy. Neurology 1996;47:711–717.
20. Ono S, Takahashi K, Jinnai K, et al. Loss of catecholaminergic neurons in the medullary reticular formation in myotonic dystrophy. Neurology 1998;51:1121–1124.
21. Ranum LPW, Rasmussen PF, Benzow KA, Koob MD, Day JW. Genetic mapping of a second myotonic dystrophy locus. Nat Genet 1998;19:196–198.
22. Ricker K, Grimm T, Koch MC, et al. Linkage of proximal myotonic myopathy to chromosome 3q. Neurology 1999;52: 170–171.
23. Mariani C, Farina E, Cappa SF, et al. Neuropsychological assessment in multiple sclerosis: a follow-up study with magnetic resonance imaging. J Neurol 1991;238:395–400.
24. Lezak MD. Neuropsychological assessment. 3rd ed. New York: Oxford University Press, 1995.
25. Friston KJ, Holmes AP, Worsley KJ, Poline JP, Frith CD, Frackowiak RSJ. Statistical parametric maps in functional imaging: a general linear approach. Hum Brain Mapp 1995;2: 189–210.
26. Talairach J, Tournoux P. Coplanar stereotactic atlas of the human brain. Dimensional proportional system: an approach to cerebral imaging. Stuttgart: Thieme, 1988.
27. Signorini M, Paulesu E, Friston K, et al. Rapid assessment of regional cerebral metabolic abnormalities in single subjects with quantitative and nonquantitative [^{18}F]FDG PET: A clinical validation of statistical parametric mapping. Neuroimage 1999;9:63–80.
28. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th ed. Washington, DC: American Psychiatric Association, 1994.
29. Thornton CA, Ashizawa T. Getting a grip on the myotonic dystrophies. Neurology 1999;52:12–13.
30. Kupferman I. Localization of higher cognitive and affective functions: the association cortices. In: Kandel ER, Schwartz JH, Jessel TM, eds. Principles of neural science. 3rd ed. New York: Elsevier Publishers, 1991:823–838.
31. Stuss DT, Benson DF. The frontal lobes. New York: Raven Press, 1986.
32. Fiorelli M, Duboc D, Mazoyer BM, et al. Decreased cerebral glucose utilization in myotonic dystrophy. Neurology 1992;42: 91–94.
33. Annane D, Fiorelli M, Mazoyer B, et al. Impaired cerebral glucose metabolism in myotonic dystrophy: a triplet-size dependent phenomenon. Neuromuscul Disord 1998;8: 39–45.
34. Moxley RT, Sansone V, Lifton A, Thornton CA. Insulin resistance in proximal myotonic myopathy (PROMM). Neurology 1997;48(suppl 3):A229. Abstract.