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Eosinophilia-myalgia syndrome: selective cognitive impairment, longitudinal effects, and neuroimaging findings

Carol Armstrong, Todd Lewis, Mark D'Esposito, Bruce Freundlich

Abstract

***Objective*—To identify the specific nature of the neurocognitive impairments of eosinophilia-myalgia syndrome (EMS) in an unselected population, and to present longitudinal patterns.**

***Methods*—A consecutive sample of 23 patients with EMS and 18 age and education matched control subjects were assessed on a comprehensive neuropsychological battery. Longitudinal results were gathered from six patients.**

***Results*—Neurocognitive impairments were found which represent a subset of deficits reported in previous group and case study reports. Deficits were limited to complex visual memory, conceptual set shifting, and attention, which suggest a selective dysexecutive syndrome. The motor slowing and verbal memory deficits previously reported were not found. Although depression, fatigue, sleep deprivation, and pain were significant symptoms, they were unassociated with deficits with the exception of an association of depression with one deficit. There was no pattern of overall decline over time in a subset of the group, although considerable heterogeneity in the longitudinal patterns of neurocognitive tests was found. Abnormalities of white matter appeared in the MRI of eight of 12 patients.**

***Conclusions*—The neurocognitive and neuroimaging findings contribute to the evidence which indicates that the neural substrate of EMS is white matter damage.**

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Keywords: eosinophilia-myalgia syndrome; neurocognitive; dysexecutive; white matter

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Eosinophilia-myalgia syndrome (EMS) was first described in the United States in 1989.[1] It was an epidemic which resulted from the ingestion of products containing a contaminated synthesised amino acid—L-tryptophan—which had been taken in many cases to aid sleep, to improve mood, and as a nutritional supplement.[2] The syndrome has been found to result in acute and chronic multisystem disorders.[3] Symptoms and raised eosinophil counts have occurred concurrently with the ingestion of L-tryptophan, as well as weeks or months after discontinuing ingestion. The course of the illness may be acute or subacute.[4–6] Symptoms include skin abnormalities (eosinophilic fasciitis, dermal sclerosis, profoundly thickened deep fascia, rash), pulmonary disorders (pneumonitis, pulmonary vasculitis resulting in respiratory failure, shortness of breath), hepatic dysfunction, systemic symptoms (severe fatigue, fever, arthralgias, oedema), sensory and motor abnormalities (paraesthesiae, polyneuropathy, severe myalgias, progressive muscle weakness), and cognitive deficits.[4 5 7–9] The pathological mechanism is not known in EMS, but includes effects of hypereosinophilia, or of a contaminant from the synthesis of the L-tryptophan which caused EMS. Proposed mechanisms for CNS injury due to hypereosinophilia are direct neural infiltration, cytotoxicity, embolic infarction, and eosinophil mediated.[10 11] A direct neurotoxic effect has not yet been ruled out.[2 12–14] Nervous system complications of EMS reported initially were limited to peripheral neuropathy, until four reports of neurological complications and MRI findings suggestive of stroke.[15–18] Neuroimaging disclosed multiple white matter lesions in these patients. In one patient the condition stabilised on withdrawal of L-tryptophan.[17]

The few studies of the cognitive deficits of patients with EMS have all identified impairments of visual and verbal memory, executive dysfunction including deficits in reasoning and processing speed, and motor slowing. Lynn *et al*[12] described in detail signs of CNS involvement in a patient with EMS, which included spastic monoparesis, gait ataxia, dysphagia, and various cognitive deficits. In this patient, neuropsychological deficits seemed to be at the more severe end of the range, including severe deficits in verbal and visual memory (free recall and recognition measures), concept formation, set shifting, tactile perception, and response speed, whereas the concurrent IQ estimate was low average to average. Magnetic resonance imaging (MRI) disclosed several small hyperintensities in the white matter of the right temporal lobe and periventricular area, which were thought to correspond to the neuropsychological patterns. Deterioration in this patient's condition over 11 months in 1989 was evidenced by an increasing number of lesions on MRI, increasing cognitive complaints, and worsening of skin and muscle symptoms.

Only three group studies of neurocognitive effects have been reported. Stanulis *et al*[13] reported on the neurocognitive results on six patients. Their findings provide evidence of

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executive dyscontrol and memory impairment, which they thought were consistent with a subcortical disease state. Hartlage and Horton,[19] reporting on nine patients, also found low average to average IQ estimates which were thought to be lower than premorbid abilities, and moderate to severe impairment on the Halstead-Reitan neurological battery. Krupp *et al*[14] studied 24 patients who were selected from a group of 32 patients with EMS,[9] based on subjective reports of cognitive impairment. They identified severe verbal and visual reasoning deficits, multisystem memory impairments, and slowed finger motor speed.[14] These reports of cognitive deficits in EMS have not argued for a distinct or focal pattern, and suggest diffuse dysfunction. The few reports of structural lesions based on neuroimaging of patients with EMS have disclosed abnormalities in the cerebral white matter and the brainstem region.[12 14 16 17]

The present study expanded the range of neurocognitive systems previously studied, identified the neuropsychological impairments in an unselected population of patients diagnosed with EMS, and gave MRI findings. We expected a comprehensive neuropsychological battery to identify impairment in executive functions (conceptual reasoning, attention, and processing speed), verbal and visual memory, and in motor speed based on previous findings in EMS, and on findings from our own laboratory on the nature of cognitive deficits in other young populations with white matter disease.[20–23] Studies of older populations with diffuse white matter disease have also consistently shown specific impairment in executive functions, attention, and motor speed.[24–28] As white matter hyperintensities have often been reported in case studies of patients with EMS and are consistent with the proposed pathogenic mechanisms of hypereosinophilia, we also expected a higher than normal rate of abnormal signal in subcortical white matter in our group as shown on neuroimages. Finally, we present longitudinal cognitive findings on six patients who received repeated batteries.

Methods

SUBJECTS

Twenty three patients with EMS who were consecutively referred by two rheumatologists to the Neuropsychology Laboratory at the University of Pennsylvania Neurology Department were studied. All patients diagnosed with EMS by a rheumatologist were referred for neuropsychological evaluation regardless of the patients' cognitive complaints, according to study protocol. Neuropsychological evaluations occurred between 20 and 75 months after symptoms emerged, the delay often because patients were receiving second opinions from the rheumatologists at the University of Pennsylvania. Neurological screening had occurred in some cases, but the neuropsychologist was blind to the neurological results. All patients met the Centers for Disease Control requirements for EMS.[7] Informed consent was obtained after the nature of the evaluation had been fully explained. Patients were between the ages of 31 to 58 years with a mean age of 46.7 years. Educational level ranged from 11 years to 20 years with a mean of 14.7 years. Seventy per cent of the sample were women. Table 1 shows the patients' reasons for exposure to L-tryptophan. Few of this cohort took L-tryptophan for mood disturbance; pain and insomnia were the most common premorbid problems cited. No patient admitted cognitive disturbance before development of EMS, and no patient described any interruption in their vocational functioning due to cognitive, emotional, or physical impairment. All patients with the diagnosis of EMS were included, and none were excluded because of history; however, no patients had histories of learning disability, head injury, other neurological disorder, diabetes, or heart surgery. Four patients had had hypertension for six, seven, 10, and 14 (borderline) years. Table 1 shows additional relevant history; three patients had histories of substance misuse, one had a diagnosis of mild obsessive-compulsive disorder, and one had a calcified meningioma which had not been operated on. No patients were currently being treated for any neurological or psychiatric disorder, nor were currently misusing drugs or alcohol. Only those patients who had preexisting neurological consultation had MRI. Table 1 summarises the results and shows that 67% of the patients' MRI included high signal intensities in the cerebral white matter and brainstem. Of those with abnormal scans, only one had hypertension.

Eighteen healthy, normal controls were recruited from relatives of patients and community volunteers. These volunteers were screened in the Department of Neurology with a comprehensive neurodiagnostic interview to exclude those with learning disability, history of head injury, major psychiatric diagnosis, current mood disorder, other neurological disorder, diabetes, heart surgery, self reported cognitive complaints, or use of medications which could compromise neurocognitive function. Controls were matched to the EMS group for age (patient mean 46.7 (SD 6.4), control mean 47.6 (SD 8.1); t (39)=0.36, P>0.73), and education (patient mean 14.7 (SD 2.7), control mean 14.8 (SD 2.5); t (39)=0.11, P>0.91). The same control subjects were used in all analyses. There were no differences between the groups in the proportions of sex and handedness.

All six subjects seen in follow up were retested between seven months to two years seven months after the initial evaluation (table 1). Patients were retested, often for medicolegal purposes; one was retested because of new white matter lesions found on a repeat MRI. This group of patients' mean age was 44.8 (range 38-56) years, and mean education was 16.3 (range 12-20) years.

PROCEDURE

Patients were administered a comprehensive neuropsychological battery including tests of sensory and motor processing, speed of information processing, attention, language, verbal learning and memory, visuospatial

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processing, visual memory, problem solving, reasoning, personality/mood, and fatigue. Control subjects were administered the same battery of tests with the exception of those indicated below. The testing of control subjects necessitated a shorter battery, and tests were eliminated if satisfactory population norms were available. The tests are listed under the appropriate headings below and were administered according to standardised rules except where indicated.

SENSORY AND MOTOR PROCESSING

Finger oscillation test;[29] Reitan-Klove tactile perception and finger agnosia examination:

Table 1 MRI findings in patients and historical factors in patients' uses of L-tryptophan (l-T)*

Patient No	*Age*	*MRI finding*	*Reason for taking L-tryptophan*	*Other history*	*MRI time from onset of symptoms*	*MRI time from neuropsychological examination*
1	31	NA	Boost metabolism and energy	None	—	—
2	38†	No abnormalities	Pain due to TMJ	None	22 months	1 month
3	42†	NA	Insomnia due to birth of baby	None	—	—
4	42	NA	Sleep	None	—	—
5	43†	Mild atrophy: slightly prominent CSF spaces	Insomnia	None	27 months	3 months
6	43†	NA	Depression	None	—	—
7	43	Multiple (> 25) white matter lesions throughout all lobes, more lobes, patchy areas in pons, single lesions right frontal region near genu of the corpus callosum	Insomnia due to work stress	None	52 months	2 months
8	43†	Multiple white matter hyperintensities	PMS	None	28 months	0.5 months
9	44	NA	Insomnia due to work	None	—	—
10	44	No abnormalities	Insomnia	History of substance misuse, no current use	60 months	6 months
11	45	NA	PMS	None	—	—
12	46	Multiple hyperintensities in white matter and pons	Insomnia	None	30 months	7 months
13	46	NA	Dietary supplement with hypertensive medications	Obsessive-compulsive history		
14	47	NA	Anxiety	Long term prescribed benzodiazepine use		
15	49	NA	Pain from orthopaedic injury	None		
16	50	Abnormally prominent Virchow-Robin spaces	Insomnia due to family illness	None	59 months	Same day
17	50	Small hyperintensities in white matter of left frontal lobe and pons	Stress due to surgery and family problems	None	80 months	28 months
18	50	No abnormalities	Pain due to orthopaedic problems	None	41 months	2 months
19	54	NA	Depressed mood, insomnia, PMS	History of alcoholism; no current use		
20	55	Multiple white matter hyperintensities bilaterally in frontal and parietal lobes, equivocal pons lesions	Aid for sleep	None	8 months	39 months
21	56	NA	Pain due to back injury	Calcified parasagittal meningioma 8 years earlier, no other abnormalities		
22	56†	Right cerebellar infarct; moderate to large areas of hyperintensities bilaterally in the mid-pons and lower pons, very small, multiple hyperintensities bilaterally in white matter of frontal, parietal, and occipital lobes, in right cerebellar cortex	Insomnia due to injury of dependent family member	None	24 months	7 months
23	58	Few small punctate lesions in frontal white matter and frontoparietal region	Stress due to political election	None	41 months	7 months

* MRI was obtained at several different imaging centres, on 1.5 Tesla magnets, with standard clinical sequences (sagittal and axial T1 weighted, axial and coronal T2 weighted images). No contrast agent was used in any scan.
† Patients available for re-evaluation.
NA = not available because patient had not been scanned; TMJ = temporomandibular joint syndrome; PMS = premenstrual syndrome.

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patients only;[29] alternating collaborative hand movements.[30 31]

REGULATORY ATTENTION AND PROCESSING SPEED

Auditory selective attention test (ASAT);[23] bells test;[32] paced auditory serial addition test: patients only (PASAT);[33] symbol digit modalities test (SDMT);[34] continuous performance test: sequential letter cancellation; patients only.[35]

VERBAL IMMEDIATE AND LONG TERM MEMORY

Digit span test (WMS-R);[36] paragraph immediate and delayed recall: patients only;[36] Rey auditory verbal learning test (using alternate forms) (RAVLT).[22]

VISUOSPATIAL PERCEPTUAL PROCESSING

Rey-Osterrieth complex figure test;[37 38] road map test;[39 40] facial recognition test.[41]

VISUOSPATIAL IMMEDIATE AND LONG TERM MEMORY

Visual memory span test;[36] Rey-Osterrieth complex figure recall test;[38] figure: immediate and delayed recall patients only.[36]

LANGUAGE

Controlled oral word association test;[42] category fluency test;[43] Boston naming test;[44–45] wide range achievement test-reading: patients only (WRAT-R).[46]

INTELLECTUAL/CONCEPTUAL PROCESSES

Wisconsin card sorting test,(WCST) one deck version;[47] similarities test, comprehension test, information test: patients only (WAIS-R);[48] written arithmetic test (WRAT-R): patients only.[46]

PERSONALITY/MOOD AND FATIGUE

Minnesota multiphasic personality inventory-2: patients only (MMPI-2);[49] fatigue severity scale: patients only.[50]

ANALYSIS

A post hoc factor analysis, based on a principal components analysis of all subjects' performances (n=41) on 15 neurocognitive tests, was used as a method of simplifying the data. We were not concerned about replicating factors, but wanted to facilitate interpretation of results by screening redundant neuropsychological variables.[51] Only those factors with eigenvalues>1 were accepted. We examined hypotheses using *t* tests, and implemented Bonferroni corrections for each factor. To search for possible associations between cognitive deficits and depression and fatigue in the patient group, analyses of covariance (ANCOVAs) and regression coefficients used the MMPI-2 scale 2 ("depression scale") and the fatigue severity scale score as covariates. To test the effects of sleep deprivation, pain, psychotropic medications, and abnormalities of white matter on MRI, subgroups of patients were compared using *t* tests to evaluate whether these factors were associated with greater impairment levels. When normal control scores were not available, T scores were calculated for an additional 10 clinical tests of cognitive processing speed, verbal and visual memory, tactile perception, and achievement, using the standardised norms corrected for age and education available from test manuals. T he T scores were also used to determine impairment in mood and fatigue; T scores have a mean of 50 and an SD of 10. To compare the mean T scores, we estimated an SEM ($s=SD/\sqrt{n}$) with a 98% confidence interval (+2.07). Thus a T score outside the range 45.7-54.3 would imply impairment. On the measures in which group analyses disclosed significant deficits, we examined individual performances to ascertain the proportion of patients who performed in a clinically impaired range. We used the criterion of 1 SD below the mean.

Six subjects were retested, and repeated measures of those test scores which were impaired in the whole patient cohort were analysed with subjects as their own controls and repeated measure analysis of variance (ANOVA). We examined whether any changes occurred in scores on the mood or fatigue measures between the first and second evaluation. We then examined other test scores to identify any other changes in cognition over time. We also examined the proportional within subject improvements and declines.

Results

NEUROCOGNITIVE IMPAIRMENTS

Eight factors with eigenvalues >1.0, accounting for 79% of the total variance, were extracted. Table 2 shows the significant differences found between the EMS and control group on five indices from three of the eight factors. Patients were not impaired on any component of factor 1, which represented word list recall (learning trials, postinterference, and recognition measures) (eigenvalue=8.9 accounting for 32.9% of the total variance). Patients were impaired on a speeded test requiring visual scanning and attention (SDMT (t (39)=3.79, P<0.0005; 74% of patients scored in the impaired range by our criterion for determining clinical impairment). Patients were not impaired in manual praxis, which, along with the SDMT comprised factor 2 (eigenvalue of 2.8 accounting for 10% of the total variance). Factor 3 (eigenvalue of 2.3 accounting for 8.5% of total variance) was comprised solely of measures requiring visuoperceptual organisation and memory, and patients were impaired on the recall, but not copy, trials of the complex figure test (immediate recall (t (39)=3.30, P<0.003; 65% of patients impaired; delayed recall (t (39)=4.33, P<0.0001; 83% of patients impaired). Subjects with EMS were impaired on both measures of the WCST which comprised factor 4 (eigenvalue of 2.0 accounting for 7.5% of total variance). They achieved fewer categories (t (39)=3.16, P<0.004; 48% of the patients impaired) and made more perseverative errors compared with the normal group (t (39)=2.54, P<0.015; 48% of the patients impaired). Patients were not impaired in visual or verbal immediate memory span (factor 5, eigenvalue of 1.5 accounting for 5.5% of the total

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Table 2 Significance of scores of patients with EMS compared with controls on the 15 principal neuropsychological components

Factor	*Neuropsychological test*	*Patient (mean(SD))*	*Controls (mean(SD))*	*t Value*	*P value*
1	RAVLT: 5th learning trial	12.65 (2.2)	13.33 (2.2)	0.99	0.33
	RAVLT: % retained after interference	83.50 (15.8)	87.22 (19.7)	0.67	0.51
	RAVLT: % retained after delay	98.33 (17.1)	99.17 (13.5)	0.17	0.87
2	Symbol digit	51.13 (9.9)	61.72 (7.3)	3.79	0.0005*
	Manual praxis	14.80 (1.9)	15.78 (0.5)	1.02	0.32
	Finger oscillation: right hand	47.83 (8.6)	51.09 (5.7)	1.34	0.19
	Finger oscillation: left hand	43.77 (8.8)	47.1 (5.5)	1.35	0.19
3	Complex figure: copy	32.22 (3.2)	33.89 (1.8)	1.98	0.06
	Complex figure: immediate recall	15.39 (6.6)	21.61 (5.1)	3.30	0.0021*
	Complex figure: delayed recall	14.87 (6.3)	22.83 (5.2)	4.33	0.0001*
1, 2, 3	Boston naming test	54.52 (5.2)	57.39 (3.0)	0.30	0.76
4	WCST: categories achieved	3.82 (1.2)	4.79 (0.7)	3.16	0.0031*
	WCST: perseverative errors	9.13 (5.2)	5.83 (2.1)	2.54	0.015*
5	Digit span: forward	7.61 (1.6)	8.39 (1.7)	1.48	0.15
	Visual memory span: forward	7.87 (1.8)	8.67 (1.8)	1.41	0.17
6	Bell's test	32.48 (3.5)	34.33 (0.9)	2.18	0.04
	Facial recognition	45.00 (4.6)	45.44 (5.1)	0.29	0.78
7	Road map test	29.48 (2.4)	30.83 (1.5)	2.10	0.05
8	Auditory selective attention test	1.48 (1.7)	0.11 (0.32)	3.35	0.002*
	Semantic fluency test	22.00 (5.9)	25.78 (5.0)	2.16	0.04
	Word fluency test	44.22 (11.6)	48.72 (12.8)	1.18	0.25

* Indicates significance at the Bonferroni corrected level.

variance). The only additional impairment was in selective attention (ASAT; (t (39)=3.35, P<0.002; 65% of patients impaired) which was the sole impaired component of factor 8 (eigenvalue of 1.1 accounting for 4.0% of the total variance). No impairments were found in visual selective attention, object naming, facial perception, or spatial rotation.

Further analyses confirmed that our group was not impaired in verbal memory. In addition to the absence of deficit in verbal supraspan list (RAVLT) recall over five trials, recall after interference, recall of the list after a delay, there was also no decrement in recognition memory, discrimination, or on verbal fluency tests, which are also speeded. They were also not impaired on paragraph and figure recall from the WMS-R, nor on any tests which correlate with premorbid intellectual achievement (such as similarities and information from the WAIS-R, nor the WRAT-R). Patients were not impaired on motor control measures such as finger tapping speed and praxis.

We examined the EMS group's T scores using published norms with age and education corrections (table 3). One other neurocognitive impairment, defined as a score which fell 2 or more SD below the mean (T<30), was identified: speed of auditory information processing in a divided attention task (PASAT; T=23.4). Ninety one per cent of patients were impaired on the PASAT.

Patients who showed white matter abnormalities on MRI were compared on the impaired scores with the patients with EMS who had not been scanned. Although the patients with abnormal scans had scores which consistently showed greater impairment, the differences were not significant. There were too few patients with normal scans to make a meaningful comparison.

The scores in the five patients with additional significant histories were examined to ascertain if they differed from the EMS group (defined as scores >1 SD below (or above) that of the EMS mean scores). The scores of the patient with obsessive-compulsive disorder were all at the mean for the EMS group; two patients with substance misuse had one of six scores below the mean (visual scanning/attention and visual memory); the third patient with substance misuse and the patient with the quiescent meningioma had three of six scores below the mean (immediate and delayed visual recall, conceptual reasoning). These five patients were compared with the rest of the cohort on the significant impairment measures (ASAT, PASAT, SDMT, complex figure recall, WCST), using age as a covariate. No significant differences or trends emerged.

Table 3 Patient's mean T scores for neuropsychological variables (mean(SD) T = 50(10))

Neuropsychological test	*T score*	*P value < 0.02*
Mean PASAT score	23.4	*
Continuous performance test	44.0	
Figure recall, immediate	53.5	
Figure recall, delayed	47.4	
Paragraph recall, immediate	52.9	
Paragraph recall, delayed	54.0	
Finger agnosia errors: right hand	38.4	
Finger agnosia errors: left hand	37.8	
Tactile perception errors: right side	58.4	
Tactile perception errors: left side	60.8	
WRAT-R: reading	51.0	
WRAT-R: arithmetic	49.9	
Information test	52.1	
Similarities test	56.6	
Comprehension test	52.2	

PERSONALITY/MOOD, FATIGUE, MEDICATIONS, SLEEP DEPRIVATION, PAIN

The EMS group had significantly higher T scores on four MMPI-2 scales which measure depression, psychological distress, and somatic symptomatology. Table 4 gives the mean scores of patients. Of those who had higher levels of emotional distress or symptomatology: 43% of patients attained a raised score on a measure of cognitive/conative/social alienation ("schizophrenia" scale), 57% of patients were raised on a measure of depression ("depression" scale), 83% of patients were raised on a measure of sensory and motor complaints ("conversion hysteria" scale), and 96% of patients endorsed high levels of somatic symptoms ("hypochondriasis" scale). Depression was not associated with the Wisconsin card sorting measures (categories achieved F(1,38)=0.34, P<0.57); perseverative errors (F(1,38)=0.32, P<0.58); auditory selective attention (F(1,38)=0.65, P<0.43); complex figure immediate recall (F(1,38)=0.05, P<0.84); or delayed recall (F(1,38)=0.15, P<0.71) scores. However, depression was associated with the subjects' performances on the symbol digit modalities test (F(1,38)=5.33, P<0.03; regression coefficient=-0.30). Depression also did not significantly correlate with any of the verbal memory measures. Table 4 shows that the fatigue severity scale scores were very high compared with normative values, resulting in a group mean of T=101 (86% of patients). Fatigue was not a significant covariate of any of the cognitive deficits found.

Twenty two of 23 patients used 73 medications, of which 10 were antidepressants

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Table 4 Patient's mean fatigue severity scale score and MMPI-2 T scores (mean(SD) T = 50(10))

MMPI-2 scales	*T score*	*P value < 0.02*
L	55.6	
F	63.4	
K	51.3	
1 "Hypochondriasis"	83.7	*
2 "Depression"	77.0	*
3 "Conversion hysteria"	87.2	*
4 "Psychopathic deviate"	62.2	
5 "Masculinity-femininity"	46.8	
6 "Paranoia"	61.3	
7 "Psychaesthenia"	69.5	
8 "Schizophrenia"	71.4	*
9 "Hypomania"	56.3	
10 "Social introversion"	51.9	
Fatigue severity scale	101.0	*

(usually tricyclic compounds); of the eight patients taking antidepressants, only three had had brain scans, and two showed structural abnormalities. Nine patients were taking 11 antianxiety agents (usually benzodiazepines), and four of the five who were scanned had abnormalities. One patient was prescribed morphine (not scanned), and many were using non-narcotic analgesics, and anti-inflammatory and antimalarial or rheumatic medications to control their symptoms. Five patients reported sleeping fewer than six hours a night with the addition of naps (range 2-13 hours a night). Pain complaints most often involved muscle spasms or pain (15 patients), joint pain (10), and headaches (seven). Three patients denied significant pain; one of these patients had been scanned, and the MRI showed cerebrovascular damage. Patients taking anxiolytic or antidepressant medications were compared in the measures of impairment (PASAT, ASAT, SDMT, WCST, complex figure recall) with the rest of the cohort, and similar comparisons were made of the subgroup of patients with sleep deprivation defined as less than six hours per night, and the subgroup of patients who reported pain symptoms. No differences between these subgroups approached significance, with the exception of the 14 patients taking anxiolytic or antidepressant medications, whose scores showed a trend towards better performance on the WCST ($t(21)=1.84$, $P<0.08$).

LONGITUDINAL FINDINGS

We tested change over the follow up interval using subjects as their own controls. The only change detected in patients' cognitive impairments was an improvement in the number of perseverative errors made on the Wisconsin card sorting test. The change from a mean of 8.7 errors in the first evaluation to a mean of 4.8 errors in the second evaluation was not significant ($F(1,10)=3.15$, $P<0.11$). Although all patient's scores were in the direction of improvement, most variance was due to one patient who showed major improvement. However, this patient at the second testing also endorsed higher levels of depression, worry, and physical symptoms on the MMPI-2. A trend towards group exacerbation of depression as measured by the MMPI-2 was found, so that the patients' mean score went from T=67 to T=81 ($F(1,10)=4.82$, $P<0.06$). Five of six patients showed a significant increase in scores, and one subject's depression score declined. Post hoc analyses disclosed no other trends in the other neuropsychological measures. When individual comparisons of scores from the two evaluations were made (significant change defined as change within the patient ≥ 1 SD), the ratio of improvements to declines was 2:1.

Discussion

We found that our patients with EMS had executive dysfunction as indicated by impairment in tests requiring conceptual set shifting and selective and divided attention: Wisconsin card sorting test (clinically impaired in 48% of patients), auditory selective attention test (65% of patients), paced auditory serial addition test (91% of patients). Patients' performances were also impaired in immediate and delayed recall of a complex figure (65% and 83% of patients respectively). However, the patient group was not impaired in visuospatial perception (though some individual patients had visuospatial deficits) nor in immediate and delayed recall of simple visual material. In addition, the patient group was not impaired in any test involving verbal retrieval (list learning, delayed retrieval, object naming, speeded verbal fluency). The patients' deficit on the symbol digit modalities test (74%) involving visual attention and speeded scanning, was weakly but significantly correlated with the MMPI measure of depression. These results are partially consistent with the findings of group[14 19] and case studies.[12 13 18] We found impaired scores on tests of processing speed, visual memory, and conceptual set shifting, but also a pronounced absence of verbal memory and motor slowing deficits. Evidence of impairment of visual memory was found only in tests involving complex material.

One contributory explanation for the lack of verbal memory and motor speed deficits could be the less conservative confidence levels used by Krupp *et al*, as they did not adopt Bonferroni corrections. Another factor in explaining the lack of impairment in verbal recall in our group is that our patients were not selected for memory complaints or by any other criterion other than diagnosis of EMS, and thus may be a more representative sample of the EMS population. The sample of Krupp *et al* was defined as the subset (75%) of the Stony Brook patients with EMS[9] who complained of cognitive difficulty, whereas our group comprised all patients diagnosed with EMS and referred by rheumatologists who referred all patients regardless of their cognitive complaints. In the study of Krupp *et al*, 62% of those patients who reported cognitive difficulty showed impairment on neuropsychological tests.[14] Lynn *et al*[12] also reported memory complaints in a patient with EMS, which seemed to correlate with severe verbal and visual memory deficits on neuropsychological testing. Thus in our patients who were not preselected for memory complaints, a lesser degree of neurocognitive impairment, particularly in memory,

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is not surprising. However, heterogeneity in the degree of neurocognitive impairment among patients with EMS also seems to be the rule.

Another explanatory factor for our findings which are inconsistent with those of Krupp *et al* may be the difference in the time of testing. Our patients were evaluated one to four years after the patients of Krupp *et al* (1991, personal communication) and later after the date that the contaminated product was on the market. Thus our group could have lesser morbidity secondary to some degree of amelioration of symptoms. We found no significant changes in cognitive function in the longitudinal results of six patients; however, individual improvements within patients occurred more often than individual decrements. Kaufman[3] reported that symptoms and abnormalities in laboratory studies are most severe during the early acute period of EMS, and others have reported at least partial resolution of some symptoms over one to two years.[4 6 52] Whereas systemic corticosteroid therapy has resulted in the complete or partial resolution of symptoms in some patients over one to two years,[6 52 53] Hertzman *et al*[52] recently reported that rates of cognitive complaints remained unchanged over 18 to 24 months of follow up. Other evidence exists that the vascular component affecting pulmonary diffusion capacity may be fully reversible.[4] Our EMS group showed deficits limited in scope, and may represent the profile of the more prolonged effects of EMS, and reflect some degree of improvement over the early stage of contamination. Further, the follow up subgroup gave evidence that whereas decline in neurocognitive function can occur in some patients, there is also frequent improvement in brain function in others during the chronic phase.

The impaired neurocognitive functions we found have been previously characterised as executive functions requiring monitoring responses[54] and divided attention.[55] In reference to memory, only visual recall of complexly organised material from long term memory was defective in our EMS group. This impairment could be due to a complexity effect[56] rather than due to the integrity of long term memory processes as they had strong performances in the verbal long term memory procedures. However, differences in the underlying cognitive processes required for deep encoding of meaningful words and abstract designs also differentiates the verbal and visual memory tests. Their visual memory deficit could also be explained by a modality specific effect in storage and retrieval of perceptual information from long term memory. However, the patients had no difficulty in the delayed recall of simple visual material from long term memory, so that a complexity effect or difficulty organising perception are better explanations of the deficits. In this case, the visual memory deficit is likely another component of a syndrome of executive dysfunction.

An explanation for the pattern of cognitive deficits we found may come from the MRI findings. For example, the idiopathic hypereosinophilia syndrome has similar effects on the cognitive state as EMS, and is known to induce CNS neurotoxicity in about 65% of patients.[11] In our group, 67% of the subjects (eight of 12) who had scans showed white matter hyperintensities on MRI, often in the frontal lobe. There are several reports of heterogeneous white matter hyperintensities in case studies of patients with EMS who did not have other neurological disease such as hypertension or diabetes which could account for the lesions. These reports have disclosed lesions in the splenium of the corpus callosum,[14] in the deep and subcortical white matter including the periventricular area,[12 15 16 57] and in the pons.[12 57] Sibbitt reported, in his review of 77 MR scans of patients with EMS, hyperintensities in 68% of his series (1993, personal communication). Herrick reported (1993, personal communication) on the postmortem pathology of four patients. In two patients the brain was normal, in one focal acute ischaemia was seen, and in the last patient various ischaemic lesions, non-multiple sclerosis demyelinating lesions, and old microscopical infarcts, were found. Estimates of the incidence of white matter hyperintensities in normal subjects are between 14% and 29% in persons younger than 50 arrayed equivalently over each decade,[58 59] 55% in 50-59 year old subjects,[59] and 46% to 65% in subjects between the ages of 45-80+.[60 61] Our patient group ranged in age between 31 and 58 years, and only one patient with white matter abnormalities had hypertension, so that the estimate of 67% in the available scans likely exceeds the population incidence. Executive dysfunction is a specific and frequent impairment related to white matter disease.[24–28 62] Deficits in processing efficiency, especially during complex operations, and conceptual set shifting are characteristic of some subcortical disorders of white matter such as multiple sclerosis,[20 63] and clinically significant leukoariaosis.[64–66] As executive dysfunction has been an invariable finding in EMS studies, and as white matter hyperintensities occur in severe cases and more often than base rates in patients with EMS, EMS seems to be a model of heterogeneous although mild cerebral white matter disease. However, conclusions about the role of white matter disease in EMS are limited, and there needs to be an investigation which involves all patients and controls the indices of MRI scanning, the epoch of scanning, repeated scans, and comparisons of MRI ratings.

Emotional distress including depression was significantly raised in our group (57%), and has often been reported in other studies of patients with EMS.[14 67] Although findings of depression in patients with EMS is common, we found little evidence to justify attributing cognitive impairment to depression. Depression was not significantly correlated with most of the deficits identified, and five of the six re-evaluated subjects reported an increase in depression on the MMPI-2 without deterioration in cognition. Gaudino *et al*[68] reported depression as a significant predictor of verbal memory, visual search, and attention in an EMS group. We also found that depression partially accounted for

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patients' deficits in a different test of visual search and attention, which provides convergent evidence of the association of depression to selective cognitive deficit. However, we found no association between depression and verbal memory. Furthermore, patients being treated for depression and anxiety showed no greater impairment than the entire group, and their cognitive performance may actually have benefited from the treatment of emotional symptoms. The studies investigating links between depression and cognitive impairment in EMS[12 69] suggest that depression and cognition are dissociated in EMS. Fatigue is sometimes thought to cause neurocognitive impairment, although we found no evidence of associations between fatigue and cognitive deficits. The results of studies of the direct affect of fatigue on cognitive versus motor responses minimise the role of fatigue in causing neurocognitive deficits.[70 71] Sleep deprivation, based on self report of hours of sleep, was not a factor in our group's cognitive performances. The impact of pain on cognitive functions was not directly assessed in our study, but the effects are expected to be limited as pain has been found to disrupt attention only to emotionally positive stimuli.[72] Our analysis of those not reporting pain as a major symptom also provided no evidence of different neurocognitive levels in those with and without EMS related pain. Future studies could attempt to clarify the interaction of pain with cognitive functioning by directly measuring pain; however, pain tends to vary in EMS ranging from headaches, to hand pain with repetitive movement, to cramping during sleep, to unpredictable "electric" sensations in the spine, and this variability of the nature and periodicity of pain would complicate analyses. The inferences from our study of the specificity of impairment from the ingestion of L-tryptophan are also limited because litigation was not directly examined. All patients with EMS were in litigation although they were at widely differing stages, and we did not use a non-litigating clinical control group.

The converging deficit in executive functions across studies may represent the critical residual neurocognitive effects of EMS. Alternatively, these cognitive functions may be the most severely affected in EMS, and may represent the residual deficits of the disease. Confirmation of executive dysfunction in EMS is needed based on further neuropsychological testing, particularly of working memory paradigms which invoke the allocation and execution of attention. A study that correlates white matter burden with cognitive deficits may help to identify whether synergistic effects of diffuse white matter injury or regionally specific injury best accounts for the executive deficits found in patients with EMS.

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Eosinophilia-myalgia syndrome: selective cognitive impairment, longitudinal effects, and neuroimaging findings

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