CME

Course and prognosis in early-onset MS

Comparison with adult-onset forms

I.L. Simone, MD; D. Carrara, MD; C. Tortorella, MD; M. Liguori, MD; V. Lepore, MD; F. Pellegrini, DStat; A. Bellacosa, MD; A. Ceccarelli, MD; I. Pavone, MD; and P. Livrea, MD

Abstract—*Objectives:* To establish the prognostic role of clinical and demographic factors in a hospital-based cohort of MS patients categorized by age at clinical onset and clinical course. *Methods:* Eighty-three patients with MS had a clinical onset of the disease in childhood (age <16 years; early-onset MS [EOMS]) and 710 in adult age (between 16 and 65 years; adult-onset MS [AOMS]). Patients were followed for a mean period of observation of 5 years. Univariate and multivariate analyses of clinical and demographic predictors for rapid progression and disability were performed using a stepwise Cox regression model with time-dependent covariates. *Results:* In EOMS, the Expanded Disability Status Scale (EDSS) evaluated at last clinical examination was lower than in AOMS, despite a longer disease duration. The probability to reach growth disability and progression was significantly lower in EOMS than in AOMS. Median times to reach EDSS score of 4 and secondary progression were longer in EOMS than in AOMS, but the age at both endpoints was significantly lower in EOMS. In EOMS and AOMS, an irreversible disability was related to a secondary progressive course, a sphincteric system involvement at onset, and an older age at onset (in EOMS only for the group >14 years); in AOMS, other unfavorable factors were a pyramidal involvement at onset and a high relapse frequency in the first 2 years. The risk of entering secondary progression was significantly influenced by a high number of relapses in EOMS and by a higher age at onset and a short interattack interval in AOMS. *Conclusion:* A slower rate of progression of disease characterized EOMS patients, suggesting more plasticity to recover in developing CNS, but the early clinical manifestation cannot be considered a positive prognostic factor.

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Retrospective analyses on MS populations have shown that the clinical onset of the disease is often insidious and its occurrence before the age of 10 years and after 50 years is considered rare. The employment of current diagnostic criteria[1,2] along with advances in biochemistry, immunology, radiology, and molecular genetics are proving to be useful to define MS diagnosis in childhood and elderly age[3] as well as to differentiate several diseases mimicking MS. In particular, the distinction between the first clinical attack of MS and acute disseminated encephalomyelitis (ADEM) is often difficult.[4,5] Most studies described single cases or small series of patients with early-onset MS (EOMS)[6-10]; the youngest of them was a 10-month-old girl.[11] A very early onset of the disease has been described in children under 6 years of age.[12] More complete information on MS in childhood derives from collaborative studies, which reported that EOMS occurs in 2.7 to 5% of all MS cases.[13-16] Similarly, there are very few studies on late MS clinical onset, which showed a highly variable frequency, ranging from 0.6 to 9.4%.[3,17,18]

Many clinical studies analyzing the prognostic factors involved in predicting the outcome of MS were carried out over the last years. In spite of some discordance, demographic and clinical variables such as age at clinical evidence of the disease, degree of first remission, interval between the first two relapses, and functional system involvement at onset were considered as reliable indicators of the disease course in different studies.[19-26] An older age at clinical onset is frequently associated with a poor prognosis; by contrast, the implication of EOMS with regard to long-term outcome is not entirely clarified. The prognostic factors in EOMS have been evaluated in few studies, performed with various methodologic approaches,[14,16,27] and the discussion about the existence of clinical courses different from that of adult-onset MS (AOMS) is still open. In a recent prospective study performed in 78 patients with EOMS, a worse prognosis was predicted by high clinical disability at onset.[28]

Based on these assumptions, we analyzed a large hospital-based historical cohort of MS patients differentiated by age at clinical onset and course to assess the long-term prognosis of selected clinical and demographic features.

From the Department of Neurological and Psychiatric Sciences (Drs. Simone, Carrara, Tortorella, Liguori, Lepore, Bellacosa, Ceccarelli, Pavone, and Livrea), University of Bari, and Department of Clinical Pharmacology and Epidemiology (Dr. Pellegrini), Istituto di Ricerche Farmacologiche Mario Negri, Consorzio Mario Negri Sud, Italy.

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Address correspondence and reprint requests to Prof. Isabella Laura Simone, Department of Neurological and Psychiatric Sciences, University of Bari, Piazza Giulio Cesare, 70124 Bari, Italy; e-mail: isasimone@neurol.uniba.it

Table 1 *Clinical and demographic features in MS population*

Variable	Not primary progressive course		Primary progressive course	
	Early-onset MS, n = 83	Adult-onset MS, n = 596	Adult-onset MS, n = 114	*p* Value*
Median (range) age at onset,† y	14.25 (1.3–15.9)	25.9 (16.1–56.1)	37.2 (16.5–65)	
Modal age at onset, y	15	24	29	
Females/males (ratio)	54/29 (1.86:1)	389/207 (1.87:1)	67/47 (1.42:1)	0.4102
Disease course at last follow-up, no. (%)				
Relapsing–remitting	71 (85.5)	453 (76)		0.0525‡
Secondary progressive	12 (14.5)	143 (24)		
Primary progressive			114	
No. of functional systems involved at onset no. (%)				0.309
One	54 (67.5)	382 (65)	66 (58.9)	
More than one	26 (32.5)	206 (35)	46 (41.1)	
Not assessed	3	8	2	
Pyramidal system at onset, no. (%)	30 (36.1)	235 (39.4)	97 (85.1)	<0.0001
Sensory system at onset, no. (%)	15 (18.1)	221 (37.1)	28 (24)	0.0003
Cerebellar/brainstem at onset, no. (%)	34 (40.9)	204 (34.2)	13 (11.4)	<0.0001
Sphincteric system at onset, no. (%)	7 (8.4)	34 (5.7)	17 (14.9)	0.0023
Cognitive or psychiatric impairment at onset, no. (%)	6 (7.2)	19 (13.9)	8 (7)	0.0577
Sexual disturbances at onset, no. (%)	—	5 (0.84)	2 (1.75)	0.3647
Optic neuritis at onset, no. (%)	19 (23)	129 (21.6)	5 (4.4)	<0.0001
Median (range) first interattack interval,† y	3.1 (0.1–27.5)	2 (0.11–21.5)		0.0035
Median (range) EDSS at last follow-up†	2.5 (0–8.5)	4 (0–9)	6 (3–9)	<0.0001
Median (range) disease duration,† y	14.1 (2.96–48)	9.6 (3.03–44.8)	11.24 (3.23–36.3)	0.0006
No. (range) of relapses in first 2 y	1 (1–9)	2 (1–9)		0.0959
Median (range) time to reach EDSS 4,† y	20.22 (4.38–47.96)	10.79 (0.5–44)	9.33 (1.08–35.25)	0.0002
Median (range) time to reach secondary progressive course,† y	16.05 (4.34–44.33)	6.88 (0.6–29.02)		0.001
Median (range) follow-up time,† y	5.31 (1.65–15.01)	6.34 (1.02–16.97)	4.74 (1.08–14.87)	

* *p* Values refer to Mann–Whitney *U* test or Kruskall–Wallis χ^2 test for continuous variables and to $2 \times \kappa$ contingency tables χ^2 test for categorical ones.
† Continuous variables.
‡ The χ^2 test refers to "not primary progressive course" only (early-onset vs adult-onset).

EDSS = Expanded Disability Status Scale.

Patients and methods. *Patients.* Seven hundred ninety-three MS patients, followed at the MS Center of the Department of Neurologic and Psychiatric Sciences of the University of Bari, Italy, were retrospectively reviewed and included in the analysis. All data were collected in a standardized European database for MS (EDMUS).[29] With use of the widely applied cutoff of age at clinical onset of the disease,[13-16,27] 83 patients had the clinical onset of the disease in early age (EOMS; <16 years) and 710 patients in adult age (AOMS; between 16 and 65 years), and 63 of them had their first symptoms in elderly age (after 45 years). Based on medical history and clinical–paraclinical evaluations, cases of early and adult onset of clinical symptoms were classified as definite MS (360 clinically definite and 433 laboratory-supported definite MS).[1] Patients were observed over a mean follow-up time of 5 years. General demographic and clinical features were evaluated in all patients (table 1). Clinical course was classified according to standardized definitions.[30] Residual neurologic disability after the first clinical attack was not considered in the analysis because it was not available in all MS patients. The time to reach an irreversible clinical disability corresponding to a degree of Kurtzke's Expanded Disability Status Scale (EDSS) score 4 (limited walking ability but able to walk without aid or rest for >500 m)[31] and the time to start a secondary progression were considered as endpoints. We focused on the disability score of 4 because only six EOMS patients reached an irreversible EDSS score of 6.

Diagnostic MRI was performed in 90% of MS patients at the time of the first clinical attack or during the clinical course, and serial MRI were carried out in several patients to evaluate the disease activity. MR findings were strongly

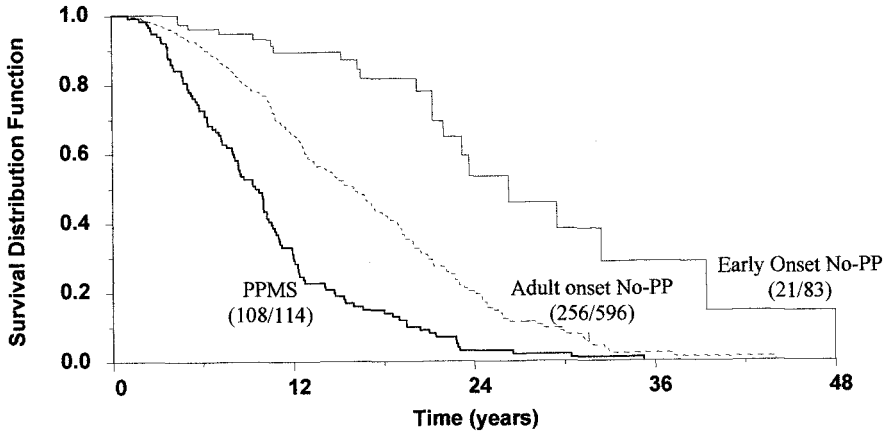

Figure 1. Kaplan–Meier survival curve for time to reach Expanded Disability Status Scale (EDSS) 4. The proportion of patients who reached EDSS 4 in each group is reported in parentheses. Log-rank test, $\chi^2 = 109.51$, $p < 0.0001$. No-PP = not primary progressive; PPMS = primary progressive MS.

suggestive of demyelinating disease; however, in this retrospective study, we did not analyze the MRI data because of the lack of standardization of MRI procedures.

Family history and associated diseases were investigated in all MS patients. Twenty-eight percent of AOMS and 5% of EOMS patients were under disease-modifying treatments; the most used were interferon-β (148 with relapsing–remitting or secondary progressive AOMS and 2 with relapsing–remitting EOMS) and azathioprine (35 with secondary progressive or primary progressive AOMS); 2 EOMS patients were treated with IV immunoglobulins. The relatively low percentage of treated patients, heterogeneity of therapy, period of treatment, and clinical course of MS patients did not allow us to analyze treated patients separately.

Statistical analysis. For statistical analysis, MS patients were categorized into groups based on 1) age at clinical onset (EOMS and AOMS groups, as described above) and 2) clinical course defined as "not primary progressive" (including relapsing-remitting and secondary progressive patients) and "primary progressive."

Comparison between clinical and demographic variables in MS groups was made by $2 \times \kappa$ contingency tables χ^2 tests for categorical variables and Kruskall–Wallis χ^2 tests for continuous ones. Considering the large difference between primary progressive and other MS clinical courses, we analyzed this group separately.

With use of time to reach irreversible EDSS 4 and time to secondary progression as survival endpoints, separate Kaplan–Meier survival curves were presented for both endpoints; differences in survival times were assessed with a log-rank test. Time-dependent Cox proportional hazards regression models were used to assess possible predictors of survival.[32] Cox models with time-dependent covariates allowed us to take into account, along with covariates at baseline, also the effect on survival of covariates changing over time (such as the clinical course, first interattack interval, and number of relapses in the first 2 years). Univariate and stepwise multivariate Cox models were tested for the two survival endpoints. In the tables, the results were expressed in terms of hazard ratios and Wald χ^2 statistics p values. All the analyses were performed using SAS/STAT (version 6.12) and some routines written in SAS Macro Language (SAS software release 6.12; Cary, NC, 1989 to 1996).

Results. *Demographic and clinical details.* The distribution by age at clinical onset in 793 MS patients showed a peak between 21 and 30 years, including in this range 367 patients (46.3%), whereas the frequency of onset in early age was 10.5%. In the EOMS group, 13 patients showed a clinical onset at <10 years (median age 8.25 years, range 1.3 to 9.88 years), 26 patients between 10 and 14 years (median age 12.78 years, range 10.24 to 13.87 years), and 44 patients at >14 years (median age 15.04 years, range 14.09 to 15.95 years). According to clinical course, 679 cases were identified as "not primary progressive" (including all of the EOMS group and 596 AOMS patients) and 114 cases as "primary progressive" (including only AOMS patients, 33 of them with onset of the disease in elderly age).

The female/male ratio did not differ in the MS groups; however, EOMS patients showed an increase of woman predominance (ratio 2.6:1) in the pubertal period (between 10 and 14 years), confirmed in the group with a clinical onset at >14 years of age (ratio 2.4:1), in contrast to a significant male predominance in the group <10 years (ratio 0.6:1). In EOMS, the relapsing–remitting course was significantly more frequent, whereas no cases was primary progressive. Cerebellar and brainstem systems at onset were involved with significantly high frequency in EOMS. The EDSS evaluated at last clinical examination was significantly lower in EOMS than in the other MS groups, despite a significant longer disease duration (see table 1).

Five patients with EOMS had a first-degree relative with MS (three sib pairs and two parent–child pairs); the frequency (6%) did not differ from that in the adult group (3.1%).

Prognostic factors. When the time to reach irreversible disability score, corresponding to EDSS 4, was considered as the endpoint, Kaplan–Meier survival curves stratified by clinical course and age at onset showed that a higher percentage of EOMS patients (75%) did not reach this disability stage at follow-up times than other MS groups (57% of AOMS "not primary progressive" and 5% of "primary progressive" course) (log-rank test, $p < 0.0001$) (figure 1). The estimated median time to reach EDSS 4 was significantly longer in the EOMS than the AOMS groups (see table 1), but the age at EDSS 4 was lower in EOMS patients (median 31.6 years, range 18.15 to 58.28 years) than in AOMS "not primary progressive" (median 41.16 years, range 21.78 to 69.22 years) and "primary progressive" (median 48.18 years, range 19.96 to 71.55 years) ($p < 0.0001$).

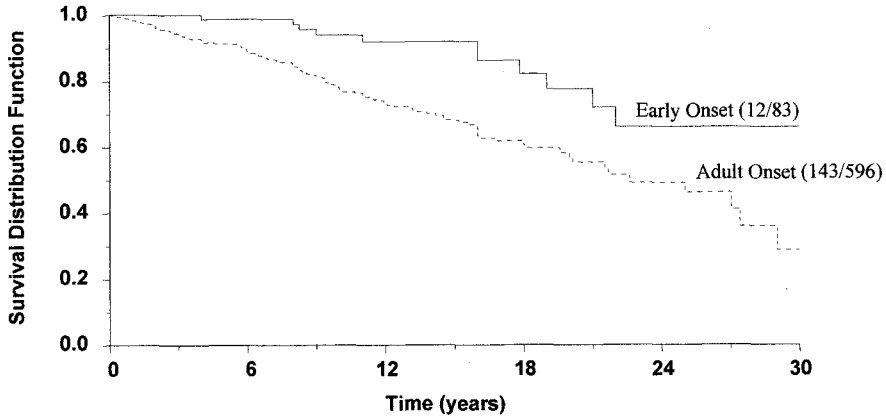

Figure 2. Kaplan–Meier survival curve for time to reach progression. The proportion of patients who reached secondary progression in each group is reported in parentheses. Log-rank test, $\chi^2 = 12.84$, $p < 0.0003$.

The probability to reach a secondary progression in a short time, evaluated only in the group of "not primary progressive" patients, was lower in EOMS patients (14.45% of events) than in AOMS patients (24% of events) (log-rank test, $p < 0.0003$) (figure 2), with an estimated median time of developing the secondary progressive phase significantly longer in EOMS (see table 1). The median age at secondary progression was lower in EOMS patients (30.7 years, range 17.6 to 52.6 years) than in AOMS patients (37.55 years, range 22.7 to 60.23) ($p < 0.002$).

In EOMS patients, a secondary progressive course and a short interval between the first and second attack were significantly unfavorable factors associated univariately with a greater risk of developing over time high clinical disability; furthermore, borderline significance was found for sphincteric system involved at onset. Testing the effects of age at onset in EOMS subgroups, only the age >14 subgroup for time to reach EDSS 4 was significant. The further step of multivariate Cox confirmed the significant association between growth disability, secondary progressive course, and sphincteric system involvement. The analysis did not retain any age subgroup for the outcome (table 2)

The risk of developing a secondary progression in EOMS was univariately associated with a first interattack interval shorter than 1 year and a high number of relapses in the first 2 years of the disease. The adverse prognostic role of a high number of relapses in the first 2 years of the disease was confirmed by multivariate analysis. The age at onset did not influence this outcome (see table 2).

In the group of AOMS "not primary progressive" patients, the risk to reach irreversible disability in a short time was greatly influenced by several factors including a higher age at onset of >45 years, an involvement of pyramidal and sphincteric systems at onset, as well as a secondary progressive course and a high number of clinical relapses

Table 2 *Univariate and multivariate survival analysis for time to reach EDSS 4 and time to reach progression in EOMS patients*

	Time to reach EDSS 4				Time to reach progression			
	Univariate		Multivariate		Univariate		Multivariate	
Prognostic variable	HR	*p* Value	HR	*p* Value	HR	*p* Value	HR	*p* Value
Age at onset subgroups (r.c.: ≤10)								
10–14 y	2.97	0.17			1.00	0.99		
>14 y	5.78	0.02			3.11	0.20		
Male sex	1.39	0.48			1.17	0.8		
No. of systems involved at onset (>1)	0.75	0.6			0.85	0.81		
Pyramidal system at onset	0.81	0.66			0.91	0.87		
Sensory system at onset	1.23	0.75			1.17	0.84		
Optic neuritis at onset	0.57	0.37			0.7	0.65		
Cerebellar/brainstem at onset	0.75	0.54			0.91	0.87		
Sphincteric system at onset	4.42	0.07	5.60	0.041	2.47	0.4		
Cognitive or psychiatric impairment at onset	1.12	0.88			1.14	0.9		
First interattack interval (<1 y)	3.09	0.035			4.27	0.021		
No. of relapses in first 2 y (>1)	1.9	0.16			4.52	0.016	4.52	0.016
Secondary progressive course	9.98	<0.001	11.07	<0.001	—	—	—	—
Events				21				12
Total				83				83

EDSS = Expanded Disability Status Scale; EOMS = early-onset MS; r.c. = reference control category; HR = hazard ratio.

Table 3 *Univariate and multivariate survival analysis for time to reach EDSS 4 and time to reach progression in AOMS patients*

	Time to reach EDSS 4								Time to reach progression			
	Not primary progressive				Primary progressive				Not primary progressive			
	Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate	
Prognostic variable	HR	*p* Value	HR	*p* Value	HR	*p* Value	HR	*p* Value	HR	*p* Value	HR	*p* Value
Age at onset >45 y	3.09	<0.001	2.12	0.001	1.37	0.15			2.95	<0.001	2.92	<0.001
Male sex	0.84	0.2			0.76	0.16			1.01	0.96		
No. of systems involved at onset (>1)	1.44	0.006			1.35	0.14			1.05	0.78		
Pyramidal system at onset	1.41	0.007	1.48	0.002	2.59	0.002	2.43	0.004	0.92	0.65		
Sensory system at onset	1.15	0.29			1.06	0.78			0.94	0.75		
Optic neuritis at onset	0.78	0.10			0.49	0.12			1.01	0.95		
Cerebellar/brainstem at onset	0.94	0.64			1.58	0.15			0.85	0.36		
Sphincteric system at onset	1.99	0.005	1.96	0.007	2.14	0.005	1.88	0.021	1.52	0.23		
Sexual dysfunction at onset	1.28	0.67			1.07	0.92			1.02	0.96		
Cognitive and psychiatric impairment	1.41	0.27			0.32	0.006			0.57	0.34		
First interattack interval (<1 y)	1.88	<0.001							1.6	0.02	1.59	0.022
No. of relapses in first 2 y (>1)	2.01	<0.001	1.73	<0.001					1.44	0.047		
Secondary progressive course	4.12	<0.001	3.4	<0.001					—	—	—	—
Events				256				108				143
Total				596				114				596

EDSS = Expanded Disability Status Scale; AOMS = adult-onset MS; HR = hazard ratio.

in the first 2 years of the disease. The significant association between irreversible growth disability and involvement of pyramidal and sphincteric system at onset was confirmed in AOMS "primary progressive" patients (table 3).

In AOMS patients, the critical factors associated with a secondary progression were a higher age at onset and a short interval between the first and second relapse (see table 3).

Discussion. The clinical expression of MS before adulthood is rare and occurs predominantly after a subclinical phase, as indicated by MRI findings. Several studies showed that 50 to 80% of patients with clinically isolated syndromes suggestive of MS have multifocal white matter lesions on MRI of the brain, suggesting that the "true" onset of the disease may precede the appearance of clinical symptoms.[33] Nevertheless, an early predisposition with clinical evidence during adolescence is demonstrated. In the current study, we found a higher frequency of EOMS (10.5%) than other authors, who reported percentages from 2.7 to 5%.[13,15,16] We think that this increase reflects a recruiting bias in a neurologic center highly specialized in MS diagnosis and treatment. Conversely, the absence of prodromal illness as well as of seizures, bilateral optic neuritis, and meningism, the finding of multiphasic clinical course during the follow-up, and the progressive deterioration over time in these patients were strongly indicative of MS and excluded a possible diagnosis of ADEM. According to previous studies, the MS diagnosis can be adequately defined only by observing the subsequent natural history of the disease; in our study, the observation was prolonged for a mean period of 5 years.[4,5]

An increased susceptibility of women was confirmed in EOMS, without significant difference in ratio with AOMS.[14-16] Nevertheless, a prevalence of women was observed in pubertal age (between 10 and 14 years), even if lower than the female overrepresentation found in our recent collaborative study.[28] Several authors reported a higher frequency of women in EOMS and in late-onset MS, emphasizing the role of hormonal factors in increasing female MS susceptibility during puberty and menopause.[34,35]

Consistent with previous studies, in EOMS, the clinical course was predominantly relapsing-remitting,[13,15,16] whereas no patient had the primary progressive course,[27,28] which was rare in other reports.[12-15] In AOMS, the frequency of the primary progressive and secondary progressive course was similar to the range in other studies,[19,20,24,25] and our data confirm that the primary progressive form occurs more frequently in later ages.[21,24,25]

In agreement with our previous collaborative studies,[16,28] symptoms suggesting an involvement of brainstem and cerebellar systems at onset were preponderant in EOMS patients, whereas the frequency of motor dysfunction was low[13-16,28] and increased with an increase of age at clinical onset, in particular, in "primary progressive" AOMS.[3,18,24,25,36-38]

In EOMS, a secondary progressive course and the involvement of sphincteric system at onset were critical elements that greatly influenced the risk of an irreversible disability score of EDSS 4. In disagreement with a recent collaborative study, which reported no association between age and disability, a higher age at onset in EOMS was univariately associated with a worse clinical disability.[28] In turn, the risk of entering secondary progression was associated with high number of relapses in the first 2 years.

In patients with "not primary progressive" AOMS, a secondary progressive course was confirmed to be associated with growth disability; however, other critical factors were an older age at onset and a short interval between the first and second attack. In line with several authors, motor and sphincter symptoms strongly influenced the risk to reach irreversible disability both in adult "not primary" and in "primary progressive" patients.[25,26,39,40] Finally, the risk of entering a secondary progressive course in AOMS patients was significantly associated with an older age at onset and a short first interattack interval.

A poor prognosis was found in few patients with EOMS, associated with a fewer number of clinical factors than AOMS. The lack of primary progressive course and a lesser incidence of motor dysfunction at onset in EOMS patients could be a favorable outcome regarding long-term disability, whereas a negative prognostic factor was a higher age at onset (>14 years). EOMS patients reached a worse clinical disability and a progression phase after long-term disease. Nevertheless, these patients get sick at a young age, and although the clinical course could be favorable for several years, they reach a more severe disease at a younger age than AOMS patients. This result is consistent with a recent report that suggests that early onset of the disease is not a favorable predictor of the outcome in all patients.[41]

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Face encoding and psychometric testing in healthy dextrals with right hemisphere language

Michael W.L. Chee, MBBS, MRCP(UK); and David Caplan, MD, PhD

Abstract—*Objective:* To document how right hemisphere language dominance in neurologically normal right-handed individuals affects lateralization of face encoding and level of performance in neuropsychological tests. *Methods:* Three healthy right-handed adults with predominantly right hemisphere language activation during single-word or sentence-level processing were identified from 210 consecutive right-handed subjects studied using blood oxygenation level-dependent contrast fMRI. These three study subjects (S1 to S3) underwent a second scanning session where they performed word and face encoding. Their functional scans were contrasted with those obtained from six healthy control subjects (C1 to C6) with left hemisphere language dominance. Psychometric tests were performed on the study subjects. *Results:* Right hemisphere-dominant language activation was reproduced in the second scanning session in the three study subjects. The extent to which the lateralization of face encoding was reversed varied. Right hemisphere language was associated with lower (but within normal) verbal IQ compared with performance IQ in two of three volunteers. Verbal and nonverbal memory scores were normal and did not differ appreciably. *Conclusion:* Right hemisphere-dominant language in healthy dextrals exists but is rare. The extent to which face encoding is reversed in these individuals is variable. Cognitive function does not appear to be significantly compromised even though some psychometric test scores are asymmetric in favor of nonverbal performance when the reversal of lateralization of face and word memory is not complete.

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Left hemisphere dominance for language is a robust brain functional asymmetry. Ninety-one percent of dextrals in an intracarotid amobarbital-based study[1] and 94% in a large fMRI-based series[2] demonstrated left cerebral hemisphere dominance for language. Right hemisphere language dominance has been reported in normal individuals using a variety of techniques including visual half-field studies, dichotic listening,[3,4] transcranial Doppler (TCD) sonography,[5-7] and fMRI,[8-10] as well as in the setting of early neurologic disorders.[11] Several studies have reported a negative impact on verbal and nonverbal functions when language is right hemisphere dominant. For example, epileptic individuals in whom right hemisphere dominance for language arose as a result of surgical or destructive lesions of the left hemisphere showed improvement in language function over time, but this never recovered to normal.[12,13] Deleterious effects on visuospatial skills have been reported when language function lateralizes to the right hemisphere as a result of neurologic disease. This has been attributed to the "crowding" of cognitive functions.[14-16] In patient-based studies, the negative impact on cognitive functions reported in association with right hemisphere language may reflect the effects of reorganization rather than development under nonpathologic conditions. It is therefore of interest to investigate if cognitive functions in neurologically normal individuals are similarly affected in the setting of right hemisphere language dominance.

From the Cognitive Neuroscience Laboratory (Dr. Chee), Singapore General Hospital; and Neuropsychology Laboratory (Dr. Caplan), Department of Neurology, Massachusetts General Hospital, Boston.

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Address correspondence and reprint requests to Dr. Michael W.L. Chee, Cognitive Neuroscience Laboratory, SingHealth Research Facility, 7th Hospital Ave., 1-11, Singapore 169611, Singapore; e-mail: mchee@pacific.net.sg

