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Neuropsychological syndromes in multiple sclerosis

Mª José Gil Moreno[1], Marta Cerezo García[2], Raluca Marasescu[2], Ana Pinel González[2], Laudino López Álvarez[3] and Yolanda Aladro Benito[2]
[1] Hospital de Móstoles, [2] Hospital Universitario de Getafe and [3] Universidad de Oviedo

Abstract

Background: Cognitive impairment in multiple sclerosis (MS) is common (45-65%).Deficits occur in speed of information processing (SIP), memory, attention, executive functions (EF) and visuoconstruction.Involvement of cognitive functions like language and gnosis is rare and lesser known. Our aim is to describe the cognitive function and the clinical and radiological features of five patients with MS and with neuropsychological syndromes (NPS). **Method:** Retrospective review of MS patients with NPS studied, using specific tests of SIP, memory, attention, EF, visuo-spatial abilities, praxis and language. **Results:** The sample included four women (3 relapsing-remitting MS/1 secondary progressive MS) and one man with primary progressive MS (aged between 30-55 years). Cognitive symptoms were the initial complaint in three cases. Three cases presented apperceptive agnosia and constructive apraxia, one case presented alexia with agraphia and the fifth patient presented motor aphasia. Four patients suffered cognitive dysfunction considered typical of MS. Magnetic resonance imaging (MR) in all cases showed high lesion volumes in T1 and T2-weighted sequences. A good correlation was observed between cognitive deficits and the location of the lesions in four patients. **Conclusions:** NPS may be the initial complaint in MS patients, often associated with other cognitive deficits, and it shows a close relationship with lesion location.

Keywords: Multiple sclerosis, neuropsychological syndrome, cognitive impairment, visual gnosis, aphasia.

Resumen

Síndromes neuropsicológicos en la esclerosis múltiple. **Antecedentes:** entre el 45-65% de los pacientes con esclerosis múltiple (EM) manifiestan déficits cognitivos en velocidad de procesamiento de la información (VPI), atención, memoria, funciones ejecutivas (FE) y visuoconstrucción. La alteración del lenguaje y la gnosis visual es infrecuente y poco reconocida. El objetivo es la descripción cognitiva, clínica y radiológica de cinco pacientes con EM con síndromes neuropsicológicos (SNPS). **Método:** revisión retrospectiva de pacientes de EM con SNPS estudiados mediante test específicos de atención, memoria, VPI, FE, visuoconstrucción, gnosis visual y lenguaje. **Resultados:** la muestra incluyó cuatro mujeres (3 EM remitente recurrente, 1 EM secundaria progresiva) y un varón con EM primaria progresiva (edades entre 30-55 años). Los déficits cognitivos fueron el síntoma inicial en 3 casos. Tres presentan agnosia aperceptiva y apraxia constructiva, uno alexia con agrafia y el quinto afasia motora. Cuatro asocian disfunción cognitiva "típica" de EM. En resonancia magnética observamos alto volumen lesional en secuencias potenciadas en T1 y T2 y correlación entre los déficits cognitivos y la localización de las lesiones en 4 de ellos. **Conclusiones:** los SNPS pueden ser la queja inicial en la EM, con frecuencia se asocian a otros déficits cognitivos y manifiestan una estrecha relación con la localización de la lesión.

Palabras clave: síndrome neuropsicológico, alteración cognitiva, gnosis visual, afasia, esclerosis múltiple.

Multiple Sclerosis (MS) is a chronic autoimmune disease of the Central Nervous System (CNS) characterized by inflammation, demyelination and axonal degeneration (Kornek & Lassmann 2004). It is the second cause of disability in young adults (Nieto, Sánchez, Barroso, Olivares, & Hernández, 2008). Typically, MS leads to disability because of cumulative motor, sensory and or visual deficit. Between 45 and 65% of the patients develop variable cognitive dysfunction over the course of the disease, being generally more frequent and severe in late phases (6 - 10%) and coexisting with physical impairment (Halligan, Reznikoff, Friedman, & La Rocca, 1988). However, cognitive dysfunction can be a major complaint and the main cause of disability in the initial stages and, in contrast to motor or sensory deficits, it does not tend to improve (Calabrese et al., 2009; Staff, Lucchinetti, & Keegan, 2009). When cognitive deterioration in MS becomes the predominant symptom, it has been named 'Cortical MS' by some authors (Zarei, Chandran, Compston, & Hodges, 2003).

Although in MS there is no specific pattern of cognitive dysfunction, the functions most commonly impaired are speed of information processing (SIP), attention, memory, executive functions (EF) and visuospatial and visuoconstructive abilities (Arango-Lasprilla, DeLuca, & Chiaravalloti, 2007; Genova, Sumowski, Chiaravalloti, Voelbel, & DeLuca, 2009; Patti, 2009). The brief batteries designed for the routine study of cognitive dysfunction in MS basically include the assessment of these functions (Boringa et al., 2001; Duque et al., 2012). The presence of neuropsychological syndromes (NPS) (cognitive and behavioural disorders observed in cerebral disease with involvement of cortical areas: agnosia, aphasia, apraxia) has only been described in isolated cases of MS, largely without regulated neuropsychological evaluation. Anecdotal cases have been published referring to acute aphasia (Devere, Trotter, & Cross, 2000), alexia with agraphia (Day, Fisher, & Mastaglia, 1987), alexia without agraphia (Dogulu,

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Corresponding author: Yolanda Aladro Benito
Servicio de Neurología
Hospital Universitario de Getafe
28905 Getafe (Spain)
e-mail: yaladro.hugf@salud.madrid.org

Kansu, & Karabudak, 1996; Mao-Draayer & Panitch, 2004), visual agnosia (Okuda et al., 1996) and patients with more than one severe cognitive symptom, with criteria for dementia (Staff et al., 2009; Stoquart-ElSankari, Périn, Lehmann, Gondry-Jouet, & Godefroy, 2010). When cognitive impairment is the initial and predominant symptom, it constitutes a diagnostic challenge (Calabrese, Filippi, & Gallo, 2010; Rinaldi, Calabrese, & Grossi, 2010).

The objective of this study is the cognitive assessment and the clinical and radiological description of five patients with MS presenting with NPS, evaluated by means of specific cognitive tests.

Method

Participants and procedure

This study was conducted in the Multiple Sclerosis Unit, at the Getafe University Hospital. From a total of 164 patients with MS (McDonald 2005 diagnostic criteria) (Polman et al., 2005) and neuropsychological evaluation, five were selected for presenting neuropsychological symptoms involving changes in cognitive processes such as language and visual gnosis.

An analysis of demographic data, course of the disease and degree of physical disability (Kurztke disability status scale, EDSS) (Kurtzke, 1983) was carried out at the moment of diagnosis of the NPS.

An estimate of the lesion volume was made by Magnetic resonance imaging (MR) axial T1- and T2-weighted sequences and coronal fluid attenuated inversion recovery (FLAIR). A low lesion volume (LV) was defined by the presence of 9 or fewer small size lesions (≤ 1 cm of larger diameter), a moderate LV by the existence of more than 9 lesions, at least 2 being large (diameter between 1 and 2 cm) and high LV if there was at least one large confluent plaque (larger than 2 cm in diameter). Cerebral atrophy was qualitatively measured by inspection of the width of sulci and of the third and the lateral ventricles in relation to age. Finally, we performed a second neuropsychological evaluation in some patients in order to estimate the progression or remission of the cognitive deficits.

Instruments

From October 2004 to March 2012, an extensive routine neuropsychological evaluation was performed including the functions typically impaired in MS (IPS, memory, learning, attention and EF), language and visuospatial abilities. The degree of anxiety and depression was also measured with the Beck Depression Inventory (BDI) and Spielberger's State-Trait Anxiety Inventory (STAI). Values lower than the normative values of each test were considered pathological.

Clinical cases

A summary of the clinical and radiological characteristics, as well as the results of the cognitive tests, is found in Tables 1-5.

Case number 1 is a 33-year-old woman. In 2001, she had the first MS symptom, consisting of motor impairment of the right hand. The second flare occurred in 2006 with motor-sensory impairment; therefore, the patient was diagnosed of relapsing-remitting MS (RRMS). Examination revealed signs of pyramidal, sensory and gait impairment (EDSS score: 3). The patient did not experience symptoms of cognitive deterioration at any time. However, a protocol neuropsychological evaluation in 2007 found a normal intelligence and low to moderate changes in IPS, attention, EF and visuoconstruction. Because difficulties at reading and writing were observed during the evaluation, additional linguistic processing was examined using the PALPA battery (Spanish version EPLA: Valle & Cuetos, 1995). The patient presented adequate phonological processing in the differentiation of sounds, letters and words independently of the imageability, frequency of use or morphology. She repeated sentences well and exhibited a good level of picture naming. Significant difficulties were observed in reading and writing, and she showed significant effects of imageability, frequency of use and inflectional morphology. The patient also had difficulties reading non-words, writing functional words and she committed errors depending on derivational morphology. These difficulties resulted in mistakes in the orthographic input lexicon and in grapheme-phoneme conversion (see Table 1). Symptoms of fatigue, anxiety and depression were also present. Cranial MR showed multiple large demyelinating lesions, some confluent in the deep white matter (WM) in both cerebral hemispheres, predominantly in the left parietal-occipital-temporal area, clear cortical atrophy and a thinning of the corpus callosum (Figure 1). At a new neuropsychological evaluation in 2009, a remission of her alexia-agraphia syndrome was observed.

Case number 2 is a 30-year-old woman with no relevant medical history. She was admitted in 2008 with a subacute left hemisphere syndrome consisting of right hemiparesis and impossible verbal expression. Neurological examination revealed a mild confusional state with a trend to agitation and a slightly decreased level of consciousness. The severity of the neurological involvement did not permit an adequate neuropsychological examination but confirmed severe motor aphasia with absence of spontaneous language and inability to repeat, name and produce automatic sequences. The patient was only able to utter two-syllable words and understood basic commands. Right unilateral visual and sensory neglect was observed together with severe right hemiparesis. MR showed an extensive lesion in the left frontal-parietal WM and two small lesions in the WM of the right hemisphere. No cortical involvement was observed (Figure 2). A brain MR after 4 months showed conversion to MS by the appearance of two new lesions, one of them active in the left occipital region, and the patient was diagnosed of RRMS. In 2009, a neuropsychological examination was carried out in another centre. The reports from this evaluation pointed out to an impairment in linguistic processing in both written and oral expression, with a slight alteration in understanding, a mild impairment in processing speed, attention, executive function (planning and working memory), memory and verbal learning, with preservation of visuospatial memory. In our centre, a neuropsychological evaluation performed in 2010 revealed a near-complete remission of the aphasia. Using the PALPA and the Boston Naming Test (BNT) (Table 2), adequate performance was observed in picture naming, phonological discrimination (words/non-words), lexical decision (depending on imageability and frequency) and linguistic understanding of sentence reading and repetition of words regardless of length, in both reading and writing. Only mild alterations in the repetition of non-words (non significant), SPI and attention were observed. In the BDI, the patient showed a slight lowering in mood, and the scores in the STAI were slightly elevated.

Case number 3 is a 43-year-old woman with secondary progressive multiple sclerosis (SPMS) of 10 years of evolution and an EDSS score 5 by impairment of walking, associated with mild decrease of visual acuity (>20/30) and fatigue. She complained of spatial disorientation, often getting lost in places close to her home. The first neuropsychological evaluation in April 2004 found difficulties in the visual perception of objects and space, and in the construction of figures under visual guidance. The patient had problems in integrating figures into a whole, in the mental rotation of figures and elements and also in using three-dimensionality. These deficits were explained by apperceptive visual agnosia, spatial agnosia and moderate constructional apraxia and were not

Table 1
CASE 1: Clinical details and cognitive results

Sex	Female
Level of education (years of schooling)	11
Age in the first neuropsychological evaluation (NPSE).	33
EDSS in the first NPSE.	3
Disease duration in the first NPSE (Years).	6
MRI:	
• *T1 lesion volume*	High
• *T2 lesion volume*	High
• *Cerebral atrophy*	Yes

TESTS	**SCORES 2007**	**SCORES 2009**	**Normative values**
***WAIS-III** (Wechsler Adult Intelligence Scale)*	*Max Score*	*Max Score*	*Max Score*
Digit Symbol-Coding	7	6	10
Block Design	4	8	10
Symbol Search	5	6	10
Letter-number sequencing	7	9	10
***WMS-III** (Wechsler Memory Scale)*	*Max Score*	*Max Score*	*Max Score*
Logical Memory I	10	13	10
Family Pictures I	13	16	10
Logical Memory II	11	13	10
Family Pictures II	12	19	10
Rey Osterrieth Figure (ROCF)	*Percentile*	*Percentile*	*Percentile*
Type of the copy	75	75	50
Accuracy of copy	60	80	50
Time of copy	75	50	50
Immediate recall condition	70	30	50
***BNT** (Boston Naming Test)*	*Raw Score*	*Raw Score*	*Raw Score*
Total Score	58	57	54
***CTMT** (Comprehensive Trail Making Test)*	*Standard. S*	*Standard. S*	*Standard. S*
Tests 1/2/3/4/5	28/29/24/19/27	26/34/37/30/29	50
Index	23	29	50
***BADS** (Behavioural Assess. of Disexecutive Syndrome)*	*Profile*	*Profile*	*Profile*
Temporal Judgement	2	2	2
Zoo Map	2	4	2
***WCST** (Wisconsin Card Sorting Test)*	*Percentile*	*Percentile*	*Percentile*
Total % of errors	90	86	50
% Perseverative Responses	94	92	50
Nº of categories completed	>16	>16	>16
Trials to complete 1st category	>16	>16	>16
Failure to maintain set	>16	>16	>16
Learning to Learn	>16	>16	>16
***PALPA** (Psycholinguistic Assessment of Language)*			
Reading	*Z score*	*Z score*	*Z score*
Letter discrimination W/NW	0.63/-2.63	0.54/-0.73	0
Visual lexical decision HIHF/HILF/LIHF/ LILF	0/-9.2/-4.2/0.55	0/0/0/0	0
Visual lexical decision. flex./deriv./non-word.	-2.8/0.33/7.9	-0.92/0.33/0.45	0
Reading HIHF/HILF/LIHF/ LILF	0.23/0.23/-3.27/0.58	0.23/0.23/0.23/0.58	0
Reading regular/Irregular.	0.35/0.1	0.35/0.1	0
Non words reading 5 letters/6 letters	-1.38/-0.62	-0.33/-0.33	0
Reading sentences	-1.91	0	0
Writing	*Z score*	*Z score*	*Z score*
Writing length 5 letters/6 letters	0/0.3	0/0.3	0
Writing to dictation HIHF/HILF/LIHF/ LILF	-1.91/-2.1/-4.25/-0.35	0.64/0.35/0.66/-0.35	0
Writing to dictation Noun/Adjective/Verb/function	-1.2/0.31/0.31/-3.4	-0.53/0.31/0.31/-0.35	0
Writing imageability. Nouns/functional W	-1.78/-3.71	-0.35/0	0
Writing to dictation Regular/ Derived/ Irregular	-3.4/-3.9/-1.68	0/0.23/-0.36	0
Writing non-words 5 letters/6 letters	0.27/-1.72	0.27/-0.95	0

justified by the degree of visual impairment (see Table 3). The patient also showed alterations in other cognitive functions: IPS, attention, EF and verbal and visual episodic memory. The cranial MR showed confluent periventricular demyelinating lesions, and other multiple non-confluent lesions in frontal and parietal and occipital areas, corpus callosum and also infratentorial, as well as signs of significant axonal damage and subcortical and cortical atrophy. In a second neuropsychological evaluation in 2009, cognitive performance was similar, and no progression of visual agnosia was found. However, she showed a slight decrease in SPI and EF. On the other hand, the patient displayed a high level of fatigue, symptoms of mild depression and mild anxiety.

Table 2
CASE 2: Clinical details and cognitive results

Sex	Female
Level of Education (years of schooling)	12
Age in neuropsychological evaluation (NPSE).	30
EDSS in NPSE.	3
Disease duration in the NPSE (years).	1.8
MRI:	
• *T1 lesion volume*	Medium
• *T2 lesion volume*	High
• *Cerebral atrophy*	No

TESTS	SCORE 2010	Normative Values
***WAIS-III** (Wechsler Adult Intelligence Scale)*	*Max Score*	*Max Score*
Digit Symbol-Coding	5	10
Block design	10	10
Symbol Search	7	10
Letter-Number sequencing	8	10
***WMS-III** (Wechsler Memory Scale)*	*Max Score*	*Max Score*
Logical Memory I	2	10
Family Pictures I	9	10
Logical Memory II	1	10
Family Pictures II	8	10
Rey Osterrieth Figure (ROCF)	*Percentile*	*Percentile*
Type of the copy	75	50
Accuracy of copy	90	50
Time of copy	50	50
Immediate recall condition	50	50
***BNT** (Boston Naming Test)*	*Raw Score*	*Raw Score*
Total Score	55	54
***CTMT** (Comprehensive Trail Making Test)*	*Standard S*	*Standard S*
Tests 1/2/3/4/5	33/29/29/29/38	50
Index	29	50
***BADS** (Behavioural Assess. of Disexecutive Syndrome)*	*Profile*	*Profile*
Temporal Judgement	1	2
Zoo Map	2	2
***WCST** (Wisconsin Card Sorting Test)*	*Percentile*	*Percentile*
Total % of errors	79	50
% Perseverative Responses	92	50
Nº of categories completed	>16	>16
Trials to complete 1st category	>16	>16
Failure to maintain set	>16	>16
Learning to Learn	>16	>16
***PALPA** (Psycholinguistic Assessment of Language processing in Aphasia)*	*Z score*	*Z score*
Discrimination minimal pairs words Equal/	0.36/0.42	0
Different Auditory lexical decision HIHF/	0/0/0.23/-0.35/-	0
HILF/LIHF/ LILF	0.6	
Repetition: Length 3L/4L/5L/6L	0.17/0.23/0.23/0	0
Repetition: non-words 3L/4L/5L/6L	-3.27/-4.33/0.31/0.53	0

Case number 4 is a 44-year-old woman with a very active form of RRMS, both clinical and radiological. She suffered her first episode of the disease in 2006, with visual problems that impeded her from moving into familiar places. In the following months, she experienced several relapses with sensory impairment and unstable gait. At a new neurological evaluation performed a year and a half later, cognitive impairment was observed together with pyramidal signs and mild cerebellar involvement, with an EDSS score of 3.5 (excluding cognitive impairment). In the neuropsychological evaluation, severe cognitive deficits were found: apperceptive visual agnosia, spatial agnosia, constructional apraxia, ideomotor apraxia and a significant alteration in coding and recovery of verbal episodic memory. She also exhibited dysfunctions in EF and naming (Table 4). A behavioural disorder was also observed, including infantilism and emotional liability. A mood disorder with marked symptoms of depression and anxiety was also present. The cranial MR showed multiple demyelinating lesions at periventricular and yuxtacortical level, with a relative predominance in the parietooccipital areas, and also an important number of lesions in the brain stem. There were an elevated number of black holes and several of the occipital lesions showed gadolinium enhancing. The patient was treated with different immunomodulating drugs from the beginning, but her cognitive dysfunction progressed incessantly to fully developed dementia. In 2011, after 5 years, the patient was in a state of absolute dependence, needing 24-hour care.

Case number 5 is a 57-year-old male patient with a history of hypertension and high levels of cholesterol. His relatives requested medical attention after observing progressive cognitive deterioration in the last 2 years, which impeded him from performing the required tasks at work. The patient, a waiter by profession, forgot the customers' orders, confused spaces at home and at work, had expression difficulties and was notably indifferent about his mistakes. The neurological exam showed only cognitive impairment (EDSS score 0, without considering cognitive impairment). The neuropsychological evaluation confirmed visual impairment in the perception of shape and space (apperceptive visual agnosia) and in colour naming (colour anomie), while maintaining perception of colour, topographical spatial disorientation, visuoconstructional impairment, preserving *gestalt* and simplification and ideomotor praxis for transitive gestures. The patient maintained verbal comprehension and the repetition of words but failed in the repetition of non-words. When dealing with spontaneous oral and verbal expression, there was a notable loss in naming abilities, construction of simple, grammatically incorrect sentences and hesitation. A decrease in the use of functional words and the presence of phonological and semantic paraphasia were also observed. Reading was considered adequate albeit slow and with some difficulty depending on the length of the sentence and presence of non-words. Verbal expression was the most affected, with difficulties with substitution, addition and omission, especially in longer and less frequent words. Spontaneous writing was characterized by grammatically incorrect sentences and a decrease in the use of functional words. These deficits resulted in difficulties in the phonological output lexicon, in acoustic-phonological conversion and in phoneme-grapheme conversion. Finally, the patient showed a low to moderate decrease in verbal episodic memory (coding), IPS, attention and EF (Table 5) as well as marked apathy. In another neuropsychological evaluation carried out 8 months later, mild progression of language disorder (anomie), semantic memory and free verbal long-term memory

were all found. In the case history file collected from the family, the great effect of these difficulties on this patient's daily life activities could clearly be seen. The MR showed multiple lesions in the periventricular WM of both hemispheres and confluent plaques in the parietal-temporal-occipital areas (Figures 3b and c). Two cerebrospinal fluid samples examined in two different laboratories showed intrathecal IgG synthesis. Another MR performed one year later showed a new large left parietal yuxtacortical lesion.

Discussion

The patients we have described herein represent a particular clinical form of MS characterized by impairment in cognitive functions rarely affected in this disease, such as aphasia, alexia, agraphia and visual agnosia. Even though these cognitive processes are generally disturbed in cortical lesions, different pathological processes of the subcortical white matter can cause similar clinical syndromes (Damasio, 1992; Naeser et al., 1982).

Table 3
CASE 3: Clinical details and cognitive results

Sex	Female
Level of education (years of schooling)	8
Age in the first neuropsychological evaluation (NPSE).	43
EDSS in the first NPSE.	5
Disease duration in the first NPSE (years).	10
MRI:	
• *T1 lesion volume*	Moderate
• *T2 lesion volume*	High
• *Cerebral Atrophy*	Yes

TESTS	Scores 2004	Scores 2009	Normative values
***WAIS-III** (Wechsler Adult Intelligence Scale)*	*Scaled Score*	*Scaled Score*	*Scaled Score*
Digit Symbol-Coding	2	2	10
Block design	5	5	10
Digit Span	8	7	10
Symbol search	5	4	10
Letter-Number sequencing	10	8	10
***WMS-III** (Wechsler Memory Scale)*	*Scaled Score*	*Scaled Score*	*Scaled Score*
Logical Memory I	7	7	10
Family Pictures I	6	6	10
Logical Memory II	5	5	10
Family Pictures II	7	7	10
Spatial Span	5	5	10
Rey Osterrieth Figure (ROCF)	*Percentile*	*Percentile*	*Percentile*
Type of the copy	50	50	50
Accuracy of copy	1	1	50
Time of copy	10	25	50
Immediate recall condition	10	1	50
***BNT** (Boston Naming Test)*	*Raw Score*	*Raw Score*	*Raw Score*
Total score	50	52	54
***CTMT** (Comprehensive Trail Making Test)*	*Standard S*	*Standard S*	*Standard S*
Tests 1/2/3/4/5	18/18/18/18/18	18/18/18/18/18	50
Index	18	18	50
***BADS** (Behavioural Assess. of Disexecutive Syndrome)*	*Profile*	*Profile*	*Profile*
Temporal Judgement	3	3	2
Zoo Map	1	1	2
Verbal Fluency	*Raw - Average*	*Raw - Average*	*Raw - Average*
Phonemic Fluency (FAS)	6	6	12-13
Semantic Fluency (animals, fruit, supermarket)	12	12	17-18
***WCST** (Wisconsin Card Sorting Test)*	*Percentile*	*Percentile*	*Percentile*
% total errors	5	3	50
% Perseverative Responses	7	1	50
Nº of categories completed	6	2	>16
Failure to maintain set	>16	6	>16
Learning to Learn	>16	-	>16
***VOSP** (Visual Object and Space Perception Battery)*	*Raw Score*	*Raw Score*	Cut-off Score
Screening Test	20	19	15
Incomplete Letters	16	11	17
Silhouettes	12	17	16
Object decision	14	10	15
Progressive Silhouettes	14	13	14
Dot counting	6	1	8
Position Discrimination	20	13	18
Number location	6	7	7
Cube analysis	4	6	6

Our first reported patient developed mild alexia with phonological agraphia in the context of a disease relapse, coincident with lesions in the left parietal and occipital areas, all evolving to complete remission at a later date. This deficit presented only a very mild repercussion in her daily life and social and occupational activities. In the second case, motor aphasia due to a large lesion in the WM of the left hemisphere was the first sign of disease, and it was not associated with any change in other cognitive functions and it also subsequently remitted. In this patient, the neuropsychological exam showed a large discrepancy between verbal and visual performance, not in accordance with spontaneous expression observed in normal conversation. This incongruence and the slight reduction in performance on SPI and attentive tasks can be explained by the elevated degree of anticipatory anxiety observed during the evaluation, as other authors have already observed (Nieto et al., 2008; Schulz, Kopp, Kunkel, & Faiss, 2006). The neuropsychological exam of the last three patients showed apperceptive agnosia and constructive apraxia in correspondence with bilateral lesions in the parietal and occipital areas. The last patient also showed alterations in linguistic processing. All but one of the cases (Case 2) exhibited cognitive impairment typical of MS, with some deficit in the encoding of verbal memory, SPI, attention and EF, similar to those described by other authors (Day et al., 1987; Devere et al., 2000; Okuda et al., 1996). We would like to highlight in three of our cases the good correlation encountered between apperceptive visual agnosia and the lesions observed in the parietal and occipital WM areas. Also remarkable is the recovery of language alterations observed in two of the patients.

Table 4
CASE 4: Clinical details and cognitive results

Sex		Female
Level of education (years of schooling)		8
Age in neuropsychological evaluation (NPSE).		44
EDSS in NPSE		3.5
Disease duration in NPSE (years).		1.5
MRI:		
• *T1 lesion volume*		High
• *T2 lesion volume*		High
• *Cerebral atrophy*		Yes
TESTS	**Score 2008**	**Normative values**
***WAIS-III** (Wechsler Adult Intelligence Scale)*	*Scaled Score*	*Scaled Score*
Picture completion	1	10
Vocabulary	9	10
Similarities	6	10
Block Design	1	10
Digit Span	5	10
***WMS-III** (Wechsler Memory Scale)*	*Scaled Score*	*Scaled Score*
Logical Memory I	3	10
Logical Memory II	1	10
Mental control	3	10
Information and Orientation	Percentile 1	Percentile 50
Verbal fluency	*Raw -Average*	*Raw -Average*
Phonemic fluency (FAS)	10	12-13
Semantic fluency (animals, fruit, supermarket)	14	17-18
***VOSP** (Visual Object and Space Perception Battery)*	*Raw Score*	*Cut-off Score*
Screening Test	18	15
Incomplete Letters	0	17
Silhouettes	2	16
Object decision	5	15
Progressive Silhouettes	20	14
Dot counting	4	8
Position Discrimination	11	18
Number location	0	7
Cube analysis	1	6

NPS may be the initial form of presentation of MS (cases 2, 4 and 5) (Devere et al., 2000; Dogulu et al., 1996; Mao-Draayer & Panitch, 2004) or, more frequently, they may appear in the course of the disease in association with physical disability involving other functional systems (Cases 1 and 3) (Day et al., 1987; Okuda et al., 1996). When they constitute the only symptom and occur progressively, as in our Case no 5, it can be difficult to establish a diagnosis of MS (Stoquart-ElSankari et al., 2010); in this setting, the presence of intrathecal synthesis of immunoglobulins may be of great help. A rapid progression of cognitive dysfunction along with severe functional deterioration and dementia over a short lapse of time has been described in some other sporadic cases, similar to our Patient 4 (Staff et al., 2009; Stoquart-ElSankar et al., 2010). Some patients with cognitive impairment also display changes in the emotional sphere, mostly euphoria, emotional instability, apathy and/or symptoms of depression, also observed in our patients (Zarei et al., 2003; Zarei, 2006).

The prevalence of NPS in MS is unknown. Possible explanations are the lack of studies focused on these specific cognitive deficits, and the fact that routine tests used in clinical practice only contemplate patterns of cognitive impairment typical of MS (Boringa et al., 2001; Duque et al., 2012). In addition, the tests may be administered by non-specialized personnel not skilled enough as to detect other possible deficits which could deserve a more specific investigation. In spite of this, their prevalence is presumably low, as these cognitive deficits demand specialized care because of the serious functional disability that they usually generate. In fact, the presence of aphasia only represented 0.8% of the 2700 MS patients tested by Larner and Lecky (2007). In spite of this probably low prevalence, it is important to consider cognitive deterioration as a main symptom of MS, even in cases where other neurological disorders are minor, given their potential repercussion on socio-occupational activities.

The substrate of cognitive impairment of MS, and in these particular NPS, is possibly brain atrophy. It may be that in the neuropsychological disorders involving typically cortical areas (aphasia, agnosia, apraxia), the grey matter (GM) atrophy is more relevant than WM atrophy. For decades, we have known that around 20% of the lesions in MS are found in the GM (Brownell & Hughes, 1962), and its clinical relevance and its important contribution to cognitive symptomatology are well recognized. Three types of lesions are found in the cerebral cortex, namely cortical-subcortical lesions involving the white and grey matter, small perivascular demyelinating intracortical lesions, and extensive subpial demyelination bands that cover several gyri and three or four layers (Rudick & Trapp, 2009). Given the strong correlation between cognitive deterioration and cortical atrophy, it is highly probable that a large part of cognitive symptoms of MS was the result of progressive damage to the GM rather than a consequence of WM atrophy (Amato et al., 2004; Benedict et al., 2006).

Cognitive impairment in MS may lead to severe and permanent disability (Wynia, Middel, van Dijk, De Keyser, & Reijneveld,

2008) with significant socio-occupational impact (Rao et al., 1991). It is therefore necessary to perform properly designed neuropsychological studies, conducted by specialized professionals, in order to diagnose and better characterize cognitive impairment in patients with MS.

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Table 5
CASE 5: Clinical details and cognitive results

Sex	Male
Level of education (years of schooling)	12
Age in the first neuropsychological evaluation (NPSE)	57
EDSS in the first NPSE	4
Disease duration in the first NPSE (years)	2.2
MRI:	
• *T1 lesion volume*	High
• *T2 lesion volume*	High
• *Cerebral atrophy*	Yes

TESTS	Score March 2012	Score November 2012	Normative values
WAIS-III *(Wechsler Adult Intelligence Scale)*	*Scaled Score*	–	*Scaled Score*
Block Design	5	–	10
WMS-III *(Wechsler Memory Scale)*	*Scaled Score*	–	*Scaled Score*
Logical Memory I	6	–	10
Logical Memory II	5	–	10
Rey Osterrieth Figure (ROCF)	*Percentile*	–	*Percentile*
Type of the copy	75	–	50
Accuracy of copy	1	–	50
Time of copy	10	–	50
Immediate recall condition	1	–	50
CTMT *(Comprehensive Trail Making Test)*	*Standard*	–	*Standard*
TEST 1	18	–	50
TEST 5	18	–	50
Verbal Fluency	*Raw Score*	–	*Raw Score*
Phonemic fluency (P)	4	–	12-13
Semantic fluency(animals)	13	–	17-18
VOSP *(Visual Object and Space Perception Battery)*	*Raw Score*	*Raw Score*	*Cut-off Score*
Screening Test	18	20	15
Silhouettes	7	12	15
Object Decision	9	7	14
Number Location	3	4	7
Cube Analysis	4	4	6
BNT *(Boston Naming Test)*	*Raw Score*	*Raw Score*	*Raw Score*
Total Score	42	37	54
M@T *(memory alteration test)*	*Raw Score*	*Raw Score*	*Cut-off Score*
Total Score	37	31	36
FAB *(Frontal Assessment Battery)*	*Raw Score*	–	*Cut-off Score*
Total Score	10	–	16

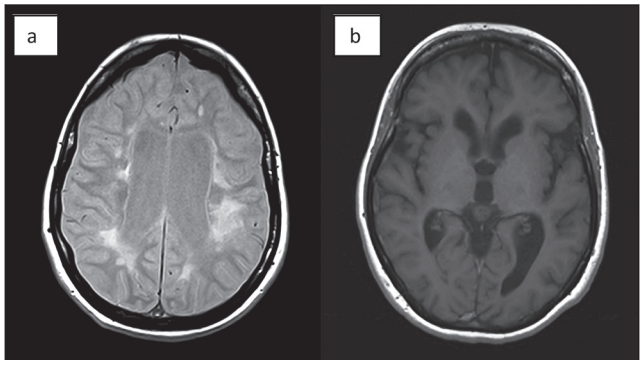

Figure 1. *Brain MRI (axial sections), case nº 1: a) Multiple demyelinating lesions, Some confluent and an extensive lesion in the left parietal region in T2 weighted sequences; y b) marked cerebral atrophy in T1 weighted sequences*

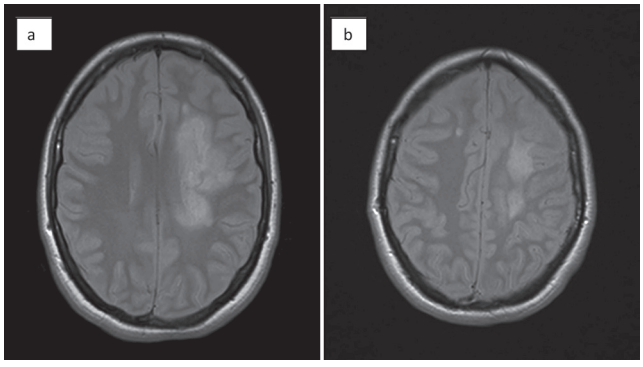

Figure 2. *Cranial MRI (Axial section in Proton Density (PD)), case nº 2: Extensive lesion in left frontal and parietal white matter. In b) Small white matter lesion in the left hemisphere is also observed*

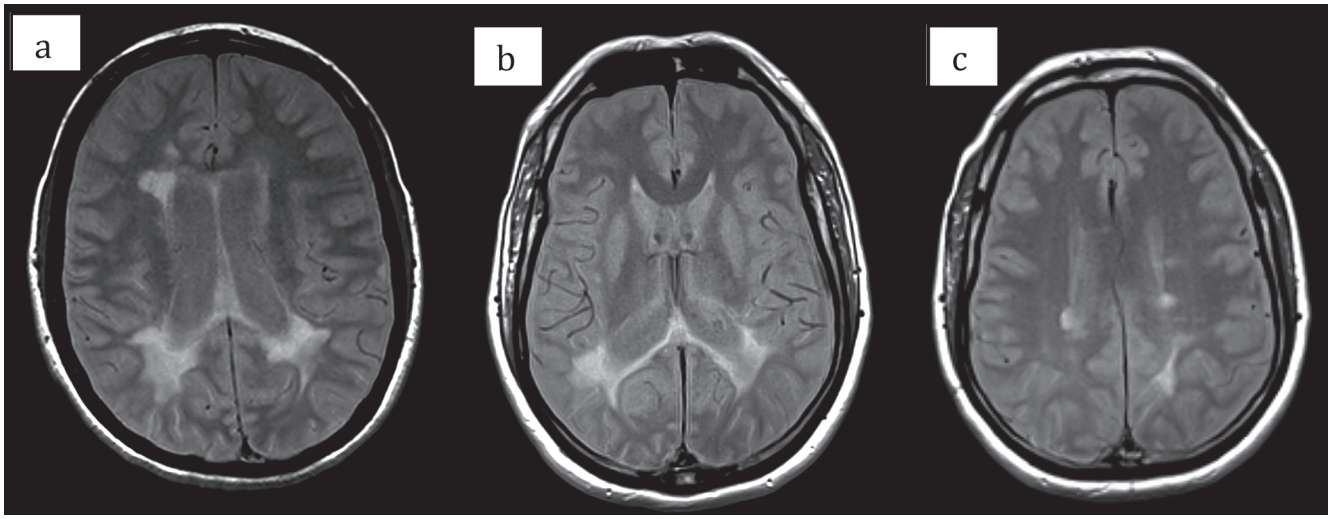

Figure 3. *Brain MRI (axial sections, PD): a) case nº 4: Multiple demyelinating lesions, with relative predominance in the parietal and occipital areas; b y c) case nº 5: periventricular lesions y confluent plaques, parietal-temporal-occipital areas*

References

Amato, M.P., Bartolozzi, M.L., Zipoli, V., Portaccio, E., Mortilla, M., Guidi, L., et al. (2004). Neocortical volume decrease in relapsing-remitting MS patients with mild cognitive impairment. *Neurology, 13*, 89-93.

Arango-Lasprilla, J.C., DeLuca, J., & Chiaravalloti, N. (2007). El perfil neuropsicológico en la esclerosis múltiple [Neuropsychological profile of multiple sclerosis]. *Psicothema, 19,* 1-6.

Benedict, R.H., Bruce, J.M., Dwyer, M.G., Abdelrahman, N., Hussein, S., Weinstock-Guttman, B., et al. (2006). Neocortical atrophy, third ventricular width, and cognitive dysfunction in multiple sclerosis. *Archives of Neurology*, *63*, 1301-1306.

Boringa, J.B., Lazeron, R.H.C., Reuling, E.W., Adèr, H.J., Pfennings, L., Lindeboom, J., et al. (2001). The Brief Repeatable Battery of Neuropsychological Tests: Normative values allow application in multiple sclerosis clinical practice. *Multiple Sclerosis, 7,* 263-267.

Brownell, B., & Hughes, J.T. (1962). The distribution of plaques in the cerebrum in multiple sclerosis. *Journal of Neurology, Neurosurgery & Psychiatry, 25*, 315-320.

Calabrese, M., Agosta, F., Rinaldi, F., Mattisi, I., Grossi, P., Favaretto, A., et al. (2009). Cortical lesions and atrophy associated with cognitive impairment in relapsing-remitting multiple sclerosis. *Archives of Neurology, 66*, 1144-1150.

Calabrese, M., Filippi, M., & Gallo, P. (2010). Cortical lesions in multiple sclerosis. *Nature Reviews Neurology, 6*, 438-444.

Damasio, A.R. (1992). Aphasia. *New England Journal of Medicine*, *326,* 531-539.

Day, T.J., Fisher, A.G., & Mastaglia, F.L. (1987). Alexia with agraphia in multiple sclerosis. *Journal of the Neurological Sciences*, *78*, 343-348.

Devere, T., Trotter, J., & Cross, A. (2000). Acute aphasia in multiple sclerosis. *Archives of Neurology, 57*, 1207-1209.

Dogulu, C.F., Kansu, T., & Karabudak, R. (1996). Alexia without agraphia in multiple sclerosis. *Journal of Neurology, Neurosurgery & Psychiatry, 61*, 528.

Duque, P., Ibáñez, J., del Barco, A., Sepulcre, J., de Ramón, E., Fernández-Fernández, O., et al. [Normalisation and validation of the Brief Neuropsychological Battery as the reference neuropsychological test in multiple sclerosis]. *Revista de Neurología, 54,* 263-270.

Genova, H.M., Sumowski, J.F., Chiaravalloti, N., Voelbel, G.T., & DeLuca, J. (2009). Cognition in multiple sclerosis: A review of neuropsychological and fMRI research. *Frontiers in Bioscience, 14,* 1730-1744.

Halligan, F.R., Reznikoff, M., Friedman, H.P., & La Rocca, N.G. (1988). Cognitive dysfunction and change in multiple sclerosis. *Journal of Clinical Psychology*, *44*, 540-548.

Kornek, B., & Lassmann, H. (2004). Neuropathology of multiple sclerosis-new concepts. *Brain Research Bulletin, 61,* 321-326.

Kurtzke, J.F. (1983). Rating neurologic impairment in multiple sclerosis: An expanded disability status scale (EDSS). *Neurology, 33*, 1444-1452.

Larner, A.J., & Lecky, B.R. (2007). Acute Aphasia in MS Revisited. *The International MS Journal, 14,* 76-77.

Mao-Draayer,Y., & Panitch H. (2004). Alexia without agraphia in multiple sclerosis: Case report with magnetic resonance imaging localization. *Multiple Sclerosis, 10*, 705-707.

Naeser, M.A., Alexander, M.P., Helm-Estabrooks, N., Levine, H.L., Laughlin, S.A., & Geschwind, N. (1982). Aphasia with predominantly subcortical lesion sites: Description of three capsular/putaminal aphasia syndromes. *Archives of Neurology, 39*, 2-14.

Nieto, A., Sánchez, M.P., Barroso, J., Olivares, T., & Hernández, M.A. (2008). Alteraciones cognitivas en etapas iniciales de la esclerosis múltiple y su relación con el estado de ánimo, variables demográficas y clínicas [Cognitive impairment in the early phase of multiple sclerosis and its relationship with mood, demographic and clinical variables]. *Psicothema, 20*, 583-588.

Okuda, B., Tanaka, H., Tachibana, H., Iwamoto, Y., Takeda M., Kawabata, K., et al. (1996). Visual form agnosia in multiple sclerosis. *Acta Neurologica Scandinavica, 94*, 38-44.

Patti, F. (2009). Cognitive impairment in multiple sclerosis. *Multiple Sclerosis, 15,* 2-8.

Polman, C.H., Reingold, S.C., Edan, G., Filippi, M., Hartung, H.P., Kappos, L., et al. (2005). Diagnostic criteria for multiple sclerosis: 2005 revisions to the "McDonald Criteria". *Annals of Neurology, 58*, 840-846.

Rao, S.M., Leo, G.J., Ellington, L., Naurertz, T., Bernardin, I., & Unverzagt, F. (1991). Cognitive dysfunction in multiple sclerosis. Impact of employment and social functioning. *Neurology, 412*, 692-696.

Rinaldi, F., Calabrese, M., & Grossi P. (2010). Cortical lesions and cognitive impairment in multiple sclerosis. *Neurological Sciences*, *31*, 235-237.

Rudick, R.A., & Trapp, B.D. (2009). Gray-matter injury in multiple sclerosis. *New England Journal of Medicine, 361*, 1505-1506.

Staff, N.P., Lucchinetti, C.F., & Keegan, M. (2009). Multiple sclerosis with predominant severe cognitive impairment. *Archives of Neurology, 66*, 1139-1143.

Stoquart-ElSankari, S., Périn, B., Lehmann, P., Gondry-Jouet, C., & Godefroy O. (2010). Cognitive forms of multiple sclerosis: Report of a dementia case. *Clinical Neurology and Neurosurgery, 112,* 258-260.

Schulz, D., Kopp, B., Kunkel, A., & Faiss, J.H. (2006). Cognition in the early stage of multiple sclerosis. *Journal of Neurology, 243,* 1002-1010.

Valle, F., & Cuetos, F. (1995). EPLA: Evaluación del Procesamiento Lingüístico en la Afasia. Hove, UK, Lawrence Erlbaum Associates.

Wynia, K., Middel, B., van Dijk J.P., De Keyser J.H., & Reijneveld S.A. (2008). The impact of disabilities on quality of life in people with multiple sclerosis. *Multiple Sclerosis, 14,* 972-980.

Zarei, M., Chandran, S., Compston, A., & Hodges, J. (2003). Cognitive presentation of multiple sclerosis: Evidence for a cortical variant. *Journal of Neurology, Neurosurgery & Psychiatry, 74*, 872-877.

Zarei, M. (2006). Clinical characteristics of cortical multiple sclerosis. *Journal of the Neurological Sciences, 245,* 53-58.