ORIGINAL PAPER

THE INTERNATIONAL JOURNAL OF CLINICAL PRACTICE

Editor's Choice

Effect of the disclosure of MS diagnosis on anxiety, mood and quality of life of patients: a prospective study

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SUMMARY

Background: In the light of the new diagnostic criteria for multiple sclerosis (MS) and currently available early treatment, this study aimed to explore whether, and to what extent, disclosure of the diagnosis of MS or clinically isolated syndrome (CIS) affects patients' anxiety, mood and quality of life (QoL). **Methods:** Eligible participants were all patients referred for the first time to the Neurological Unit who had manifested symptoms suggestive of MS for no more than 6 months. All patients were evaluated for (i) QoL (SEIQoL and MS-QoL54), (ii) Anxiety (STAI) and Depression (CMDI) on study inclusion (T0), 30 days after diagnosis disclosure (T30), and after 1 (T1y) and 2 (T2y) years' follow-up. **Results:** Two hundred and twenty-nine patients were enrolled; 93 of these were unaware of their diagnosis. Patients who already knew their diagnosis (100 with CIS and 22 with MS) were excluded from the main analyses and used to perform control analyses. At the end of the screening, an MS diagnosis was disclosed to 18 of the 93 patients, whereas a CIS diagnosis was disclosed to 62 patients (12 patients received a diagnosis other than MS or CIS). Thirty days after diagnosis disclosure, irrespective of the diagnosis disclosed, both QoL and Anxiety and Depression were significantly rated as better compared to the start of screening, ($p_s < 0.03$), and this improvement remained stable over the two annual follow-ups. However, as suggested by a significant 'Time' × 'Diagnosis' interaction with regard to both QoL and Anxiety and Depression ($p_s < 0.02$), the effect of the disclosure in the short term differed depending on CIS or MS diagnosis. Specifically, on MSQoL, which is a health-related QoL scale, we found a statically significant improvement, immediately after the diagnosis disclosure, in both the MS and CIS groups ($p_s < 0.01$). Differently, on SEIQoL, which is a non health-related QoL measure, and on the anxiety scale, we observed a statistically significant improvement only in the group which received a MS diagnosis ($p_s < 0.03$). **Conclusions:** This first prospective study provides objective data showing that early disclosure of MS diagnosis improves both the patient's QoL and psychological well-being. In addition, the results seem to suggest that CIS disclosure does not lead to the same favourable effects.

What's known

Very few studies have investigated the effect of MS diagnosis disclosure on psychological well-being and QoL. It is suggested that there is a significant improvement in QoL and psychological well-being following disclosure, but the fact that the patients' mood and QoL were assessed only when diagnosis disclosure had already taken place poses an important methodological limit to these studies. A comparison with the previous phase in which the patients were unaware of the diagnosis, therefore, is missing.

What's new

This is the first prospective study providing objective data concerning the short-term (30 days after diagnosis disclosure) and long-term (after 1 and 2 year follow-ups) effects of MS diagnosis disclosure on QoL and psychological well-being. This study disambiguates differences in those patients who were told they have CIS from those who were told they have a specified clinical disease, which could lead to a more serious diagnosis such as MS.

Introduction

How and when to disclose a diagnosis of multiple sclerosis (MS), or even the suspicion of MS, to patients is a matter of long-standing controversy.

The introduction of the newer, less conservative, diagnostic criteria for MS (1,2) allows a definite diagnosis in the earlier stages of the disease. However, establishing MS does not entail a clear prognosis. This, together with the collective imagination of the disease, could cause the patient significant psychological distress.

Regardless of the new diagnostic criteria according to McDonald et al. (1) and the neurologist's actions, the effect of early disclosure of MS diagnosis is still to be determined. What has not been clearly studied in a prospective experimental design is how the disclosure of MS diagnosis can affect patients'

Int J Clin Pract, May 2012, **66**, 5, 504–514. doi: 10.1111/j.1742-1241.2012.02912.x

psychological well-being and quality of life (QoL). Most studies (3–5) have assessed patients' mood and QoL retrospectively, after a diagnosis had already been disclosed, therefore missing a comparison with the previous phase in which patients were unaware of the diagnosis.

We undertook a prospective 2-year follow-up study to explore whether, and to what extent, disclosure of a diagnosis of MS affects patients' anxiety, depression and their QoL in the short (immediately after diagnosis disclosure) and long term (1 and 2 years after diagnosis disclosure). Based on past research of patient preferences (4,5), we predicted a significant improvement in QoL and psychological well-being after MS diagnosis disclosure. In addition, we aimed to explore whether this improvement occurs immediately following the diagnosis disclosure or over a more prolonged time period. On the contrary, however, we cannot exclude the fact that the ongoing disease may interfere with the QoL and psychological well-being of the individual over the long term.

As many patients who have symptoms which point to MS are told by neurologists that they have a clinically isolated syndrome (CIS) (6), a second aim of the present study was to disambiguate differences in those patients who were told generically that they have a CIS from those who were told they have a more specific clinical disease, which could lead to a more serious diagnosis such as MS.

Method

The present study is part of a more extensive project (7) on the prognosis of MS (Gruppo Emiliano-Romagnolo Neurologi In Multiple Sclerosis - G.E. Ro.N.I.Mu.S.). The investigation was conducted in 16 Neurological Units. The protocol was approved by the Ethical Committee on Human Research at the Hospital affiliation of each of the Units involved, and informed consent was obtained from all participants.

Participants

Eligible participants were all patients referred for the first time to a general Neurological Unit [i.e. not specific for MS, although in four units there was a specific consulting room for central nervous system (CNS) disease] between December 2004 and July 2007 with symptoms suggestive of MS which had started no more than 6 months previously. Exclusion criteria were: (i) age under 18 years; (ii) cognitive impairment that could prevent patients filling in questionnaires; (iii) impossibility to undergo MRI necessary for MS diagnosis according to the criteria of McDonald et al. (1).

Assessment

Quality of life was assessed using the Italian version of the Multiple Sclerosis QoL-54 (MSQoL-54) (8), and the schedule for the evaluation of individual QoL – Visual Analogue Scale (SEIQoL-VAS) (9). MSQoL-54 is a self-administered questionnaire that focuses on the impact of the disease on patients' QoL and provides two composite scores: physical (MSQoL-Phy) and mental (MSQoL-Mental) health score. SEIQoL-VAS is a semi-structured interview in which patients are invited to freely nominate the five domains they currently consider to be the most important in their lives, followed by a rating and weighting procedure on a VAS.

Anxiety and Depression was assessed by the State-Trait Anxiety Inventory (STAI) (10) and the Italian version of the Chicago Multiscale Depression Inventory (CMDI) (11). None of the questionnaires mentioned the term MS. Demographic and clinical information was collected by means of an electronic case report form. The topics covered are: age, education, gender, work, place of residence, comorbidities, symptoms at onset, neurological examination, Expanded Disability Status Scale (EDSS) (12), drug treatments.

Study procedure

Initially, patients received written and oral information on the study from a senior neurologist. Participants were asked to take part in a study on the effect of diagnosis disclosure on QoL. Neither the interview nor the written documents mentioned a probable diagnosis of MS in order to avoid informing patients with the study materials.

Patients were assessed at study inclusion (T0), 30 days after diagnosis disclosure (T30) and after 1 (T1y) and 2 (T2y) years of follow-up from diagnosis disclosure. The study procedure affected neither the patient's diagnosis and care routine nor the timing of the diagnosis disclosure. On enrolment, in order to exclude patients who already knew their diagnosis, or had clear suspicion of their diagnosis, from the main study group, the neurologist asked them, through an unstructured interview, what they knew about their symptoms and diagnosis. Diagnosis of MS was established according to the criteria McDonald et al. (1) and considered disclosed after the neurologist had informed the patient of the nature of the condition, therapeutic procedures, including possible alternatives, and possible outcome. A diagnosis of CIS was given to those patients who did not meet the diagnostic criteria of MS according to McDonald et al. (1), and when there was insufficient evidence for other causes of CNS lesions. In order to avoid affecting the patient's clinical work-up and the care routine undertaken by the neurologist, the disclosure

***G.E.Ro.N.I.Mu.S.** coinvestigators are listed in the Appendix.

Disclosures
The authors declare no conflict of interest.

of CIS was not standardised, as it was for MS, but driven mostly by the necessity to explain to patients that they would require follow-up investigations (e.g. follow-up scan to screen for additional lesions).

All patients were interviewed with symptoms resolved or with residual symptoms. In each phase, the study included an interview with a psychologist whose purpose was to administer the questionnaires. To avoid an effect on SEIQoL-VAS responses, questionnaires were administered in a strict order: SEIQoL, which was scored by an interview, followed by STAI, MSQoL-54 and CMDI, which were self-report questionnaires. The questionnaires were confidential and could not be viewed by the unit's staff. Following compilation, the data were sent to the contract research organisation that was responsible for data management and monitoring. In order to reach the greatest possible uniformity, the neurologists were trained to conduct the study at the outset.

Statistical analyses

Three scores were entered in all QoL analyses (i.e. MSQoL-Phy, MSQoL-Mental and SEIQoL). To emphasise the effect of diagnosis disclosure on patients' mental profile, all analyses of Anxiety and Depression included the CMDI Mood subscale and the STAI Y1 (state anxiety inventory), which provide more conservative indications of depression and anxiety than the total CMDI score and STAI Y2.

From the end of the diagnostic work-up to the second year of follow-up, patients' diagnoses could change (e.g. from CIS to MS) altering the number of patients in each group. Group numbers were therefore established *post hoc* on the basis of the type of diagnosis disclosed at each assessment. For this reason, and also in order to reach maximum statistical power, we conducted two separate analyses, one for the short-term and one for the long-term effect of diagnosis disclosure.

p values ($\alpha = 0.05$) were corrected by Greenhouse-Geisser epsilon, if appropriate. Partial eta squared (η_p^2) was reported as an estimate of effect size. Contrasts were made to characterise the significant effect of diagnosis disclosure timing and disease type. A Bonferroni confidence interval adjustment correction was applied, when appropriate, on multiple pair-wise comparisons among the adjusted means. Details of the analyses are as follows.

Short-term effect of diagnosis disclosure (T0 vs. T30)

Two separate repeated measure 2×3 MANCOVAs were performed on patients who did not know their diagnosis at enrolment (NK group) taking 'Time' (T0 vs. T30) as a within-subjects factor, and 'Diagnosis' at the end of the screening (i.e. T30) as a between-subjects factor [NK who received MS disclosure (NK → MS group) vs. NK who received CIS disclosure (NK → CIS group) vs. NK who were given other diagnoses (NK → OTH group)]. We did not exclude NK patients with other diagnoses (NK → OTH) but kept them as a control group. Disability by means of EDSS score at T0 and T30 was placed as a covariate.

We assigned each patient to the NK → MS, NK → CIS or NK → OTH groups when the clinical documents explicitly stated the diagnosis, or according to the investigator's reports on the colloquium with the patients.

Long-term effect of diagnosis disclosure (T0 vs. T30 vs. T1y vs. T2y)

Two separate repeated measure 4×2 MANCOVAs were performed on invariant NK → CIS and NK → MS groups in all scheduled follow-ups. We took 'Time' (T0 vs. T30 vs. T1y vs. T2y) as a within-subjects factor and 'Diagnosis' as a between-subjects factor (NK → CIS vs. NK → MS). Disability by means of EDSS score (T0, T30, T1y and T2y) was placed as covariate.

Control analyses

In order to gain a better understanding of the modulation of disclosed diagnosis type on patients' QoL, Anxiety and Depression, two control analyses were performed. QoL, Anxiety and Depression were compared at T0 between the NK group and two post-hoc-created control groups (i.e. patients who already had an MS diagnosis – MS group – or CIS diagnosis – CIS group – on enrolment as disclosed by a previous centre and who were therefore excluded from the NK group) by means of two separate one-way MANOVAs, taking 'Communicative State at T0' (NK vs. CIS group vs. MS group) as a between-subjects factor and EDSS as covariate. According to the clinical routine, for these two control groups, T0 was the beginning of follow-ups. The assessment at T30 was scheduled only when there was a change in diagnosis (from MS to another illness, or from CIS to MS), otherwise they were assessed at the 1 and 2 year follow-up.

Two separate one-way repeated measure MANOVAs were also performed as control analyses on the CIS group and patients with MS diagnosed at the end of the screening (CIS → T30MS), taking 'Time' (T0 vs. T30) as a within-subjects factor and EDSS in T0 and T1 as covariate.

Results

Patients

Two hundred and twenty-nine patients were included (see Figure 1). Twelve of them declined to

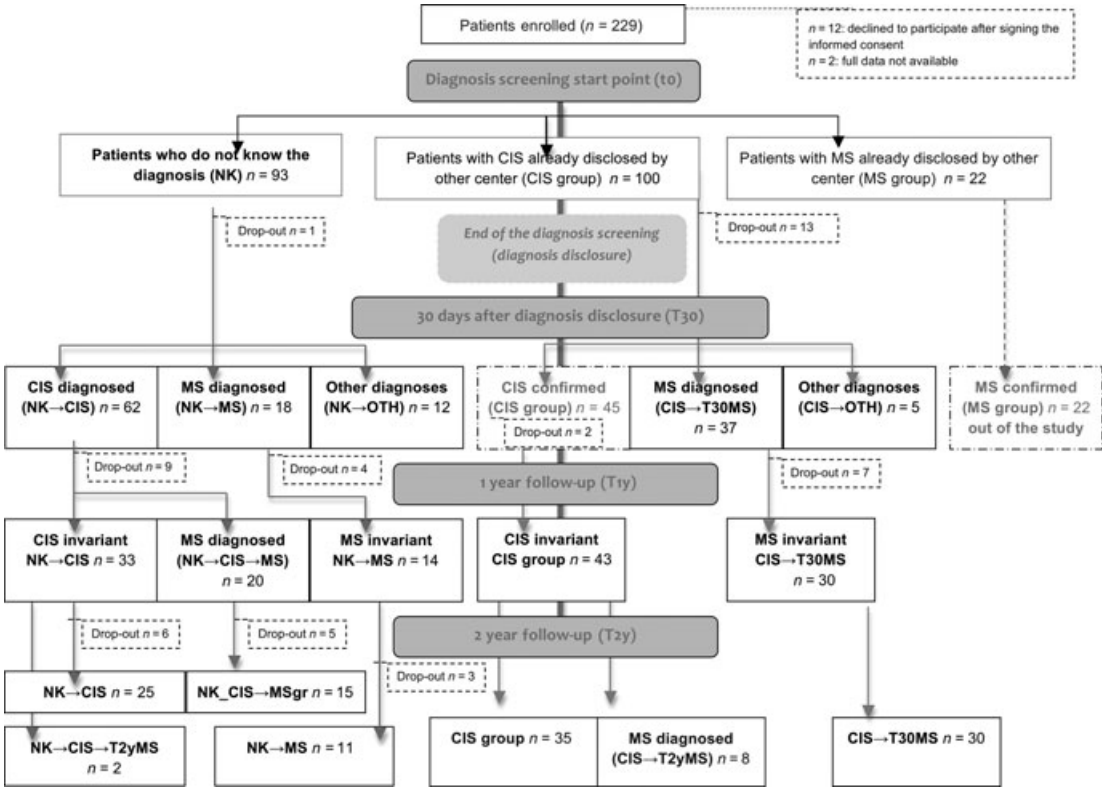

Figure 1 Study design and patients' group progression in several phases of the study. Dashed boxes indicate patients for whom the assessment was not scheduled or drop-out patients, as specified. Inactive units and withdrawal of informed consent were the main causes of drop-out after enrolment and before the end of the screening phase. Migration to other neurological units or health improvement and consequent tendency to skip the follow-up were the main causes of drop-out after the end of screening. When full psychometric data were unavailable, patients were excluded from the analysis. NK → OTH group includes: two peripheral neuropathy (one ulnar nerve and one trigeminal nerve), two unexplained neurological symptoms, two psychogenic syndrome, one myelopathy, one vertebral artery dissection, one meningoradiculitis, one drug abuse-induced vasculitis, one Chiari malformation type I, one Menière syndrome plus myopic retinochoroiditis. NK group mean (± SD) days between T0 and T30: 122 ± 133

participate after signing the informed consent and for two patients, full data were not available.

Specifically, three neurological units recruited more than twenty patients, seven units recruited more than 10 and six Units recruited fewer than 10 patients.

Of the 215 patients who completed the initial screening, 144 were female (mean age 33.18 ± 8.42; mean years of education 12.75 ± 3.49) and 71 male (mean age 34.46 ± 8.20; mean years of education 12.51 ± 3.66)[1].

Analyses

In order to be more concise, we did not report most *F* values of factors (or interactions), which failed to reach statistical significance. Levene's test of equality of error variance was conducted, showing that dependent variables in each analysis met the assumptions of homogeneity of variance.

Short-term effect of diagnosis disclosure (T0 vs. T30)

At the end of the screening, an MS diagnosis was disclosed to 18 of the 93 patients enrolled who did not know their diagnosis. Clinical and MRI characteristics of patients are reported in Table 1. A CIS diagnosis was disclosed to 62 patients and a diagnosis other than MS or CIS was given to 12 patients (see Figure 1 for more details). Symptoms started 51.84 ± 49.90 days before T0 (range: 2–187 days). Mean (± SD) interval between T0 and T30 was 122 days (± 133), median was 65 days. The long interval of time between T0 and T30 was mainly due to the time required to book and carry out all the necessary tests, especially the CSF analysis (Oligoclonal Bands), on the National Health Service. The patient was also free to return at their convenience to the Neurological Unit with the completed test. On top of this there were 30 days between the diagnosis disclosure and the T30 evaluation.

[1]We explored the effect of gender, which did not reach statistical significance in any analyses performed. Detailed results are available on request.

Table 1 Clinical, MRI characteristics and therapies of patients who did not know their diagnosis at study inclusion (T0) and who became MS (NK → MS) or CIS (NK → CIS) disclosed at the end of the screening

Group			T0	T30	T1y	T2y
NK → MS group	**EDSS**	0.0–2.5	16/18	17/18	13/14	8/11
	No. pts	3.0–6.0	2/18	1/18	1/14	3/11
		> 6.0	0/18	0/18	0/14	0/11
	MRI lesions,	T2 lesions	11 (3–21)			
	median (IQR)	Gd-enhancing lesions	0 (0.5)			
	CSF	Positive CSF	11/18			
	No. pts					
	Treatment	IV steroid	11/18		5/14	3/11
	No. pts	Immunomodulatory	0/18		7/14	9/11
		Other	0/18		2/14	3/11
NK → CIS group	**EDSS**	0.0–2.5	48/62	56/62	32/33	24/25
	No. pts	3.0–6.0	13/62	7/62	1/33	1/25
		> 6.0	1/62	0/62	0/33	0/25
	MRI lesions,	T2 lesions	4.50 (1–10.25)			
	median (IQR)	Gd-enhancing lesions	0 (0–1)			
	CSF	Positive CSF	42/62			
	No. pts					
	Treatment	IV steroid	44/62		2/33	3/25
	No. pts	Immunomodulatory	0/62		3/33	3/25
		Other	4/62		0/33	0/25

IQR, interquartile range; CSF, cerebral spinal fluid; Gd-enhancing lesions, gadolinium enhancing lesions; immunomodulatory drugs, beta-interferon and Glatiramer acetate; Other, immunomodulatory drugs other than beta-interferon and Glatiramer acetate.

A preliminary analysis evaluating the homogeneity-of-regression (slopes) assumption indicated that the relationship between the covariate (i.e. EDSS at T0 and EDSS at T30) and the dependent variables (i.e. QoL and Anxiety and Depression) did not differ significantly as a function of Time (respectively: $F(3,85) > 1.624$; $p_s > 0.190$, $\eta_p^2{}_s > 0.054$; $F(2,86) > 0.054$; $p_s > 0.900$), $\eta_p^2{}_s > 0.001$). Moreover, as expressed by η_p^2, in accordance with the Cohen guidelines (13), the effect of Time, when statistically significant, is consistent enough to allow us to make some interesting inferences about the effect of diagnosis disclosure in the short-term period. Specifically, a significant main effect of diagnosis disclosure (Time) was found both on QoL, $F(3,85) = 13.151$; $p = 0.001$, $\eta_p^2 = 0.317$, and on Anxiety and Depression, $F(2,86) = 3.841$; $p = 0.025$, $\eta_p^2 = 0.082$. Univariate analyses showed a significant main effect of 'Time' on MSQoL-Phy and, most importantly, on MSQoL-Mental and SEIQoL, $F(1,87) > 13.732$; $p_s < 0.01$, $\eta_p^2{}_s > 0.136$, STAI Y1, $F(1,87) = 7.567$; $p = 0.008$, $\eta_p^2 = 0.085$, and CMDI mood subscale, $F(1,87) = 4.008$; $p = 0.048$, $\eta_p^2 = 0.044$. Specifically, as illustrated in Figure 2, 30 days after the diagnosis disclosure, regardless of the diagnosis, all QoL and Anxiety and Depression questionnaires were rated as better compared to the start of screening.

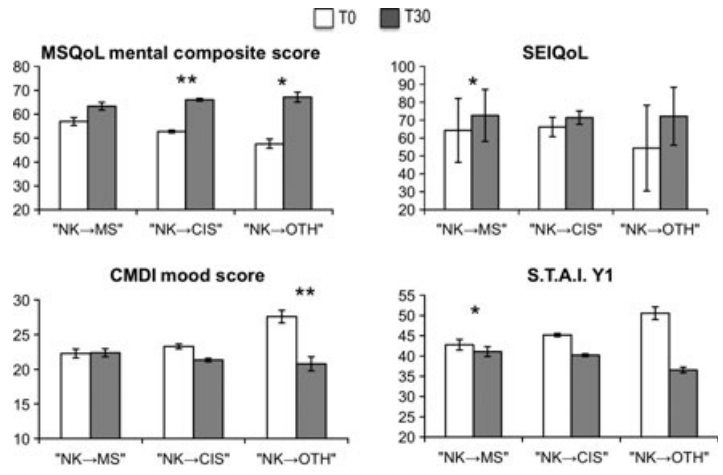

Figure 2 Short-term mean changes and confidence interval (CI) in QoL (MSQoL-Mental and SEIQoL), Anxiety and Depression (CMDI Mood Score and STAI-Y1) between the Diagnosis Screening Start Point (T0) and 30 days after the Diagnosis Disclosure (T30). *p < 0.05; **p < 0.01; when not specified p is > 0.05. On MSQoL-Mental and SEIQoL a high score indicates better results. On CMDI and STAI-Y1, a high score indicates worse functioning.

The main effect of 'Time' was qualified by a significant interaction 'Time' × 'Diagnosis' regarding both QoL, $F(6,170) = 2.632$; $p = 0.018$, $\eta_p^2 = 0.085$, and

Anxiety and Depression, $F(4,174) = 3.135$; $p = 0.016$, $\eta_p^2 = 0.068$. Subsequent analyses conducted separately in each of the three groups indicated that 'Time' significantly modulates QoL and Anxiety and Depression in the NK → CIS and NK → MS groups, although in different measures, but not as far as the NK → OTH group is concerned (see also Table 2 for means, adjusted means and other detailed results). Specifically, in the NK → MS group, Time significantly affected QoL, $F(3,13) = 4.109$; $p = 0.03$, $\eta_p^2 = 0.487$, both in the MSQoL-Phy score, $F(1,15) = 7.710$; $p = 0.01$, $\eta_p^2 = 0.339$ and in the SEIQoL, $F(1,15) = 5.265$; $p = 0.03$, $\eta_p^2 = 0.260$. The effect of Time on Anxiety and Depression was nearly significant, $F(2,14) = 3.078$; $p = 0.07$, $\eta_p^2 = 0.305$. When exploring univariates, we observed a significant effect of MS diagnosis disclosure only on STAI Y1, $F(1,15) = 5.798$; $p = 0.03$, $\eta_p^2 = 0.279$. As far as the NK → CIS group is concerned, we obtained a significant main effect of Time only on QoL, $F(3,57) = 7.257$; $p = 0.001$, $\eta_p^2 = 0.276$, and specifically on the MSQoL-Phy score, $F(1,59) = 21.376$; $p = 0.001$, $\eta_p^2 = 0.266$, and MSQoL-Mental score, $F(1,59) = 15.095$; $p = 0.001$, $\eta_p^2 = 0.204$.

Long-term effect of diagnosis disclosure (T0 vs. T30 vs. T1y vs. T2y)

At the 2 year follow-up, seven of eighteen patients with MS diagnosis (NK → MS) dropped out of the study thus leaving 11 MS patients for analysis. Of the 62 patients to whom CIS had been disclosed (NK → CIS), 25 patients did not receive an altered diagnosis, and thus were valid for analysis (see Figure 1 for more details).

A nearly significant main effect of 'Time' was found on QoL, $F(9,22) = 2.049$; $p = 0.082$, $\eta_p^2 = 0.456$, whereas a non-significant effect was found on Anxiety and Depression, $F(6,25) = 1.081$; $p = 0.485$, $\eta_p^2 = 0.206$.

In order to explore the consistency with previous short-term analyses (i.e. T0 vs. T30), we examined univariate analyses and pair-wise comparisons. Regardless of the diagnosis disclosed (refer also to Table 3 for means and adjusted means): (i) MSQoL-Phy, $F(3,90) = 5.114$; $p = 0.006$, $\eta_p^2 = 0.146$, was significantly lower in T0 compared to T30 ($p < 0.01$), T1y ($p < 0.01$) and T2y ($p < 0.01$); (ii) MSQoL-Mental, $F(3,90) = 2.185$; $p = 0.104$, $\eta_p^2 = 0.068$, was significantly lower in T0 compared to T30 ($p < 0.02$), T1y ($p < 0.01$) and T2y ($p < 0.01$); SEIQoL score, $F(3,90) = 2.329$; $p = 0.088$, $\eta_p^2 = 0.072$, was significantly lower in T0 compared to T1y ($p < 0.02$); CMDI Mood score, $F(3,90) = 0.952$; $p = 0.952$, $\eta_p^2 = 0.031$, was significantly higher in T0 compared to T1y ($p < 0.01$) as for the STAI Y1 scores, $F(3,90) = 1.308$; $p = 0.377$, $\eta_p^2 = 0.031$, which are significantly higher in T0 compared to T1y ($p < 0.02$). No significant main effect of 'Diagnosis' or significant interaction was found.

Control analyses

Comparison between NK group and different patients who are already aware of their diagnosis upon enrolment (MS group, n = 22 and CIS group, n = 100): A

Table 2 Scores (mean ± SD, adjusted mean ± SE) and statistical results* obtained on QoL, Anxiety and Depression at T0 and T30 by patients who did not know their diagnosis at study inclusion (T0) and who became MS (NK → MS) or CIS (NK → CIS) or other disease (NK → OTH) disclosed at the end of the screening

Group (*no. patients*)	Domain	Questionnaire	T0 Mean ± SD (adjusted mean ± SE)	T30 Mean ± SD (adjusted mean ± SE)	*F*(df)	p (η_p^2)
NK → MS (*n* = 18)	QoL				*F* (3,13) = 4.109	0.030 (0.487)
		MSQoL-Phy	62.6 ± 13.8 (61.4 ± 3.6)	68.3 ± 18.1 (67.5 ± 3.1)	*F* (1,15) = 7.710	0.014 (0.339)
		MSQoL-Mental	56.9 ± 15.6 (56.5 ± 4.0)	63.3 ± 14.9 (62.3 ± 3.8)	*F* (1,15) = 3.260	0.081 (0.179)
		SEIQoL	64.3 ± 16.4 (64.0 ± 40.0)	72.6 ± 13.3 (72.4 ± 28.4)	*F* (1,15) = 5.265	0.037 (0.260)
	Anxiety and Depression				*F* (2,14) = 3.078	0.078 (0.305)
		STAI Y1	42.7 ± 12.01 (42.7 ± 2.9)	41.1 ± 11.03 (40.8 ± 2.4)	*F* (1,15) = 5.798	0.029 (0.279)
		CMDI mood	23.3 ± 5.9 (23.8 ± 2.3)	22.4 ± 5.2 (22.6 ± 1.7)	*F* (1,15) = 0.705	0.414 (0.045)
NK → CIS (*n* = 62)	QoL				*F* (3,57) = 7.257	0.001 (0.276)
		MSQoL-Phy	58.5 ± 16.3 (59.1 ± 1.9)	73.9 ± 14.1 (74.6 ± 1.7)	*F* (1,59) = 21.376	0.001 (0.266)
		MSQoL-Mental	52.7 ± 18.2 (53.1 ± 2.1)	66.1 ± 17.4 (66.6 ± 2.0)	*F* (1,59) = 15.095	0.001 (0.204)
		SEIQoL	66.2 ± 17.1 (66.3 ± 21.4)	72.4 ± 11.8 (71.5 ± 15.2)	*F* (1,59) = 1.865	0.177 (0.031)
	Anxiety and Depression				*F* (2,58) = 1.765	0.180 (0.057)
		STAI Y1	45.2 ± 12.6 (45.1 ± 1.5)	40.2 ± 10.5 (40.2 ± 1.3)	*F* (1,59) = 1.158	0.286 (0.019)
		CMDI mood	28.1 ± 11.1 (27.9 ± 1.2)	21.3 ± 7.9 (21.2 ± 0.9)	*F* (1,59) = 3.589	0.063 (0.057)

**F* and p values refer to the multivariate and univariate analyses of variance for the 'Time' factor. SD, standard deviation; SE, standard error.

Table 3 Scores (mean ± SD, adjusted mean ± SE) and statistical results* obtained on QoL, Anxiety and Depression in each assessment scheduled, by patients who did not know their diagnosis at study inclusion (T0) and who became MS or CIS disclosed at the end of the screening (T30), remaining stable in the annual follow-up

		T0	T30	T1y	T2y	Pair-wise comparisons ($p < 0.02$)
Domain	**Questionnaire**	**Mean ± SD (adjusted mean ± SE)**				
QoL	MSQoL-Phy	55.1 ± 15.8 (57.2 ± 2.7)	71.1 ± 15.6 (71.6 ± 2.7)	75.8 ± 13.3 (77.2 ± 1.9)	76.8 ± 14.3 (77.3 ± 2.4)	T0 < T30,T1y, T2y
	MSQoL-Mental	51.7 ± 17.5 (53.8 ± 3.3)	65.5 ± 15.9 (64.7 ± 2.9)	71.7 ± 14.5 (71.4 ± 2.8)	70.8 ± 16.1 (71.1 ± 2.9)	T0 < T30,T1y, T2y
	SEIQoL	66.3 ± 16.7 (65.8 ± 3.2)	71.4 ± 12.6 (73.3 ± 2.1)	73.6 ± 14.1 (74.5 ± 2.5)	71.5 ± 12.9 (73.2 ± 2.3)	T0 < T1y
Anxiety and	STAI Y1	44.4 ± 12.3 (43.5 ± 2.4)	39.2 ± 10.5 (39.6 ± 2.1)	38.3 ± 10.3 (36.9 ± 1.9)	38.1 ± 10.2 (37.8 ± 1.9)	T0 > T1y
Depression	CMDI mood	29.1 ± 12.1 (26.9 ± 2.4)	21.9 ± 6.7 (22.2 ± 1.3)	19.9 ± 7.6 (19.3 ± 1.4)	20.6 ± 8.9 (21.0 ± 1.7)	T0 > T1y

*p values refer to 'Time' factor pair-wise comparisons regardless of the 'Diagnosis'. Only $p < 0.05$ comparisons were reported. SD, standard deviation; SE, standard error.

significant main effect of 'Communicative State at T0' was found on QoL, $F(6,418) = 4.260$; $p = 0.001$, $\eta_p^2 = 0.058$, and Anxiety and Depression, $F(4,420) = 2.621$; $p = 0.024$, $\eta_p^2 = 0.024$. Subsequently univariate analyses and pair-wise comparisons showed (see Figure 3) that: (i) the MSQoL-Phy, $F(2,211) = 10.272$; $p = 0.001$, $\eta_p^2 = 0.089$, was significantly lower in NK compared to CIS ($p < 0.01$) and MS ($p < 0.01$) groups (58.9 ± 15.6 vs. 68.7 ± 13.3 vs. 72.8 ± 18.3 respectively); (ii) the MSQoL-Mental, $F(2,211) = 5.509$; $p = 0.005$, $\eta_p^2 = 0.050$, was significantly lower ($p < 0.01$) in NK (53.1 ± 16.9) compared to CIS (61.8 ± 15); (iii) the CMDI mood score, $F(2,211) = 3.085$; $p = 0.048$, $\eta_p^2 = 0.028$, was significantly higher in NK compared to both CIS ($p < 0.03$) and MS ($p < 0.03$) groups (27.1 ± 9.7 vs. 23.7 ± 7.2 vs. 22.5 ± 10.2 respectively); (iv) the STAI Y1 score, $F(2,211) = 4.816$; $p = 0.009$, $\eta_p^2 = 0.044$, was significantly higher in the NK group compared to the MS ($p < 0.03$) group and nearly significantly higher in the NK group compared to the CIS ($p < 0.07$) group (45.3 ± 12.2 vs. 37.9 ± 11.7 vs. 41.1 ± 9.6 respectively).

Comparison with patients who already knew of their CIS diagnosis upon enrolment (CIS group) and who were given an MS disclosure at the end of the screening (CIS → T30MS, n = 37): No significant 'Time' modulation was seen in CIS → T30MS patients either on QoL or Anxiety and Depression.

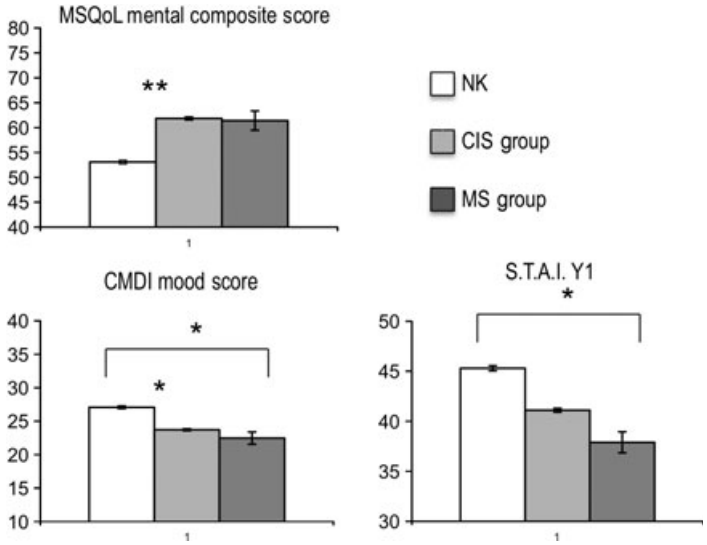

Figure 3 T0 means and confidence interval (CI) comparison in QoL (MSQoL-Mental), Anxiety and Depression (CMDI Mood Score and STAI-Y1) between patients who do not know their diagnosis at enrolment (NK) and two control groups such as patients enrolled with CIS (CIS group) and MS (MS group) already disclosed by another centre. *$p < 0.05$; **$p < 0.01$; when not specified p is > 0.05

Discussion

In this first prospective study a large sample of patients presenting with symptoms suggestive of MS were enrolled in the early phase of the disease (i.e. who had manifested symptoms suggestive of MS for no more than 6 months) and evaluated for QoL and psychological well-being at study inclusion, coinciding with the diagnosis screening start point, and in three further main steps: immediately after diagnosis disclosure and during 2 years of follow-up.

The prospective assessment of patients from when they were unaware of their diagnosis until the disclosure of MS, showed a significant improvement in patients' QoL together with a significant reduction in anxiety after the disclosure of MS diagnosis. This improvement was already significant in the immediate period after diagnosis disclosure and, with the caution due to the small size of the sample, it seems to have remained stable over the two subsequent annual follow-up visits when patients were assumed to have developed a more precise concept of the disease and disease-coping strategies. These findings were further strengthened by comparing the patients awaiting diag-

nosis with a different group of patients who already knew their MS diagnosis. In fact, patients who already knew their MS diagnosis showed a better QoL and lower levels of anxiety and depression than diagnostic work-up patients. Several types of reasons may be responsible for this positive effect of MS diagnosis disclosure. The first may be concerned with providing patients with accurate information and clarification as to the origin of the symptoms. Reassurance and sharing with the medical staff may be just as important, and stress management appears to be particularly valuable in the setting of chronic medical disease (14).

The pattern of results is less clear when patients received disclosure of a more general diagnosis like CIS. The MSQoL-Mental scale revealed a significant improvement in QoL after CIS diagnosis disclosure compared to the condition of not knowing. However, assessing QoL by means of SEIQoL, a non-health-related measure, CIS diagnosis disclosure did not seem to improve patients' QoL in either the short or long term. Furthermore, there was no significant decrease in anxiety and only a marginally significant reduction in depressive symptoms after CIS disclosure. It is reasonable to assume that disclosure of a generic diagnosis like CIS, although less serious than MS, keeps patients in a state of uncertainty which affects mood and QoL, especially if measured subjectively and not in relation to health status. Patients presenting with CIS are at a high risk of developing MS and hence are not in a situation of reduced anxiety. When patients present with CIS, clinicians are also faced with many questions and uncertainties (e.g. is the CIS due to a disorder other than MS? What is the likelihood that the person will develop MS?), which will probably have an impact on patients. The patients will undoubtedly have their own questions and fears, which may cause some of their anxiety. These findings suggest that CIS could also be a critical disclosure to take into serious consideration probably because of the high degree of uncertainty in which the disclosure leaves the patients about the disease and its future development. However, some caution is needed in defining the diagnosis of CIS as it is likely to keep the patient in a state of psychological distress. Although statistically weaker, a control analysis showed a better QoL, but again only when measured by MSQoL, and a lower level of depression and anxiety in patients who already knew of their CIS diagnosis compared to the NK group. Moreover, it is true that the disclosure of CIS, compared to that of MS, is less uniform due to the very nature of the condition. This could have created an unintentional bias in the study despite our attempt to reach the greatest possible uniformity by training the neurologist, at the outset of the study, in giving disclosure of CIS. It is worth bearing in mind that the discussion, which follows a disclosure of CIS, is more personalised due to the differing nature of patient interaction, but this is certainly true also for the disclosure of MS.

Before reaching conclusions, some methodological limits must be discussed and caution must be taken when considering the above results. These limits derive mainly from the necessity to avoid interference with clinical practice, leaving it to take its natural course as far as possible. For example, as discussed above, it is impossible to completely control the uniformity of the discussion between the neurologist and patient during disclosure of both MS and CIS. Also, one cannot be certain that, in the NK phase of the study, some patients did not harbour a strong, but unexpressed, suspicion regarding the nature of their diagnosis. Another important consideration is that, notwithstanding the fact that we corrected analyses by disability and patients were interviewed on enrolment with symptoms resolved or with residual symptoms, we cannot exclude the fact that residual symptoms could have influenced the results of the questionnaire, and thus, increased differences compared to the evaluation carried out immediately after the diagnosis disclosure.

However, keeping in mind the methodological limits, the most striking findings overall seem to suggest that the condition of diagnostic uncertainty is characterised by the worst QoL and the greatest psychological distress compared to the end of the screening work-up and therefore to the period after diagnosis disclosure. The increased sense of control conferred by knowledge of a diagnosis of MS or CIS, albeit weaker in the case of CIS rather than MS, seems to have a counter-regulatory effect on patients' stress levels. The results obtained in the second control analysis in patients who already had a CIS diagnosis that changed to MS at the end of the screening, support the finding that the end of uncertainty, rather than diagnosis of MS alone, could be the main factor improving patients' QoL and psychological well-being. Apparently, findings in patients given a diagnosis other than MS or CIS do not support the positive effect of an end to uncertainty. However, the NK $\rightarrow$ OTH group had heterogeneous diagnoses, large SD and a higher age than the NK $\rightarrow$ MS and NK $\rightarrow$ CIS groups. Further studies may determine the combined effect of the end to uncertainty and the type of diagnosis on patients' QoL and psychological well-being. Most available studies concern the effect of diagnosis disclosure in cancer, but findings are controversial. Some data support a positive effect of the knowledge of a cancer diagnosis (15,16), whereas others suggest that diagnosis worsens patients' QoL (17) or does not affect the way patients respond to a QoL questionnaire (18). Differences in the questionnaire, study design and cultural backgrounds could account for these divergent results.

In line with retrospective QoL assessments and the preferences of MS patients (3–5), this prospective study provides objective data supporting the importance of an early disclosure of MS diagnosis. In keeping with recent studies on shared decision-making in the relationship with MS patients (19), our results highlight the importance of an earlier diagnosis disclosure together with the provision of disease information to reduce the stressful condition of uncertainty and enhance the process of adaptation to the disease with an improvement in psychological well-being. It is also important to consider patients' constantly changing access to medical information (e.g. via websites). Patients who are uncertain about their condition are more likely to seek additional information and attempt a sort of self-diagnosis often accompanied by inaccurate information frequently affecting confidence and compliance. These factors inevitably redefine patient–doctor communication in general and have an impact on the timing of diagnosis disclosure.

In conclusion, it can be argued that early disclosure of MS diagnosis is not only useful for prompt treatment of MS but will also improve patients' well-being, QoL and, no less importantly, the patient–doctor relationship.

Acknowledgements

We dedicate this paper to the memory of the late Professor Pasquale Montagna who greatly encouraged our study. We are indebted to Eleonora Romagnoli, Silvia Canala and YGHEA staff for their precious technical assistance and study group supervision, to Daniel Zilio and Melissa Stott for English help, and to anonymous reviewers for their helpful suggestions. We would like to thank each patient and all medical staff of the Neurological Units. This study was supported by the Department of Neurological Science of the University of Bologna, Italy and by Biogen Dompe' s.r.l. None of the authors has financial relationships with the sponsor.

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Mattarozzi Katia was involved in concept/design, data analysis/interpretation and drafting the article. Vignatelli Luca was involved in concept/design, critical revision and approval of the article, and statistics. Baldin Elisa and Lugaresi Alessandra were involved in critical revision of the article and data collection. Pietrolongo Erika and Calzoni Silvia were involved in data collection. Tola Maria Rosaria, Granella Franco, Galeotti Massimo, Santangelo Mario and Malagu' Susanna were involved in approval of the article and data collection. Motti Luisa and Neri Walter were involved in approval of the article. Fiorani Laila, Guareschi Angelica and Scandellari Cinzia were involved in data collection. D'Alessandro Roberto was involved in concept/design, critical revision and approval of the article.

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Paper received September 2011, accepted February 2012

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