Impact of a Cognitive Behavioral Treatment Group on Multiple Sclerosis Patient's Quality of Life: A Clinical Trial (MARINA SEP)

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Introduction

MARINA SEP was a French multi-center clinical trial which evaluates the effects of a group Cognitive Behavioral Therapy (CBT) on Multiple Sclerosis (MS) Patients Quality of Life (QoL) [1-3].

One year multi-center controlled multivariate-matched study was organized on Relapsing Remitting MS (RRMS) patients with Expanded Disability Status Scale (EDSS) <4, MS duration <2 years, treated by interferon (Iβ) in 11 French centers (Figure 1) [4-8].

It was impossible to organize a double blind randomized clinical pilot trial, so we moved to a in comparison of a patient in the center which uses in daily life the CBT, with the two best matching patients in the others centers [the Nearest Neighbours (NN)] [9-17].

New Scales

In France, Iβ belongs to the first front of MS treatment, our objective was to investigate the QoL benefit of a group CBT in a prospective controlled trial compared with standard therapy in a homogeneous MS population (Figure 1) [18-25].

The essential concern of QoL in MS motivated us to provide further investigation on the beneficial effect of CBT. Aware of the methodological problems, we postponed the therapy trial, in concentrating first to the development of adapted measurement tools: a literature review showed that there was no scale of QoL or coping conducted in the same time adapted to routine practice [26,27]. A first cross-sectional study of 331 consecutive patients identified a short MS optimized QoL scale of 10 items (TLS-QoL 10) easy to use and easy to score in the routine practice (Figure 2 and 3) [26].
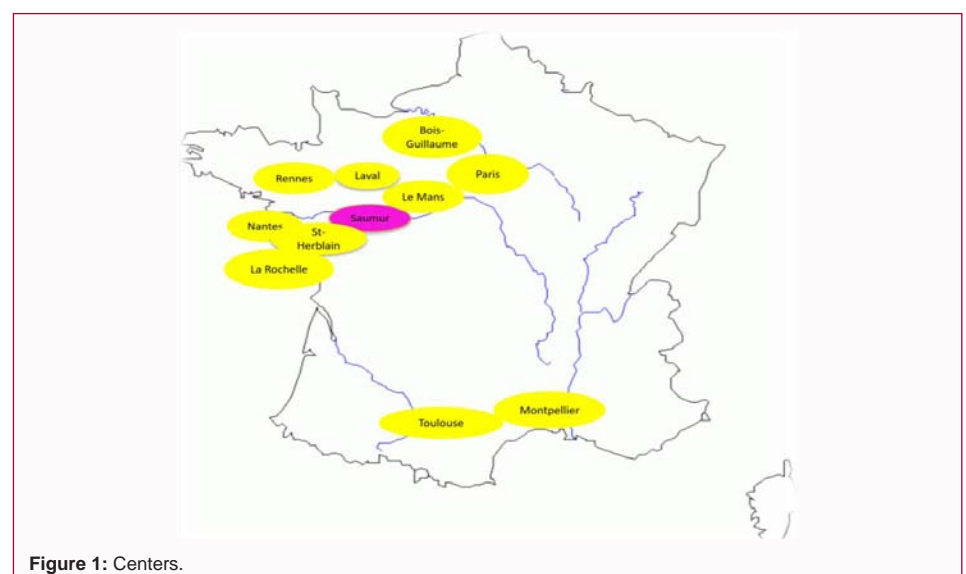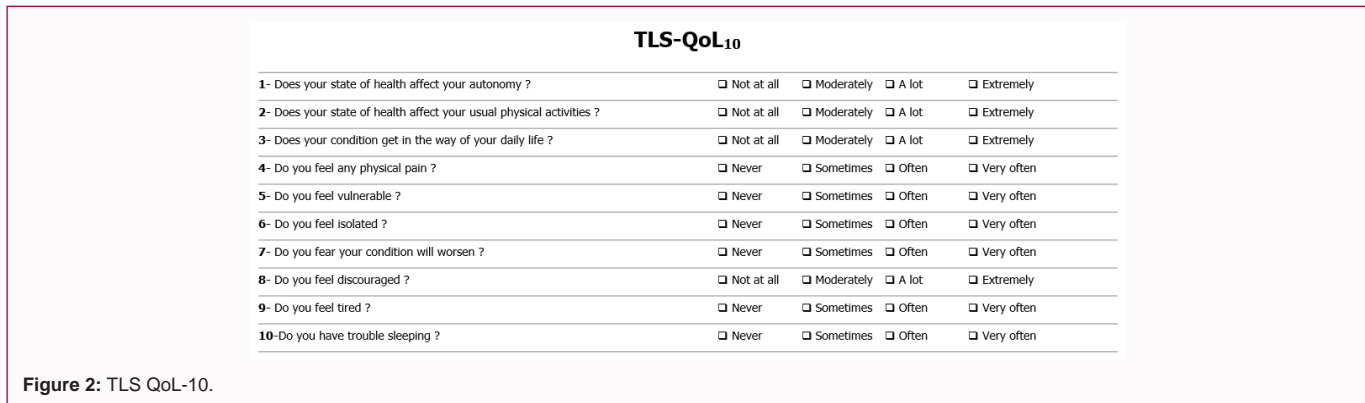
Figure 1: Centers.
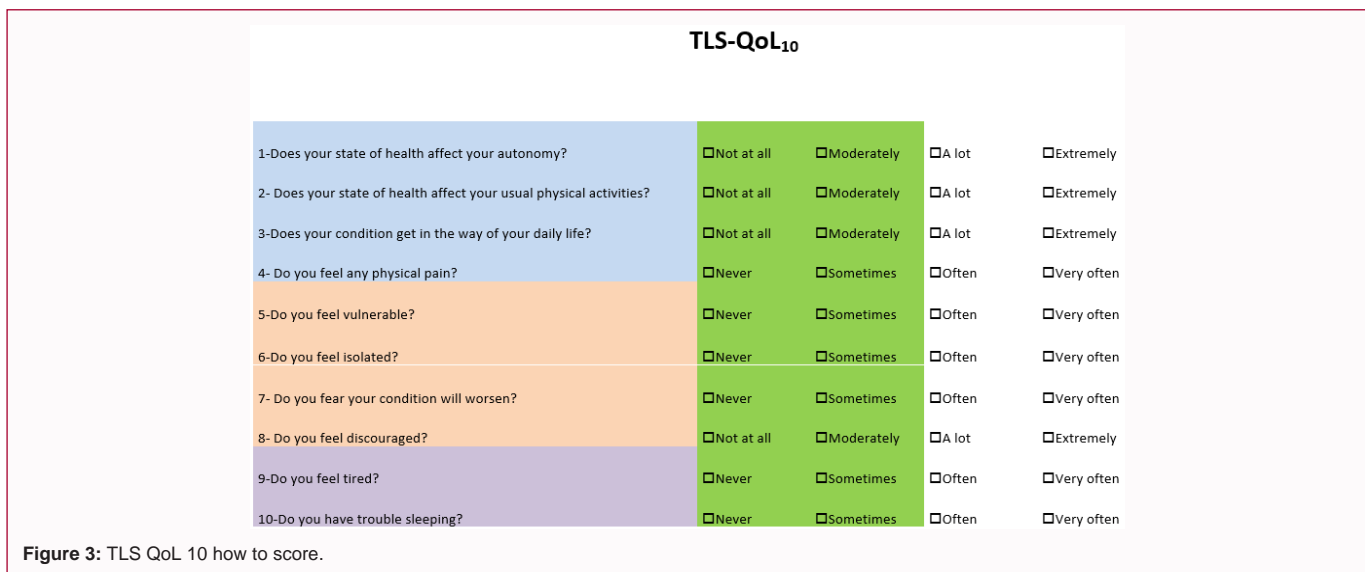
Figure 2: TLS QoL-10.
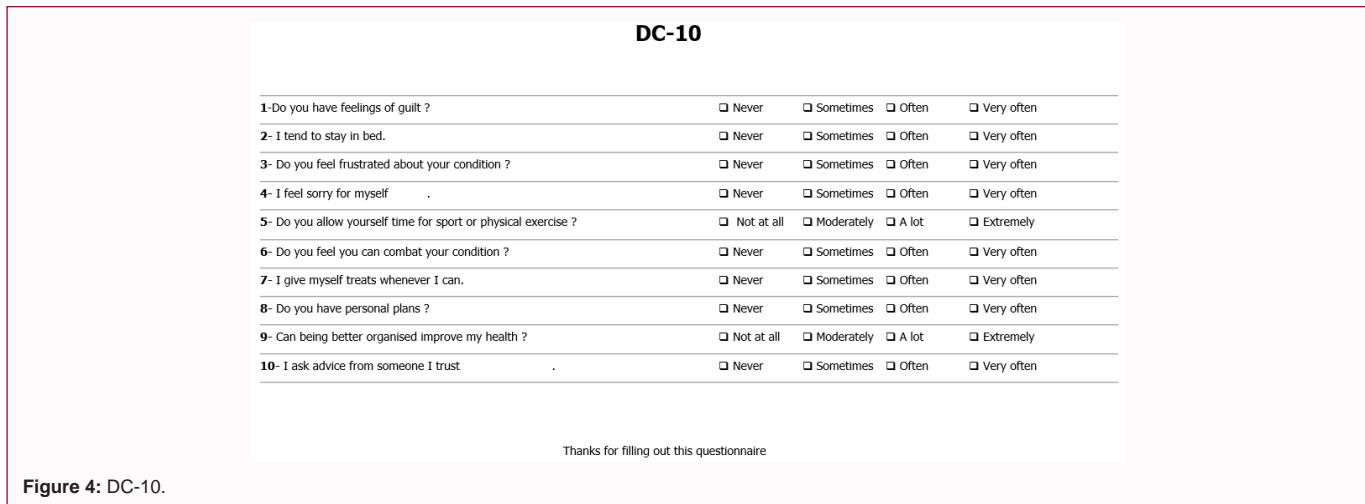

Figure 3: TLS QoL 10 how to score.

Figure 4: DC-10.

In the study, the authors developed an optimized short MS-specific coping scale, measuring the negative and positive coping and providing a total score (Devy Coping Scale: DC-10) [27]. We highlighted a statistical link between coping score and QoL score in MS context (Figure 4 and 5). So the authors led internal and external validations respecting all the steps of the psychometric rules to validate definitely these two brand new scales with 331 + 521 MS patients.

A Pilot Clinical Trial

Once these measurement tools were validated, we organized the clinical trial to assess the impact of CBT on MS QoL [28,29].

Hypotheses generated in the first studies constituted secondary objectives.

- Has the studied CBT a beneficial effect on QoL?

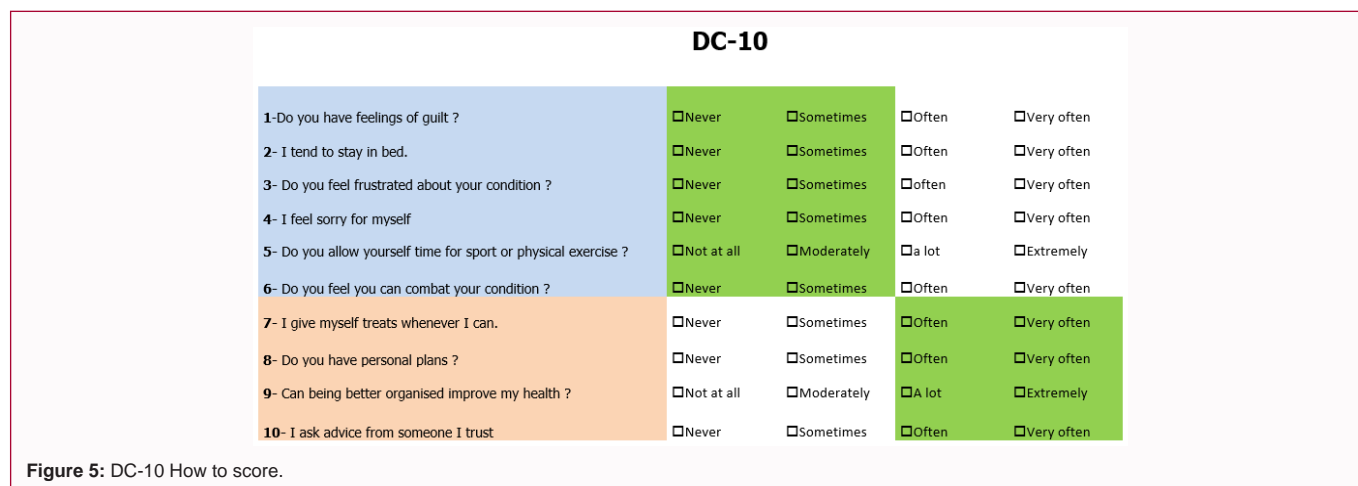- Does this coping have an effect on QoL?
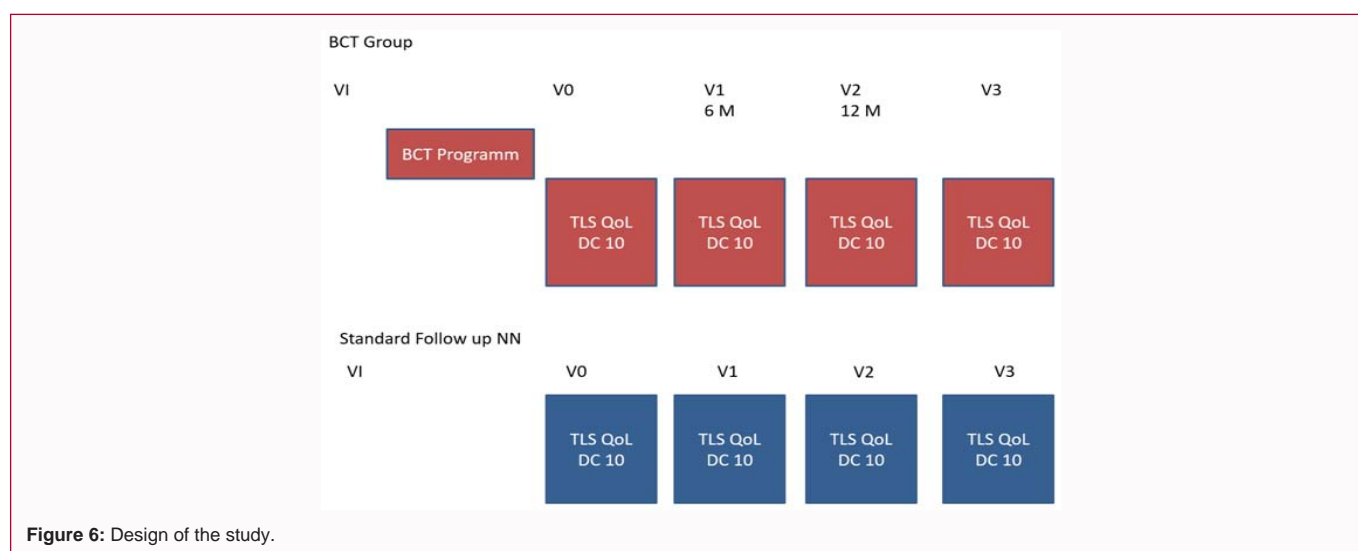
Figure 5: DC-10 How to score.

Figure 6: Design of the study.

And as a consequence to which extent the presumable benefit of CBT on QoL can be explained by an improvement of coping caused by the CBT?

QoL was strongly correlated with the disease severity which was essentially interpreted as QoL deterioration caused by disease progression. However, another interpretation in the opposite direction was suspected in which improving QoL may be slow disease development and delay disease progression.

Ethical Committees

This clinical trial has been accepted by 3 French Ethical committees (Brittany, Loire Valley, Languedoc Roussillon) as a pilot study and as a non-interventional trial.

Design

The design was based on One Year observational multi-center controlled multivariate-matched study in RRMS. Patients selected were 18-65 years aged, EDSS <4 and MS diagnosed since less than 2 years (Figure 6).

Patients with major psychiatric or other central nervous system disorders were excluded (one Patient was excluded because of a bipolar psychosis; all the patients with depression were included). The follow-up duration was 15 months CBT was administrated from month 0 (M0) to M3 in one center constituting the studied treatment CBT aim. Standard therapy was identically administered in the two groups during the whole duration of the trial with visits to king place at M0, M3, M6, M9, and M5.

For each recruited patient in the CBT group, constitute a neurological Identity Card, than the two best matching patients (nearest-neighbour) were selected in the others centers based on five matching severity variables (age, gender, EDSS, mood, disease duration). The standard therapy means 2 visits to a neurologist a year and 1 MRI a year. At initiation, each patient selected 3 personal objectives highlighted by a psychological positive test. These objectives have been used as the stimulus reference during the whole therapy.

CBT

During the first three months, the group CBT consisted in 12 group sessions of 2 hours concentrating in a particular coping theme (self-esteem, managing stress or anger) animated by two CBT experts (a psychologist and an expert in relaxation).

Measurements, at baseline, were based on alexithymia scale (TAS-20) (Beck Depression Inventory, Anxiety: STAI Y-A, Emotional distress: POMS; assertiveness and self-esteem scales). Neuropathy pain scale (DN4), Severity Fatigue Scale (FSS), sleeping disorder scales (Epworth), EDSS and self-filled validated short TLS-QoL10 and DC-10 scales were used at every visit [30].
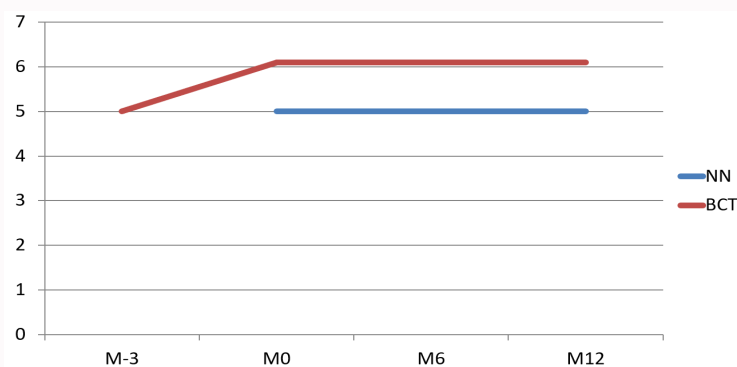
Figure 7: Impact of BCT on QoL (TLS QoL-10).

Table 1: Comparison by treatment group and unadjusted QoL and Coping values.
All the patients had RRMS without progressive form.

	Control (n=32)		CBT (n=19)		Total (n=51)	
Age[0.788]	42.03	± 10.42	42.74	± 6.44	42.3	± 9.04
EDSS[0.128]	1.58	± 1.06	2.03	± 0.89	1.75	± 1.01
Illness Duration (year)[0.161]	4.97	± 4.33	7	± 5.82	5.74	± 4.99
N of Relapses per Year[0.827]	0.66	± 0.47	0.64	± 0.40	0.65	± 0.44
Walking Distance (m)[0.557]	4.19	± 3.52	3.65	± 2.15	3.98	± 3.06
Gender[0.564]	19	61.30%	10	52.60%	29	58.00%
Medullary Relapse[0.348]	19	61.30%	9	47.40%	28	56.00%
QoL V0[1.000]	6.58	± 1.89	6.58	± 1.95	6.58	± 1.90
Final Q0L[0.102]	6.44	± 1.86	7.25	± 1.33	6.75	± 1.71
Qolf-Qol0[0.060]	-0.14	± 1.52	0.67	± 1.37	0.17	± 1.50
Qol responder	5	16.10%	8	42.10%	13	26.00%
CP at Baseline[0.116]	4.97	±1.43	4.32	± 1.42	4.72	± 1.44
Cp Final[0.607]	4.9	± 1.39	4.7	± 1.18	4.83	± 1.30
Cp Final-Cp at Baseline[0.123]	-0.06	± 0.99	0.39	± 1.01	0.11	± 1.01
CN baseline (CNb)[0.673]	1.81	± 1.33	2	± 1.86	1.88	± 1.53
CN Final (CNf)[0.122]	1.8	± 1.08	1.26	± 1.31	1.59	± 1.19
CNf-CNb[0.017]	-0.01	± 1.00	-0.74	± 1.04	-0.29	± 1.06
Coping Total Baseline (Cb)[0.202]	3.16	± 2.22	2.32	± 2.31	2.84	± 2.27
Coping Total Final (Cf)[0.557]	3.11	± 1.97	3.44	± 1.75	3.23	± 1.88
Cf-Cb[0.013]	-0.05	± 1.61	1.12	± 1.50	0.39	± 1.66

Table 2: Baseline and CBT effect on Quality of Life, positive, negative and Total coping (effect, [95%CI] P value. Baseline effect estimates the ratio between Post/pre baseline values for the control group. CBT effect estimates the difference between CBT and control group adjusted for baseline effect. The four studied endpoints were standardized to range [0,10].

	Baseline effect			CBT effect		
Quality Of Life	0.93	[0.863, 1.006]	<0.001	1.104	[0.310, 1.898]	0.009
Positive Coping	0.95	[0.887, 1.016]	<0.002	0.592	[0.070, 1.114]	0.032
Negative Coping	0.99	[0.796, 0.834]	<0.003	-0.44	[0.898, 0.019]	0.067
Total Coping	0.76	[0.624, 0.895]	<0.004	1.431	[0.715, 2.417]	<0.001

Objectives

Our main objective was to assess the efficacy of CBT compared to standard therapy alone to prevent QoL deterioration.

Our secondary objectives were the assessment of:

- The effect of CBT on coping improvement.

- The association between QoL and Coping to determine the possible interaction between Coping and QoL with a possible delay in time [31].

- The association between QoL and disease progression and the extent to which a QoL deterioration is a consequence of disease progression on QoL or/and QoL may have a per-se effect on disease progression.
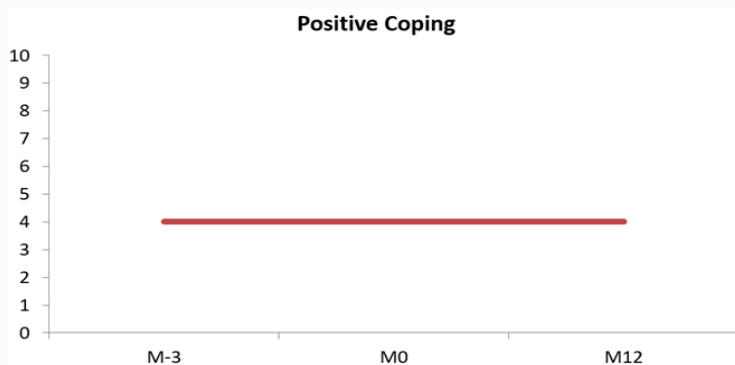
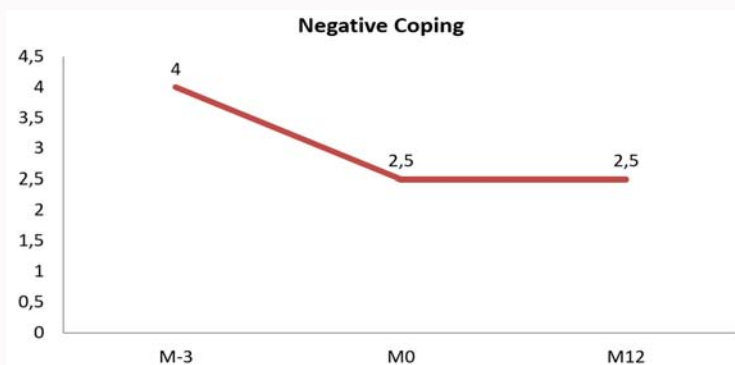**Figure 8:** Impact of BCT on coping strategy (DC-10).

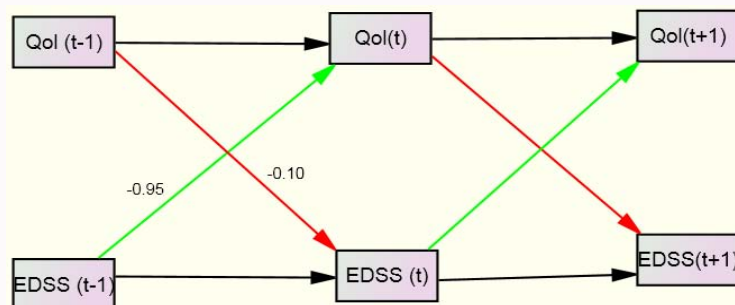**Figure 9:** Impact of BCT on coping strategy (DC-10).

Figure 10: Bidirectional effect QoL-EDSS.

Statistical Analysis

The intent to treat included all the selected patients and was our unique study selection. By using a mixed linear model, the post-baseline summary means on QoL between M3 and M15 was adjusted for QoL between M3 and M15 was adjusted for QoL baseline with matching block used as random factor, and CBT treatment compared standard therapy as a fixed factor [32].

Sample Description

19 patients were recruited in the pilot center and were matched to one or two patients among the control centers. A total of 51 patients were recruited in 11 centers. The two groups were found comparable on all baseline variables (Table 1) [33].

Results

The effect of CBT on quality of life was 1, 10 (0, 31, 1.89) p=0.009) on TLS-QoL scale (Table 2 and Figure 7).

Similar significant results were found for positive and negative coping (Figure 8 and 9). The effect of CBT on QoL can be explained essentially by coping. We investigated the direction of the association between QoL and illness progression. We found a bidirectional effect QoL-EDSS (Figure 10).

Discussion

Our results have limitations because this trial is a pilot study with CBT expertise in a unique center but our study has strength QoL and Coping have been measured with specific scales, validated within a routine practice environment.

Effect of a CBT on QoL

We confirmed the results obtained in previous studies. The mean improvement effect in the CBT group adjusted for baseline was 1.10 on TLS-QoL 10 (Table 2 and Figure 7).

Path	Meaning of paths	Coef (%)	95%	CI	Pval
C	Total effect CBT → QOL	1.10	1.31	1.89	.009
a	Effect CBT → Coping (%)	1.43	.715	2.14	<.001
b	Effect coping → QOL	.52	.36	.74	.003
a.b	Mediating effect CBT → QOL (= 1.43*.62)	.88	.61	1.25	.005
a.b/c	ratio of PAD mediation in total CBT effect =.88/1.10	.81	.57	1	.005

Figure 11: Statistical Univariate Mediation model (regression adjusted for SSI at baseline). Treatment CBT effect can apportioned into its indirect effect on QoL through coping and/or putative residual effect on QoL. Path 'a' is the effect of CBT on coping, whereas path 'b' is the effect of coping portialling out the effect of CB. If paths are quantified with unstandardized regression coefficients, the indirect effect of CBT on QoL through coping is estimated by the product of 'a' and 'b'. As the total effect CBT QoL is quantified by 'c', we can write c=c'+ab, thus ab/c estimates the indirect effect size of CBT through coping mediator.

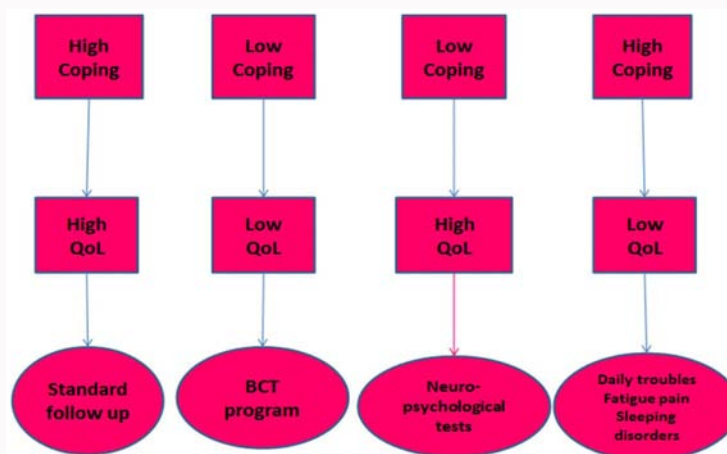Figure 12: Guidelines using Coping and QoL in the routine medical practice.

Effect of CBT on Coping

We found a highlight significant effect of CBT on total coping with a decrease of 1.43 on the DC10-Coping scale. The CBT effect was to strength and maintain positive coping score and to decrease negative coping score (Figure 8 and 9).

Coping as a result or a consequence of QoL we confirmed the significant effect of the Coping: QoL

QoL must be considered as a consequence of coping instead of a cause.

Coping as the mediating effect of CBT on QoL

We showed the indirect relationship CBT coping QoL constituted 81% of the direct effect CBT QoL (Figure 11).

The recursive effect of QoL and MS progression

Disease progression was expected to have an important deterioration effect on QoL.

Our study provides evidence of a feedback of QoL on disease progression: a deteriorated QoL during the previous period should accelerate disease progression while at the opposite a better QoL should reduce the natural progression of the disease.

Conclusion

Our original findings are:

1.   Better than any pharmacological treatment used alone, CBT adjuvant has a clinically relevant benefit on QoL.

2.   Coping has a direct effect on QoL (not the opposite) and constitutes the essential mediation effect of a CBT on QoL.

3.   Although the effect of disease progression was hypothesized, the unexpected beneficial effect of QoL on disease progression was identified.

The results highlighted the facts that there is no opposition between Modifying Disease Drugs (MDD) and CBT. In the contrary, especially in the window of opportunity CBT and MDD are synergistic to increase the effect of MDD (higher observance, lower side effects)
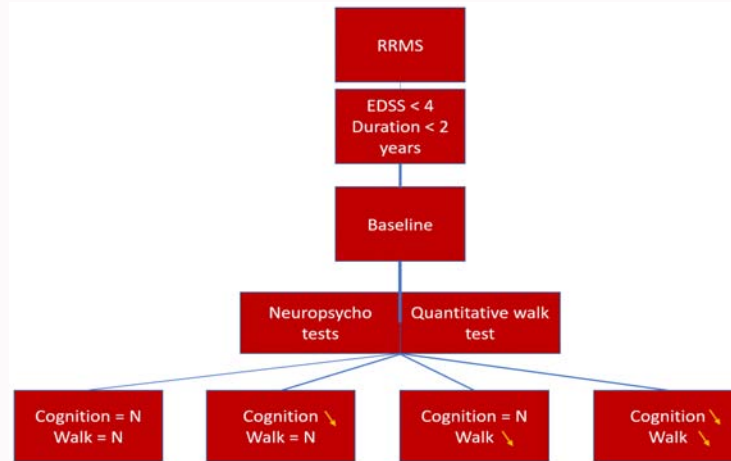
Figure 13: Guidelines improving MS Patient's assessment before treatment.

and to join a better QoL for MS patients. Single Patients perspective reinforces MDD effect [34]. The clinical trial meets to be validated on a larger sample. These results could make the neurologists looking after the link between cognitive status and coping strategy [35]. The neurologists, at the baseline, should improve MS patient's evaluation (EDSS, Coping strategy, QoL, Cognitive status and quantitative walk measurement). With the official guidelines based on EDSS score we should treat MS patients at the beginning of their disease with a validated strategy. Assessing coping strategy and MS Patient's QoL, it could be effective to optimize the impact of this treatment, and to help the patient to reach his blossoming [35]. New guidelines could help neurologists to reach a personalized way of treatment, validated scales easy to use and easy to score in the routine medical practice (Figure 12). Lastly, we observed that at the beginning all the patients of this trial could be including in a homogenous EDSS group. In fact, using EDSS, QoL, Coping, Cognitive status and quantitative walk assessment. This precise MS patient-s assessment could help the neurologist to reinforce the quality of the follow-up with a guideline adapted to the reality of MS patient's status (Figure 13).

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