ISSN: 2638-9231

Gratis

Research Article

Annals of Behavioral Neuroscience

A Group Cognitive Behavioural Therapy Improves Quality of Life of Multiple Sclerosis Patients and Delays Disease Progression: A Multi-Centre Controlled Trial

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Received: June 26, 2018; Accepted: September 06, 2018; Published: September 11, 2018

Abstract

Background: Multiple Sclerosis (MS) affects quality of life (QoL). Pharmacological treatments demonstrated benefits on clinical endpoints without improving QoL. We evaluated the effects of a group Cognitive Behavioural Therapy (CBT) on QoL disease progression.

Methods: One-year multi-centre controlled multivariate-matched study was organised on Relapsing-Remitting MS (RRMS) patients with Expanded Disability Status Scale (EDSS) < 4, MS duration < 2 years, treated by interferon Iβ in 11 French centres. For each new patient, the two best-matching patients for age, gender, EDSS, mood, illness duration baseline variables were selected in the other centres. The self-filled Two Lives Scale (TLS)-QoL10 was used at months (M) 0-3-6-9-12-15; the post-baseline mean QoL was the endpoint. We compared CBT + Iβ to Iβ alone. The effect of disease progression on QoL was evaluated by modelling, for each visit, the effect of EDSS on QoL at later visits.

Results: 19 + 32 patients were recruited. Compared to placebo, improvements of 1.10 (95%CI [0.31-1.89], p = 0.009) and 1.43*** [0.72, 2.15] were observed in the CBT group on QoL and coping scales, respectively. Coping explained 81%*** [57, 100] of the effect of CBT on QoL. QoL was negatively affected by disease progression (0.95*** [-1.21; 0.63]), whereas EDSS was influenced by QoL values (-0.10*** [-0.14; -0.06]).

Conclusions: We observed a clinically significant beneficial effect of CBT on QoL, the effect of CBT essentially explained by an increase of coping, a positive influence of QoL on disease progression. QoL is both the most important target for patients and a factor of slowing disease progression.

Keywords: Quality of life, Multiple sclerosis, Behavioral cognitive therapy

Introduction

Multiple Sclerosis (MS) severely affects Quality of Life (QoL) [1-3]. Interferon β1a and β1b provide evidence of benefits in reducing the number of exacerbations or delaying disease progression [4-8], however without proving a significant effect on QoL [1]. Conversely, pioneer studies provided first evidence that a group Cognitive Behavioural Therapy (CBT) used as add-on treatment to standard therapy may have beneficial effect on QoL [9-17], by improving the adaptation or coping of patients

towards the illness [18-25]. The Coping is a cognitive adaptation which has been activated by a stressful event [26].

These studies had limitations, such as uncontrolled design [13], comparison limited between CBT [9],[10],[14] or heterogeneous recruitment [12]. Important methodological concerns were met in measuring QoL and coping. In particular, the effect of a CBT may considerably vary depending on the conditions of medical practice, thus evaluating its effect requires studies within a routine medical environment, directly generalizable to every day practice.

The essential concern of QoL in this pathology motivated us to provide further investigation on the beneficial effect of CBT. Aware of these methodological problems, we postponed the therapy trial, in concentrating first to the development of adapted measurement tools: a literature review [27],[28] showed that there was no scale of QoL or coping conducted in the same time specific to MS and adapted to routine practice. A first cross-sectional study of 331 patients [27] identified a short MS-specific optimized QoL scale of 10 items (TLS-QoL 10). In the same study, the authors developed an optimized short MS-specific coping scale [28], measuring the negative and positive coping and providing a total score (Devy Coping Scale (DC-10)). The two scales were validated by an independent second study in 521 MS patients, providing accurate, specific and short questionnaires for both QoL and coping, fully adapted to routine medical practice.

Once these measurement tools were validated, 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. Hypotheses generated in the first studies constituted secondary objectives: (1) has the studied CBT a beneficial effect for improving coping?, (2) does this coping has an effect on QoL?, (3) 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 disease severity, which was essentially interpreted as QoL deterioration caused by disease progression [1],[5],[7]. However, another interpretation in the opposite direction was suspected [28], in which improving QoL may be slow disease development and delay disease progression.

Material and Methods

Interferon Beta (Iβ), a currently used standard therapy in MS, demonstrated a significant delay of disease progression and relapse reduction [8], however without benefit on QoL. The present study assessed the extent to which a CBT added to standard therapy is superior to standard therapy alone in preventing QoL deterioration.

The principal Investigator belongs to a multidisciplinary Care association “Douleur-Neurologie-Saumur” DNS.

The scientific committee of Britany (Pr G. EDAN) is the main supervisor.

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

Design

One-year observational multi-centre controlled multivariate-matched study in Relapsing Remitting MS (RRMS) patients [29],[30] was organised. Patients selected were 18-65 years aged, with a baseline Kurtzke [29] EDSS < 4 and MS diagnosed since less than 2 years. Patients with major psychiatric or others 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 administered from month 0 (M0) to M3 in one centre constituting the studied treatment CBT arm. Standard therapy was identically administered in the two groups during the whole duration of the trial with visits taking place at M0, M3, M6, M9 and M15. For each recruited patient in the CBT group, the two best-matching patients (Nearest-Neighbour NN) were selected in the other centres based on five baseline matching severity variables (Age, gender, EDSS, mood, disease duration).

Treatment

The standard therapy was accurately described in a manual to warrant as far as possible its administration as homogeneously as possible across the two arms in all centres. At initiation, each patient selected 3 personal objectives used as the stimulus reference during the whole therapy. 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 (one psychologist and one expert in relaxation). Each session started with a discussion of the previous session, followed by the presentation of a new theme,

and terminating with a relaxation period [12]. The groups were constituted to distribute the QoL and coping values.

Measurements

At baseline, we measured alexithymia (TAS-20) scale [31], Beck Depression inventory [31], Anxiety STA-I [31], emotional distress (POMS) [31], assertiveness and self-esteem scales [31],[32]. Neuropathic pain scale (DN4), severity fatigue scale (FSS), sleeping disorder scales (Epworth), EDSS [33] and self-filled validated short TLS-QoL 10 [27] and DC10 [28] scales were used at every visit. All the scales were administered in conformity with CBT. The scales EDSS, DN4, TLS-QoL 10 and DC10 have been validated in MS context. TLS QoL and DC10 are brand new scales validated in MS context respecting internal and external validation and psychometric process using especially Cronbach's alpha measurement [27],[28].

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: (a) the effect of CBT on coping improvement, (b) the association between QoL and coping to determine the possible interaction between coping and QoL, with a possible delay in time (b) 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.

Statistical Analysis

The intent to treat sample included all the selected patients and was our unique study selection. By using a mixed linear model, the post-baseline summary mean of QoL between M3 and M15 (QoL_p, main endpoint) was adjusted for QoL baseline (QoL_b), with matching block used as random factor, and CBT treatment compared standard therapy as a fixed factor. Response to therapy was defined as an increase of QoL_p of at least 1 point on TLS-QoL 10 (demonstrated as a minimum clinically relevant difference [26]). Secondary endpoints (negative, positive and total coping) were analysed following the same model. The study was powered to detect a difference of QoL of 1 point with a power of 80% at 95% two-sided confidence level with a 1:2 sample size ratio.

To estimate the extent to which the improvement of coping potentially generated by CBT may contribute to QoL change, we used a univariate mediation model [34].

By measuring disease progression by EDSS at each visit, the effect of EDSS on QoL (EDSS $\rightarrow$ QoL) was assessed by a mixed model, assuming an auto-regressive level 1 model for assessing the effect of $EDSS_t$ at a visit t on QoL_{t+1} measured at time t+1, whereas the opposite effects of QoL on EDSS (QoL $\rightarrow$ EDSS) was assessed by the same model but assessing the effect of QoL_t at visit t on $EDSS_{t+1}$ at visit t+1.

Results

Sample description and between group comparison

19 patients were recruited in the tested centre and were matched to one or two patients among the control centres. A total of 51 patients were recruited in 11 centres. The two groups were found comparable on all baseline variables (Table 1).

Effect of CBT on Quality of Life

In the control group, the post-baseline mean QoL_p value was slightly reduced compared with its QoL_b baseline value (Table 2), estimated ratio $QoL_p/QoL_b = 0.93$ ([.86, 1.006], $p < 0.001$). The mean estimated effect of CBT effect was 1.10 ([0.31, 1.89], $p = 0.009$) on TLS-QoL scale. By defining therapy response when QoL increased of at least 1 point on TLS-Qol Scale, the unadjusted proportions of responders were 16% (5/31) and 42% (8/19) on the control and tested groups (Risk Ratio RR = 2.58 ([1.10, 6.02], $p < 0.033$).

Similar significant results were found for positive, negative and total coping. The three endpoints were observed to decrease in the control group, with significant beneficial effect of CBT for positive and total coping (Table 2). To investigate the direction of the observed association between coping and QoL, a significant increase of 0.621 per CP level ([.436, 0.804], $p = 0.003$) was found when assessing the effect of coping at each visit t on QoL at next visit t+1. Conversely, a non-significant increase of 0.15 per QoL level ([-0.015, 0.368], $p = 0.153$) was found when assessing the effect of QoL at every visit t on coping at visit t+1.

Coping mediation to explain treatment effect on QoL

The extent to which the benefit of CBT on QoL can be explained by a benefit of CBT on coping was our second objective. In conformity with a univariate mediation model (Table 3), the positive effect of CBT on QoL increase was

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)	
Age0.788	42.03	± 10.42	42.74	± 6.44	42.30	± 9.04
EDSS0.128	1.58	± 1.06	2.03	± 0.89	1.75	± 1.01
Illness Duration (year)0.161	4.97	± 4.33	7.00	± 5.82	5.74	± 4.99
N of Relapses per Year0.827	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
gender0.564	19	61.3%	10	52.6%	29	58.0%
Medullary Relapse0.348	19	61.3%	9	47.4%	28	56.0%
QoL V01.000	6.58	± 1.89	6.58	± 1.95	6.58	± 1.90
Final QoL0.102	6.44	± 1.86	7.25	± 1.33	6.75	± 1.71
Qolf-Qol00.060	-0.14	± 1.52	0.67	± 1.37	0.17	± 1.50
QoL responder0.041	5	16.10%	8	42.10%	13	26.00%
CP at Baseline0.118	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 Baseline0.123	-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	-0.05 ± 1.61	1.12	± 1.50	0.39	± 1.66

Values: All the patients had RRMS without progressive form.

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	0.934	[0.863, 1.006]	<.001	1.104	[0.310, 1.898]	0.009
Positive Coping	0.952	[0.887, 1.018]	<.001	0.592	[0.070, 1.114]	0.032
Negative Coping	0.99	[0.796, 0.834]	<.001	-0.439	-[0.898, 0.019]	0.067
Total Coping	0.759	[0.624, 0.895]	<.001	1.431	[0.715, 2.147]	<.001

c = 1.10 [031, 1.89], p = 0.009 (Table 2). We estimated the effect of CBT on coping to a = 1.43 ([0.715, 2.14], p < 0.001) and the effect of coping on QoL to b = 0.52 ([.36, 0.74], p = .003. Thus, the indirect effect of CBT mediated by coping is a×b = 1.43×0.62 = 0.886 ([0.61, 1.25], p = 0.005). Given the ratio of the indirect/direct a×b/c = 0.88/1.10 = 0.81%, the effect of CBT on QoL can be essentially explained by coping.

Assessing the causes and consequences of MS progression on QoL

We investigated the direction of the association between QoL and illness progression (measured by EDSS). First, the consequence of illness progression on QoL (EDSS →, QoL) was estimated in assessing the effect of $EDSS_t$ at each visit t on QoL_{t+1} at the following visit t+1 (Figure 1). At one visit t+1, QoL_{t+1} is estimated by the sum of the effect of QoL_t (previous visit) and a deteriorating effect proportional to EDSS following the model $QoL_{t+1} = 0.97 \times QoL_t - 0.92 \times EDSS_t$. At the opposite, the effect of QoL on EDSS (QoL → EDSS) was found in testing the effect of QoL_t for each visit t on EDSS measured at the next visit (t+1). At one visit t+1, $EDSS_{t+1}$ is estimated by the sum of the effect of $EDSS_t$ (previous visit) and a beneficial effect

of QoL at time t following the model $EDSS_{t+1} = 1.03 \times EDSS_t - 0.1 \times QoL_t$ was found.

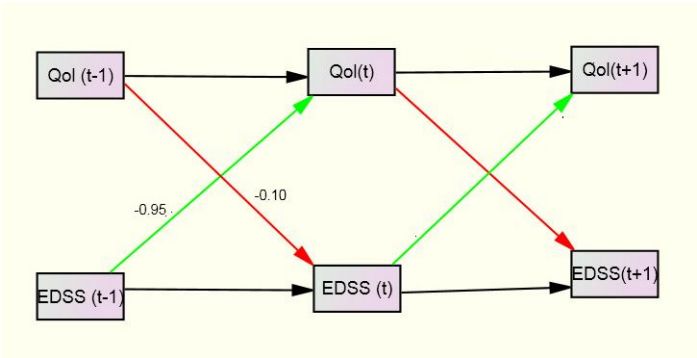

Figure 1: Bidirectional effect QoL-EDSS

Discussion

Limitations and strengths

Our results have limitations: the CBT effect was confounded with the centre effect. Stratifying treatment by centre was not feasible in this study, as the studied CBT expertise was exclusively available in one centre. We managed to reduce this bias: the standard therapy was administered homogeneously in the two groups, and baseline patients heterogeneities between centres were minimized through nearest neighbour matching, and further adjustment for baseline.

However, our study has strengths: QoL and coping have been measured with specific scales validated within a routine practice environment, providing evidence of external validity of this study, thus generalizable to every day medical practice [27],[28].

Effect of a CBT on QoL

We confirmed and completed the results obtained in previous studies [21],[23],[25]. The mean improvement effect in the CBT group adjusted for baseline was 1.10 on TLS-QoL 10. This value exceeds the validated [27] 1 point minimum clinically relevant difference. On the other hand, the proportion of responders on CBT was more than doubled compared with standard therapy alone (RR = 2.58). We conclude to a statistically and clinically meaningful effect of CBT addition to standard therapy, compared with standard therapy alone. The standard therapy means a classical follow up (an appointment with the neurologist twice a year and a brain MRI once a year.

Effect of CBT on Coping

Similarly to QoL, we found a highly significant effect of CBT on total coping with a decrease of 1.43 on the DC 10-coping scale. The CBT effect was similar for positive or negative coping and both effects cumulated to the total coping score, with a highly significant decrease of 1.43, taking into account the baseline coping value of 2.82

Table 3: Statistical Univariate Mediation model (regressions adjusted for SSI at baseline). Treatment CBT effect can be 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 partialling out the effect of CBT. 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.

Path	Meaning of paths	Coef (%)	95%	CI	P- value
c	Total effect CBT → QOL	1.1	1.31	1.89	0.009
a	Effect CBT → Coping (%)	1.43	0.715	2.14	<.001
b	Effect coping → QOL	0.52	0.36	0.74	0.003
a.b	Mediating effect CBT → QOL (= 1.43*.62)	0.88	0.61	1.25	0.005
a.b/c	ratio of PAD mediation in total CBT effect = .88/1.10	0.81	0.57	1	0.005

Case	GA	UV connection	Prenatal sonographic findings/associated anomalies	Karyotype	Outcome	Postnatal/Post-mortem findings
1	13+0	PV	Apparent retrognathia. No other obvious changes in echoanatomy.	NP	VD at 39w	Male, 3285gr, 50cm, Apgar 9/10/10.
2	13+6	RA	Congenital heart defect with cardiac chambers disproportion with a smaller LV, hypoplastic aortic arch, great arteries disproportion, moderate to severe VSD, small aortic valve. Bilateral pyelectasis.	46,XY	VD at 39w+6d NND	Male, 3300gr, 53cm, Apgar 8/10/10. Corrective cardiac surgery at 14d, died in the intra-operative period. Autopsy: hypoplastic LV, hypoplastic aortic valve (bicuspid), ascending aorta and aortic arch, RA and RV hypertrophy, large ventricular meso-septal defect. Bilateral pyelectasis. Lymphangiectasis
3	22+5	RA	Mild cardiomegaly, no usual vascular pattern of the portal system is observed, suspected portal vein agenesis, Blake's pouch cyst with normal cerebellar vermis, IUGR.	46,XY	CD at 34w+3d	Male, 1700gr, 41cm, Apgar 9/10/10, no dysmorphic features.
4	14+5	RA	SUA, tetralogy of Fallot with hypoplastic pulmonary artery.	46,XX	TOP at 25w	Autopsy: confirmed the DVA, biometric parameters adequate for GA, severe hypoplastic PuV (quasi-atresia), hypoplastic pulmonary trunk, abnormal RV morphology, lightly hypoplastic ductus arteriosus, sub-aortic VSD and SUA.

GA, Gestational age; UV, umbilical vein; PV, portal vein; NP, not performed; VD, vaginal delivery; RA, right auricle; LV, left ventricle; VSD, ventricular septal defect; RV, right ventricle; IUGR, intrauterine growth restriction; CD, caesarean delivery; SUA, single umbilical artery; TOP, termination of pregnancy; DVA, ductus venosus agenesis; PuV, pulmonary valve.

(Table 1), providing a relative benefit of 50.1% compared to standard therapy alone.

Coping as a result or a consequence of QoL

We assessed the direction of the association between coping and QoL, in comparing the two longitudinal models QoL → coping and coping → QoL. The significant superiority of the coping → QoL effect provides evidence that QoL must be considered as a consequence of coping instead of a cause.

Coping as the mediating effect of CBT on QoL

This simultaneous effect on QoL and coping supports the hypothesis that QoL change can be explained by an improvement of coping [21],[24],[25] . We demonstrated the effect of CBT on QoL through the indirect or mediating effect of coping by a mediation model: by estimating the relationship a = CBT → coping and b = coping → QoL, we showed that the combination a×b of the indirect relationship CBT → coping → QoL constituted 81% of the direct effect CBT → QoL (Table 3).

The recursive effect of QoL and MS progression

Disease progression (EDSS baseline) was expected to have an important deterioration effect on QoL [1],[2],[21],[24],[25]. Our study provides the first 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.

This recursive effect of QoL on EDSS has important practical implications:

- This feedback effect may generate the hypothesis that at the accelerated deterioration at Secondary Progressive MS (SPMS) stage [5],[7],[29] (where both QoL and EDSS are deteriorated), the EDSS increase impacts QoL which as a feedback impacts EDSS.
- The consequences of these results may suggest to the neurologists that the combination between standard therapy and CBT could be synergistic and could increase the global treatment efficacy just after MS diagnosis and during the "window of opportunity" [4],[6],[7],[30]. Single patient perspective reinforces modifying disease drugs effect.
- Although in this trial all the patients were treated indistinctly with CBT and to improve benefit/risk, only patients with a low coping or QoL score should be treated. From this viewpoint, a regular monitoring of QoL and coping of MS patients might be useful to anticipate further damage caused by QoL deterioration, needing a CBT to rebalance QoL. This monitoring should only trigger a CBT when needed, thus reducing health costs.
- How to explain this surprising influence of QoL on disease progression? A possible effect not studied was that an adequate constructive coping inducing QoL increase may also increase the compliance of prescribed treatment (Iβ in this study), which may have a positive effect on disease progression, increase of the confidence of the patient, adequate functioning of endomorphism, etc.

Conclusion

Our original findings are: (a) better than any pharmacological treatment used alone, CBT adjuvant has a clinically relevant benefit on QoL; (b) coping has a direct effect on QoL (not the opposite) and constitutes the essential mediation effect of a CBT on QoL; (c) although the effect of disease progression was hypothesised, the unexpected beneficial effect of QoL on disease progression was identified.

MARINA SEP is a pilot study with few patients. This clinical trial needs to be validated on a larger sample. This result could make the neurologists looking after the link between cognitive status and Coping strategy.

Acknowledgements

For the neurologists who belong to "The MARINA SEP Group"

"On behalf of Prof. D. Laplaud (Chu Nantes), Dr. S. Wiertlevski (Chu Nantes), Dr. P. Cormier (Laval), Dr. A. Legout (Chr Le Mans), Dr. A. Gueguen (The Rothschild Foundation, Paris), Prof. E. Thouvenot (Chu Montpellier), Prof. D. Brassat (Chu Toulouse), Dr. V. De Burghgraeve † (Chu Rennes), Prof. G. Edan (Chu Rennes), Dr. I. Bernard (Cholet), Dr. L. Iasci (Bois Guillaume), Dr. J. Augustin (Bois Guillaume), Dr. O. Anne (Chr La Rochelle), Dr. G. Hinzelin (Saint Herblain), The MARINA SEP Group".

This work has been funded in part by DNS association and by Merck Serono Research Fund.

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Gratis

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