Brainstem volume changes related to cognitive behavior therapy in postcancer fatigue patients

H. Prinsen[1], H. W.M. van Laarhoven[1], G. Bleijenberg[2], M. J. Zwarts[3], M. van der Graaf[4,5], M. Rijpkema[6], and A. Heerschap[4]

[1]Medical Oncology, Radboud University Nijmegen Medical Centre, Nijmegen, Gelderland, Netherlands, [2]Expert Centre Chronic Fatigue, Radboud University Nijmegen Medical Centre, Nijmegen, Gelderland, Netherlands, [3]Clinical Neurophysiology, Radboud University Nijmegen Medical Centre, Nijmegen, Gelderland, Netherlands, [4]Radiology, Radboud University Nijmegen Medical Centre, Nijmegen, Gelderland, Netherlands, [5]Clinical Physics Laboratory, Radboud University Nijmegen Medical Centre, Nijmegen, Gelderland, Netherlands, [6]Nuclear Medicine, Radboud University Nijmegen Medical Centre, Nijmegen, Gelderland, Netherlands

Introduction

Postcancer fatigue (PCF) is a frequently occurring, severe, and invalidating problem, impairing quality of life.[1-2] Cognitive behavior therapy (CBT) addresses the perpetuating factors of PCF and has a clinically relevant effect in reducing fatigue and functional impairments in severely fatigued cancer survivors.[3] However, until now, little is known about (neuro)physiological factors determining postcancer fatigue. For non-cancer patients with chronic fatigue syndrome (CFS), some characteristics of brain morphology, metabolism, and perfusion have already been identified.[4-10] A generalized reduction of brain perfusion has been observed in CFS patients, with a particular pattern of hypoperfusion of the brainstem.[9] Furthermore, a recent study reported a strong correlation between brainstem gray matter volume and pulse pressure, which suggests impaired cerebrovascular autoregulation.[10] Thus, changes in brain physiology, structure, and function could contribute to chronic fatigue and impaired cognitive function in CFS. As the brainstem seems to be an important link in the pathogenesis of fatigue in general, it may also be of importance for PCF. **Aim:** to assess CBT related structural changes in the brain using brainstem volumetry in PCF.

Methods

Twenty severely fatigued cancer survivors were included in this randomized controlled trial. Participants had completed treatment of a malignant, solid tumor minimal one year earlier and had no evidence of disease recurrence. Patients with a brain tumor in the past or with a co-morbidity that could explain fatigue were excluded. Fatigue severity was measured by the fatigue severity subscale of the Checklist Individual Strength (CIS-fatigue).[11] Severely fatigued patients (35 points or more on this subscale) were randomly assigned to either the intervention condition (CBT, n=12) or the waiting list condition (WL, n=8). Both patient groups were assessed two times, at baseline and six months later. MR measurements were performed on a 3T MR system (Siemens, Erlangen) using the accompanying circularly polarized birdcage head coil. High-resolution T1-weighted images (voxel size 1mm^3, TR=2300 ms, TE=3.16 ms) of the whole brain were acquired using a magnetization prepared rapid acquisition gradient echo sequence. Normalizing, bias-correcting, and segmenting into gray and white matter was performed using the voxel-based morphometry toolbox in the SPM5 package (http://www.fil.ion.ucl.ac.uk/spm/software/spm5).[12] Automatic segmentation of the brainstem (defined as medulla, pons, and midbrain, bordering the ventral diencephalon, the fourth ventricle, and the cerebellum) was performed using the FIRST module of FSL 4.1.4 (http://www.fmrib.ox.ac.uk/fsl/first/).[13] Brainstem volumes were expressed as a percentage of total brain volume (TBV, gray matter volume plus white matter volume).

Results

At baseline, both brainstem volume (Figure 1) and TBV were not significantly different (p>0.05) between patients in the WL and the CBT group (Table 1). CIS-fatigue scores showed a significant decrease (p<0.001) from pre- to post-treatment, whereas the CIS-fatigue scores of patients in the WL condition remained high (Table 1). CBT led to a significant (p=0.008) increase in brainstem volume from baseline to post CBT, whereas in the WL condition no change (p>0.05) in brainstem volume was observed from baseline to post WL (Table 1). The change in brainstem volume from baseline to follow-up was significantly larger (p=0.032, Figure 2) in the CBT condition (0.031±0.033) compared to the WL condition (-0.006±0.038). There was no significant change (p>0.05) in TBV from baseline to follow-up, neither in the CBT condition nor in the WL condition (Table 1).

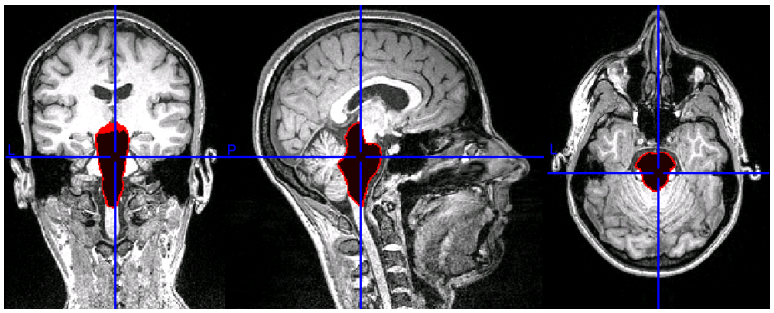

Figure 1. Example of segmentation of the brainstem in red in a patient with PCF. From left to right in coronal, sagittal, and transversal plane.

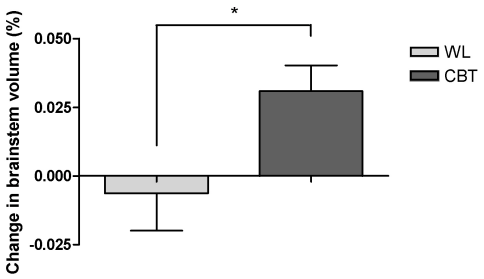

Figure 2. Effect of WL and CBT on brainstem volume (expressed as a percentage of TBV). There is a significant increase in brainstem volume in the CBT condition, but not in the WL condition. *p=0.032

Table 1. Comparison of baseline and follow-up data of the WL and CBT condition

	WL	CBT
Brainstem volume (% of TBV) baseline	1.983 ± 0.147	1.921 ± 0.178
Brainstem volume (% of TBV) follow-up	1.976 ± 0.124	1.952 ± 0.186
TBV (ml) baseline	1195.3 ± 155.4	1199.8 ± 168.9
TBV (ml) follow-up	1192.0 ± 155.7	1191.7 ± 171.8
CIS-fatigue score baseline	46.12 ± 5.69	46.58 ± 5.74
CIS-fatigue score follow-up	42.75 ± 4.53	26.08 ± 8.28

Discussion and conclusion

This is the first study to report on the effect of CBT on brainstem volume in a randomized controlled trial in patients suffering from PCF. At baseline, TBV and brainstem volume were similar between the different groups, underlining the adequacy of randomization. CBT resulted in a significant decrease in fatigue score and a significant increase in brainstem volume. This increase in brainstem volume could not be explained by a change in TBV and was not observed in patients after six months of waiting for CBT. These findings suggest that the central nervous system, and in particular the brainstem, plays a central role in the pathophysiology of fatigue in PCF.

References

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