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Neuroinflammation in HCV-infection – Peril or protection?

To the Editor:

We have read with interest the article by Byrnes *et al.* [1], who prospectively evaluated the effect of HCV clearance with pegylated interferon/ribavirin (PegIFN/RBV) therapy on cerebral metabolism as well as cognitive function in 15 non-cirrhotic HCV positive patients.

In their study, cerebral metabolites were measured with ^{1}H magnetic resonance spectroscopy (MRS) before, during, and 12 weeks after treatment, and neurocognitive dysfunction was assessed by a psychometric test battery. In contrast to non-responders or relapsers (NR/R; n = 5) patients with sustained viral response (SVR; n = 8) showed a significant reduction of the choline/creatine and the myoinositol/creatine ratio in the basal ganglia as well as improvement in verbal learning, memory and visuo-spatial memory. Consequently, the authors concluded that SVR was associated with a decrease of neuroinflammation and an improvement of cognitive function. Indeed, this finding of improvement with viral clearance fits the expectation that viral clearance should improve HCV-associated cognitive impairment. However, a note of caution might be worthwhile.

We recently found MRS markers of neuroinflammation to be increased in HCV patients with only mild neuropsychiatric symptoms in contrast to those with severe symptoms, suggesting a neuroprotective effect of the inflammatory response [2]. Thus, our findings are in contrast to the conclusion drawn by Byrnes *et al.*, who hypothesize that their MRI results reflected reduced neuroinflammation as a consequence of HCV eradication and that reduced neuroinflammation caused the improvement of the psychometric test results observed in their patient group.

Stimulated by the paper of Byrnes *et al.* [1], we had a second look at our data and performed additional analyses. Firstly, we compared MRS data and psychometric test results of the 53 PCR positive patients described before [2], to data of 9 PCR negative patients who had undergone the same study protocol. Secondly, we compared the non-responders in our patient group (n = 18) to patients with SVR after PegIFN/RBV therapy (n = 6). Chosen regions of interest were basal ganglia (BG), parietal white matter (PWM), occipital cortex (OC) and pons. Spectra were analysed using LC model as described in [2].

Table 1. Comparison of mean brain metabolite levels and psychometric results for PCR+ *vs.* PCR– patients and for sustained responders *vs.* non-responders.

Patients	Spectroscopy							
	Choline		Creatine		Myo-Inositol		N-Acetylaspartate	
	PWM	OC	PWM	OC	PWM	OC	PWM	OC
PCR+	1.49 ± 0.40	0.96 ± 0.25	4.87 ± 1.20	6.06 ± 1.51	4.24 ± 1.08	4.34 ± 1.27	8.30 ± 2.19	8.59 ± 1.95
PCR-	1.18 ± 0.19	0.84 ± 0.18	3.79 ± 0.46	5.27 ± 0.42	3.46 ± 0.73	3.60 ± 0.65	7.62 ± 0.98	7.66 ± 0.90
p value	0.001	n.s.	0.000	0.005	0.047	n.s.	n.s.	0.035
SVR	1.23 ± 0.13	0.80 ± 0.16	3.86 ± 0.51	5.26 ± 0.46	3.71 ± 0.64	3.62 ± 0.76	7.79 ± 0.95	8.00 ± 0.60
NR	1.20 ± 0.24	0.78 ± 0.18	3.96 ± 0.67	5.01 ± 0.81	3.44 ± 0.55	3.67 ± 1.19	6.72 ± 1.07	7.38 ± 1.35
p value	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	0.044	n.s.

Patients	Psychometric tests				
	FIS	SF36 phys	SF36 mental	PsychScore	WBGT-Words z
PCR+	73.54 ± 39.42	156.90 ± 77.96	155.36 ± 82.71	0.38 ± 0.19	0.17 ± 1.21
PCR-	93.56 ± 39.81	166.33 ± 89.98	164.42 ± 93.40	0.38 ± 0.12	-0.22 ± 0.52
p value	n.s.	n.s.	n.s.	n.s.	n.s.
SVR	94.71 ± 44.87	134.86 ± 61.75	166.21 ± 106.34	0.43 ± 0.14	0.08 ± 0.83
NR	88.67 ± 33.15	164.88 ± 72.38	152.80 ± 84.98	0.37 ± 0.20	-0.03 ± 1.15
p value	n.s.	n.s.	n.s.	n.s.	n.s.

PWM, parietal white matter; OC, occipital cortex; SVR, sustained viral responders; NR, non-responders; FIS, Fatigue Impact Scale; SF36 phys, Short Form 36 physical sum score; SF 36 mental, Short Form 36 mental sum score; Psych Score; Attention test sum score; WBGT-words z, Z-score word-figure-memory test words; n.s., not significant. Metabolite levels of the basal ganglia and pons are not shown since we did not observe significant group differences in these regions.

Importantly, no differences were found for the basal ganglia. In contrast, the PCR negative patients showed significantly lower choline (Cho), myoinositol (mI) and creatine (Cr) levels in PWM, and significantly decreased creatine and N-acetylaspartate (NAA) levels in OC compared to the PCR positive patients, while they tended to score worse in the psychometric tests, especially the Fatigue Impact Scale and the memory for words (Table 1). Non-responders and SVR patients did not significantly differ except for a significantly higher NAA level in the latter in PWM. Our new observations (summarized in Table 1) again do not support the hypothesis suggested by Byrnes *et al.* that SVR is accompanied by a decrease in neuroinflammation thereby leading to an improvement in cognition.

We believe that different factors might have biased the work of Byrnes *et al.* If their concept was true, shouldn't patients with NR/R have shown a lack of improvement? However, both groups in their study (patients with SVR and NR/R patients) showed an improvement of psychometric test results with repetitive testing. In addition, the two patient groups are far too small with 7 and 4 subjects, respectively, for analysing treatment effects on the test results during follow-up. Conflicting results from different studies [2,3] suggest that more efforts and research resources need to be allocated to address the true impact of HCV eradication on neuropsychiatric symptoms in patients with hepatitis C. In the future, interferon associated with non-interferon associated viral clearance and potential differences on mental performance should be compared.

Concerning the MRS results, we would like to address additional caution. Significant metabolite changes have been observed in the basal ganglia, only by Byrnes *et al.* [1]. As shown in their Fig. 1, the voxel of basal ganglia they used, contains a component of the anterior limb of the internal capsule and surrounding white matter (WM). It is known that the metabolite distribution in WM and gray matter (GM) is quite different [4]. Therefore, a voxel placement containing such a partial volume effect will reduce the reproducibility of the results by a study with follow-ups. In addition, it has to be considered that the metabolite Cr, which has been used by the authors as internal calibration factor, is a glial marker and thus cannot be considered as a control metabolite – especially not in a study dealing with neuroinflammation.

Conflict of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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