Combining fMRI with qMRS for understanding the etiology of periodic hypersomnia

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Introduction:

Kleine–Levin Syndrome (KLS) is a rare, but relatively well-defined disorder characterised by excessive sleep periods (periodic hypersomnia) [1,2,3] The etiology of KLS is unknown, however, a few studies have implicated thalamic involvement [4,5]. In a previous study we studied 8 patients with KLS and 12 healthy controls were examined with functional Magnetic Resonance Imaging (fMRI) using a paradigm that investigated the response to increasing working memory load. KLS patients showed working memory hyperactivity in left thalamus (TH) compared to healthy controls (Fig. 1). The objective in this work was to examine if the hyperactivity were due to neurological damage of thalamus. For this purpose Absolute Quantitative Magnetic Resonance Spectroscopy (qMRS) were used.

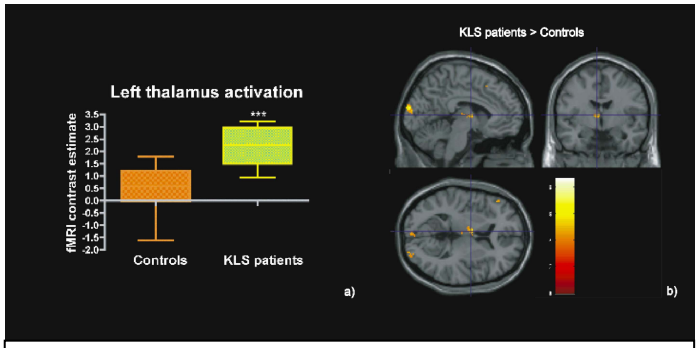

Fig 1. Results from previous study showing hyperactivity in left thalamus

Materials and Methods:

5 patients suffering from periodic hypersomnia were included. at the time of writing 3 patient were diagnosed with KLS, one was under investigation and one was diagnosed as non KLS. (males = 3; females = 2) and 6 healthy volunteers (males = 4; females = 2) were included. All measurements were performed on an Achieva 1.5 T MR-scanner (Philips Medical Systems, The Netherlands).

fMRI: A verbal working memory paradigm with increasing difficulty level was applied. Functional images were acquired with a BOLD-sensitive echo planar imaging (EPI) sequence (TE = 40 ms, TR = 2.7 s, flip angle 90°, number of slices = 32, 3 X 3 X 3; 302 dynamics). The fMRI images were preprocessed and analysed using SPM5 software (Wellcome Department of Imaging Neuroscience, University College, London, UK), using image realignment, normalisation, and smoothing with 8 mm Gaussian kernels. Second level analysis was performed using a random effect model. The threshold was set at $p < 0.001$, uncorrected for family wise errors. Activation in areas with five or more activated voxels was taken into account.

MRS: The MR spectra were acquired using PRESS (TE 25 ms, TR 3 s, NSA 128) and water suppression. An internal reference of unsuppressed MRS signal (NSA 8) was obtained using the same preparation. Four single voxels were measured: two VOI in Parietal Normal Appearing White Matter (NAWM) and two VOI in thalamus (TH), the voxels were placed bi-laterally. Quantitative MRI (qMRI) were measured using QRAPMASTER [6] the images were postprocessed using SyMRI Brain Studio (SyMRI, Sweden). Absolute metabolite concentrations were calculated using LCModel (Provencher, Canada) using water scaling, the attenuation of the internal water due to relaxation was calculated from the quantitative T1, T2 and PD images obtained using QRAPMASTER.

Statistics: Pearson correlation coefficients were calculated between the activations in left TH, and the absolute concentrations of tCr, mIns, tCho and tNAA. The correlations were considered to be significant if $p < 0.05$. The differences in concentrations of myo Inositol (mIns), N-acetyl aspartate (NAA) and compounds containing Creatine (tCr), Choline (tCho) between the patient and the control group and the difference between left and right voxels where determined using an two factor ANOVA [7] additive model. Variances with a p value < 5% were considered significant.

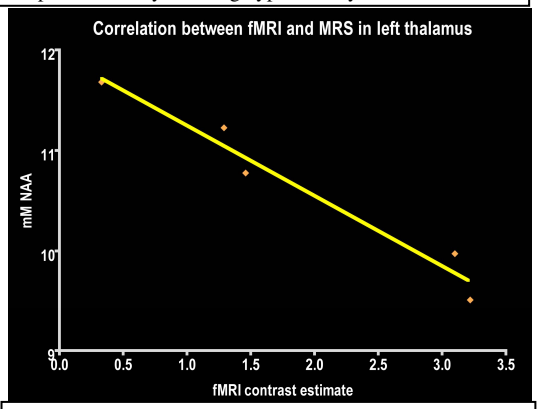

Fig 2. NAA conc V. activation in left thalamus in the patient group. Correlation coefficient r=-0.984

Table 1: Absolute Concentrations Average and (standard error)				
	TH			
	Controls (n=2*5)		Patients(n=2*5)	
tCr	7.25	(0.22)	7.41	(0.30)
tCho	2.37	(0.15)	3.32	(0.10)
mIns	4.90	(0.37)	5.13	(0.61)
NAA	10.48	(0.51)	10.35	(0.38)
	NAWM			
	Controls		Patients	
tCr	5.89	(0.16)	6.19	(0.33)
tCho	2.52	(0.18)	2.46	(0.09)
mIns	4.11	(0.42)	5.46	(0.60)
NAA	10.71	(0.43)	10.11	(0.67)

Results

Correlation: A strong correlation r = -0.984 p = 0.0024 was observed in the patient group between activation during working memory load test in left TH and NAA concentration in left TH, see Fig. 2. In contrast, no significant correlation between activation and concentration of tCr, mIns and tCho was observed.

MRS: One healthy control was excluded due to movement. No significant differences between left and right VOIs were found thus the MRS measurement form left and right VOIs can be seen as two observation of the same tissue. The group mean and standard errors of metabolite concentrations in TH and NAWM are shown in Table 1. No significance difference in metabolite concentrations between patients and control subjects was observed in TH. In NAWM a significant difference in mIns concentration at a significance level of p = 0.02 was found, but non of the concentrations of the other metabolites were significantly different.

Conclusion

The strong correlation between NAA concentration and fMRI activation during the working memory test indicates a damage of the thalamus in the patient group. Increased mIns are a sing of phospholipids break down which can be interpret as membrane damage, analogous with demyelization in MS [8].

References [1] Arnulf I,.et al Brain 2005 128:2763. [2] Landtblom et al, Acta Neurol Scand 2003 108:363. [3] Landtblom et al, Acta Neurol Scand 2002;105:318 [4] Huang et al, Sleep 2005 28:955. [5] Billiard M. et al, Sleep 2005 28:915. [6] Warntjes et al, MRM 2008 60:320.[7] Montgomery, et al, Design and analysis of experiments, Wiley, 2005. [8] Landtblom et al, Acta. Radiol 1996 37:278.