Metabolic changes in the thalamus of Restless Legs Syndrome patients: preliminary ^{1}H-MRS findings.

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Introduction

Restless legs syndrome (RLS) is a common disorder with a prevalence in the general population between 3% and 9%. It is characterised by an irresistible urge to move the legs, associated with unpleasant paraesthesias in the legs and sometimes in the arms (1,2). These sensations occur at rest, in particular in the evening or at night, and are relieved by movement. Many patients also have periodic limb movements in sleep (PLMS) (1,2). The pathophysiology of RLS is poorly understood. Clinical and pharmacological observations point towards a central role for the dopaminergic system and iron metabolism. Recent studies have suggested a potential thalamic involvement in RLS. Functional MRI has demonstrated an activation of the cerebellum, thalamus, red nuclei and brainstem (3). A voxel-based morphometry (VBM) study detected a bilateral gray matter increase in the medial and posterior portion of the thalamus (4). A PET study using [^{11}C]FLB 457 investigated extrastriatal dopaminergic regions, reporting a higher binding potential in RLS patients at the level of the anterior cingulate cortex and of the medial and posterior subregions of the thalamus (5). We evaluated the same thalamic region in RLS patients using H^{1}-MRS.

Methods

We recruited ten patients with a diagnosis of RLS (age 47±7 years, mean±SD) following the diagnostic criteria of the International Restless Legs Syndrome Study Group (IRLSSG) (2), and nine age-matched healthy volunteers (46±12). The severity of RLS was assessed using the revised IRLSSG rating scale (6). Single voxel ^{1}H-MRS spectra were acquired using the PRESS sequence. A spectrum at short echo-time (TE = 35ms; TR = 4 s; number of acquisitions = 128) was acquired in the medio-posterior region of the thalamus (Figure 1-A).

N-acetyl-aspartate (NAA), creatine (Cr), choline-containing compounds (Cho) and myo-inositol (mI) resonances were analysed using LCModel method (7). The metabolite ratios relative to Cr were calculated. Moreover absolute concentrations were estimated by LCModel for all metabolites using the resonance area of the unsuppressed water signal as reference (7).

Statistical analyses were performed using nonparametric tests with SPSS 12.0 for Windows, assuming a significant *P*-value <0.05. The Mann-Whitney U test was used to evaluate differences between the two groups. For correlations we used the Spearman rank test.

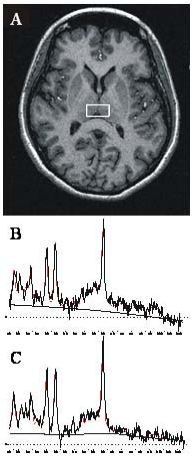

Fig. 1. (A) thalamic VOI. Spectra from (B) a RLS patient and (C) from an healthy subject.

Patient	NAA/ Cr	Cho/ Cr	mI/ Cr	[NAA] (mM)	[Cr] (mM)	[Cho] (mM)	[mI] (mM)
1	0.96	0.29	0.61	6.95	7.28	2.12	4.40
2	1.24	0.25	0.62	8.26	6.67	1.69	4.09
3	1.13	0.27	0.69	6.03	5.34	1.44	3.67
4	1.21	0.27	0.79	7.99	6.60	1.80	5.18
5	1.39	0.26	0.89	8.37	6.03	1.55	5.32
6	1.15	0.27	0.79	8.07	7.07	1.88	5.59
7	0.99	0.28	0.77	7.32	7.37	2.04	5.61
8	1.14	0.31	0.76	8.75	5.67	1.96	4.84
9	1.23	0.31	0.91	5.68	4.63	1.44	4.20
10	1.55	0.35	0.86	6.61	5.80	1.77	4.39
Mean ± SD	1.20 ± 0.17	0.29 ± 0.03	0.77 ± 0.10	7.40 ± 1.05	6.25 ± 0.90	1.77 ± 0.24	4.73± 0.68
Controls (n=9)	1.38 ± 0.12	0.31 ± 0.04	0.81 ± 0.15	9.05 ± 1.25	6.65± 1.16	2.01 ± 0.21	5.16± 0.31
P value	0.01	NS	NS	0.008	NS	NS	NS

Table. Thalamic metabolite ratios and concentrations (mM) in RLS patients and in healthy controls.
NAA = N-acetyl-aspartate, Cr = creatine, Cho = choline, mI = myoinositol, NS = not significant.

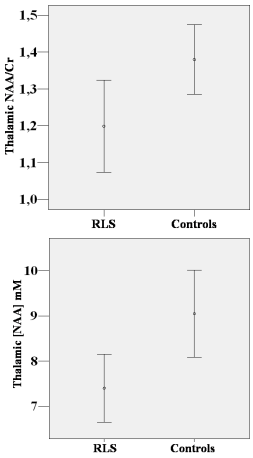

Fig. 2. Mean NAA/Cr ratio (upper) and mean NAA concentration (lower) in RLS patients and healthy volunteers. Error bars indicate standard deviation.

Results

Mean values and standard deviations of age at onset, disease duration and IRLSSG score in RLS patients were 33±11 years, 13±11 years and 24±2 respectively. Six patients never took therapy and four patients were free from dopaminergic drugs from at least 3 weeks before scan. The NAA/Cr ratios and the absolute concentrations of NAA were significantly lower in the thalamus of RLS patients compared with the healthy controls (figure 1-B/C, figure 2 and table). We did not detect statistical differences in the other ratios and metabolite concentrations. The reduction in NAA/Cr and in the absolute NAA concentrations in the thalamus of the patients did not correlate with the clinical variables considered (age at onset, disease duration, revised IRLSSG rating scale for symptoms severity).

Discussion

Using ^{1}H-MRS we detected metabolic changes in the medio-posterior region of the thalamus. In the same localization a previous VBM study detected a bilateral gray matter increase, interpretated as a primary neuronal change, or a consequence of chronic increase in afferent input. A PET study with the high-affinity D2-receptors radioligands [^{11}C]FLB 457 reported a higher thalamic binding potential in RLS patients, at the level of the medial and posterior portions (5). Our preliminary ^{1}H-MRS data confirm a thalamic involvement in RLS patients where the reduction in NAA content, in general observed not only in pathological processes where neuronal loss occurs but also in the presence of neuronal dysfunction, likely reflects neuronal functional changes.

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