Cerebellar involvement in Essential Tremor with and without resting tremor: a Diffusion Tensor Imaging study

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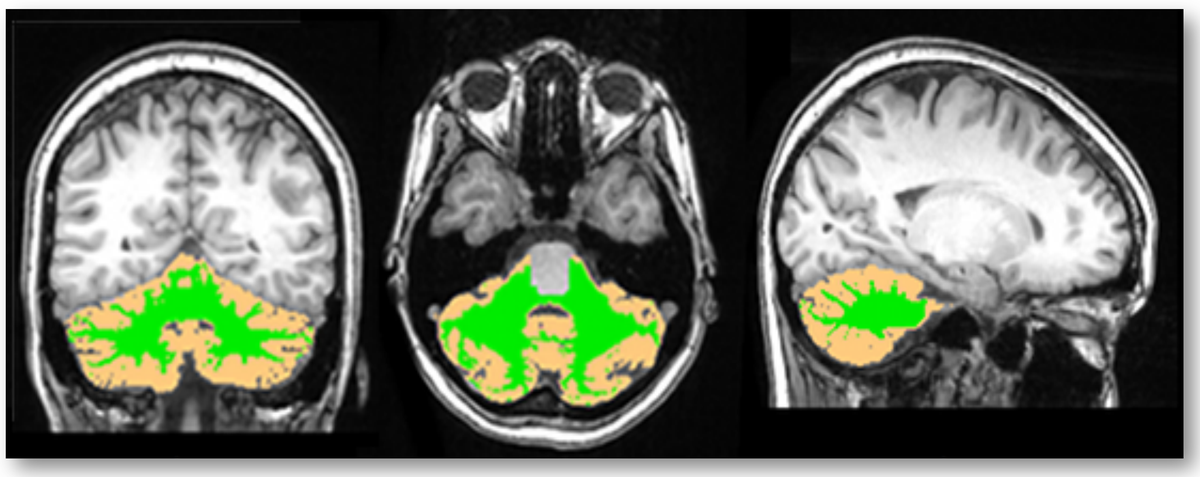
OBJECTIVE: Essential Tremor with rest tremor (rET) is a debated and poorly understood clinical phenotype. The prominent theory proposed to explain the pathophysiology of classical ET is that neurodegeneration of the cerebellum represents a fundamental mechanism of this disorder, but it is not known if cerebellar changes also occurs in patients with rET.
The aim of our study was to evaluate cerebellar microstructure in patients with rET, in comparison to ET patients without resting tremor and healthy controls by MR Diffusion Tensor Imaging (DTI).

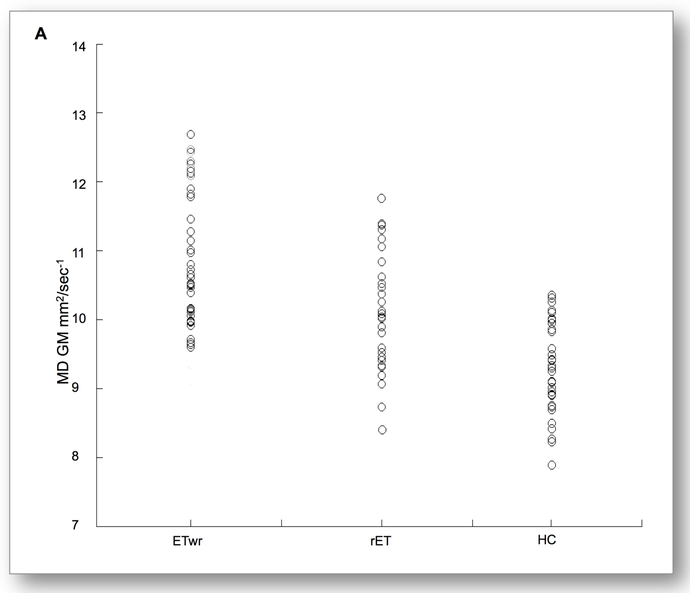
MATERIALS AND METHODS: We studied 67 patients with ET and 39 age-matched healthy controls (HC). An accurate evaluation of clinical characteristics of tremor was performed in all patients and ET subjects were divided in ET with- (rET) and without rest tremor (ET) (rET:29 and ET:38). The severity of tremor was assessed according to Fahn-Tremor-Rating-Scale (Fahn-TRS). All participants underwent the same 3T-MRI protocol, including DTI. FSL was used to perform image post-processing and cerebellar segmentation. For each subject, fractional anisotropy (FA) and mean diffusivity (MD) values were extracted from the cerebellum in white and grey matter (WM, GM).

RESULTS: Age and sex distribution were not different between different groups. The mean score of Fahn-TRS was significantly higher in rET (15.50±4.04) than in ET (9.46±5.6) (p=0.010).
MD was significantly higher in the cerebellar GM of ET patients (10.39 ±0.87) in comparison with HC (9.90±0.71) (p=0.0027). Interestingly, MD was significantly different in the GM of cerebellum when ET without resting tremor (10.48±0.77) were compared with HC (p=0.0017), whereas a trend toward significance were found between rET (10.29±0.99) and HC (p=0.067). No differences among groups were found in MD of cerebellar WM and in FA values neither in the WM nor in the GM.

CHARACTERISTIC	ET total group (n= 67)	ET without rest tremor (ETwr n= 38)	ET with rest tremor (rET n= 29)	HC (n= 39)	p-Value
Age (mean ± SD)	65.64 ± 10.48	66.65 ± 9.38	64.3 ± 11.8	64.56 ± 9.4	0.635†
Men n. (%)	38 (56.7)	22 (57.8)	16 (55.1)	21 (53.8)	0.964‡
Age at onset (mean ± SD)	54.88 ± 15.32	55.42 ± 12.76	54.17 ± 14.38	_	0.221°
Duration of disease (mean ± SD)	11.09 ± 10.32	11.23 ± 10.80	10.88 ± 9.80	_	0.309°
Familial history n.(%)	21 (36.2)	16 (35.5)	(38.4)	_	0.888‡
Fhan-Tolosa part A (mean ± SD)	11.4 ± 4.72	9.46 ± 5.6	15.50 ± 4.04	_	0.015*
TOTAL CEREBELLUM GM					
MD (x 10^{-4} mm^2/s^{-1})	10.39 ± 0.87	10.46 ± 0.77	10.29 ± 0.98	9.90 ± 0.71	0.025#
FA	0.226 ± 0.02	0.224 ± 0.01	0.229 ± 0.01	0.229 ± 0.02	0.277
TOTAL CEREBELLUM WM					
MD (x 10^{-4} mm^2/s^{-1})	8.10 ± 0.84	7.90 ± 0.49	8.31 ± 0.90	7.93 ± 0.50	0.642
FA	0.382 ± 0.03	0.387 ± 0.02	0.374 ± 0.04	0.392 ± 0.02	0.314
RIGTH HEMISPHERE GM					
MD (x 10^{-4} mm^2/s^{-1})	10.38 ± 0.90	10.44 ± 0.82	10.31 ± 0.98	9.78 ± 0.69	0.020*
FA	0.227 ± 0.01	0.226 ± 0.01	0.230 ± 0.01	0.228 ± 0.01	0.317
RIGTH HEMISPHERE WM					
MD (x $10^{-3}$$mm^2/s^{-1}$)	8.21 ± 0.85	7.84 ± 0.42	8.20 ± 0.78	7.82 ± 0.50	0.642
FA	0.385 ± 0.04	0.386 ± 0.03	0.369 ± 0.04	0.388 ± 0.02	0.314
LEFT HEMISPHERE GM					
MD (x 10^{-4} mm^2/s)	10.39 ± 0.82	10.45 ± 0.75	10.29 ± 0.82	9.89 ± 0.65	0.022†
FA	0.228 ± 0.02	0.224 ± 0.01	0.228 ± 0.01	0.227 ± 0.02	0.317
LEFTHEMISPHERE WM					
MD (x 10^{-4} mm^2/s^{-1})	8.12 ± 8.4	7.93 ± 3.9	8.30 ± 1.19	7.88 ± 0.50	0.642
FA	0.383 ± 0.02	0.378 ± 0.01	0.377 ± 0.02	0.387 ± 0.01	0.314

MD: mean diffusivity; FA: fractional anisotropy; GM: grey matter; WM: white matter.
§ Comparison among ETwr, rET and HC (Kruskal-Wallis test)
#ETwr vs HC p= 0.0017, rET vs HC p= 0.067; ETwr vs rET p=0.468, Mann-Whitney U test with Bonferroni correction.
*ETwr vs HC p= 0.0014, rET vs HC p= 0.069; ETwr vs rET p=0.389, Mann-Whitney U test with Bonferroni correction.
†ETwr vs HC p= 0.0016, rET vs HC p= 0.060; ETwr vs rET p=0.346, Mann-Whitney U test with Bonferroni correction





CONCLUSIONS: Our results demonstrate the presence of microstructural changes in the cerebellum of patients with ET. It is noteworthy that rET showed intermediate values to that of HC and ET without resting tremor, revealing the presence of microstructural cerebellar involvement, but less prominent than ET. This is an interesting finding in the debate on the underlying basis for rest tremor in ET and the correct nosologic classification of this disorder. Our results suggest that rET shares part of the pathophysiological mechanisms of ET, but cerebellar involvement seems do not fully account for rET, leading to hypothesize that in addition to the cerebellar loops, other networks may play a role in rET pathophysiology.

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