PEAK WIDTH OF SKELETONIZED MEAN DIFFUSIVITY (PSMD), A NOVEL IMAGING MARKER FOR CEREBRAL SMALL VESSEL DISEASE: PRELIMINARY RESULTS IN A CADASIL POPULATION

C. Vinciguerra, A. Giorgio, J. Zhang, I. Di Donato, M.L. Stromillo, M.T. Dotti, A. Federico, N. De Stefano

Department of Medicine, Surgery and Neuroscience, University of Siena, Siena

OBJECTIVE

To apply in a population of patients with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencepahalopathy (CADASIL) a new, fully automated and robust imaging marker named as peak width of skeletonized mean diffusivity **(**PSMD). A recent study described that increases in PSMD were linked to vascular but not to neurodegenerative disease. In longitudinal analysis, PSMD captured cerebral small vessel disease (CSVD) progression better than the other imaging markers [1].

MATERIALS AND METHODS

We included thus far in the study 63 subjects, of whom 24 CADASIL (20 patients and 4 asymptomatic subjects, age: 48±10 years, 37.5% female) and 39 normal controls (NC, age: 51.3±14.43 years, 46.2% female) (Table). Diagnosis of CADASIL was based on clinical, genetic, neuropathological and MRI data [2]. Clinical and neuropsychological assessment in CADASIL was performed with Rankin scale (0.29±0.75) and Mini-Mental State Examination (MMSE: 28.5±4.8).

MRI data (conventional MRI and diffusion tensor imaging [DTI]) were acquired on a 1.5 T clinical scanner. All the subsequent analysis of MRI data was mostly performed with tools of the FMRIB Software Library (FSL, www.fmrib.ox.ac.uk/fsl/, Oxford, UK). A sagittal survery image was used to identify the anterior and posterior commissures. Sequences were acquired in the axial plane parallel to the commissural line. A dual-echo, turbo spin-echo sequence (repetition time [TR]/echo time [TE]1/TE2 = 2,075/30/90 ms, voxel size= 1x1x 3 mm) yielded proton density and T2-W images. DTI data consisted of echo-planar imaging (EPI) (TR=8,500 ms;TE= 100 ms; voxel size =2.5 mm^3), with diffusion weighting distributed in 32 directions and b-value =1,000 sec/mm^2). Lesion volume (LV) was computed by a single observer using a semiautomated segmentation technique based on local thresholding (Jim 6.0, Xinapse System, Leicester, UK). DTI data were corrected for MRI eddy currents and head motion, then images were brain-extracted using Brain Extraction Tool (BET) and entered into the program DTIFIT which fits a diffusion tensor model at each voxel and creates DTI images, including mean diffusivity (MD) and fractional anisotropy (FA). DTI processing was performed using tract-based spatial statistics (TBSS). We computed PSMD from DTI data through “skeletonization” of white matter (WM) tracts and histogram analysis (Fig 1 and 2), as previously described [1]. Data were compared with those obtained from the DTI of NC with Mann-Whitney test. PSMD data of CADASIL patients were correlated with clinical measures and LV using Spearman correlation. The level of statistical significance for all analyses was set at $p<0.05$.

RESULTS

Age and sex were similar in both groups (p=0.28 and p=0.60). In CADASIL, LV was 33±32 cm^3. CADASIL subjects showed higher (p<0.001) PSMD values (4.76±1.4 x 10^{-4} mm^2/sec in the whole population, 4.81±1.41 x 10^{-4} mm^2/sec in patients and 4.48±1.4 x 10^{-4} mm^2/sec in asymptomatic subjects) than NC (2.9±0.4 x 10^{-4} mm^2/sec). Moreover, PSMD values of CADASIL subjects correlated with LV (r=0.80, p<0.001), MMSE (r=-0.57, p=0.003) and Rankin scale (r=0.48, p=0.016).

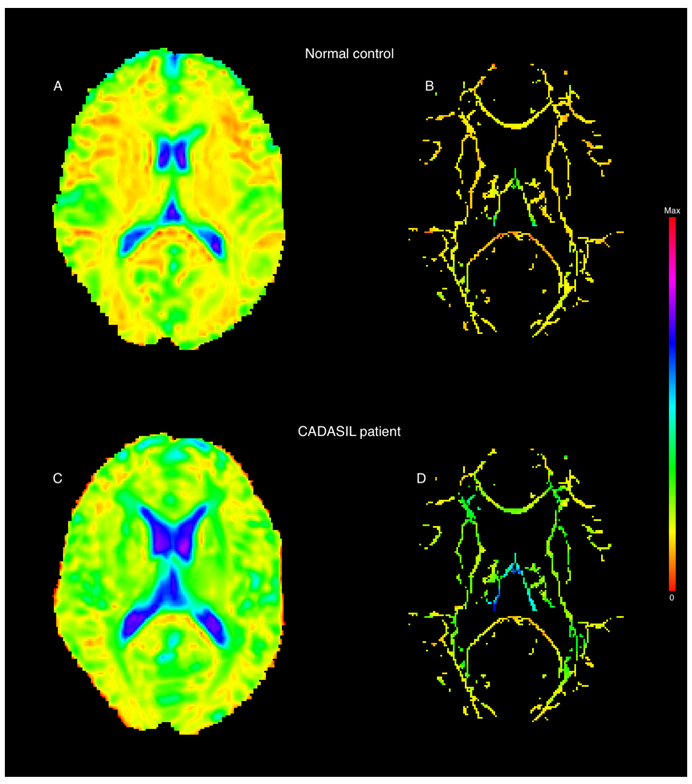

Figure 1
Illustrative examples of MD maps projected onto the standard WM skeleton from a normal control (A-B) and a CADASIL subject (C-D)

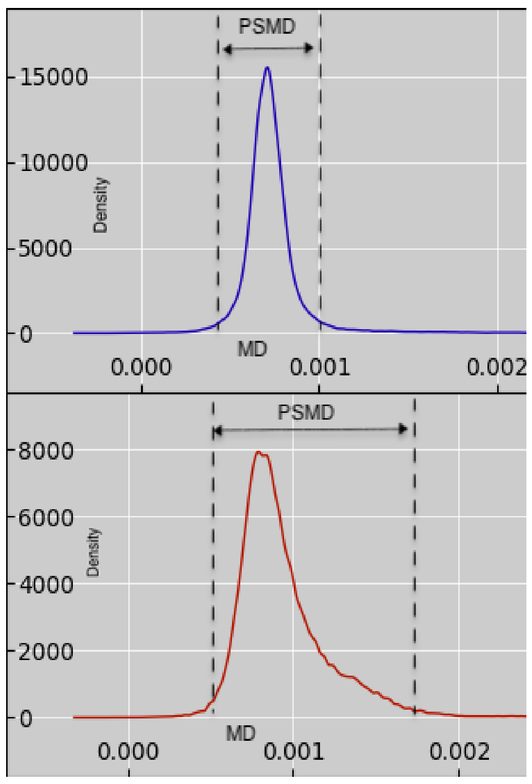

Figure 2. Histogram analysis of the same MD data as in Figure 1. Peak width of skeletonized MD (PSMD) is calculated as the difference between the 95th and 5th percentiles

GROUP	VARIABLES	
CADASIL	AGE (years)	47.9910 ± 10.0328
	MALE (number, [percent])	15 (62.50%)
	LV (cm^3)	32.9795 ± 32.1516
	PSMD (x 10^{-4} mm^2 /sec)	4.7561 ± 1.3886
	MMSE	28.5 ± 4.8544
	RANKIN SCALE	0.2917 ± 0.7506
NORMAL CONTROLS	AGE (years)	51.3337 ± 14.4383
	MALE (number, [percent])	21 (53.85%)
	PSMD (x 10^{-4} mm^2 /sec)	2.9 ± 0.3911

Table. Clinical-demographic variables and PSMD values of CADASIL subjects and normal controls

CONCLUSIONS

CSVD is an important cause of clinical disability and cognitive impairment. The understanding and management of CSVD has been hampered, at least partially, by the lack of a good disease marker. In this scenario, PSMD can represent a robust imaging marker for quantitatively assessing microstructural tissue damage in these patients. Our on-going study provides further evidence that PSMD can be a marker of great utility for both research studies and clinical use in CSVD, including CADASIL.

References
[1] Baykara E, Gesierich B, Adam R, Tuladhar AM, Biesbroek JM, Koek HL, Ropele S, Jouvent E; Alzheimer's Disease Neuroimaging Initiative, Chabriat H, Ertl-Wagner B, Ewers M, Schmidt R, de Leeuw FE, Biessels GJ, Dichgans M, Duering M. ”A Novel Imaging Marker for Small Vessel Disease Based on Skeletonization of White Matter Tracts and Diffuse Histograms. Ann Neurol 2016. 80:581-592..
[2] Di Donato I, Bianchi S, De Stefano N, Dichgans M, Dotti MT, Duering M, Jouvent E, Korczyn AD, Lesnik-Oberstein SA, Malandrini A, Markus HS, Pantoni L, Penco S, Rufa A, Sinanović O, Stojanov D, Federico A. “Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL) as a model of small vessel disease: update on clinical, diagnostic, and management aspects”. BMC Medicine 2017 15:41.