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White Matter Hyperintensities progression over 2 years in CADASIL is associated with age, sex, migraine status, initial hyperintensities volume and diastolic blood pressure: a longitudinal study in 214 patients

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CONTEXT & AIM OF THIS STUDY

White matter hyperintensities (WMH) represent a key imaging marker of cerebral Small Vessel Diseases (cSVD) [1]. In **CADASIL**, a severe and archetypal genetic form of ischemic cSVD, the variability of WMH load, shape, location or intensity is wide. Thus, their exact clinical consequences are still poorly understood [2,3]. Nevertheless, these lesions correspond to the **earliest manifestation of the disease** and could develop long before the occurrence of clinical symptoms. Longitudinal studies are then crucial to better characterize the exact progression of WMH, to assess their variability and, if any, their potential predictors. Herein, we aimed to **assess the progression of WMH over 2 years in a large sample of CADASIL patients and identify the main predictors of this progression and potential clinical correlates** [4,5].

MATERIAL & METHODS

Acquisitions

Sagittal T1w-MRI and FLAIR were acquired on a 3T SIEMENS scanner (Table1), on CADASIL patients followed every 2 years (<https://www.cervco.fr>)

Image processing

- All MRIs were bias corrected [6] and normalized for intensity range.
- Intra-cranial cavity volume (ICC) and Brain Parenchymal Fraction (BPF) were measured from T1-w MRI [7].
- WMH were segmented with **BIANCA** [8] using 20 3DFLAIR-based reference masks including various load of WMH for the baseline visit, and subject-specified training set including the baseline dataset and follow-up dataset with baseline WMH mask registered to the follow-up data for the follow-up [9]. All probability maps were thresholded using a value automatically fixed from a clustering process and masks were manually corrected by a trained scientist (MS).

Analysis

- Potential predictors of annualized WMH changes** normalized by the ICC over 2 years (data collected at baseline): BPF, volume of WMH normalized by the ICC, systolic and diastolic blood pressure, sex, mutation location in EGF_r domains, history of hypertension, diabetes, hypercholesterolemia and migraine with aura. Continuous predictors were scaled between 0 and 1.
- The best model was based on a stepwise procedure removing the non significant predictors and selecting the minimal AIC.

Table1

FLAIR	TR/TE/TI(ms)	6000/387/2200	5000/393/1600	5000/378/1650
	resolution(mm ³)	0.5x0.5x0.9	1.0x1.0x1.0	0.5x0.5x1.0
T1	TR/TE/TI(ms)	2000/3.2/900	1800/2.4/907	2200/2.4/900
	resolution(mm ³)	0.4x0.4x0.4	0.4x0.4x0.9	1.0x1.0x1.0

RESULTS

- The study was conducted on 214 patients who had their 2 first visits over 2 years (mean age at baseline visit 54.2 ± 11.9 years)
- Normalized WMH volumes at baseline and follow-up visits were labeled according to baseline measures on Fig1.
- 3 main baseline predictors were significantly associated with WMH increase: age, male sex, and lack of migraine with aura. The increase of WMH with age was reduced in presence of larger WMH load and higher diastolic blood pressure measured at baseline. The increase of WMH according to the baseline WMH load became significant with increasing diastolic blood pressure (Fig2).



Fig1

OLS Regression Results					
Dep. Variable:	WMH variations norm ICC	R-squared:	0.102		
Model:		OLS Adj. R-squared:	0.076		
Method:		Least Squares F-statistic:	3.936		
No. Observations:	214	Prob (F-statistic):	0.000951		
Df Residuals:	207	Log-Likelihood:	-146.65		
Df Model:	6	AIC:	307.3		
Covariance Type:	nonrobust	BIC:	330.9		
	coef	std err	t	P> t	[0.025 0.975]
Intercept	-0.0294	0.119	-0.246	0.806	-0.264 0.206
Sex[T.m]	0.1890	0.070	2.710	0.007	0.052 0.327
Migraine with aura at baseline[T.yes]	-0.1501	0.073	-2.065	0.040	-0.293 -0.007
Age at baseline	1.1459	0.382	3.002	0.003	0.393 1.899
Age at baseline : WMH norm ICC at baseline	-1.5195	0.556	-2.733	0.007	-2.616 -0.423
Age at baseline : Diastolic pressure at baseline	-1.2806	0.512	-2.502	0.013	-2.290 -0.272
WMH norm ICC at baseline : Diastolic pressure at baseline	1.9947	0.705	2.831	0.005	0.606 3.384
Omnibus:	30.741	Durbin-Watson:	1.934		
Prob(Omnibus):	0.000	Jarque-Bera (JB):	104.706		
Skew:	0.508	Prob(JB):	1.83e-23		
Kurtosis:	6.273	Cond. No.	39.1		

Notes:
[1] Standard Errors assume that the covariance matrix of the errors is correctly specified.

Fig2

DISCUSSION & CONCLUSION

This study showed that in CADASIL, **WMH changes measured over 2 years widely vary across patients**. This variation was found **independently related to age, sex and to migraine with aura**. The effect of age on these changes varied with the normalized WMH volume and diastolic pressure, and that of normalized WMH volume became significant when the diastolic pressure increased. Vascular risk factors were not found involved. These results must be interpreted with caution. The factors associated with WMH changes could differ over a much longer observation period. Lesions progression could also differ according to the location of WMH in the brain tissue as they might be related to different underlying mechanisms [3]. Additional investigations are obviously needed to better understand how the predictors and their interactions could influence the progression of WMH during the course of this condition. The low R² value of our multivariate model rather suggests that other unknown predictors might have significant effects on WMH changes.

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[7] Avants, Neuroinformatics 2011 [8] Griffanti, NeuroImage 2016 [9] Leberberg, ISMRM 2024

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