The CADASIL Scale: an update of the experience in the Florence VAS-COG clinic

Rinnoci V[1], Pescini F[2], Salvadori E[1], Nannucci S[1], Donnini I[1], Valenti R[1], Fierini F[1], Pasi M[1], Chiti G[1], Bianchi S[3], Federico A[3], Dotti MT[3], Pantoni L[1]

[1] *Department of NEUROFARBA, University of Florence, Italy*
[2] *Stroke Unit, Emergency Department, Azienda Ospedaliero Universitaria Careggi, Florence, Italy*
[3] *Department of Neurological and Behavioural Sciences, University of Siena, Italy*

Background

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is the most common cause of genetic small vessel disease (SVD). Specific clinical and neuroimaging features are considered typical but not pathognomonic of the disease. The genetic test remains the diagnostic gold standard, but it is costly and time-consuming. Consequently, a screening tool to select patients for *NOTCH3* gene analysis, the CADASIL scale (range 0-25, cut-off ≥15), was proposed in 2012 [1].

Clinical Features

Neuroimaging Features

Family History

Table 4. CADASIL Scale

Migraine	1
Migraine with aura	3
TIA or stroke	1
TIA/stroke onset ≤50 y	2
Psychiatric disturbances	1
Cognitive decline/dementia	3
Leukoencephalopathy	3
Leukoencephalopathy extended to temporal pole	1
Leukoencephalopathy extended to external capsule	5
Subcortical infarcts	2
Family history* in at least 1 generation	1
Family history* in at least 2 generations	2

The total score (ranging from 0 to 25) is obtained by the sum of the score attributed to each variable. A total score ≥15 is predictive of CADASIL diagnosis.

CADASIL indicates cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy.

*For at least 1 of the typical disturbances (headache, transient ischemic attack/stroke, cognitive decline, psychiatric disturbances).

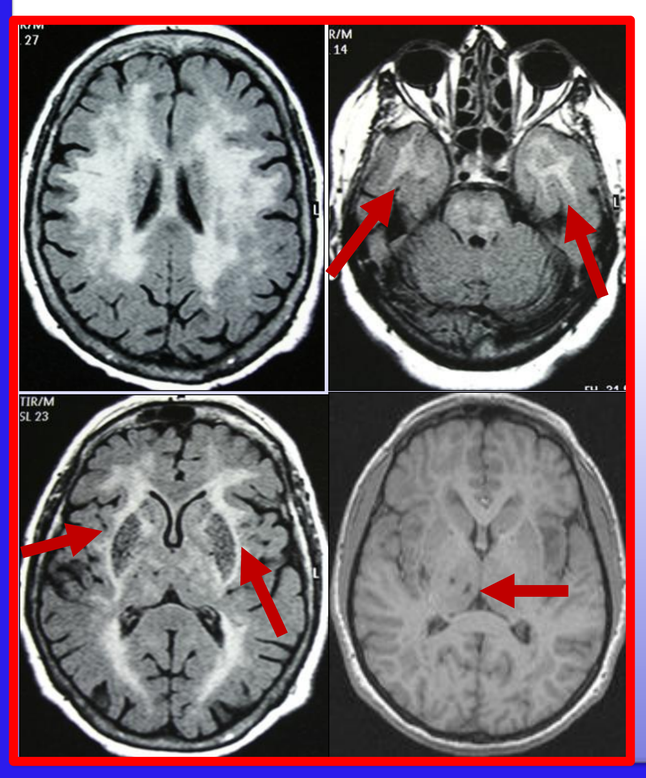

Figure 1: Typical neuroimaging features of CADASIL patients

Materials and Methods

After its publication, the use of the CADASIL scale was implemented in our center routine work-up of patients with suspected forms of genetic SVD and we selected patients for *NOTCH3* gene analysis after its systematic compilation. From 2012 to 2016, we performed genetic testing in 33 probands.

[1] Pescini F *et al. Stroke* 2012; 43(11):2871-6.
[2] Nannucci S *et al*. *Acta Neurol Scand* 2015; 131(1):30-6.

Results

Ten patients had a CADASIL score <15 but genetic testing was nonetheless performed because this was considered appropriate by the clinician. The total CADASIL score ranged from 9 to 22. Out of the 33 probands, 4 were diagnosed with CADASIL while 29 were *NOTCH3*-negative patients. Among the latter, 20 patients had a CADASIL score ≥15 and were defined as CADASIL-like [2]. Comparing CADASIL and both *NOTCH3*-negative and CADASIL-like patients, we did not find any significant difference in the mean CADASIL score. One CADASIL patient had a CADASIL score of 14. In this series, the CADASIL scale (cut-off: 15) predicted the diagnosis with 75% sensitivity, 31% specificity, 13% positive predictive value and 90% negative predictive value.

Table 1: Differences between CADASIL, *NOTCH3* negative and CADASIL-like patients

	CADASIL (n=4)	*NOTCH3* neg (n=29)		CADASIL vs *NOTCH3* neg (P)	CADASIL vs CADASIL-like** (P)
			CADASIL-like** (n=20)		
Male sex, %	50	38	40	NS	NS
Age, mean ± SD	64±6	69±11	70±10	NS*	NS*
Age at first stroke/TIA, mean ± SD	(n=3) 56±15	(n=13) 64±12	(n=8) 65±13	NS*	NS*
Migraine, %	50	48	55	NS	NS
Migraine with aura, %	25	14	20	NS	NS
TIA or stroke, %	75	48	45	NS	NS
TIA/stroke onset < 50 yrs, %	25	3	5	NS	NS
Psychiatric disturbances, %	0	70	65	<0.05	<0.05
Cognitive decline/dementia, %	75	52	60	NS	NS
Leukoencephalopathy, %	100	100	100	n.a.	n.a.
L. extended to temporal pole, %	75	55	40	NS	NS
L. extended to external capsule, %	100	80	95	NS	NS
Subcortical infarcts, %	75	83	95	NS	NS
Family history (one generation), %	100	100	100	n.a.	n.a.
Family history (two generations), %	50	83	90	NS	NS
CADASIL Score, mean ± SD	17±2.4	15±3.0	17±2.0	NS*	NS*
CADASIL Score ≥15, %	75	69	100	--	--

* Mann-Whitney
** CADASIL-like: *NOTCH3* negative patients with a CADASIL score ≥15

Conclusions

This study confirms that patients with a CADASIL score≥15 present a high suspicion of CADASIL. However, in this series, the CADASIL scale (at the set cut-off) presented lower values of sensitivity and specificity compared to the original paper [1], and this could be partially explained by the small sample size. It should be noted that if we would have restricted the genetic testing only to probands with a CADASIL score ≥15 we would have missed one CADASIL diagnosis. The application of the CADASIL scale on other and larger series is needed not only to verify its accuracy but also to apply possible constructive changes.