Jugular venous reflux and brain lesion volume in CADASIL: a pilot study

Diogo Melo Maleita[1] and Gustavo C Santo[2], MD; João Sargento-Freitas[2], MD; Miguel Pereira[2], MD; Ricardo Varela[2], MD; José Coelho[2], MD; Carlos Ferreira[3]; Otília Almeida[3]; César Nunes[4], MD; Miguel Castelo-Branco[1,3],MD, PhD; Luís Cunha[1,2], MD, PhD; António Freire Gonçalves[1,2], MD, PhD

1. Faculdade de Medicina da Universidade de Coimbra, Coimbra, Portugal

2. Serviço de Neurologia do Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal

3. Instituto de Ciências Nucleares Aplicadas à Saúde, Coimbra, Portugal

4. Serviço de Neurorradiologia do Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal

Table of contents

Abbreviations

CADASIL: Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leucoencephalopathy

JVR: Jugular venous reflux

CHUC: Centro Hospitalar e Universitário de Coimbra

D-US: Doppler-ultrasonography

CBF: Cerebral blood flow

VBF: Venous blood flow

IJV: Internal jugular vein

VM: Valsalva manoeuvres

MRI: Magnetic Resonance Imaging

SVD: Small vessel disease

GOM: Granular osmiophilic material

WMH: White matter hyperintensities

FLAIR: Fluid-attenuated inversion recovery

CNS: Central nervous system

ARWMC: Age-related white matter changes

BMI: Body mass index

HT: Arterial hypertension

DM: Diabetes mellitus

CAD: Coronary artery disease

PAD: Peripheral artery disease

AF: Atrial fibrillation

HF: Heart failure

TIA: Transient ischemic attack

ICNAS: Instituto de Ciências Nucleares Aplicadas à Saúde, Coimbra, Portugal

w/: with

IJVV: Internal jugular vein valve

CVP: Central venous pressure

Abstract

Background and Purpose: CADASIL (Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leucoencephalopathy) is currently the most common hereditary cause of stroke and vascular dementia in adults. This study aims to compare the clinical, cerebral hemodynamic and imagiologic characteristics of CADASIL patients with healthy volunteers and to investigate, in those with the disease, if there is an association between the presence of jugular venous reflux (JVR) and brain lesion´s volume.

Methods: We included willing patients with CADASIL followed in the outpatient clinic at the Neurology Department of Centro Hospitalar e Universitário de Coimbra (CHUC). The control population was composed by healthy volunteers. We collected data on vascular risk factors. Patients and controls underwent extra- and transcranial Doppler-ultrasonography (D-US) study, including analysis of cerebral blood flow (CBF), venous blood flow (VBF) and internal jugular vein (IJV) flow during Valsalva manoeuvres (VM). Magnetic Resonance Imaging (MRI) (3-Tesla) was also applied and a lesion growth algorithm calculation was used to determine brain lesion volume. $\chi 2$ test was used for nominal variables (or Fisher's exact test when appropriate) and t-test for continuous variables. When adjustment for confounding variables was needed, binary logistic regression (nominal variables) and linear regression (continuous variables) were used. Statistical significance was set at two-sided p values <0.05.

Results: A total of 55 subjects (28 CADASIL patients and 27 controls) were enrolled. In this study, 30.9% had JVR (all detected during VM). CADASIL was not associated with a higher prevalence of JVR compared with the control group (OR 1.04; CI 95%: 0.22 – 5.00; p=0.958) nor there was a statistically difference in CBF or VBF between this two groups. In patients,

the presence of JVR appeared to be associated with higher lesion volume (β 11.86; CI 95%: -6.74 – 30.46; p=0.201) and a lower number of lesions (β -4.22; CI 95%: -13.36 – 4.92; p=0.350), although not statistically significant. This association was significantly increased in the subpopulation of patients aged 40 years or older (β 22.14; CI 95%: 6.47 – 37.82; p=0.008).

Conclusion: Our population of Portuguese CADASIL patients had the same typical clinical characteristics of others described before. The prevalence of JVR seems to be identical in CADASIL patients compared to healthy controls. However, it appears to be a trend for higher lesion volume in CADASIL patients with JVR, particularly in those aged 40 or more. JVR might be a non-documented risk factor for disease progression.

Key-Words: CADASIL; JUGULAR VENOUS REFLUX; BRAIN LESION VOLUME.

Resumo

Introdução: CADASIL (Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leucoencephalopathy) é atualmente a causa hereditária mais comum de acidente vascular cerebral (AVC) e demência vascular nos adultos. Este estudo tem como objetivo comparar as características clínicas, hemodinâmicas e imagiológicas dos doentes com CADASIL com voluntários saudáveis e investigar, naqueles com a doença, se há associação entre a presença de refluxo jugular venoso (RJV) e o volume lesional cerebral.

Métodos: Foram incluídos doentes com CADASIL acompanhados na consulta de Risco Vascular do Serviço de Neurologia do Centro Hospitalar e Universitário de Coimbra (CHUC). A população controlo foi composta por voluntários saudáveis. Foram recolhidos dados sobre os fatores de risco vascular. Os doentes e os controlos foram submetidos ao estudo vascular extra e intracraniano recorrendo a ultrassonografia-Doppler, que incluiu análise do fluxo sanguíneo cerebral (CBF), fluxo sanguíneo venoso (VBF) e fluxo da veia jugular interna (IJV) durante as manobras de Valsalva. Os participantes também foram submetidos a estudo de imagem cerebral, com recurso a ressonância magnética (3-Tesla) tendo sido utilizado um algoritmo de cálculo de crescimento de lesão para determinar o volume lesional cerebral. O teste $\chi 2$ foi usado para variáveis nominais (ou o teste exato de Fisher, quando apropriado) e o t-test para variáveis contínuas. Quando o ajuste para variáveis confundentes foi necessário, a regressão logística binária (variáveis nominais) e a regressão linear (variáveis contínuas) foram utilizadas. Significância estatística foi considerada em todos os resultados com um $p<0.05$.

Resultados: Foram incluídos 55 participantes (28 doentes com CADASIL e 27 controlos). Neste estudo, 30.9% apresentaram RJV (todos detetados durante manobras de Valsalva). A presença de RJV foi semelhante nos doentes com CADASIL quando comparados com o grupo controlo (OR 1.04; CI 95%: 0.22 – 5.00; p=0.958). Também não foi observada uma diferença estatisticamente significativa no fluxo sanguíneo cerebral ou fluxo sanguíneo venoso entre os dois grupos. Na população doente, a presença de RJV pareceu estar associada a maior volume lesional (β 11.86; CI 95%: -6.74 – 30.46; p=0.201) e menor número de lesões (β -4.22; CI 95%: -13.36 – 4.92; p=0.350), embora não estatisticamente significativo. No subgrupo com idade igual ou superior a 40 anos a associação foi estatisticamente significativa (β 22.14; CI 95%: 6.47 – 37.82; p=0.008).

Conclusões: A nossa população de doentes com CADASIL apresentou as mesmas características clínicas típicas anteriormente descritas. A prevalência de RJV parece ser idêntica em doentes com CADASIL em comparação com controlos saudáveis. No entanto, parece existir uma tendência para o aumento de volume lesional em doentes com CADASIL e com RJV, particularmente naqueles com 40 anos ou mais. RJV pode ser um fator de risco não documentado para a progressão da doença.

Palavras-chave: CADASIL; REFLUXO JUGULAR VENOSO; VOLUME LESIONAL CEREBRAL

Introduction

CADASIL (*Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leucoencephalopathy),* acronym coined in 1993, is a small vessel disease (SVD) with an autosomal dominant inheritance pattern(1–5). It is caused by mutations in NOTCH3 gene and is currently the most common hereditary cause of stroke and vascular dementia in adults(1,2,5–7). Its prevalence is low but it is probably underestimated in several countries as there is a high variability between them (around 1.5-5.0 per 100,000 adults in Western Europe)(5,8–10). CADASIL is the prototype of SVD and its study is considered essential for the understanding of this group of disorders(1,6,11–13). Genetic testing is the gold standard for the diagnosis, and only symptomatic treatment is available(2,9,10).

In this disease, there is a progressive loss of vascular smooth muscle cells of small penetrating arteries, arterioles, capillaries and venules, that are replaced by granular osmiophilic material (GOM), resulting in chronic white matter ischaemia and lacunar infarcts(5,8,10,14).

Clinically, it is characterized by subcortical ischaemic events, migraine with aura, mood disturbances and progressive cognitive decline associated with gait and balance dysfunction, which becomes more prominent with ageing(2,7,9,15). Ischaemic events are the most frequent manifestations in CADASIL, occurring in 60–85% of patients. In addition, when compared to the general population, ischaemic events in these patients occur earlier in life, tipically starting on the fifth decade(2,4). Migraine is present in near half of the patients (54.5%), mostly migraine with aura and it is usually the first clinical symptom of the disease, with a mean age of onset of 30 years old(2,16). While some patients have severe manifestations of the disease early in life, others remain asymptomatic until the 5-6th decade. This variability in the clinical manifestations occurs between and within families, even when the same mutation is involved(1,2,4,10,12,17–19). The mechanisms underlying this

variability are not well understood. Some studies considered classic vascular risk factors as unimportant(2,8,9,18,19). However recent ones pointed out smoking and hypertension as possible risk factors for disease severity(1,9,17). Thus, much effort has been put to find out predictors of clinical worsening.

Except for very rare cases of early migraine with aura and normal Magnetic Resonance Imaging (MRI) at onset, MRI changes precede the onset of other symptoms by 10–15 years. These changes appear at a mean age of 30 years, increase with age, and are present in all individuals carrying the mutation during the 4^{th} decade of life(2,15,19,20). The most frequent changes are white matter hyperintensities (WMH) in temporopolar areas, external capsule and periventricular regions on T2-weighted imaging or fluid-attenuated inversion recovery (FLAIR), which tend to increase in size and to converge(2,5,18–20). Microbleeds, lacunes, dilated perivascular spaces and cerebral atrophy are observed later with the progression of the disease(2,5,7,18). The presence of lacunar infarcts and cerebral atrophy seem to be associated with cognitive decline(2,5,7,18–20).

There is increasing evidence that cerebrovascular autoregulation is progressively affected in this disease, as well as the cerebral blood flow (CBF), leading to chronic cerebral hypoperfusion, which, in turn, precedes changes in MRI(5,6,13,15,21–24). Chronic cerebral hypoperfusion seems to be related with the presence and volume of WMH, as well as the cognitive deficit(13,15,21,22,24).

Although little is known about the compromise of the venous vasculature in CADASIL, some studies have shown that both small arteries and small veins are affected within white matter lesions in cerebral small vessel diseases(3,14). It was also reported that in CADASIL, GOM are present in cerebral veins, and venous density and integrity may be altered(3,14). For this

reason it seems reasonable to admit that this is a disease involving the entire small cerebral vascular system(3,14).

Until recently, the understanding of the pathophysiology of the extracranial venous system was limited and overlooked. Thus, the impact of cerebral venous drainage abnormalities in a variety of central nervous system (CNS) disorders are probably underestimated(25,26). Internal jugular vein (IJV) is the main venous outflow pathway for cerebral venous drainage (24,27,28). Recent studies suggest that jugular venous reflux (JVR), a condition which prevalence is known to increase after the 5^{th} decade of life, particularly in the left vessel, may cause a repetitive or sustained retrograde-transmitted venous pressure into the cerebral venous system, especially during Valsalva manoeuvres (VM)(24,29–33). This may affect cerebral blood flow and result in accumulated insults to structure and function of cerebral small vessels and blood-brain barrier. Therefore this could be the cause of, or at least contribute to, cerebral white matter lesions (WMH)(24,29–33).

The association of JVR, a condition that increases with age(24,30,32–34), and some clinical disorders, such as transient global amnesia, age-related white matter changes (ARWMC) and Alzheimer's disease has been previously studied(25,28,31). However, it has not yet been investigated in CADASIL patients.

The first objective of the study was to compare the clinical, hemodynamic and imagiologic characteristics of our CADASIL patients with healthy volunteers. Secondly, and most important, we aimed to investigate if there was an association between the presence of JVR and brain lesion´s volume within the population with the disease and also in a subpopulation of patients aged 40 or more.

Materials and Methods

Study population

In this study we included all willing patients with CADASIL followed in the outpatient clinic at the Neurology Department of Centro Hospitalar e Universitário de Coimbra (CHUC). The control population was composed by healthy volunteers. The exclusion criteria were the impossibility of performing MRI, previous cerebral venous thrombosis, known thrombophilia, and CADASIL patients with cortico-subcortical lesions. All were informed of data collection for clinical studies and were free to withdraw consent.

Demographic data and risk factors

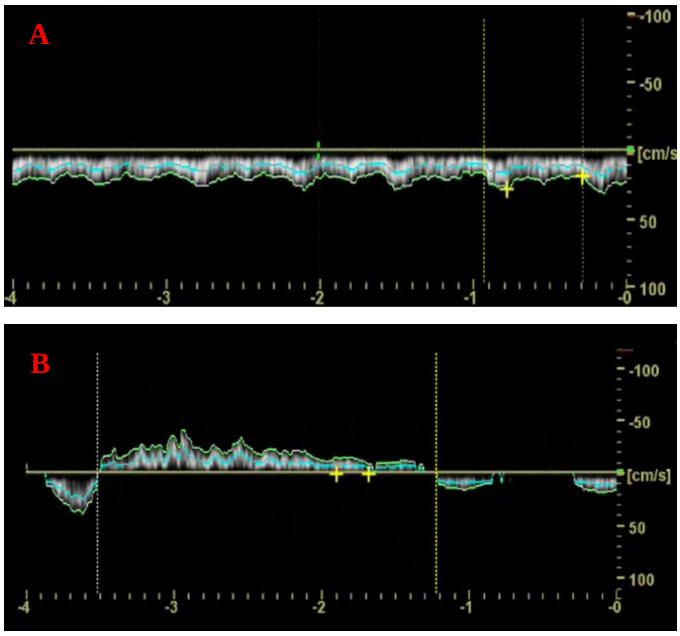
We collected data on vascular risk factors: age, sex, body mass index (BMI), alcoholism (proven alcohol abuse and dependence), smoking (present or past), arterial hypertension (HT), diabetes mellitus (DM), dyslipidaemia (current or history of abnormal plasma high-/low-density cholesterol or triglycerides values), chronic kidney disease, coronary artery disease (CAD) (history of angina pectoris or acute myocardial infarction, or evidence from coronary artery catheterization), peripheral artery disease (PAD) (history of intermittent claudication, ischemic ulcers or gangrene, or evidence of peripheral artery narrowing on ultrasound examination), atrial fibrillation (AF) (paroxysmal, permanent or persistent episodes of atrial fibrillation), heart failure (HF) (previous history with or without recent exacerbation), history of previous strokes or transient ischemic attack (TIA), migraine with or without aura, according to the International Classification of Headache Disorders, 3rd edition (2013)(35).

Doppler Ultrasonography (D-US)

Patients and controls underwent arterial and venous cervical, as well as an intracranial D-US study by the same physician, experienced in the technique and blind for the clinical diagnosis, at the Neurology department of CHUC. The ultrasound device used was a General Electric Logiq 7® with a 11MHz linear probe for extracranial evaluation and a 3MHz sector probe for transcranial examination(29,36,37).

Before the examination, subjects remained in the supine position with the best cervical alignment achievable for 2 minutes, while performing deep breaths, and persisted in this position with the neck mildly extended for the rest of the study. The carotid, jugular and vertebral images were obtained with the patient in this position with the head rotated contralaterally to the side exanimated and the flows of each vessel were recorded. CBF and venous blood flow (VBF) were then calculated using these measures. The intracranial assessment was performed through an optimal transtemporal window in the middle third of the M1 segment of both Middle Cerebral Arteries. Then IJVs were assessed during VM. VM were always performed 3 times for each vessel, and a VM was considered valid if it lasted more than 5 seconds and led to an increase of more than 1 cm the IJV diameter. Jugular venous insufficiency was considered in cases of flow reversal with duration greater than 0.88 seconds in at least one vein(36,38,39).

Figure 1. A - Normal venous flow in internal jugular vein (IJV), during Valsalva manoeuvre. **B -** Transient inversion of venous flow (2.30 seconds) in the IJV, during Valsalva manoeuvre.



During the study, precautions were taken to avoid jugular venous compression, using a generous amount of ultrasound gel and making the lowest possible compression with the echograph probe(29,30,36,37,40). The protocol of this study is provided in supplemental material.

Magnetic Resonance Imaging (MRI):

Using a 3.0 MRI scanner MRI (3-Tesla) from Instituto de Ciências Nucleares Aplicadas à Saúde, Coimbra, Portugal (ICNAS), a complete set of diffusion-weighted imaging, T1-weighted imaging, FLAIR, DP and T2-weighted imaging (3-mm-thick contiguous interleaved sections) were obtained. T2-hyperintense lesions were segmented by the lesion growth algorithm from a combination of T1 and FLAIR images as implemented in the LST toolbox version 2.0.15 (www.statisticalmodelling.de/lst.html) for SPM 12. We established the initial threshold of 0.25ml, to obtain the lesion probability maps and estimate automatically the number and volume of lesions(41). The results were validated by an experienced stroke neuroradiologist, blinded to the ultrasound findings and other clinical issues.

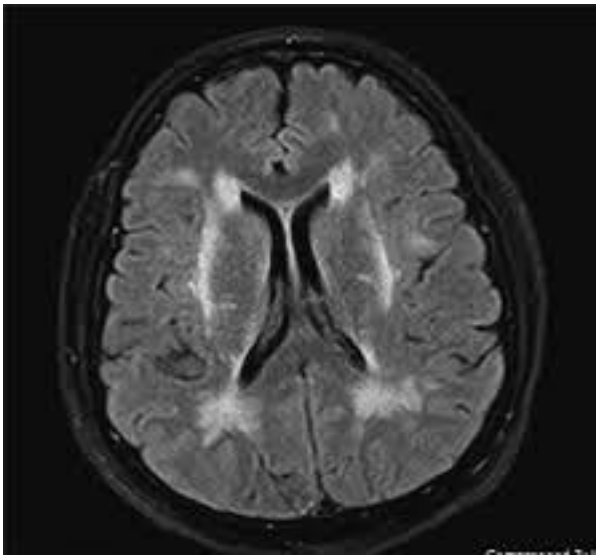


Figure 2. Brain MRI findings in a patient with CADASIL. FLAIR images demonstrate hyperintense lesions in bilateral periventricular and subcortical white matter and bilateral external capsules. In this study, the number of lesions and lesion volume were obtained using the lesion growth algorithm for lesion segmentation.

Abbreviations: CADASIL – Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leucoencephalopathy; FLAIR – fluid attenuated inversion recovery.

Statistical analysis:

We performed univariate analysis of the study population regarding demographical data and risk factors. These variables were compared between CADASIL patients and the control group (Table 1). The variables were also compared between patients w/ no-JVR and w/ JVR (Table 3) and in the subgroup of patients w/ 40 years or more, w/ no-JVR and w/ JVR (Supplemental material - Table 5). $\chi 2$ test was used for nominal variables (or Fisher's exact test when appropriate) and t-test for continuous variables.

The relations between CADASIL and the presence of JVR, lesion volume, number of lesions, CBF and VBF were analysed using binary logistic regression (nominal variables) and linear regression (continuous variables), adjusted for the confounding variables. Univariate comparison was also included.

Continuous variables are presented as mean (standard deviation) and dichotomous variables as frequency (percentage). Statistical significance was set at two-sided p values <0.05.

Results

A total of 55 subjects (28 CADASIL patients and 27 controls) were enrolled, mean age of 48.13 ± 13.79 years, 27 men (49.1%). Baseline characteristics, as well as a comparison between CADASIL patients and the control group are summarized in Table 1. Hypertension, previous stroke / TIA, migraine and migraine with aura differed among the CADASIL and control groups.

In this study, 17 subjects (30.9%) had JVR (all detected during VM), 10 CADASIL patients and 7 controls (Table 2A). Thirteen subjects had left-sided JVR (76.5%) (10 unilateral and 3 bilateral JVR).

As can be seen in Table 2B, CADASIL was not associated with a higher prevalence of JVR compared with the control group (OR 1.04; CI 95%: 0.22 – 5.00; p=0.958) nor there was a statistically difference in CBF or VBF between this two groups. Lesion volume and the number of lesions was highly associated with CADASIL (p=0.007 and p=0.000 respectively).

In Table 3 a comparison between the characteristics of the CADASIL patients w/ JVR and w/ no-JVR is resumed. Dyslipidaemia was the only variable that differed between the 2 groups in univariate analysis.

Cerebral MRI findings of the JVR group and the no-JVR group were then compared. A trend for more lesion volume (means of 31.58mL, 19.70mL respectively) (β 11.86; CI 95%: -6.74 – 30.46; p=0.201) and less number of lesions (means of 15.70, 20.78 respectively) (β -4.22; CI 95%: -13.36 – 4.92; p=0.350) was observed, as shown in Graph 1 and 2. However, these differences were not statistically significant.

A subgroup of CADASIL patients aged 40 years or more was also investigated regarding the possible association between JVR and lesion volume in this population. In this group, lesion

volume was statistically significantly higher in the patients with JVR compared with the no-JVR group (β 22.14; CI 95%: 6.47 – 37.82; p=0.008) as can be seen in Table 4 and Graph 3. Baseline characteristics of this subgroup is provided in supplemental material in Table 5.

Table 1. Baseline characteristics of the study population and univariate comparison between CADASIL patients and the control group.

	Total (n=55)	CADASIL (n=28)	Controls (n=27)	p
Age (years, mean±SD)	48.13 (±13.79)	51.18 (±13.80)	44.96 (±13.29)	0.095
Male gender	27 (49.1%)	15 (53.6%)	12 (44.4%)	0.498
Overweight	37 (67.3%)	21 (75.0%)	16 (59.3%)	0.214
Hypertension	17 (30.9%)	13 (46.4%)	4 (14.8%)	**0.011**
Smoking	19 (34.5%)	8 (28.6%)	11 (40.7%)	0.343
Alcoholism	15 (27.3%)	7 (25.0%)	8 (29.6%)	0.700
Diabetes Mellitus	4 (7.3%)	3 (10.7%)	1 (3.7%)	0.611
Dyslipidaemia	22 (40.0%)	14 (50.0%)	8 (29.6%)	0.123
Atrial Fibrillation	1 (1.8%)	0 (0.0%)	1 (3.7%)	0.491
Coronary artery disease	0 (0.0%)	0 (0.0%)	0 (0.0%)	-
Peripheral artery disease	0 (0.0%)	0 (0.0%)	0 (0.0%)	-
Heart Failure	1 (1.8%)	1 (3.6%)	0 (0.0%)	1.000
Previous Stroke / TIA	8 (14.5%)	8 (28.6%)	0 (0.0%)	**0.003**
Chronic kidney disease	0 (0.0%)	0 (0.0%)	0 (0.0%)	-
Migraine	19 (34.5%)	15 (53.6%)	4 (14.8%)	**0.003**
Migraine with aura	11 (20.0%)	10 (35.7%)	1 (3.7%)	**0.003**

Abbreviations: CADASIL – Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leucoencephalopathy; SD – Standard deviation; TIA – Transient ischemic attack

Table 2 A /B. Hemodynamic and imagiologic associations between CADASIL patients and healthy controls. Continuous variables are presented as mean (standard deviation).

A. Univariate comparison

	Total (n=55)	CADASIL (n=28)	Controls (n=27)	p
JVR	17 (30.9%)	10 (35.7%)	7 (25.9%)	0.432
LV	12.31 (±18.82)	23.95 (±20.54)	0.25 (±0.59)	**0.000**
NoL	10.96 (±11.16)	18.96 (±10.03)	2.67 (±3.69)	**0.000**
CBF	630.4 (±153.3)	615.5 (±157.6)	645.8 (±150.0)	0.468
VBF	489.3 (±212.7)	479.8 (±251.7)	498.8 (±169.2)	0.746

B. Multivariate comparison

	OR	CI 95%	p
JVR	1,04	0.22-5.00	**0.958**
	β	CI 95%	p
LV	11.86	3.33 – 20.39	**0.007**
NoL	13.95	8.79 – 19.11	**0.000**
CBF	- 4.61	-111.925 – 102.71	0.932
VBF	- 95.37	-247.84 – 57.10	0.215

Abbreviations: CADASIL – Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leucoencephalopathy; LV – Lesion volume; NoL – Number of lesions; CBF – cerebral blood flow; VBF – Venous blood flow; OR – Odds ratio; CI – Confidence interval; β – regression coefficient

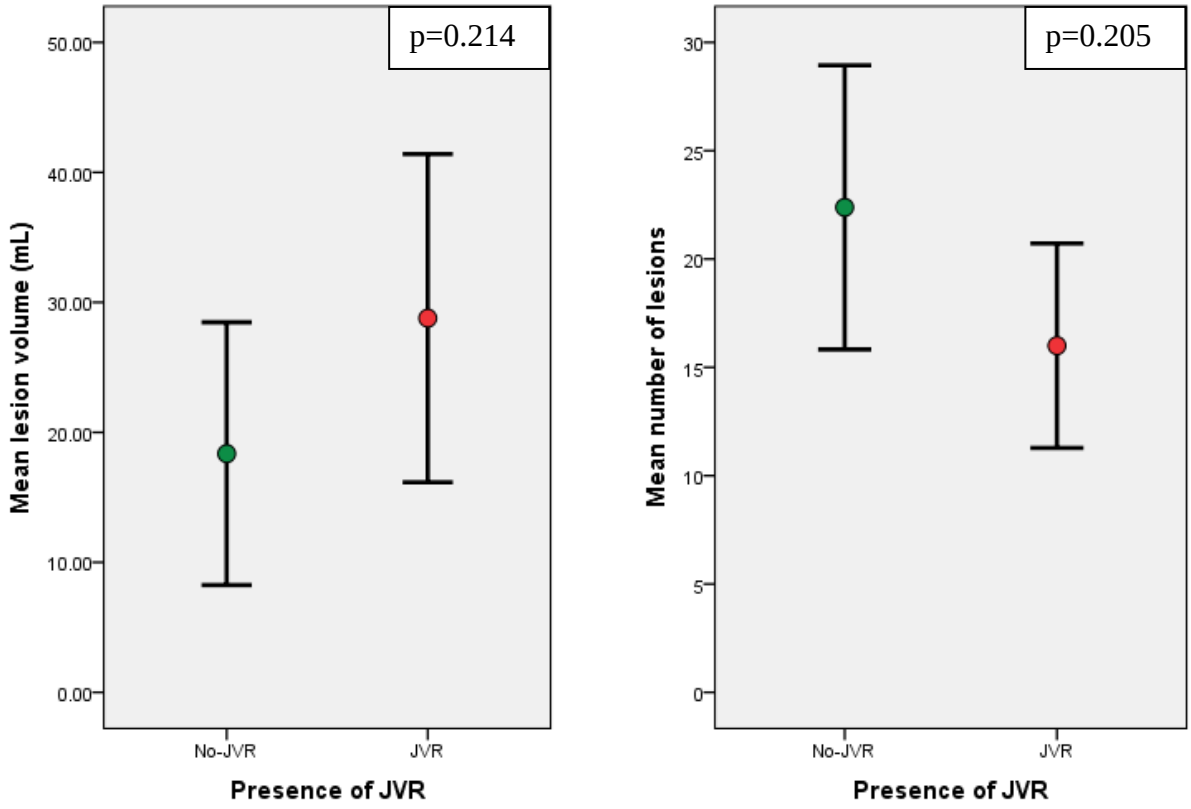
Table 3. Characteristics of the CADASIL patients and univariate comparison between JVR and no-JVR patients

	CADASIL (n=28)	no-JVR (n=18)	JVR (n=10)	p
Age (years, mean±SD)	51.18 (±13.80)	51.11(±12.77)	51.3 (±16.21)	0.973
Male gender	15 (53.6%)	9 (50.0%)	6 (60.0%)	0.705
Overweight	21 (75.0%)	15 (83.3%)	6 (60.0%)	0.207
Hypertension	13 (46.4%)	9 (50.0%)	4 (40.0%)	0.705
Smoking	8 (28.6%)	4 (22.2%)	4 (40.0%)	0.400
Alcoholism	7 (25.0%)	3 (16.7%)	4 (40.0%)	0.207
Diabetes Mellitus	3 (10.7%)	3 (16.7%)	0 (0.0%)	0.533
Dyslipidaemia	14 (50.0%)	6 (33.3%)	8 (80.0%)	**0.018**
Atrial Fibrillation	0 (0.0%)	0 (0.0%)	0 (0.0%)	-
Coronary artery disease	0 (0.0%)	0 (0.0%)	0 (0.0%)	-
Peripheral artery disease	0 (0.0%)	0 (0.0%)	0 (0.0%)	-
Heart Failure	1 (3.6%)	1 (5.6%)	0 (0.0%)	1.000
Previous Stroke / TIA	8 (28.6%)	3 (16.7%)	5 (50.0%)	0.091
Chronic kidney disease	0 (0.0%)	0 (0.0%)	0 (0.0%)	-
Migraine	15 (53.6%)	10 (55.6%)	5 (50.0%)	1.000
Migraine with aura	10 (35.7%)	6 (33.3%)	4 (40.0%)	1.000

Abbreviations: CADASIL – Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leucoencephalopathy; JVR – Jugular venous reflux; SD – Standard deviation; TIA – Transient ischemic attack

Graph 1(left) In the CADASIL group, the relation between JVR and lesion volume.

Graph 2(right) In the CADASIL group, the relation between JVR and number of lesions.



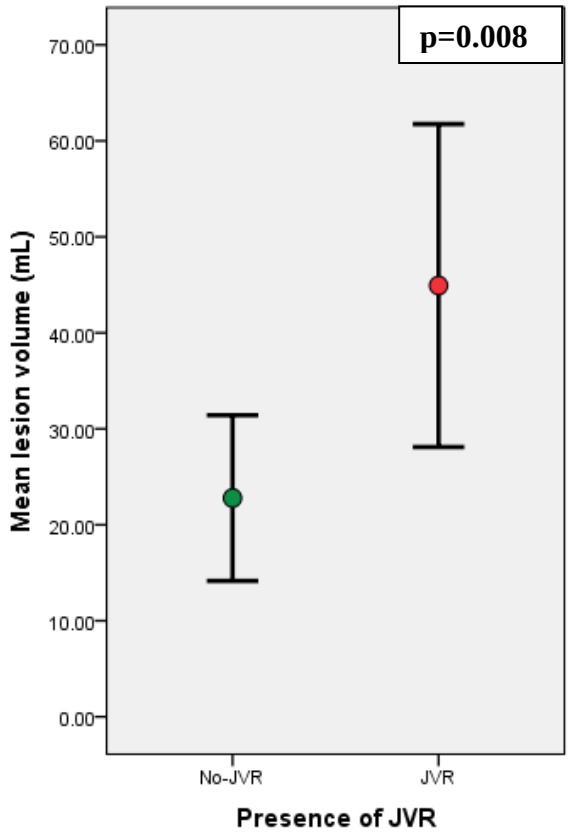
Abbreviations: JVR – Jugular venous reflux.

Table 4. Imagiologic associations of CADASIL patients aged 40 years or more, univariate comparison between w/ JVR and w/ no-JVR in this population. Continuous variables are presented as mean (standard deviation).

	A. Univariate comparison				**B. Multivariate comparison**		
	CADASIL ≥ 40y (n=22)	No-JVR (n=15)	JVR (n=7)	p	β	CI 95%	p
Lesion volume	29.83 (±19.18)	22.78 (±15.59)	44.93 (±18.19)	**0.008**	22.14	6.47 – 37.82	**0.008**
Number of lesions	22.05 (±8.49)	23.27 (±9.23)	19.43 (±6.45)	0.335	-3.84	-11.95 – 4.27	0.335

Abbreviations: CADASIL – Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leucoencephalopathy; β – regression coefficient; CI – Confidence interval

Graph 3. In the CADASIL patients aged ≥ 40y, the association between JVR and lesion volume.



Abbreviations: JVR – Jugular venous reflux

Discussion

To our knowledge, this is the first study that investigates the association between JVR and cerebral imagiologic changes in patients with CADASIL.

The first finding is that, as would be expected, these patients had higher prevalence of previous strokes/TIA, migraine and migraine with aura compared with healthy volunteers. In fact, the prevalence of migraine and migraine with aura in CADASIL patients was similar to other studies (migraine – 53.6% vs 54.5%, migraine with aura 35.7% vs 45.8%)(16). Unsurprisingly, CADASIL patients also had a greater lesion volume and number of lesions compared to healthy volunteers.

Growing interest has been given to hemodynamic changes in CADASIL, particularly to CBF reduction, thought to be one of the factors leading to the chronic cerebral hypoperfusion that is well documented in the disease(6,21,23). Nonetheless, compared with the cerebral arterial system, the cerebral venous one has not been so thoroughly described and studied. An insufficient description contributes to a poor understanding of physiology, which may lead to an underestimation of cerebral venous dysfunction in various clinical disorders(26). For this reason, the CBF and also the VBF of the patients were determined and, as in other studies, it was found to be slightly reduced compared with healthy controls, although not at a statistically significant level(6,21,23).

As mentioned before, the IJV is the main drainage route for cerebral venous outflow(24,27,28). The IJV valve (IJVV), in turn, serves an important role in preventing the backflow of venous blood and backward venous pressure into the cerebral venous system during conditions of increased central venous pressure (CVP), such as the VM(42,43).

Without a competent IJVV or with a reversed gradient pressure that exceeds the competence of the IJVV, JVR occurs. If the extent of venous hypertension exceeds the ability of venous dilatation to compensate for it and compromises the competence of the jugular venous valve, the direction of venous flow will be reversed(42,44).

A key finding of this study is that there was no difference between the prevalence of JVR in CADASIL patients and in the control group (OR 1.04; CI 95%: 0.22 – 5.00; p=0.958). This is an important result, as this association had never been studied before. It is also worth mentioning, that the prevalence of JVR was similar to other studies, in different populations, using the same cut-off (>0.88s) (30.9% vs 29.3% and 30%)(36,38).

It has been previous shown that cerebral venous drainage impairment results in decreased cerebral perfusion and brain oedema, leading to cerebral dysfunction(24,30,44,45).

Interestingly, it was observed that, as a whole, in CADASIL patients with JVR, a trend for more lesion volume (means of 31.58mL, 19.70mL respectively) (β 11.86; CI 95%: -6.74 – 30.46; p=0.201) and less number of lesions (means of 15.70, 20.78 respectively) (β -4.22; CI 95%: -13.36 – 4.92; p=0.350) was observed, although neither statistically significant. This is a curious finding since, with time, white matter lesions in CADASIL usually tend to converge, thus increasing lesion volume and decreasing the lesion number(19). Of note, regarding lesion volume, is that this association became noticeably stronger within the subpopulation of patients aged 40 years or more (β 22.14; CI 95%: 6.47 – 37.82; p=0.008). The subgroup of patients with 40 years or more was studied individually, as there is some evidence that JVR prevalence increases predominantly after the 5^{th} decade(29,30).

There are no conclusive explanations for this interesting finding. The retrograde-transmitted pressure, caused by JVR, to the already dysfunctional and weakened cerebral microvasculature and blood-brain barrier of CADASIL patients seems to be a reasonable explanation(6,24). Although with several differences in physiopathology, this theory is similar to the recent discoveries in cardio-renal syndrome, in which the worsening of renal function in patients with acute HF seems to be more attributable to venous congestion than to reduced cardiac output. The same explanation is considered to be valid about liver dysfunction in chronic HF, where the transmission of elevated CVP to the hepatic venous system leads to passive hepatic congestion(46,47).

Other questions should be considered following the results of this study. One of them is whether the higher lesion volume associated with JVR is reflected in the clinical manifestations of these patients. The side of JVR and its implications may be relevant in SVDs like CADASIL, as unlike the arteries which supply blood flow to the cerebral hemisphere ipsilateral to each carotid artery, each IJV usually affects either deep cerebral

venous system drainage (usually the left IJV) or cortical cerebral venous drainage (usually the right IJV)(30).

There are some limitations in this pilot study, as it was carried out in a single centre, it had a relatively small sample size, mainly due to the rarity of this disease. The duration and severity of risk factors, as well as the medication of the subjects were not considered, which might interfere with the results. The lesion volume measure, being made by an automatic lesion growth algorithm may have its flaws. Therefore, our findings should be interpreted with caution and no firm conclusions should be made. However, we do not think that the above mentioned limitations significantly compromise the validity of our findings.

Little is known about the hemodynamic physiopathology of CADASIL and the determinants of disease progression and clinical severity, but the JVR seems to be a variable to take into account, particularly in the population aged 40 or more.

This work reinforces the importance of a more profound study of the jugular venous reflux and its impact in CADASIL, as it might be a non-documented risk factor for disease progression.

Conclusion

In summary, our population of Portuguese CADASIL patients had the same typical clinical characteristics of others described before. The prevalence of JVR seems to be identical in CADASIL patients compared to healthy controls. However, it appears to be a trend for higher lesion volume in CADASIL patients with JVR, particularly in those aged 40 or more. JVR might be a non-documented risk factor for disease progression.

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Supplemental Material

Table 5. Baseline characteristics of CADASIL patients aged 40 years or more and univariate comparison between these patients w/ JVR and w/ no-JVR.

	CADASIL ≥40y (n=22)	no-JVR (n=15)	JVR (n=7)	p
Age (years, mean±SD)	57.05 (±8.45)	55.47 (±8.52)	60.43 (±7.81)	0.207
Male gender	12 (54.5%)	7 (46.7%)	5 (71.4%)	0.381
Overweight	17 (77.3%)	13 (86.7%)	4 (57.1%)	0.274
Hypertension	12 (54.5%)	9 (60.0%)	3 (42.9%)	0.652
Smoking	7 (31.8%)	3 (20.0%)	4 (57.1%)	0.145
Alcoholism	7 (31.8%)	3 (20.0%)	4 (57.1%)	0.145
Diabetes Mellitus	3 (13.6%)	3 (20.0%)	0 (0.0%)	0.523
Dyslipidaemia	11 (50.0%)	5 (33.3%)	6 (85.7%)	0.063
Atrial Fibrillation	0 (0.0%)	0 (0.0%)	0 (0.0%)	-
Coronary artery disease	0 (0.0%)	0 (0.0%)	0 (0.0%)	-
Peripheral artery disease	0 (0.0%)	0 (0.0%)	0 (0.0%)	-
Heart Failure	1 (4.5%)	1 (6.7%)	0 (0.0%)	1.000
Previous Stroke / TIA	8 (36.4%)	3 (20.0%)	5 (71.4%)	0.052
Chronic kidney disease	0 (0.0%)	0 (0.0%)	0 (0.0%)	-
Migraine	11 (50.0%)	8 (53.3%)	3 (42.9%)	1.000
Migraine with aura	8 (36.4%)	6 (40.0%)	2 (28.6%)	1.000

Abbreviations: CADASIL – Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leucoencephalopathy; JVR – Jugular venous reflux; SD – Standard deviation; TIA – Transient ischemic attack

Doppler-Ultrassonography protocol:

A) Procedimentos preparatórios:

1. Doente colocado em posição supina com o melhor alinhamento cervical possível;

2. Antes da realização da avaliação, o doente deve permanecer nesta posição durante 2 minutos, enquanto realiza inspirações profundas.

3. Evitar a compressão venosa jugular.

4. Utilização de quantidade generosa de gel.

5. Efetuar a menor compressão possível com a sonda do ecógrafo.

6. Excluir avaliação de fluxo em zonas de contacto artério-venoso.

B) Estudo Extracraniano

Avaliação morfológica

1. Modo B - Insonação da veia jugular nos seus planos transversal e longitudinal. Identificar o bulbo venoso jugular e atentar a alterações morfológicas do septo ou válvula venosa.

2. Modo cor - Critérios de oclusão venosa: Ausência de sinal de Doppler após várias inspirações profundas.

Avaliação hemodinâmica / Quantificações de fluxo:

1. Cerebral Blood Flow (ACI's + AV's)

2. Venous Blood Flow (VJI's e VV's)

C) Estudo Transcraniano

Condições técnicas: Filtros *off***.** Diminuição PRF adequado a estudo venosa

Estruturas venosas a avaliar

1. Veias basais de Rosenthal

Planos: Segmento médio (plano mesencefálico); Segmento distal (plano talâmico)

Porção proximal - Lateral a P2; Fluxo no sentido da sonda

Porção distal - Supero-medial a P2; Fluxo no sentido oposto à sonda

2. Veia de Galeno

Plano axial talâmico

Posterior à glândula pineal (hiperecogénica)

D) Avaliação de refluxo venoso jugular (bulbo) no contexto de manobra de Valsava

1. Realizar 3 manobras de Valsava (Critérios de qualidade da manobra de Valsava: Duração > 5 segundos; Aumento do diâmetro da veia jugular interna >1 cm).

2. Refluxo jugular venoso: se fluxo invertido durante pausa respiratória com duração >0.88segundos.

E) Avaliação do fluxo das mesmas estruturas de C) no contexto de manobra de Valsava