Carotid atherosclerosis and cerebral small vessel disease

Canadian Atherosclerosis Imaging Network (CAIN) Project 1



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Background

Combining in vivo imaging of vessel wall disease with imaging of occult end-organ disease, and the acquisition of clinical-pathological end points, CAIN's central goal is to move innovations in clinical evaluation and therapeutic interventions aimed at cardiac and neurological diseases [1].



Given the increasing burden of vascular diseases world-wide with population aging, the CAIN Project 1 is a unique pan-Canadian brain and carotid imaging project focused on understanding the natural history of carotid disease and associations with cerebrovascular outcomes.

Objective

The goal of Project 1 is to recruit and serially image approx. 450 subjects with non-surgical carotid disease (stenosis between 30 and 95%).

We describe results from a preliminary analysis aimed to evaluate the role of carotid atherosclerosis in cerebral small vessel disease on a subsample (n=93) data acquired at baseline.

These preliminary cross-sectional results suggest a potential relationship between carotid atherosclerosis and end-organ cerebral small vessel disease.

In addition to MRI-derived measures for brain volume and distribution of ischemic cerebral white matter disease, future analyses will include:

- Progression analyses from serial assessments
- Predictive modelling of end-organ and clinical outcomes 11) using 3D carotid MRI features of vessel disease and other vascular risk factors
- iii) Evaluation of carotid plaque components, specifically intraplaque hemorrhage

Results

	Demographics
	Age, years
	Sex, n (%) male
	Medical History
la il auto radio ante a la aval	H_{V} nortonsion $n(%)$

Stenosis (bilateral)			Stenosis (left only)			
Yes (n=40)	No (n=53)	Left hemisphere	Yes (n=62)	No (n=31)	Р	
74.5 (9.0)	74.2 (9.0)	Grey matter (GM)	276.4 (21.3)	270.2 (25.5)	n.s.	
24 (60.0)	30 (56.6)	White matter (WM)	211.3 (31.0)	204.7 (28.0)	n.s.	
		Ventricular cerebrospinal fluid (vCSF)	19.2 (9.3)	18.7 (9.0)	n.s.	
34 (89.5) ^a	48 (92.3) ^c	Subcortical hyperintensities (SH)	4.2 (6.3)	2.4 (4.4)	p=0.066	
12 (30.8) ^b	12 (22.6)	Deep white (dwSH)	0.7 (1.0)	0.3 (0.5)	p=0.007	
37 (92.5)	47 (90.4) ^c	Periventricular (pvSH)	3.6 (5.7)	2.1 (4.3)	n.s.	
14 (35.0)	13 (25.0) ^c	Lacunes, mm ³	126.3 (273.1)	59.4 (151.7)	n.s.	
2 (5.0)	-		Stenosis (right only)			
5 (12.5)	17 (32.7) ^c	Right hemisphere	Yes (n=53)	No (n=40)	Р	
4 (10.0)	3 (5.7) ^c	Grey matter (GM)	280.9 (23.7)	273.8 (24.7)	n.s.	
2 (5.0)	2 (3.8)	White matter (WM)	212.7 (31.4)	206.3 (27.8)	n.s.	
-	2 (3.5) ^c	Ventricular cerebrospinal fluid (vCSF)	18.3 (8.8)	18.5 (8.6)	n.s.	
4 (10.0)	1 (1.9)	Subcortical hyperintensities (SH)	4.1 (6.1)	2.5 (4.5)	n.s.	
3 (7.5)	-	Deep white (dwSH)	0.6 (0.9)	0.3 (0.4)	n.s.	
2 (5.0)	-	Periventricular (pvSH)	3.5 (5.7)	2.2 (4.3)	n.s.	
Stenosis	(bilateral)	Lacunes, mm ³	144.3 (309.9)	80.6 (160.7)	n.s.	
	Stenosis Yes (n=40) 74.5 (9.0) 24 (60.0) 34 (89.5) ^a 12 (30.8) ^b 37 (92.5) 14 (35.0) 2 (5.0) 5 (12.5) 4 (10.0) 2 (5.0) - 4 (10.0) 3 (7.5) 2 (5.0) Stenosis	Stenosis (bilateral)Yes (n=40)No (n=53) $74.5 (9.0)$ $74.2 (9.0)$ $24 (60.0)$ $30 (56.6)$ $34 (89.5)^a$ $48 (92.3)^c$ $12 (30.8)^b$ $12 (22.6)$ $37 (92.5)$ $47 (90.4)^c$ $14 (35.0)$ $13 (25.0)^c$ $2 (5.0)$ - $5 (12.5)$ $17 (32.7)^c$ $4 (10.0)$ $3 (5.7)^c$ $2 (5.0)$ - $2 (5.0)$ 2 (3.8)- $2 (3.5)^c$ $4 (10.0)$ $1 (1.9)$ $3 (7.5)$ - $2 (5.0)$ -Stenosis (bilateral)	Stenosis (bilateral) Left hemisphere Yes (n=40) No (n=53) Left hemisphere 74.5 (9.0) 74.2 (9.0) Grey matter (GM) 24 (60.0) 30 (56.6) White matter (WM) Ventricular cerebrospinal fluid (vCSF) Subcortical hyperintensities (SH) 12 (30.8) ^b 12 (22.6) Deep white (dwSH) 37 (92.5) 47 (90.4) ^c Periventricular (pvSH) 14 (35.0) 13 (25.0) ^c Lacunes, mm ³ 2 (5.0) - - 5 (12.5) 17 (32.7) ^c Right hemisphere 4 (10.0) 3 (5.7) ^c Grey matter (GM) 2 (5.0) - - - 2 (3.5) ^c Ventricular cerebrospinal fluid (vCSF) 4 (10.0) 3 (5.7) ^c Grey matter (WM) - 2 (3.5) ^c Ventricular cerebrospinal fluid (vCSF) 4 (10.0) 1 (1.9) Subcortical hyperintensities (SH) 3 (7.5) - Deep white (dwSH) 2 (5.0) - Periventricular (pvSH) 2 (5.0) - Deep white (dwSH) <	Stenosis (bilateral)StenosisYes (n=40)No (n=53)Left hemisphereYes (n=62) $74.5 (9.0)$ $74.2 (9.0)$ Grey matter (GM) $276.4 (21.3)$ $24 (60.0)$ $30 (56.6)$ White matter (WM) $211.3 (31.0)$ $24 (60.0)$ $30 (56.6)$ White matter (WM) $211.3 (31.0)$ $24 (60.0)$ $30 (56.6)$ White matter (WM) $211.3 (31.0)$ $24 (60.0)$ $30 (56.6)$ White matter (WM) $211.3 (31.0)$ $24 (60.0)$ $30 (56.6)$ Uentricular cerebrospinal fluid (vCSF) $19.2 (9.3)$ $34 (89.5)^a$ $48 (92.3)^c$ Subcortical hyperintensities (SH) $4.2 (6.3)$ $12 (30.8)^b$ $12 (22.6)$ Deep white (dwSH) $0.7 (1.0)$ $37 (92.5)$ $47 (90.4)^c$ Periventricular (pvSH) $3.6 (5.7)$ $14 (35.0)$ $13 (25.0)^c$ Lacunes, mm ³ $126.3 (273.1)$ $2 (5.0)$ -Stenosis (Stenosis ($5 (12.5)$ $17 (32.7)^c$ Right hemisphereYes (n=53) $4 (10.0)$ $3 (5.7)^c$ Grey matter (GM) $280.9 (23.7)$ $2 (5.0)$ $2 (3.8)$ White matter (WM) $212.7 (31.4)$ $ 2 (3.5)^c$ Ventricular cerebrospinal fluid (vCSF) $18.3 (8.8)$ $4 (10.0)$ $1 (1.9)$ Subcortical hyperintensities (SH) $4.1 (6.1)$ $3 (7.5)$ $-$ Deep white (dwSH) $0.6 (0.9)$ $2 (5.0)$ $-$ Periventricular (pvSH) $3.5 (5.7)$ $2 (5.0)$ $-$ Periventricular (pvSH) $3.5 (5.7)$	Stenosis (bilateral)Stenosis (left only)Yes (n=40)No (n=53)Left hemisphereYes (n=62)No (n=31)74.5 (9.0)74.2 (9.0)Grey matter (GM) $276.4 (21.3)$ $270.2 (25.5)$ 24 (60.0)30 (56.6)White matter (WM) $211.3 (31.0)$ $204.7 (28.0)$ $34 (89.5)^a$ 48 (92.3)^cSubcortical hyperintensities (SH) $4.2 (6.3)$ $2.4 (4.4)$ 12 (30.8) ^b 12 (22.6)Deep white (dwSH) $0.7 (1.0)$ $0.3 (0.5)$ 37 (92.5)47 (90.4) ^c Periventricular (pvSH) $3.6 (5.7)$ $2.1 (4.3)$ 14 (35.0)13 (25.0) ^c Lacunes, mm ³ $126.3 (273.1)$ $59.4 (151.7)$ 2 (5.0)-Stenosis (right only)5 (12.5)17 (32.7) ^c Right hemisphereYes (n=53)No (n=40)4 (10.0)3 (5.7) ^c Grey matter (GM) $280.9 (23.7)$ $273.8 (24.7)$ 2 (5.0)-2 (3.5) ^c Ventricular crebrospinal fluid (vCSF) $18.3 (8.8)$ $18.5 (8.6)$ 4 (10.0)1 (1.9)Subcortical hyperintensities (SH)4.1 (6.1) $2.5 (4.5)$ 3 (7.5)-Deep white (dwSH) $0.6 (0.9)$ $0.3 (0.4)$ 2 (5.0)-Periventricular (pvSH) $3.5 (5.7)$ $2.2 (4.3)$	

The left only stenosis group had

The bilateral stenosis group had significantly greater SH volumes (p<0.05), attributed primarily to deep white SH (p<0.01) rather than periventricular SH (n.s.).

> No significant between group differences were demonstrated for brain tissue atrophy measures.

Diabetes Mellitus, n (%)	12 (30.8) ^b	12 (22.6)	
Hyperlipidemia, n (%)	37 (92.5)	47 (90.4) ^c	
Coronary Artery Disease, n (%)	14 (35.0)	13 (25.0) ^c	
Mitral Insufficiency, n (%)	2 (5.0)	-	
Peripheral Vascular Disease, n (%)	5 (12.5)	17 (32.7) ^c	
Atrial Fibrillation, n (%)	4 (10.0)	3 (5.7) ^c	
Cardiac Valve Disease, n (%)	2 (5.0)	2 (3.8)	
Hepatic, n (%)	-	2 (3.5) ^c	
Renal, n (%)	4 (10.0)	1 (1.9)	
Amaurosis Fugax, n (%)	3 (7.5)	-	
Hyperhomocysteinemia, n (%)	2 (5.0)	-	
	Stenosis (bilateral)		
Volumetric Analysis	Stenosis	(bilateral)	
Volumetric Analysis Whole brain	Stenosis Yes (n=40)	(bilateral) No (n=53)	Р
Volumetric Analysis Whole brain TIC	Stenosis Yes (n=40) 1258.7 (113.3)	(bilateral) No (n=53) 1225.2 (113.6)	P n.s.
Volumetric Analysis Whole brain TIC BPF%	Stenosis Yes (n=40) 1258.7 (113.3) 78.7 (4.7)	(bilateral) No (n=53) 1225.2 (113.6) 78.4 (3.7)	P n.s. n.s.
Volumetric Analysis Whole brain TIC BPF% Grey matter (GM)	Stenosis Yes (n=40) 1258.7 (113.3) 78.7 (4.7) 557.3 (44.7)	(bilateral) No (n=53) 1225.2 (113.6) 78.4 (3.7) 544.0 (50.0)	P n.s. n.s. n.s.
Volumetric Analysis Whole brain TIC BPF% Grey matter (GM) White matter (WM)	Stenosis Yes (n=40) 1258.7 (113.3) 78.7 (4.7) 557.3 (44.7) 424.0 (62.3)	(bilateral) No (n=53) 1225.2 (113.6) 78.4 (3.7) 544.0 (50.0) 411.0 (55.6)	P n.s. n.s. n.s. n.s.
Volumetric Analysis Whole brain TIC BPF% Grey matter (GM) White matter (WM) Ventricular cerebrospinal fluid (vCSF)	Stenosis Yes (n=40) 1258.7 (113.3) 78.7 (4.7) 557.3 (44.7) 424.0 (62.3) 37.5 (17.5)	(bilateral) No (n=53) 1225.2 (113.6) 78.4 (3.7) 544.0 (50.0) 411.0 (55.6) 37.2 (16.9)	P n.s. n.s. n.s. n.s. n.s.
Volumetric Analysis Whole brain TIC BPF% Grey matter (GM) White matter (WM) Ventricular cerebrospinal fluid (vCSF) Subcortical hyperintensities (SH)	Stenosis Yes (n=40) 1258.7 (113.3) 78.7 (4.7) 557.3 (44.7) 424.0 (62.3) 37.5 (17.5) 8.3 (12.4)	(bilateral) No (n=53) 1225.2 (113.6) 78.4 (3.7) 544.0 (50.0) 411.0 (55.6) 37.2 (16.9) 4.9 (8.8)	P n.s. n.s. n.s. n.s. n.s. p=0.036
Volumetric Analysis Whole brain TIC BPF% Grey matter (GM) White matter (WM) Ventricular cerebrospinal fluid (vCSF) Subcortical hyperintensities (SH) Deep white (dwSH)	Stenosis Yes (n=40) 1258.7 (113.3) 78.7 (4.7) 557.3 (44.7) 424.0 (62.3) 37.5 (17.5) 8.3 (12.4) 1.3 (1.9)	(bilateral) No (n=53) 1225.2 (113.6) 78.4 (3.7) 544.0 (50.0) 411.0 (55.6) 37.2 (16.9) 4.9 (8.8) 0.5 (0.9)	P n.s. n.s. n.s. n.s. n.s. p=0.036 p=0.007
Volumetric Analysis Whole brain TIC BPF% Grey matter (GM) White matter (WM) Ventricular cerebrospinal fluid (vCSF) Subcortical hyperintensities (SH) Deep white (dwSH) Periventricular (pvSH)	Stenosis Yes (n=40) 1258.7 (113.3) 78.7 (4.7) 557.3 (44.7) 424.0 (62.3) 37.5 (17.5) 8.3 (12.4) 1.3 (1.9) 7.0 (11.3)	(bilateral) No (n=53) 1225.2 (113.6) 78.4 (3.7) 544.0 (50.0) 411.0 (55.6) 37.2 (16.9) 4.9 (8.8) 0.5 (0.9) 4.4 (8.5)	P n.s. n.s. n.s. n.s. n.s. p=0.036 p=0.007 p=0.083

Data are presented as Mean (SD) unless otherwise stated. Raw volumes are presented for transparency, statistical analyses were performed on normalized (log transformed), head size corrected data. Volumetrics are reported in cubic centimetres (cc) unless otherwise stated.

n.s.	^a Data available for 38/40 subjects
0.036	^b Data available for 39/40 subjects
0.007	^c Data available for 52/53 subjects
0.083	Abbreviations: TIC=total intracranial capacity, BPF=brain parenchymal fraction
n.s.	

significantly more left hemisphere deep white SH volumes than the non-left stenosis group



Methods



Lesion Explorer

Quantification of cerebral small vessel disease: periventricular (pvSH), deep white (dwSH), and lacunar infarcts [2-3].



References

1. Tardiff et al. (2013). Can J Cardiol. 2. Ramirez et al. (2011). Neurolmage. 3. Ramirez et al. (2014). J Vis Exp. 4. Singh et al. (2013). Int J Cardiovasc Imaging.

Main Study Reference 5. CAIN: www.canadianimagingnetwork.org/

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Fig. 1 (a) SH segmentation overlayed on axial T1; (b) Axial T2weighted; (c) 3D surface volume rendering from above and, (d) from angled side views.

Left hemisphere SH depicted in purple, lacunar infarcts depicted in red, periventricular infarcts depicted in white. Right hemisphere SH depicted in yellow, lacunar infarcts depicted in green, periventricular infarcts depicted in blue. (a&b displayed in radiological convention; c&d displayed in neurological convention).



Fig. 2 Baseline carotid stenosis was assessed using routine clinical imaging and confirmed with MRI.

After head-size correction and normalization of skewed data, brain atrophy and small vessel disease burden was compared between bilateral and unilateral stenosis (>50%) groups controlling for sex and age.

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