Vascular Disease Risk Factors and MS Progression: A study of brain metabolism

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Background

- There is growing evidence that vascular disease risk factors (VDRF), such as hyperlipidemia, hypertension, obesity, diabetes, and heart disease, can significantly increase the risk of disability progression in MS.
- Recent research has shown MS subjects with one or more VDRF (VDRFP) at diagnosis required unilateral assistance to walk at earlier times (a median of 6 years) than those without any VDRF (VDRFN).[1]
- There also appeared to be a dose-response relationship between VDRF and MS disability with presence of a single VDRF increasing the risk of early gait disability by 51% and presence of 2 of these conditions increasing the risk by 228%.[1]

Objectives

Specific Aim 1: Determine whether VDRFP subjects in comparison with VDRFN have decreased cerebral blood flow and volume detected by MRI and high energy phosphate metabolites in cerebral gray matter assessed by ^{31}P magnetic resonance spectroscopic imaging (MRSI).

Specific Aim 2: Determine if brain atrophy progresses faster in VDRFP subjects compared to VDRFN and whether ^{31}P MRSI and cerebral blood flow deficits are associated with this increased rate of brain atrophy (yet to be analyzed).

Specific Aim 3: Determine if clinical impairment, disability and quality of life deteriorates faster in VDRFP than VDRFN subjects and whether ^{31}P MRSI and cerebral blood flow deficits are associated with clinical measures of an increased rate of disease progression.

Table 1: Baseline demographic ((N(SD) or (N(%))

	Total	Positive	Negative
	50	28	22
Age	54.5 (6.9)	56.4 (6.9)	52.2 (7.8)
Female	36 (72%)	23 (82%)	13 (59%)
MS Subtype			
RRMS	36 (72%)	18 (36%)	18 (36%)
SPMS	8 (16%)	6 (12%)	2 (4%)
PPMS	6 (12%)	4 (8%)	2 (4%)
MS Medication			
None	19 (38%)	9 (18%)	10 (20%)
Tecfidera	14 (28%)	8 (16%)	5 (10%)
Avonex	7 (14%)	4 (8%)	3 (6%)
Copaxone	8 (16%)	6 (12%)	1 (2%)
Other (Rebif, Plegridy)	4 (8%)	1 (2%)	3 (6%)

Methods

- This is a three year long observational study, mixed design (cross-sectional and longitudinal) with two study arms (VDRFP & VDRFN)
- The presented data is cross-sectional analysis of baseline data. 7T MRI data will be collected at 12, 24 and 36 months.
- Brain parenchymal volume (normalized for head size) was assessed using SIENAX.[2]
- For specific aim 1, a volume of interest in parietal brain region was analyzed for changes in phosphate metabolites (Figure 1).

Figure 1:a. axial plane b. coronal plane

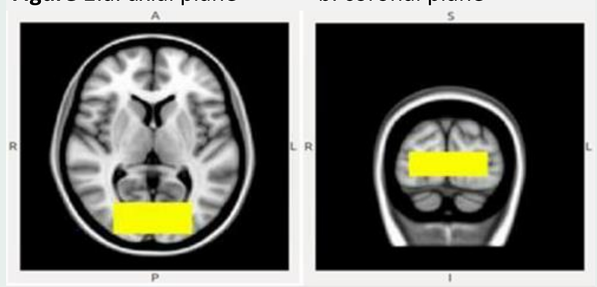
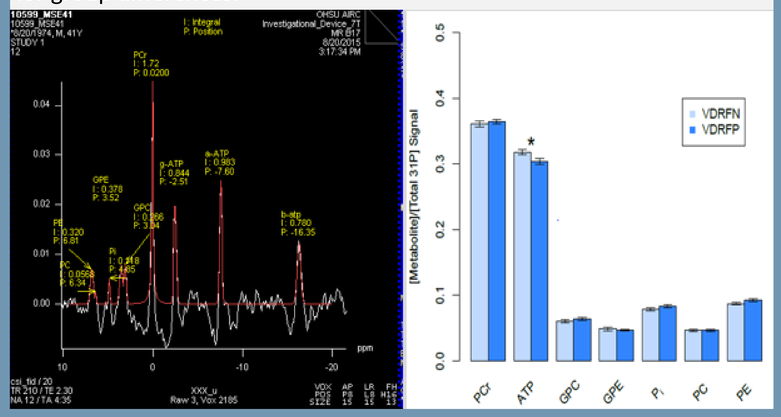


Figure 2: Phosphate metabolite signals (phosphocreatine (PCr), (α,β,γ)-adenosine triphosphate(ATP), glycerophosphocholine(GPC), glycerophosphoethanolamine (GPE), inorganic phosphate (P_i), phosphocholine (PC), phophoethanolamine (PE), were fitted using jMRUI-3.0 from each voxel in a volume of interest from parietal lobe. These fitted signals were normalized by total signal and compared for group differences.



Results

- Data is available in 50 of the original 60 subjects enrolled.
- Adenosine triphosphate (ATP) to total phosphate signal ratio is decreased in VDRFP subjects by 4.5% (P<0.05).
- VDRFP female subjects' normalized brain tissue volume was 3.9% less than VDRFN female subjects (P=0.02, N1=23,N2=13,one-tailed Student's t-test).
- VDRFP males show a similar trend in normalized brain volume, but were limited by sample size (N1=5, N2=9).
- Our baseline data supports the view of an impaired metabolic state in VDRFP MS subjects.

Table 2: Clinical and quality of life measurements (N (SD)

	Total	Positive	Negative
	N=50	N=28	N=22
BMI*	27.3 (5.8)	30.3 (5.7)	23.5 (2.8)
Waist Circumference*	96.6 (13.5)	103.5 (12.6)	87.9 (8.7)
Thigh Circumference*	53.7 (6.9)	56.1 (7.9)	50.6 (3.6)
Expanded Disability Status Scale (EDSS)*	3.9 (1.2)	4.2 (1.1)	3.6 (1.3)
Insulin (mIU/ml)*	9.7 (7.7)	12.4 (9.4)	6.6 (2.8)
Hemoglobin A1C	5.4 (0.6)	5.4 (0.7)	5.3 (0.3)
Cholesterol (mg/dl)*	191.8 (17.4)	199.2 (37.7)	182.7 (28)
HDL (mg/dl)	65.9 (17.4)	65.3 (17.4)	66.6 (17.7)
LDL (mg/dl)	105.8 (29.9)	111.0 (32.1)	99.6 (26.3)
Triglycerides (mg/dl)*	100.3 (48.8)	114.7 (57.8)	82.7 (27.0)
Blood Pressure	124/79	124/80	124/77
Timed Walk (seconds)	6.6 (2.6)	6.7 (1.9)	6.4 (3.3)
9 Hole Peg Test (seconds)			
Dominant Hand	24.4 (6.5)	24.7 (6.9)	24.1 (7.1)
Non-Dominant Hand	25.3 (5.9)	26.0 (6.1)	24.4 (5.7)
Symbol Digit Modality Test	50.7 (13.8)	51.6 (14.2)	49.5 (13.5)
PASAT (% Correct)	69 (20.7)	71 (21.6)	67 (20.0)
Food Frequency Questionnaire			
Fat % of Cal	38 (6.6)	37.5 (6.2)	38.6 (7.1)
Saturated Fat % of Cal	12.2 (3.9)	12.5 (3.6)	11.8 (4.3)
Protein % of Cal	16.1 (2.5)	16.0 (2.6)	16.1 (2.5)
Carbs % of Cal	45.1 (8.3)	46.1 (7.4)	43.8 (9.3)
Becks Depression Questionnaire	8.3 (7.6)	8.8 (7.8)	7.7 (7.5)
Fatigue Severity Scale	4.8 (1.5)	5.0 (1.5)	4.5 (1.4)

*p-value<0.05 for two-tailed student's t-test.

References:
[1]Marrie RA, Rudick R, Horwitz R, et al. Vascular comorbidity is associated with more rapid disability progression in multiple sclerosis. Neurology. 2010;74(13):1041-1047.
[2] S.M. Smith, Y. Zhang, M. Jenkinson, J. Chen, P.M. Matthews, A. Federico, and N. De Stefano. Accurate, robust and automated longitudinal and cross-sectional brain change analysis. NeuroImage, 17(1):479-489, 2002.

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