

Total sodium concentration is increased in lesions and normal appearing white matter in Multiple Sclerosis

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Introduction: Recent histological and animal studies suggest that intra-axonal sodium accumulation may lead to neuro-axonal loss in multiple sclerosis (MS)¹. Increase in the number of voltage gated sodium channels in demyelinated axons may cause increased sodium influx, and mitochondrial functional disruption may reduce available ATP to power Na/K/ATPase leading to a failure to export sodium from the axon.² Sodium is normally distributed into intra and extra cellular compartments in the brain. Whilst around 80% of sodium is within the intracellular compartment, this is at a lower concentration (15mM) as compared to the extracellular compartment (140mM).³ Increases in total sodium could reflect increase in concentration of the intracellular compartment, or could reflect increase in the proportion of the extracellular compartment. In either case an increase in sodium could reflect important pathophysiological processes in MS, i.e., (i) increased intracellular sodium leading to axonal death, and (ii) increased proportion of extracellular sodium resulting from axonal loss. A previous study demonstrated increased total sodium concentration in lesions and normal appearing white matter (NAWM) in patients with relapsing remitting MS.⁴ We created whole brain sodium maps and applied them in a preliminary clinical study of patients with both relapsing remitting and secondary progressive MS and healthy controls.

Methods: MRI images were acquired in 10 patients with MS (mean age 44.8, 4M, 6F, 6 relapsing remitting, 4 secondary progressive) and 6 controls (mean age 43.9, 3M, 3F). The study was approved by the local research ethics committee.

MRI protocol: A 3 Tesla Philips Achieva scanner was used (Philips Healthcare, Best). Sodium scans were performed using a single resonant ²³Na RX/TX birdcage head coil (Rapid, Rimpac, Germany). Sodium scans were acquired using a 2D radial UTE sequence with non-selective 90° block excitation pulse. Parameters were TR=120ms, nominal isotropic voxel size of 4mm, FOV=240mm², 1 average, acquisition time 23 minutes. Two phantoms of concentration 66mmol/L and 33mmol/L were placed adjacent to the skull. ¹H T₁ and T₂ weighted scans were performed immediately afterwards with the same positioning using a 32 channel receive coil. T₁ weighted image was acquired using an MPRAGE sequence with parameters: voxel size 1x1x1, FOV 256x256, TE 3.1ms, TR 6.9ms, TI 824.5ms, Acquisition time 6 minutes 31s. T₂ weighted images were obtained using the 4th echo of a fast multi echo spin echo sequence (equivalent to TE of 64ms) acquired with parameters: voxel size 1x1x2, FOV 240x180x152, TE1 7.1ms ΔTE 6.3ms, TR 5667ms, NEX 1, acquisition time 8 min 47s,

Post processing: Signal intensities from the calibration tubes were obtained and were used to create a two-point linear calibration curve, and this was applied to the sodium intensity images to create total sodium concentration maps.⁵ The T₂ weighted and sodium map image were registered to the T₁ image using in house software. Using the region of interest (ROI) toolkit of JIM 6 (Xinapse systems, www.xinapse.com), 38 anatomically defined ROI 38mm² in area were placed in normal appearing white matter (NAWM) on the T₁ weighted image, 8 in temporal lobe, 14 in frontal lobe, 8 in the parietal lobe, 8 in occipital lobe and 10 in the corpus callosum. MS lesions were identified using the registered T₂ weighted image and outlined using a semi-automated technique based upon local threshold. ROI were applied to the registered total sodium map to calculate mean sodium concentration for NAWM and lesions. Results are presented as mean +/- SD

Results: Sodium was increased in lesions as compared to the NAWM (48.6mM +/- 6.5 vs 36.6mM +/- 2.6, p<0.001 paired t test). Sodium was also increased in the NAWM in patients as compared to controls (36.6mM +/- 2.6 vs 32.2mM +/- 1.8, p=0.005 unpaired t test). There was a trend towards increase in sodium in NAWM in patients with secondary progressive as compared to relapsing remitting MS (38.1mM +/- 1.5 vs 35.5mM +/- 2.7, p=0.09 unpaired t test).

Discussion: Our finding of increased total sodium concentration in lesions and NAWM may represent increase in intra-axonal sodium concentration or increase in proportion of extracellular fluid. Increase in intracellular sodium concentration may be due to increase in sodium channel concentration in demyelinated axons with insufficient ATP production to power sodium export via Na/K/ATPase.^{1,2} Increase extracellular fluid proportion could be secondary to secondary to increased blood volume, oedema, or axonal loss.¹ The only previous sodium imaging study in MS was in relapsing remitting MS⁴ and the trend for higher NAWM sodium in SPMS in our study suggests the potential total sodium concentration to be a marker of clinical disability and progression in MS. Further studies of larger cohorts will be undertaken to definitively study sodium abnormalities in MS clinical sub-groups and the relationship with disability.

References.

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Figure 1: T2 weighted and sodium map from a 60 year old patient with secondary progressive MS. Large increase in sodium can be seen in a large lesion (arrowed)

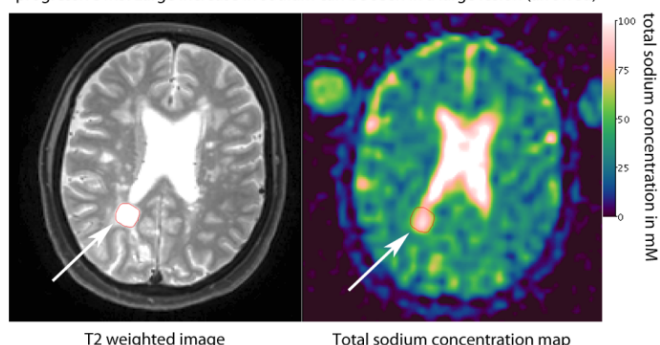


Figure 2: Graph of total sodium concentration in patients and controls

