Blood permeability imaging of proximal nerve segments in peripheral neuropathies

Progress Report

Dr E J Rodrigues MBChB FRACP Neurology

Background

Immune mediated inflammatory peripheral neuropathies such as Guillain Barre Syndrome (GBS), and Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP) are an important group of treatable conditions in neuromuscular medicine. There is no gold standard test to diagnose these neuropathies and no biomarker to monitor disease progression and / or treatment response. Although electrophysiological criteria to diagnose demyelination have evolved over the last 40-50 years especially with regard to CIDP, these criteria were still designed originally for research purposes rather than to select patients who are treatment responsive. (1-4) There is also considerable overlap in electromyography (EMG) findings in patients with CIDP and late onset genetic demyelinating neuropathies as well as neuropathies due to diabetes and paraproteinemic neuropathies. (4-7) In addition to these recently described nodopathies and paranodopathies may have axonal changes rather than demyelinating changes on EMG. (8,9) Thus, misdiagnosis of CIDP in patients with genetic or other disorders may lead to inappropriate use of immunomodulatory agents or inadequate therapy in neuropathies that may not be responsive to first line agents.

Disruption of the blood nerve barrier (BNB) is an important common pathway in the pathogenesis of all inflammatory neuropathies. In-vivo assessment of BNB disruption in patients with inflammatory neuropathies especially in proximal nerve segments may have potential to as a biomarker in the diagnosis and management of these disorders. (10-12) Regional blood flow and blood nerve perfusion in proximal nerve segments where the BNB may be more susceptible may be a surrogate for BNB disruption in patients with inflammatory neuropathies. CT and MRI techniques have been used successfully to define cerebral blood perfusion and select patients who may benefit from reperfusion therapy. Whilst there have been several studies that have used MRI imaging in the evaluation of peripheral nerves in inflammatory neuropathies such as chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) and multifocal motor neuropathy (MMN), only a few studies have used perfusion imaging techniques to study the blood flow in proximal nerve segments.(13-17) These studies have demonstrated increased blood nerve permeability in proximal nerve segments in large fibre neuropathies using DCE MRI.(16,17) MRI perfusion may have potential as a biomarker in the diagnosis and management of patients with inflammatory neuropathies.

The aim of this study was to investigate the utility of DCE MRI techniques to examine the blood permeability of proximal nerve segments in patients with peripheral neuropathies. We hypothesize that blood nerve permeability measures will enable differentiation of genetic from inflammatory demyelinating neuropathies, correlate with disease relapse and stability.

Methods

We recruited patients from the Alfred inpatient and outpatient departments with inflammatory and genetic neuropathies. Patients who were undergoing gadolinium enhanced MRI scans post lumbar discectomy surgery formed the control group for our study. The inclusion and exclusion criteria were as follows.

Inclusion Criteria	***Exclusion criteria***
1. Age > 18 2. Diagnosis of genetic demyelinating neuropathy with known genetic mutation	1. Contraindications to MRI being performed including presence of possible metallic foreign bodies

3. Diagnosis of definite or probable CIDP according to the EFNS / PNS criteria[1] including MADSAM, Ig A and Ig G paraproteinemic demyelinating neuropathy 4. Diagnosis of definite or probable MMN with conduction block 5. Patients yet to commence treatment with IVIG or patients who are stable on IVIG treatment. 6. Significant disability with adjusted ONLS score of at least two for patients with new diagnosis. 7. Patients who have been on IVIG treatment for 12 months without any changes to frequency or IVIG dose in the preceding 6 months. 8. Consent	2. Claustrophobia or need for a general anaesthetic to tolerate an MRI 3. Respiratory involvement requiring mechanical ventilation 5. Known allergic reaction to Gadolinium or other contrast agents 6. Malignancy or active infection including Hepatitis B, Hepatitis C or HIV infection 7. Unstable ischemic heart disease or Heart failure – NYHA class III or above 8. Liver disease (ALT or AST 3x greater than normal) and renal failure (creatinine 1.5 x) 9. Diabetes with HbA1C > 6.0 10. Pregnant or breast-feeding women or female patients planning pregnancy in the following six months.

TABLE 1: Inclusion and Exclusion criteria

MRI examinations were carried out at 3T magnetic field strength. T-2 weighted sequence of the spine for imaging of the lumbosacral plexus from the second lumbar vertebrae to the coccyx, with fat saturation will be obtained for recognition and segmentation of the nerve roots, dorsal root ganglion (DRG) and mixed spinal nerve. A T1-weighted DCE volume interpolated breath-hold (VIBE) sequence examination sequence was acquired for detection of before and after contrast administration at the same position to aid further quantitative analysis. MRI contrast medium (Gadavist- Bayer) will injected at a rate of 5 mL/s followed by a 20-mL bolus of sodium chloride solution at 5 mL/s. A total of 100 images will be acquired at 10-second intervals with the injection occurring at the 10th image. Regional nerve blood permeability (K^{trans}) maps for nerve roots, DRG and mixed spinal nerve were generated using a modified Patlak linearized regression mathematical analysis. The arterial input function (AIF) was derived from the aorta in each patient instead of using an average value from the inferior vena cava to determine tracer concentration in blood. Region of interest analysis was performed in these nerve segments to derive the K^{trans}. We have performed DCE MRI previously on various pathologies such as brain gliomas to hippocampi in patients with Alzheimer's disease. We are choosing a Patlak modeling approach in this setting over a Toft 2-compartment pharmaco-kinetic model for example because the permeability is felt to lie somewhere between a very leaky tumor versus a slowly leaking – non enhancing hippocampus in neurodegenerative diseases.

We calculated the ratio of the Ktrans in the DRG to the Motor root (DRG Ratio) and the Mixed spinal nerve to the Motor root (MSN Ratio) in patients with genetic neuropathies and CIDP as well as controls bilaterally at the L4, L5 and S1 levels. Patients with CIDP included patients with active disease (new diagnosis or relapse) and patients who were stable on treatment. The medians between the groups were compared with the Kruskal-Wallis Test.

Results

We analyzed MRI scans of six patients with genetic neuropathies, six controls and 8 patients with CIDP. Of these 8 patients 3 had stable disease and the remainder were patients with active disease (new diagnosis or relapse)

The Ktrans ratio of the DRG to the motor root was similar in patients with genetic neuropathies, controls, and patients with active CIDP. Patients with stable CIDP had higher Ratio DRG ($P<0.05$). The Ktrans ratio of the mixed spinal nerve to the motor root was higher in patients with stable CIDP ($P<0.05$). There was a trend to lower MSN ratios in the genetic patients and higher MSN ratios in the active CIDP patients respectively, but these differences did not meet statistical significance.

The MSN ratio was similar to the DRG ratio in patients with genetic neuropathies and controls. However, in patients with active CIDP and stable CIDP the MSN ratio was higher than the DRG ratio, but again with the current numbers of patients analysed, this difference failed to meet statistical significance.

In patients with active disease there was moderate correlation between objective measures of disease severity and the MSN ratio but weak or no correlation between subjective measures of disease severity and the MSN ratio.

Conclusions

These results further support our hypothesis that the blood nerve barrier is most vulnerable at the level of the mixed spinal nerve in patients with CIDP. Patients with genetic neuropathies had blood nerve permeability that was comparable to that of our controls and lower than patients with CIDP. Blood nerve permeability at the level of the mixed spinal nerve may be indicative of patients with stable CIDP and could be used to as another parameter to monitor disease relapse especially in patients being weaned or trialed off immunomodulatory treatment. DCE MRI imaging of nerve roots and mixed spinal nerves may offer more objective measures in addition to nerve root enhancement and hyperintensity in patients with CIDP.

References

1. Bromberg MB. Review of the evolution of electrodiagnostic criteria for chronic inflammatory demyelinating polyradicoloneuropathy. Muscle and Nerve. 2011;43(6):780-94.
2. Van den Bergh PY, Hadden RD, Bouche P, Cornblath DR, Hahn A, Illa I, et al. European Federation of Neurological Societies/Peripheral Nerve Society guideline on management of chronic inflammatory demyelinating polyradiculoneuropathy: report of a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society - first revision. Eur J Neurol. 2010;17(3):356-63.
3. Van den Bergh PYK, van Doorn PA, Hadden RDM, Avau B, Vankrunkelsven P, Allen JA, et al. European Academy of Neurology/Peripheral Nerve Society guideline on diagnosis and treatment of chronic inflammatory demyelinating polyradiculoneuropathy: Report of a joint Task Force-Second revision. J Peripher Nerv Syst. 2021;26(3):242-68.
4. Sharma KR, Cross J, Farronay O, Ayyar DR, Shebert RT, Bradley WG. Demyelinating neuropathy in diabetes mellitus. Arch Neurol. 2002;59(5):758-65.

5. Bril V, Blanchette CM, Noone JM, Runken MC, Gelinas D, Russell JW. The dilemma of diabetes in chronic inflammatory demyelinating polyneuropathy. Journal of Diabetes and its Complications. 2016;30(7):1401-7.
6. Mathis S, Magy L, Diallo L, Boukhris S, Vallat J-M. Amyloid neuropathy mimicking chronic inflammatory demyelinating polyneuropathy. Muscle Nerve. 2012;45(1):26-31.
7. Tracy JA, Dyck PJ, Klein CJ, Engelstad JK, Meyer JE, Dyck PJB. Onion-bulb patterns predict acquired or inherited demyelinating polyneuropathy. Muscle Nerve. 2019;59(6):665-70.
8. Mathey EK, Park SB, Hughes RA, Pollard JD, Armati PJ, Barnett MH, et al. Chronic inflammatory demyelinating polyradiculoneuropathy: from pathology to phenotype. J Neurol Neurosurg Psychiatry. 2015;86(9):973-85.
9. Querol L, Devaux J, Rojas-Garcia R, Illa I. Autoantibodies in chronic inflammatory neuropathies: diagnostic and therapeutic implications. Nature Reviews Neurology. 2017;13(9):533-47.
10. Kanda T. Biology of the blood-nerve barrier and its alteration in immune mediated neuropathies. J Neurol Neurosurg Psychiatry. 2013;84(2):208-12.
11. Shimizu F, Kanda T. Breakdown of blood-nerve barrier in immune-mediated neuropathy. Clinical and Experimental Neuroimmunology. 2015;6(2):139-48.
12. Shimizu F, Sawai S, Sano Y, Beppu M, Misawa S, Nishihara H, et al. Severity and patterns of blood-nerve barrier breakdown in patients with chronic inflammatory demyelinating polyradiculoneuropathy: correlations with clinical subtypes. PLoS ONE. 2014;9(8):e104205.
13. Hofstadler B, Bäumer P, Schwarz D, Kronlage M, Heiland S, Bendszus M, et al. MR Neurography: Normative Values in Correlation to Demographic Determinants in Children and Adolescents. Clinical Neuroradiology. 2020;30(4):671-7.
14. Kronlage M, Bäumer P, Pitarokoili K, Schwarz D, Schwehr V, Godel T, et al. Large coverage MR neurography in CIDP: diagnostic accuracy and electrophysiological correlation. J Neurol. 2017;264(7):1434-43.
15. Kronlage M, Pitarokoili K, Schwarz D, Godel T, Heiland S, Yoon MS, et al. Diffusion Tensor Imaging in Chronic Inflammatory Demyelinating Polyneuropathy: Diagnostic Accuracy and Correlation with Electrophysiology. Investigative Radiology. 2017;52(11):701-7.
16. Kronlage M, Schwehr V, Schwarz D, Godel T, Heiland S, Bendszus M, et al. Magnetic Resonance Neurography: Normal Values and Demographic Determinants of Nerve Caliber and T2 Relaxometry in 60 healthy individuals. Clinical Neuroradiology. 2019;29(1):19-26.
17. Bäumer P, Reimann M, Decker C, Radbruch A, Bendszus M, Heiland S, et al. Peripheral nerve perfusion by dynamic contrast-enhanced magnetic resonance imaging: Demonstration of feasibility. Investigative Radiology. 2014;49(8):518-23.