2328 THE LANDSCAPE OF PERIPHERAL NEUROPATHY GENETICS: WHEN COMMON CAUSES ARE NOT ACTUALLY THE CAUSE

Mona Saleh*, [1]Jennifer Roggenbuck, [2]Asia Mitchel, [2]Ana Morales, [2]Molly Stetler, [2]Chris Tan, [2]Swaroop Aradhya, [2]Dianalee McKnight, [2]Tom Winder, [2]Edward D Esplin. *[1]The Ohio State University, Columbus, Ohio, USA; [2]Invitae, San Francisco, CA, USA*

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Objectives Peripheral neuropathies (PN) have a prevalence of up to 8% in individuals > 55 years. Consensus suggests clinical evaluation of PN should include screening for acquired causes followed by genetic testing for *PMP22*, *MFN2*, *GJB1*, and *MPZ* in individuals with a positive family history and symptom onset <50 years. We report outcomes from a retrospective analysis of a sequential cohort of affected individuals referred for genetic testing.

Methods 6,849 adult probands underwent PN multigene panel testing. A molecular diagnosis was defined as either a single pathogenic/likely pathogenic (P/LP) variant in an autosomal dominant or X-linked gene, or two P/LP (homozygous) variants in a recessive gene.

Results Of 6,849 probands, 899 (13.1%) had P/LP variants. *PMP22*, *MFN2*, *GJB1*, *MPZ*, and *TTR* accounted for 73% of molecular diagnoses. Of those who tested positive, 84% (231/275) had a positive family history and symptoms appeared at 31.1 years on average. 73/573 (12.7%) could have been missed if genetic testing was not pursued due to: first documented symptoms at age = or > 50; an explicitly stated negative family history; or documentation of a presumed acquired aetiology. 152/573 (26.5%) would be missed if testing was restricted to *PMP22*, *MFN2*, *GJB1*, and *MPZ*. 225/573 (39.3%) of molecular diagnoses would have been missed if only published indications for genetic testing had been followed.

Conclusion Genetic testing may identify P/LP results in up to 13% of individuals affected with PN. Nearly half of those with P/LP variants would be missed by published genetic testing recommendations.

2329 INNOVATIVE COMPARATIVE STUDY ASSESSING THE EFFECT OF SIPONIMOD ON REACTIVE MICROGLIA/ASTROCYTES IN PATIENTS WITH SECONDARY PROGRESSIVE MULTIPLE SCLEROSIS: STUDY DESIGN

[1]Robert Walker*, [2,3,4]Robert Zivadinov, [2]Bianca Weinstock-Guttman, [2]Ralph Benedict, [2,3,4]Michael G Dwyer, [2,3,4]Ferdinand Schweser, [3]Dejan Jakimovski, [2,3]Niels Bergsland, [5]Daniela Piani-Meier, [5]Harold Kropshofer. *[1]Novartis, Macquarie Park, NSW, Australia; [2]Department of Neurology, University at Buffalo, Buffalo; [3]Buffalo Neuroimaging Analysis Centre, Buffalo; [4]Center for Biomedical Imaging, Clinical and Translational Science Institute, University at Buffalo, Buffalo; [5]Novartis Pharma AG, Basel*

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Objective To assess the effect of siponimod, compared to ocrelizumab, on reactive microglia/astrocytes using positron emission tomography (PET) and magnetic resonance imaging (MRI) in patients with active secondary progressive multiple sclerosis (aSPMS).

Methods An open-label, single-blinded (MRI analysis), observational, comparative, prospective, 36-month, adaptive study will be conducted in aSPMS patients (aged 18–60 years with evidence of clinical and/or MRI disease activity [Lublin 2014 Criteria] and EDSS of 3.0 to 6.5). Following enrollment of each SPMS patient starting siponimod treatment, a matching (ratio 1:1) of SPMS patient starting ocrelizumab treatment will be enrolled. PET, MRI, serum biomarker, and clinical and cognitive assessments will be conducted at 0, 6, 12, 24 and 36 months.

Results The study plans to enroll 60 patients with aSPMS who are treatment-naïve to siponimod/ocrelizumab. The primary endpoint is change from baseline in PET-activation of PBR06 in lesional/non-lesional normal appearing (NA) WM, NAGM, and peri-plaque area of chronic lesions. Secondary endpoints include change in PET-activation of PBR06 in these areas between siponimod and ocrelizumab groups, and cumulative number of ultra-small superparamagnetic particle iron oxide-positive lesions on MRI between two treatment arms. First and second interim-analyses are planned after 50% and 100% of ongoing patients have reached month 12. The first-patient-first-visit is scheduled in October 2021.

Conclusions This is the first and largest PET/MRI imaging/biosignature study in MS evaluating siponimod's effect on microglia/astrocyte activation compared with ocrelizumab.

2331 CHALLENGES OF MANAGING CRYPTOCOCCAL MENINGITIS IN PREGNANCY

[1]Sophie Chatterton*, [2]James Montgomery, [2]Eunice Liu, [1]Michal Lubomski. *[1]Department of Neurology, Royal North Shore Hospital, Sydney, NSW, Australia; [2]Department of Microbiology and Infectious Diseases, Royal North Shore Hospital, St Leonards, NSW, Australia*

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A 33 year-old female at 32/40 (G1P0) presented with refractory headaches. Medical history included asthma and her pregnancy had been previously uncomplicated, aside from two flares of asthma requiring brief courses of prednisone. Regular medication included inhaled fluticasone propionate/formoterol fumarate. She was diagnosed with migraines and discharged after high dose aspirin. She represented the following day with worsening headaches, nuchal rigidity and fevers. CSF evaluation showed opening pressures of 31 mmH_2O and predominant mononuclear pleocytosis. *Cryptococcus gattii* was subsequently detected from fungal cultures. Directed treatment included liposomal amphotericin and flucytosine. Initial MRI brain showed no evidence of raised intracranial pressure or cryptococcomas. During her prolonged admission, she experienced refractory headaches and raised ICP requiring successive therapeutic lumbar punctures and later insertion of a lumbar drain. Sequential MRIs demonstrated evolution of multiple cryptococcomas throughout her basal ganglia, supratentorial brain and cerebellum without significant mass effect. Immunosuppression screening was unremarkable. After three weeks of antifungal therapy her headaches settled. Complications of induction therapy included amphotericin-induced nephrotoxicity and peripartum hypokalaemia. She delivered a healthy newborn by elective caesarean section at 37+ 5 weeks and was discharged home without neurological deficit with HITH. Progress MRIs with gadolinium (postpartum) continue to show significant improvement in her cryptococcomas and resolving leptomeningeal changes. Notably, she did not develop cryptococcal-IRIS postpartum. After six weeks she was changed to fluconazole, which she will remain on for a further 12–18 months.

Conclusions *C. gattii* meningitis in pregnancy is uncommon, poses many therapeutic challenges and requires a collaborative multidisciplinary approach.