Young Investigators Presentation Abstracts

1 PATIENT-DETERMINED DISEASE STEPS IS NOT EQUIVALENT TO THE EXPANDED DISABILITY STATUS SCALE IN MILD TO MODERATE MULTIPLE SCLEROSIS

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Background Patient Determined Disease Steps(PDDS) is a common patient-reported outcome(PRO) in multiple sclerosis(MS). However, concerns remain over its validity and reliability in mild to moderate disability, longitudinal performance and confounding due to mood disorders.

Objectives We aimed to examine the psychometric properties of the PDDS in people with MS(pwMS), to explore longitudinal associations between expanded disability status scale(EDSS) and PDDS, and examine the impact of mood on PDDS.

Methods We prospectively enrolled relapsing-remitting multiple sclerosis(RRMS) patients with mild to moderate disability. Participants completed an iPad-based version of the PDDS, other PROs and EDSS 6-monthly. Test-retest reliability and validity was assessed. Longitudinal data was examined with mixed effect modelling.

Results We enrolled 904 RRMS patients with a median age of 40.9years, median EDSS of 1.5 and median PDDS of 0. The baseline correlation between PDDS and EDSS was weak. Correlations between functional systems(FS), age, disease duration and processing speed test(PST) and EDSS were stronger compared to PDDS. Conversely, correlations between PROs and PDDS were stronger. PDDS test-retest reliability was good to excellent. Longitudinally, PDDS was weakly associated with EDSS, depression and quality-of-life scores. Higher EDSS was associated with greater progression in PDSS. The magnitude of these associations were small.

Conclusion The PDDS differs from the EDSS in its psychometric properties, and should not be used interchangeably. The discordance in the aspects of disability that the PDDS measures may explain the small magnitude of longitudinal and cross-sectional associations. Modifying the PDDS to better detect under-reported symptoms such as bladder and bowel dysfunction may improve its validity.

2 VALIDATION OF DAYS ALIVE AND OUT OF HOSPITAL AS A MEASURE OF STROKE OUTCOME IN PATIENTS RECEIVING HYPERACUTE STROKE INTERVENTION

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Objectives Patient outcome after stroke is frequently assessed with the modified Rankin Scale score, which is a 7-level ordinal scale from 0 – no disability, to 6- dead. The mRS can be prone to bias and can have significant inter-rater variability. Days alive and out of hospital at 90 days (DAOH-90) is an objective, readily available outcome measure that accounts for survival, time spent in hospital or rehabilitation settings, readmission, and institutionalisation. We aimed to assess the criterion and construct validity of DAOH.

Methods Consecutive ischemic stroke patients treated with thrombolysis or endovascular thrombectomy were used in this analysis. DAOH-90 was calculated from the national minimum dataset. mRS was assessed with in-person or telephone interviews. Simple descriptive statistics were applied (median [IQR]). The ability of DAOH-90 to distinguish between the commonly applied cut-points of mRS-90 was assessed using the area under the receiver operating curve (AUROC).

Results 1278 ischemic stroke patients (714 male, median age 70 [59–79], median NIHSS 14 [9–20]) were included in this study. There was a strong association between mRS-90 and DAOH-90 (spearman rho correlation – 0.78, $p<0.001$). AUROC (95% CI) for predicting mRS>0, mRS>1, mRS>2 were 0.86 (0.84–0.88), AUC 0.88 (0.86–0.90), AUC 0.90 (0.89–0.92) respectively. DAOH-90 was significantly correlated with age (rho -0.13, $p<0.001$), admission NIHSS (rho -0.44, $p<0.001$) and Alberta stroke programme early CT score (spearman rho 0.24, $p<0.001$).

Conclusion DAOH is an objective, patient-centric outcome measure that can be determined from large datasets and therefore its place in stroke research warrants further study.

3 DEEP LEARNING CLASSIFICATION OF POSTERIOR CIRCULATION INFARCTION USING CT PERFUSION

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Objectives Posterior circulation infarction (POCI) is a common but frequently missed diagnosis. Hyper acute POCI is poorly visualised using traditional CT and MRI sequences. Deep learning is a branch of artificial intelligence, which facilitates automated detection of imaging features not readily identified by clinicians. We aimed to develop a novel convolutional neural network (CNN) to classify POCI using CT perfusion (CTP).

Methods Data were analysed from the International-stroke-perfusion-registry (INSPIRE). Patients with baseline multimodal-CT and follow up diffusion-weighted MRI at 24–48 hours were included. Patients with POCI on follow up MRI were identified. A reference group of randomly selected patients with non-POCI diagnosis were collated to form a dataset in a 1:4 POCI to reference-ratio. A 3D-DenseNet was trained to classify participants into POCI or non-POCI using CTP deconvolved maps.

Results Eighty-eight patients with POCI were included (median age: 69 with interquartile range [60- 78]; NIHSS at baseline: 8 [5–14]; DWI lesion volume: 3 [0.6–16] ml). Three-hundred-two patients were included in the reference group (median age: 72.5 [61–80.8]; NIHSS at baseline: 12 [6–17]; DWI lesion volume: 15.1 [3–50] ml). Optimal model performed was achieved using Delay Time (DT) maps with an accuracy of 0.89 (sensitivity: 0.77; specificity: 1). Mean Transit Time and Cerebral Blood Flow yielded lower but acceptable accuracies of 0.83 (sensitivity/specificity: 0.61/0.97) and 0.80 (sensitivity/specificity: 0.51/0.97), respectively.

Conclusions Classification of POCI using a CNN is highly accurate. Optimal model performance was achieved using DT maps. A CNN classification model may aid in the rapid and accurate diagnosis of POCI.

4 SERUM NEUROFILAMENT LIGHT CHAIN IN HEREDITARY TRANSTHYRETIN AMYLOIDOSIS: A VALIDATION STUDY

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Objectives Sensitive biomarkers of disease and progression are needed in hereditary transthyretin amyloidosis (ATTRv). Neurofilament light chain (NfL) has emerged as a potential biomarker, however, appropriate cut-off values, alteration longitudinally and applicability in real-world settings requires evaluation.

Methods NfL levels were measured longitudinally (2015–2022), in presymptomatic and symptomatic ATTR variant carriers. Correlations between NfL and demographics, renal function, examination, and staging scores were performed. ROC analyses were performed to determine cut-off values. NfL changes longitudinally were explored, pre-treatment, in asymptomatic and symptomatic cohorts, and converters to sensory or motor neuropathy via mixed-effect models.

Results 59 individuals with mixed ATTR variants (26=T60A, 12=V30M, 21=other [including G47V/V112I/S77Y/A97S]) and PND scores (0=18, 1=19, 2=9, >3=13) were studied over maximum follow-up of 4.75 years.

No correlations were found between NfL and age, creatinine, eGFR, gender or mutation. NfL correlated with CMTNS (r=0.56, p=0.002), NIS (r=0.5, p=0.0014), and MRC scores (r=-0.57, p<0.001). NfL significantly differed between PND0 and PND2, PND3A and PND3B (all p<0.003), and PND1 and PND3B (p= 0.047). NfL differed between FAP2 and FAP0 (p= 0.001) and FAP1 (p=0.03). Patients with PND>2, were discriminated from PND0–1, by NfL>52.2pg/ml (AUC=0.83; 95%CI:0.71–0.95; sensitivity=100%, specificity=55.5%).

NfL was higher in symptomatic and motor converters, than in asymptomatic or sensory converters, irrespective of time (all p<0.001). Symptomatic or motor converters were discriminated from asymptomatic by NfL>64.5pg/ml (AUC=0.95; 95%CI:0.90–0.99; sensitivity= 91.9%, specificity=88.5%).

Conclusions This study proposes NfL cut-off values for conversion to symptomatic disease and validates the use of NfL to monitor disease activity and progression in ATTRv.

5 AHSCT AS IMMUNE RECONSTITUTION THERAPY FOR MS – RESETTING THE IMMUNE SYSTEM OR DEPLETING EBV RESERVOIRS?

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Objectives It is established that autologous haematopoietic stem cell transplant (AHSCT) is a high-efficacy form of therapy for MS patients who have active disease despite pharmacotherapy; inducing protracted disease remission. Despite the import of EBV in MS pathogenesis no study has reviewed the effect of AHSCT on EBV viraemia, anti-EBV T and B cell immunity, nor latent viral load. Here, we study immune reconstitution which follows AHSCT to parse the role of EBV infection, anti-EBV immunity and its impact on MS.

Methods Bio-banked peripheral blood mononuclear cells (PBMCs) and platelet depleted plasma (PDP) were collected from MS patients enrolled in a phase 2 clinical trial (ACTRN12613000339752) pre-AHSCT, and at months 3, 6, 12, 24 and 36 post-AHSCT, n=22. Repertoire sequencing of TCRb chains were amplified from FAC-sorted CD4/CD8 naïve and memory cells. Longitudinal EBV-avid TCR responses were assessed through HLA-restricted repositories (VDJdb.com). EBNA IgG titres were analysed using the Abbott EBNA IgG kit. EBV viraemia and EBV genome load per cell was calculated using qPCR.

Results EBV DNAemia was rare beyond 3 months post-AHSCT, occurring in 3/22 individuals. DNAemia correlated with detectable EBV-specific T cell responses, clonal expansions of CD8+45RO+ T cells targeting both lytic and latent EBV epitopes. EBNA1 titres were preserved in 19 patients, and fell in 3 patients, all of whom relapsed post-AHSCT. EBV genome load within memory B cells increased concurrent with relapse in a single patient, 13 months post-AHSCT.

Conclusions Perturbations in EBV viral load and anti-EBV immunity appear to associate with relapse post-AHSCT.