Parallel Session 4: Muscle/NMJ/Peripheral Nerve

Thu 7 May, 17:15 - 18:15

Hall 5

1. Evaluating the Genetic Mutations in ALS: **Adithya Ajith**
2. A novel gene therapy for motor neuron disease (MND): **Puja Mehta**
3. Efgartigimod efficacy and safety in refractory myasthenia gravis: multi-centre, longitudinal experience in the United Kingdom: **Aravindhan Baheerathan**
4. Quantitative MRI of forearm muscles as a biomarker in inclusion body myositis: **Sharfaraz Salam**
5. The Outcome of Guillain-Barre Syndrome in ICU: A Retrospective Single Centre Cohort: **Rachel Young**
6. How is CIDP managed in the UK? A cross-sectional survey of peripheral nerve experts: **Stephen Keddie**

Evaluating the Genetic Mutations in ALS

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Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disorder with substantial clinical and genetic heterogeneity. Multiple genes have already been identified as being involved in ALS pathogenesis, many of which are implicated in protein trafficking, neuroinflammation, and RNA metabolism.

This project aimed to characterise genetic variants identified through the NECTAR screening programme within the AMBRoSIA cohort and assess their potential importance in the pathophysiology of ALS.

Anonymised samples were analysed using next-generation sequencing with a 42-gene ALS/FTD panel. Variants were evaluated using MutationTaster for predicted functional impact and gnomAD for population frequency and annotation. Majority of the variants were predicted to be benign or likely benign, with a few found to be of uncertain significance.

Seventeen variants were identified, including missense, synonymous, intronic, and repeat expansion variants. Several showed discordant pathogenicity predictions across databases, highlighting challenges in variant classification. The DCTN1 variant remains of uncertain significance despite involvement in axonal transport and autophagy pathways, while the SQSTM1 variant is likely benign but occurs in a gene central to proteostasis. These findings underline the complexity of ALS genetics and the need for integrated genetic, functional, and clinical approaches to improve variant interpretation and biomarker development.

A novel gene therapy for motor neuron disease (MND)

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Background: Motor neuron disease (MND) is a paralysing, rapidly fatal neurodegenerative illness, with one globally licensed disease-modifying treatment for most, prolonging survival by ~2-3 months.

>97% of patients exhibit 'TDP-43 proteinopathy' (nuclear-to-cytoplasmic mislocalisation of the RNA-binding protein, TDP-43). This nuclear loss is a key disease-driver, via mis-splicing of pre-mRNAs and erroneous inclusion of usually intronic sequences, termed 'cryptic exons' (CEs). Specifically, this results in loss of two proteins with critical roles in neurite outgrowth (STMN2) and synaptic transmission (UNC13A).

Therapeutic U7 snRNAs ('tU7s') have shown promise in other disorders of splicing. Their small size affords unique advantages over other technologies: i) multiple disease-relevant CEs can be targeted simultaneously; and ii) tU7s can be packaged into a non-pathogenic viral vector for stable expression, meaning a single lumbar puncture provides lifelong benefit, compared with treatments prone to degradation requiring repeated delivery.

Results: Our 'Combined-2x-tU7' corrects STMN2 and UNC13A mis-splicing simultaneously. Using TDP-43-depleted human stem cell-derived motor neurons to model MND in vitro, our STMN2-tU7 rescues neurite outgrowth, and our UNC13A-tU7 rescues synaptic activity. Furthermore, tU7s demonstrate target engagement in vivo in mice

Conclusion: These promising pre-clinical data position single-use tU7s as a state-of-the-art technology with exciting translational potential for people with MND.

Efgartigimod efficacy and safety in refractory myasthenia gravis: multi-centre, longitudinal experience in the United Kingdom

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Despite advances in therapeutics, 15-25% of patients with generalised myasthenia gravis (gMG) remain refractory to standard therapeutics. Efgartigimod is efficacious, safe and well tolerated in patients with treatment-resistant gMG. This multi-centre observational study aims to provide long-term real-world experience of patients treated with efgartigimod across the UK. Prospective data was collected from November 2022 to August 2025 in patients treated with efgartigimod within selected centres. 106 patients were treated with efgartigimod across 9 centres. Mean disease duration was 13.3 years (1-43 years), mean MG-ADL pre treatment was 11.1 (3-20) and mean prednisolone dose was 16mg (0-60). 41 (38.7%) patients had previously been treated with rituximab.

The mean number of treatment cycles was 8.22 (1-37), 35% were treated intravenously whilst the remainder were treated subcutaneously. 26.4% of patients achieved minimal symptom expression at some stage during their treatment. 43.4% of patients reduced their prednisolone dose with a mean reduction of 14.3mg (1-55mg) 9.4% of patients were able to reduce or stop their non-steroidal immunosuppression. 10.3% of patients required rescue treatment with IVIg or TPE as rescue treatment. 73.5% of patients continue treatment. Treatment with long-term efgartigimod is consistently efficacious, safe and well tolerated in patients with treatment resistant gMG.

Quantitative MRI of forearm muscles as a biomarker in inclusion body myositis

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Our group has demonstrated quantitative MRI (qMRI) of the lower limb muscles to be a valid and responsive outcome measure. Weakness of the finger flexors is a characteristic clinical feature of inclusion body myositis (IBM), especially flexor digitorum profundus (FDP). We aimed to characterise changes within the forearm muscles of IBM participants using qMRI measurements and assess the utility of forearm qMRI as a biomarker.

Twenty-one IBM participants and fourteen matched healthy volunteers underwent qMRI at baseline and 12 months, including measurements of fat-fraction (FF), remaining muscle area (RMA), muscle water T2 (T2m) and apparent fat-fraction (FFa). IBM participants underwent clinical assessments of upper limb strength and function.

qMRI measurements for the whole forearm compartment were significantly different in IBM participants compared to healthy controls ($p<0.001$). FF, RMA, and FFa measurements of the forearm showed high construct validity, supported by strong correlations with clinical assessments. FF, RMA and FFa of the whole forearm and FDP demonstrated large responsiveness to disease progression (SRMs>0.9; $p<0.001$) at follow-up. Longitudinal changes in the RMA of FDP correlated strongly with changes in grip myometry ($p<0.05$).

qMRI measurements of the forearm muscles particularly FDP, revealed progressive fat accumulation and atrophy in IBM, emerging as promising biomarkers.

The Outcome of Guillain-Barre Syndrome in ICU: A Retrospective Single Centre Cohort

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Background: Guillain–Barré syndrome (GBS) is an autoimmune polyradiculoneuropathy that causes acute flaccid paralysis. Severe cases require critical care admission due to respiratory failure, bulbar weakness, and dysautonomia. Early prognostication may aid risk stratification and reduce mortality.

Methods: We retrospectively reviewed patients with GBS admitted to critical care at Salford Royal Hospital from 02/08/2022 to 28/02/2025. Data was extracted from electronic records and included demographics, severity scores, treatment, respiratory support, complications, and outcomes. Continuous variables were summarised as mean ± standard deviation and compared using Student's t-test. Categorical variables were analysed using Fisher's exact test.

Results: Nine patients were included; mortality rate was 22.2% (n=2). Non-survivors were older and frailer than survivors (mean age 74.5 vs 53.1 years, p=0.048), with higher EGOS scores (11.5 vs 7.0) and severe weakness at presentation (MRC sum ≤30 in 100% vs 14.3%). Axonal subtypes, preceding illness, and cardiac dysautonomia were only observed amongst non-survivors. Intravenous immunoglobulin was the predominant treatment. All non-survivors required prolonged invasive ventilation and nutritional support. Pneumonia occurred in all non-survivors and 71.4% of survivors.

Conclusions: Older age, greater disease severity, dysautonomia, prolonged respiratory dependence, and pneumonia were associated with poorer outcomes. Larger multicentre studies are required to validate these findings.

How is CIDP managed in the UK? A cross-sectional survey of peripheral nerve experts

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Background: CIDP diagnosis and management is challenging. Although guidelines exist, practice amongst peripheral nerve specialists remains varied. This study explores current diagnostic and treatment practices in the UK and identifies factors contributing to this variability.

Methods: Cross-sectional survey of British Peripheral Nerve Society members, focusing on diagnostic approaches and treatment strategies.

Results: 30 peripheral nerve experts responded. EFNS/PNS guidelines were used by 63% to establish diagnosis. 40% reported using lumbar puncture in most to all cases (75-100%) for diagnosis, while neurophysiology was considered essential by all. IVIG was the preferred first-line therapy (70%), due to effectiveness and rapid onset. Most clinicians (65%) administer two IVIG courses (2 g/kg) separated by 4–6 weeks and use deterioration to define dosing interval. When patients deteriorate, 36% increase dose and 24% increase frequency. In clinically stable patients, 36% stop IVIG abruptly, and 40% reduce dosage over time.

Steroids were the commonest second-line therapy (67%), with pulsed oral methylprednisolone used most. In treatment-resistance, mycophenolate and rituximab were preferred third-line (both 62%).

Subcutaneous immunoglobulin was available to 66%, though used in only 10% of patients.

Conclusion: CIDP management is diverse. Work is underway to explore factors influencing treatment decisions, including IVIG optimisation and transition to SCIg.