Platform Presentations

Grand Plenary Abstracts

GP.01

Childhood obesity and multiple sclerosis susceptibility: a Mendelian randomization study

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Background: Observational studies have reported an association between childhood obesity and a higher risk of multiple sclerosis (MS). However, the difficulties to fully account for confounding and long recall periods make causal inference from these studies challenging. The objective of this study was to assess the contribution of childhood obesity to the development of MS through Mendelian randomization, which uses genetic associations to minimize the risk of confounding. **Methods:** We selected 23 independent genetic variants strongly associated with childhood body mass index (BMI) in a genome-wide association study (GWAS) which included 47,541 children. The corresponding effects of these variants on risk of MS were obtained from a GWAS of 14,802 MS cases and 26,703 controls. Standard two-sample Mendelian randomization methods were performed, with additional sensitivity analyses to assess the likelihood of bias from genetic pleiotropy. **Results:** The inverse-variance weighted MR analysis revealed that one standard deviation increase in childhood BMI increased odds of MS by 26% (odds ratio=1.26, 95% confidence interval 1.10-1.45, p=0.001). There was no significant heterogeneity across the individual estimates. Sensitivity analyses were consistent with the main findings and provided no evidence of pleiotropy. **Conclusions:** This study provides genetic support of a role for increased childhood BMI in the development of MS.

GP.02

Neuronal expression of Ubiqulin-2 mutant exacerbates TDP-43 aggregation in ALS mouse mode

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Background: Mutations in the gene encoding Ubiquilin-2 (UBQLN2) are linked to amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD). UBQLN2 plays a central role in ubiquitin proteasome system (UPS) and UBQLN2 up-regulation exacerbates TDP-43 cytoplasmic aggregates. **Methods:** To analyse interaction between UBQLN2 and TDP-43 and to produce a relevant ALS animal model, we have generated a new transgenic mouse expressing UBQLN2^{P497H} under the neurofilament heavy (NFH) gene promoter. The mice were then bred with our previously described TDP-43^{G348C} mice to generate double transgenic mice. **Results:** With low expression UBQLN2, the double transgenic mice developed TDP-43 cytosolic accumulations in motor neurons starting at 5 months of age. These double transgenic mice exhibited motor neuron loss, muscle atrophy, as well as motor and cognitive deficits during aging. The microglia from double transgenic mice were hyperresponsive to lipopolysaccharide (LPS). *In vivo* and *in vitro* analyses suggested that extra UBQLN2 proteins can exacerbate cytoplasmic TDP-43 accumulations by competing with the UPS for binding to ubiquitin. Thus, increasing the pool of ubiquitin promoted the UPS function with ensuing reduction of TDP-43 aggregation. **Conclusions:** In conclusion, the double transgenic UBQLN2^{P497H}; TDP-43^{G348C} mice provides a unique mouse model of ALS/FTD with enhanced TDP-43 pathology that can be exploited for drug testing.

GP.03

Diagnostic yield of next generation sequencing and myositis autoantibody panels in patients with axial myopathy

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Background: Axial myopathy is a rare neuromuscular disorder of variable etiology characterised by preferential involvement of the paraspinal muscles. We reviewed clinical features of patients with axial myopathies and the diagnostic yield of myositis-associated antibodies and targeted next generation sequencing panels. **Methods:** We performed a retrospective review of patients presenting with axial myopathy at the Montreal Neurological Hospital from 2011-2018. Data collection included clinical presentation, disease course, results of electromyography, imaging, laboratory and genetic testing, and histopathology on muscle biopsy. **Results:** Twenty-five patients were identified. Initial manifestation of axial weakness was head drop (15), camptocormia (8), and rigid spine (2). Autoimmune myositis was diagnosed in 9 patients, seropositive in 7 out of 7 tested for myositis-associated antibodies. Genetic testing was consistent with oculopharyngeal muscular dystrophy in one patient and RYR-1 (ryanodine receptor 1) related core myopathy in another. Local radiotherapy or spine surgery preceded the onset of axial weakness in 1 and 6 patients, respectively. Muscle biopsies were available in 17 patients and revealed myopathic changes (16), inflammatory changes (6), and myopathy with vacuoles (3). **Conclusions:** Recent advancements in genetic and antibody testing, combined with paraspinal muscle biopsy, allow for more precise classification and identification of potentially treatable axial myopathies.