Welcome to the latest issue of Neurology Research Review.

This month we report a potential prognostic marker of neurodegeneration in patients with Huntington’s disease, promising findings for orally active olesoxime in patients with spinal muscular atrophy, and epidemiological evidence of an association between migraine and chronic exposure to high altitude. We also report that maternal obesity is a modifiable risk factor for epilepsy, and present evidence that GON blockade may be an effective treatment for chronic migraine.

We hope you find these and the other selected articles interesting and look forward to any feedback you may have.

Kind Regards,
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Neurofilament light protein in blood as a potential biomarker of neurodegeneration in Huntington’s disease

Authors: Byrne L et al.

Summary: This retrospective cohort study investigated whether neurofilament light protein (NfL) in blood is a potential prognostic marker of neurodegeneration in patients with Huntington’s disease. Baseline and follow-up plasma samples were analysed for 97 controls and 201 carriers of CAG expansion mutations in HTT who were participating in the 3-year international TRACK-HD study. Mean plasma NfL levels at baseline were significantly higher in HTT mutation carriers than in controls (2.68 vs 2.68 log pg/ml; p<0.0001), and the difference increased from one disease stage to the next. At any given time-point, plasma NfL levels correlated with clinical and magnetic resonance imaging findings. In longitudinal analyses, baseline plasma NfL levels correlated significantly with subsequent decline in cognition, total functional capacity, and brain atrophy.

Comment: Neurofilament light chains have been proposed as a biomarker for many neurodegenerative diseases. A further advantage of their potential is that blood and cerebrospinal fluid levels of neurofilament light chains tend to correlate very closely. Although retrospective, this study suggests that neurofilament light chain levels reflect progression and onset of cognitive dysfunction in Huntington’s patients. This would make them a useful biomarker in drug trials for Huntington’s.

Reference: Lancet Neurol 2017;16(8):601-09
Abstract

Safety and efficacy of olesoxime in patients with type 2 or non-ambulatory type 3 spinal muscular atrophy

Authors: Bertini E et al., for the Olesoxime SMA Phase 2 Study Investigators

Summary: This multicentre phase 2 study investigated the safety and efficacy of olesoxime in patients with type 2 or non-ambulatory type 3 spinal muscular atrophy (SMA). 165 patients aged 3–25 years were randomised 2:1 to receive an oral liquid suspension of olesoxime (10 mg/kg/day) or placebo for 24 months in a double-blind design. The change from baseline to month 24 for the primary outcome (functional domains 1 and 2 of the Motor Function Measure) was 0.18 for olesoxime and −1.82 for placebo (p=0.0676). Olesoxime was safe and generally well tolerated, and had an adverse event profile similar to that of placebo. The most frequently reported adverse events with olesoxime were pyrexia, cough, nasopharyngitis, and vomiting. Two patients died in each group but the deaths were not considered to be related to the study treatment.

Comment: SMA is one of the few genetic neuromuscular conditions in which significant breakthroughs in treatment have been achieved in recent times. Olesoxime is different to other treatments in that it is oral and aims to maintain mitochondrial function. Further, patients included in this phase 2 trial were older (up to 25 years). Although a significant result was not reached, this drug may augment the effects of other treatments and could maintain motor function in older SMA patients in whom other treatments may not be useful or when intrathecal treatment is not possible.

Abstract
Early predictors of outcome after mild traumatic brain injury (UPFRONT)  
Authors: van der Naalt J et al.  
Summary: This population-based cohort study investigated predictors of functional outcome after mild traumatic brain injury (TBI). Over a 2-year period, data were collected for 910 patients who presented with mild TBI at an emergency department (ED) in the Netherlands. When assessed 2 weeks after the injury, 76.4% of patients had post-traumatic complaints and 414 (45%) showed emotional distress. After 6 months, 56% of patients had complete recovery and 44% had incomplete recovery. Logistic regression analyses showed that psychological factors (emotional distress and maladaptive coping at 2 weeks) in combination with pre-injury mental health problems, education, and age were important predictors of recovery at 6 months.  
Comment: The long-term effects of TBI are very topical and concussion is now clearly assessed in all codes of rugby and in cricket in Australia with clear guidelines for return to play. However, most data available on head injury outcome are from American College Football players. This prospective study looked at various factors in a cohort presenting to an ED and so provides data for all TBI and not just sports-related injury. The associations with poor recovery are similar to those in previous studies and so these patient characteristics need to be considered when arranging patient follow-up and deciding on treatment.  
Reference: Lancet Neurol 2017;16(7):532-40  
Abstract

Association of long-term opioid therapy with functional status, adverse outcomes, and mortality among patients with polyneuropathy  
Authors: Hoffman E et al.  
Summary: This retrospective cohort study examined the prevalence of long-term opioid use (≥90 continuous days) in patients with polyneuropathy, and evaluated the association of long-term opioid use with functional status and adverse outcomes. Analysis of prescription data for 2892 patients with polyneuropathy and 14,435 controls in ambulatory practice showed that more patients than controls received long-term opioids (18.8% vs 5.4%). Patients with polyneuropathy who were receiving long-term opioids had multiple functional status markers that were poorer than those of controls, even after adjusting for medical comorbidity. Adverse outcomes were more common among patients with polyneuropathy receiving long-term opioids, including depression (adjusted HR, 1.53), opioid dependence (2.85), and opioid overdose (5.12).  
Comment: This study highlights the fact that polyneuropathy significantly affects patient quality of life and can be associated with multiple functional deficits and co-morbidities. Optimal management of polyneuropathy-associated pain using newer non-opioid agents should be considered and patients should be referred to specialist pain services to avoid the complications and adverse effects of opioids described in this cohort of patients. The lack of efficacy of opioids in nerve pain and the adverse events described in this study support the findings of previous studies and have resulted in the Centers for Disease Control and Prevention (CDC) guidelines stating that opioids not be used first line in the management of neuropathic pain.  
Reference: JAMA Neurol 2017;74(7):733-79  
Abstract

Migraine associated with altitude  
Authors: Linde M et al.  
Summary: This population-based study investigated the association between migraine and chronic exposure to high altitude. A representative sample of 2100 Nepali-speaking adults was visited at home by trained interviewers using a culturally adapted questionnaire. 52.4% of participants lived at an altitude >1000m and 22.4% lived at ≥2000m. Migraine prevalence (standardised for age and gender) increased from 27.9% to 45.5% at an altitude of 0 to 2499m, and decreased to 37.9% at ≥2500m. The likelihood of having migraine was greater at all higher altitudes compared with <500m. All symptoms (attack frequency, duration, and pain intensity) increased with altitude across the range <500m to 2000–2499m, and showed a downward trend above 2500m.  
Comment: This study population showed that migraine is more common in those living at altitude and the higher the altitude that people live at, the more likely they are to have migraine. Similar results were found in a study in Peru. This is an interesting phenomenon as migraine/headache is a prominent component in altitude sickness yet these people are chronically exposed to the high altitude. There may therefore be an effect of atmospheric pressure or oxygen intensity in the triggering of headache.  
Abstract

Maternal body mass index in early pregnancy and risk of epilepsy in offspring  
Authors: Razaz N et al.  
Summary: This population-based cohort study investigated the association between BMI in early pregnancy and the risk of childhood epilepsy. 1,441,623 live single births in Sweden in 1997–2011 were included in the analysis. The overall incidence of epilepsy in children aged 28 days to 16 years was 6.79 per 10,000 child-years. Compared with offspring of normal-weight mothers, adjusted HRs for epilepsy were 1.11, 1.20, 1.30 and 1.82 for maternal overweight (BMI 25 to <30), obesity grade I (BMI 30 to <35), obesity grade II (BMI 35 to <40), and obesity grade III (BMI ≥40), respectively. The rates of epilepsy were increased for children with malformations of the nervous system (adjusted HR, 46.4), hypoxic ischaemic encephalopathy (23.6) and neonatal convulsions (33.5). The rates of epilepsy were doubled among children with neonatal hypoglycaemia or respiratory distress syndrome.  
Comment: Obesity in pregnancy has negative effects for both maternal and foetal health. It increases the risk of gestational diabetes and pre-eclampsia as well as the risk of stillbirth and foetal anomalies. There are also long-term effects for both the mother and child including increased risk of obesity and diabetes in the child. This study reports that the risk of epilepsy is increased in maternal obesity. However this large community-based study did not show an association between known pregnancy- and foetal-related effects of obesity and the risk of epilepsy. The risk of epilepsy however showed an increased incidence with increasing maternal obesity. Therefore maternal obesity is a modifiable risk factor for epilepsy.  
Reference: JAMA Neurol 2017;74(6):668-76  
Abstract

Immunotherapies in neuromyelitis optica spectrum disorder: efficacy and predictors of response  
Authors: Stellmann J-P et al.  
Summary: This retrospective German study analysed predictors for relapses and the number of attacks with different immunotherapies in patients with neuromyelitis optica spectrum disorder (NMOSD). Eligible patients were those with aquaporin-4-antibody-positive or aquaporin-4-antibody-negative NMOSD. 265 treatment episodes with a mean duration of 442 days in 144 patients were analysed. The most common treatments were rituximab (n=77), azathioprine (n=52), beta-interferon (n=32), mitoxantrone (n=34) and glatiramer acetate (n=17). Azathioprine and rituximab significantly reduced the attack risk compared with beta-interferon (HR, 0.4 and 0.6, respectively) whereas mitoxantrone and glatiramer acetate did not. Patients who were aquaporin-4-antibody-positive had a higher risk of attacks (HR, 2.5; p=0.009). Every decade of age was associated with a lower risk of attacks (HR, 0.8; p=0.039), and a previous attack under the same treatment tended to be predictive of further attacks.  
Comment: The optimal treatment for NMOSD is still uncertain as there are no randomised controlled trials. However, given the nature and incidence of the condition, randomised controlled trials are unlikely to occur. Although this is a fairly large study it is retrospective and has a few other biases. The standard annualised relapse rate (ARR) was that of the beta-interferon group and this ARR was lower than that reported in other NMOSD cohorts. Further, there was a bias to using azathioprine in subjects with more attacks. Nevertheless, the study still provides some useful information in that mitoxantrone and beta-interferon appeared ineffective in patient management.  
Reference: J Neurol Neurosurg Psychiatry 2017;88(8):639-47  
Abstract
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The efficacy of greater occipital nerve blockade in chronic migraine

Authors: Gul H et al.

Summary: This placebo-controlled study evaluated the use of GON blockade in patients with chronic migraine. 44 patients were randomised to receive GON blockade with bupivacaine or saline once a week for 4 weeks, and were followed up for a further 3 months. The bupivacaine group showed a significant decrease in the frequency of headache and visual analogue scale (VAS) pain scores at the first, second, and third months of follow-up. The placebo group also showed a significant decrease in the frequency of headache and VAS scores after the first month of follow-up, but not after the second and third months.

Comment: This small but well-designed study provides some evidence that GON blockade may be a long-term effective treatment in chronic migraine, a condition with significant morbidity and effect on quality of life. The placebo effect appeared to be lost after the first saline injection. A larger randomised trial is needed to confirm these effects.


Abstract

High-intensity interval training in facioscapulohumeral muscular dystrophy type 1

Authors: Andersen G et al.

Summary: This study determined the safety and efficacy of high-intensity training in patients with facioscapulohumeral muscular dystrophy type 1 (FSHD1). Thirteen untrained adults with genetically verified FSHD1 who were able to perform cycle-ergometer exercise were randomised to either 8 weeks of supervised high-intensity training (three 10-min cycle-ergometer high-intensity training sessions per week) or usual care. All patients then underwent 8 weeks of unsupervised high-intensity training. Both supervised and unsupervised training improved fitness, but had no effect on other outcomes. Patients preferred high-intensity training over strength and moderate-intensity aerobic training. High-intensity training had no effect on plasma creatine kinase levels or pain scores.

Comment: It was previously thought that over-exercising patients with inherited neuromuscular disorders may have an adverse effect by increasing fatigue and/or accelerating the disease process. This is yet another study that demonstrates that high intensity exercise is beneficial in a host of inherited neuromuscular conditions and need not be undertaken only under supervision. This is good news for those affected individuals who are motivated and keen to optimise their function. High intensity exercise not only has important physical effects but may help to improve the mood, cognition and quality of life in these patients.

Reference: J Neurol 2017;264(6):1099-1106

Abstract

Effects of different doses of triazolam in the middle-of-the-night insomnia

Authors: Ferini Strambi L et al.

Summary: This study evaluated the use of different dosages of triazolam in patients with middle-of-the-night (MOTN) insomnia. 24 patients were randomised to take 1 of 3 dosages of triazolam (0.0625mg, 0.125mg, or 0.250mg) after a MOTN awakening with difficulty returning to sleep. A significant improvement in total sleep time and sleep efficiency, and a reduction of wake after sleep onset and number of awakenings was observed after the first dose of triazolam compared with baseline, irrespective of dosage. After 2 weeks' treatment, insomnia severity significantly improved in all 3 groups compared with baseline, without any diurnal residual effects.

Comment: As the authors of the study note, MOTN insomnia is a common problem with few proven remedies. These people do not have difficulty falling asleep but rather have trouble staying asleep or returning to sleep if roused. While the results of this study are encouraging, longer term data are needed to determine whether the effect is long lasting or whether patients require increasing dosages of the drug for the same effect. Further, it would be interesting to determine if the drug could be withdrawn without the recurrence of MOTN insomnia.

Reference: J Neurol 2017;264(7):1362-69

Abstract