Insight Ten: Top MS & NMO Research Monthly

Welcome to the inaugural issue of Insight Ten, the European Charcot Foundation's premier publication designed to distill and disseminate the most significant findings in the fields of Multiple Sclerosis (MS) and Neuromyelitis Optica (NMO) to neurologists and neuroscience professionals worldwide.

As a monthly digest, Insight Ten is carefully crafted to present a selection of the ten most impactful papers recently published. Our mission extends beyond mere information sharing; we aim to foster a spirit of excellence and innovation in neurological care and research.

Our editorial team, consisting of esteemed neurology experts, meticulously reviews a wide range of journals and publications. We seek out studies that offer the potential to reshape our understanding and treatment of MS and NMO. Whether it's through reporting on revolutionary clinical trials, providing analyses of comprehensive reviews, introducing novel diagnostic methods, or discussing the latest therapeutic interventions, Insight Ten is dedicated to bringing you the forefront of neurological science.

For our first edition, we are thrilled to offer a synopsis of the top ten articles for October 2023. These summaries distill the core findings and clinical implications of each paper, allowing you to grasp the critical advancements in the field without the need to navigate through the extensive literature yourself.

Stay with us on this journey of exploration and knowledge as Insight Ten becomes your monthly beacon, illuminating the most noteworthy research in MS and NMO.

1. **Neurofilament and GFAP After Treatment Discontinuation in MS (Bose G, et al. - Neurol Neuroimmunol Neuroinflamm)**
    - **Summary**: The decision to discontinue disease-modifying therapy (DMT) in stable MS patients carries the risk of disease reactivation. This study investigated whether serum neurofilament light chain (sNfL) and serum glial fibrillary acidic protein (sGFAP) levels could serve as biomarkers to predict disease activity after DMT discontinuation. The researchers found that increases in these biomarkers were associated with a higher risk of MS disease activity, suggesting their potential utility in guiding clinical decisions regarding the discontinuation of DMT. The ability to stratify risk using these biomarkers could lead to more personalized management of MS, helping to identify patients who might safely discontinue therapy versus those who should continue treatment to prevent disease reactivation.
    - **Expert View**: The potential of sNfL and sGFAP as biomarkers for monitoring disease activity post-treatment discontinuation could be a game-changer in personalized MS management strategies.
2. **Plasma Lipids, Statins, and MS Risk and Severity (Almramhi MM, et al. - Neurology)**
    - **Summary**: This study used a genetic approach known as Mendelian randomization to investigate the relationship between plasma lipid levels, statin use, and the risk and severity of multiple sclerosis (MS). The researchers looked at genetic variants associated with the effects of statins, which are drugs commonly used to lower cholesterol, to determine if there was any association with the development of MS. The findings suggested that certain genetic factors that mimic the effects of statins could be linked to a reduced risk of MS. This indicates that cholesterol management, potentially through statin use, might influence the pathophysiology of MS. The study opens the door to further research into whether statins

could be used not only for managing cholesterol but also as a potential preventive or therapeutic measure for MS.
    - **Expert View**: The implications of this study for the potential use of statins in MS prevention or management are profound, warranting further investigation into statin therapy as a modifiable risk factor for MS.
3. **mRNA COVID-19 Vaccination in MS Patients (Blanco Y, et al. - Neurol Neuroimmunol Neuroinflamm)**
    - **Summary**: With the rollout of mRNA COVID-19 vaccines, there was concern about how these vaccines would affect people with multiple sclerosis (pwMS), particularly in terms of disease exacerbation. This longitudinal study monitored pwMS after mRNA COVID-19 vaccination, looking for any changes in MS symptoms or the induction of neural antibodies, which could suggest an adverse immune response. The study found that the vaccines were generally safe for pwMS, with no significant exacerbation of MS symptoms or induction of neural antibodies observed. This provides important evidence supporting the safety profile of mRNA COVID-19 vaccines in pwMS, which is crucial for vaccine uptake and protection against COVID-19 in this vulnerable group.
    - **Expert View**: The findings provide reassurance about the safety of COVID-19 vaccines for pwMS, which is vital for vaccine uptake and protection against COVID-19 in this vulnerable population.
3. **Low Protection from SARS-CoV-2 in Ocrelizumab-Treated MS Patients (Novak F, et al. - J Neurol Neurosurg Psychiatry)**
    - **Summary**: Ocrelizumab is a medication used to treat multiple sclerosis (MS) that works by depleting a specific type of immune cell known as B cells. This study aimed to assess the effectiveness of mRNA COVID-19 vaccines in MS patients being treated with ocrelizumab. The researchers found that these patients had a higher rate of breakthrough COVID-19 infections compared to the general population, even after full vaccination. However, the infections in the vaccinated MS patients were generally mild. The study underscores the potential need for additional protective measures against COVID-19 for MS patients on ocrelizumab, such as booster vaccinations, continued mask-wearing, and social distancing. It also raises questions about the timing of vaccination relative to ocrelizumab treatment to optimize immune response.
    - **Expert View**: This research is crucial for informing MS patients and healthcare providers about the potential need for additional COVID-19 preventative strategies, especially for those on immunosuppressive therapies.
4. **Quantitative MRI in Postmortem MS Brains (Galbusera R, et al. - Brain Pathol)**
    - **Summary**: Magnetic resonance imaging (MRI) is a crucial tool in diagnosing and monitoring multiple sclerosis (MS), but its ability to reflect the underlying pathology can sometimes be limited. This study aimed to improve the correlation between MRI findings and the actual histological changes in the brain tissue of MS patients. Researchers performed quantitative MRI (qMRI) on postmortem brain samples from MS patients and compared the imaging results with detailed histological analyses. They found that qMRI could differentiate between various types of MS lesions, especially those that had undergone remyelination. The study demonstrated that qMRI measures correlate with histological markers of myelin, axons, and astrocytes, suggesting that qMRI could be a powerful tool for assessing different pathological processes in MS and potentially guiding treatment decisions.
    - **Expert View**: The ability of qMRI to differentiate MS lesion types, including remyelinated lesions, could significantly enhance the understanding of MS pathology and the monitoring of disease progression and treatment effects.
4. **Quantitative MRI Reflects Myelin Densities in MS (Wiggermann V, et al. - Brain Pathol)**
    - **Summary**: The study aimed to validate the use of quantitative MRI (qMRI) techniques to measure myelin density in the brains of multiple sclerosis (MS) patients. By comparing qMRI data with histopathological analyses, the researchers sought to determine how well qMRI could reflect actual myelin content in MS lesions. The results indicated that qMRI measures

were closely aligned with myelin densities, providing a non-invasive means of assessing myelin integrity in vivo. This has significant implications for the diagnosis and monitoring of MS, as it suggests that qMRI could be used to track changes in myelin over time, evaluate the effectiveness of remyelinating therapies, and improve the understanding of disease progression.
    - **Expert View**: The study's confirmation of qMRI's ability to measure myelin density could revolutionize the monitoring of MS progression and the evaluation of remyelinating treatments.
5. **Reference Resources for Neurofilament Light Chain Levels in MS (Sotirchos ES, et al. - Neurology)**
    - **Summary**: Neurofilament light chain (NfL) levels in the blood are emerging as a promising biomarker for multiple sclerosis (MS), reflecting neuronal damage and disease activity. This study compared different reference resources for measuring NfL levels in MS patients to assess their agreement and reliability. The researchers found significant variability in NfL levels depending on the reference resource used. This variability could lead to inconsistencies in how NfL levels are interpreted in clinical practice and research. The study emphasizes the need for standardization in the measurement of NfL levels, which would ensure that this biomarker can be reliably used to monitor disease progression and response to therapy in MS patients.
    - **Expert View**: This study highlights the importance of standardizing biomarker assessments in MS, which is critical for the consistent monitoring of disease progression and response to therapy.
6. **B Cell Receptors in Neuromyelitis Optica Spectrum Disorder (Kim HJ, et al. - J Neuroinflammation)**
    - **Summary**: Neuromyelitis optica spectrum disorder (NMOSD) is an autoimmune condition that affects the central nervous system, distinct from multiple sclerosis. B cells, a type of immune cell, are implicated in the pathogenesis of NMOSD. This study utilized high-throughput sequencing to analyze the B cell receptors (BCRs) in NMOSD patients compared to those with other central nervous system inflammatory demyelinating diseases (CIDDs). The researchers discovered unique features in the BCR repertoire of NMOSD patients, suggesting a distinct B cell-mediated humoral immune response in this disease. These findings could have implications for the development of B cell-targeted therapies in NMOSD and enhance the understanding of the disease's underlying immune mechanisms.
    - **Expert View**: Understanding the unique BCR characteristics in NMOSD could lead to more targeted therapies that specifically address the aberrant immune response in this disease.
6. **Comprehensive Metabolic Fingerprints Characterize Neuromyelitis Optica Spectrum Disorder (Chen W, et al. - ACS Nano)**
    - **Summary:** In this study, researchers developed a novel diagnostic tool that utilizes nanoparticle-enhanced laser desorption/ionization mass spectrometry to analyze the metabolic fingerprints of patients with neuromyelitis optica spectrum disorder (NMOSD). By examining both plasma and cerebrospinal fluid samples, the researchers were able to identify specific metabolic patterns that are characteristic of NMOSD. The assay proved to be rapid and sensitive, distinguishing NMOSD from healthy controls with high accuracy. Furthermore, it could differentiate NMOSD from a similar condition, myelin oligodendrocyte glycoprotein associated disorder (MOGAD), which is often challenging to distinguish due to overlapping clinical features. The study's use of machine learning algorithms to analyze the complex data sets was crucial in achieving these results. This diagnostic approach is particularly valuable in regions where conventional antibody assays are not readily available, offering a potential new standard for NMOSD diagnosis that is both efficient and cost-effective.
    - **Expert View**: This research is significant because it provides a novel, rapid diagnostic tool for NMOSD, which could lead to earlier and more accurate treatment interventions, potentially improving patient outcomes.

7. **Microfibrillar-Associated Protein 4 as a Potential Marker of Acute Relapse in Inflammatory Demyelinating Diseases of the CNS (Samadzadeh S, et al. - Mult Scler)**
    - **Summary**: This research investigates the role of microfibrillar-associated protein 4 (MFAP4), an extracellular matrix protein, in the central nervous system (CNS) and its potential as a biomarker for acute relapse in inflammatory demyelinating diseases like multiple sclerosis (MS). The study examined MFAP4 expression in CNS tissues from autopsy cases and measured its levels in cerebrospinal fluid (CSF) and serum. The researchers found that MFAP4 was localized to the meninges and vascular/perivascular spaces, with intense presence in the optic nerve. Interestingly, at sites of active inflammation, MFAP4 reactivity was reduced, particularly in neuromyelitis optica spectrum disorder (NMOSD) and acute MS, and to a lesser extent in progressive MS. CSF levels of MFAP4 were lower during relapse and at disease onset compared to healthy controls. These findings suggest that MFAP4 could serve as a biomarker for disease activity, with reduced CSF levels indicating active inflammation during relapses in demyelinating diseases.
    - **Expert View**: MFAP4's potential as a biomarker for acute relapse in demyelinating diseases could be a game-changer for early intervention and treatment personalization.
8. **Gasdermin D Activation Drives Inflammatory Demyelination in Progressive MS (Pollock NM, et al. - Brain Behav Immun)**
    - **Summary**: Progressive multiple sclerosis (P-MS) is characterized by a continuous decline in neurological function, and inflammation plays a significant role in its pathogenesis. This study investigated the involvement of gasdermin D (GSDMD), a protein known for its role in a form of cell death called pyroptosis, in P-MS. Researchers found that GSDMD expression was elevated in brain tissue samples from P-MS patients. They proposed that the activation of GSDMD in cells such as oligodendrocytes, which are responsible for myelin production, and microglia, the CNS's resident immune cells, contributes to the demyelination and neuroaxonal injury observed in P-MS. The study's findings suggest that GSDMD could be a driver of the chronic inflammation seen in P-MS and that targeting GSDMD activation may offer a new therapeutic strategy for treating this debilitating form of MS.
    - **Expert View**: The identification of GSDMD's role in P-MS could be a breakthrough in understanding the disease's progression and may lead to the development of new treatments aimed at inhibiting this pathway.
9. **Assessing Neuroprotective Effects of Diroximel Fumarate and Siponimod via Modulation of Pacemaker Channels in an Experimental Model of Remyelination (Vinnenberg L, et al. - Exp Neurol)**
    - **Summary**: The study explores the neuroprotective effects of diroximel fumarate (DRF) and siponimod, two drugs used in the treatment of multiple sclerosis (MS), focusing on their impact on neuronal excitability and pacemaker channel activity. Using a cuprizone (CPZ) mouse model to induce changes in axonal myelination, the researchers investigated how these substances affect the hyperexcitability and activity of hyperpolarization-activated and cyclic nucleotide-gated (HCN) channels in the thalamocortical (TC) system. They found that DRF reduced the current density of HCN channels in thalamic neurons, counteracting the increased excitability seen during early remyelination. Siponimod had a differential effect, reducing HCN channel activity in thalamic neurons under normal conditions but not affecting auditory cortex neurons. It also modulated action potential firing differently in these regions. Computational models suggested that both drugs could normalize thalamic bursting patterns during early remyelination. These findings indicate that DRF and siponimod may exert their therapeutic effects in MS by modulating neuronal excitability and pacemaker channel activity, which could be beneficial in the treatment of demyelinating diseases.
    - **Expert View**: The research provides promising evidence that DRF and siponimod may modulate neuronal excitability, offering insights into their therapeutic effects in MS and guiding future treatment approaches.
10. **A20 Regulates Lymphocyte Adhesion in Murine Neuroinflammation (Johann L, et al. - J Clin Invest)**

- **Summary**: The protein A20 plays a critical role in the immune system's regulation, particularly in the context of inflammation. This study focused on the function of A20 in the central nervous system (CNS) and its implications for neuroinflammatory diseases like multiple sclerosis (MS). By genetically modifying mice to delete A20 specifically in CNS endothelial cells, the researchers observed an increase in the adhesion of lymphocytes to the endothelial cells and their subsequent migration into the CNS. This process is a key pathological feature of MS, where immune cells infiltrate the CNS and cause damage. The findings suggest that A20 helps to maintain the integrity of the blood-brain barrier and regulates the immune response, preventing excessive inflammation. The study provides a deeper understanding of the molecular mechanisms that underlie MS and points to A20 as a potential target for therapeutic intervention to control neuroinflammation.
- **Expert View**: This article provides valuable insights into the molecular mechanisms of MS, potentially opening up new avenues for therapeutic targets that could modulate the immune response in neuroinflammatory diseases.