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# Efficacy and Safety of Inebilizumab Among Non-White Demographic Groups with Neuromyelitis Optica Spectrum Disorder: N-MOmentum Study Subgroup Analysis

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Background:

There is a need for efficacy and safety information of disease modifying therapies on Neuromyelitis Optica Spectrum Disorder (NMOSD) in non-White demographic groups. Inebilizumab (INEB), an anti-CD19 B cell depleting antibody, is approved for the treatment of NMOSD in adults seropositive for aquaporin-4 antibody (AQP4+).

Methods:

N-MOmentum (NCT02200770) was a double-blind, phase 2/3 trial that assessed the efficacy and safety of INEB in adults with NMOSD, with a 28-week randomized controlled period (RCP) (intravenous INEB 300 mg or placebo [PBO] on days-1 and 15) and an open-label period (OLP) of ≥2 years.

Results:

Participants receiving INEB in the RCP were less likely to have an attack compared to PBO (Hazard Ratio[95%CI], p-value): Asian 0.20[0.06, 0.66], p=0.01; H/L 0.25[0.06, 1.01], p=0.05; B/AA 0.33[0.02, 5.31], p=0.44; White 0.27[0.11, 0.66], p=0.004. Expanded Disability Status Scale (EDSS) worsening from baseline to last RCP visit for participants receiving INEB vs PBO (Odds Ratio[95%CI], p-value): Asian 0.58[0.09, 3.63], p=0.56; H/L 0.50[0.09, 2.70], p=0.4; White 0.37[0.14, 0.95], p=0.04; and B/AA participants receiving INEB (0/15) did not experience EDSS worsening compared to 20% of PBO (1/5) participants. Participants who received any INEB during the study (combined RCP/OLP), the annualized attack rate [95% CI] was: Asian 0.10[0.05, 0.18]; H/L 0.07[0.04, 0.15]; B/AA 0.05[0.01, 0.33]; White 0.08[0.05, 0.13]. Among INEB participants, ≥1 investigational product-related treatment-emergent adverse event was reported: Asian(16/46); H/L(12/40); B/AA(12/19); White(48/120).

Conclusions:

Non-White NMOSD participants receiving inebilizumab had improved outcomes when compared to placebo and were similar to White participants although evaluation of larger populations is needed to confirm these results.

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# Impaired Cerebrospinal fluid circulation and cerebral lymphatic drainage in a rat model of chronic Hydrocephalus

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The cerebrospinal fluid (CSF) not only protects the brain but also maintains homeostasis by removing metabolic waste produced by brain activity. This study hypothesizes that chronic CSF circulatory dysfunction, such as normal pressure hydrocephalus (NPH), may be a critical condition in neurodegenerative diseases associated with metabolic waste accumulation. To investigate the glymphatic system and cerebral lymphatic drainage in a rat model of chronic hydrocephalus nduced by kaolin injection, we performed time-dependent evaluations of intraparenchymal injection of tracers or intra-cisterna magna, as well as intraventricular injection of Evans blue. The study systemically evaluated the dysfunction of CSF circulation and lymphatic drainage in the brain from various perspectives, including the glymphatic system, transependymal CSF flow, subarachnoid CSF flow, meningeal lymphatic drainage, and peripheral lymphatic drainage to deep cervical lymph nodes. The results indicated delayedglymphatic and cerebral lymphatic drainage in he kaolin-induced hydrocephalus model. Based on these findings, our research indicated that dysfunction of CSF circulation, as observed in conditions such as NPH, may act as an initiating or exacerbating factor in neurodegenerative diseases. This can lead to the accumulation of metabolic waste, as seen in Alzheimer`s disease. Our research can help identify risk factors and provide insight into the underlying pathophysiology of neurodegenerative diseases, which may lead to the development of novel therapeutic strategies.

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# Spinocerebellar Ataxia Type 2 (SCA2) confirmed with memory impairment as the only clinical manifestation

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Spinocerebellar Ataxia Type 2 (SCA2) is an autosomal dominant disorder characterized by gait disturbances, limb ataxia, dysarthria, eye movement disorders, and neuropathy. In the later stages of the disease, extrapyramidal symptoms, along with dementia, may develop. The author reports a patient with a family history of spinocerebellar ataxia who exclusively complained of memory impairment, and was diagnosed with SCA2 through genetic testing.

A 56-year-old woman began to experience memory issues approximately 5 years ago. Around 4 years ago, she started having difficulty remembering dates and became disoriented, often getting lost on familiar routes. Her mother was diagnosed with spinocerebellar ataxia after experiencing symptoms such as hand tremors, muscle wasting, and difficulty walking at a young age. Neurological testing revealed cognitive impairments, including deficits in memory, attention, and executive functions (Table 1), but no significant physical signs of ataxia. Despite a normal brain MRI (Fig) and no clear clinical signs of SCA, genetic testing confirmed the diagnosis of SCA2 due to an abnormal CAG repeat expansion in the ATAXIN2 gene (Table 2).

This case highlights that cognitive decline in SCA2 can occur without prominent cerebellar motor symptoms, and emphasizes the importance of considering family history and performing genetic testing for accurate diagnosis, particularly when symptoms suggest conditions like early-onset Alzheimer`s. The article also discusses the broader impact of SCA on cognitive functions, including its association with dementia and memory impairment, and introduces the concept of cerebellar cognitive affective syndrome (CCAS), in which cerebellar dysfunction affects higher cortical functions.

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# Exploring the link between neurodevelopmental vulnerabilities and neurodegenerative manifestations

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Primary progressive aphasia (PPA) is a clinical manifestation characterized by gradual decline in language functions secondary to neurodegenerative processes affecting language areas or networks in the brain. Two studies have found an association between the occupation of teaching and development of PPA (Jiskoot et al., 2024, Josephs et al., 2013). Two possible hypotheses have been proposed to explain this association. One, by nature of their occupation, teachers are sensitive to subtle changes in their verbal abilities, and the other that they are at risk for developing these disorders due to their frequent use of verbal and written communication (Josephs et al., 2013). Jiskoot et al (2024) refer to the latter as the "wear and tear hypothesis." In this presentation, I explore the possibility that an extraneous variable could have explained the association between the occupation of teaching and development of PPA. Specifically, I propose an alternative hypothesis that teachers who have a neurodevelopmental vulnerability (e.g., learning disability) are the ones at risk for developing PPA. This hypothesis is primarily derived from the finding that there is a high frequency of learning disability in patients with PPA and their first-degree relatives (e.g., Rogalski et al., 2008). I will discuss the clinical and theoretical implications of exploring this alternative hypothesis.

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# Peripheral neuromotor system disorders in Alzheimer`s disease

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Degenerative diseases with cognitive dysfunction and peripheral neuromotor system abnormalities predominate in older people. We decided to study the function of peripheral nerves in Alzheimer`s patients to identify a correlation between these two processes and the potential use of peripheral lesions as biomarkers for Alzheimer`s disease.

Material and methods. 10 patients with mild cognitive dysfunction (5 men and 5 women), 4 patients with Alzheimer`s disease (2 men and 2 women) and 10 healthy people (5 women and 5 men) were examined. The age of all patients ranged from 60 to 80 years. Alzheimer`s disease and mild cognitive dysfunction were diagnosed using MoCA. Sensor and motor fibers of the n.medianus, n. peroneus and n. tibialis, n. suralis and n. peroneus superficialis were examined. Nerve conduction velocity, amplitude and latency of S- and M-responses were studied. The ENMG study was performed using a Keypoint electromyograph from Metronics.

Result. The slowing of conduction velocities in the n.medianus and n.peroneus motor fibers was qualitatively greater in patients with Alzheimer`s disease than in those with mild cognitive dysfunction. In older adults without cognitive dysfunction, the nerve conduction velocities in the motor fibers of these two nerves were higher than in those with mild cognitive dysfunction persons.

Conclusion:It can be assumed that the rate of NCV decrease along motor fibers of peripheral nerves increases as cognitive function declines. Whether peripheral nerve function can be used as an early diagnostic marker for Alzheimer`s disease requires further elucidation, although it opens new avenues for future biomarker research.

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# Wernicke's Encephalopathy: A Case Report of Alcohol-Related Thiamine Deficiency

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Wernicke's encephalopathy (WE) is a severe neurological disorder caused by thiamine deficiency, most commonly associated with chronic alcohol misuse. We present the case of a 63-year-old male with a history of prolonged alcohol dependence who acutely developed confusion, gait ataxia, and memory deficits after abrupt cessation of alcohol consumption.

Neurological examination revealed horizontal gaze palsy, severe ataxia, and disorientation. MRI demonstrated symmetrical T2 hyperintensities in the periaqueductal gray matter, mammillary bodies, and thalami, consistent with Wernicke's encephalopathy. Laboratory workup confirmed marked thiamine deficiency and microcytic anemia linked to chronic gastrointestinal bleeding.

The patient received high-dose intravenous thiamine, leading to partial improvement in gait stability and alertness. However, persistent amnestic symptoms reflected irreversible damage due to delayed intervention.

This case underscores the necessity of prompt recognition and treatment of thiamine deficiency in alcohol-dependent patients. Early thiamine administration remains the cornerstone of management to prevent irreversible neurodegeneration. Clinicians should maintain a high index of suspicion for WE in patients presenting with the classic triad of ophthalmoplegia, ataxia, and confusion, even if all features are not initially evident. This report highlights the preventable nature of WE and the critical role of early intervention in mitigating long-term morbidity.

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# Sleep Disorders as Non Motor Symptoms in GBA parkinson`s patients in Albania

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*Background* Parkinson`s disease (PD) is the second most common neurodegenerative movement disorder. The etiology of the disease is unknown, but number of monogenic forms for PD were described over the last 2 decades. More frequently are identified pathologic variants in GBA, LRRK2, SNCA,PARK2. Sleep disorders is also a significant characteristics of PD, as rapid eye movement sleep behavior disorder (RBD), restless legs syndrome (RLS), excessive daytime sleepiness (EDS), insomnia, obstructive sleep apnea (OSA) and circadian rhythm disturbances.

*Methods* In the study are included 41 patients fullfill all criteria of Parkinson disease. These are divided into to groups. In the first group are included 9 patients carring mutations of GBA1 heterozigotes or compound heterozigote, 1 patient LRRK2 and in the second group are included 31 patients with PD without presence of GBA patologic variants.

Results In the first group with 10 patients carring mutations of GBA heterozigotes or compound heterozigotes and 1 patient LRRK2 and second group 31 patients NMS. Sleep disorders RBD 30%, RLS 30%, EDS 20%, insomnia 10 % of all PD patients carring mutation of GBA, PD patient with mutation LRRK2 has RBD. In the second group 19 % has RBD, 16% has RLS, EDS 16 %, and insomnia 13%.

*Conclusion* Sleep disorders, such as RBD, RLS, EDS and insomnia, are the most common non-motor feature of PD and often antedate PD, suggesting that sleep disorders are closely related to PD pathophysiology. Non motor symptoms are more prominent in GBA PD patients compared with PD patients

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# Improvements in Pain and Disability Contribute to Improved Quality of Life After Inebilizumab Treatment in Attack-Free Neuromyelitis Optica Spectrum Disorder (NMOSD) Participants

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Background:

Chronic pain and disability are enduring effects of NMOSD and contribute to decreased quality of life (QoL). Here we evaluated Pain and QoL improvement in attack-free, inebilizumab-treated participants over 3-years to determine improvements in non-attack related Pain and QoL.

Methods:

N-MOmentum (NCT02200770) was a phase 2/3 trial in 230 participants (randomized 3:1, inebilizumab 300mg:placebo), with an open-label extension of ≥2 years. Year-over-year changes in pain (SF-36-Bodily-Pain-Score [BPS]), QoL (SF-36-physical-component-summary [PCS]), and disability (Expanded-Disability-Status-Scale [EDSS]) were assessed for significance using mixed linear models in participants who were attack-free with ≥3-years of inebilizumab. Sensitivity analysis was conducted in participants who were attack-free for ≥6 months prior to inebilizumab treatment to control for acute attack-related recovery.

Results: At Baseline, (36/95) participants reported an abnormal QoL score (SF36-PCS40), (32/36) of these participants reported increased pain (SF36-BPS40) and (18/36) reported significant disability (EDSS≥5). After 3-years of inebilizumab, QoL scores improved in (32/36) of attack-free participants with an abnormal baseline QoL score. (37/95) of participants had abnormal pain scores (SF36-BPS40) at baseline and improvements were reported in (29/37) p0.001 after 3-years of inebilizumab. SF36-PCS and BPS scores improved in participants with normal (≥40) baseline scores after 3-years of inebilizumab. Improvements in EDSS from baseline to 3-years of inebilizumab were observed in (40/91) of participants including (25/69) with less disability (5 EDSS) and (15/22) with greater disability (≥5 EDSS) at baseline. Results were consistent with the sensitivity analysis.

Conclusions

Year-over-year improvements in Pain, QoL, EDSS and FSS were observed in attack-free participants on inebilizumab and independent of acute attack-related recovery.

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# Case of Myotonic Dystrophy type 1

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Introduction. Myotonic dystrophy (MD) is a type of muscular dystrophy, a group of genetic disorders that cause progressive muscle loss and weakness. In MD, muscles often fail to relax after contraction..

Case summary. The presented patient is a 30-year-old man with complaints of noticeable gait disturbance (foot drop), weakness in the distal parts of the upper and lower extremities, spasm during movement, difficulty starting movement.

Neurological status: Deformity of the chest - sunken sternum. The configuration of the spine is altered. The shoulders and scapulae are asymmetrical, muscle hypotrophy of the shoulder girdle, upper arm, forearm, lower leg (more on the left).

Gait is impaired, when walking, the right foot hangs down.

Muscle tone decreased. Muscle strength in the shoulder girdle is 5 points (proximally), in the shoulder flexors - 4 points, in the extensors of the hand - 2 points. Muscle strength in the proximal part of the lower extremities is 5 points, in the distal part 2-3 points. Percussion myotonic reactions are positive on both sides.

Reflexes from m. biceps and m. triceps is symmetrically decreased, periosteal reflexes are absent. Knee and Achilles reflexes are absent.

In the Romberg pose, he is stable, in the complicated Romberg pose - slight rocking. He performs the heel-knee test well. Coordination tests - minor disturbances.

Electromyography: the impulse conduction velocity in the motor nerves (ICVeff) is slow, the amplitude of the M-potentials is reduced. The values of ICVaff and S-potentials are normal. Needle EMG revealed positive waves at rest and "myotonic" discharges. The amplitude of the motor unit potensial (MUP) is reduced. Echocardiography: Segmental motor failure of the left ventricle.

Conclusion. Based on clinical and EMG data, the patient was diagnosed with myotonic dystrophy type 1 and received drug (tegretol, etc.) and physiotherapy treatment.

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# Nonfluent/Agrammatic Primary Progressive Aphasia in the Context of Accelerated Post-COVID-19 Neurodegeneration: A Case Report

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Background: Primary Progressive Aphasia (PPA) is a rare neurodegenerative disorder characterized by progressive impairment in language, often linked to frontotemporal lobar degeneration (FTLD). The nonfluent/agrammatic variant (naPPA) is distinguished by effortful speech, agrammatism, and apraxia of speech. Viral infections, including COVID-19, may act as triggers or accelerators of neurodegeneration.

Case Presentation: A 56-year-old female presented with progressive speech and language impairment over 7–8 months. Several months before the appearance of cognitive symptoms she had confirmed COVID-19 infection two times. Initial symptoms included word-finding difficulty and sentence construction issues, progressing to severe deficits in speech production, reading, and writing. Due to these, it was impossible to conduct MMSE and MOCA tests. Neurological examination revealed slow, hypokinetic gait, diminished arm swing, ideomotor apraxia, amimic face, pseudobulbar affect, and dysphagia.

Investigations: EEG demonstrated paroxysmal activity in the left temporal lobe with rhythmic beta slowing. MRI revealed cortical atrophy in the left temporal and parietal lobes, with globus pallidus hypointensity, and mild chronic periventricular leukoencephalopathy. CSF analysis was unremarkable, excluding infectious and autoimmune causes.

Conclusion: In summary, this case highlights the clinical evolution and diagnostic challenges of naPPA, underscoring the importance of multimodal imaging and EEG in evaluation. The possible connection between COVID-19 and accelerated tauopathy calls for further investigation. Prompt diagnosis and a multidisciplinary strategy are essential for optimal patient management.