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Demyelinating Disorders 1

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Demyelinating Disorders 1
Role of MRI in prognostic prediction of clinically isolated syndrome in Japanese patients

H. Yano, F. Katada, S. Sato, H. Shibayama, T. Fukutake. *Neurology, Kameda Medical Center, Kamogawa, Japan*

Background: The recognition of clinically isolated syndrome (CIS) and the early use of disease-modifying therapies are considered to be of great prognostic importance in the Western population. However, there is little consensus on the prognostic evaluation with MRI among the Asian population, including Japanese.
Objective: We examined clinical findings in Japanese CIS patients and compared them with those of clinically definite multiple sclerosis (CDMS) patients at the first presentation.
Patients and methods: The study was based on the medical records of patients diagnosed with CIS using 2010 Revised McDonald Diagnostic criteria between November 2008 and April 2014. All patients were negative for AQP4 antibodies at the onset. They were divided into two groups according to whether they developed CDMS (progressive CIS) or not (non-progressive CIS). The age of onset, symptoms, Expanded Disability Status Scale, findings in cerebrospinal fluid, and lesion distribution on the initial MRI (both cranial and spinal) were compared.
Results: Fourteen patients were diagnosed with CIS of which 7 developed MS (50%). The mean age at onset and follow-up period for progressive and non-progressive CIS patients were 27.4 ± 13.8 vs 38.8 ± 11.5 year-old and 54.7 ± 14 vs 48.5 ± 18 months respectively. Comparative analysis of MRI findings at the first attack revealed that progressive CIS patients have more intracranial lesions (6.4 ± 3.6 vs 2.1 ± 3.5, $p < 0.05$) and brainstem lesions (0.8 ± 0.7 vs 0.1 ± 0.4, $p < 0.05$).
Conclusion: In our study, CIS patients with more intracranial and brainstem lesions have higher risks for conversion to CDMS.

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Use of multiple biomarkers to improve the prediction of multiple sclerosis in patients with clinically isolated syndromes

V. Martinelli, G. Dalla Costa, M. Messina, G. Di Maggio, L. Moiola, M. Rodegher, B. Colombo, R. Furlan, L. Leocani, G. Comis. *Neurology, San Raffaele Hospital, Milan, Italy*

Background: The early identification of patients at high risk of Clinically Definite Multiple Sclerosis (CDMS) represents the main purpose of diagnostic criteria and of clinicians in everyday clinical practice.
Objective: To investigate whether the incorporation of different biomarkers in a model with established MRI criteria improves the prediction of MS.
Methods: We evaluated baseline clinical data as well as MRI, multimodal evoked potentials and cerebrospinal fluid (CSF) data of patients with a first demyelinating episode. We used discrimination and calibration characteristics and reclassification of risk categories to assess incremental utility of different biomarkers for CDMS prediction.
Results: During follow-up (median 7.2 years), 127 of the 243 participants in our study (mean age 31.6 years) developed a second clinical attack (CDMS). In Cox proportional-hazards models adjusted for established MRI criteria, age at onset, number of T1 lesions and presence of CSF oligoclonal bands significantly predicted the risk of developing MS within 2 and 5 years. The C-statistic increased significantly when the three biomarkers were incorporated into a model with established MRI criteria, both at 2 years (C-statistic with biomarkers vs. without biomarkers, 0.74 vs. 0.69) and at 5 years (0.66 vs. 0.70). The use of multiple biomarkers led to a 29% net-reclassification improvement at 2 years ($p < 0.001$) and 30% at 5 years ($p < 0.001$).
Conclusions: The simultaneous addition of several biomarkers improves the risk stratification for MS in patients with clinically isolated syndromes beyond that of a model that is based only on MRI criteria.

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Efficacy for remyelination and safety of anti-lingo-1 monoclonal antibody (biib033) in acute optic neuritis: results from the renew study

N. Kurukulasuriya[a], O. Fernandez[b], L. Balcer[c], S. Galetta[c], O. Aktas[d], T. Ziemssen[e], L. Vanopdenbosch[f], H. Butzkueven[g], F. Ziemssen[h], L. Massacesi[i], Y. Chai[j], L. Xu[j], S. Freeman[k], D. Cadavid[l]. [a]*Global Medical, Biogen, Cambridge, USA;* [b]*Institute of Clinical Neurosciences IBIMA, Hospital Regional Universitario, Malaga, Spain;* [c]*Department of Neurology, NYU Langone Medical Center, NY, USA;* [d]*Department of Neurology, Heinrich-Heine-Universität Düsseldorf, Düsseldorf, Germany;* [e]*MS Center Dresden, University Hospital Carl Gustav Carus, Dresden, Germany;* [f]*Department of Neurology, AZ Sint Jan Brugge Oostende, Brugge, Belgium;* [g]*Melbourne Brain Centre, Royal Melbourne Hospital, Parkville, Australia;* [h]*Eye Clinic, Universitätsklinikum Tuebingen, Tuebingen, Germany;* [i]*Department of Neurosciences Drug Research and Child's Health, University of Florence, Florence, Italy;* [j]*Biostatistics, Biogen, Cambridge, USA;* [k]*Drug Safety, Biogen, Cambridge, USA;* [l]*Medical Research, Biogen, Cambridge, USA*

0022-510X/$ – see front matter.

Background: Anti-LINGO-1 is a monoclonal antibody antagonist of LINGO-1, an oligodendrocyte differentiation and myelination suppressor.
Objective: To determine the efficacy/safety of anti-LINGO-1 for CNS remyelination.
Methods: Subjects with a first unilateral acute optic neuritis episode were treated with high-dose steroids and randomized to 100mg/kg anti-LINGO-1 IV or placebo every 4 weeks (NCT01721161). Subject and IRB approval were obtained. Nerve conduction latency recovery using full-field visual evoked potential (FF-VEP) in the affected eye over time versus unaffected eye at baseline assessed remyelination (pre-specified primary endpoint). Between-treatment comparisons were evaluated by ANCOVA and mixed-effect model repeated measure (MMRM) in subjects who completed the study and did not miss >1 study dose or receive MS modifying therapy (pre-specified per-protocol population). Safety/tolerability was evaluated in those who received ≥1 study dose and included adverse event (AE) and clinical laboratory result assessments.
Results: Anti-LINGO-1-treated subjects (n = 33) showed improved latency recovery versus placebo (n = 36): mean (95% confidence interval) −7.55ms (−15.12 to 0.01) at Week 24 ($P = 0.05$); −9.13ms (−16.11 to −2.14; $P = 0.01$) at Week 32. 54% of anti-LINGO-1 subjects had no/mild latency delay at Week 24 (affected eye FF-VEP latency ≤10% worse than baseline fellow eye) versus 27% of the placebo group ($P = 0.036$). Additional subgroup analyses will be presented. 34/41 in each group experienced any AE, serious AEs occurred in 2 placebo and 5 anti-LINGO-1 subjects, and there were 3 treatment-related serious AEs.
Conclusions: Improvement in FF-VEP latency is consistent with the first evidence of remyelination in a Phase 2 trial. Anti-LINGO-1 was generally well tolerated.

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Granulocyte-macrophage colony-stimulating factor: Increased expression by immune cells of patients with multiple sclerosis

C. Constantinescu, J. Aram, R. Tanasescu, B. Gran. *Neurology, University of Nottingham, Nottingham, United Kingdom*

Background: Recent evidence suggests that GM-CSF Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF), a proinflammatory cytokine with multiple roles in the immune system, has a role in MS pathogenesis. In the experimental model of MS, experimental autoimmune encephalomyelitis, expression of GMCSF by T cells is essential for disease induction. Our aim was to evaluate the expression of GM-CSF by different peripheral blood mononuclear cells (PBMC) subtypes in MS patients and controls.
Materials and methods: PBMCs were isolated 21 MS and 14 control subjects and stimulated. NK cells were isolated and cultured with different stimuli for 3 days. Cells were phenotyped using flow cytometry.
Results: There was higher GM-CSF expression in Phorbol Myristate Acetate/Ionomycin (PMA/I)-stimulated monocyte-gated PBMCs, and natural killer T (NKT) cells in MS patients compared to healthy controls. Th17, NK, and cytotoxic T-gated cells expressed similar GM-CSF levels in MS and controls In MS, 40–45% of gated CD4+ and CD8 cells expressing GM-CSF; 10–20% of these are also IFN-γ+. About 50% of NKT cells are GMCSF+, and 45% of these were IFN-γ+. In controls, these proportions were lower. Isolated NK cells stimulated with IL-15+IL-18, and IL-15+IL-1β were noticed to have more GM-CSF expression than the unstimulated and mono-stimulated CD56+ NK cells (MS n = 6, controls n = 6).
Conclusion: T cells (both CD4+ and CD8+), NK, and NKT cells are all high GM-CSF producers in MS. GM-CSF is a potential therapeutic target in MS. The recent safety and tolerability results of a phase I trial of a monoclonal antibody in MS are encouraging.

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Enhancement dynamics of tumefactive demyelinating lesions on brain MRI associated with clinical course

J.G. Liu[a], M. Ren[a], X.K. Qi[a], F. Qiu[a], K.H. Zheng[a], C.J. Sun[a], H.L. Zhao[b], D.Y. Xia[a]. *[a]Department of Neurology, Navy General Hospital, Beijing, China; [b]Neurosurgery Department, Navy General Hospital, Beijing, China*

Objectives: The evolutionary characteristics of the lesions of tumefactive demyelinating lesions (TDL) on contrast-enhanced T_1-weighted images, were evaluated and summarized to facilitate the diagnosis of TDL.
Methods: The brain MRI imagings of 60 patients pathologically diagnosed with TDL (≥20 mm in diameter) were assessed. The course of the disorder was classified as acute phase (≤2 weeks), subacute phase (>2 weeks, but ≤6 weeks), and chronic phase (≥7 weeks) according to its clinical course.
Results: (1) The diameters of lesions ranged 21–85 mm, and the mean diameter was 45 ± 22 mm. (2) We summarized the neuroimaging features of TDL on MRI in different clinical phases as the following: a) For acute phase (≤2 weeks), the images of contrast enhancement brain MRI were available for 18 cases. In 17 of the 18 cases, their images showed variable degrees of contrast enhancement. The patterns of enhancement were patchy (n = 5), nodular (n = 7), complete ring (n = 3), open ring (n = 4), flame-like (n = 2) and dilated venular (n = 3). b) For subacute phase (3–6 weeks), contrast enhancement MRI images were available for 54 cases. 52 of the 54 cases showed marked contrast enhancement and patterns of enhancement were open ring-like (n = 18), complete ring-like (n = 14), irregular round (n = 18), patchy (n = 21), nodular (n = 8), flame-like (n = 5) and dilated venular in a dense array (n = 25). c) For chronic phase (≥7 weeks), contrast enhancement MRI were available for 28 cases. 13 of the 28 cases showed mild contrast enhancement, such as mild patchy (n = 8), open ring-like (n = 4), and complete ring-like (n = 4).
Conclusion: Different manifestations of the lesions on contrast-enhanced MRI develop in different clinical stages of TDL. Dynamic evolution of the enhanced MRI may be more important to facilitate the diagnosis of TDL.

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Comparison of the features of MRI of tumefactive demyelinating lesions and glioma

J.G. Liu[a], W.Y. Qiao[b], X.K. Qi[a], H.L. Zhao[c], K.H. Zheng[d], H.R. Qian[a], S. Yao[a], S. Yao[a], F. Duan[a], F. Qiu[a], D.Y. Xia[a], Y.X. Y[a], C.J. Sun[a]. *[a]Department of Neurology, Navy General Hospital, Beijing, China; [b]Emergency Center, Beijing Chaoyang Hospital (Jingxi Campus), Beijing, China; [c]Department of Neurosurgery, Navy General Hospital, Beijing, China; [d]Department of Imaging, Navy General Hospital, Beijing, China*