Neuroimmunology

EP4154
Comparative case series of GABA(B) and AMPA receptor antibodies associated with limbic encephalitis

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Background: We present clinical and paraclinical features of antibodies (abs) to GABA(B) and AMPA receptors associated with limbic encephalitis (LE).

Methods: Serum and CSF samples of 12 patients who were suspected to have LE were tested for a broad panel of antineural abs and found to be positive for GABA(B) and AMPA receptor abs. Clinical data were retrospectively compiled.

Results: In nine patients we detected abs to GABAB receptor (GABAB(R)). Median age was 65.1. All female and 3/6 male patients were diagnosed with small cell lung cancer. GABAB(R)abs were found in serum samples of all patients but only in 6 CSF samples. Intrathecal GABAB(R) ab synthesis was found in 2/4 patients with sufficient data available (median ab-index: 71,2). On MRI we found bilateral mediotemporal and in one case cortical abnormalities, EEG revealed encephalopathy. 3 patients died, 1 patient showed slight improvement and in 5 patients bodily and cognitive functions declined gradually. AMPA receptor (AMPA) abs were detected in three patients with mnestic disturbances (1 female). Median age was 60.7. The only female patient was diagnosed with ovarian cancer. AMPAR abs were present in all serum samples but only in 1 CSF sample without intrathecal AMPARab synthesis. MRI findings showed mediotemporal abnormalities, EEG was normal in all patients.

Discussion: Our data reveal that GABABR abs more likely lead to full clinical picture of LE with a poor outcome. Patients with AMPAR abs were less impaired with less pronounced abnormalities on MRI and EEG pointing to a more confined cerebral process.

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EP4155
CD138+ plasma cells predominate in the cerebrospinal fluid of patients with anti-N-methyl-D-aspartate receptor encephalitis

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Introduction: Anti-N-methyl-D-aspartate receptor (NMDA-R) encephalitis is a recently described autoimmune panencephalitis with characteristic clinical features that include neuropsychiatric symptoms, seizures, abnormal movements and autonomic instability. Antibodies cause a reversible selective cross-linking and internalization of surface NMDA-Rs and subsequent disturbance of synaptic transmission and plasticity. Here, we studied the composition of the cellular infiltrates in the cerebrospinal fluid in patients with NMDA-R encephalitis before and during the course of the disease using flow cytometry.

Methods: A total of 8 patients with NMDA-R encephalitis underwent detailed analysis of the cellular composition of blood and cerebrospinal fluid samples before and during the course of the disease using flow cytometry and were compared to a cohort of 35 patients with psychogenic neurological symptoms.

Results: We found exceedingly increased numbers of activated B cells i.e. CD138+ plasma cells in the cerebrospinal fluid of patients with NMDA-R encephalitis compared to controls, whereas numbers of activated HLA DR+ CD4+ and CD8+ T cells were only slightly increased. The fraction of CD138+ plasma cells in the cerebrospinal fluid decreased under immunotherapy in parallel to clinical improvement during the disease course.

Conclusions: CD138+ plasma cells represent the major fraction of activated lymphocytes in the cerebrospinal fluid of patients with NMDA-R encephalitis may serve as a marker of response to immunotherapy.

Disclosure: Nothing to disclose
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Cytotoxic CD8+ T-cells predominate in the cerebrospinal fluid of patients with limbic encephalitis associated with antibodies to the voltage-gated potassium channel complex

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Introduction: Limbic encephalitis (LE) associated with antibodies to voltage-gated potassium channel (VGKC) complex usually presents with rapidly progressive short-term memory deficits, neuropsychiatric symptoms, and temporal lobe seizures. Antibodies disrupt the presynaptic and para-/juxtanodal VGKC complex consisting of the VGKC and associated proteins leucine-rich glioma-inactivated 1 (LGI1) and contactin-associated protein-like 2 (CASPR2) and thus cause altered synaptic transmission and neuronal excitability. Here, we studied the composition of the cellular infiltrates in the cerebrospinal fluid in patients with anti-VGKC complex LE before and during the course of the disease using flow cytometry.

Methods: A total of 6 patients with anti-VGKC complex LE underwent detailed analysis of the cellular composition of blood and cerebrospinal fluid samples before and during the course of the disease using flow cytometry and were compared to a cohort of 35 patients with psychogenic neurological symptoms.

Results: We found predominantly increased numbers of activated HLADR+ CD8+ T-cells in the cerebrospinal fluid of patients with anti-VGKC complex LE compared to controls, whereas numbers of activated B cells i.e. CD138+ plasma cells were only slightly increased.

Conclusions: Predominantly increased numbers of activated HLADR+ CD8+ T-cells may in the cerebrospinal fluid of patients with anti-VGKC complex LE may point towards a pathogenic role of these cells.

Disclosure: Nothing to disclose

EP4157

Three cases with familial Mediterranean fever and multiple sclerosis

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Introduction: FMF is an autosomal recessive inflammatory disease and characterized by recurrent episodes of fever and serositis or synovitis. Few cases having both MS and FMF have been reported.

Methods:
Case 1: 27 years old woman diagnosed with Familial Mediterranean fever (FMF) 10 years ago and treated with colchicine presented with headache and urinary incontinencia. She had two siblings who had FMF. The magnetic resonance imaging (MRI) of brain showed a hyperintense enhancing lesion at the bilateral cerebral white matter and mesensephalon.

Case 2: 45 years old man diagnosed with FMF 15 years ago and treated with colchicine. He admitted to our clinic for left arm weakness and numbness. The cervical MRI showed hyperintense lesion alt the left side at the level of C3-4 and C6-7.

Case 3: 34 years olds male admitted to our clinic with fever, arthralgia and vertigo. He was diagnosed with FMF 17 years ago. Complete visual loss observed on his left eye and partial visual loss observed on the right eye. He was diagnosed as an optic neuritis. MRI of brain showed a hyperintense, demyelinizan lesion at the bilateral cerebral periventricular white matter. Pattern VEP response distal latency was delayed at the right side. Tibial and median sensory evoked potential responses were not obtained.

Results: All of their oligoclonal bands were positive.

Conclusions: Here we assess three cases with both FMF and MS, in order to clarify any relationship between FMF and MS, and to evaluate disease characteristics.

Disclosure: Nothing to disclose
EP4158
Expression of apoptosis-related genes in relapsing-remitting multiple sclerosis and clinically isolated syndrome
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Introduction: The pathogenesis of multiple sclerosis (MS) involves failure of lymphocyte apoptosis leading to persistence of neuroinflammation. Identifying mediators that govern apoptotic pathways is critical for better understanding of MS as well as for the discovery of new therapies and biomarkers. Our aim was to identify a new prognostic biomarker that would predict conversion from clinically isolated syndrome (CIS) to MS.
Methods: The study included 46 subjects (11 RRMS, 20 CIS, 16 controls) that were studied neurologically and the blood samples were collected. The expression of apoptotic genes in mononuclear cells was analysed with Taqman array in two separate cohorts. First, 96 transcripts were measured in patients with RRMS and controls. Thereafter, such transcripts that appeared to be upregulated in RRMS were studied in patients with CIS annually over four years.
Results: We detected 11/93 upregulated transcripts in RRMS. They belong to the Bcl-2 family (BBC3, BAD, BCL2L14, BIK, BOK), death receptor pathway (TNFRSF25, FADD) and NF-KB family (IKBKE, NFKBID). In CIS, half of the patients fulfilled the diagnostic criteria for MS, but none of the studied genes was associated with conversion to MS. Longitudinal analysis of subjects with CIS showed marked intra- and interindividual variability in the levels of gene expression.
Conclusions: Proapoptotic gene changes are detectable in patients with clinically silent early MS. Most likely such changes are consistent with peripheral immune activation and proapoptotic gene changes may also be responsible for worsening of MS. However, in CIS, the upregulated transcripts did not predict conversion to MS.
Disclosure: Nothing to disclose

EP4159
New mouse model mimicking IFN-alpha-related depression in hepatitis C virus infected patients
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Introduction: We have previously identified 15 genes (DRIIs) that are associated with the development of severe depressive episodes during the standard therapy with interferon alpha (IFN-α) and ribavirin in the peripheral blood of hepatitis C virus (HCV) infected patients. Hereby, through direct intracerebroventricular application of IFN-α and poly(I:C) in mice, we mimic the depression conditions affecting HCV patients and the genetic response of DRIIs and cytokines.
Methods: Miniosmotic pumps were implanted into the lateral ventricle of 10-12-weeks-old C57Bl6/j mice for administration of saline, recombinant mouse IFN-α (mIFNα) and/or poly(I:C) during 14 days. After the treatment animals underwent behavioral tests: open field test (OFT) for 20 minutes, tail suspension test (TST) for 6 minutes and forced swim test (FST) during 6 minutes/session. Hippocampus and prefrontal cortex were dissected to assess the expression of nine of the DRIIs, Ccl5, Cxcl1 and Timp-1 by RT-PCR.
Results: The TST and FST showed that concomitant administration of mIFNα and poly(I:C) promoted a depression-like behavior which was not detectable with the single treatments. Additionally, the OFT revealed a strong tendency to anxious-like behavior. Except Mef2A, the rest of the DRIIs and cytokines showed a significant or strong upregulation, especially with costimulation treatment and in hippocampus.
Conclusions: Intracerebroventricular administration of mIFNαA and poly(I:C) in mice may partially mimic the neural environment present in depressed-HCV patients undergoing IFN therapy. As suggested by our previous ex vivo studies, the upregulation of selective DRIIs and production of inflammatory cytokines may be involved in the pathophysiological mechanisms underlying IFN-α-associated depression.
Disclosure: Nothing to disclose
EP4160

Refractory IgG4-related intracranial hypertrophic pachymeningitis

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Introduction: IgG4-related disease is usually described in gastrointestinal/respiratory systems. Involvement of the central nervous system is uncommon, with principal neurological manifestations including hypophysitis and HP. Leptomeningeal disease has also been reported. Generally, it does not affect the brain parenchyma. In some cases, previously known idiopathic-HP may represent IgG4-related-HP, affecting the intracranial and/or intraspinal dura. Most cases resolve with surgery and/or steroid therapy; other reports describe efficacy of radiation therapy and anti-tumor necrosis factor antibodies. Only three cases of recurrent IgG4-related-HP have been described, one case treated with rituximab with excellent clinical response, and two cases treated with mycophenolate mofetil (MMF) producing stable clinico-radiological findings after 12 and 18 months respectively.

Methods: We report a rare case of IgG4-related intracranial-HP, initially presenting with seizures, complicated subsequently with multiple cranial neuropathies. This disease has been refractory to steroids, azathioprine, methotrexate and did not improve with MMF. We have been closely following this patient at the UTMB since 2003.

Results: After initial presentation with seizures, the patient developed cranial neuropathies. Most recent brain MRI demonstrated progressive dural enhancement along the falx, bilateral frontotemporal convexities and around the right cavernous sinus. Serum IgG fractionation showed elevation of systemic IgG4 levels. Biopsy of the affected dura revealed many inflammatory B-cells, though no evidence of lymphoma, there was over 25% of immunostain-positive IgG4-mast cells. Despite treatment with steroids, azathioprine, methotrexate and MMF, lesions continued to grow into the right cavernous sinus and maxillary sinus.

Conclusions: This case highlights a refractory IgG4-related intracranial-HP. Rituximab has been initiated.

Disclosure: Nothing to disclose

EP4161

Non-stiff anti-amphiphysin syndrome: clinical manifestations and their favorable outcome after immunotherapy

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Introduction: Classically, anti-amphiphysin antibody causes paraneoplastic stiff-person syndrome. However, the antibody is responsible for various neurological manifestations, and here we investigated the clinical spectrum of non-stiff anti-amphiphysin syndrome (NSAS) and their responses to immunotherapies.

Methods: From October 2012 and September 2013, patients with encephalomyelitis, limbic encephalitis, brainstem encephalitis, subacute ataxia, dysautonomia, or polyneuropathy of unknown etiology were screened for classical paraneoplastic or autoimmune synaptic encephalitis antibodies. Patients who are positive for anti-amphiphysin antibody were included and the clinical features, laboratory findings and radiological tests were analyzed.

Results: Total 21 patients had anti-amphiphysin antibody. The most common neurological manifestation was limbic encephalitis, followed by dysautonomia, cerebellar dysfunction, brainstem encephalitis, peripheral neuropathy, and myelitis. Cancer was detected in 7 patients but not in the majority of the patients (mean follow-up period: 2.8 years). Immunotherapy was performed in 13 patients, and most of the patients demonstrated favorable response to the treatment. Intravenous immunoglobulin or steroid treatment was effective in majority of the patients. Three patients improved only after rituximab treatment.

Conclusions: Anti-amphiphysin antibody can be detected in non-stiff encephalomyelitis, and is partially associated with cancer. Active immunotherapy improved the symptoms, and novel immune modulating therapies including rituximab might be beneficial to treat the disease.

Disclosure: Nothing to disclose
EP4162

CLIPPERS – a case report with atypical MRI-findings

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Introduction: Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS) is an inflammatory central nervous system (CNS) disorder which is increasingly diagnosed in the last years. The aetiology is up to now unknown. Pathological marks are infiltrations of T-lymphocytes predominantly in the perivascular spaces of the brainstem. Characteristics are a number of typical clinical features with a favorable responsiveness to immunotherapy and gadolinium enhancing punctiform lesions in the brainstem in the magnetic resonance images.

Case report: We report the clinical, magnetic resonance imaging (MRI) and brain biopsy findings of a 68 year old Italian man who presented with dysphagia, numbness and paresthesia in his right face and a progressive gait ataxia. Brain and spine MRI showed a lesion in pons at the junction of the medulla oblongata with a second lesion in the cervical spinal cord. Several analyses could not give evidence for a neoplastic, infectious or different inflammatory process. Histopathology showed a blood vessel associated inflammation indicative for CLIPPERS.

Conclusion: Previous reports in the literature show cases of CLIPPERS with a spread of lesions in MR imaging and discuss the nosological position of CLIPPERS. The current case demonstrated an atypical MRI feature suggesting that CLIPPERS can present with heterogeneous morphological properties.

Disclosure: Nothing to disclose

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EP4163

Development of Guillain-Barré syndrome in patients receiving ganglioside treatment

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Introduction: The acute motor axonal neuropathy (AMAN) model has been successfully established by sensitizing Japanese white rabbits with a bovine brain ganglioside mixture including GM1 and the pathological findings in the peripheral nerves of the immunized rabbits were similar to pathological changes in patients with AMAN. However, observational studies on the relationship between the incidence of Guillain-Barré syndrome (GBS) and the intravenous use of ganglioside failed to reveal a positive correlation. Thus far, the relationship between ganglioside and occurrence of GBS remains controversial.

Methods: We presented five cases who developed GBS following ganglioside treatment. Additionally, we reviewed the literatures on the relationship between GBS and ganglioside therapy.

Results: All the five patients developed GBS after receiving ganglioside treatment range from five to fourteen days, without antecedent infectious. Three of them were prescribed ganglioside because of trauma or surgery. They all presented with acute or progressively flaccid paralysis. And the cervical MRI scan was normal which ruled out acute paralysis of the limbs caused by acute cervical myelopathy. The cerebrospinal fluid (CSF) examination showed an increase in protein level with cell count within the normal range. The diagnosis of GBS was further confirmed by electrophysiological examinations.

Conclusions: Ganglioside treatment, which is widely prescribed in China with few reports on the side effects, is suspected to be related to the development of GBS in our opinion. The history of trauma or surgery might made a patient prone to develop GBS after receiving exogenous ganglioside through influencing the human immunity.

Disclosure: Nothing to disclose
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Demographic description of Guillain-Barré syndrome: a retrospective analysis of 516 patients in Northeast China

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Introduction: Guillain-Barré syndrome (GBS) is generally considered as an immune-mediated disorder in the peripheral nervous system. Although the prognosis is generally favorable, mortality is up to 10% and approximately 20% of patients are left with severe disability.

Methods: We retrospectively analyzed the characteristics of 516 inpatients diagnosed as GBS in the First Hospital of Jilin University between 2003 and 2012.

Results: The median age of the subjects was 39.1 years, and 60.47% of them were male. About 57.56% had an antecedent infection and 36.43% developed GBS between April and June. Hyporeflexia or areflexia was present in 91.47% of all patients. Additionally, cranial nerves were involved in 40.31% of patients, among whom the glossopharyngeal nerves and the facial nerves were frequently involved, accounting for 70.19% and 53.37%. Sensory and autonomic deficits were present in 42.83% and 44.38% of all patients, while disturbances of consciousness and paralysis of respiratory muscles occurred in 3.3% and 24.61%. The cerebrospinal fluid (CSF) examinations were performed 2-4 weeks after disease onset. The albumin-cytologic dissociation was noted in 73% of patients. The electrophysiological check revealed that impairment of axonal, demyelinating and both involved accounted for 23%, 52% and 25%, respectively. The Hughes Functional Grading Scale (HFGS) score was used to access the severity of GBS. HFGS scores from 1-6 corresponded to 10%, 10%, 21%, 46%, 12% and 1% of all patients.

Conclusions: GBS is commonly triggered by antecedent infection, occurs with seasonal predilection and mainly affects males. The most common subtype is demyelinating form. Glossopharyngeal nerves are frequently involved.

Disclosure: Nothing to disclose