NEUROIMMUNOLOGY

FP75

CLINICAL OUTCOMES IN CHILDREN YOUNGER THAN 12 YEARS WITH MULTIPLE SCLEROSIS TREATED WITH SUBCUTANEOUS INTERFERON BETA-1A: SUBGROUP ANALYSIS OF A RETROSPECTIVE STUDY (REPLAY)

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Introduction: Data on efficacy of interferon (IFN) beta are limited in pediatric multiple sclerosis (MS). In the REPLAY study, subcutaneous (sc) IFN beta-1a (44 and 22 mcg, three times weekly) was well tolerated in the subgroup of patients aged <12 years at treatment initiation (Tenembaum et al 2013). Data on the impact of treatment on clinical relapses in these young children are presented here.

Methods: Medical records were retrospectively reviewed for patients with demyelinating events who received ≥1 injection of sc IFN beta-1a when aged <12 years. Clinical outcomes were annualized relapse rate (ARR) and time to first medically confirmed clinical relapse.

Results: In total, 50 patients with MS were <12 years at the time of their first sc IFN beta-1a injection. The median observation time (range) was 1.3 (0.1–6.9) and 2.4 (<0.1–12.5) years before and after starting sc IFN beta-1a therapy. The ARR (95% confidence interval [CI]) was 2.00 (1.81, 2.22) prior to treatment initiation, 0.27 (0.20, 0.37) during treatment, and 0.62 (0.39, 1.00) from stopping treatment until end of observation. Prior to sc IFN beta-1a initiation, the median time from first demyelinating event to first relapse (95% CI) was 6.1 (4.4, 8.7) months. Median time to first relapse after starting sc IFN beta-1a therapy (95% CI) was 70.1 (31.6, not estimated) months.

Conclusion: Although this retrospective study was not designed to evaluate efficacy, treatment with sc IFN beta-1a appeared to reduce relapses in patients with MS starting therapy when aged <12 years.

FP76

DIAGNOSING CHILDHOOD SMALL VESSEL CNS VASCULITIS: A PROPOSED HISTOLOGICAL TOOL.

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Introduction: Primary small vessel CNS vasculitis is an increasingly recognized, devastating inflammatory brain disease in children. An elective brain biopsy is mandatory to confirm the diagnosis. However, no standardized evaluative approach for brain biopsies has been defined. The study aimed to develop and validate a histological scoring tool for the diagnosis of small vessel CNS vasculitis on brain biopsies.

Methods: A comprehensive, evaluative instrument was drafted and reviewed by 7 expert neuropathologists across Canada. The refined tool was applied to cases and epilepsy controls diagnosed at Sick kids, Toronto. Stains included Hematoxylin & Eosin and immunohistochemistry for all immune cell subsets (CD3, 4, 8, 20 and 68). A consensus-meeting panel reviewed the results and finalized the tool for prospective validation.

Results: A total of 40 evaluations were included, 25 cases, 15 controls. Cortical inflammation was present in 68% of the cases vs. 24% of the controls (p=0.002) Perivascular small vessel inflammation was noted in 60% of cases vs. 20% of controls (P.04). Cortical vessel inflammation was predominantly T-cell mediated (79% CD3+, 96% CD8 +). White matter inflammation was present in 54% of cases vs. 3% of controls (p=0.01), correspondingly, white matter inflammation was primarily T-cell mediated (86% CD3+, 90% for CD8+), only 27% were CD20+. Myelin loss was rare in both cases and controls. Leptomeningeal inflammation was noted in 47% of cases and 45% of controls.

Conclusion: Canadian expert neuropathologists agreed on a consensus approach towards diagnosing small vessel CNS vasculitis including brain biopsy quality recommendations and a histological assessment tool.

FP77

NON-TRAUMATIC ACUTE MYELOPHATY: A SERIES OF 76 CASES

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Introduction: To describe our experience in the etiology, evolution, and sequelae of non-traumatic acute myelopathy (NTAM).

Material and methods: A retrospective, observational study of medical records of 76 patients who presented with NTAM was conducted. NTAM was defined as spinal cord involvement with motor and/or sensory deficits and/or sphincter dysfunction that reaches its nadir over the course of 3 weeks.

Results: Patients were classified into 4 groups according to etiology: A (n=11) tumour compression, being PNET the most-frequent tumour. B (n=9) vascular: 3 spinal AVM; 6 ischemic (4 procedure-related, 2 idiopathic). C (n=10) infectious: 2 mycobacterium; 1 bacterium; 1 CMV; 1 arbovirus; 4 enterovirus; 1 histoplasmosis. D (n=46) inflammatory/ demyelinating: 31 ADEM, NMO, MS; 12 idiopathic transverse myelitis; 3 lupus. The most frequent clinical presentation in all groups was gait abnormality and sphincter dysfunction. A rapid symptom onset (within hours) was characteristic of group B (p=0.00). Visual and sensory impairment and relapses were exclusively seen in group D. Sequelae were the most frequent in group A and the least frequent in group D (p=0.025). The most-common sequelae in all groups was paraparesis. CSF parameters of inflammation and a contrast-enhancing spinal cord MRI were only found in group C and D.

Conclusions: In the face of an NTAM patient, abroad range of possible causes should be considered. These causes should guide the request of complementary studies and treatment strategy. An inflammatory/ demyelinating etiology was most frequently observed in our series and was associated with better outcome.

FP78

UTILITY AND SAFETY OF RITUXIMAB IN PEDIATRIC AUTOIMMUNE AND INFLAMMATORY CNS DISEASE

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Introduction: Rituximab causes B cell depletion and is increasingly used off-label to treat autoimmune and inflammatory disorders of the CNS in children, adolescents and adults.

Methods: Multicentre retrospective review of the utility and safety of Rituximab treatment in children and adolescents with autoimmune and inflammatory CNS disorders.

Results: 144 children and adolescents (103 females, mean age 7.8 yrs, median 8, range 0.7-17) with NMDAR encephalitis (n=39), opsoclonus myoclonus ataxia syndrome (n=32), neuromyelitis optica (n=20), neuropsychiatric lupus (n=18), and other neuro-inflammatory disorders (n=35); were studied with a mean follow-up of 2.16 years. Infusion

adverse events were recorded in 18/144 (12.5%) including Grade 4 (anaphylaxis) in three, and all were transient and uncomplicated. 11 patients (7.6%) had an adverse infectious events. A definite, probable or possible benefit was reported in 125 of 144 (87%) patients. 17.4% of patients had a modified Rankin scale (mRS) of 0-2 at Rituximab initiation, compared to 73.9% at outcome. For the four main indications, the change in mRS 0-2 was larger in patients given early Rituximab compared to those treated later.

Conclusion: Rituximab is being used as a second line agent in children with severe autoimmune and inflammatory CNS disease. While limited by the retrospective nature of this analysis, our data suggest a role for the off-label use of Rituximab in severe autoimmune CNS disease. This safety data will help inform risk versus benefit discussions with families.

FP79

CLINICAL AND DEMOGRAPHIC FEATURES OF 389 CHILDREN WITH OMS: AN INTERNATIONAL COHORT

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Introduction: Opsoclonus-myoclonus syndrome (OMS) is a serious orphan disease in need of neuroepidemiological studies.

Methods: 24-year, IRB-approved, observational study at NPMC. N=357 U.S./32 other countries. Statistical analysis: medians (with IQR). Follow-up:1.9 y (1-3.4).

Results: Age 2.7 y (1.9-4). Gender: 215 females/174 males (1.2:1). Race: 85%-White, 10%-Black, 3%-Asian/Oceanic, 1%-Native American, 0.2%-Indian. Ethnicity 15%-Hispanic. OMS onset age: 1.5y (1.2-2). Time to diagnosis: 1.2 mo (0.7-3). At initial evaluation, 25%-acute, 32%-subacute, 43%-chronic; 18%-untreated, 22%-only-previously-treated, 60%-on-treatment (25%-monotherapy/14%-multimodal). Severity scores (OMES):39%-mild, 34%-moderate, 17%-severe. Tumor frequency was 50%:58%-abdominal/26%-thoracic/6%-pelvic/2%-cervical. Tumor type: 73%-neuroblastoma/22%-ganglioneuroblastoma/5%-ganglioneuroma. Neuroblastoma INNS stage 58%-I/35%-II/5%-III/2%-IV. Neuroblastoma: commonest type in young (p =. 004), more Stage I (p =. 002). Patients with tumour not distinguishable by prodromal symptoms, onset age, OMS severity, relapse rate, rank order of OMS sign appearance, or geographic distribution. OMS was non-relapsing (monophasic) in 59%, relapsing-remitting in 36%, relapsing-progressive in 5%. 53% of relapsers had 1 relapse, 20%-2, 27%-3-or-more (annualized rate 0.1/y). First relapse trigger (48%-treatment-taper/40%-infection/12%-both/other) predictive of subsequent ones. A single relapse carried a 47% risk of another/2 relapses-57%/3 relapses-35%. OMS duration at first relapse was 1.5 y (0.7-2.5); at last relapse 2.3 y (1.4-4). Chronic relapsers could not be predicted initially on clinical grounds. Of the 7% of OMS that never attained remission (Total-Score ≤ 6), 73% had cognitive impairment; 73% had relapsed at least once.

Conclusions: In this largest reported series, OMS has a propensity for relapse. Failure to remit and relapses were the main associations with cognitive impairment. A different approach to OMS based on the tumor vs idiopathic dichotomy was not supported. Biomarkers for relapse prediction and better prevention measures are needed.

FP80

PHARMACODYNAMICS OF IMMUNOTHERAPY FOR OPSOCLONUS-MYOCLONUS SYNDROME: IMPACT ON CYTOKINES/CHEMOKINES

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INTRODUCTION: The purpose was to evaluate the capacity of immunotherapies to normalize several putative inflammatory biomarkers of disease activity in OMS.

METHODS: BAFF and APRIL and a variety of chemokine ligands for CXCR3, CXCR5, CCR4, CCR7 were measured in cerebrospinal fluid (CSF) and serum by ELISA in 433 children: 296 OMS/109 controls/28 other inflammatory neurological disorders (OIND). A blinded scorer rated motor severity on the validated OMS Evaluation Scale.

RESULTS: In untreated OMS, elevations of CSF BAFF (+57%), CXCL10 (+2.7-fold), CXCL13 (+16.5-fold) and serum CCL22 (+55%) and CCL17 (+121%) were significant ($P < 0.0001$). In cross-sectional comparisons of treated groups, three different pharmacodynamic patterns emerged. Corticotropin (ACTH) was associated with lower production of CSF BAFF (-61%) and CXCL13 (-91%) and serum CCL22 (-51%) and CCL21 (-32%); response to corticosteroids was similar. In contrast, the IVIg group showed no such effects, but serum APRIL was higher (+6.7-fold), remaining normal in CSF. Rituximab-treated, not cyclophosphamide-treated, groups had higher serum BAFF (+2.6-fold), normalizing after B cell repopulation. Treatment with front-loaded ACTH, IVIg, and rituximab dropped CSF BAFF (-41%) and CXCL13 (-84%), and serum CCL22 (-34%), by 6-8 months, and diminished severity score (71%). By one week, serum CCL22 dropped 81% and CCL21 59%, with slow decline in CXCL13. Concentrations normalized over 12 weeks of ACTH tapering. Serum APRIL increased 2.9-fold after 1-2 g/kg IVIg monotherapy ($P = 0.0003$).

CONCLUSIONS: Striking distinctions in immunotherapy effects on BAFF/APRIL, CXCL13/CXCR5, CCL22/CCR4, and CCL21/CCR7 signalling were found. The contrasting pharmacodynamic patterns may offer utility as treatment biomarkers.

FP81

VOLTAGE GATED POTASSIUM CHANNEL (VGKC)-COMPLEX ANTIBODIES IN CHILDREN: WHAT DO THEY MEAN?

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Introduction: In adults, VGKC-complex antibodies are associated with limbic encephalitis (LE), neuromyotonia and Morvan's Syndrome. Many of the antibodies bind to the VGKC-associated proteins LGI1 and CASPR2[1]. In children, the VGKC-complex antibodies have been identified in a wider range of encephalopathies, seizure disorders and autistic regression. Our objective was to systematically identify the associated clinical phenotypes in 2 London paediatric neurology centres.

Method: From 2007-2013, 363 serum samples were tested for VGKC-complex antibodies. Patient notes were reviewed retrospectively and patients were grouped independently by their primary diagnosis to either inflammatory (n= 159) or non-inflammatory (n=204) aetiologies.

Results: 39/363 (11%) of the patients tested were VGKC-complex antibody positive, and presented with encephalopathy (n=18), acute demyelinating syndrome (n=6), movement disorder (n=4), neuromuscular syndromes (n=5), seizure disorders (n=3) and others (n=3). These antibodies were positive in 31/159 patients with inflammatory conditions compared with only 8/204 in the non-inflammatory group. (p <0.0001, Fisher's exact). Only one child who presented with GBS was positive for the associated proteins (LGI1 and CASPR2). Of the 18 VGKC-antibody positive patients with encephalopathy; 3 had LE (one with additional neuromyotonia). An additional antibody was present: NMDAR in one, GAD in one and TPO in three. None had an underlying neoplasm.

Conclusion: Positivity of VGKC-complex antibodies in children does not indicate a specific clinical syndrome and the VGKC-associated proteins are mostly negative. Nevertheless, these antibodies are identified more frequently in primary inflammatory disorders and can be a non-disease specific biomarker of an inflammatory condition that may be immunotherapy-responsive.

FP82

THE CLINICAL IMPACT OF ACUTE DEMYELINATION OF THE CENTRAL NERVOUS SYSTEM IN CHILDREN

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Background: Acute demyelinating syndromes (ADS) of the central nervous system (CNS) in children may occur as an isolated illness with rapid resolution, may result in permanent neurological disability, or may represent the first clinical manifestation of chronic diseases such as multiple sclerosis (MS).In a national prospective cohort study we delineate the clinical features, acuity, medical management, and clinical outcome of children with incident ADS.

Results: 299 eligible children were followed prospectively from ADS presentation: 71 (24%) with monofocal optic neuritis, 61 (21%) with clinically monofocal transverse myelitis, 36 (12%) with monofocal deficits extrinsic to the optic nerve and spinal cord, 75 (25%) with acute disseminated encephalomyelitis (ADEM), and 54 (18%) with polyfocal deficits without encephalopathy. Hospitalization at the time of first attack was required for 258 participants (87%) with a median length of stay of 6 (range 1-99) days. At onset, 75 children were profoundly encephalopathic with polyfocal deficits, 69 were unable to ambulate independently, and 48 had severely impaired vision. Twelve patients with monoADS and one patient with MS experienced severe sequelae following their incident attacks of demyelination.

Conclusions: ADS is a serious illness in Canadian children, with 87% of children requiring hospitalization due to severe neurological deficits during acute illness. Over 95% of children recovered physically from their ADS event. However, permanent visual and spinal cord impairment occur in a small proportion of children, and 17% were diagnosed with MS within the first few years post ADS.

FP83

SPECTRUM OF MOG AUTOANTIBODY-ASSOCIATED DEMYELINATING DISEASES IN PEDIATRIC PATIENTS

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Background: Myelin oligodendrocyte glycoprotein (MOG) has been a candidate target antigen in acquired demyelinating diseases of the CNS. The presence of MOG antibodies has been described in children with different demyelinating syndromes.

Aim: To describe the clinical spectrum of children seropositive for MOG IgG antibodies, clinically identified at a single centre in Buenos Aires.

Methods: Between 2009 and 2012 serum and CSF samples collected from 105 consecutive children with an acute CNS inflammatory/ demyelinating event were sent to Oxford for AQP4-IgG and MOG-IgG antibody testing using immunofluorescence on live HEK cells transfected with either human M23-Aquaporin-4 or human MOG. Clinical and MRI features of MOG-IgG seropositive children were reviewed and their disease classified using 2013 consensus definitions.

Results: Twenty-five patients (24%) were positive for MOG-IgG antibodies and negative for IgG-AQP4; 13 were boys (52%) and median age at onset was 7 years (1.75-16). Longitudinal myelitis was identified in 19 (76%) children; thalamic involvement in 15 (60%); and tumefactive brainstem lesions in 13 (52%). Using the classification, nine children had NMOSD, nine had ADEM, four had optic neuritis, two a brainstem syndrome, and one an acute myelopathy. Ten (40%) children relapsed and seven of them were treated with azathioprine. Longitudinal analysis of available samples showed persisting MOG-IgG in 10/12 children.

Conclusion: These results suggest that the presence of MOG antibodies may help define a subgroup of children with acquired demyelinating diseases. The heterogeneity of these children suggests that spectrum of an antibody mediated disease is not necessarily restricted to a single clinical phenotype.

FP84

MYELIN OLIGODENDROCYTE GLYCOPROTEIN (MOG) ANTIBODIES IN CHILDREN WITHOUT OLIGOCLONAL BANDS PREDICT A NON-MS COURSE OF ACQUIRED DEMYELINATION SYNDROME (ADS).

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Introduction: MOG-Abs are found in children with ADS but their significance is not clear.

Method: Acute serum samples from 66 children with first episode ADS (12 ADEM, 24 optic neuritis, 18 transverse myelitis, 12 other CIS) were tested for MOG-Abs by cell-based assay. MOG-Abs and oligoclonal bands (OCBs) were used in a classification and regression decision tree analysis (RDTA) to predict progression to MS at one year.

Results: 24/66 (36%) children had MOG-Abs. When compared to the MOG-Ab negative group (n=32), the positive patients presented with ON (50% vs 29%), TM (17% vs 33%), ADEM (17% vs 19%) or other CIS (17% vs 19%). CSF OCB positivity at onset was higher in the MOG-Ab negative group (14/35 vs 1/17, p=0.011). Subsequently 16 MOG-Ab negative patients were diagnosed with MS (15 clinical, 1 radiological) compared to 3 positive patients (2 clinical, 1 radiological) (p=0.046). In the RDTA model, a positive test result (negative MOG-Ab with positive OCB) resulted in positive likelihood ratio of 11.0 (95% CI 2.7-45) for development of MS, whereas a negative test result (positive MOG-Ab, or negative MOG-Ab with negative OCB) resulted in a negative likelihood ratio of 0.44 (95% CI 0.26 to 0.76).

Conclusions: MOG-Abs are found at presentation in 36% of patients with childhood ADS, across a range of demyelinating disorders. When combined with negative OCB results they help to distinguish those children who will not develop MS from those, with negative MOG-Abs and positive OCBs, who are at high risk.

FP85

THERAPEUTIC PLASMA EXCHANGE IN PAEDIATRIC NEUROLOGY: INDICATIONS, SIDE EFFECTS AND OUTCOMES FROM FOUR UK TERTIARY CENTRES

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Introduction: Therapeutic plasma exchange (TPE) is increasingly used in a range of neurological illnesses in children characterised by the presence of autoantibodies or suspected immune dysregulation. Our aim was to ascertain the indications, side effects and outcomes for children receiving TPE.

Methods: Multicentre retrospective case review of 58 paediatric neurology patients undergoing TPE from 2005-2013. Outcome was assessed using modified Rankin Scale (mRS) for children (http://www.neuropaediatrie.ch/snpsr/Modified%20Rankin%20Scale.pdf).

Results: Median age at treatment was 9.2 years (range 1.3-16.0) with 23 days elapsed since onset of neurological symptoms (range 1 day-12.5 years). Indications included transverse myelitis (n=16), ADEM (n=9), myasthenia gravis (n=8), NMDAR encephalitis (n=7), Guillain-Barré syndrome (n=5), CIDP (n=4), VGKC encephalitis (n=3) and FIRES (n=2). A median 2 treatments were tried before TPE (range 0-4) including steroids (88%) and IVIG (70%). Courses comprised a median 6 exchanges (range 2-179) given over 8 days (range 3-466). 36% of courses were initiated in PICU. Reported complications included hypocalcaemia (n=13), suspected line infection (n=8), anaemia (n=6), coagulopathy (n=5) and hypotension (n=5). 73% of patients were severely disabled (mRS=5) at treatment initiation. There was a statistically significant improvement in mRS score immediately following treatment, with improvement in 21% of patients and no change in 79% (Wilcoxon signed-rank test, p<0.001). Treating clinician's impression of effect was positive in 65%. Median mRS at follow-up was 3 (moderate disability); 9% were severely disabled (n=4) or dead (n=1).

Discussion: This study provides safety and efficacy information on TPE for clinicians and families and provides a basis for future prospective studies.

FP86

CLINICAL CHARACTERISTICS OF IRISH NARCOLEPSY PATIENTS FOLLOWING H1N1 INFLUENZA EPIDEMIC AND VACCINATION IN 2009/2010

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Introduction: Following the H1N1 influenza epidemic of 2009/2010, we noted an increase in the number of children presenting with narcolepsy. This has been examined nationally with a link to H1N1 vaccine identified. We compared patients who had received H1N1 vaccination to those patients who had no significant vaccine exposure.

Methods: We prospectively collected data on referrals with narcolepsy received between December 2009 and December 2012, in addition to retrospective review of all cases from January 2006 to December 2009. We examined data for symptom complex experienced, investigation results, vaccine exposure, and if positive, time lag from vaccination to symptom onset.

Results:48 patients were diagnosed with narcolepsy, 43 had a history of H1N1 vaccination prior to symptom onset.Average age of symptom onset was 10.05 years, with a lag from vaccine to symptom onset of 0.38 years in those who had received vaccination.Average age of symptom onset in unvaccinated patients was 8.25 years. Incidence of cataplexy was 3 in 4 for vaccinated patients, versus 4 in 5 unvaccinated patients. Where results are available to date, 34/35 had positive HLA typing for DQB1:0602 in vaccine related patients, and 4/5 unvaccinated patients were positive.

Conclusion: There is an increased incidence of narcolepsy related to H1N1 vaccination, likely to have an immune aetiology.Vaccinated and unvaccinated groups present as homogenous in terms of symptoms experienced and investigation results.

FP87

AUTOIMMUNE ENCEPHALITIS IN CHILDREN: EXPERIENCE OF A TERTIARY CARE TEACHING HOSPITAL IN NORTH INDIA

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Introduction: Autoimmune encephalitis is a spectrum of disorder manifested by epileptiform encephalopathy, neuropsychiatric manifestations and extrapyramidal features. Anti NMDA receptor and Basal ganglia encephalitis are two such entities encountered in the pediatric age group.[1]

Material and Methods: Fourteen cases of proven autoimmune encephalitis (upto 18 years of age) presented to a tertiary care hospital in north India between January 2010 and August 2013.

Results: In the 11 patients with anti NMDA receptor encephalitis (average age 9 years, male female ratio 1:1.2), the common modes of presentation were progressive extrapyramidal syndrome and epileptiform encephalopathy. Sixty four percentage (7/11) showed significant response to combination therapy of steroids and intravenous immunoglobulin. The 3 cases with basal ganglia encephalitis (all males, aged 8, 6 and 10 years) presented with acute onset parkinsonian features, chronic progressive generalized dystonia and acute onset motor tics respectively. The first 2 cases had abnormal brain MRI in the form of bilateral striatal signal changes with additional cerebellar and occipital changes in the first, the third patient's MRI was normal. The first and third case showed near complete response to steroids and intravenous immunoglobulin. The second case was already 2 years into the illness and had irreversible bilateral striatal cystic changes on MRI with no significant response to immunotherapy.

Conclusion: In upto two-third patients with encephalitis like presentation, a specific infectious etiology is not found.[2] Autoimmune encephalitis should always be considered if there are specific clinical pointers in view of possible favourable response to early immunotherapy.