Summary Plenary Topic I: ***Am I missing something? Is it MS? Is it NMO?***

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The audience/membership

The aim of the first plenary session was to bring into focus selected topics in the expanding field of childhood MS.

The definition or diagnostic criteria of Paediatric MS

In the first lecture A. Waldmann, CHOP, reviewed the IPMSSG consensus definitions from 2007 and 2013 for pediatric inflammatory-demyelinating diseases and highlighted the changes recently made. In 2007 the main goal was to define a common terminology in regards to MS, ADEM and NMO and a classification system to facilitate prospective research studies. For the diagnosis of ADEM for example the presence of encephalopathy and multifocal neurological signs were included and less emphasis was put on imaging criteria. Although it is known that children with MS can present with an encephalopathy at the first demyelinating event a study by Banwell 2011 (Lancet Neurology) showed that due to the new criteria only 3.3% in children less than 12 years with an ADEM phenotype developed MS. The following changes were made in the 2013 revision: The term polysymptomatic was changed to polyfocal neurological symptoms, the term recurrent ADEM was omitted and included under the umbrella of multiphasic ADEM. It was also appreciated that other phenotypes of relapsing episodes after ADEM can occur such as ON (ADEMON).

Dr. Waldmann also stated that children who fulfill McDonald criteria at disease onset do not have a more aggressive clinical course which supported by recent data that children who met the 2010 McDonald criteria at the time of first attack did not experience more frequent subsequent relapses (van Pelt et al, JNNP, 2013) and did not develop earlier physical disability when compared to pediatric MS patients who did not meet criteria at the time of the first attack

(Bigi et al, 2013). In her summary she emphasizes that careful characterisation of children with an acute demyelinating event will allow for improved diagnostics and eventually the development of prognostic markers in addition to the need for further validation of pediatric neuroinflammatory disorders such as ADEM-ON, CRION in collaborative studies.

2. “Prognostic markers in pediatric MS - are we able to tell a child's fortune?“

D. Pohl addressed the following aspects: Risk factors for pediatric MS susceptibility in general, markers predicting MS after an initial demyelinating event, markers for the severity of the further course of the disase or the response to treatment. She pointed out that female gender, high BMI, parental smoking, low Vit D level, remote EBV-infection and the presence of more than one HLA-DRB1 alleles (review Waldmann, 2014) are independant risk factors for the development of childhood MS. Factors influencing the likelyhood of pediatric MS after the first event are older age, an MRI with hypointense lesions and OCBs in CSF (Banwell et al, 2011; Verhey et al, 2011).
A substantial number of children will eventually have significant disease burden at a younger age. Dr. Pohl stated that prognostic factors for „early severity“ in Pediatric MS are a short intervall between 1st and 2nd MS attack, which is also associated with low serum level of Vit D (Mowry et al,2010) or incomplete recovery from a severe 1st attack (Fay et al, 2012; Harding et al, 2014). Data to predict response to treatment (e.g. relapses in first year(s) of treatment, or MRI activity at 12 months of treatment) are not yet available due to the lack of randomized trials in children. In the future, the talk concludes, it would be desirable to have individual prognostic markers at hand in order to tailor immunmodulatory treatment accordingly.

3. Pathology in demyelination

In the third lecture Dr. Brück, Göttingen, presented the differential diagnosis of children with an acute demyelinating event based on their pathological findings in children who had a brain biopsy taken. The cohort consisted of 30 children with median age at first attack of 12.6 years. Median duration between symptom-onset and biopsy was 39 days, the clinical presentation

was polysymptomatic in the majority of cases with a median follow up 3.9 years. Nearly 80% were finally diagnosed with MS/CIS, 17% with NMO, 3% with ADEM. The histopathological results in children with CIS/MS were similar to findings in adults characterized by an even more prominent perivascular and parenchymal Inflammation with mainly T cells (CD8 > CD4), few B cells and plasma cells in addition to an abundance of macrophages/microglia. Other important features were confluent demyelination with active signs of remyelination, acute axonal damage and activated astrocytes. Interestingly also children with NMO showed prominent signs of inflammation eosinophilic granulocytes, confluent demyelination, axonal and oligodendrocyte loss. In addition children with NMO and AQP4 antibodies revealed dystrophic astrocytes and loss of the protein aquaporin-4 loss and up regulation of MOG-protein. One improtant difference in children with ADEM is that the inflammation is mainly perivascular not as extensive as in MS or NMO. Also demyelination is restricted to the perivascular spaces and axons are preserved. He concluded that also demyelinating disorders such as ALD or MLD show signs of inflammation and confluent demyelination but often reveal inclusions in astrocytes and macrophages which should be then further studied by electronmicroscopy.

4. MOG antibodies in demyelination

K. Rostasy, Innsbruck discussed the role of serum MOG antibodies in the differential diagnosis of inflammatory demyelinating diseases. Autoantibodies have recently gained attention, because of the role of AQP-4 antibodies in the diagnosis and pathogenesis of NMO. B-cells have long been implicated in various inflammatory-demyelinating diseases. CSF chemokine CXCL13- a B-cell chemoattractant predicts for example conversion to MS. Oligoclonal bands and MRZ reaction are a constant finding also in children with CIS/MS. Recently a number of articles were published looking at the frequency of MOG antibodies in serum of children with an ADE. Pooling data from these studies it appears that ¼ of all children has detectable autoantibodies against MOG-protein, which is expressed on the outermost surface of the myelin sheath. Human MOG-antibodies have been shown to induce complement mediated cytotoxicity in-vitro, but convincing evidence for their pathogenicity

is missing. Initially thought to play a role in CIS/MS, MOG antibodies have been found in particular in children with ADEM, recurrent ON and NMOSD with absent AQP4-antibodies (Rostasy et al, 2012). Studies suggest that there is a certain overlap between these disease entities (e.g ADEM followed by ON, (Huppke et al, 2012)). It appears that children with ADEM and MOG antibodies that decline overtime have a sole episode only with a characteristic MRI pattern and a better prognosis (Proebstel et al, 2011; Bauman et al, 2014). Children with high and persiting MOG antibodies are more likely to develop further episodes (e.g ON, NMOSD). Little is known about the longterm outcome and the appropriate therapy in particular in children with a NMOSD phenotype and MOG antibodies. The role of MOG antibodies and the spectrum of MOG associated diseases needs to be further defined.

5. The new NMO diagnostic criteria

In the last lecture Silvia Tenembaum introduced the new NMO criteria. After describing the clinical and pathological hallmarks of NMO, she focussed on the evolving diagnostic criteria overtime ending with the recent recommendation made by the expert group „International panel of NMO diagnosis“. According to the panel's recommendation children and adults will be allocated into two groups based on the AQP4 antibody status measured with is a cell-based assay (CBA): (1) NMO Spectrum Disorder (NMOSD) with AQP4 antibodies or (2) NMOSDr without AQP4 antibodies.

NMOSD with AQP4 antibodies requires a positive test for AQP4 IgG , ≥ 1 core clinical characteristic and no better explanation for the clinical syndrome. Core clinical characteristics for seropositive patients include ON, TM, area postrema syndrome (episodes of unexplained nausea, vomiting, or hiccups) acute brainstem syndrome, symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD- typical diencephalic MRI lesion or symptomatic cerebral syndrome with NMOSD-typical brain lesions.

NMOSD without AQP4 antibodies or not known antibody status need to have at least 2 core clinical characteristics, meeting all of the following: (1) At least

1 core characteristic must be ON, LETM, or area postrema syndrome (2) dissemination in space. (3) Fulfillment of additional MRI requirements (as applicable) which includes for example for acute ON a brain MRI showing (A) normal findings or non-specific white matter lesions and (B) T2 or T1-w gad-enhancing lesion extending over >1/2 optic nerve length or involving the optic chiasm. Acute myelitis needs to expand over >3 contiguous segments (LETM) or >3 contiguous segments of spinal cord atrophy in patients with prior history compatible with acute myelitis. Area postrema syndrome requires associated dorsal medulla/area postrema lesion.

Differences between pediatric and adult NMO appear are that AQP-4 antibodies are less prevalent in monophasic disease course. In children also the presence of LTEM is less predictive of NMO compared to adults and can occur in children with MS and ADEM as well. Overall clinical outcome in children seems better and cerebral MRI changes are more often reported.