Immunological Insights into Pediatric MS

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Brigham and Women’s Hospital

Associate Professor in Neurology
Harvard Medical School

WHY STUDY THE IMMUNOLOGY (BIOLOGY) OF PEDIATRIC MS?

1) Pediatric MS may provide novel insights into environmental risk factors for MS

2) Identify mechanisms of disease initiation and disease progression

3) Pediatric MS may provide us with novel insights into the early immune mechanisms of MS

1) Pediatric MS may identify factors related to disability accrual

2) To optimize treatment selection for children with MS
Why Study the Immunology (Biology) of Pediatric MS?

1. Pediatric MS may provide novel insights into environmental risk factors for MS

Does pediatric MS present clinically closer to the true biological onset of MS?
NIH-sponsored study – US Network of Pediatric MS Centers
Environmental and Genetic risk factors in pediatric MS
(PI: Emmanuelle Waubant)

- Target enrollment 500 children with MS from 15 pediatric MS Centers in US
- 1500 age and sex and center-matched controls

- Environmental and dietary exposures questionnaire
- DNA and serum sample

- (Substudy – gut microbiome in pediatric MS-NMSS funded)

- www.clinicaltrials.gov

ENVIRONMENTAL RISK FACTORS

- Serological evidence for remote EBV infection in pediatric MS patients vs. controls
  - 83% MS, 42% controls (Aloitaibi et al., JAMA 2004)
  - 99% MS, 72% controls (Pohl et al, Neurology 2006)
  - 86% MS, 64% controls (Banwell et al., Lancet 2007)
  - 88% MS, 56% controls (Lunemann, Neurology 2008)

- Remote infection with CMV associated with lower risk of pediatric MS; HSV effect ≈ HLA status (Waubant, Neurology 2011)

- Decreased Vitamin D levels in patients under 20 years of age correlated with MS susceptibility
  (Munger and Ascherio, JAMA 2006)

- Parental cigarette smoking increases MS risk in children (RR=2.12)
  (Mikaeloff et al. Brain 2007)
**Obesity in MS**

- Women who are obese (BMI>30kg/m²) at the age of 18 had a greater than two-fold increased risk of MS compared to those with normal BMI (Munger, Neurology 2009)

- Childhood obesity was associated with 2X risk of MS in females only (Munger, MSJ 2013)

- Obese girls are twice as likely to develop MS as normal weight girls (Langer-Gould, Neurology 2013)

**MIGRATION DATA**

- When people from low risk areas move to high risk areas before the age of 15 - their risk of MS is the same as those living in the high risk area

- When people from low risk areas move to high risk areas after the age of 15 - their risk of MS stays the same as people from their original low risk country

⇒ The period before age 15 is a susceptibility period for developing MS

Ascherio, 2005 review
AGE and GENDER DISTRIBUTION OF PEDIATRIC MS

• Before puberty (0-12)
  • Less than 20% of cases

• After puberty (13-18)
  • >80% of cases

• Gender distribution
  0.9:1 female before age 14 years
  2.2:1 after age 14 years

(Pohl et al., Eur J. Pediatrics 2007)

Is puberty the key risk period for the development of MS?
WHY STUDY THE IMMUNOLOGY (BIOLOGY) OF PEDIATRIC MS?

2. Identify mechanisms of disease initiation and progression

AGE INCREASES THE RISK OF MS AFTER OPTIC NEURITIS

Meta-analysis of 14 studies, 223 pediatric patients with ON. Age and abnormal MRI scan increases risk of MS

Waldmann, J. AAPOS, 2011
### Predictors of MS in Children?

**Banwell, Lancet Neurology 2011**

#### Overall vs. MS

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Overall (n=205)</th>
<th>MS (n=16)</th>
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Perivenous demyelination is characteristic of ADEM

Young, Brain 2011
Pediatric vs. adult MS: EAE studies

Model: Passive transfer of MOG-transgenic T cells into B6 mice

Ongoing

Pediatric vs. Adult EAE model:
Limited inflammatory infiltrate limited to perivascular area in younger mice

2 wk old  4 wk old  6 wk old

T-spine

Work in progress
• Can the difference or progression from ADS → MS inform us about the mechanisms of developing MS?

Implication of perturbed axoglial apparatus in early pediatric multiple sclerosis

Increased gliomedin (GLDN) in CSF of children with MS after ADS

Dhaunchak, Annals of Neurology 2012
WHY STUDY THE IMMUNOLOGY (BIOLOGY) OF PEDIATRIC MS?

2. Pediatric MS may provide us with novel insights into the early immune mechanisms of MS

Relevant studies on reactivity to myelin peptides

Several studies have demonstrated differential T cell responses to myelin peptides in adult MS subjects

Children with inflammatory CNS demyelination, remote CNS injury, as well as children with type I diabetes exhibited heightened PBMC responses to a wide array of self-antigens – (Banwell, Ann Neurol 2008)

CD4+ T cell responses to MBP and MOG peptides in adult and pediatric MS: no differences between the two groups – (Correale et al. Mult Scler 2006)
Increased T cell responses to myelin peptides in pediatric MS compared to adult MS and healthy children

Vargas-Lowy, Clin Imm. 2013

PMS > PHC (p = 0.0107 for MP1; p = 0.0133 for MP10)
PMS > AMS (p = 0.002 for MP1; p = 0.0002 for MP10).

Increased IL-17 producing CD62Lhi CD4+ cells in pediatric MS vs. healthy children

• IL17+IFNγ- CD4+CD62L high (MP10)
PMS > PHC (p < 0.05)

• IL-17+IFNγ+ CD62L high (MP1)
PMS > PHC (p < 0.05)

two-way ANOVA, Bonferroni post test

Vargas-Lowy, Clin Imm. 2013
Central memory cells have been shown to be prevalent in the CSF of MS patients and in MS lesions – (Kivisakk Proc Natl Acad Sci U S A 2003, Kivisakk et Ann Neurol 2004)

Younger children with MS had increased CSF neutrophils c/w IL-17 production (Chabas, Neurology 2009)

Th17 cells are crucial for penetration of the blood-brain barrier and may be important in initiation of disease within the CNS — (Kebir, Nat Med 2007)

Suppression of migration from lymph nodes of Th17 central memory cells is one mechanism of action of S1P1 antagonist, fingolimod in MS – (Mehling Neurology 2010)
Increased proportion of memory T cells in pediatric MS vs. HC
And normalize with the addition of DMT

Ballint B et al. Neurology 2013;81:784-792

ELUCIDATING THE SPECTRUM OF MOG ANTIBODY ASSOCIATED DISEASE IN CHILDREN

O’Connor, Nature Medicine 2007
MOG antibodies are increased in pediatric-onset MS, particularly in children<10

McLaughlin, J. Immunology 2009

MOG antibodies persist in children who develop multiple sclerosis (MS).

Pröbstel A et al. Neurology 2011;77:580-588
13/83 (15%) are MOG seropositive; and are younger than seronegative patients.

MOG seropositive patients present with a bimodal distribution:
- an older group (13-18 years) presenting with optic neuritis
- a younger group (ages 4-8) presenting with encephalopathy

Seropositives were found in all disease categories – MS, CIS, ADEM, NMO
Higher CSF WBC in MOG seropositive patients.
Corpus callosum lesions were absent in seropositive patients.
Relapse rate and EDSS score at 2 years did not differ between both groups.

Fernandez-Carbonell, submitted
Figure 1 Serum reactivity to KIR4.1 in children with acquired demyelinating diseases. Protein-based ELISA was used to detect anti-KIR4.1 serum autoantibodies.

Kraus V et al. Neurology 2014;82:470-473

SUMMARY OF IMMUNE FEATURES OF PEDIATRIC MS

- INCREASED MYELIN-REACTIVE CD4+ T CELL PROLIFERATION
- INCREASED MEMORY T CELL COMPARTMENT
- INCREASED CENTRAL MEMORY TH17 PRODUCING T CELLS
- INCREASED MOG (KIR1.4?) ANTIBODY PRODUCTION
WHY STUDY THE IMMUNOLOGY (BIOLOGY) OF PEDIATRIC MS?

6. Pediatric MS may identify factors related to disability accrual

CHILDREN PROGRESS SLOWER ON PHYSICAL DISABILITY SCALE THAN ADULTS

- Simone et al., Neurology 2005
  - Time to reach EDSS 4 was 20.2 years (adults 10.8 years)
  - Mean age to EDSS 4 was 31.6 years old (adults 41.2 years old)

- Boiko et al., Neurology 2002
  - Time to EDSS 3.0 - 16.03±1.17 years (adults 7.69 y)
  - Time to EDSS 6.0 - 19.39±1.43 years (adults 14.97 y)

- Renoux et al., NEJM 2007
  - Longer time to EDSS 4, 6, 7 in children vs. adults
  - Despite this, children reach given EDSS at younger ages than adults

HOWEVER AT ANY GIVEN AGE, PEDIATRIC ONSET PATIENTS HAVE MORE DISABILITY THAN ADULT-ONSET MS PATIENTS
Better recovery from ON in children vs. adult MS

- Younger age associated with better recovery

<table>
<thead>
<tr>
<th>Attack N (%)</th>
<th>ACMS</th>
<th>POMS</th>
<th>Unadjusted P-value</th>
<th>Adjusted P-value</th>
</tr>
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<tbody>
<tr>
<td>Mild (1)</td>
<td>29 (11.5)</td>
<td>5 (13.16)</td>
<td>0.77</td>
<td>0.67</td>
</tr>
<tr>
<td>Moderate (2)</td>
<td>101 (58.9)</td>
<td>13 (4.21)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe (3)</td>
<td>123 (48.6)</td>
<td>20 (52.03)</td>
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<table>
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<tr>
<th>Recovery N (%)</th>
<th>Complete (1)</th>
<th>Fair (2)</th>
<th>Poor (3)</th>
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<tr>
<td></td>
<td>202 (79.8)</td>
<td>23 (8.1)</td>
<td>28 (11.1)</td>
<td>0.041</td>
<td>0.029</td>
</tr>
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Malik, Neurology 2014

SLOWER ACCRUAL OF DISABILITY IN CHILDREN WITH MS

PERIPHERAL IMMUNE SYSTEM?
- Adaptive immune changes
- Innate immune changes
- Hormone/cytokine milieu

CNS?
- Glial cell features
- Axonal integrity
- Mitochondrial health
- Remyelinating capacity

FOUNTAIN OF YOUTH?
Less axonal damage, and improved remyelination in younger mice

Reviewed: Vargas-Lowy and Chitnis, Clin Imm 2012

Hampton, AJP 2012
WHY STUDY THE IMMUNOLOGY (BIOLOGY) OF PEDIATRIC MS?

5. To optimize treatment selection

Is pediatric MS the same disease as adult MS?

<table>
<thead>
<tr>
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<td>- Similar disease course – relapses, progression</td>
<td>- &quot;Children are not small adults&quot;</td>
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<td>- Similar risk factors – Vitamin D, EBV, smoking, obesity</td>
<td>- More inflammatory disease course - relapse rate, MRI lesions</td>
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<tr>
<td>- Generally respond to same treatments</td>
<td>- Biological differences: MOG antibodies, Th17 responses</td>
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<td>- Cognitive disability prominent</td>
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<td>- Impact of disease during key physical, mental, educational and social developmental period</td>
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**TAILORING MS THERAPIES – PERSONALIZED MEDICINE**

**MS MECHANISMS**
- T Cell activation
- APC activation
- Epitope spreading
- B cell stimulation
- Antibody production
- Cortical lesions and gray matter pathology
- Dying back axonopathy
- Diffuse activation of glial cells – microglia and astrocytes
- Mitochondrial dysfunction and oxidative stress
- Presence of meningeal follicles
- Impaired CNS repair processes

**MECHANISMS MS THERAPIES**
- B-IFN
- Increase Th2 response
- Decrease Th1/Th17 responses
- Enhance Tregs
- T, B cell cytostatics
- Modify APC function
- Prevent immune cell migration/BBB penetration
- Stabilize mitochondria
- Modify microglial, astrocyte function
- Enhance neuroprotection
- Enhance remyelination

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Patients and their families

Funding:
National MS Society
Peabody Foundation
NIH