PEDIATRIC MULTIPLE SCLEROSIS
CLINICAL AND TRANSCRIPTIONAL ASPECTS

Gurevich M.
PEDIATRIC MS

- Pediatric MS is defined as onset MS under the age of 18 years
- Pediatric MS occurs in about 3% of MS cases
- MS onset before puberty (<12 years) is defined as childhood and between 12-18 years is defined as juvenile Pediatric MS
- Phenotype: Relapsing-remitting MS >98%, Primary Progressive <2%
- As compared to adult patients, Pediatric MS is characterized by a more aggressive initial course, but better recovery and slower disease progression (Renoux C, et al. 2007)
GENDER EFFECTS IN ADULT MS

• Higher prevalence of MS in females

• Amelioration of MS during pregnancy (Finkelsztein A, 2011, meta-analysis of 22 reports, 13,141 women, ~70% suppression of RR)

• Sex hormones demonstrate anti-inflammatory and neuroprotective effects in MS clinical trials (Voskuhl RR, et al, 2016).

• Oestriol reduces MRI activity in RRMS females, testosterone reduces brain tissue loss and improved cognition (Kurth, F., et al. 2014).

• Clinical phenotype in pediatric MS patients could be affected by pubertal transition.

• Effects of puberty on pediatric MS clinical presentation could be different in males and females.
OUR HYPOTHESIS

• Hormonal changes associated with puberty in Pediatric MS patients could ameliorate the disease.

• The expected effect of puberty could be gender dependent.
EFFECTS OF AGE AND GENDER ON DISEASE PROGRESSION IN PEDIATRIC MULTIPLE SCLEROSIS POPULATION

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SHEBA MEDICAL CENTER
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METHODS

- Data of Pediatric MS patients followed prospectively in Sheba MS Center from 1995-2016 were analyzed. Patients were diagnosed according to 2010 McDonald criteria.
- Queried for onset of puberty by Tanner stage.

We examined the differences between childhood (< 12 years) and juvenile (12-18 years) MS patients as follows:

- Onset parameters:
  - number and volume of brain MRI lesions, EDSS, EDSS presenting symptoms.
- Clinical outcome parameters:
  - time to second relapse, time to EDSS 3.0, 5 years ARR, EDSS at 5, 10, 15 and 20 years from onset.
RESULTS
DISTRIBUTION OF PEDIATRIC MS PATIENTS BY AGE AT ONSET, N=133
DISTRIBUTION OF PEDIATRIC MS PATIENTS BY GENDER

Pediatric MS onset
- N=133
- onset: 15.0 ± 0.3 Y
- F:M 1.7

Juvenile MS onset
- N=116
- onset: 15.9 ± 0.1 Y
- F:M 1.9

Childhood MS onset
- N=17
- onset: 8.8 ± 0.7 Y
- F:M 0.9
  - females
    - N=8
    - onset: 8.6 ± 0.6 Y
  - males
    - N=9
    - onset: 9.0 ± 1.2 Y

females
- N=76
- onset: 15.9 ± 0.2 Y

males
- N=40
- onset 14.8 ± 0.5 Y
AGE EFFECT: DISABILITY AT ONSET IS NOT AFFECTED BY AGE

Disability at onset

No differences in MRI parameters at onset

Proportion of EDSS functional systems

Number of EDSS functional systems
AGE EFFECT IN MALES: SEVERITY OF ONSET IS NOT AFFECTED BY PEDIATRIC MALE AGE

Disability at onset

Proportion of EDSS functional systems

No differences in MRI parameters at onset

EDSS

<table>
<thead>
<tr>
<th>EDSS</th>
<th>Childhood</th>
<th>Juvenile</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td></td>
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</tr>
<tr>
<td>2</td>
<td></td>
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<tr>
<td>3</td>
<td></td>
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p = 0.1

Number of EDSS functional systems

<table>
<thead>
<tr>
<th>System</th>
<th>EDSS Parameter</th>
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<tbody>
<tr>
<td>Pyramidal</td>
<td>p = 0.01</td>
</tr>
<tr>
<td>Sensory</td>
<td>p = 0.02</td>
</tr>
<tr>
<td>Visual</td>
<td>p = 0.5</td>
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<tr>
<td>Brainstem</td>
<td>p = 0.01</td>
</tr>
<tr>
<td>Cerebellar</td>
<td>p = 0.01</td>
</tr>
<tr>
<td>Bladder</td>
<td>p = 0.5</td>
</tr>
</tbody>
</table>

p = 0.01
AGE EFFECT IN FEMALES: DISABILITY AT ONSET
NOT AFFECTED BY AGE

Disability at onset

No differences in MRI parameters at onset

Proportion of EDSS functional systems

<table>
<thead>
<tr>
<th>System</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyramidal</td>
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<tr>
<td>Sensory</td>
<td>0.8</td>
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<tr>
<td>Visual</td>
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<tr>
<td>Brainstem</td>
<td>0.01</td>
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<tr>
<td>Cerebellar</td>
<td>0.01</td>
</tr>
<tr>
<td>Bladder</td>
<td>0.01</td>
</tr>
</tbody>
</table>
GENDER EFFECTS CHILDHOOD MS: SEVERITY OF ONSET NOT AFFECTED BY GENDER IN CHILDHOOD MS

Disability at onset

No differences in clinical outcome parameters
GENDER EFFECTS IN JUVENILE MS: SEVERITY OF ONSET AND CLINICAL OUTCOME NOT AFFECTED BY GENDER IN JUVENILE MS

No changes in others onset and clinical outcome parameters
AGE EFFECT: BETTER CLINICAL OUTCOME IN JUVENILE PATIENTS

<table>
<thead>
<tr>
<th>Clinical parameters</th>
<th>Childhood MS N=17</th>
<th>Juvenile MS N=116</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>EDSS at 5 years</td>
<td>2.3 ± 0.6 (N=13)</td>
<td>1.5 ± 0.3 (N=64)</td>
<td>0.05</td>
</tr>
<tr>
<td>EDSS at 10 years</td>
<td>3.6±0.7 (N=12)</td>
<td>2.9 ± 0.4 (N=52)</td>
<td>0.1</td>
</tr>
<tr>
<td>EDSS at 15 years</td>
<td>5.2 ± 0.7 (N=12)</td>
<td>3.3 ± 0.4 (N=43)</td>
<td>0.01</td>
</tr>
<tr>
<td>EDSS at 20 years</td>
<td>5.7 ± 0.9 (N=8)</td>
<td>3.5 ± 0.1 (N=41)</td>
<td>0.01</td>
</tr>
</tbody>
</table>
AGE EFFECT IN MALES: JUVENILE MALES HAVE BETTER CLINICAL OUTCOME

5 years ARR

Disease progression

No differences in other outcome parameters
CONCLUSIONS:

- In pediatric patients disability at onset is not affected by age or gender.
- Juvenile patients and especially juvenile males have better clinical outcome.

Our findings might be explained by the protective immunomodulatory effect of sex hormones during puberty.
GENE-EXPRESSION ANALYSIS OF PEDIATRIC PATIENTS WITH MULTIPLE SCLEROSIS TREATED WITH NATALIZUMAB

BRACHA ROBINSON
NATALIZUMAB

- Humanized monoclonal Antibody targeting α4 subunit of α4β1-integrin
- FDA approved therapy for adults
- In children similar efficacy to adults
  - Fewer relapses
  - No enhancing lesions on MRI
  - No association with PML (unlike adults)
- Effect on childhood development is not fully understood
OUR GOAL

- To determine whether Natalizumab induces changes in gene expression in pediatric MS similar to adult MS patients
- To determine whether Natalizumab treatment affects the expression of essential childhood and adolescent developmental genes
PATIENT CHARACTERISTICS

- 18 Patients treated with Natalizumab
  - Of these, 10 patients were sampled for gene expression analysis

<table>
<thead>
<tr>
<th></th>
<th>Total n=18</th>
<th>Female n=10</th>
<th>Male n=8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age MS onset</td>
<td>13.9±0.8</td>
<td>13.8±1.0</td>
<td>14.1±1.2</td>
</tr>
<tr>
<td>Age Tx start</td>
<td>14.8±0.6</td>
<td>14.5±0.8</td>
<td>15.1±1.1</td>
</tr>
<tr>
<td>EDSS before Tx</td>
<td>1.67±0.27</td>
<td>1.95±0.36</td>
<td>1.31±0.38</td>
</tr>
<tr>
<td>Annual Relapse Rate before Tx</td>
<td>1.33±0.26</td>
<td>1.20±0.31</td>
<td>1.48±0.45</td>
</tr>
</tbody>
</table>
CLINICAL RESULTS: NATALIZUMAB INDUCES CLINICAL EFFICACY

1 – before treatment
2 – one year after Natalizumab treatment

Switch of Annual EDSS rate by Natalizumab treatment

p=3.7E-05

PCA of Blood gene expression
Red = Before treatment
Blue = After treatment
COMPARISON TO ADULTS (FUNCTIONAL ANALYSIS)
NATALIZUMAB ALTERS GENE EXPRESSION IN CHILDREN AND ADULTS IN SIMILAR WAYS

<table>
<thead>
<tr>
<th>Diseases or Functions Annotation</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>differentiation of pre-B lymphocytes</td>
<td>3.05E-09</td>
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<tr>
<td>differentiation of B lymphocytes</td>
<td>5.34E-07</td>
</tr>
<tr>
<td>arrest in differentiation of B lymphocytes</td>
<td>1.37E-06</td>
</tr>
<tr>
<td>proliferation of B lymphocytes</td>
<td>4.23E-06</td>
</tr>
<tr>
<td>development of B lymphocytes</td>
<td>5.22E-06</td>
</tr>
<tr>
<td>development of pre-B lymphocytes</td>
<td>1.37E-05</td>
</tr>
<tr>
<td>expansion of B lymphocytes</td>
<td>0.000104</td>
</tr>
<tr>
<td>proliferation of pre-B lymphocytes</td>
<td>0.000245</td>
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<tr>
<td>lifespan of B lymphocytes</td>
<td>0.000486</td>
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<tr>
<td>differentiation of plasma cells</td>
<td>0.000611</td>
</tr>
<tr>
<td>development of follicular B lymphocytes</td>
<td>0.000835</td>
</tr>
</tbody>
</table>

It has been previously shown that in adults, Natalizumab alters expression of genes related to B cell activity.
WEIGHTED GENE CO-EXPRESSION NETWORK ANALYSIS (WGCNA)

- Developed by Steve Horvath and Peter Langfelder of UCLA in 2008
- This method creates clusters of highly correlated genes which can be related to external traits

1. **Step 1: Construct a Network**
   Quantify connection and determine interaction patterns between genes

2. **Step 2: Identify Modules**
   Find gene clusters

3. **Step 3: Relate Modules to External Information**
   Find biologically interesting modules
WGCNA: GENE CLUSTERS

Each black line represents one gene

Each color represents one cluster

We merged highly-related clusters together
WGCNA: COMPARISON TO EXTERNAL TRAITS

Names of clusters

Clinical traits

Red = positive correlation
Green = negative correlation
(p-values in parentheses)
Circles = \( p \leq 0.05 \)

Clusters that are correlated with treatment are not the same clusters that are correlated with age, gender, and Tanner scale → Natalizumab does not affect age-related genes
CONCLUSIONS

Natalizumab treatment is an effective treatment in pediatric patients

Natalizumab does not affect gene expression modules that are associated with childhood development.