PEDIATRIC MULTIPLE SCLEROSIS CLINICAL AND TRANSCRIPTIONAL ASPECTS

MULTIPLE SCLEROSIS CENTER

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PEDIATRIC MS

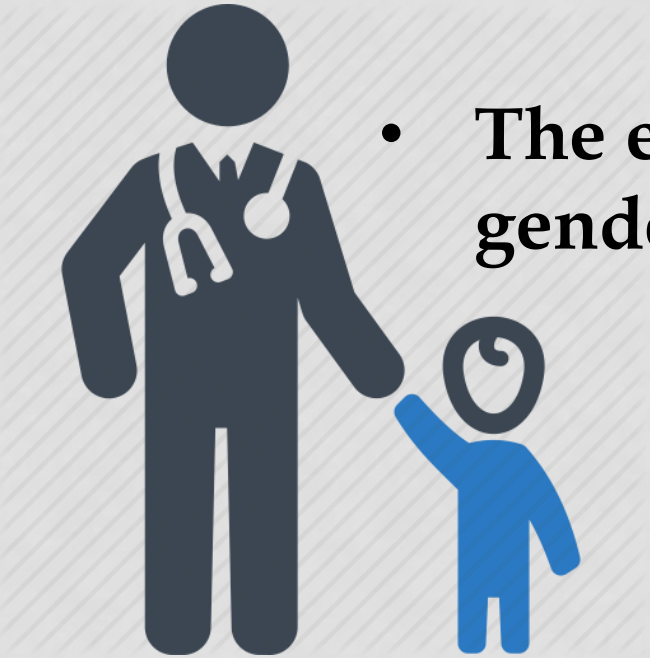
- **Pediatric MS is defined as onset MS under the age of 18 years**
- **Pediatric MS occurs in about 3% of MS cases**
- **MS onset before puberty (<12 years) is defined as childhood and between 12-18 years is defined as juvenile Pediatric MS**
- **Phenotype: Relapsing-remitting MS >98%, Primary Progressive <2%**
- **As compared to adult patients, Pediatric MS is characterized by a more aggressive initial course, bur 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

KHAVKIN YULIA

MULTIPLE SCLEROSIS CENTER
SHEBA MEDICAL CENTER
ISRAEL

METHODS

- **Data of Pediatric MS patients followed prospectively in Sheba MS Center from 1995-2016 were analyzed.**

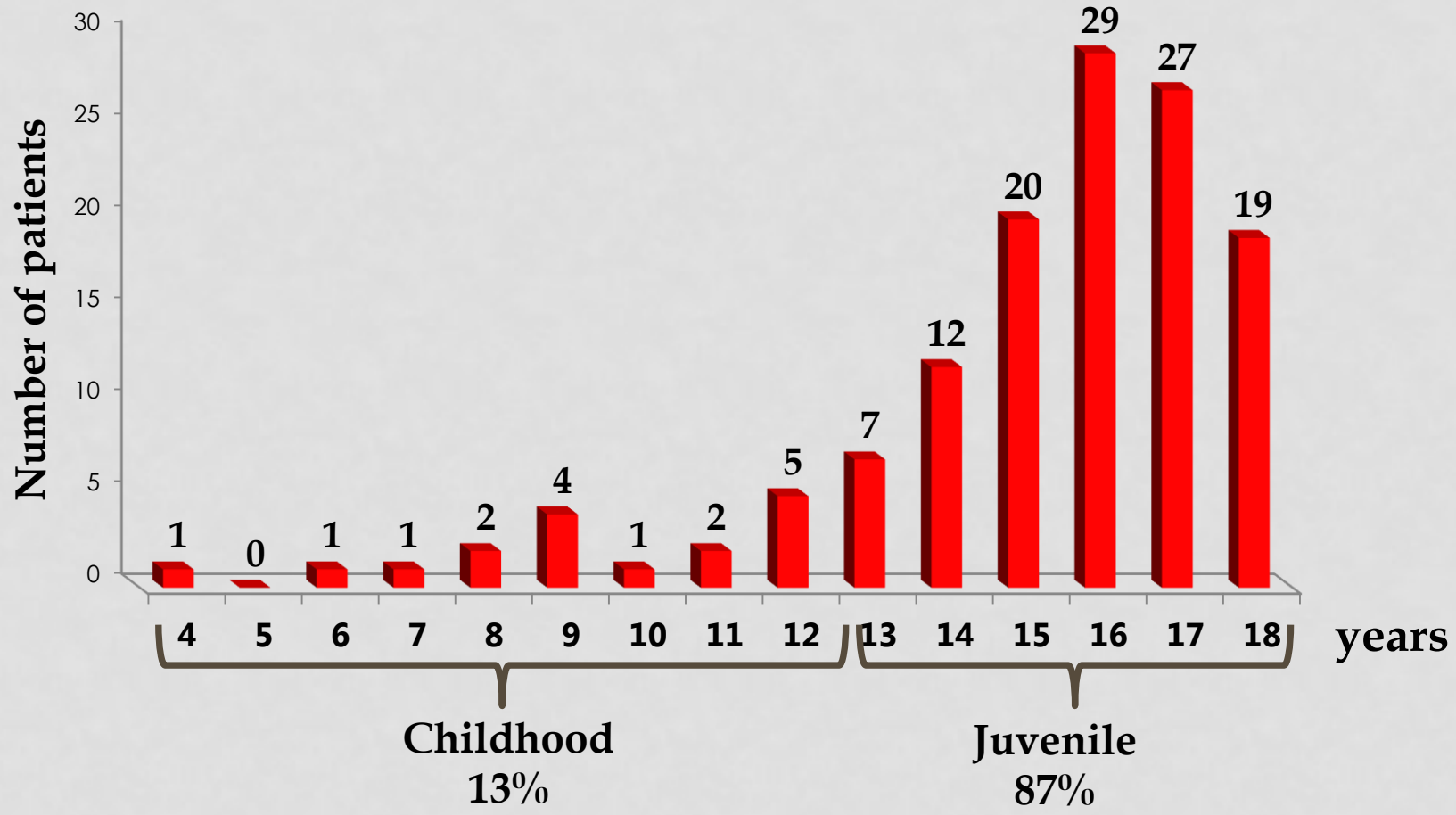
Patients were diagnosed according to 2010 McDonald criteria

- **Queried for onset of puberty by Tanner stage.**

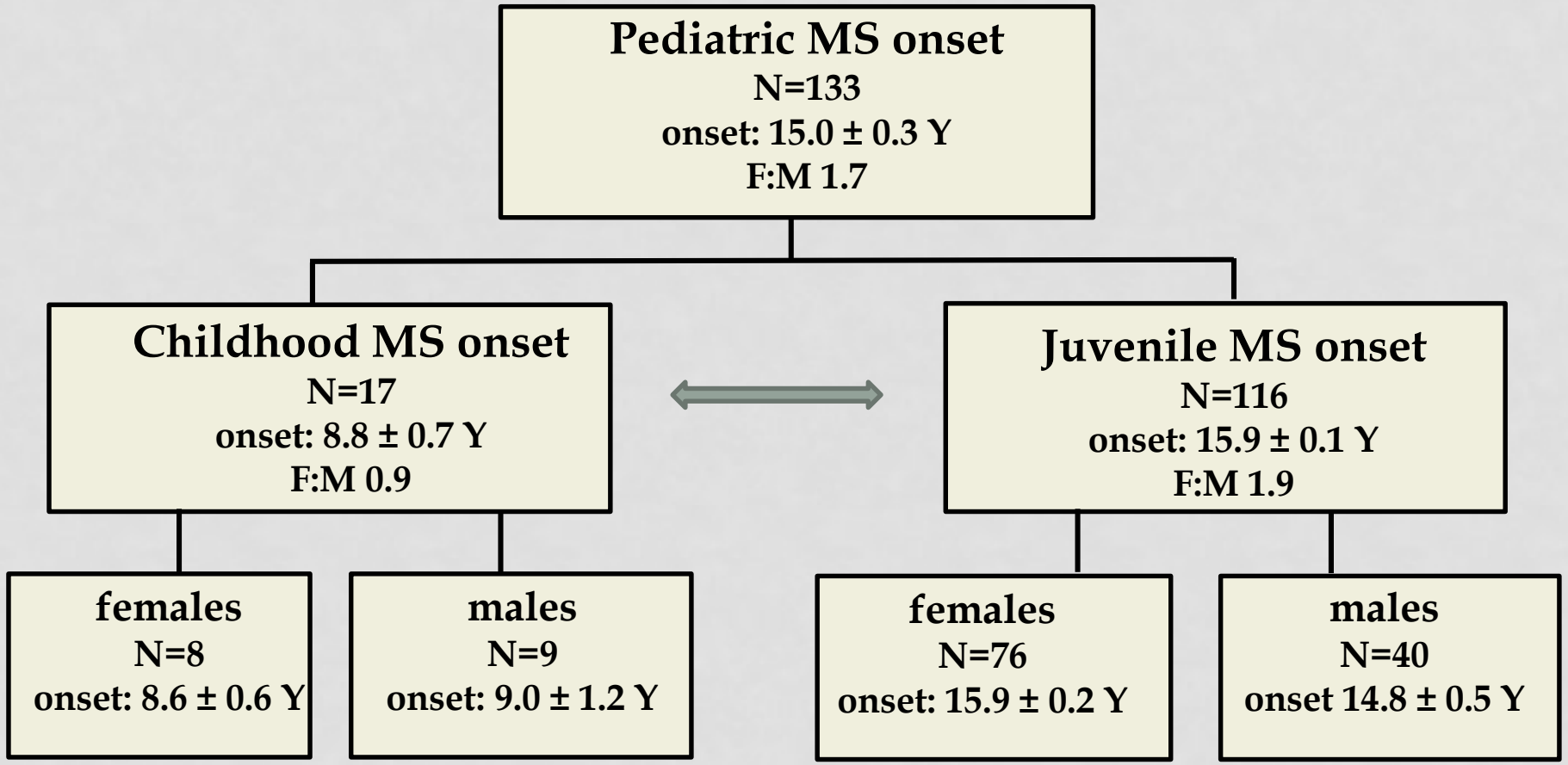
We examined the differences between childhood (< 12 years) and juvenile (12-18 years) MS patients as follows:

- **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.

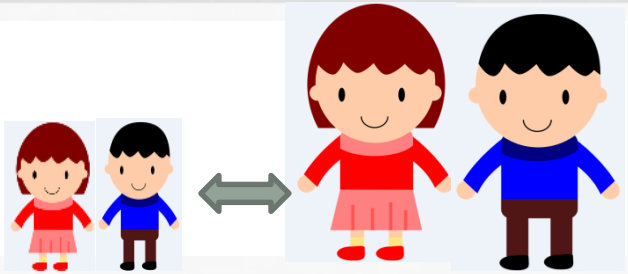
RESULTS
DISTRIBUTION OF PEDIATRIC MS PATIENTS BY AGE AT ONSET, N=133



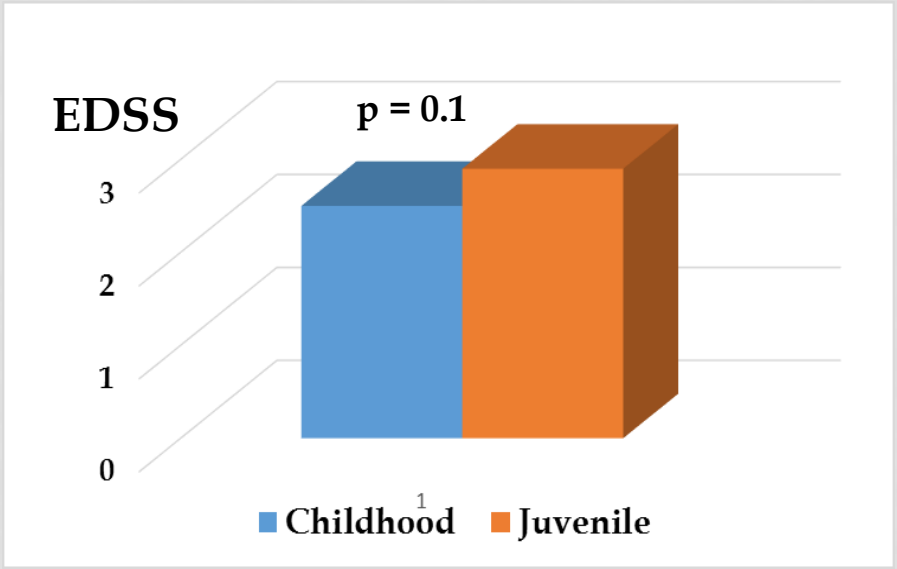
DISTRIBUTION OF PEDIATRIC MS PATIENTS BY GENDER



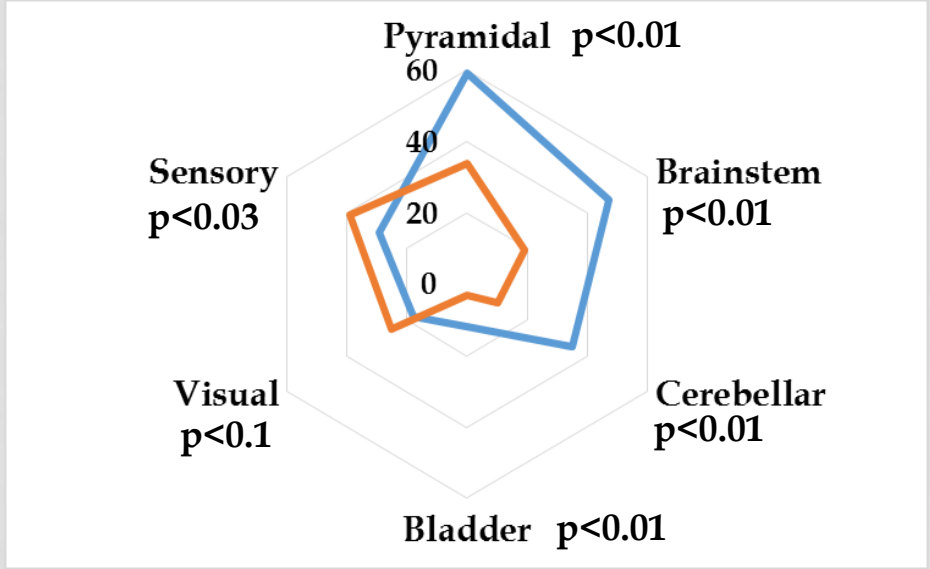
AGE EFFECT: DISABILITY AT ONSET IS NOT AFFECTED BY AGE



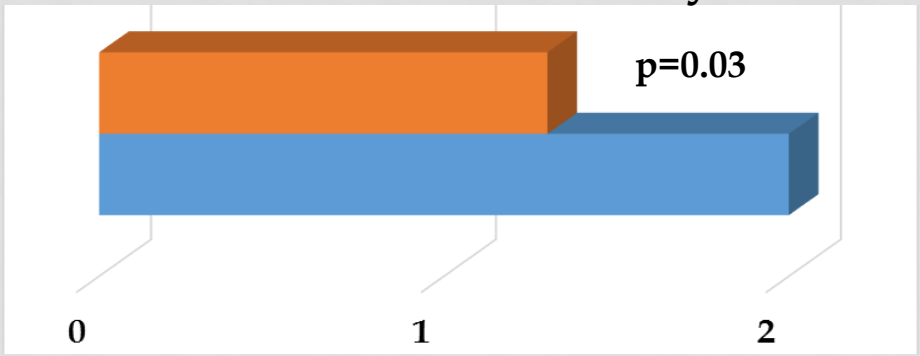
Disability at onset



Proportion of EDSS functional systems

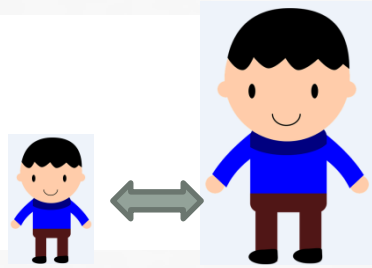


Number of EDSS functional systems

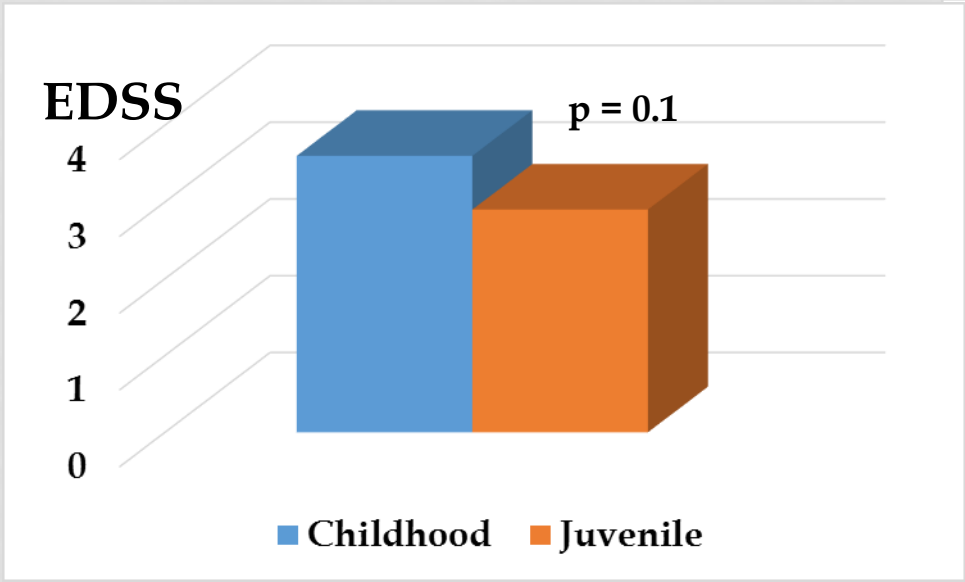


No differences in MRI parameters at onset

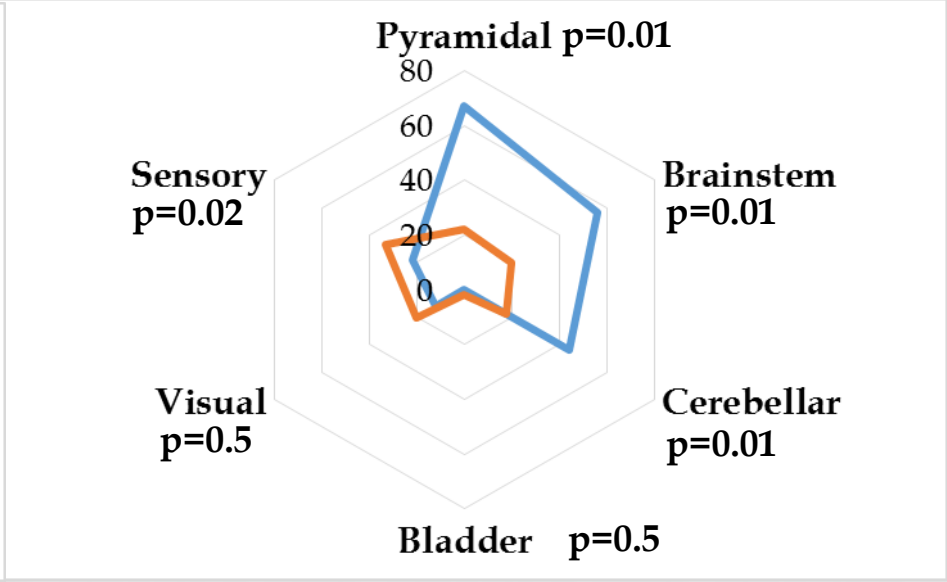
AGE EFFECT IN MALES: SEVERITY OF ONSET IS NOT AFFECTED BY PEDIATRIC MALE AGE



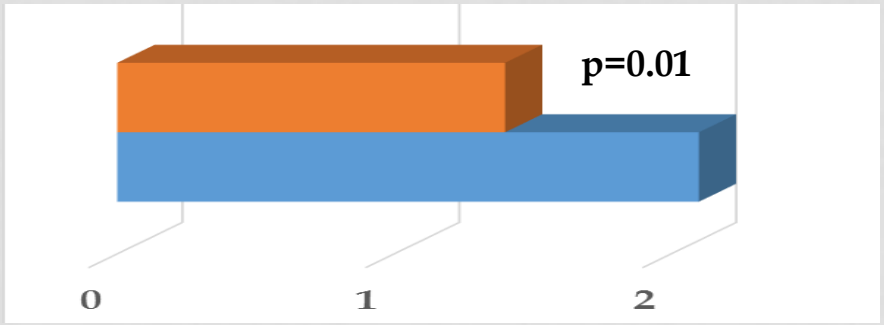
Disability at onset



Proportion of EDSS functional systems

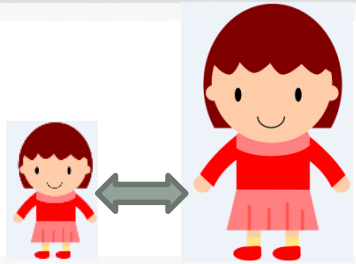


Number of EDSS functional systems

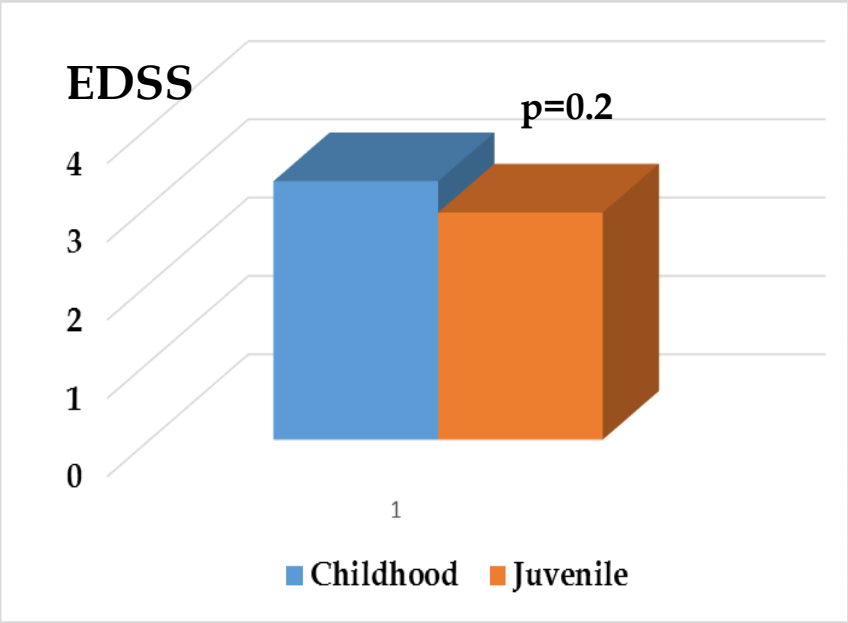


No differences in MRI parameters at onset

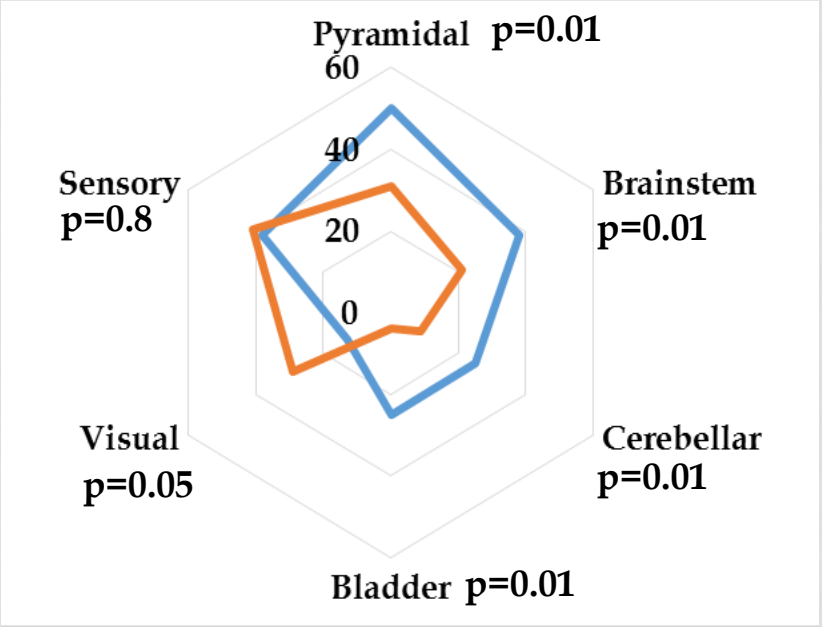
AGE EFFECT IN FEMALES: DISABILITY AT ONSET NOT AFFECTED BY AGE



Disability at onset

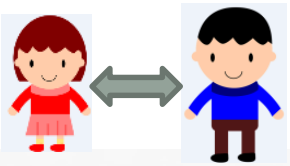


Proportion of EDSS functional systems

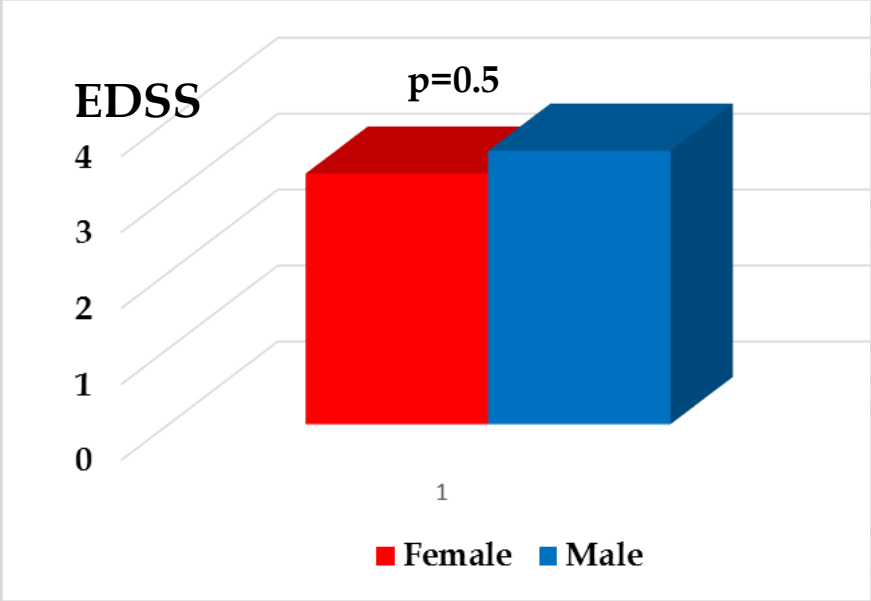


No differences in MRI parameters at onset

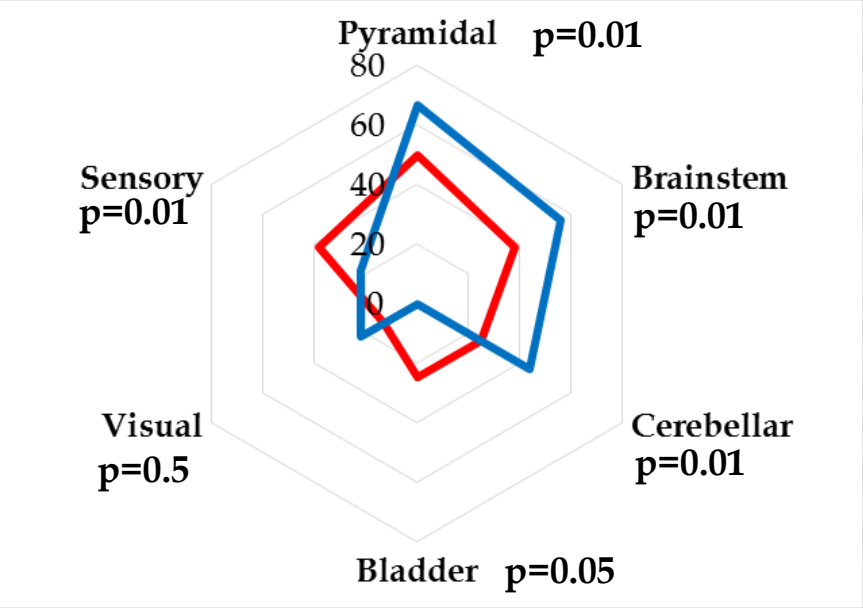
GENDER EFFECTS CHILDHOOD MS: SEVERITY OF ONSET NOT AFFECTED BY GENDER IN CHILDHOOD MS



Disability at onset

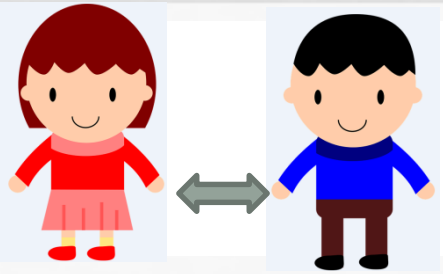


Proportion of EDSS functional systems

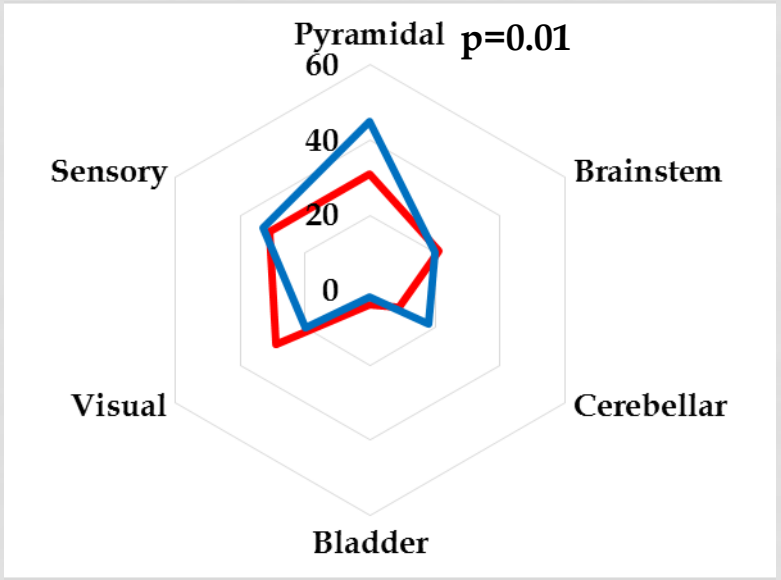


No differences in clinical outcome parameters

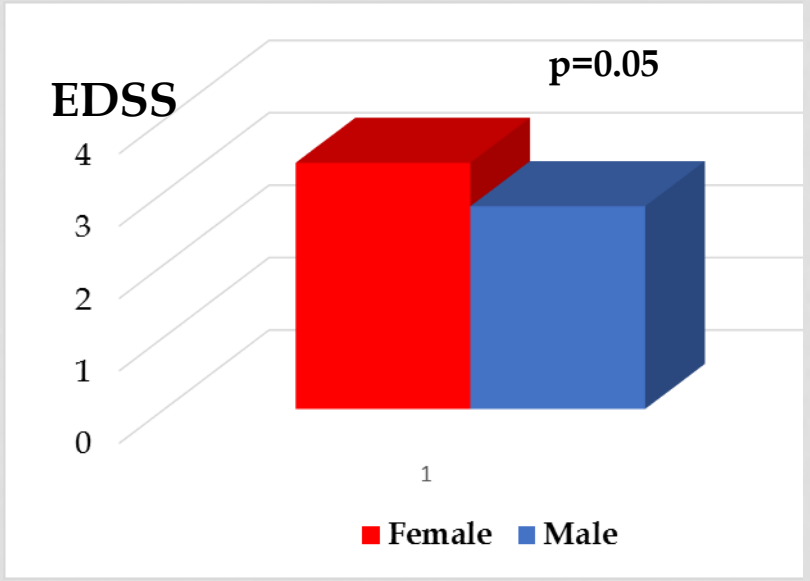
GENDER EFFECTS IN JUVENILE MS: SEVERITY OF ONSET AND CLINICAL OUTCOME NOT AFFECTED BY GENDER IN JUVENILE MS



Proportion of EDSS functional systems at onset

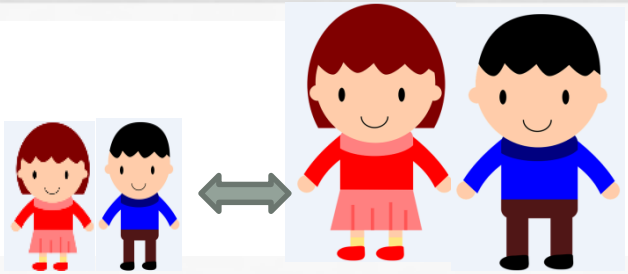


EDSS after 10 years

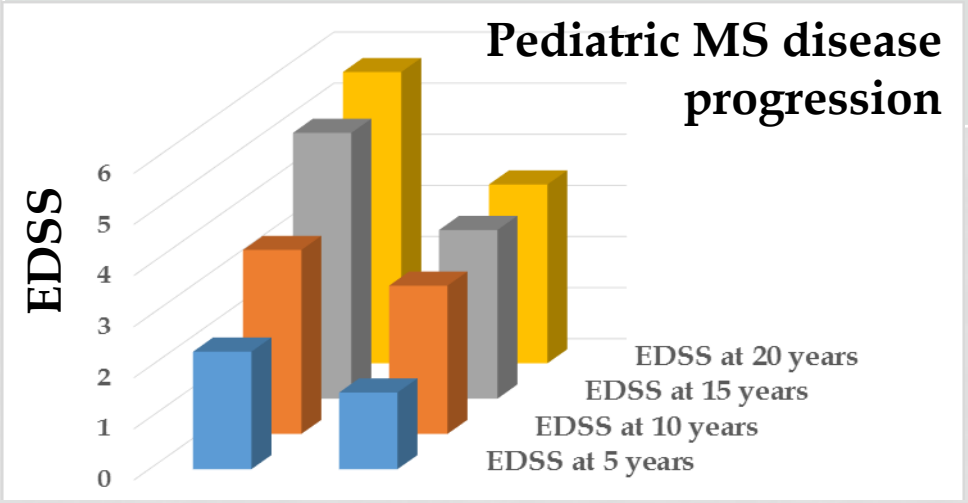


No changes in others onset and clinical outcome parameters

AGE EFFECT: BETTER CLINICAL OUTCOME IN JUVENILE PATIENTS

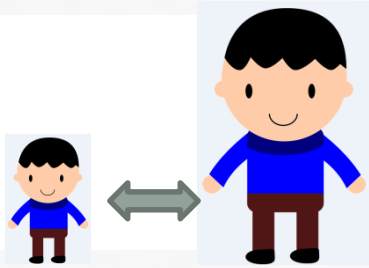


Clinical parameters	Childhood MS N=17	Juvenile MS N=116	p value
EDSS at 5 years	2.3 ± 0.6 (N=13)	1.5 ± 0.3 (N=64)	0.05
EDSS at 10 years	3.6±0.7 (N=12)	2.9 ± 0.4 (N=52)	0.1
EDSS at 15 years	5.2 ± 0.7 (N=12)	3.3 ± 0.4 (N=43)	0.01
EDSS at 20 years	5.7 ± 0.9 (N=8)	3.5 ± 0.1 (N=41)	0.01

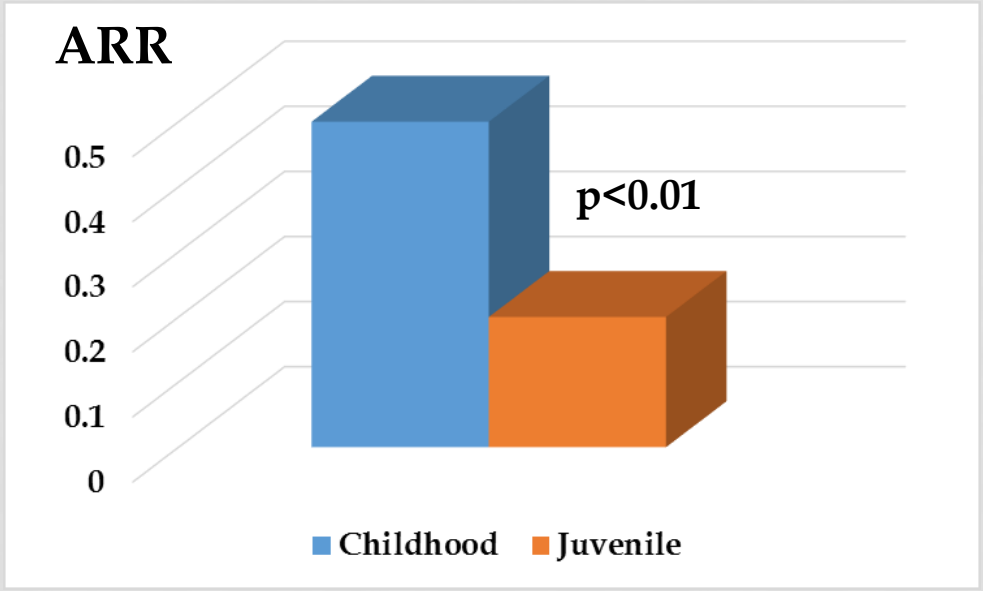


No differences in other outcome parameters

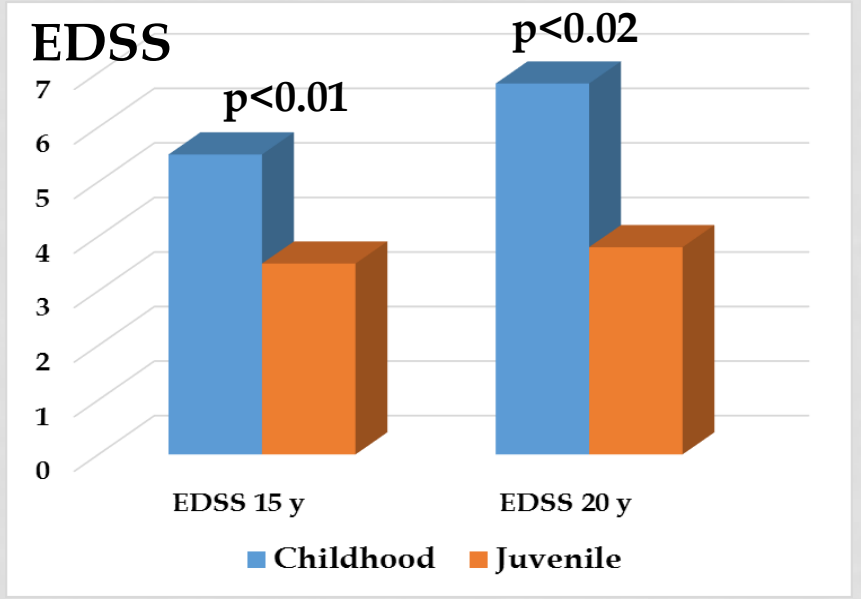
AGE EFFECT IN MALES: JUVENILE MALES HAVE BETTER CLINICAL OUTCOME



5 years ARR



Disease progression

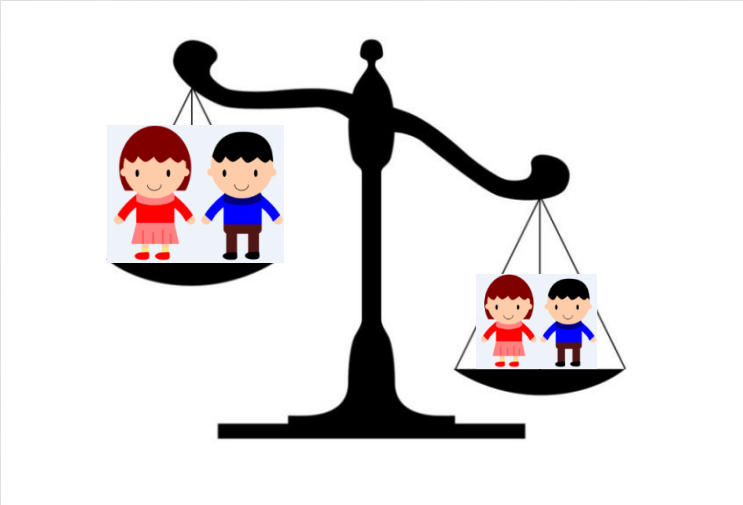


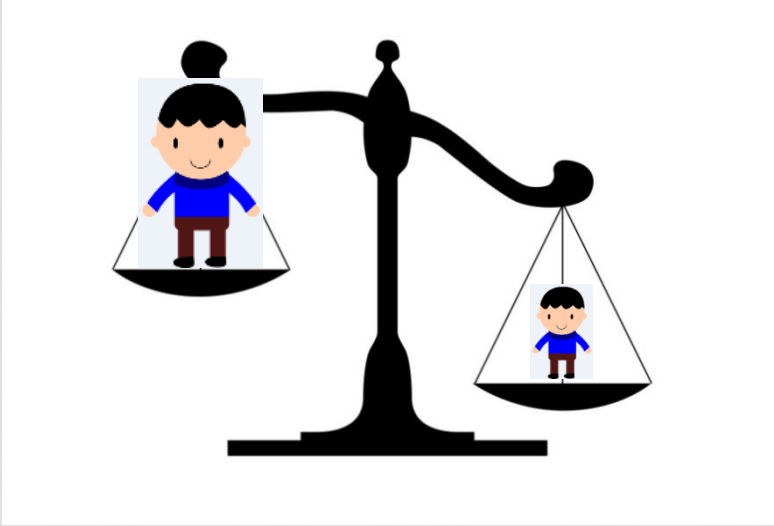
No differences in other outcome parameters

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

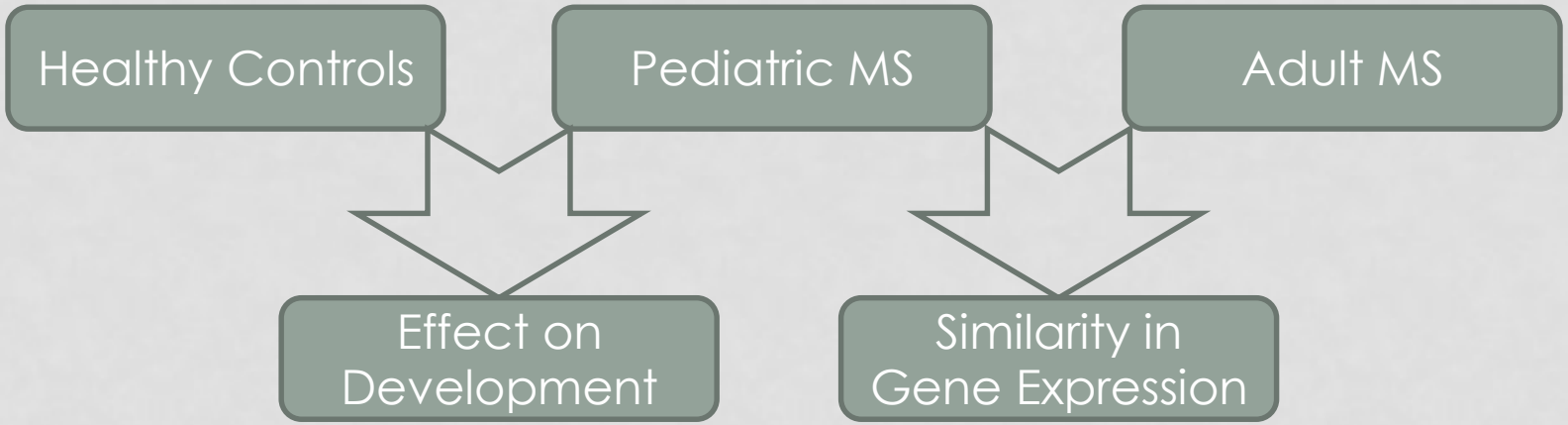
BRACHA ROBINSON

NATALIZUMAB

- **Humanized monoclonal Antibody targeting a4 subunit of a4b1-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

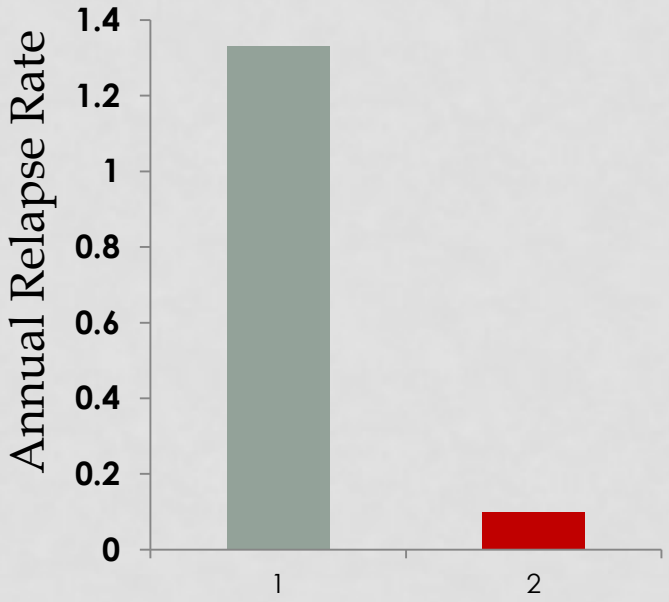


PATIENT CHARACTERISTICS

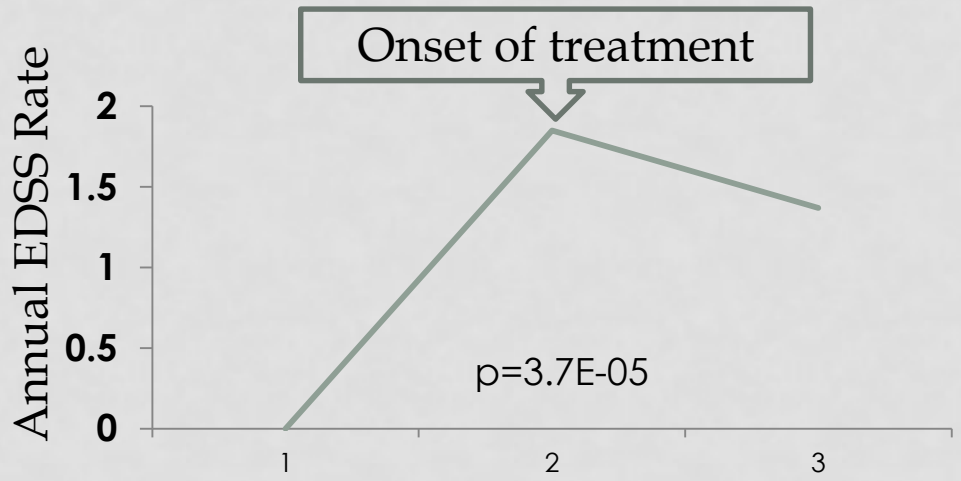
- 18 Patients treated with Natalizumab
  - Of these, 10 patients were sampled for gene expression analysis

	Total n=18	Female n=10	Male n=8
Age MS onset	13.9±0.8	13.8±1.0	14.1±1.2
Age Tx start	14.8±0.6	14.5±0.8	15.1±1.1
EDSS before Tx	1.67±0.27	1.95±0.36	1.31±0.38
Annual Relapse Rate before Tx	1.33±0.26	1.20±0.31	1.48±0.45

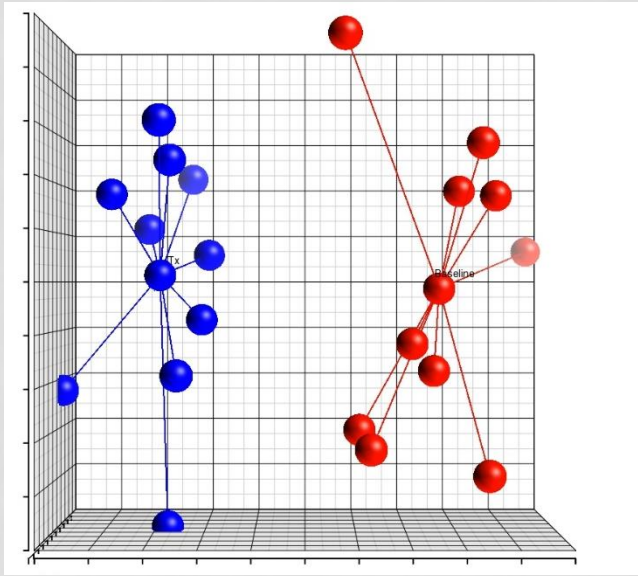
CLINICAL RESULTS: NATALIZUMAB INDUCES CLINICAL EFFICACY



1 – before treatment
2 – one year after Natalizumab treatment



Switch of Annual EDSS rate by Natalizumab treatment



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

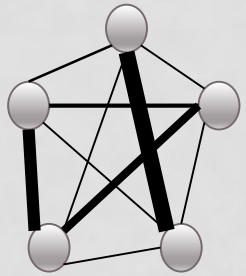
Diseases or Functions Annotation	p-Value
differentiation of pre-B lymphocytes	3.05E-09
differentiation of B lymphocytes	5.34E-07
arrest in differentiation of B lymphocytes	1.37E-06
proliferation of B lymphocytes	4.23E-06
development of B lymphocytes	5.22E-06
development of pre-B lymphocytes	1.37E-05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

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

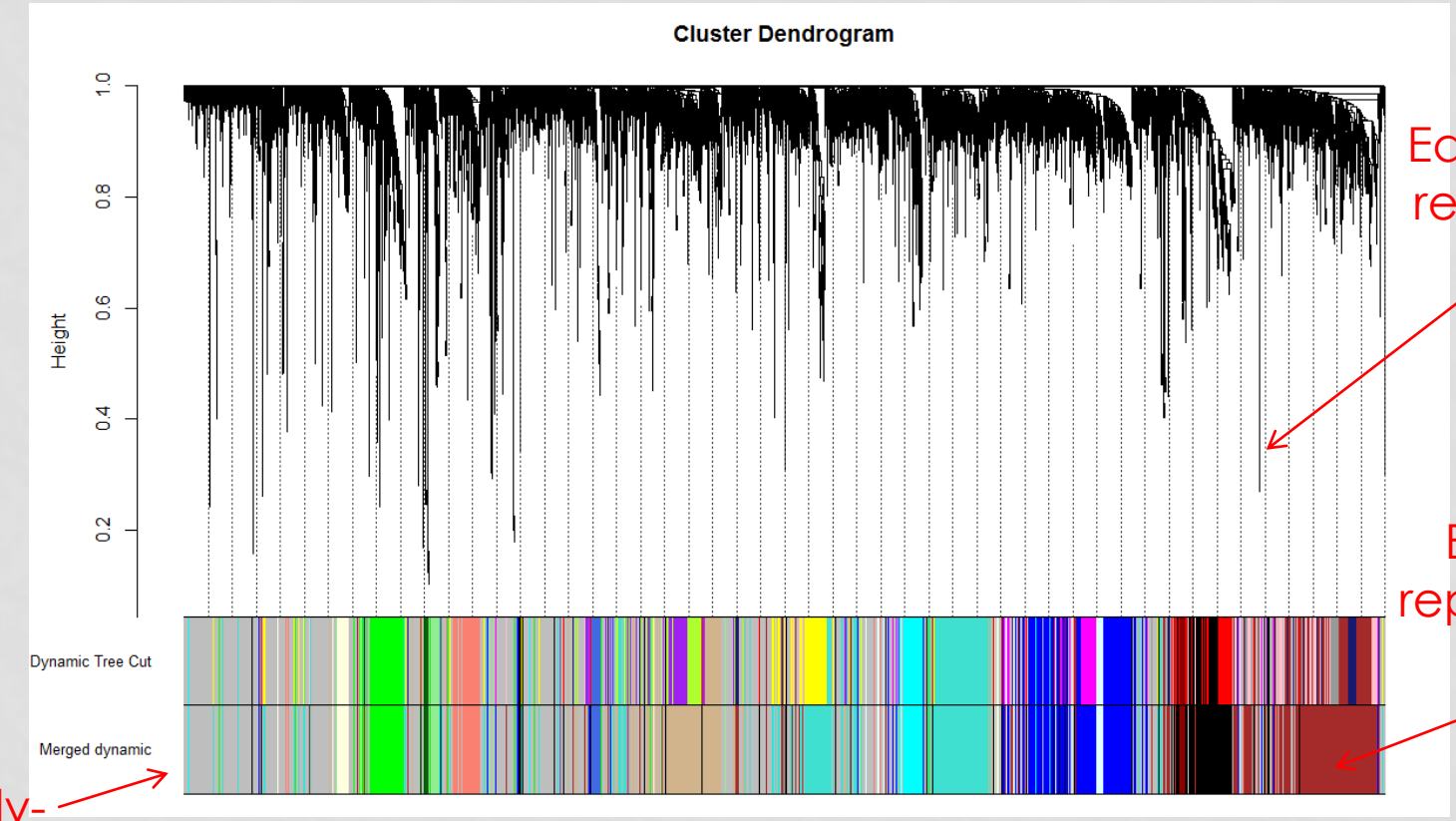
Step 1: Construct a Network
Quantify connection and determine interaction patterns between genes



Step 2: Identify Modules
Find gene clusters

Step 3: Relate Modules to External Information
Find biologically interesting modules

WGCNA: GENE CLUSTERS



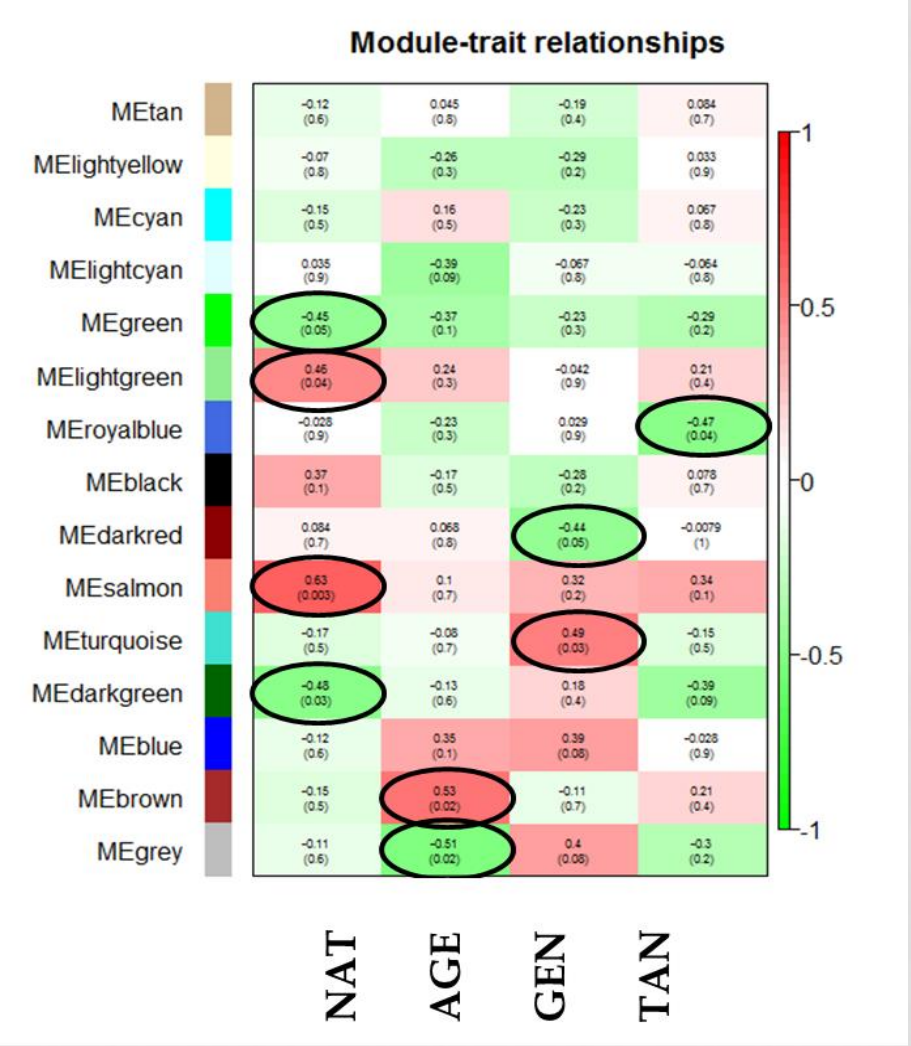
Each black line represents one gene

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.