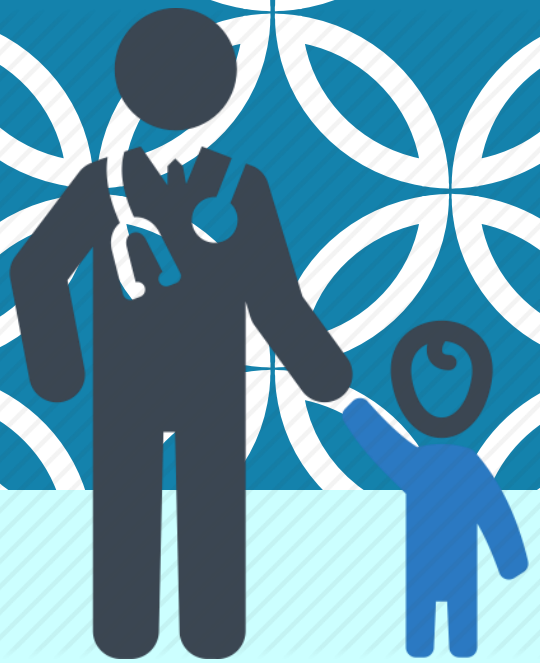
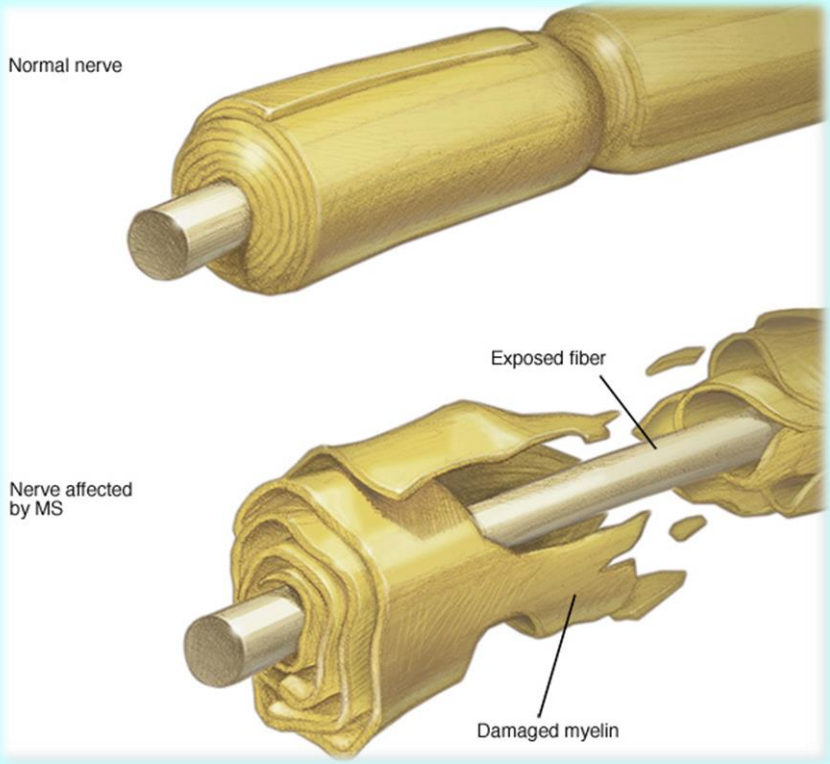
GENDER EFFECTS ON DISEASE PROGRESSION IN PEDIATRIC MS POPULATION



Yulia Khavkin
Mentor: Dr. Michael Gurevich

MULTIPLE SCLEROSIS

Multiple sclerosis (MS) is the most common immune-mediated inflammatory demyelinating disease of the central nervous system

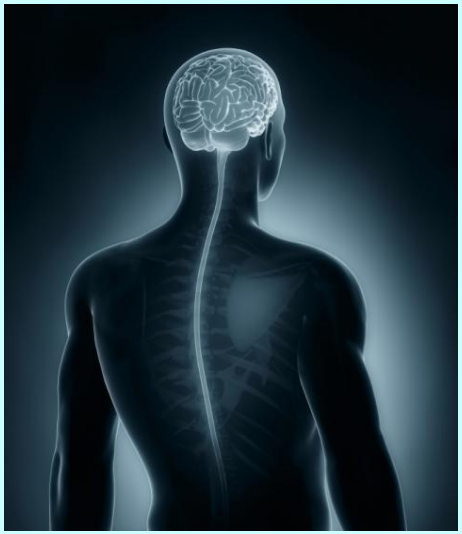


MULTIPLE SCLEROSIS

visual disturbance

gait & balance problems

sensory symptoms



vertigo

motor symptoms

bowel & bladder problems

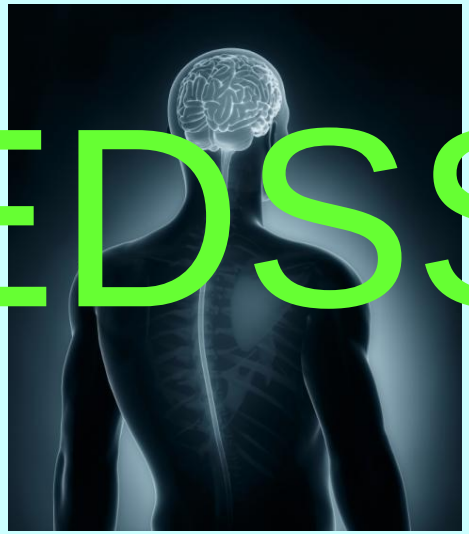
fatigue

MULTIPLE SCLEROSIS

visual disturbance

gait & balance problems

sensory symptoms



EDSS

vertigo

motor symptoms

bowel & bladder problems

fatigue

MULTIPLE SCLEROSIS

- Diagnosis is based on McDonald's criteria (2010) – dissemination in time and space expressed in imaging (MRI) and clinical features
- The estimated female to male ratio of MS incidence is 2:1
- The disease onset typically occurs at ages 20-40
- 2%-5% of MS onsets occur under the age of 18. These cases are defined as **pediatric MS**.

MOTIVATION

- The majority of pediatric MS data compares pediatric and adult MS
- Although the pediatric group is heterogeneous, differences between subgroups within this group are less researched
- Our project compares clinical features and outcomes in childhood and juvenile pediatric MS patients, and evaluates gender effects on disease progression

< 12

12-18

female

male

METHODS

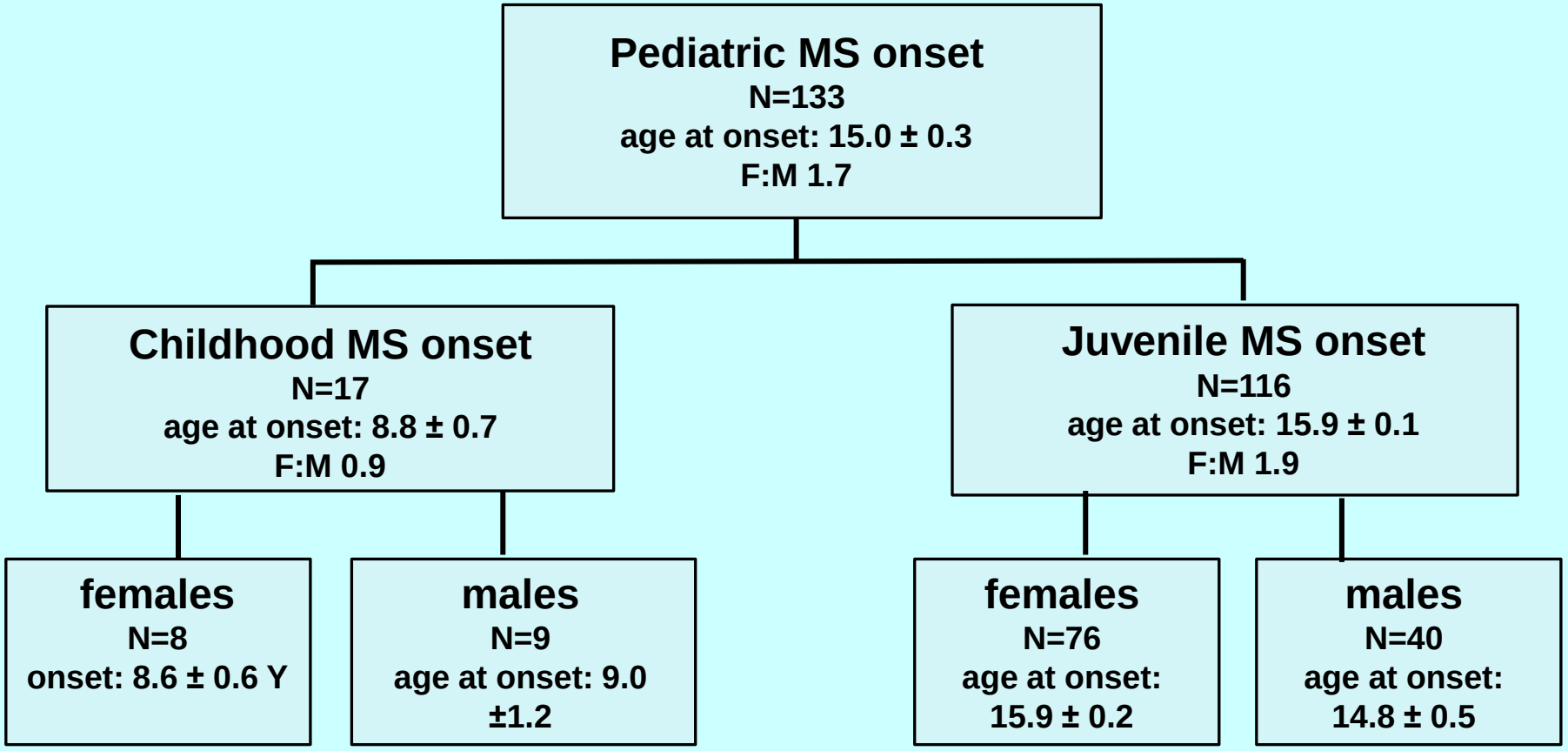
- A retrospective study was made on 133 Pediatric MS patients

- All patients were diagnosed with RRMS

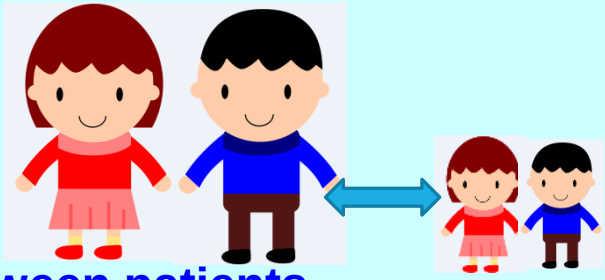
- We compared:
  - **Parameters at onset:** EDSS, presenting symptoms, number and volume of brain MRI lesions at onset.
  - **Clinical outcome parameters:** time to second relapse, time to EDSS 3.0 and 6.0, EDSS at 5, 10, 15 and 20 years from onset, annual relapse rate (ARR) at the first 5 years, 5-10 years and at 10 years of disease

RESULTS

Distribution of pediatric MS patients according to age of onset and gender



RESULTS



Clinical variables that differed between patients with childhood and juvenile MS onset

At onset patients with childhood MS onset were characterized by:

- Higher number of functional systems involved
- higher prevalence of pyramidal, brainstem, cerebellar and bowel and bladder involvement , but less sensory involvement.

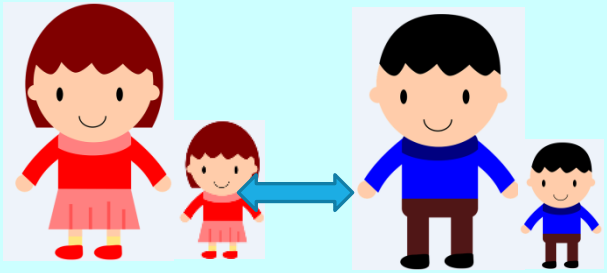
The clinical outcome of childhood MS onset patients was characterized by :

- Higher EDSS after 5, 15 and 20 years from onset as compared to juvenile-onset patients

Clinical variables that differ between patients with childhood and juvenile MS onset

Clinical parameters	Childhood MS n=17	Juvenile MS n=116	P value
presenting symptoms, n (%)			
visual	18	25	0.1
pyramidal	59	34	0.0001
brainstem	47	19	0.0001
cerebellar	35	10	0.0001
sensory	29	39	0.03
bowel & bladder	12	3	0.0001
number of functional systems involved at onset	2.0 ± 0.3	1.3 ± 0.1	0.001
EDSS at 5 years	2.3 ± 0.6 (n=13)	1.5 ± 0.3 (n=64)	0.05
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

RESULTS



Clinical variables that differed between female and male pediatric MS patients

At onset female patients differed from male by:

- higher volume of brain MRI lesions

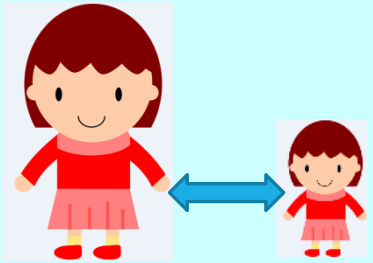
The clinical outcome of female patients compared to male patients was characterized by:

- longer time to second relapse
- higher ARR at 5-10 years from onset
- higher EDSS at 10 years from onset

Clinical variables that differed between pediatric female and male patients

Clinical parameters	Females n=84	Males n=49	P value
presenting symptoms (%)			
visual	27	20	0.2
pyramidal	33	45	0.01
brainstem	20	27	0.1
cerebellar	11	18	0.06
sensory	41	33	0.09
bowel & bladder	5	2	0.2
brain MRI flair volume at onset	7.1 ± 1.8	3.3 ± 0.8	0.05
years to second relapse	4.8 ± 0.3	3.4 ± 0.5	0.05
EDSS after 10 years	3.5 ± 0.1 n=39	2.8 ± 0.4 n=23	0.02
ARR at 5-10 years of disease	0.8 ± 0.2	0.5 ± 0.1	0.03

RESULTS



Clinical variables that differed between female childhood and juvenile MS onset patients

At onset female patients with childhood onset MS, compared to female patients with juvenile onset MS, were characterized by:

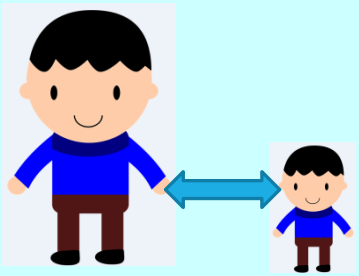
- higher prevalence of pyramidal, brainstem, cerebellar and bowel and bladder symptoms
- lower prevalence of visual symptoms

No differences were found in the **clinical outcome** variables

Clinical variables that differed between females with childhood and juvenile MS onset

Clinical parameters	Childhood n=8	Juvenile n=86	P value
presenting symptoms (%)			
visual	13	29	0.0004
pyramidal	50	31	0.0001
brainstem	38	21	0.0001
cerebellar	25	9	0.0001
sensory	38	41	0.5
bowel & bladder	25	4	0.0001

RESULTS



Clinical variables that differed between male childhood and male juvenile MS onset

At onset males with childhood onset MS, compared to males with juvenile onset MS were characterized by:

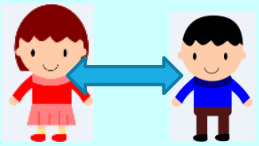
- higher number of functional systems involved
- higher prevalence of pyramidal, brainstem and cerebellar symptoms, lower prevalence of sensory symptoms
- higher prevalence of EDSS=3.0 and above at onset

No differences were found in the **clinical outcome** variables

Clinical variables that differed between male childhood and juvenile MS onset

Clinical parameters	Childhood n=9	Juvenile n=40	P value
presenting symptoms (%)			
visual	22	20	0.6
pyramidal	67	45	0.0001
brainstem	56	20	0.0001
cerebellar	44	18	0.0001
sensory	22	33	0.02
bowel & bladder	0	2	0.9
number of functional systems involved	2.1 ± 0.3	1.4 ± 0.1	0.002
EDSS ≥ 3.0 at onset, %	67	42	0.0001

RESULTS



Clinical variables that differed between females and males with childhood MS onset

At onset male patients with childhood onset, compared to females with childhood onset, were characterized by:

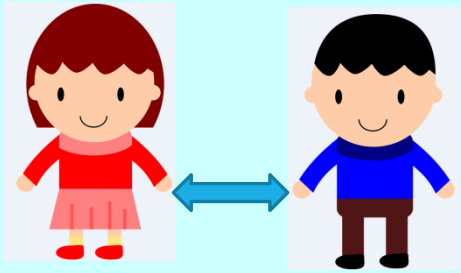
- higher prevalence of pyramidal , brainstem , cerebellar and visual symptoms and higher prevalence of sensory and bowel & bladder symptoms
- higher prevalence of EDSS 3 and above at onset

No differences were found in the **clinical outcome** variables

Clinical variables that differed between females and males patients with childhood MS onset

Clinical parameters	Female n=8	Male n=9	P value
presenting symptoms (%)			
visual	13	22	0.03
pyramidal	50	67	0.0003
brainstem	38	56	0.0001
cerebellar	25	44	0.0001
sensory	38	22	0.0001
bowel & bladder	25	0	0.0001
EDSS ≥ 3 at onset, %	50	67	0.0003

RESULTS



Clinical variables that differed between females and males with juvenile MS onset

At onset female patients with juvenile onset, compared to male patients with juvenile onset, were characterized by:

- lower prevalence of pyramidal and cerebellar symptoms
- higher prevalence of EDSS 3 and above

The clinical outcome of female patients compared to male patients was characterized by:

- higher EDSS at 10 years from onset
- higher ARR at 5-10 years from onset

Clinical variables that differed between female and male patients with juvenile MS onset

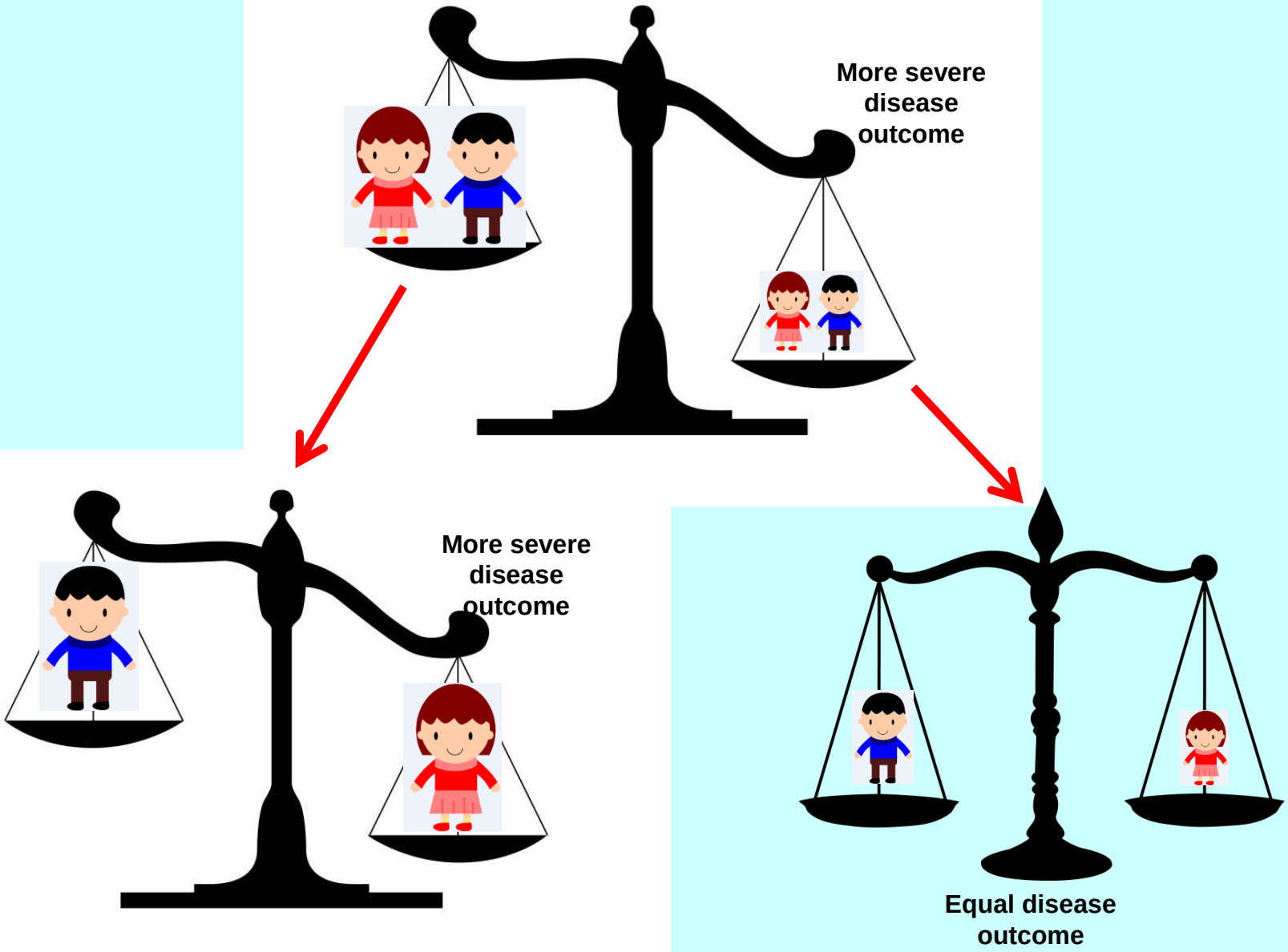
Clinical parameters	Female n=76	Male n=40	P value
presenting symptoms (%)			
visual	29	20	0.6
pyramidal	31	45	0.005
brainstem	21	20	0.8
cerebellar	9	18	0.002
sensory	41	33	0.08
bowel & bladder	4	2	0.1
EDSS ≥ 3 at onset (%)	53	42	0.03
EDSS after 10 years	3.4 ± 0.4 n=31	2.8 ± 0.3 n=17	0.02
ARR 5-10 years after onset	1.3 ± 0.2	0.6 ± 0.1	0.01

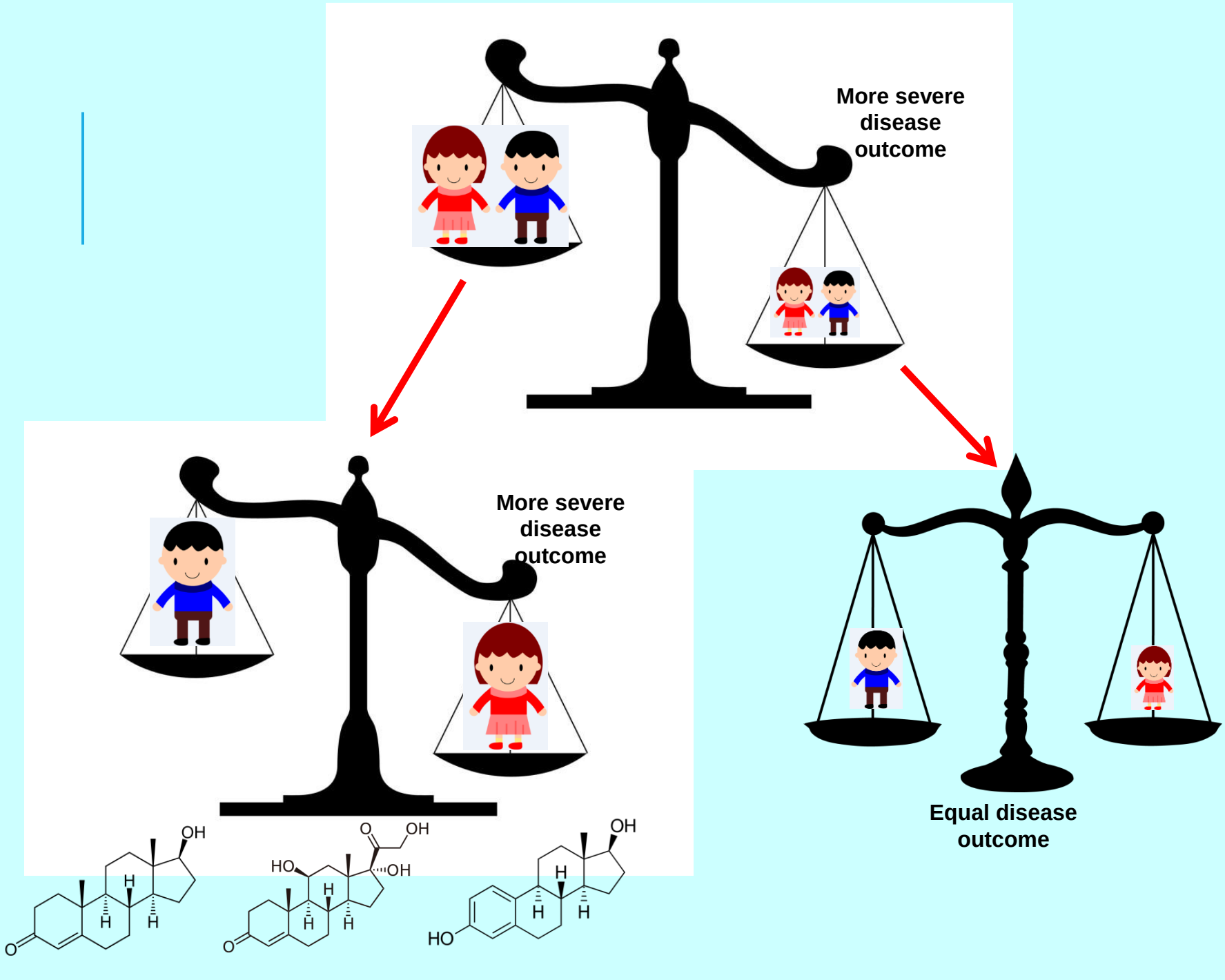
CONCLUSIONS: onset

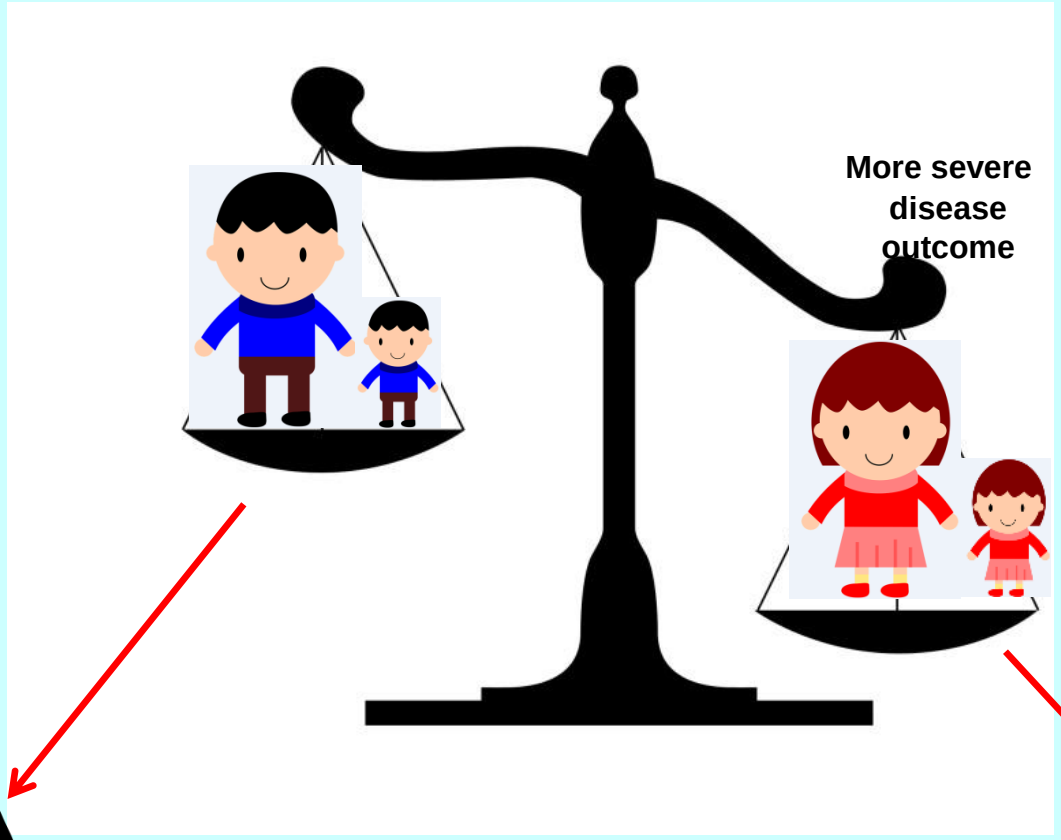
- **Patients with childhood onset MS are characterized by more severe onset than juvenile MS patients**
- **Male patients with childhood onset MS are characterized by the most severe clinical presentation**

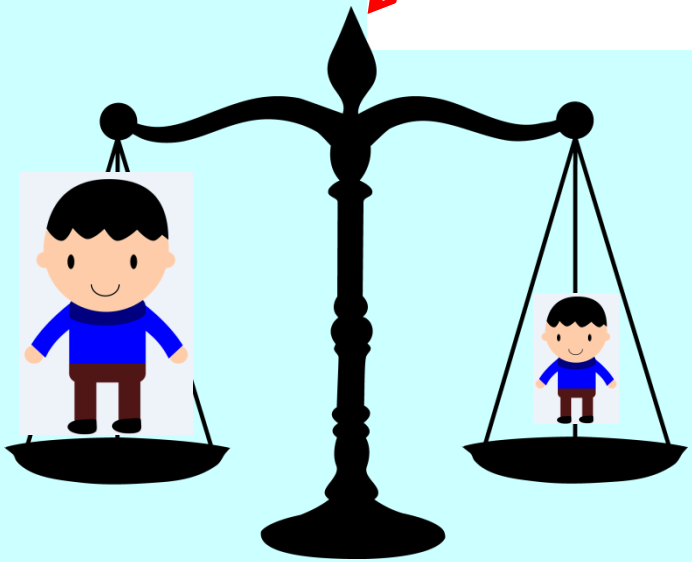
CONCLUSIONS: outcome

- **Patients with childhood onset MS are characterized by worse disease outcome compared to juvenile patients**
- **Female patients are characterized by worse disease outcome compared to male patients**

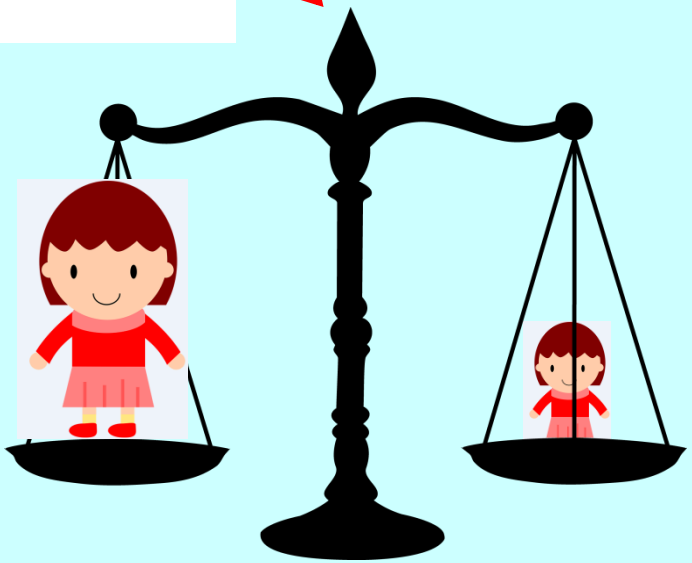

More severe disease outcome
More severe disease outcome
Equal disease outcome


More severe disease outcome
More severe disease outcome
Equal disease outcome
OH
H
H
H
O
HO
O
OH
OH
H
H
H
O
OH
H
H
H
HO





Equal disease outcome



Equal disease outcome

Gender effects on disease progression in pediatric multiple sclerosis population

[1,2] A. Achiron MD, PhD, [1,2] S. Menascu MD, [1] D. Magalashvili MD, [1,2] Y. Havkin MD, [1] M. Dolev Dolgopiat, [1] M. Gurevich

[1]Multiple Sclerosis Center, Sheba Medical Center, Tel-Hashomer, [2]Sackler School of Medicine, Tel-Aviv University, ISRAEL

Background

- The onset of multiple sclerosis (MS) under the age of 18 occurs in 3%-5% of cases and is defined as pediatric MS disease.
- Males and females differ in their immunological response and show distinctions in innate and adaptive immunity.
- These sex-based immunological differences as well as childhood and adolescent age at onset could contribute to variations in the clinical features and may have an impact on disease related long-term outcomes.

Methods

- Pediatric MS patients followed prospectively in the Sheba MS Center, from 1995-2016 were evaluated.
- All patients were diagnosed according to the criteria of the International Pediatric Multiple Sclerosis Study Group (IPMSSG, 2012 http://ipmssg.org/others/education/ipmssg-publications/).
- The Sheba Institutional Review Board approved the study.
- We examined the differences between childhood (< 12 years) and juvenile (12-18 years) MS patients as follows:
- At onset in relation to gender, EDSS, EDSS functional systems scores, and number and volume of T1, T2 and flair brain MRI lesions.
- Clinical outcome parameters including time to second relapse, time to EDSS 3.0 and 6.0, EDSS at 5, 10, 15 and 20 years from onset, and annual relapse rate (ARR) at the first 5 years, 5-10 years and at 10 years of disease.
- Statistical analysis was performed using Chi Square and T-tests.

Results

- 133 pediatric MS patients, 84 females (F/M ratio 1.71) with juvenile onset MS (N=116, 76 females, F/M ratio 1.9, mean age of onset 15.9 ± 0.1) and childhood onset MS (N=17, 8 females, F/M ratio 0.9, mean age of onset 8.8 ± 0.7) were included in the study, Figure 1.

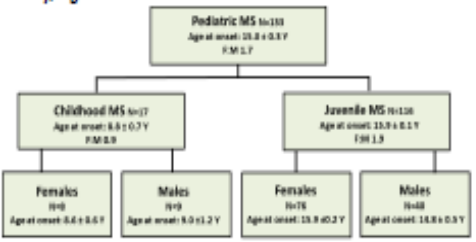


Figure 1. Distribution of pediatric MS patients according to age of onset and gender

Clinical variables that differed between patients with childhood and juvenile MS:

At onset patients with childhood MS were characterized by:

- Higher number of functional systems involved at onset.
- Higher prevalence of pyramidal, brainstem, cerebellar and bowel and bladder involvement that associated with lower sensory involvement.
- Higher pyramidal EDSS score while other EDSS functional scores did not differ, Table 1.

Clinical outcome of patients with childhood MS were characterized by:

- Higher EDSS after 5, 15 and 20 years from onset as compared to juvenile-onset patients.
- Time to 2nd relapse and MRI variables did not differ between groups, Table 1.

Table 1. Clinical variables that differed between patients with childhood and juvenile MS

Clinical parameters	Childhood n=17	Juvenile n=116	P value
presenting symptoms, n (%)			
visual	18	25	0.1
pyramidal	59	54	0.0001
brainstem	47	19	0.0001
cerebellar	35	10	0.0001
bowel & bladder	12	3	0.0001
number of functional systems involved at onset	2.0 ± 0.3	1.3 ± 0.1	0.001
EDSS at 5 years	2.5 ± 0.6 (n=13)	1.5 ± 0.3 (n=64)	0.05
EDSS at 15 years	5.2 ± 0.7 (n=12)	3.3 ± 0.4 (n=61)	0.01
EDSS at 20 years	5.7 ± 0.9 (n=8)	3.5 ± 0.1 (n=41)	0.01

Clinical variables that differed between female and male pediatric MS patients:

At onset pediatric female patients differed from male patients by:

- Lower prevalence of pyramidal symptoms.
- Higher volume of brain FLAIR MRI lesions.

Clinical outcome in pediatric female patients was characterized by:

- Longer time to second relapse.
- Higher ARR at 5-10 years.
- Higher EDSS at 10 years, Table 2.

Table 2. Clinical variables that differed between pediatric female and male patients

Clinical parameters	Females n=84	Males n=49	P value
presenting symptoms (%)			
visual	27	20	0.2
pyramidal	88	65	0.01
brainstem	20	27	0.1
cerebellar	11	18	0.06
sensory	41	33	0.09
bowel & bladder	5	2	0.2
brain MRI flair volume at onset	7.1 ± 1.8	3.3 ± 0.8	0.05
years to second relapse	4.8 ± 0.3	8.4 ± 0.5	0.05
EDSS after 10 years	3.5 ± 0.1 n=59	2.8 ± 0.4 n=23	0.02
ARR at 5-10 years of disease	0.8 ± 0.2	0.5 ± 0.1	0.03

Clinical variables that differed between female childhood and female juvenile MS patients:

At onset female patients with childhood onset MS were characterized by:

- Higher prevalence of pyramidal, brainstem, cerebellar and bowel and bladder symptoms and lower prevalence of visual symptoms.
- Higher pyramidal EDSS.

Clinical outcome: No differences were found in the clinical outcome variables, Table 3.

Table 3. Clinical variables that differed between females with childhood and juvenile MS

Clinical parameters	Childhood n=8	Juvenile n=86	P value
presenting symptoms (%)			
visual	13	29	0.0004
pyramidal	50	31	0.0001
brainstem	38	21	0.0001
cerebellar	25	9	0.0001
sensory	38	41	0.5
bowel & bladder	25	4	0.0001

Clinical variables that differed between male childhood and juvenile MS:

At onset male patients with childhood MS onset were characterized by:

- Higher prevalence of pyramidal, brainstem and cerebellar symptoms, lower prevalence of sensory symptoms.
- Higher number of functional systems involved.
- Higher prevalence of EDSS=3.0 and above at onset, Table 4.
- **Clinical outcome:** No differences were found in the clinical outcome variables.

Table 4. Clinical variables that differed between male childhood and juvenile MS

Clinical parameters	Childhood n=9	Juvenile n=40	P value
presenting symptoms (%)			
visual	22	20	0.6
pyramidal	67	45	0.0001
brainstem	56	20	0.0001
cerebellar	44	18	0.0001
sensory	22	33	0.02
bowel & bladder	0	2	0.9
number of functional systems involved	2.1 ± 0.3	1.4 ± 0.1	0.002
EDSS ≥ 3.0 at onset, %	67	42	0.0001

Clinical variables that differed between females and males with childhood MS:

At onset female patients with childhood onset were characterized by:

- Lower prevalence of pyramidal, brainstem, cerebellar and visual symptoms and higher prevalence of sensory and bowel & bladder symptoms.
- Lower prevalence of EDSS 3 and above at onset, Table 5.
- **Clinical outcome:** No differences were found in the clinical outcome variables.

Table 5. Clinical variables that differed between females and males patients with childhood MS

Clinical parameters	Female n=8	Male n=9	P value
presenting symptoms (%)			
visual	13	22	0.05
pyramidal	50	67	0.0003
brainstem	38	56	0.0001
cerebellar	25	44	0.0001
sensory	38	22	0.0001
bowel & bladder	25	0	0.0001
EDSS ≥ 3 at onset, %	50	67	0.0003

Clinical variables that differed between female and male patients with juvenile MS:

At onset female patients with juvenile onset were characterized by:

- lower prevalence of pyramidal and cerebellar symptoms.
- higher prevalence of EDSS 3 and above.
- higher volume of FLAIR lesions.
- higher EDSS at 10 years from onset.
- higher ARR at 5-10 years from onset, Table 6.

Clinical outcome No differences were found in the clinical outcome variables.

Table 6. Clinical variables that differed between female and male patients with juvenile MS

Clinical parameters	Female n=76	Male n=40	P value
presenting symptoms (%)			
visual	29	20	0.6
pyramidal	31	45	0.005
brainstem	21	20	0.8
cerebellar	9	18	0.002
sensory	41	33	0.08
bowel & bladder	4	2	0.1
EDSS ≥ 3 at onset (%)	53	42	0.05
EDSS after 10 years	3.4 ± 0.4 n=31	2.8 ± 0.3 n=17	0.02
ARR 5-10 years after onset	1.3 ± 0.2	0.6 ± 0.1	0.01

Conclusions

MS ONSET:

- Patients with childhood MS are characterized by a more severe onset than juvenile MS patients.
- Male patients with childhood MS are characterized by more severe clinical presentation as demonstrated by multiple functional systems involvement.

MS OUTCOME:

- Patients with childhood MS are characterized by worse disease outcome as compared to juvenile MS patients, Figure 7a.
- Female patients with pediatric MS have worse disease outcome manifested by higher relapse rate and disability within 10 years from onset disease, Figure 7b.

Figure 7a

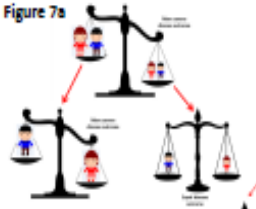
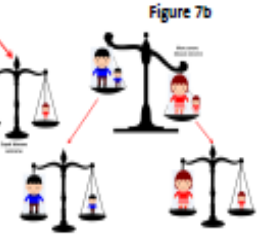


Figure 7b



THANK YOU