Pediatric onset clinically isolated syndrome suggestive of Multiple Sclerosis patients benefits from early disease modifying treatment

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Background

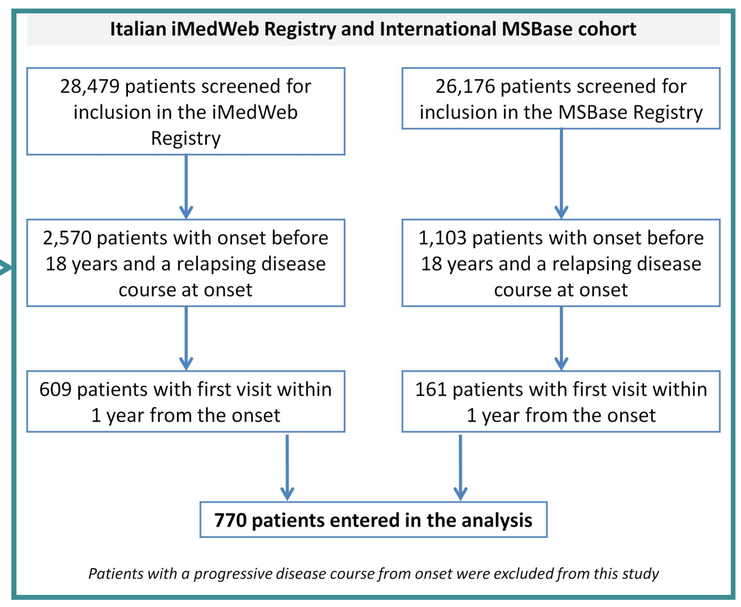
Pediatric onset MS (POMS) – before the age of 18 years – is a rare disease, occurring in 3 to 10% of cases. POMS usually starts with the occurrence of a first attack of demyelination, termed pediatric clinically isolated syndrome (pCIS).

Objectives

To assess the effect of an early disease modifying treatment on time to second clinical attack and on time to first disability worsening event (confirmed EDSS progression) in a large cohort of pCIS patients.

Methods

Patients selection from feeder databases



Variables included in the analysis

- **Demographics (age at onset; gender)**
- **pCIS topography at onset**
- **EDSS score at first visit**
- **Brain MRI features classified as 0-2 lesions, > 2 lesions**
- **Presence/absence of CSF OB**
- **DMD treatment prescription and relapses occurring before progression were included as a time-dependent covariate.**

Statistical analysis

Multivariate Cox proportional hazard regression models

to identify predictive factors for shorter time to second attack and to first 3 months confirmed EDSS progression

RECursive Partitioning and AMalgamation (RECPAM)

to identify distinct subgroups of patients at different risk of reaching EDSS progression

Backward Cox regression analysis with the RECPAM classes forced-in

to study the effect of time-dependent covariates (DMD exposure and relapses) on the risk classes provided by the recpam analysis

EDSS progression definition:

A minimum 1 point EDSS increase if the baseline value was 1-5.5, or 1.5 point increase if the baseline EDSS score was 0, and 0.5 point increase if the baseline EDSS score was ≥ 6. A confirmation at repeat assessment at least 3 months later was required to confirm the EDSS worsening event.

Results

A cohort of 770 patients with pCIS was extracted from the Italian iMedWeb registry (44 contributing MS centers) and the MSBase registry (32 contributing MS centers) in June 2015. Demographic and clinical characteristics of this cohort are shown in table 1 and 2.

Table 1. Baseline Characteristics

Sex, F/M	544/226
Age at Onset (years) median (IQR)	16.0 (14.1 - 17.2)
Classes of Age at Onset (years) n (%)	
0 - ≤ 12	92 (12.0)
> 12 - ≤ 15	190 (24.7)
> 15 - ≤ 18	487 (63.3)
pCIS topography, n (%)	
Isolated Optic Neuritis	196 (26.2)
Isolated Brain-Stem Syndrome	149 (19.9)
Isolated Spinal Syndrome	101 (13.5)
Isolated Supratentorial Syndrome	173 (23.1)
Multifocal	129 (17.3)
Patients with CSF examination, n (%)	493 (64.0%)
Patients with CSF OB, n positive OB/total (%)	399/493 (80.9)
Patients with MRI examination, n (%)	494 (64.2%)
Patients with number of brain MRI T2 lesions: 0 – 2	58 (11.7)
Patients with number of brain MRI T2 lesions: > 2	436 (88.3)
First EDSS Evaluation mean (SD)	1.9 (1.4)

Table 2. Follow-up features

Follow-up, year, median (IQR)	5.4 (1.9 - 10.8)
Patients with a 2nd attack during the follow-up, n (%)	602 (78.2)
Patients with an EDSS worsening during the follow-up, n (%)	299 (24.3)
Patients treated with at least one DMD during the follow-up	614 (79.7)
Patients with a first drug prescription before 2° Attack, n (%)	200 (26.0)
Patients with a first drug prescription before first EDSS worsening event, n (%)	156 (52.2)

The multivariate model for the outcome "second clinical attack" showed a significant lower risk in patients who started DMDs before the 2nd attack. Moreover, this model indicates female sex and a multifocal disease onset as independent risk factors for a second attack. (Fig. 1).

The multivariate model for the outcome "first EDSS worsening event" indicates that age at onset younger than 15 years, a supratentorial symptoms at onset, DMDs exposure before the EDSS worsening all prolonged the time to confirmed disability progression, whereas the occurrence of relapses was the only significant risk factor associated with a shorter time to EDSS worsening. (Fig. 2).

Using the RECPAM we identified 3 heterogeneous risk classes for EDSS progression (Fig. 3). The first node, in red, at the top of the figure indicates the most important variable in discriminating the risk of EDSS progression which was the pCIS topography. The lowest incidence of disability progression was found in patients with a supratentorial syndrome at onset and born before 1990. In comparison with patients belonging to class 3, those with a supratentorial symptom at onset and born after 1990 had a two-fold increased risk and those with all the other possibility of symptoms at onset had a 5.4-fold higher incidence of EDSS progression.

Results

Figure 1. Risk of a second clinical attack

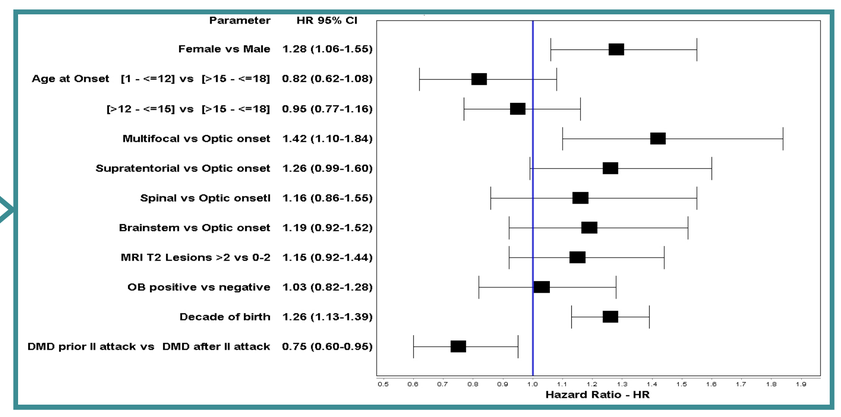


Figure 2. Risk of attaining 3-months confirmed EDSS worsening

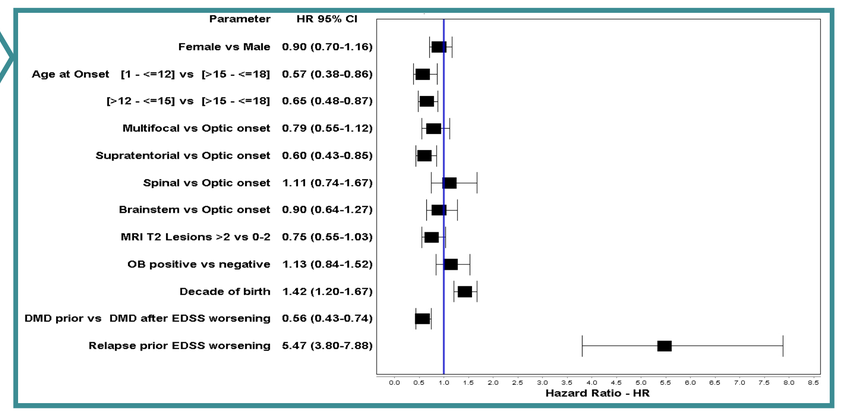
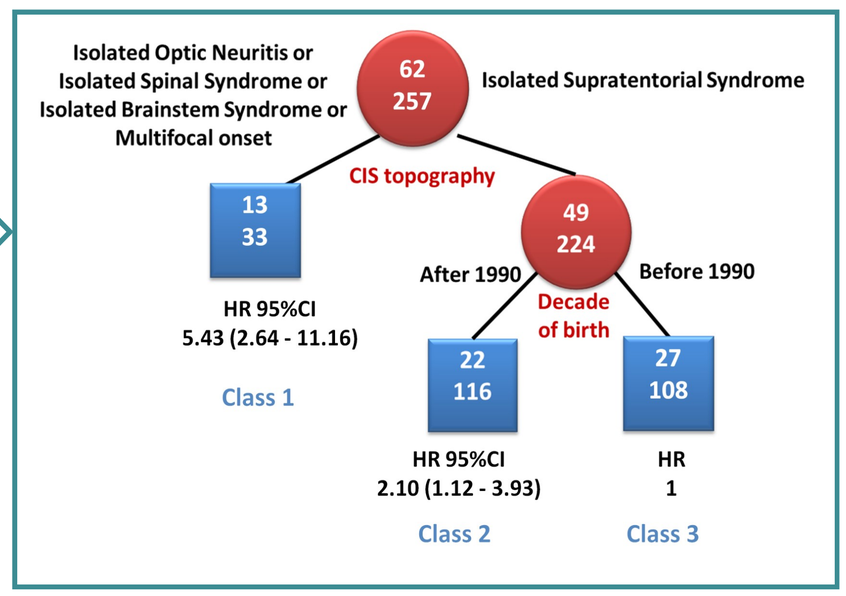


Figure 3. RECPAM Risk classes from a "pruned" tree: 3-months confirmed EDSS worsening



The characteristics for each class were reported in table 3. The highest risk class included pediatric CIS patients who were less frequently treated with DMDs in comparison to patients belonging to the Classes 2 and 3; more frequently than the other 2 classes had more additional relapses after the first attack. They were older at the onset and more frequently than those in the Classes 2 and 3 have had an isolated spinal or ON as onset symptoms. Notably they also more frequently than patients belonging to the other 2 classes had more than 2 Brain T2 lesions at the first MRI.

The final backward Cox regression model with RECPAM classes forced-in, performed to highlight the role of additional time dependent covariates (treatment and relapses before progression), confirmed DMDs exposure as the most important protective factor against EDSS worsening events (HR = 0.22, 95% CI 0.13 - 0.38) in this pCIS population (Table 4).

Table 3. RECPAM Risk classes characteristics

	Risk of disability progression: High	Medium	Low	
VARIABLE	Class 1	Class 2	Class 3	p
Females, n (%)	23 (69.7)	77 (66.4)	84 (77.8)	0.16
Classes of Age at Onset, years, n (%)				
0 - ≤12	1 (3.0)	24 (20.7)	9 (8.3)	0.0023
> 12 - ≤15	6 (18.2)	33 (28.5)	22 (20.4)	
> 15 - ≤18	26 (78.8)	59 (50.9)	77 (71.3)	
CIS topography, n (%)				
Isolated Optic Neuritis	10 (30.3)	24 (20.7)	22 (20.4)	0.0003
Isolated Brain-Stem Syndrome	7 (21.2)	29 (25.0)	20 (18.5)	
Isolated Spinal Syndrome	11 (33.3)	11 (9.5)	9 (8.3)	
Isolated Supratentorial Syndrome	0 (0.0)	31 (26.7)	25 (23.2)	
Multifocal	5 (15.2)	21 (18.1)	32 (29.6)	
First DMD start before EDSS worsening, n (%)	18 (54.6)	91 (78.5)	77 (71.3)	0.0241
Patients with > 2 Brain MRI T2 lesions, n (%)	32 (97.0)	101 (87.1)	103 (95.4)	0.0394
OB Positive (n = 493)	29 (87.9)	98 (84.5)	90 (83.3)	0.8197
Relapse/s before EDSS Worsening, n (%)	13 (39.4)	7 (6.0)	0 (0.0)	<0.0001

Table 4. Post-RECPAM backward Cox regression model with RECPAM classes forced-in

VARIABLE	HR (95% CI)	p
RECPAM Class 1 vs 3	3.89 (1.89 - 7.98)	0.0002
RECPAM Class 2 vs 3	2.73 (1.45 - 5.15)	0.0019
DMD exposure before EDSS worsening	0.22 (0.13 - 0.38)	<0.0001

Conclusions

Our results confirm the beneficial effect of an early DMD exposure in reducing the risk of a second clinical attack and in preventing disability accumulation in pCIS patients. Females and patients with a multifocal onset are both prone to having a second clinical attack in a shorter time. Young age and a supratentorial syndrome at onset both predict a longer time to reach disability accumulation. Moreover, relapses are the major risk factor for disability accrual in the middle term in pCIS patients.