



Original article

Clinical characteristics and use of disease modifying therapy in the nationwide Danish cohort of paediatric onset multiple sclerosis



Julie Laub Erdal^{a,*}, Tine Iskov Kopp^c, Morten Blinkenberg^b, Thor Petersen^d,
Per Soelberg Sørensen^b, Melinda Magyari^{b,c}

^a University of Copenhagen, Faculty of Health and Medical Sciences, Blegdamsvej 3B, 2200 Copenhagen, Denmark

^b Danish Multiple Sclerosis Center, Department of Neurology, Rigshospitalet, Copenhagen University Hospital, Blegdamsvej 9, 2100 Copenhagen, Denmark

^c Danish Multiple Sclerosis Registry, Department of Neurology, Rigshospitalet, Copenhagen University Hospital, Tagensvej 22, 2200 Copenhagen, Denmark

^d Department of Neurology, Aarhus University Hospital, Palle Juul-Jensens Boulevard 99, 8200 Aarhus, Denmark

A B S T R A C T

Background: Several disease-modifying therapies (DMT) are being used in paediatric patients with multiple sclerosis (MS) despite the limited number of randomised controlled clinical trials leading to approved indication in children.

Objectives: The aim of this study was to describe clinical characteristics of the Danish population of paediatric onset MS, and the patterns of DMT utilisation in patients who started treatment before the age of 18 years.

Methods: We conducted a nationwide population-based cohort study, including 347 children with paediatric-onset MS (< 18 years). Subjects were followed until their 25th birthday or end of follow-up.

Results: Median age at onset and diagnosis was 15.8 years and 17.2, respectively. The majority of the children had monosymptomatic presentation. In total, 140 children received DMT before the age of 18. Most started treatment with a moderate-efficacy drug (90%) of which interferon-beta was the most used (80%). However, since oral treatments became available, these have increasingly been used. During follow-up, 108 children switched or discontinued DMT. Fingolimod was prescribed more frequently than natalizumab as escalation therapy.

Conclusion: We present that use of DMT in POMS varies over the observed period concurrently with the availability of disease modifying drugs with progressive use of oral and high-efficacy therapies.

1. Introduction

Multiple sclerosis (MS) is an immune-mediated disease in the central nervous system. It is characterized by inflammation causing disseminated plaques with demyelination and axonal loss. Clinical manifestations of MS before the age of 18 years are uncommon. The proportion of paediatric onset MS (POMS) varies between countries from 2.7% to 10% of all MS patients (Dell'Avvento et al., 2016). A Danish nationwide population-based study from 2017 found a POMS incidence rate of 0.79 per 100,000 children, accounting for 2.3% of the total Danish MS population between 1977 and 2015, with increasing incidence seen after puberty, especially in girls (Boesen et al., 2017).

POMS has a higher frequency of relapses as well as a higher lesion load on magnetic resonance imaging (MRI) compared to adult onset MS (Ghezzi et al., 2016, Gorman et al., 2009). Patients with POMS recover initially better from relapses and have a slower progression of disease compared to adult onset MS (Yeh et al., 2009, Renoux et al., 2007, Alroughani and Boyko, 2018), but reach milestones of disability earlier

in life, and present early with cognitive and behavioural deficits (Amato et al., 2008, Amato et al., 2016).

Relatively little is known about the use of disease-modifying therapy (DMT) in children and adolescent with MS. However, a consensus statement from the International Paediatric Multiple Sclerosis Study Group (IPMSSG) recommends that all paediatric patients with active relapsing-remitting (RR) MS should be considered for treatment with DMT (Chitnis et al., 2012). An increasing number of DMTs are now available, but due to the limited number of randomized clinical trials (RCT) and subsequent approved indication in children, several are being used off-label in POMS (Chitnis et al., 2016). Observational studies including retrospective and open-label studies have reported presumed effectiveness, high tolerance and safety of moderate-efficacy DMTs such as glatiramer acetate (GA) and interferon beta (IFN- β), in addition to high-efficacy natalizumab (Ghezzi et al., 2009, Ghezzi et al., 2013, Kornek et al., 2013, Pohl et al., 2005, Tenembaum et al., 2013). Until now only two RCTs have been published in POMS patients; FOCUS evaluating safety and efficacy of dimethyl fumarate (DMF) and

* Corresponding author.

E-mail addresses: pgd966@alumni.ku.dk (J.L. Erdal), tine.iskov.kopp@regionh.dk (T.I. Kopp), Morten.Blinkenberg@regionh.dk (M. Blinkenberg), thorpete@rm.dk (T. Petersen), Per.Soelberg.Soerensen@regionh.dk (P.S. Sørensen), melinda_magyari@dadlnet.dk (M. Magyari).

<https://doi.org/10.1016/j.msard.2019.101431>

Received 26 June 2019; Received in revised form 7 September 2019; Accepted 4 October 2019

2211-0348/© 2019 Elsevier B.V. All rights reserved.

PARADIGMS comparing fingolimod with IFN- β -1a (Chitnis et al., 2018). In 2018 fingolimod became the first DMT to be approved by Food and Drug Administration (FDA) for paediatric MS patients of 10 years or older.

The aim of this study is to report the clinical characteristics of POMS in a Danish population-based study, and to describe the pattern of DMT utilisation in patients who started treatment before the age of 18 years.

2. Materials and methods

2.1. Study population

We conducted a cohort study based on prospectively collected data from The Danish Multiple Sclerosis Registry (DMSR). We included all multiple sclerosis patients with onset of MS prior to age 18, starting from 1979 and up until data was extracted on February 9, 2018. As the first DMT became available in Denmark in 1996, the beginning date of inclusion (1st of January 1979) was chosen to ensure that all patients had the possibility of receiving treatment before their 18th birthday.

The dataset comprised year of onset and year of diagnosis, with the specific day of month arbitrarily set to the 1st of January.

The diagnostic criteria were until 1994 those of Allison and Millar (1954); from 1994–2004, Poser et al. (1983); and from 2001, the revised McDonald criteria moderated by the guidelines of IPMSSG (Krupp et al., 2013). Multifocal onset was defined as: (a) registered multifocal diagnosis or (b) optic pathway + any other symptom; or (c) cerebellar + any other symptom; or (d) brainstem + any other symptom; or (e) sphincter + any other symptom that was not sensory or pyramidal symptoms.

3. Sub-cohort

In a sub-cohort we included all POMS patients that started DMT before their 18th birthday and described treatment patterns of this group. Furthermore, we evaluated the use of moderate-efficacy treatments as primary choice in patients starting before and after 2006, when more efficacious treatments became available. Finally, we compared the sub-cohort with the group of patients that started DMT between age 18 and 25, to investigate differences in baseline demographic and clinical characteristics.

3.1. Data sources

The DMSR is a nationwide population-based registry, virtually comprising data on all Danish persons with MS. It was formally established in 1956 and has since performed a continuous registration of all cases of MS. Reporting of patients treated with DMT has been mandatory since 1996. In Denmark only 14 departments of neurology are authorized to treat with DMTs and reporting to the database is done by the treating physician, which ensures a high level of completeness and validity (Magyari et al., 2016).

3.2. Follow-up and outcomes

The entire POMS cohort was followed until their 25th birthday, death, emigration or date of data extraction (February 9, 2018), whichever came first. Throughout treatment, patients were monitored during scheduled clinical visits (three months after treatment start and every six months thereafter) at which different clinical features and outcomes were recorded. We excluded few cases treated with intravenous immunoglobulin or pulsed corticosteroid therapy, but other off-label DMTs (rituximab, ofatumumab and mitoxantrone) were included. For assessment of the annualized relapse rate (ARR) before and after treatment initiation, patients were followed from the day they started their first DMT until end of follow-up. Individual ARR were

calculated as the total number of relapses in the follow-up period divided by person-years.

3.3. Statistical methods

Descriptive statistics of the cohort are presented as frequencies with corresponding percentages for categorical variables and median with their range (interquartile (IQR)) or mean values with their standard deviation for continuous variables. ARR at baseline was analysed by Poisson regression whereas ARR during follow-up was analysed by negative binomial regression due to over-dispersed data and are presented as least square means. Log person-years were used as an offset in the model with ARR during follow up as an outcome.

Statistical analyses were performed using the statistics program SAS, version 9.4 (SAS Institute, Cary, NC).

4. Results

4.1. Baseline clinical and demographic characteristics

We identified a final cohort of 347 patients with onset of MS before the age of 18 years (Fig. 1). The female to male ratio was 2.6 (Table 1). All children presented with RR course. The first demyelinating event occurred at a median age of 15.8 years (IQR: 14.4–16.9 years). Onset at ≤ 12 years of age was seen in 50 children (14%), and at ≤ 10 years of age in 13 children (4%), with the youngest patient aged 3.0 years. The median age at diagnosis was 17.2 years (IQR: 15.5–19.3 years). Of the 347 children, 214 (62%) received the diagnosis of MS before turning 18 years old.

As shown in Fig. 2, we observed a continuous reduction in the mean latency period between onset of symptoms and time of diagnosis, decreasing from 5.6 years for patients with onset before 1994 to 0.4 year for patients with onset after 2015.

Among girls, sensory symptoms were the most common presenting symptom, found in 88 of the 251 patients (35%), whereas this was only seen in 19% of the boys (Fig. 3). Onset with both sensory and pyramidal symptoms was found in 23 girls (9%) and seven boys (7%). Multifocal clinical presentation according to the definition in this study was found in 17% of the girls and 25% of the boys. Only four children had sphincter symptoms at onset, all were girls and had coexisting sensory and/or pyramidal symptoms (in Fig. 3 they are only included in the group of sphincter symptoms). Onset symptoms were missing for 5% boys and 4% girls.

4.2. Disease-modifying therapies in children and adolescents

Of the 214 patients diagnosed in childhood or adolescent, 140 started DMT before their 18th birthday (Fig. 1). On average, each child was treated with 2.3 DMTs during follow-up (median: 2; IQR: 1–3). Fig. 4 show, that the majority of the children started treatment with a moderate-efficacy drug (90%) of which IFN- β was the most frequently used (80% of all patients). IFN- β -1a 22 or 44 microgram subcutaneously (sc.) was the DMT most commonly used between 1996 and 2005 (53% of treated patients during that period), but decreased to 13% in 2011–2018. Conversely, the prescription of IFN- β -1a intramuscularly (im.) increased to be the most used DMT between 2006 and 2010 and between 2011 and 2018 (56% and 51% respectively). Natalizumab became available in Denmark in 2006 but was not prescribed as first line treatment in children before 2011, after which nine patients received it. Mitoxantrone was prescribed as induction therapy in only two patients. For oral medications, fingolimod was approved in Denmark in 2011 and teriflunomide and DMF in 2013 and 2014. Since the approval, oral treatments have been increasingly used. From 2013 to 2018, oral DMTs was prescribed as first DMT in 26% of children.

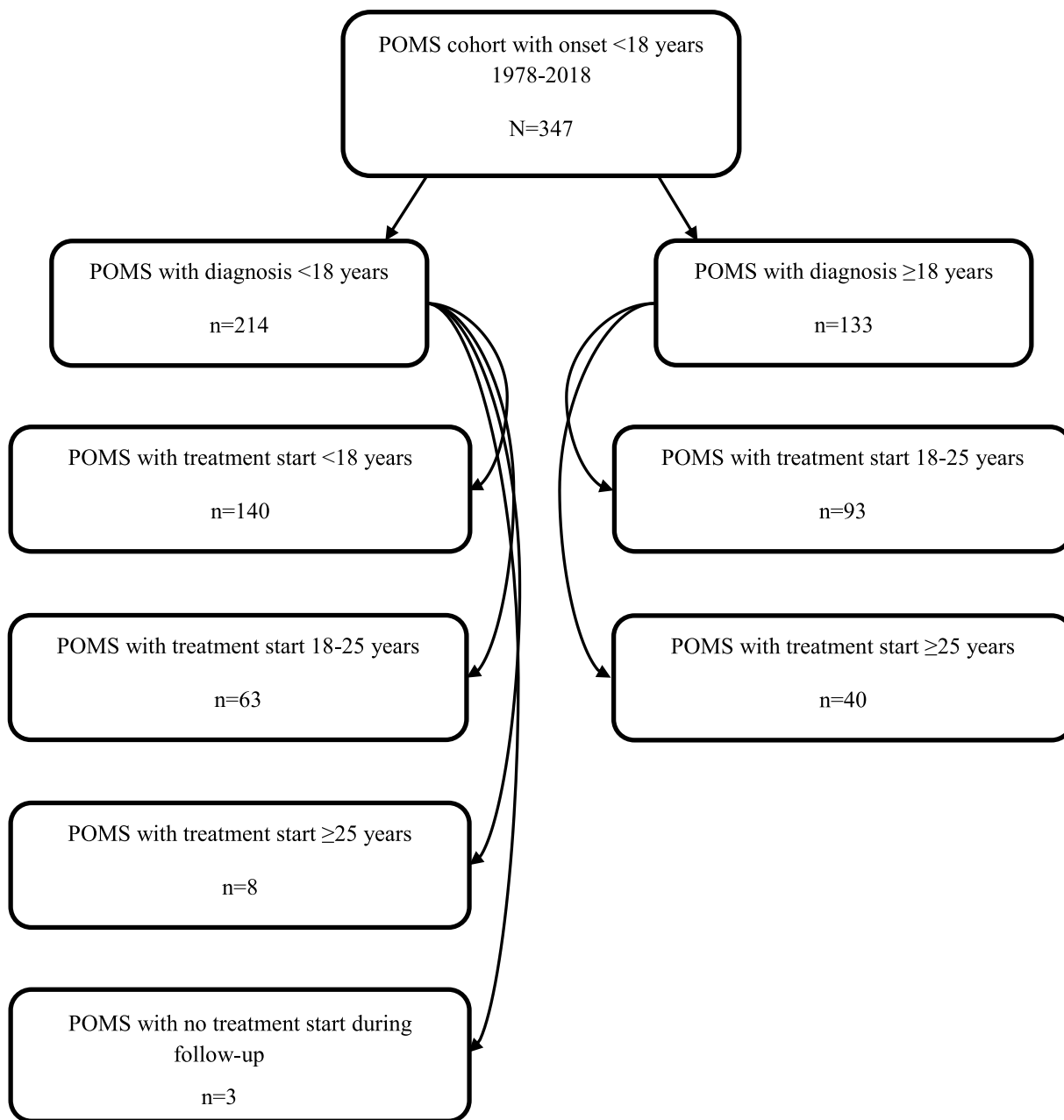


Fig. 1. Flow charts of the POMS cohort based on age at diagnosis and treatment start.

Table 1
Demographic and clinical characteristics of the full cohort with POMS.

Characteristics	POMS cohort (N = 347)
Females, n (%)	251 (72)
Age at onset, median (IQR)	15.8 (14.4–16.9)
Age at diagnosis, median (IQR)	17.2 (15.5–19.3)
Onset symptom, n (%)	
Monofocal	264 (76)
Multifocal	67 (19)
Unknown	16 (5)
Calendar year at onset, median (IQR)	2005 (2000–2010)
Diagnostic delay, years, median (IQR)	1.0 (0.0–3.0)
Total follow-up time from date of onset, years, median (IQR)	8.2 (7.1–9.8)

IQR, interquartile range; POMS, paediatric onset multiple sclerosis.

4.3. Discontinuation and switch of DMT

At the time of data extraction, 108 (77%) patients had discontinued their first treatment, seven of them within the first three months of treatment. The reasons for discontinuation were pregnancy ($n = 2$), adverse events ($n = 26$), development of neutralising antibodies ($n = 3$), lack of clinical response ($n = 47$) or unspecified reason ($n = 30$).

In total, adverse events during first treatment period were reported in 90 out of 140 patients. Of the 108 patients who discontinued their first treatment, 103 started treatment with another DMT during follow-up and further one patient started on the same DMT after a one-year break. Of the 103 patients switching therapy, 46 were lateral switches (41 moderate-to-moderate and 5 high-to-high) and 55 where escalations from a moderate- to a high-efficacy drug. The remaining two who received mitoxantrone as induction therapy switched to a moderate-efficacy drug.

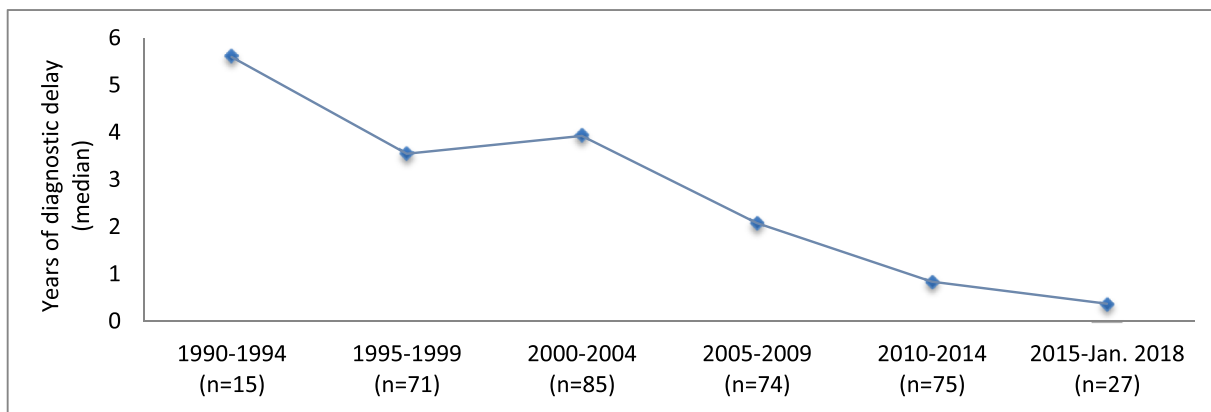


Fig. 2. Comparison of diagnostic delay in POMS (median number of years), based on year of onset.

Of the 60 patients receiving high-efficacy therapy as second DMT, fingolimod and natalizumab were prescribed in 30 and 24 cases, respectively. Further two patients received ocrelizumab (in 2016 and 2017), one patient rituximab and three patients mitoxantrone as escalation therapy (all between 2000 and 2006). When only considering treatment initiated after 2011, fingolimod was prescribed more often than natalizumab when escalation of therapy was indicated (25 versus 14). In total, 48 children had received more than one DMT at age < 18 and the remaining 55 patients between age 18–25.

Of the 140 children receiving treatment with DMT prior to age 18,

38 (27%) initiated treatment before 2006, and 102 (73%) after 2006. When only considering patients, who received a moderate-efficacy drug as first treatment, we found that a larger proportion of the patients who started DMT after 2006, switched or discontinued treatment during follow-up, compared to those starting before 2006 (86% vs. 67%). Also, median treatment length before switch or cessation of therapy was shorter for those starting a moderate-efficacy therapy after 2006 compared to those starting before 2006 (17.9 months vs. 25.1 months).

We compared the clinical characteristics of the present cohort (treatment start < 18 years) with the 156 POMS patients who started

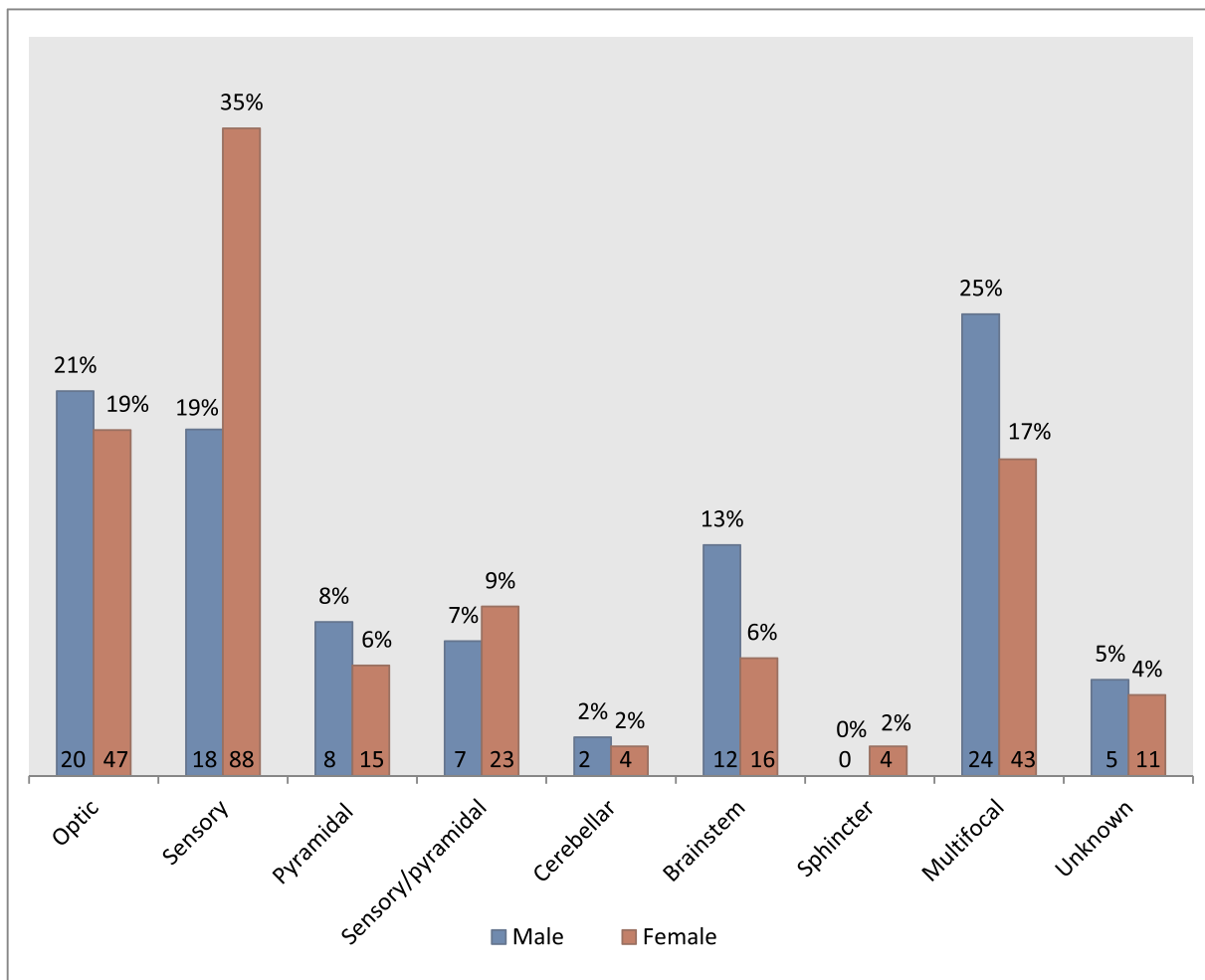


Fig. 3. Clinical presentation of children and adolescents with MS (n = 347).

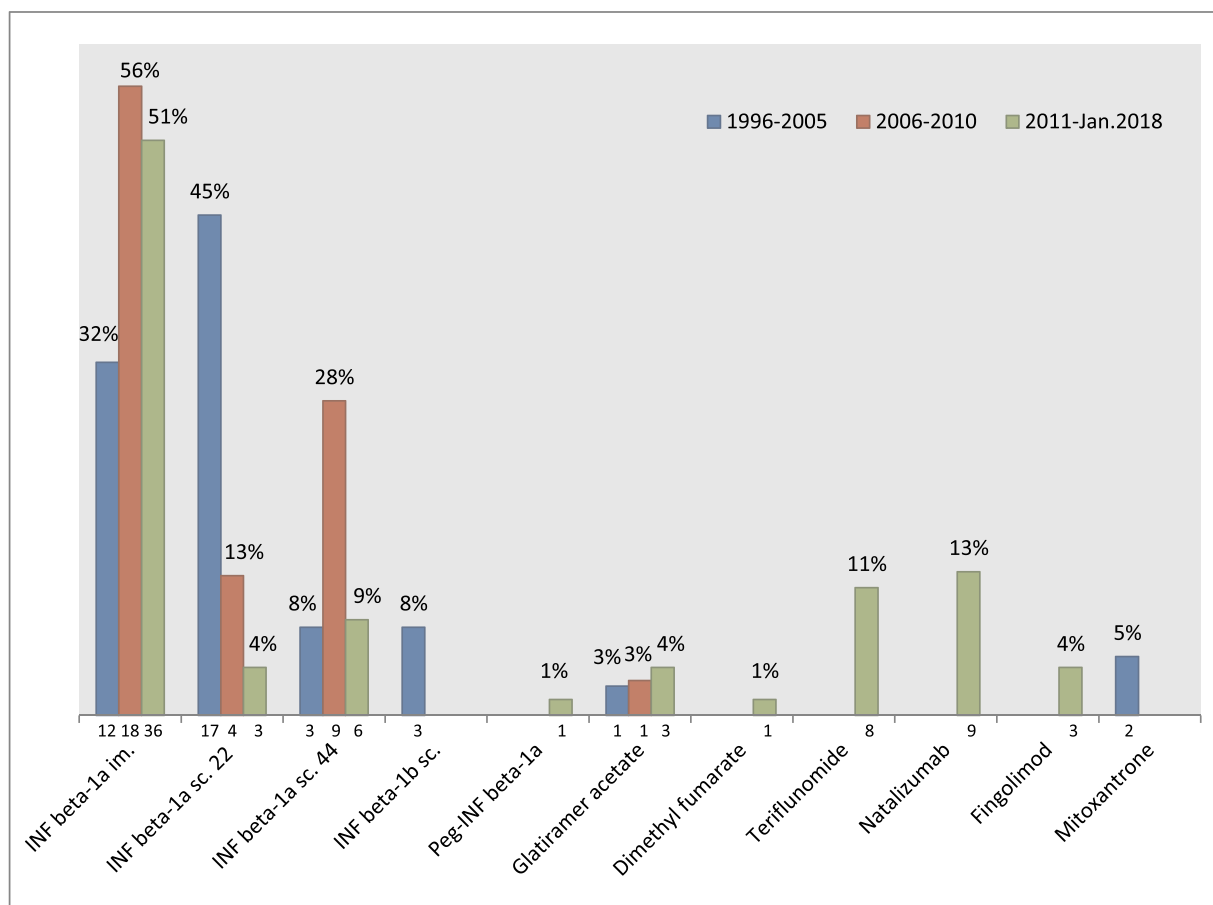


Fig. 4. Choice of first DMT for POMS in Denmark based on period of treatment start ($n = 140$). Percentage and in numbers.

treatment between age 18 and 25 and found, that the latter group were older at onset (16.1 vs. 14.8) and at diagnosis (18.5 vs. 15.4) (Table 2). Notable, they also had a longer diagnostic delay than those who started treatment before their 18th birthday (2.0 vs. 0.0 and 3.6 vs. 1.3, respectively) and were diagnosed at an earlier point in time. No other significant differences in clinical characteristics were found and they were not further investigated in this study.

4.4. Clinical outcomes

ARR differed slightly between boys (0.77) and girls (0.98) during the 24 months prior to treatment start, without reaching statistical significance ($p = 0.23$), whereas the difference among sexes was statistically significant after treatments start ($p = 0.0007$) (Table 3). ARR decreased from 0.98 (95% CI: 0.8–1.2) to 0.33 (95% CI 0.26–0.41) among girls, whereas boys experienced a reduction in ARR from 0.77 (95% CI 0.54–1.09) to 0.13 (95% CI 0.08–0.21).

5. Discussion

This study describes demographic and clinical characteristics of Danish patients with paediatric onset MS and the use of DMT in this cohort since 1996. As MS in children is rare, our cohort is relatively small, although still one the largest reported in POMS.

First of all it is important to underline that the distribution of demographic and clinical characteristics depends on the size and completeness of the presented cohort, as well as the organisation of paediatric MS care. When comparing median age at clinical milestones in different populations, age definition of paediatric onset must be taken into account, as this differs from country to country. The median age of

onset (15.8 years) found in this study, was similar to what is seen in a population-based study from Slovenia (Bizjak et al., 2017) and a retrospective single-centre study from USA (Yamamoto et al., 2018), both defining paediatric onset as age < 18 years. Different age definitions of paediatric onset also affect the female to male ratio between paediatric MS populations, because the gender discrepancy starts at puberty. Therefore, cohorts including persons with onset < 18 years report a higher female to male ratio than those only including patients with onset < 15 years. The higher proportion of girls (ratio 2.6) in the present cohort is in line with what is seen in other studies (Stark et al., 2008).

The majority of our population (76%) presented with a mono-symptomatic episode at onset, which differs from a Belgian cohort of 21 cases, where two thirds of children had multifocal onset (Verhelst et al., 2017), and the population from Slovenia, where 61 patients (59%) had multifocal onset (Bizjak et al., 2017). In our cohort, only 19% presented with multifocal onset, which is more in line with an Italian study of 97 patients, reporting 29% multifocal onset (Baroncini et al., 2019). Disease course was relapsing-remitting in all included cases, which is in line with the literature (Banwell et al., 2007).

The mean diagnostic delay decreased considerably during the follow-up period, partially due to several updates of the diagnostic criteria and earlier access to clinical care and DMT. Of the 347 cases with POMS, 214 received the diagnosis before the age of 18 years, of whom 140 started DMT before turning 18. The low proportion of DMT initiation before age 18 could partly be explained by the median age of diagnosis at 16.1 years (IQR 14.6–16.9) (for patients diagnosed < 18), which is close to adulthood, as well as the uncertainty in relation to exact date of diagnosis, leading to a risk of patients falsely being registered as diagnosed before age of 18 (since diagnosis date was

Table 2

Baseline demographic and clinical characteristics of the treated paediatric onset multiple sclerosis cohort stratified by age at treatment start ($N = 296$).

Characteristics	Treatment start < 18 years ($n = 140$)	Treatment start 18–25 years ($n = 156$)
Females, n (%)	99 (71)	114 (73)
Age at onset, median (IQR)	14.8 (13.1–15.9)	16.1 (15.6–17.5)
Age at diagnosis, median (IQR)	15.4 (14.0–16.4)	18.5 (17.5–19.9)
Age at treatment start, median (IQR)	16.4 (15.2–17.3)	19.9 (18.8–21.8)
Onset symptom, n (%)		
Monofocal	104 (74)	118 (76)
Multifocal	29 (21)	31 (20)
Unknown	7 (5)	7 (4)
Calendar year at onset, median (IQR)	2009 (2004–2013)	2004 (1998–2009)
Diagnostic delay, years, median (IQR)	0.0 (0.0–1.0)	2.0 (0.0–4.0)
Disease duration, years, median (IQR)	1.3 (0.9–2.0)	3.6 (1.8–6.3)
Relapse rate 24-months pre-therapy, mean (\pm SD)	1.8 (1.2)	2.0 (1.2)
EDSS at treatment start, median (IQR) ^a	2.0 (1.0–3.0)	2.0 (1.0–2.5)
First choice of treatment, n (%)		
Interferon β	112 (80)	116 (74)
Teriflunomide	8 (6)	10 (6)
Dimethyl fumarate	1 (1)	8 (5)
Glatiramer acetate	5 (4)	10 (6)
Natalizumab	9 (6)	10 (6)
Fingolimod	3 (2)	2 (1)
Mitoxantrone	2 (1)	0 (0)

EDSS, Expanded Disability Status Scale; IQR, interquartile range; SD, standard deviation.

^a Patients with missing EDSS baseline values were $n = 8$ among those treated before 18 years of age, and $n = 7$ among those treated between 18 and 25 years of age.

arbitrary sat to 1. of January). DMT was initiated between 18 and 25 years of age in 156 POMS. Further 48 cases started treatment after age 25, leaving only three cases untreated within follow-up.

In accordance with reports from other populations, IFN- β was widely used in our cohort, and was the first choice of treatment in 80% of the POMS population. Comparably, IFN- β was given as initial treatment in 83% of patients in an American POMS cohort followed from 2002 to 2015 (Yamamoto et al., 2018), in 82% of children in a German population (Stark et al., 2008), and in 71% of children in a cohort from Belgium (Verhelst et al., 2017). However, the pattern of DMT during the 22 years of follow-up period also reflects the increased drug availability. Over the last years a tendency towards prescribing the new and more convenient oral therapies has been seen, which is in line with recommendations from the Danish national treatment guidelines for adults with MS. A RCT from 2018 (FOCUS) found that efficacy and safety profile of oral DMF in children is consistent with what is seen in adults, which encourages use in POMS (Alroughani et al., 2018). The fact that the majority of patients still received injectable IFN- β shows reluctance in shifting to more convenient drugs, possibly due to safety considerations and longer experience with IFN- β . The safety profile of IFN- β , has been reported favourable in several studies, including a study with 44 children from seven countries treated with IFN- β 1b

Table 3

Annualised relapse rate before and after treatment start.

Sex	N	Before treatment start	p -value	After treatment start	p -value
Male	41	0.77 (95% CI 0.54–1.09)	0.23	0.13 (95% CI 0.08–0.21)	0.0007
Female	99	0.98 (95% CI 0.80–1.20)		0.33 (95% CI:0.26–0.41)	

(Banwell et al., 2006).

The presented data moreover demonstrate that many patients switched from moderate- to high-efficacy therapies over the observed period, which reflects breakthrough disease in these children and the need for more effective DMTs. Several case and cohort studies have discussed the use of high-efficacy therapy in children (Huppke et al., 2008, Ghezzi et al., 2015). Fingolimod has now been approved based on the PARADIGMS study, and other two studies; TERIKIDS (teriflunomide) and CONNECT (DMF vs. IFN- β 1a) involving moderate-efficacy DMTs are reaching final stages [ClinicalTrials.gov [Internet] 2019]. In line with this, the larger proportion of treatment switches and the shorter treatment duration seen in primary treatments initiated after 2006 could be explained by the availability of a higher number of DMTs.

Girls had a slightly higher ARR than boys before start of DMT, and the difference between the sexes was more pronounced on treatment. But for both groups a reduction in ARR was registered after treatment start. This observation is in accordance with a German study, which found that a high proportion of patients were relapse-free after treatment start (Stark et al., 2008). However, different studies reported a mean ARR during IFN-treatment of POMS ranging from 0.21 to 1.63, demonstrating a variability in treatment response and/or in the reporting of relapses (Banwell et al., 2011). Moreover, relapse rates decrease over time as a natural consequence of the disease course, which could explain some of the reduction in ARR found in our study, although the follow-up period in the present study is rather short.

DMT has been used in the treatment of POMS despite the lack of RCT-guided evidence. But our results also reflect a caution in prescribing newly approved DMT, including oral medications, which indicate that more RCTs are needed to make evidence-based decisions on both initiation and sequencing of DMT. Furthermore, most POMS patients become adults soon after diagnosis. Therefore, longitudinal follow-up studies of efficacy and safety of DMT initiated before the age of 18 years would provide physicians with greater confidence in starting DMT early in children.

There are several possible limitations. First, our study is based on registry data, and an important limitation of the study is the lack of completeness in reporting of magnetic resonance imaging. We were not able to complete missing data from the medical records. Strengths of this study include the nationwide population-based design and the completeness of the study population. In addition, the Danish public health care system is tax-funded minimizing the risk of referral bias. Diagnostic and clinical care of paediatric MS is organised in only three MS clinics at University Hospitals, ensuring continuity and sufficient experience of the neurologist. Data collection on all patients with MS treated with DMT is mandatory in order to get reimbursement.

Disclosures

Julie Laub Erdal: has nothing to disclose.

Tine Iskov Kopp: has nothing to disclose.

Morten Blinkenberg: has served on scientific advisory boards for Sanofi-Genzyme, Roche, Biogen, Merck, Novartis and Teva; has received speaker honoraria from Sanofi-Genzyme, Biogen, Merck, Novartis, Teva and Roche; has received consulting honoraria from the Danish Multiple Sclerosis Society, Sanofi-Genzyme, Biogen, Teva, Roche and Merck; and has received funding for travel from Sanofi-Genzyme, Roche and Biogen.

Thor Petersen: has received research grant support from Merck, Alexion, Roche, Genzyme, Biogen, Novartis and Sanofi.

Per Soelberg Sørensen: has received personal compensation for serving on scientific advisory boards, steering committees, independent data monitoring committees or have received speaker honoraria for Merck, Novartis, TEVA, GlaxoSmithKline, MedDay Pharmaceuticals, SanofiAventis/Genzyme, and Celgene.

Melinda Magyari: has served on scientific advisory board for Biogen, Sanofi, Teva, Roche, Novartis, Merck, has received honoraria for lecturing from Biogen, Merck, Novartis, Sanofi, Genzyme, has received research support and support for congress participation from Biogen, Genzyme, Teva, Roche, Merck, Novartis.

Role of funding source

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of Competing Interest

None

Acknowledgements

We would like to acknowledge the Danish Multiple Sclerosis Group for continuous data collection.

References

- Allison, R., Millar, J., 1954. Prevalence and familial incidence of disseminated sclerosis (a report to the Northern Ireland hospitals board on the results of a three year study). *Ulster Med. J.* (23), 29–49.
- Alroughani, R., Boyko, A., 2018. Pediatric multiple sclerosis: a review. *BMC Neurol.* 18 (Mar(1)), 27.
- Alroughani, R., Das, R., Penner, N., Pultz, J., Taylor, C., Eraly, S., 2018. Safety and efficacy of delayed-release dimethyl fumarate in pediatric patients with relapsing multiple sclerosis (FOCUS). *Pediatr Neurol* 83 (Jun), 19–24.
- Amato, M.P., Goretti, B., Ghezzi, A., Lori, S., Zipoli, V., Portaccio, E., et al., 2008. Cognitive and psychosocial features of childhood and juvenile MS. *Neurology* 70 (May(20)), 1891–1897.
- Amato, M.P., Krupp, L.B., Charvet, L.E., Penner, I., Till, C., 2016. Pediatric multiple sclerosis: cognition and mood. *Neurology* 87 (Aug(9 Suppl 2)), S82–S87.
- Banwell, B., Bar-Or, A., Giovannoni, G., Dale, R.C., Tardieu, M., 2011. Therapies for multiple sclerosis: considerations in the pediatric patient. *Nat. Rev. Neurol.* 7 (2), 109–122 Feb.
- Banwell, B., Ghezzi, A., Bar-Or, A., Mikaeloff, Y., Tardieu, M., 2007. Multiple sclerosis in children: clinical diagnosis, therapeutic strategies, and future directions. *Lancet Neurol.* 6 (Oct(10)), 887–902.
- Banwell, B., Reder, A.T., Krupp, L., Tenembaum, S., Eraksoy, M., Alexey, B., et al., 2006. Safety and tolerability of interferon beta-1b in pediatric multiple sclerosis. *Neurology* 66 (Feb (4)), 472–476.
- Baroncini, D., Zaffaroni, M., Moiola, L., Lorefice, L., Fenu, G., Iaffaldano, P., et al., 2019. Long-term follow-up of pediatric MS patients starting treatment with injectable first-line agents: a multicentre, Italian, retrospective, observational study. *Mult. Scler. Houndmills Basingstoke Engl.* 25 (Mar(3)), 399–407.
- Bizjak, N., Osredkar, D., Perković Benedik, M., Šega Jazbec, S., 2017. Epidemiological and clinical characteristics of multiple sclerosis in paediatric population in Slovenia: a descriptive nation-wide study. *Mult. Scler. Relat. Disord.* 18 (Nov), 56–59.
- Boesen, M.S., Magyari, M., Koch-Henriksen, N., Thygesen, L.C., Born, A.P., Uldall, P.V., et al., 2017. Pediatric-onset multiple sclerosis and other acquired demyelinating syndromes of the central nervous system in Denmark during 1977–2015: a nationwide population-based incidence study. *Mult. Scler Houndmills Basingstoke Engl.* (Jun).
- Chitnis, T., Arnold, D.L., Banwell, B., Brück, W., Ghezzi, A., Giovannoni, G., et al., 2018. Trial of fingolimod versus interferon beta-1a in pediatric multiple sclerosis. *N. Engl. J. Med.* 379 (11), 1017–1027.
- Chitnis, T., Ghezzi, A., Bajer-Kornek, B., Boyko, A., Giovannoni, G., Pohl, D., 2016. Pediatric multiple sclerosis Escalation and emerging treatments. *Neurology* 87 (Aug (9 Supplement 2)), S103–S109.
- Chitnis, T., Tenembaum, S., Banwell, B., Krupp, L., Pohl, D., Rostasy, K., et al., 2012. Consensus statement: evaluation of new and existing therapeutics for pediatric multiple sclerosis. *Mult. Scler. J.* 18 (Jan(1)), 116–127.
- ClinicalTrials.gov [Internet]. [cited 2019 Apr 10]. Available from: <https://clinicaltrials.gov/>.
- Dell'Avvento, S., Sotgiu, M.A., Manca, S., Sotgiu, G., Sotgiu, S., 2016. Epidemiology of multiple sclerosis in the pediatric population of Sardinia, Italy. *Eur. J. Pediatr.* 175 (Jan(1)), 19–29.
- Ghezzi, A., Amato, M., Annovazzi, P., Capobianco, M., Gallo, P., La Mantia, L., et al., 2009. Long-term results of immunomodulatory treatment in children and adolescents with multiple sclerosis: the Italian experience. *Neurol. Sci.* 30 (Jun(3)), 193–199.
- Ghezzi, A., Amato, M.P., Makhani, N., Shreiner, T., Gärtner, J., Tenembaum, S., 2016. Pediatric multiple sclerosis Conventional first-line treatment and general management. *Neurology* 87 (Aug(9 Supplement 2)), S97–102.
- Ghezzi, A., Moiola, L., Pozzilli, C., Brescia-Morra, V., Gallo, P., Grimaldi, L.M.E., et al., 2015. Natalizumab in the pediatric MS population: results of the Italian registry. *BMC Neurol.* 15 (Sep), 174.
- Ghezzi, A., Pozzilli, C., Grimaldi, L., Moiola, L., Brescia-Morra, V., Lugeschi, A., et al., 2013. Natalizumab in pediatric multiple sclerosis: results of a cohort of 55 cases. *Mult Scler J* 19 (Jul(8)), 1106–1112.
- Gorman, M.P., Healy, B.C., Polgar-Turcsanyi, M., Chitnis, T., 2009. Increased relapse rate in pediatric-onset compared with adult-onset multiple sclerosis. *Arch. Neurol.* 66 (Jan(1)), 54–59.
- Huppke, P., Stark, W., Zürcher, C., Huppke, B., Brück, W., Gärtner, J., 2008. Natalizumab use in pediatric multiple sclerosis. *Arch. Neurol.* 65 (Dec(12)), 1655–1658.
- Kornek, B., Aboul-Enein, F., Rostasy, K., Milos, R.-I., Steiner, I., Penzien, J., et al., 2013. Natalizumab therapy for highly active pediatric multiple sclerosis. *JAMA Neurol.* 70 (Apr(4)), 469–475.
- Krupp, L.B., Tardieu, M., Amato, M.P., Banwell, B., Chitnis, T., Dale, R.C., et al., 2013. International Pediatric Multiple Sclerosis Study Group criteria for pediatric multiple sclerosis and immune-mediated central nervous system demyelinating disorders: revisions to the 2007 definitions. *Mult. Scler. J.* 19 (Sep(10)), 1261–1267.
- Magyari, M., Koch-Henriksen, N., Sørensen, P.S., 2016. The Danish multiple sclerosis treatment register. *Clin. Epidemiol.*
- Pohl, D., Rostasy, K., Gärtner, J., Hanefeld, F., 2005. Treatment of early onset multiple sclerosis with subcutaneous interferon beta-1a. *Neurology* 64 (5), 888–890 Mar 8.
- Poser, C.M., Paty, D.W., Scheinberg, L., McDonald, W.I., Davis, F.A., Ebers, G.C., et al., 1983. New diagnostic criteria for multiple sclerosis: guidelines for research protocols. *Ann. Neurol.* 13 (Mar(3)), 227–231.
- Renoux, C., Vukusic, S., Mikaeloff, Y., Edan, G., Clanet, M., Dubois, B., et al., 2007. Natural history of multiple sclerosis with childhood onset. *N. Engl. J. Med.* 356 (25), 2603–2613.
- Stark, W., Huppke, P., Gärtner, J., 2008. Paediatric multiple sclerosis: the experience of the German Centre for Multiple Sclerosis in Childhood and Adolescence. *J. Neurol.* 255 (Dec(Suppl 6)), 119–122.
- Tenembaum, S.N., Banwell, B., Pohl, D., Krupp, L.B., Meinel, M., Rocak, S., et al., 2013. Subcutaneous interferon beta-1a in pediatric multiple sclerosis: a retrospective study. *J. Child Neurol.* 28 (Jul(7)), 849–856.
- Verhelst, H., De Waele, L., Deconinck, N., Ceulemans, B., Willekens, B., Van Coster, R., 2017. Multiple sclerosis in Belgian children: a multicentre retrospective study. *Eur. J. Paediatr. Neurol.* 21 (Mar(2)), 358–366.
- Yamamoto, E., Ginsberg, M., Rensel, M., Moodley, M., 2018. Pediatric-Onset multiple sclerosis: a single center study. *J Child Neurol* 33 (Jan(1)), 98–105.
- Yeh, E.A., Chitnis, T., Krupp, L., Ness, J., Chabas, D., Kuntz, N., et al., 2009. Pediatric multiple sclerosis. *Nat. Rev. Neurol.* 5 (Nov(11)), 621–631.