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Influence of Age at Onset and Obesity on Pediatric Multiple Sclerosis

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Hiermit erkläre ich, die Dissertation mit dem Titel "Influence of Age at Onset and Obesity on Pediatric Multiple Sclerosis" eigenständig angefertigt und keine anderen als die von mir angegebenen Quellen und Hilfsmittel verwendet zu haben.

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List of Abbreviations

ADEM	acute disseminated encephalomyelitis
AGA	Arbeitsgemeinschaft Adipositas im Kindes- und Jugendalter
ARR	annualized relapse rate
BMI	body mass index
CI	confidence interval
CNS	central nervous system
CSF	cerebrospinal fluid
DIS.	dissemination in space
DIT	dissemination in time
DMT	disease-modifying therapy
DXA	dual-energy X-ray absorptiometry
ECOG	European Childhood Obesity Group
EDSS	expanded disability severity scale
EOMS	early-onset multiple sclerosis
GA	glatiramer acetate
IFN-β	interferon-beta
IOTF	International Obesity Task Force
IPMSSG	International Pediatric Multiple Sclerosis Group
IQ	intelligence quotient
KiGGS	Studie zur Gesundheit von Kindern und Jugendlichen in Deutschland (German Health Interview and Examination Survey for Children and Adolescents)
MRI	magnetic resonance imaging
MS	multiple sclerosis
NEDA	no evidence of disease activity
OCB	oligoclonal bands
OR	odds-ratio
POMS	pediatric-onset multiple sclerosis
SAS	Statistical Analysis System
vs	versus
WMW	Wilcox-Mann-Whitney
WHO	World Health Organization

1 Introduction

Pediatric multiple sclerosis (MS) has been receiving growing worldwide recognition and attention over the last two decades due to improved neuroimaging techniques and advances in disease modifying treatments. This thesis presents the findings of two studies that have focussed on different aspects of pediatric multiple sclerosis. The first study compares clinical features of an MS manifestation before puberty with an onset in adolescence. The second study examines the effect of elevated body mass index (BMI) on pediatric MS risk, treatment response and disease course.

1.1 Pediatric multiple sclerosis

MS is a chronic immune-mediated demyelinating and neurodegenerative disorder of still unclear aetiology that targets the central nervous system (CNS), causing significant disability throughout the disease course and reducing life expectancy. At more than 2.2 million cases globally, it is predominantly an adult-onset disorder of young to mid-adult life, affecting women approximately two to three times more often than men (Collaborators 2019; Duquette et al. 1992). Less well known is that MS can also manifest in childhood, whereby it is generally referred to as pediatric MS, although several other terms such as pediatric-onset MS (POMS), early-onset MS (EOMS) and juvenile MS have also been used in the literature. In the past, variable age definitions have been used to define pediatric MS, so in an attempt to unify terminology for research purposes, the International Pediatric Multiple Sclerosis Study Group (IPMSSG) has proposed a working definition of a disease manifestation before18 years of age (Krupp et al. 2007).

1.1.1 Epidemiology and demographic

Pediatric MS is very uncommon. Approximately as little as two to five percent of all MS cases present with a disease manifestation before 16 years of age while a manifestation before puberty, frequently defined as 10 years or younger, is considered extremely rare (0.1 - 0.7%) (Boiko et al. 2002; Duquette et al. 1987; Ghezzi et al. 1997; Ruggieri et al. 2004). In Germany, the MS incidence for children under 16 years of age has been estimated at 0.64 per 100,000 person years and as low as 0.09/100,000 for those younger than 11 year (Reinhardt et al. 2014). The scarcity of pre-pubertal MS cases makes this subgroup particularly challenging to study while also suggesting that reproductive age influences disease immunopathogenesis. Further suggestive that sexual maturation plays a decisive role in disease risk is the well-recognized observation that female preponderance, a hallmark of adult MS, is only apparent after puberty while a more balanced sex ratio is evident before puberty (Ruggieri et al. 2004). A proinflammatory effect of the adipokine leptin, a hormonal regulator of body fat and

sexual maturation, on the adaptive immune system in the peri-pubertal period, is thought to play a contributory role in MS susceptibility in females, while protective effects of testosterone have been demonstrated in animal models of MS (Bebo et al. 1998; Dalal et al. 1997; Garcia-Mayor et al. 1997; Matarese et al. 2001).

1.1.2 Diagnosis

As in adults, the diagnosis of pediatric MS is made on the basis of clinical, paraclinical and magnetic resonance imaging (MRI) evidence of CNS demyelinating lesions that are disseminated in both space (DIS) and time (DIT) as defined by the McDonald criteria and secondly, by careful exclusion of other possible neurological disorders resembling MS (Krupp et al. 2013; McDonald et al. 2001). Prompted by advancements in disease modifying therapies, the McDonald diagnostic criteria for MS, first proposed in 2001, have undergone three revisions (2005, 2010 and 2017) in an effort to improve diagnostic accuracy, promote early diagnosis and reduce treatment delays (Polman et al. 2005; Polman et al. 2011; Thompson et al. 2018). Unchanged throughout all revisions is that two clinical attacks, each lasting longer than 24 hours and at least 30 days apart, are sufficient for a diagnosis of MS (Poser et al. 1983). Both the 2005 and 2010 revisions have made changes to the MRI requirements for DIS and DIT. A notable achievement of the 2010 revision has been to make it possible to diagnosis MS at the time of a first clinical attack based on a single MRI scan if evidence of DIS (T2-hyperintense lesions in at least two of four characteristic CNS areas: periventricular, juxtacortical, infratentorial, spinal cord) and DIT (concurrent asymptomatic gadolinium-enhancing and non-enhancing lesions) can be found (Polman et al. 2011). Since 2017, the MRI criteria for DIS also include cortical grey matter lesions and positive oligoclonal bands in cerebrospinal fluid have been allowed as a substitute for DIT (Thompson et al. 2018). While the revised criteria are largely considered sufficient for diagnosing MS in the adolescent age group, the IPMSSG advises caution in applying these criteria in the younger child as clinical presentation and MRI findings can sometimes be difficult to distinguish from other acute CNS inflammatory demyelinating disorders, in particular acute disseminated encephalomyelitis (ADEM) (Banwell B et al. 2007b; Chabas et al. 2008). Consensus criteria by the IPMSSG released in 2013 recommend that the diagnostic criteria for MS based on a single MRI scan at the time of the first attack should not be applied for children 11 years or younger (Krupp et al. 2013). Furthermore, the group advises that in the circumstance of an ADEM-like first attack, one non-encephalopathic clinical event at least 90 days later in combination with new MRI lesions consistent with MS is necessary to confirm MS.

A balanced sex ratio and an ADEM-like first attack in pre-pubertal MS patients are distinct features that indicate an influence of age at onset on clinical presentation.

1.1.3 Course

Almost all children with MS have an initial relapsing-remitting disease course, progressive symptoms from the outset are exceedingly rare (Boiko et al. 2002; Renoux et al. 2007). Compared to adults, children exhibit a more inflammatory course in the early stages of disease, experiencing more frequent relapses and showing greater disease activity on MRI (Benson et al. 2014; Gorman et al. 2009; Waubant et al. 2009). Nevertheless, recovery between relapses is generally better than in adult MS and both accrual of disability as well as evolution of secondary progressive disease is considerably slower (Renoux et al. 2007; Simone et al. 2002). A greater capacity for remyelination and repair as well as enhanced adaptability and plasticity of the younger brain may explain this finding. Far less favourable, however, is that although patients with pediatric MS take longer to reach disability milestones, they reach these milestones much earlier in life than adult MS patients due to their considerably younger age at disease onset (Harding et al. 2013; McKay et al. 2019; Renoux et al. 2007).

1.1.4 Treatment

In pediatric MS it is recommended that a disease-modifying therapy (DMT) be initiated as early as possible with the aim of achieving a state free of clinical or MRI disease activity (Chitnis et al. 2012; Ghezzi et al. 2010). DMTs approved for adult MS are also, despite regulatory restrictions, being used to treat pediatric patients and are generally classed as either first- or second-line immunomodulatory agents. Conventional first-line DMTs used in children are interferon-beta-1a and -1b (IFN-β-1a/-1b) and glatiramer acetate (GA). A number of studies indicate that these agents are effective, safe and generally well-tolerated in the pediatric population (Ghezzi et al. 2009; Kornek et al. 2003; Tenembaum et al. 2013). Second-line DMTs, including agents such as natalizumab, fingolimod, teriflunomide, rituximab, alemtuzumab and daclizumab, have been shown more potent and effective in the treatment of cases poorly responding to first-line therapy but their application is limited by more serious adverse effects (Chitnis et al. 2018; Ghezzi et al. 2015; Yousry et al. 2006). The current approach is to begin with a first-line drug and escalate to a second-line medication if treatment response is unsatisfactory and breakthrough disease is identified. While no international consensus definitions exist for when to escalate pediatric patients, signs of an inadequate treatment response in an adequately dosed and compliant patient are ongoing or increasing relapses, the presence of continued disease activity on MRI and incomplete recovery following attacks with worsening neurologic function (Chitnis et al. 2016a).

1.2 Obesity

1.2.1 Definition of obesity / Body Mass Index

The worldwide prevalence of obesity among children and adolescents has risen considerably in the past four decades making it an important global public health issue (Collaboration 2017). The International Obesity Task Force (IOTF), and the European Childhood Obesity Group (ECOG) both recommend employing body mass index (BMI) as a clinical screening tool to identify obesity in children (Bellizzi and Dietz 1999; Cole et al. 2000; Poskitt 1995). BMI is a crude measure of body fatness, but has been shown a good predictor of overweight in children correlating well with body fat measured by dual-energy X-ray absorptiometry (DXA) and has the advantage that it is simple and inexpensive to obtain (Mei et al. 2002; Pietrobelli et al. 1998). It is derived by dividing body weight by body height squared and is expressed as kg/m^2. In adults, the World Health Organization (WHO) defines overweight as a BMI of greater than or equal to 25 and obesity as a BMI of 30 or higher, irrespective of age and sex. Such fixed cut-off values are not appropriate for children for whom age and sex dependent changes to height and body composition, in particular skeletal mass, muscle mass and body fatness, must be taken into account. Consequently, age- and sex- specific BMI references are routinely used to determine if a child is overweight or obese. As ethnicity also influences the relationship between BMI and body fat, BMI references specific to the target population, if available, appear preferable to universal global references (Dugas et al. 2011). BMI references for German children were first compiled in 2001 following a meta-analysis of 17 different regional studies between 1985 and 1999 that reported BMI data of 34,422 German children under the age of 18 years (Kromeyer-Hauschild 2001). Here, BMI data were stratified by sex and age and expressed as percentiles which were calculated using the LMS method of Cole (Cole 1990). The guidelines of the "Arbeitsgemeinschaft Adipositas im Kindes- und Jugendalter" (AGA) recommends the use of the Kromeyer-Hauschild BMI references for defining overweight and obesity in German children and defines overweight as a BMI above the 90^{th} percentile and obese as a BMI over the 97^{th} percentile (Wabitsch and Kunze 2015). These chosen cut-off points comply with ECOG recommendations and also closely approximate IOTF definitions which are based on percentiles that at the age of 18 correspond to a BMI value of 25 and 30 kg/m^2, namely the recognized cut offs for overweight and obesity in adults, respectively.

1.2.2 Obesity trends in German children

In 2007, the first nationwide assessment of BMI trends within the German pediatric population was performed by the "German Health Interview and Examination Survey for Children and Adolescents" (KiGGS) (Kurth and Schaffrath Rosario 2007). Findings revealed a 50% increase in the overall prevalence of children and adolescents exceeding the 90^{th} BMI percentile (15%) and a doubling of obesity (6.3%) compared to the two previous decades.

The greatest increase in obesity was observed in the age group 14 to 17 years (8.5%). These findings were based on BMI data of 14,747 healthy German children aged 3 to 17 years, collected between 2003 and 2006, and sex- and age-stratified according to 2001 Kromeyer-Hauschild references. Since then, two follow-up surveys carried out from 2009 to 2012 and 2014 to 2017 have shown that the rates of overweight and obesity in German children have plateaued (Brettschneider et al. 2015; Brettschneider et al. 2017; Schienkiewitz et al. 2019). Interestingly, this finding matches trends in many high income countries (Collaboration 2017).

1.2.3 Obesity and MS risk

The first description of a link between obesity in adolescence, and increased MS risk appeared in 2009 in a study of 200,000 women in the United States which reported that a BMI of 30 or higher at age 18 years doubles the risk of developing MS in adult life (Munger et al. 2009). These findings have since been validated by multiple studies, with some suggesting that childhood is also a critical period within which a high BMI impacts future adult MS risk (Gianfrancesco et al. 2014; Hedstrom et al. 2016; Liu et al. 2016; Mokry et al. 2016; Munger et al. 2013; Wesnes et al. 2015). Findings in men are less conclusive with some studies showing either no or only attenuated risk related to adolescent obesity while significant male risk was found within the Swedish population (Hedstrom et al. 2012, 2016; Liu et al. 2016; Munger et al. 2013; Xu et al. 2021). The relationship between obesity and pediatric MS risk is not well studied. Prior to our study, one small study found increased risk of pediatric MS in obese adolescent girls but not in younger children and not in boys (Langer-Gould et al. 2013). A larger study comparing 254 pediatric MS cases with 420 healthy controls showed a BMI association in postmenarcheal girls but not premenarcheal girls, but additionally reported elevated risk in boys in general (Chitnis et al. 2016b). Both studies listed small numbers of males and younger children as limitations and called for validation of results in larger datasets.

Almost nothing is known about the effect of obesity on disease course and treatment response in children with MS.

1.3 Aims of the Studies

The aim of the first study was to determine clinical features that distinguish a pre-pubertal onset of pediatric MS from a post-pubertal onset.

The purpose of the second study was to validate and quantify obesity associated pediatric MS risk in a large cohort and to investigate whether obesity influences treatment and disease course in pediatric MS.

2 Methods

Both studies were retrospective single center cohort studies. All study patients were selected from the database of the German Center for Multiple Sclerosis in Childhood and Adolescence at the University Medical Center Göttingen, which serves as a tertiary referral center for children with CNS inflammatory demyelinating disease up to the age of 18 years. After this time, ongoing care is performed by adult neurologists. All study patients satisfied consensus definitions for pediatric MS as defined by the 2010 revised McDonald criteria and the criteria of the IPMSSG (Krupp et al. 2013; Polman et al. 2011).

2.1 Clinical features of a pre- and post-pubertal onset of MS

For the study, patients were classified as having a pre-pubertal MS onset if the first attack occurred at ten years or younger and no clinical evidence of secondary sexual development was documented at the time of the attack. As a comparative cohort, adolescents with an MS manifestation between 14 and 16 years of age were chosen to ensure sufficient follow-up information. Further inclusion criteria were a well-documented first attack, a relapsing-remitting MS disease course and a minimum follow-up of four years.

Data collected from the MS database and hospital records encompassed race, sex, family history of MS, infection history in month prior to first presentation, age at onset, clinical features of the first attack (symptoms, attack severity, recovery), time interval to second attack, relapse rate, choice of therapy and progression of disability.

Symptoms of the first attack were assigned to a functional system defined as either motor, sensory, optic, brainstem, cerebellar, sphincter or cognitive. An attack was considered polysymptomatic if more than one functional system was involved. Cases presenting with altered consciousness or behavioural changes but no documented fever or a systemic illness were classified as encephalopathic (Krupp et al. 2007). An attack was defined as severe if loss of ambulation or complete visual loss in at least one eye occurred during the episode and recovery from the attack was classified as incomplete if persisting neurological sequelae were detected six months or longer after the attack.

Disease course was assessed using annual relapse rate (ARR) and disability progression as parameters. A relapse was defined as an episode with new or worsening neurologic symptoms lasting at least 24 hours and unaccompanied by fever or intercurrent illness and occurring at least 30 days after a previous attack (Poser et al. 1983). Disability progression was assessed using the Kurtzke Expanded Disability Severity Scale (EDSS) (Kurtzke 1983). EDSS is a widely used parameter to grade residual neurological deficit in MS and is routinely documented at follow-up evaluation of patients in Göttingen. The scale ranges from zero to ten and increases in increments of 0.5. At a score below two the patient has no clinical disability while a score of four or more indicates significant disability usually involving some degree of gait impairment. In the study, an attack-free interval of at least six months prior to

EDSS assessment was required for inclusion of EDSS data. For patients lost to follow-up an attempt was made to re-establish contact. Where successful, current EDSS status was assessed by means of a telephone interview employing a standardized questionnaire.

2.2 Influence of BMI on pediatric MS

Study inclusion criteria were a confirmed diagnosis of relapsing-remitting MS, a first attack before 18 years and a reliably documented height and weight within six months of diagnosis. Body mass index (BMI (kg/m^2) was used as a surrogate measure of body fatness. All BMIs were standardized for sex and age based on Kromeyer-Hauschild data (2001). Children in the study with a BMI at or below the 90^{th} percentile(≤P90) were classified as non-overweight, children with a BMI between the 90^{th} and the 97^{th} percentile(>P90 - 97) as overweight, and children with a BMI over the 97^{th} percentile(>P97) as obese, as recommended for German children (Wabitsch and Kunze 2015).

In choosing a healthy control group the possibility of increasing BMI trends over time influencing results was considered. In Germany, rising BMI trends in children were observed throughout the 1990s and into the first decade of the 21^{st} century, as demonstrated by the findings of the 2003 to 2006 KiGGS study (Kurth and Schaffrath Rosario 2007). Since then, follow-up studies have positively shown that overweight and obesity prevalence in German children have stagnated (Brettschneider et al. 2015; Brettschneider et al. 2017). MS onset in the study cohort ranged from 1990 to 2016, thus the BMI data of the14,747 children in the 2003 - 2006 KiGGS study was considered representative as control data for the study. Patients with a disease onset before 2003 were considered unlikely to falsely elevate odds ratio (OR) estimates as obesity prevalence was lower in this period.

Comparative data collected from the MS database and medical charts included age at MS onset, first inter-attack interval, time to DMT initiation, relapses before and during first-line treatment with IFN-β and GA, escalation to a second-line DMT (fingolimod, natalizumab, alemtuzumab, rituximab), BMI at escalation, EDSS score after two years and at last follow-up.

Disease activity was evaluated on cranial and spinal MRIs performed within six months of MS diagnosis. Assessed were number of T2 hyperintense and gadolinium-enhanced lesions. Lesion volume was not analyzed. Acquisition of MRI data is described in publication two.

First-line therapy response was evaluated using annualized relapse rate (ARR) under therapy and frequency of escalation to a second-line therapy. Only cases with at least six months treatment with IFN-β or GA were included in the analysis of ARR. Prior to 2010, escalation to a second-line therapy was uncommon in pediatric patients, thus a subgroup of cases with disease onset from 2010 onwards and a minimum follow-up of 12 months were used to calculate escalation frequency. Patients recommended for second-line therapy at last consultation were counted as escalated.

2.3 Statistical Analysis

2.3.1 Clinical features of a pre- and post-pubertal onset of MS

As outlined in the publication, both cohorts were compared using the nonparametric Wilcoxon-Mann-Whitney (WMW) test with an outcome considered statistically significant at a two-sided $P < 0.05$. For comparative analysis of binomial data the two-sided Fischer's exact test was applied, for categorical data with more than two outcomes the Pearson χ^2-Test. Metric data was analysed using the Student's t-Test for unequal variances, ordinal data with the WMW test, and count data with Poisson regression using number of years as an offset to adjust for potential over-dispersion. Computation was done using SAS 9.3 or Statistica 10.

2.3.2 Influence of BMI on pediatric MS

BMI data of children with MS and healthy controls were stratified for age and compared. Frequencies for overweight and obesity between the groups were reported with 95% Clopper-Pearson CIs. Odds of MS was tested using the Fischer exact test and reported with 95% CIs. For the MS cohort, mean, median as well as interquartile range were reported for each BMI category. Group comparisons were performed with unpaired, 2-tailed Welch *t* test or Wilcoxon rank sum test, as appropriate. Relapses and MRI lesion counts were compared between groups using a negative binomial regression model with relapse rate adjusted for different follow up times and including 95% CIs. An outcome was considered statistically significant at two-sided $P < 0.05$. Computation was done with R Stat, version 3.4.3 (R Foundation for Statistical Computing).

3 Results

3.1 Clinical features of a pre- and post-pubertal onset of MS

3.1.1 Patients

47 children ten years or younger (mean age 8.4 years, range 2.5 - 10.9 years) and 41 adolescents aged 14 - 16 years, with year of MS onset ranging from 1986 to 2008 (mean 1999) and 1990 to 2007 (mean 2003), respectively, were included. Mean follow-up was 10.4 years (range 3 - 23 years) for the younger patients and only 5.6 years for the adolescent group. Transfer of care to adult neurologists at age 18 years explains the shorter follow-up interval in this group. No significant differences between the two groups were shown for race, family history of MS and infection history preceding MS onset.

3.1.2 Characteristics of the first attack

The adolescent group showed a marked female preponderance (73%) compared to the pre-pubertal group (55%). Pre-pubertal patients presented more commonly with a polysymptomatic (48.9% vs 36.6%, $P = 0.24$) onset and had a higher frequency of motor (44.7% vs 26.8%, $P = 0.08$) and brainstem symptoms (42.5% vs 26.8%, $P = 0.12$) as opposed to a predominance of sensory (46.3% vs 25.5%, $P = 0.04$) and optic lesions (31.7% vs 14.9%, $P = 0.06$) in the adolescent group. Encephalopathy was notably more common among younger patients (12.8% vs 2.5%, $P = 0.08$) and sphincter dysfunction (6.4%) and seizures (6.4%) were only documented in this group. A severe first attack was more than twice as likely among pre-pubertal children (26.8% vs 10.5%, $P = 0.06$); loss of ambulation was the reason in virtually all cases (10/11 pre-pubertal, 3/4 adolescents). Pre-pubertal boys and girls showed no significant differences in presenting features, recovery from the first attack or first inter-attack interval, however, a trend towards more brainstem symptoms in boys (57% vs 31%, boys vs girls, $P = 0.08$) at the first attack and sphincter symptoms in girls (5% vs 27%, boys vs girls, $P = 0.06$) over the first two years was noted.

3.1.3 Disease course

An incomplete recovery 6 months or longer after the first attack was more common in younger patients (17.4% vs 5.1%, $P = 0.08$), associated predominantly with minimal or mild motor sequelae (80%). No significant difference was found for the first inter-attack interval (mean 15 vs 13.9 months, pre-pubertal vs adolescents) with approximately two thirds of all patients experiencing a second attack within 12 months. Over the course of the first two years of disease, motor (68% vs 46%, $P = 0.04$) and brainstem (60% vs 39%, $P = 0.05$) symptoms remained significantly more common symptoms in the pre-pubertal cohort and sensory (40% vs 73%, $P = 0.002$) and optic (25.5% vs 73%, $P = 0.04$) symptoms in the

adolescent group (pre-pubertal vs post-pubertal, respectively)(Figure 1). Sphincter dysfunction was almost only reported in the pre-pubertal group (17% vs 2.4%, $P = 0.024$). For a quarter of the younger patients (25.5%) cognitive disturbances were documented within the first two years of disease compared to only 7.3% of adolescents ($P = 0.023$); 66% experienced concentration problems, 42% a decline in school performance.

Relapse rate was not significantly different between the two cohorts, however, ARR was generally higher in the pre-pubertal group at all time intervals possibly explained by the longer delay till treatment initiation in this group and changing treatment modalities. ARR after five years was 1.1 in the pre-pubertal cohort versus 0.8 in the adolescent cohort ($P = 0.39$).

One in four of the pre-pubertal patients showed some mild disability (EDDS 2 - 3.5) two years after disease manifestation while over 90% of the adolescents had no disability (EDSS < 2). High number of relapses in the first two years correlated significantly with a poorer EDSS outcome after 5 years in the pre-pubertal group ($P = 0.0032$). Insufficient data was available for the adolescent group. Disability five years after MS onset was not significantly different between the two groups, however. A follow-up period of longer than 10 years was available for 20 of 47 pre-pubertal patients. Disability levels remained low for the majority of these patients with a mean EDSS of 2.6 (median 2, range 0 – 7.0) after a mean follow-up of 14.8 years (range 11 – 23 years).

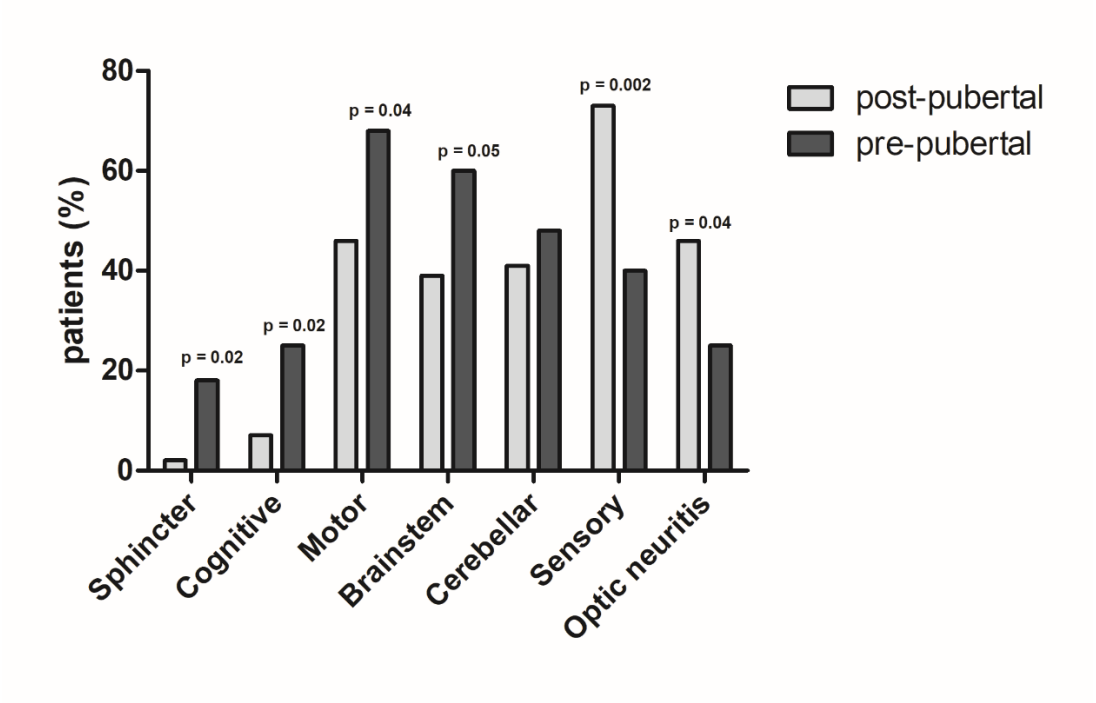

Figure 1: MS symptoms in the first two years of clinical disease

3.1.4 Treatment

Changing treatment modalities prevented comparative interpretation of treatment data. 87% pre-pubertal and 83% adolescent patients received at least one DMT, however, considerably longer time delay till initiation of therapy was observed in the pre-pubertal group (median 24 months vs 9 months). Survival analysis showed no significant difference for duration of treatment with the first agent between the two groups, median survival time was approximately 50 months for the whole collective.

3.2 Influence of BMI on pediatric MS

3.2.1 Characteristics of the total cohort

453 (306 females, 67.5%) cases identified in the database fulfilled inclusion criteria. Year of MS onset ranged from 1990 to 2016 with 400 cases (88%) first presenting after 2000. Mean age at diagnosis was 13.7 years (median 14.3) and mean age at BMI measurement 13.9 years (median 14.5). 62 children (13.7%) were under 11 years of age at MS onset. This subgroup showed an even ratio of girls (53%, 33/62) and boys compared to a female preponderance (70%) in children 11 years and older. 28% of all children had a high BMI (>P90, n = 126) at MS diagnosis; 15% were obese (>P97, n = 67). Mean follow-up for the cohort was 38.4 months (range 1 - 158), ARR excluding first attack was 0.85 and mean EDSS 0.9 (median 0, range 0 - 6).

3.2.2 BMI and odds of pediatric MS

Obesity was associated with significant two-fold odds of pediatric MS in both sexes (obese girls odds ratio (OR): 2.19; 95% CI, 1.5 - 3.1; $P < 0.001$ vs obese boys OR: 2.14; 95% CI, 1.3 - 3.5; $P = 0.003$) (Figure 2). Furthermore, the association between BMI and MS risk showed a dose dependent relationship with odds of MS of 1.37 (95% CI, 1.0 - 1.8; $P = 0.03$) in overweight participants rising to 2.2 (95% CI, 1.7 - 2.9; $P < 0.001$) in obese patients, an outcome seen equally for boys and girls. Higher rates of overweight and obesity were observed among both younger (7 - 10 years) and older children (11 - 17 years) with MS compared with controls. Boys aged seven to ten years showed the highest rate of overweight and obesity (40% combined).

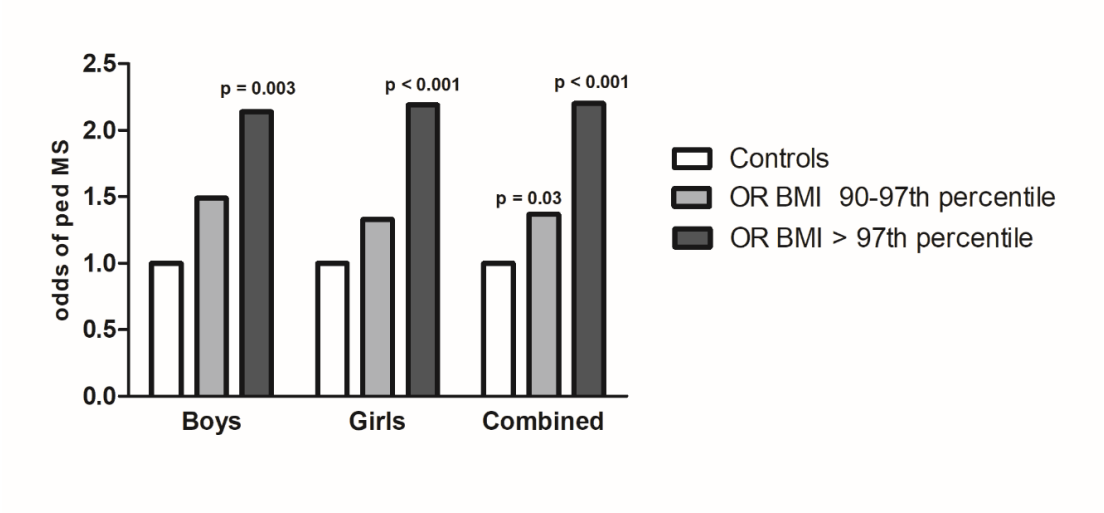

Figure 2: BMI and odds of MS

3.2.3 BMI and response to first-line therapy with IFN-β and GA

277 of the 453 patients were treated with IFN-ß (n = 249) and/or GA (n = 51) for six months or longer. 28% had a BMI above the 90th percentile matching that of the total cohort. Time to initiation of a DMT and treatment duration with IFN-β and GA were not statistically different between non-overweight, overweight and obese patients. Despite similar relapse rates prior to initiation of treatment, obese children had significantly more relapses on treatment with IFN-β and GA compared with their non-overweight counterparts (ARR, 1.29 (95% CI, 1.1 - 1.6) vs 0.72 (95% CI, 0.6 - 0.8); $P < 0.001$) (Figure 3). This finding was significant for children under 11 years at MS onset and for the age group aged 11 - 17 years.

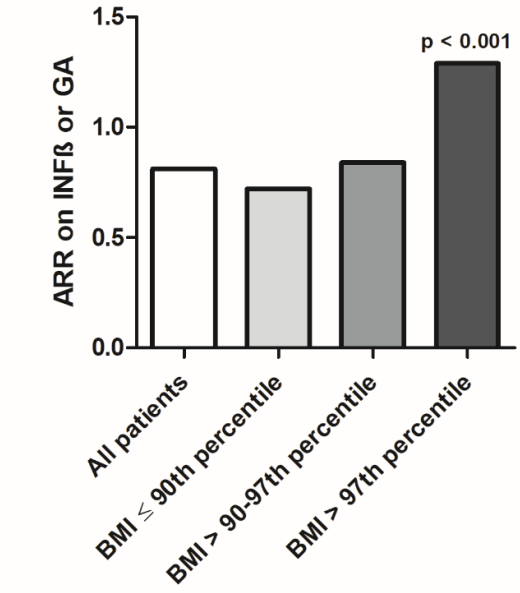

Figure 3: BMI and annual relapse rate (ARR) on treatment with interferon-beta or glatiramer acetate

3.2.4 BMI and escalation to second-line therapy

181 children had an MS onset after 2010 and at least 12 months follow-up. Mean follow-up was 35.4 months (median 17.7) with no significant difference in follow-up interval between weight categories. From 181 children, 78 (43%) were switched to a second-line therapy; natalizumab (n = 53), fingolimod (n = 31), alemtuzumab (n = 2), rituximab (n = 2). BMI at initiation of second-line therapy was available for 76 of the 78 patients. 91% had not changed their weight category since diagnosis and none of the children who were obese at diagnosis had normalized their weight. Switch frequency to a second-line therapy was approximately 50% higher in obese children compared with non-overweight (56.8% vs 38.7%; $P = 0.06$) (Figure 4).

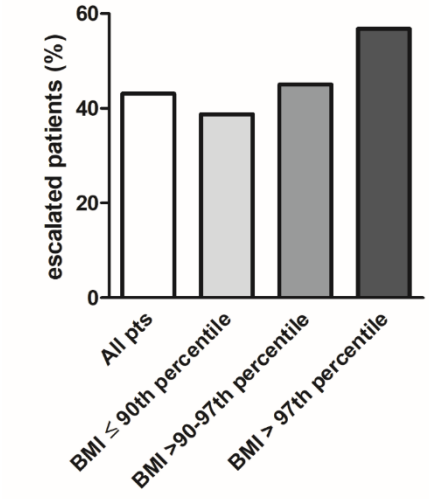

Figure 4: BMI and escalation frequency to a second-line therapy

3.2.5 BMI and disease activity and disability

No correlation was shown between BMI and initial MRI disease activity, first inter-attack interval or EDSS. Disease duration was not significantly different between weight classes.

4 Discussion

The findings of both studies contribute to the growing body of knowledge on pediatric MS. Two particular areas of focus in the studies were features associated with a pre-pubertal onset of MS and the influence of obesity on pediatric MS risk, treatment and disease course.

4.1 Clinical features of a pre- and post-pubertal onset of MS

Consistent with the literature, the first study showed a more even sex distribution in the pre-pubertal group and a female preponderance in adolescence, a finding that has been well described and strongly suggests that hormonal changes associated with puberty influence disease immunopathogenesis (Chitnis et al. 2016b; Ruggieri et al. 2004). Several other observations in the study also suggest that regional changes in vulnerability to inflammatory processes within the developing brain may influence the clinical presentation of MS in children. Pre-pubertal patients were more likely to have a polysymptomatic first attack, present with an encephalopathy and showed a predominance of motor and brainstem symptoms compared with more sensory and optic dysfunction in adolescent children. Additionally, seizures and sphincter dysfunction were only reported in pre-pubertal patients at onset. In pediatric MS, no absolute consensus can be found in the literature as to the most common presenting symptoms or their frequency at clinical onset (Ness et al. 2007). Moreover, very few studies have stratified for age effects or included significant numbers of young children. Nevertheless, there are several reports that support our results. In a study of 49 MS children under the age of six years at onset of MS, optic nerve involvement was also observed to increase with age while ataxia was found the most common presenting symptom (Ruggieri et al. 1999). In another small group of children under 10 years, frequent brainstem and motor symptoms were also reported whereas two large pediatric studies with almost 90% of participants 11 years or older both showed a preponderance of sensory and optic symptoms, matching our findings (Boiko et al. 2002; Duquette et al. 1987; Gusev et al. 2002). Since our study, a large multicentre prospective study of 490 children and adolescents has also presented similar findings showing a higher propensity for encephalopathy, motor and coordination symptoms in children under 12 years and significantly more sensory symptoms in adolescent children (Belman et al. 2016). It must be considered, however, that under-reporting of mild sensory or visual disturbances may be more likely in younger patients who are possibly less likely to vocalize such symptoms. Encephalopathy is well-recognized as a more common presenting feature in young children, making the distinction between ADEM and MS often problematic in this age group, particularly in patients presenting with multifocal neurological deficits (Banwell B et al. 2007a; Mikaeloff et al. 2004). It is estimated that as many as 29% of children initially diagnosed with ADEM will inevitably be diagnosed with MS (Mikaeloff et al. 2004).

A less favourable study finding was that pre-pubertal children were considerably more likely to experience a severe first attack, often involving loss of ambulation during the episode, and were, subsequently, also less likely to make a full recovery from the attack compared to their adolescent counterparts. Indeed, as many as one in four of the young study patients experienced a severe first attack and 17% were still displaying neurological deficits 6 months or longer after the initial attack, mostly minimal or mild motor disturbances. It has been suggested that lesion location may influence both inflammation and repair processes (Mowry et al. 2009b). Poorer recovery resulting in mild disability after the first attack in the very young child under six years of age has been reported once before and at a similar frequency (19%), however, attack severity was not assessed in the study (Mikaeloff et al. 2006). Conversely, in the large multicentre study of 490 children, disease severity at presentation was reportedly similar between older and younger children based on EDSS at the time of first visit to the clinical center, however, a variation in timing between disease onset and visit to the center was noted but not further specified (Belman et al. 2016). Nevertheless, EDSS 2 years post-onset was also similar between the groups in the study. In adult studies, younger age at onset has been associated with higher odds of a more severe first attack as well, while a severe demyelinating first event has been shown a significant predictor of incomplete recovery and possibly also indicative of severity and poor recovery of subsequent events in both adults and children (Fay et al. 2012; Mowry et al. 2009b; West et al. 2006).

Interestingly, the distinctive pattern of predominating symptoms at clinical manifestation in each of the cohorts was maintained over the first two years supporting the notion that lesion location of the first attack may influence the site involved in ensuing relapses (Mowry et al. 2009a). It also may explain why mild sequelae were still a more common finding in young children two years after onset. Similar symptoms during consecutive attacks has also been shown in an earlier Göttingen cohort as well as in adult MS studies, however, the underlying mechanisms to explain this observation remain unclear (Mowry et al. 2009a; Stark et al. 2008; Tsantes et al. 2020). Notably, two factors found predictive of disease progression in a recent large study that evaluated disease severity and disability in 873 pediatric MS patients, were having a motor relapse and EDSS at one year (Santoro et al. 2020). No convincing evidence was found in our study to suggest that the described clinical differences in pre-pubertal patients were significantly influenced by the higher percentage of males in this group.

Although cognitive function was not quantified in the study, particularly relevant was a higher reporting of concentration problems and decline in school performance in the pre-pubertal group suggesting an increased vulnerability for cognitive dysfunction. Cognition is commonly affected in pediatric MS. It has been shown that up to a third of pediatric MS patients display cognitive impairment within two to three years of disease onset with frequently affected domains involving memory, attention, speed of information processing, executive functions and verbal comprehension (Amato et al. 2008; Banwell BL and Anderson 2005; Charvet et al. 2014; Julian et al. 2013). A greater risk of cognitive decline has been linked to younger age at onset in two of the studies, matching the general observation in our

study (Amato et al. 2008; Banwell BL and Anderson 2005). Cognitive impairment can have a deleterious effect on school achievement and impact future academic success stressing the value of prompt diagnosis and treatment of MS in young patients. Disadvantageously, considerably longer delay to treatment initiation was certainly evident in the younger patients in this study and is a recognized problem in general (Belman et al. 2016). An interesting observation made in one study evaluating therapies in pediatric MS patients with refractory disease was that younger children are less likely to change therapy as a result of non-compliance or poor medication tolerability (Yeh et al. 2011). Our study, however, showed no significant difference in treatment duration with the first drug between cohorts on survival analysis. A recent Italian study of long-term DMT use in pediatric patients also notably reported a better response to DMTs as evidenced by fewer relapses and slower disability progression in younger children compared to children 12 years and older (Baroncini et al. 2019). Unfortunately, due to changing treatment modalities a comparison of treatment response was not possible in our study.

Despite a higher likelihood of a severe first attack and poorer initial recovery, there was no clinical evidence to indicate greater disease activity overall in younger children compared to adolescents, consistent with other reports (Belman et al. 2016; Boiko et al. 2002; Ruggieri et al. 1999). After five years of disease, younger children did not show worse levels of disability compared to the adolescent group and EDSS remained low over the following decade. Slow disability progression in pediatric MS is known and most likely indicates a generally better capacity for remyelination and more plasticity of the younger brain (Franklin et al. 2002; Renoux et al. 2007; Simone et al. 2002). A decline in remyelination capacity later in adolescence between the ages of 16 and 20 years has been demonstrated in one study of lesion recovery that used magnetization transfer ratio MRI to quantify changes in myelin (Brown et al. 2014). Patients aged 18 to 20 years showed recovery levels closely comparable with adult MS.

4.2 Influence of BMI on pediatric MS

Although the exact aetiology of MS remains unexplained, MS risk is considered to be under the influence of both genetic and environmental factors. The second study revealed significantly higher rates of overweight and obesity among children with MS compared to healthy controls, in support of a relevant role of obesity in pediatric MS risk. A dose dependent relationship was observed with higher BMIs associated with greater MS risk. Indeed, obese children showed more than twofold odds of MS, similar to the magnitude of adult female risk related to a high BMI in adolescence (Hedstrom et al. 2016; Munger et al. 2009). Although a link between obesity in adolescence and MS susceptibility in adult males remains less conclusive, our study revealed an equally elevated MS risk in both obese boys and girls (Gianfrancesco et al. 2014; Gunnarsson et al. 2015; Hedstrom et al. 2012; Liu et al. 2016; Munger et al. 2013; Wesnes et al. 2015). Pediatric findings are still very limited in this

area, but relevant risk in boys has been reported at least twice (Chitnis et al. 2016b; Milles et al. 2021). Increased male risk may be specific to the pediatric population, but, may also simply signify more reliable data collection, as some adult studies of BMI association have relied on recall of body size in adolescence limiting their findings (Gianfrancesco et al. 2014; Wesnes et al. 2015). Male obesity has been associated with reduced testosterone levels possibly due to heightened aromatase activity in adipose tissue promoting conversion of androgens to oestrogens (de Boer et al. 2005; Glass et al. 1977). Altered sex hormone profiles in obese males my play a role in increased MS risk.

While BMI in adolescence rather than early childhood has been described as the most critical period for impacting adult MS risk, our study also revealed higher rates of overweight and obesity in MS children aged 7 - 10 years (Hedstrom et al. 2016). Small numbers possibly limited significance. It has recently been shown that BMI trajectories in children with MS are significantly higher up to a decade before clinical manifestation compared to healthy controls (Brenton et al. 2019). Significantly higher BMI levels were already demonstrated by age 3 years in boys and age 4 in girls, suggesting that a long exposure period might be relevant for influencing MS manifestation. Although the exact pathologic mechanisms to explain obesity associated MS risk remain uncertain, it is thought that altered adipokine secretion is involved. In particular leptin has been suggested to play a pivotal role (Marrodan et al. 2021; Matarese et al. 2001; Sanna et al. 2003). Leptin is an adipokine produced by adipocytes and exerts an effect on both the innate and adaptive immune system. Its levels correlate well with BMI and are higher in women than in men (Blum et al. 1997; Chow and Phoon 2003; Falorni et al. 1997; Marrodan et al. 2021; Monti et al. 2006). Leptin promotes a state of chronic low grade inflammation by enhancing proliferation and survival of autoreactive T-cells, promoting production of proinflammatory cytokines and down regulating the circulation of Treg-cells which suppress immune response (Marrodan et al. 2021; Matarese et al. 2001). Additional factors associated with a high BMI that possibly also impact MS risk are lower serum vitamin D levels, deregulated gut microbiota, synergistic interaction with HLA-risk genes linked to MS susceptibility, and earlier start of menses (Chitnis et al. 2016b; Gianfrancesco et al. 2017; Hedstrom et al. 2014; Huitema and Schenk 2018; Smotkin-Tangorra et al. 2007). Taken together, promoting a healthy weight in all children, irrelevant of age and sex, appears relevant for mitigating pediatric MS risk.

The influence of obesity on first-line treatment with IFN-β or GA has not been studied in children before. Obese children were found to experience nearly twice as many relapses during treatment with IFN-β or GA compared with non-overweight MS patients. This finding was true for children younger than 11 years and older than 11 years at MS onset. Accordingly, the switch rate to a second-line DMT was approximately 50% higher among obese patients. At the time of escalation over 90% of children had not changed their weight category and none of the escalated children who were obese at diagnosis had normalized their weight suggesting that BMI trends in MS patients persist throughout childhood and adolescence, a finding supported by a recent pediatric study (Brenton et al. 2019). Obesity in

adulthood has also been shown to correlate well with childhood and adolescent obesity, indicating a continuation of the trend beyond childhood (Simmonds et al. 2016).

This is the first study to describe an association between high BMI and poorer response to first-line therapy with IFN-β or GA in pediatric patients. Higher relapse rates in general in overweight and obese children have been reported in one small pediatric cohort of 60 patients, but response to treatment was not specifically investigated (Yamamoto et al. 2018). Interestingly, an international retrospective analysis of 298 pediatric MS patients form eight different countries reported higher relapse rates under treatment with IFN-β-1a and a higher switch rate to another DMT among US patients (Krupp et al. 2016). They also reported substantially higher BMIs among US patients, however, noted that BMI data was lacking for the majority of the patients. An association with therapy response was not specifically analysed. In adults, worse therapy response to IFN-β has also been related to obesity in a small study which evaluated MRI activity and no evidence of disease activity (NEDA), a composite measure defined as no relapses, an absence of radiological disease activity and no disability progression, during treatment (Kvistad et al. 2015). In the study, it was suggested that the pro-inflammatory effects related to obesity might promote a more inflammatory disease process overall in obese patients explaining the poorer response to IFN-β. Although this hypothesis seems plausible the investigators reported no association between BMI and MRI activity or EDSS prior to commencement of IFN-β, which speaks against the presence of heightened disease activity in this group. Matching these findings, our study also showed no evidence of increased disease activity prior to treatment in obese children with respect to baseline MRI findings, first inter-attack interval or relapse rate. One small study of 50 pediatric cases likewise reported no positive association between BMI and disease activity (Krysko et al. 2016). No studies have evaluated the effect of elevated BMI on GA in children.

An alternative explanation for the suboptimal treatment response is that obesity may influence the pharmacokinetic properties of IFN-β or GA. Very little is known in general about how obesity influences drug pharmacokinetics in children and no studies have specifically investigated the effect of obesity on the pharmacokinetics of IFN-β or GA in children. A very small study of the pharmacokinetics of interferon-alpha in six obese and five nonobese adult patients showed findings that suggested a stronger biologic response in nonobese patients (Lam et al. 1997). Despite a paucity of information on the subject, there is evidence to suggest a relevant impact in children. In 2015, a study reviewed the last four decades of literature for studies that had evaluated drug pharmacokinetics in obese children (Harskamp-van Ginkel et al. 2015). 20 studies with pharmacokinetic data on 21 drugs were isolated. No MS medication was described among the studies. For two thirds of the drugs clinically significant alterations in pharmacokinetic properties were observed in obese children, involving either volume of distribution or clearance. Compared to non-obese children, pharmacokinetic alterations in obese children resulted in suboptimal therapeutic exposure in 38% of the studied drugs. Drug lipophilicity, however, was not correlated with obesity associated changes in volume of distribution or clearance. All of the studies were

limited by size and not stratified for age while some studies grouped overweight and obese children together possibly underestimating the effect. Establishing dosing recommendations in obese patients certainly requires more standardized pharmacokinetic studies.

4.3 Limitations

The Göttingen University Hospital is a tertiary care center for children with MS and as such may draw patients with more severe disease which may have influenced results. Findings are also limited by the retrospective nature of both studies and may only be specific to German children and not applicable to other ethnicities and countries.

As BMI is not an exact measure of excess body fatness, misclassification of some individuals in the BMI study cannot be excluded. Nevertheless, BMI has been shown to have a moderately high sensitivity (70 - 80%) and high specificity (95%) for identifying obese children, thus it is unlikely that children with a healthy weight were falsely classified as obese (Freedman and Sherry 2009). As BMI was measured after MS onset, a reverse association could be postulated, in other words, MS is a risk factor for the development of obesity in children. Factors speaking against a radical change in BMI status after disease onset include a short mean time between disease manifestation and BMI measurement, limited steroid treatment, very low level of disability as well as little change in BMI status in the time interval between manifestation and therapy escalation in subgroup analysis. The recent finding of higher BMI trajectories in children with MS up to a decade before disease onset also makes a reverse association unlikely (Brenton et al. 2019). Although recognized MS risk factors such as vitamin D deficiency, exposure to Epstein-Barr virus or genetic susceptibility were not considered in the study, a causal relationship between BMI and MS in children has been previously confirmed even after controlling for these variables (Gianfrancesco et al. 2014; Gianfrancesco et al. 2017). Finally, as lesion count not lesion volume was assessed on baseline MRI, disease activity may have been misrepresented in the occasional case with large confluent lesions but a low overall lesion count.

4.4 Conclusion

Several findings presented in this thesis are relevant for the evaluation of children presenting with pediatric MS. Both pre- and post-pubertal MS children presented with a specific pattern of symptoms at clinical manifestation that was maintained over the first two years. Young children showed a propensity for motor and brainstem symptoms and older children sensory and visual symptoms. Less favourable for the younger patient, however, were a higher likelihood of a severe first attack, a higher frequency of mild sequelae following the first attack and a greater vulnerability for cognitive involvement in the first two years compared to adolescent patients. This underscores the importance of minimizing delays in DMT initiation in young patients, a problem that was also more common in this age group. More

positively, disease activity and disability progression were not worse overall in pre-pubertal cases compared to post-pubertal.

The second study confirmed a positive association between BMI and pediatric MS risk with significant two-fold odds of developing MS related to obesity in both sexes. Furthermore, patients who were obese at onset were likely to remain obese and twice as likely to relapse on conventional first-line therapies increasing the likelihood of therapy escalation. A more inflammatory underlying disease process, however, was not demonstrated in obese patients suggesting a role of altered pharmacokinetics in poor treatment response. In short, promoting a healthy weight in childhood appears beneficial for mitigating pediatric MS risk and improving treatment outcomes in MS patients.

5 Summary

Pediatric multiple sclerosis has many parallels to adult multiple sclerosis, however, the initial disease course is generally associated with more relapses yet better recovery and slower disability progression than in adults. Two distinctive features of pediatric multiple sclerosis indicate that age at onset in children has clinical relevance. Firstly, female preponderance, a hallmark of adult multiple sclerosis, first becomes apparent after puberty suggesting that multiple sclerosis risk in girls is unfavourably influenced by sexual maturation, Secondly, in younger pediatric patients the first attack can be difficult to distinguish from other inflammatory central nervous system demyelinating disorders often leading to delays in diagnosis and treatment initiation. A relatively recent link between obesity in adolescence and increased multiple sclerosis risk in adulthood also appears relevant for pediatric multiple sclerosis but studies are very limited. Moreover, almost nothing is known about the influence of obesity on disease modifying therapy and disease course in children. This thesis presents the findings of two retrospective single center cohort studies which explore firstly, the effect of a pre-pubertal onset of multiple sclerosis on clinical features and, secondly, the influence of obesity on pediatric multiple sclerosis risk, treatment response and disease course.

In the first study, presenting features, relapse rate and disability progression of 47 pre-pubertal children at disease onset were compared with 41 adolescents aged 14 to 16 years at onset. Findings showed a specific pattern of symptoms at clinical manifestation in both patient groups that was maintained over the first two years of disease suggesting that regional changes in vulnerability to inflammatory processes in the developing brain affect presentation. Multifocal symptoms, a propensity for motor and brainstem symptoms and encephalopathy were all more common in pre-pubertal cases at clinical onset compared to sensory and visual symptoms in adolescent cases. Less favourably, children with a pre-pubertal onset had a higher likelihood of a severe first attack, a higher frequency of mild sequelae following the attack and a greater vulnerability for cognitive involvement in the early course of disease. Nevertheless, relapse rate and disability progression after five disease years, were not significantly different between pre-pubertal and post-pubertal onset cases.

In the second study, a cohort of 453 children with multiple sclerosis were categorized as non-overweight, overweight or obese according to their body mass index within six months of their first multiple sclerosis attack. The weight groups were then compared with body mass index data of 14,747 healthy German controls. Resultingly, obesity was associated with significant twofold odds of multiple sclerosis in both sexes. Weight categories were then compared within the multiple sclerosis cohort. Obese children with multiple sclerosis were significantly more likely to relapse on first-line therapy with interferon beta and glatiramer acetate and, subsequently had a higher switch rate to a second-line therapy. Furthermore, patients who were obese at onset were likely to remain obese. Findings did not indicate a more inflammatory underlying disease process or worse disability progression in obese patients, suggesting a possible role of altered pharmacokinetics in poor treatment response.

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Clinical presentation of pediatric multiple sclerosis before puberty

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Background and purpose: Multiple sclerosis (MS) onset before puberty is extremely rare and establishment of diagnosis is often difficult due to atypical presentation. The study aims to identify the typical presentation of MS in this age group.

Methods: Pediatric MS patients were identified from the database of the Center for Multiple Sclerosis in Childhood and Adolescence at the University Medical Center Göttingen, Germany. Inclusion criteria were a relapsing–remitting initial disease course and minimum disease duration of 4 years.

Results: Forty-seven pre-pubertal (<11 years) and 41 post-pubertal (14–16 years) MS patients were compared. Before puberty an even gender ratio was found. The pre-pubertal patients were more likely to have a polysymptomatic severe first attack with motor and brainstem involvement, sphincter dysfunction, cognitive disturbances and milder residual neurological sequelae after the first episode whilst the post-pubertal patients predominantly presented with optic neuritis and sensory symptoms. The initial symptom pattern prevailed over the first 2 years of disease. Presentation of pre-pubertal boys and girls did not differ significantly.

Conclusions: To facilitate early diagnosis it is important to recognize that pre-pubertal MS presents with a specific pattern of symptoms that is maintained over the first two disease years.

Introduction

Multiple sclerosis (MS) before the age of 16 years is uncommon with prevalence rates between 2.2% and 5.0% reported; a manifestation prior to puberty is extremely rare (<10 years: 0.1%–0.7%) [1–5]. Despite a more inflammatory early course, initial recovery is reportedly better and disease progression slower in children than in adult onset disease [4,6–8]. Nevertheless, significant disability is attained much earlier in life in the pediatric patient emphasizing the importance of early diagnosis and optimal therapeutic management. Childhood, however, is a period of intense development and the influence of biological changes on disease risk and disease expression must be considered. Atypical presentation at onset is a frequent cause of diagnostic uncertainty and is more commonly seen in the younger child.

Studies of pre-pubertal children remain challenging and are frequently limited by small sample size. Study groups of more than 40 pre-pubertal children are rare. The main objective of our study was to establish the characteristic features of an onset of MS before puberty and to explore the effect of pubertal transition on phenotype.

Methods

Pre-pubertal and post-pubertal onset MS patients were selected retrospectively from the database of the Center for Multiple Sclerosis in Childhood and Adolescence at the University Medical Center Göttingen, Germany (approved by the ethics committee of the University Medical Center Göttingen, Ethic approval number 21/12/03). An assessment in the Pediatric Neurology Department in Göttingen at least once, a minimum disease duration of 4 years and a relapsing–remitting disease course were criteria for inclusion. Children up to and including the age of 10 years with no clinical evidence of secondary sexual development at first clinical manifestation of disease were defined as pre-pubertal. Adolescents aged 14–16 years at disease onset were defined as post-pubertal. All subjects satisfied consensus definitions for pediatric MS as defined by the International Pediatric MS

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Group [9]. In all at least one MRI was compatible with the diagnosis.

The following variables were obtained: race, gender, family history of MS, age at onset, reported infection in month prior to first manifestation, presenting symptoms, severity of first attack, cerebrospinal fluid (CSF) analysis, initial recovery, first inter-attack interval, functional system involvement in the first 2 years, relapses, Expanded Disability Severity Score (EDSS) progression and disease-modifying therapies. Symptoms were grouped as motor, sensory, optic, brainstem, cerebellar, sphincter and cognitive corresponding with the functional systems in the EDSS [10]. The disease manifestation was considered polysymptomatic if more than one functional system was affected at onset. Encephalopathy required the presence of behavioral change or alteration in consciousness according to consensus definitions [9]. The initial attack was graded as severe if a loss of ambulation or complete visual loss in at least one eye occurred during the episode. A complete recovery was defined as the absence of persistent neurological sequelae at a follow-up examination no less than 6 months after the first attack. In those patients with an inter-attack interval of <6 months the first available attack-free period of at least 6 months was assessed. Complete remission was assigned to those cases with no evidence of a deficit attributable to the first episode. Documentation of functional system involvement over the first 2 years included the first episode. If multiple attacks involving the same system occurred the system was only recorded once per patient. Cognitive data were gathered from questioning at visits about concentration problems, school performance and behavioral changes.

Relapse rate was recorded for the first year and each subsequent year thereafter for as long as documentation was available. The initial attack was included in the first year. EDSS was evaluated at time intervals of 2, 5, 10 and 15 years after disease onset. A detailed neurological examination performed either within the Pediatric Neurology Department in Göttingen or by another neurologist for these time periods and an attack-free interval of at least 6 months was mandatory; in the absence of either, no EDSS was calculated.

Comparing two groups by means of the nonparametric Wilcoxon–Mann–Whitney test at the usual two-sided significance level of 5%, sample sizes of at least 41 subjects give a power in excess of 80% provided that the probability that an observation in one group is smaller than an observation in the other is at least 68%.

Comparisons between groups of pre- and post-pubertal subjects as well as between gender were made with a two-sided Fisher's exact test for binomial data. For categorical data with more than two outcomes Pearson χ^2 test was applied. Metric data were evaluated according to Student's *t*-test for unequal variances, ordinal data (e.g. EDSS status) according to a Wilcoxon–Mann–Whitney test and count data (e.g. number of relapses) according to a Poisson regression adjusted for potential over-dispersion with the number of years of follow-up as offset. Correlation coefficients including 95% confidence intervals (CI) were calculated stratified between the two groups. *P* values below 0.05 were considered statistically significant. All calculations were performed with SAS 9.3 (SAS, Heidelberg, Germany) or Statistica 10 (Tulsa, StatSoft, OK, USA).

Results

Forty-seven children under 11 years of age presenting between 1986 and 2008 (mean 1999) with a mean follow-up of 10.4 years (range 3–23 years) and 41 adolescents aged 14–16 years presenting between 1990 and 2007 (mean 2003) with a mean follow-up of 5.6 years (range 0.5–21 years) documented in the database fulfilled the inclusion criteria. At age 18 pediatric MS patients are transferred to the care of adult neurologists and consequently are more easily lost to follow-up explaining the shorter follow-up interval in this group. In the pre-pubertal cohort mean age was 8.4 years (range 2.5–10.9 years) (Table 1); 35 children were <10 years and 17 were <8 years at onset. Female preponderance was demonstrated in the post-pubertal group (female : male: pre-pubertal 1.24, 95% CI 0.70, 2.20; post-pubertal 2.73, 95% CI 1.37, 5.44; $P = 0.12$). Ethnic distribution was similar with a Caucasian majority (>90%) in both groups. No significant difference in familial cases of MS and history of antecedent infection was seen.

Pre-pubertal children presented more commonly with a polysymptomatic onset (49% vs. 37%, $P = 0.24$) and a preponderance of motor (44.7% vs. 26.8%) and brainstem (42.5% vs. 26.8%) symptoms; 95% of brainstem symptoms were diplopia (55%) and facial weakness (40%). Sensory (46.3% vs. 25.5%) and optic lesions (31.7% vs. 14.9%) predominated in the post-pubertal group. Statistical significance was achieved for sensory symptoms ($P = 0.04$) and near significance for motor ($P = 0.08$) and optic lesions ($P = 0.06$). An encephalitic manifestation (12.8% vs. 2.5%, $P = 0.08$) and a severe first attack (26.8% vs. 10.5%, $P = 0.06$) were notably more common in the younger child with near significance for both. Ten of 11 pre-pubertal and three of four post-pubertal patients suffered loss of ambulation. Seizures (6.4%)

Table 1 Demographic, clinical and paraclinical characteristics at onset in patients under 11 years of age and 14–16 years of age with pediatric onset MS

	Onset <11 year (n = 47)	Onset 14–16 years (n = 41)	P value
Demographics			
Female : male ratio	1.24 (26/21)	2.73 (30/11)	0.12
First-degree relative with MS, % (n)	10.6 (5)	12.2 (5)	1.0
Combined first and second relatives with MS, % (n)	19.1 (9)	19.5 (8)	1.0
First attack			
Prior infections, % (n)	27.7 (13)	19.5 (8)	0.37
Polysymptomatic presentation, % (n)	48.9 (23)	36.6 (15)	0.24
Motor symptoms, % (n)	44.7 (21)	26.8 (11)	0.08
Sensory symptoms, % (n)	25.5 (12)	46.3 (19)	0.04
Optic neuritis, % (n)	14.9 (7)	31.7 (13)	0.06
Brainstem symptoms, % (n)	42.5 (20)	26.8 (11)	0.12
Cerebellar symptoms, % (n)	27.7 (13)	19.5 (8)	0.37
Sphincter dysfunction, % (n)	6.4 (3)	0 (0)	0.1
Seizures, % (n)	6.4 (3)	0 (0)	0.1
Encephalopathy, % (n)	12.8 (6)	2.5 (1/40)	0.08
Severe first attack, % (n)	26.8 (11)	10.5 (4)	0.06
Incomplete recovery, % (n)	17.4 (8/46)	5.1 (2/39)	0.08
First inter-attack interval, mean months (median, range)	15 (6, 1–68)	13.9 (8, 2–69)	0.98
OCBs, % (n)	60.1 (28/46)	73.2 (30/41)	0.26
OCBs including testing at later attacks, % (n)	91.3 (42/46)	85.3 (35/41)	0.51
Pleocytosis > 4/μl, % (median, range)	59.5 (13/μl, 5–92)	63.2 (12.5/μl, 5–50)	0.73

and sphincter dysfunction (6.4%) at onset were only seen in the pre-pubertal group.

Over the first 2 years of disease the initial symptom pattern at onset was reinforced, reaching significance for all variables except cerebellar involvement (Fig. 1). Motor (68.1% vs. 46.3%, $P = 0.039$), brainstem (59.6% vs. 39%, $P = 0.054$), sphincter (17% vs. 2.4%, $P = 0.024$) and cognitive disturbances (25.5% vs. 7.3%, $P = 0.023$) afflicted significantly more pre-pubertal patients and sensory (40.4% vs. 73.2%, $P = 0.002$) and optic lesions (25.5% vs. 46.3%, $P = 0.04$) more post-pubertal patients. Cognitive impairment was documented for a quarter of pre-pubertal patients: 66% experienced concentration problems, 42% a decline in school performance and 42% behavioral changes and mood swings.

No significant difference was found for first inter-attack interval: mean 15 months (median 6 months) vs. 13.9 months (median 8 months) in pre- and post-pubertal patients, respectively. Sixty-six percent of pre-pubertal children and 61% of adolescents experienced a relapse within the first year. Mild residual neurological deficits after the first attack were three times more common in the pre-pubertal group (17.4% vs. 5.1%), showing near significance ($P = 0.08$). Mild motor deficits were most common (80%); EDSS was ≤2.0 for six of eight affected pre-pubertal children after 2 years with no EDSS > 4.0.

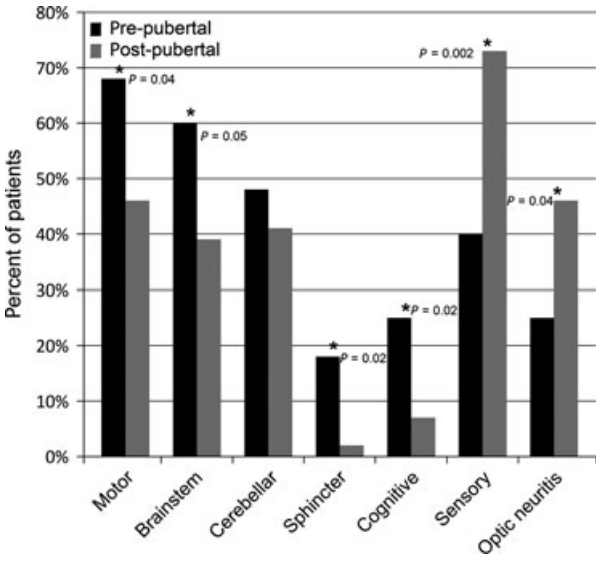

Figure 1 Symptoms in the first 2 years after onset of disease. Percentage of pre- and post-pubertal patients who present at least once with a specific neurological symptom.

Cerebrospinal fluid analysis showed a slightly lower oligoclonal band (OCB) detection rate initially in the pre-pubertal group (60% vs. 73%, pre- vs. post-); however, subsequent retesting improved the rate to above that in the post-pubertal group (91% vs. 85%,

Table 2 Mean relapses in the first 5 years, annualized relapse rate after 5, 8 and 10 years and EDSS progression

	Onset < 11 year (n = 47)	Onset 14–16 years (n = 41)	P value
Relapses, mean (range) (n)			
Year 1	2.1 (1–6) (47)	1.8 (1–5) (40)	0.23
Year 2	1.0 (0–8) (46)	0.94 (0–4) (36)	0.75
Year 3	0.91 (0–4) (46)	0.65 (0–3) (32)	0.29
Year 4	0.88 (0–5) (43)	0.73 (0–2) (27)	0.52
Year 5	0.79 (0–4) (42)	0.42 (0–2) (20)	0.15
Annualized relapse rate (n)			
5 years	1.11 (42)	0.76 (18)	0.39
8 years	0.93 (23)	0.54 (8)	0.28
10 years	0.65 (15)	0.47 (6)	0.93
EDSS mean (median, range) (n)			
2 years	0.95 (0, 0–4) (43)	0.50 (0, 0–5.5) (35)	0.099
5 years	1.1(1.0, 0–3.5) (42)	1.0 (0, 0–6.5) (13)	0.136
10 years	1.2 ((1.0, 0–3.5) (16)	1.2 (0.5, 0–3.5) (6)	0.971
15 years	2.5 (2.0, 0–6.0) (10)		

Table 3 Comparison of clinical characteristics of boys and girls in the pre-pubertal group

	Boys (n = 21)	Girls (n = 26)	P value
First attack			
Mean age, years	8.6	8.2	0.51
Polysymptomatic presentation, % (n)	57.1 (12)	42.3 (11)	0.39
Motor symptoms, % (n)	38.1 (8)	50 (13)	0.56
Sensory symptoms, % (n)	28.6 (6)	23.1 (6)	0.74
Optic neuritis, % (n)	14.3 (3)	15.4 (4)	1.0
Brainstem symptoms, % (n)	57.1 (12)	30.8 (8)	0.084
Cerebellar symptoms, % (n)	28.6 (6)	26.9 (7)	1.0
Sphincter dysfunction, % (n)	4.8 (1)	7.7 (2)	1.0
Seizures, % (n)	4.8 (1)	7.7 (2)	1.0
Encephalopathy, % (n)	14.3 (3)	11.5 (3)	1.0
Severe first attack, % (n)	14.3 (3)	30.8 (8)	0.30
Incomplete recovery, % (n)	14.3 (3)	19.2 (5)	0.72
First inter-attack interval, mean months (median, range)	14.5 (8, 1–68)	15.5 (6, 1–60)	0.84
Symptoms in the first 2 years			
Motor symptoms, % (n)	80.1 (17)	57.7 (15)	0.121
Sensory symptoms, % (n)	38.1 (8)	42.3 (11)	1.0
Optic neuritis, % (n)	33.3 (7)	23.1 (6)	0.52
Brainstem symptoms, % (n)	71.4 (15)	50 (13)	0.23
Cerebellar symptoms, % (n)	47.6 (10)	46.2 (12)	1.0
Sphincter dysfunction, % (n)	4.8 (1)	27 (7)	0.059
Cognitive symptoms, % (n)	33.3 (7)	19.2 (5)	0.33

pre- vs. post-). No difference in CSF pleocytosis was observed at onset.

No significant difference in yearly relapses was found between the groups; however, slightly more relapses were observed in the pre-pubertal group at all time intervals (Table 2). Relapses were highest in the early course of disease decreasing with increasing disease duration in both groups; mean relapse rate fell from 2.1 in the first year to 0.79 in the fifth year for pre-pubertal subjects and from 1.8 to 0.42 for post-pubertal subjects. Annualized relapse rate after 5 and 8 years was 1.11 vs. 0.76 and 0.93 vs. 0.54 for the pre- and post-pubertal patients, respectively. Two patients in each group developed secondary progressive disease, two pre-pubertal patients after 10 and 12 years and two post-pubertal patients after 5 and 16 years.

Changing treatment modalities between 1986 and 2008 prevented comparative interpretation of treatment data (Table S1). Eighty-seven percent pre-pubertal and 83% post-pubertal patients received at least one disease-modifying therapy after a mean untreated duration of 37.5 months (median 24 months) and 22.5 months (median 9 months) and mean relapses of 3.4 and 2.3, respectively. Survival analysis showed no significant difference for duration of treatment with the first agent between the two groups with a median survival time for the whole collective of approximately 50 months.

No significant difference in EDSS outcome was found between the two cohorts (Table 2). More mild disability was seen in the pre-pubertal cohort after 2 and 5 years, however: EDSS < 2.0, 72% vs. 91%; EDSS 2.0–3.5, 26% vs. 5.7% after 2 years; and EDSS < 2.0, 71% vs. 85%; EDSS 2.0–3.5, 29% vs. 0%; EDSS ≥ 4.0, 0% vs. 15% after 5 years (pre-pubertal versus post-pubertal, respectively). EDSS progression was slow in both groups over the first 10 years with mean EDSS 1.2 for both groups after 10 years (P = 0.97). Ten-year data were small, however. Twenty pre-pubertal patients had a follow-up longer than 10 years. Mean EDSS was 2.6 (median 2, range 0–7.0) after a mean follow-up period of 14.8 years (range 11–23 years): 30% EDSS < 2, 50% EDSS 2–4 and 20% EDSS > 4.

A significant correlation was found between high number of relapses in the first 2 years and poorer EDSS outcome after 5 years for the pre-pubertal group (P = 0.0032, correlation coefficient r = 0.45, 95% CI 0.13, 0.68) and for the collective as a whole (P = 0.0031, correlation coefficient r = 0.40, 95% CI 0.12, 0.62). Insufficient data were available for the post-pubertal patients.

Comparison of pre-pubertal boys and girls showed no significant differences for presentation at first attack and symptoms during the first 2 years (Table 3).

Discussion

Increased female risk after puberty, a finding also evident in our study (female : male 1.24 vs. 2.73 pre- vs.

post-), is characteristic of pediatric MS and highlights a difference between pre- and post-pubertal onset MS. With this study the typical features of a pre-pubertal manifestation of MS are described.

Both genetic and environmental factors have been considered relevant in MS etiology. One could assume that a younger manifestation of MS is associated with a greater familial risk of disease. However, no evidence of this was found with a similar number of familial cases reported in each of our cohorts. An infective episode preceding MS onset was slightly more frequent in the pre-pubertal group (28% vs. 20%, pre- vs. post-) but not as frequent as that reported by Mikaeloff *et al*.[11] in children under 10 (41%). Both findings may simply reflect a higher infection rate in children under 10 years of age rather than an enhanced role in MS pathogenesis.

Comparison of clinical characteristics at onset revealed a distinctive pattern of symptom predominance in each of the cohorts that was maintained over the first two disease years, becoming significant for almost all observed variables. The first attack of the pre-pubertal patient was more commonly polysymptomatic with a preponderance of motor and brainstem symptoms. It was also more than twice as likely to be severe with an incomplete initial recovery three times more common than in the post-pubertal group. Sphincter dysfunction at onset was only seen in the pre-pubertal group and remained significantly more frequent during the first 2 years. Furthermore, an increased vulnerability for cognitive dysfunction was evident with more pre-pubertal patients presenting with encephalopathy at onset and significantly more reporting cognitive impairment over the first 2 years, predominantly concentration difficulties. A decline in school performance was documented in nearly half the cases. An unfavorable association between lower age at onset and cognitive impairment has been previously described [12–14]. Adolescent patients, in contrast, displayed more sensory and optic symptoms both at first presentation and within the first 2 years. Many pediatric MS studies have evaluated clinical presentation but only few have stratified for age [4,6,11,13,15–18]. Gusev *et al*.[16] also found motor and brainstem involvement more frequent in the younger child (4–8 years) and optic neuritis in older children (9–15-year-olds), consistent with our findings; however, only eight children were under 8 years of age in this study. More mild disability after the first clinical episode in the very young child (<6 years) has also been described [11].

Cerebrospinal fluid analysis revealed a lower detection rate of OCBs at the time of first attack in the pre-pubertal patients, a finding previously reported in children with MS [11]. Subsequent retesting at a later episode, however, resulted in a marked rise in positive cases amongst pre-pubertal patients.

Despite more severity of first presentation and poorer initial recovery amongst our pre-pubertal patients, disease course was not found to differ statistically significantly between the pre- and post-pubertal cohorts. In contrast to the findings of Mikaeloff *et al*.[11] a similar first inter-attack interval was observed in both groups. Furthermore, no statistically significant difference in relapse frequency was shown, a finding also reported by Boiko *et al*. who compared children under 11 years at onset with adolescents [1]. A higher number of relapses in the first 2 years was associated with a poorer disability outcome after 5 years in the pre-pubertal group ($P = 0.003$) and in the collective as a whole, a previously described association [1,8,16,19,20]. EDSS progression was very slow in both groups and no significant effect of age at onset was seen on EDSS outcome after any of the designated time intervals, consistent with previous reports [1,4,17,20,21]. More mild disability was seen in the pre-pubertal group early in the course of the disease, however.

Lastly, whether the clinical differences observed in our study could be explained by differences in gender distribution between the groups was considered. However, no evidence was found for this. Age at presentation was similar between pre-pubertal boys and girls, as was the presentation at first attack and symptoms in the first 2 years. The only symptoms nearing statistical significance were more brainstem symptoms at presentation in boys and sphincter dysfunction within the first 2 years in girls.

This study has limitations mostly arising from its retrospective nature. Broader inclusion dates at clinical onset in the pre-pubertal group resulted in therapeutic differences between the two groups. Consequently comparative interpretation of treatment data was not possible. Longer initial untreated periods and evolving treatment modalities in the younger child may explain the slightly higher relapse rate and EDSS outcome in this group. Finally, small post-pubertal sample size beyond 5 years due to loss of follow-up limited comparison after this time period.

The picture evolving from our data and other studies is that presenting and early clinical phenotype are influenced by pubertal transition most probably reflecting regional changes in vulnerability within the developing brain to inflammatory processes. High initial relapse rate and slow EDSS progression relative to adult onset MS, on the other hand, appear characteristic of pediatric MS, irrespective of age at onset, representing a highly active immune process in a brain that is recovering well.

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Disclosure of conflicts of interest

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Disease-modifying therapy in pre-pubertal and post-pubertal patients.

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JAMA Neurology | Original Investigation

Association of Obesity With Multiple Sclerosis Risk and Response to First-line Disease Modifying Drugs in Children

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IMPORTANCE Obesity reportedly increases the risk of pediatric multiple sclerosis (MS), but little is known about its association with disease course.

OBJECTIVE To investigate the association of obesity with pediatric MS risk and with first-line therapy response among children with MS.

DESIGN, SETTING, AND PARTICIPANTS This single-center retrospective study used the medical records and database at the Center for MS in Childhood and Adolescence, Göttingen, Germany. The study included 453 patients with relapsing-remitting pediatric MS and body mass index (BMI) measurement taken within 6 months of diagnosis. Onset of the disease occurred between April 28, 1990, and June 26, 2016, and the mean disease duration was 38.4 months. Data were collected from July 14, 2016, to December 18, 2017.

MAIN OUTCOMES AND MEASURES Data on BMIs were stratified by sex and age using German BMI references and compared with the BMI data of 14 747 controls from a nationwide child health survey for odds ratio (OR) estimates. Baseline magnetic resonance imaging findings, intervals between first and second MS attacks, annualized relapse rates before and during treatment with interferon beta-1a or -1b and glatiramer acetate, frequency of second-line treatment, and Expanded Disability Status Scale (EDSS) scores were compared between nonoverweight (BMI≤90th percentile), overweight (BMI>90th-97th percentile), and obese (BMI>97th percentile) patients.

RESULTS In total, 453 patients with pediatric MS were included, of whom 306 (67.5%) were female, and the mean (SD) age at diagnosis was 13.7 (2.7) years. At diagnosis, 126 patients (27.8%) were overweight or obese, with obesity associated with statistically significant twofold odds of MS in both sexes (girls OR, 2.19; 95% CI, 1.5-3.1; $P < .001$ vs boys OR, 2.14; 95% CI, 1.3-3.5; $P = .003$). Obese patients, compared with nonoverweight patients, had statistically significantly more relapses on first-line treatment with interferon beta and glatiramer acetate (ARR, 1.29 vs 0.72; $P < .001$) and a higher rate of second-line treatment (21 [56.8%] of 37 vs 48 [38.7%] of 124; $P = .06$). Baseline neuroimaging, interval between first and second MS attacks, pretreatment relapses, and EDSS progression scores were not correlated with BMI.

CONCLUSIONS AND RELEVANCE In this study, increased pediatric MS risk appeared to be associated with obesity, and obese patients did not respond well to first-line medications; altered pharmacokinetics appeared to be most likely factors in treatment response, suggesting that achieving healthy weight or adjusting the dose according to BMI could improve therapy response.

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The prevalence of overweight and obesity is on the rise worldwide, with the most substantial increase in the past 3 decades being observed among children and adolescents.[1-4] This global phenomenon has attracted international attention as obesity has been consistently associated with increased mortality and several deleterious health outcomes, including greater susceptibility to inflammatory and autoimmune diseases.[5-8]

A plausible association between obesity and multiple sclerosis (MS) risk was first established in a 2009 study of the association between body size and MS in a cohort of more than 200 000 women in the United States.[9] In that study, a more than twofold increased risk of developing adult-onset MS was associated with obesity (body mass index [BMI] of 30 or higher; calculated as weight in kilograms divided by height in meters squared) at age 18 years. These results have since been validated in other adult studies, with a growing body of evidence indicating that a high BMI in adolescence and possibly in early life increases MS risk.[10-18] This association is evident even after controlling for established genetic and environmental risk factors and has been described in both sexes, although a stronger association has been repeatedly shown in females.[16] The exact underlying pathologic mechanisms still require elucidation, but lower serum vitamin D levels, altered adipokine profiles favoring a proinflammatory state, deregulated gut microbiota, unfavorable interaction with HLA-risk genes in puberty, and earlier start of menses have all been suggested to play a role in obesity-associated MS risk.[19-25]

In the pediatric setting, to date, only a few studies on small cohorts have assessed the association between BMI and risk of pediatric MS; nevertheless, their findings also indicate substantially higher rates of overweight and obesity among children with MS compared with their healthy counterparts.[14,25,26] At the Center for MS in Childhood and Adolescence in Göttingen, Germany, in which more than 150 pediatric patients with MS are followed up yearly, we have observed that many obese patients do not respond well to first-line therapy with interferon beta-1a or -1b and glatiramer acetate. This study was conducted to (1) ascertain whether obese patients have a worse response to first-line therapy, and (2) confirm increased pediatric MS risk associated with obesity in a large cohort.

Key Points

Question Is obesity associated with multiple sclerosis risk and response to first-line therapy in a pediatric population in Germany?

Findings In this single-center study of 453 German children with a multiple sclerosis diagnosis, obesity was associated with twofold greater odds of the disease and more frequent failure of first-line treatment with interferon beta-1a or 1b and glatiramer acetate, thereby increasing the number of patients on second-line treatment.

Meaning Obesity appeared to be statistically significantly associated with increased risk of pediatric multiple sclerosis and with worse treatment response to first-line treatment; a healthy weight may potentially optimize treatment outcomes and reduce the disease burden and costs.

Methods

This single-center analysis of MS cases (with onset between April 28, 1990, and June 26, 2016) received ethical approval from the University Medical Center Goettingen. All data were derived from database and medical record review and were deidentified; thus, informed consent was waived by the University Medical Center Goettingen. Data were collected from July 14, 2016, to December 18, 2017.

Study inclusion criteria were a confirmed diagnosis of relapsing-remitting MS, as defined by the revised McDonald criteria and the International Pediatric MS Study Group criteria[27,28]; an MS onset before 18 years of age; and a reliably documented height and weight measurement within 6 months of first clinical presentation to a medical institution. We performed a database search (W.S.) and validated those data by medical records review (B.H.). We standardized BMI for sex and age according to Kromeyer-Hauschild[29] data, the recommended BMI references for German children. These data originated from a meta-analysis of 34 422 German children (aged <18 years) pooled from 17 different regional studies between 1985 and 1999.[29]

Patients were grouped by BMI category using the definitions recommended by the European Childhood Obesity Group.[30] Nonoverweight was defined as BMI at or below the 90th percentile; overweight, BMI above the 90th to 97th percentile; obese, BMI above the 97th percentile; and extremely obese, BMI above the 99.5th percentile. These BMI cutoff points approximate the International Obesity Task Force definitions, which are based on percentiles that correspond to the World Health Organization adult (18 years of age) cutoffs for overweight (BMI of 25) and obesity (BMI of 30).[31]

For MS risk assessment, the outcome of increasing BMI trends over time was considered in choosing the control collective for odds ratio (OR) estimates. Patient BMIs were compared with the BMI data of 14 747 healthy children aged 3 to 17 years who participated in the 2003 to 2006 German Health Interview and Examination Survey for Children and Adolescents (KiGGS).[32] The data in KiGGS were sex- and age-stratified according to the Kromeyer-Hauschild[29] reference values and were presented in a 2007 Federal Health Bulletin,[32] which reported a 50% increase in overweight and obesity in that period compared with the 2 previous decades. Studies[33,34] have shown a stagnation in prevalence rates in Germany since the KiGGS survey; thus, the KiGGS data are still representative of current BMI trends among German children. Patients with MS onset before 2003 were not considered likely to falsely elevate ORs.

The Center for MS in Childhood and Adolescence in Göttingen is a tertiary referral center for pediatric MS. Referred patients are assessed every 6 months until age 18 years. Documented at these visits are new relapses (defined as the presence of new or worsening neurologic symptoms lasting at least 24 hours and occurring more than 30 days after a previous clinical event); Expanded Disability Status Scale (EDSS) score (range: 0-10, with the highest score indicating death from MS and the lowest score indicating normal neurological examination); laboratory findings; and results of ophthalmic

examination, evoked potentials, nerve conduction studies, and brain magnetic resonance imaging (MRI).[35] Spinal MRIs are done yearly unless indicated earlier. For comparison between weight categories, data on the following were collected: age at diagnosis, baseline MRI findings, interval between first and second MS attacks, time to initiation of a disease-modifying therapy (DMT), relapses before and during first-line treatment with interferon beta and glatiramer, initiation of second-line DMT (fingolimod, natalizumab, alemtuzumab, or rituximab), BMI at second-line DMT initiation, and EDSS score at 2 years and last consultation.

Annualized relapse rate (ARR), reported in person-years, was used to measure first-line therapy response; only patients with at least 6 months of treatment with interferon beta or glatiramer were included in the analysis. In general, patients were treated with doses according to the drug manufacturer's recommendations. The standard doses for subcutaneous glatiramer, 20 mg daily, and for intramuscular interferon beta-1a, 30 µg weekly, were not reduced. Subcutaneous interferon beta-1a was dosed at 44 µg 3 times weekly, and subcutaneous interferon beta-1b was dosed at 250 µg every other day. In patients who developed intolerable adverse effects, subcutaneous interferon beta-1a was reduced to 22 µg 3 times weekly, and subcutaneous interferon beta-1b was reduced to 187.5 µg, 125 µg, or 62.5 µg every other day. If concerns of noncompliance (medication taken irregularly over a 6-month period) were documented at follow-up, the noncompliant patients were excluded.

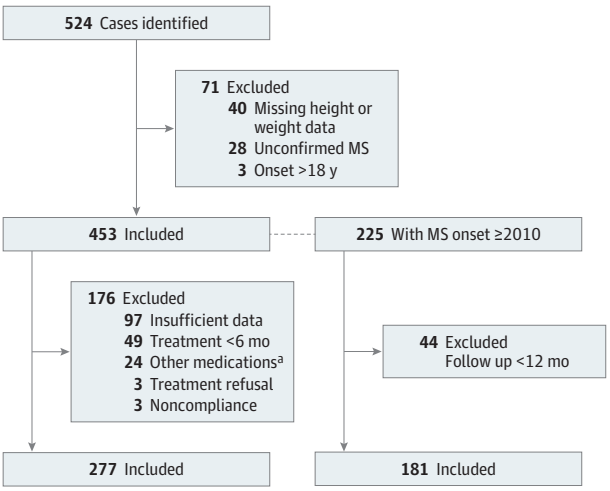
Analysis of second-line therapy included only patients presenting from 2010 and with a minimum of 12 months of follow-up, unless escalated in less than 12 months. Patients recommended for second-line therapy at last consultation were counted as escalated. The year 2010 was chosen as the cutoff because the practice of escalating pediatric patients before this time was less common.

The variables used to define disease activity were baseline MRI findings, interval between first and second MS attacks, and EDSS score. A brain or spine MRI within 6 months of first presentation was considered a baseline MRI. T2 axial images as well as sagittal and coronal images, if available, were evaluated for T2 and gadolinium lesion counts. Magnetic resonance imaging data were acquired on a clinical 1.5-T or 3-T MRI scanner with the following parameters: axial T2-weighted turbo spin echo (T2w) sequences (echo time [TE], 80-132 milliseconds; repetition time [TR], 2111-6290 ms; slice thickness, 3-5 mm; gap, ≤1 mm) and axial T1-weighted sequences (T1w; TE, 2.1-25 milliseconds; TR, 150-873 milliseconds; slice thickness, 2-6 mm; gap, ≤1 mm) before and 5 minutes after standard single-dose gadolinium injection. Lesions were analyzed manually and independent of the analysis of the clinical history (by B.H. and H.H.) and were reevaluated in case of conflicting results (by P.H. and J.G.).

Statistical Analysis

We reported frequencies, including 95% Clopper-Pearson CIs for predefined categories of obesity and categorical outcomes. Comparisons between groups were performed with the Fisher exact test and reported with 95% CIs for the OR. For continuous and ordinal data, we reported mean, median, and 25% and 75% quantiles. Group comparisons were performed with unpaired, 2-tailed Welch *t* test or Wilcoxon rank sum test, as appropriate. For count data, including relapse rates and lesions, a negative binomial regression model was used, allowing for different follow-up times as offset. Adjusted relapse rates along with 95% CIs were thus estimated and comparisons between groups were tested. Two-sided $P < .05$ was considered statistically significant. Analyses were conducted with R Stat, version 3.4.3 (R Foundation for Statistical Computing).

Figure. Patient Selection



MS indicates multiple sclerosis.

[a] Other medications were azathioprine sodium (n = 10), dimethyfumarate (n = 2), and only second-line therapy (n = 12).

Results

Of the 524 patients identified, 71 (13.5%) were excluded and 453 (86.5%) were included (**Figure**). Among the 453 patients, 306 (67.5%) were female and the mean (SD) age at diagnosis was 13.7 (2.7) years (**Table 1**).

The onset of MS occurred from April 28, 1990, to June 26, 2016, with 400 cases (88.3%) manifesting after 2000. Sixty-two patients (13.7%) were younger than 11 years at MS onset, a group with a lower female preponderance compared with the group of children 11 years or older (33 [53.2%] vs 273 [69.8%]). The mean (SD) age at BMI measurement was 13.9 (2.7) years. In total, 126 patients (27.8%) had a BMI greater than the 90th percentile, 59 (13.0%) of these patients had a BMI greater than the 90th to 97th percentile (grouped as overweight), and 67 (14.8%) had a BMI greater than the 97th percentile (grouped as obese). Mean (SD) follow-up was 38.4 (28.9) months, ARR excluding first attack was 0.85 (1239 relapses; 17 504 months; n = 452), and mean (SD) EDSS score was 0.9 (1.2).

High BMI was associated with statistically significantly increased odds of pediatric MS in both sexes (obese girls OR, 2.19; 95% CI, 1.5-3.1; $P < .001$ vs obese boys OR, 2.14; 95% CI, 1.3-3.5; $P = .003$). This association was dose dependent and had

Table 1. General Characteristics of the Cohort

Variable	All Patients (N = 453)	BMI ≤90th Percentile (n = 327)	BMI >90th-97th Percentile (n = 59)	BMI >97th Percentile (n = 67)
Age at diagnosis, y				
Mean (SD)	13.7 (2.7)	13.6 (2.8)	13.2 (2.6)	14.2 (2.0)
Median (range)	14.3 (2.2-17.8)	14.4 (2.2-17.8)	13.7 (5.5-16.7)	14.4 (9.1-17.7)
P value	NA	1 [Reference][a]	.27	.06
Female, No./total No (%)				
Total cohort	306/453 (67.5)	222/327 (67.9)	38/59 (64.4)	46/67 (68.7)
P value	NA	1 [Reference]	.65	>.99
<11 y at MS onset	33/62 (53.2)	25/44 (56.8)	6/12 (50.0)	2/6 (33.3)
P value	NA	1 [Reference]	.75	.39
≥11 y at MS onset	273/391 (69.8)	197/283 (69.6)	32/47 (68.1)	44/61 (72.1)
P value	NA	1 [Reference]	.86	.76
Interval first attack to DMT, mo				
Mean	11.7	11.9	11.8	10.6
Median	6.2	6.0	7.0	6.0
No.	352	258	40	54
P value	NA	1 [Reference]	.97	.48
Follow-up duration, mo				
Mean	38.4	39.1	36.8	36.4
Median (range)	31 (1-158)	31 (1-158)	31 (1-139)	30 (2-100)
No.	453	327	59	67
P value	NA	1 [Reference]	.62	.39

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); DMT, disease-modifying therapy; NA, not applicable.

[a] 1 [Reference], reference group for *P* value.

an OR of 1.37 (95% CI, 1.0-1.8; *P* = .03) in overweight participants and rose to 2.2 (95% CI, 1.7-2.9; *P* < .001) in those with obesity, an outcome seen equally in boys and girls. Higher rates of overweight and obesity were seen among both younger (7-10 years) and older (11-17 years) children with MS compared with controls, although statistical significance was not achieved in all age categories. Boys aged 7 to 10 years had the highest rate of overweight and obesity (10/25 [40.0%]) (**Table 2**). To control for secular changes in BMI, patients with MS onset between 2003 and 2006 (n = 56) were analyzed; 8 (14.3%) of these patients were obese (BMI>97th percentile). This figure was consistent with the findings for the whole cohort (14.8%).

Of the 453 patients, 352 (77.7%) received a DMT. For 6 months or longer, 277 patients were treated with interferon beta (n = 249) and/or glatiramer (n = 51). Interferon beta-1a (Rebif; EMD Serono Inc), provided to 126 children, and interferon beta-1b (Betaferon; Bayer PLC), provided to 107, were the most commonly used medications, followed by glatiramer (Copaxone; Teva Neuroscience Inc), provided to 51 patients, and interferon beta-1a (Avonex; Biogen), provided to 27.

Seventy-seven (27.8%) of the 277 patients had a BMI higher than the 90th percentile at diagnosis. Time to initiation of a DMT and treatment duration while receiving therapy with interferon beta and glatiramer were not statistically significantly different between weight categories (**Table 3**). Although the relapse rate prior to treatment was similar between nonoverweight (ARR, 1.13; 95% CI, 0.69-1.31), overweight (ARR, 1.17; 95% CI, 0.39-1.61), and obese (ARR, 1.2; 95% CI, 0.5-1.5) patients, statistically significantly more relapses were recorded for obese patients during treatment with interferon beta and glatiramer compared with those recorded for their nonoverweight counterparts (ARR, 1.29 [95% CI, 1.1-1.6] vs 0.72 [95% CI, 0.6-0.8]; *P* < .001) (Table 3). This finding was statistically significant for both children younger than 11 years and adolescents aged 11 to 17 years. Extremely obese patients (BMI>99.5th percentile; n = 20) had the worst response to interferon beta and glatiramer therapy (ARR, 1.37; 95% CI, 1.0-1.9; *P* < .001).

Overall, 181 patients had MS onset in 2010 or later and had 12 months or more of follow-up. Mean (SD) follow-up for these patients was 35.4 (17.7) months with no statistically significant difference between weight categories. Seventy-eight patients (43.1%) either received or were recommended for second-line treatment. Fifty-three (29.3%) received natalizumab; 31 (17.1%), fingolimod; 2 (1.1%), alemtuzumab; and 2 (1.1%), rituximab. Ten patients (5.5%) received 2 or more second-line agents. Thirty (38.5%) of the 78 patients had a high BMI at diagnosis, and 21 (26.9%) were obese. The likelihood of receiving a second-line DMT was approximately 1.5 times higher among obese (21 [56.8%] of 37) and extremely obese (11 [61.1%] of 18) patients compared with nonoverweight patients (48 [38.7%] of 124). Body mass index data at the time of second-line DMT initiation were available for 76 of 78 cases. Most patients (69 of 76 [90.8%]) had not changed their weight categories. Twenty-seven (93.1%) of 29 patients who had displayed a high BMI at first clinical presentation were still displaying a high BMI at escalation. By the time of therapy escalation, none of the obese patients had a weight below the 90th percentile, whereas 2 initially overweight patients had a weight below the 90th percentile, and 4 nonoverweight patients had become overweight.

Table 2. Odds of Pediatric Multiple Sclerosis

Variable[a]	Controls With BMI >90th-97th Percentile, % (95% CI)[b]	Patients With MS With BMI >90th-97th Percentile		OR (95% CI)	*P* Value	Controls With BMI >97th Percentile, % (95% CI)[a]	Patients With MS With BMI >97th Percentile (95% CI)		OR (95% CI)	*P* Value
		% (95% CI)	No./Total No.				% (95% CI)	No./Total No.		
Age 7-10 y										
Boys	8.9 (7.6-10.4)	24.0 (9.4-45.1)	6/25	2.45 (0.8-6.3)	.06	7.0 (5.8-8.3)	16.0 (4.5-36.1)	4/25	2.11 (.5-6.3)	.10
Girls	9.0 (7.6-10.7)	18.2 (5.2-40.3)	4/22	1.83 (0.5-5.5)	.30	5.7 (4.7-6.9)	9.1 (1.1-29.2)	2/22	1.50 (.2-6.3)	.60
Total	9.0 (8.0-10)	21.3 (10.7-35.7)	10/47	2.3 (1.1-4.5)	.04	6.4 (5.6-7.3)	12.8 (4.8-25.7)	6/47	1.85 (.6-4.5)	.20
Age 11-17 y										
Boys	9.1 (8.9-11.0)	12.6 (7.2-19.9)	15/119	1.14 (0.6-2.0)	.70	7.7 (6.8-8.6)	14.3 (8.5-21.9)	17/119	1.7 (.9-2.9)	.05
Girls	9.4 (8.4-10.4)	12.0 (8.4-16.5)	33/274	1.15 (0.8-1.7)	.50	8.2 (7.3-9.2)	16.1 (11.9-21.0)	44/274	1.79 (1.2-2.6)	.002
Total	9.7 (9.0-10.4)	12.2 (9.1-15.9)	48/393	1.13 (0.8-1.6)	.50	7.9 (7.3-8.6)	15.5 (12.1-19.5)	61/393	1.8 (1.3-2.4)	<.001
Age 3-17 y										
Boys	8.8 (8.0-9.7)	14.5 (9.2-21.3)	21/145	1.49 (0.9-2.4)	.10	6.3 (5.6-7.0)	14.5 (9.2-21.3)	21/145	2.14 (1.3-3.5)	.003
Girls	8.5 (7.9-9.2)	12.5 (9.0-16.7)	38/305	1.33 (.9-1.9)	.10	6.4 (5.8-7.1)	4615.1 (11.3-19.6)	46/305	2.19 (1.5-3.1)	<.001
Total	8.7 (8.2-9.2)	13.1 (10.1-16.6)	59/450	1.37 (1.0-1.8)	.03	6.3 (5.8-6.9)	14.9 (11.7-18.5)	67/450	2.2 (1.7-2.9)	<.001

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); OR, odds ratio.

[a] Patient data for age category 3 to 6 years (n = 10) are not shown. This group contained only 1 overweight and 0 obese children; the findings were insignificant. Three patients were excluded from this analysis for being younger than 3 years of age at BMI measurement.

[b] The control group consisted of 14 747 healthy German children aged 3 to 17 years from the KiGGS (German Health Interview and Examination Survey for Children and Adolescents) study.[32]

No BMI association was shown for disease activity on baseline brain or spine MRI, interval between first and second MS attacks, or EDSS score progression (**Table 4**). Mean disease duration was not statistically significantly different between weight classes.

Discussion

Many of the obese patients who were treated at the Center for MS in Childhood and Adolescence have not responded to first-line medications. Although obesity has been previously associated with increased risk of pediatric MS, its association with treatment response has not been studied to date. A great advantage of studies in the pediatric population is that MS onset and the association with BMI can be more reliably addressed because of more reliable data collection and reduced recall bias (unreliable data collection and recall bias are common problems in adult investigations).

In the first part of this study, aimed at confirming the association between obesity and increased pediatric MS risk, we analyzed 453 patients, which, to our knowledge, was the largest cohort to date. We found that the rate of overweight and obesity among pediatric patients with MS was statistically significantly higher than among healthy controls, with obesity increasing MS susceptibility twofold. The outcome was dose dependent, with MS odds rising from 1.37 in overweight children to 2.2 in obese children. The magnitude of MS risk associated with obesity was similar for boys and girls. Findings for female patients matched those in the literature, which indicated that obesity has consistently been associated with a 1.6 to 2.4 increase in MS risk, but the degree of male risk has been disputed.[9-11,14,16,26] Most adult studies have shown either no risk or only attenuated risk in males.[10,11,13,16,36] Pediatric findings are scarce, but a study has also reported statistically significant male risk (n = 59; BMI>85th percentile; OR, 1.43; *P* = .01).[14] This finding may be specific to pediatric cohorts or may reflect more reliable data collection owing to reduced recall bias. Another possibility is the implication of increasing BMI trends over time given that adult MS studies most likely reflect BMI data from an earlier generation of men with lower obesity rates. Two previous pediatric MS studies did not show any relevant association between BMI and MS risk in prepubertal children (aged 2-11 years), but we found a high rate of overweight or obesity among younger patients with MS (aged 7-10 years), particularly boys.[14,26]

In the second part of the study, we analyzed the association of obesity with response to first-line therapy in 277 patients treated with interferon beta or glatiramer. Supporting our observation, patients who were obese at diagnosis experienced nearly twice as many relapses while being treated with these medications, compared with nonoverweight patients. Consistent with this finding, the switch rate to a second-line DMT was approximately 50% higher. All children who were obese at diagnosis were still displaying high BMIs at therapy escalation. To our knowledge, the association between BMI and treatment response in pediatric MS has never been investigated before. Yamamoto et al,[37] however, did observe higher

Table 3. Comparison of Treatment Responses

Variable	All Patients	BMI		
		≤90th Percentile	>90th-97th Percentile	>97th Percentile
Months to start of DMT				
Mean	11.7	11.9	11.8	10.6
Median	6.2	6.0	7.0	6.0
No.	352	258	40	54
P value	NA	1 [Reference][a]	.97	.48
First-line therapy[b]				
Interferon beta-1a, 1b, and glatiramer acetate				
ARR (95% CI)	0.81 (0.7-0.9)	0.72 (0.6-0.8)	0.84 (0.7-1.1)	1.29 (1.1-1.6)
No.	277	200	32	45
P value	NA	1 [Reference]	.24	<.001
Patients <11 y at MS onset				
ARR (95% CI)	0.55 (0.4-0.7)	0.49 (0.4-0.6)	0.37 (0.2-0.7)	1.22 (0.7-2.0)
No.	43	32	6	5
P value	NA	1 [Reference]	.45	<.001
Patients ≥11 y at MS onset				
ARR (95% CI)	0.90 (0.8-1.0)	0.79 (0.7-0.9)	1.04 (0.8-1.4)	1.31 (1.1-1.6)
No.	234	168	26	40
P value	NA	1 [Reference]	.07	<.001
Interferon beta-1a and 1b				
ARR (95% CI)	0.79 (0.7-0.9)	0.7 (0.6-0.8)	0.89 (0.7-1.2)	1.22 (1.0-1.5)
No.	249	180	27	42
P value	NA	1 [Reference]	.12	<.001
Glatiramer acetate				
ARR (95% CI)	0.89 (0.7-1.1)	0.82 (0.6-1.1)	0.47 (0.2-1.1)	1.86 (1.1-3.0)
No.	51	31	11	9
P value	NA	1 [Reference]	.17	.004
Mean duration of treatment with interferon beta and glatiramer acetate, y	2.1	2.1	2.3	1.9
P value	NA	1 [Reference]	.63	.25
Frequency of second-line therapy, No./total no. (%)[c]	78/181 (43.1)	48/124 (38.7)	9/20 (45.0)	21/37 (56.8)
P value	NA	1 [Reference]	.63	.06

Abbreviations: ARR, annualized relapse rate (relapses per person-years); BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); DMT, disease-modifying therapy; NA, not applicable.

[a] 1 [Reference], reference group for *P* value.

[b] Only patients with 6 or more months treatment duration.

[c] Only patients with first presentation in 2010 or later and at least 12 months of follow-up since first attack unless escalated in 12 months or less. Second-line medications: fingolimod, natalizumab, alemtuzumab, and rituximab.

relapse rates, in general, among overweight and obese children in a study describing 60 pediatric patients with MS, but treatment response was not investigated. An association between high BMI and worse therapy response to interferon beta has been described in a small adult cohort of 86 patients.[38] In that study, Kvistad et al[38] found that obese patients were substantially less likely to reach no evidence of disease activity under interferon beta treatment. Kvistad et al[38] postulated that obesity-associated proinflammatory outcomes promote a state of chronic low-grade systemic inflammation, thereby leading to greater disease activity in these patients. We considered this possibility and extended this study to analyze disease activity in the total cohort of 453 patients.

To exclude the confounders of treatment, we assessed MRI activity at diagnosis, interval between first and second MS attacks, relapse pretreatment, and disability progression as measures of disease activity. Contrary to our expectation, we found no evidence that a high BMI was associated with a more active inflammatory process. The association between obesity and disease activity in pediatric MS has, to our knowledge, been described in only one study with a small cohort (n = 50), which analyzed ARR and new lesions on MRI.[39] Consistent with our findings, BMI at diagnosis was not correlated with disease activity. Kvistad et al[38] also did not find an association between BMI and MRI disease activity or EDSS score prior to interferon beta treatment. Without evidence of higher disease activity, the suboptimal treatment response observed in this study may be associated with altered drug pharmacokinetics in obese patients. No pharmacokinetic data are available on the absorption of interferon beta and glatiramer after subcutaneous application in obese patients with MS, but studies of other medications such as enoxaparin sodium and insulin have shown slower but complete absorption in obese patients.[40,41] Increased adipose tissue mass and lean body mass as well as the physiochemical properties of the drug, such as lipophilicity, also alter drug distribution.[42] To our knowledge, this distribution has not been studied for interferon beta or glatiramer, but a reduction of interferon alfa serum concentrations

Table 4. Comparison of Disease Severity

Variable	All Patients (n = 453)	BMI		
		≤90th Percentile (n = 327)	>90th-97th Percentile (n = 59)	>97th Percentile (n = 67)
MRI ≤6 mo of first clinical presentation				
T2 Cranial lesions				
Median	15.0	14.0	15.5	15.0
No.	385	278	50	57
P value	NA	1 [Reference][a]	.93	.32
Gadolinium				
Median	1.0	1.0	1.0	1.0
No.	366	259	49	58
P value	NA	1 [Reference]	.06	.60
T2 Spinal lesions				
Median	1.0	1.0	1.0	1.0
No.	333	233	46	54
P value	NA	1 [Reference]	.26	.34
Gadolinium				
Median	0.0	0.0	0.0	0.0
No.	295	206	40	49
P value	NA	1 [Reference]	.54	.13
Interval between 1st and 2nd attack, mo				
Mean	9.2	9.1	7.9	10.9
Median	5.5	5.2	5.0	6.0
No.	361	254	45	62
P value	NA	1 [Reference]	.40	.41
EDSS at 2 y				
Mean	0.8	0.8	.70	.80
Median	0.0	0.0	0.0	0.0
No.	308	220	36	52
P value	NA	1 [Reference]	.71	.85
EDSS at last consultation				
Mean	0.9	0.9	0.7	1.0
Median	0.0	0.0	0.0	1.0
No.	433	318	53)	62
P value	NA	1 [Reference]	.41	.30

Abbreviations: EDSS, Expanded Disability Status scale (range: 0-10, with the highest score indicating death from MS and the lowest score indicating normal neurological examination); NA, not applicable.

[a] 1 [Reference], reference group for *P* value.

in obese patients has been described before.[43] Studying the association of obesity with the pharmacokinetics of first-line DMTs may improve the understanding of treatment response in obese patients and possibly even enable the development of BMI-adjusted dosing recommendations.

Strengths and Limitations

A strength of this study was the large cohort size. All previous BMI studies of children with MS had considerably smaller sample sizes, particularly with respect to the number of male and prepubertal children.

This study has several limitations. First, because the Center for MS in Childhood and Adolescence is a tertiary referral center for pediatric MS, it may have attracted a higher number of patients with less benign disease, which in turn may have changed the outcome measures. Furthermore, some relapses were treated in local hospitals and therefore not verified at the center. Second, patient BMI measurements were taken within 6 months of diagnosis and thus may not truly reflect pre-disease BMI or changes in status over the study period. Factors against a radical change from pre-disease BMI status in our patients were that the mean time between MS diagnosis and height and weight measurement was only 2.4 months; the steroid exposure was not prolonged; and the EDSS score was low, indicating minimal disability. Subgroup analysis of BMI at initiation of second-line therapy also indicated little change in BMI status over the study period. Moreover, 2 adult studies have shown no association between MS and BMI status, with a baseline EDSS score also not a predictor of BMI change in one of these studies.[12,44] In the analysis of MS risk, the implica-

tions of recognized MS risk factors such as pre-disease levels of serum Vitamin D, exposure to Epstein-Barr virus, or genetic factors were not considered; however, a causal relationship between BMI and onset of adult and pediatric MS has been confirmed even after controlling for these variables.[16,25]

Disease activity assessment was limited by 2 factors. First, MRI data were based on lesion count and not lesion volume; thus, disease activity was underrepresented in patients with large confluent lesions yet low overall lesion count, whereas a degree of inaccuracy was possible in patients with high lesion counts. Second, follow-up was short and EDSS scores generally were low in all patients, a common finding in pediatric MS that limits the value of this variable. Because only German children were evaluated, the findings may not be reflective of children of other race/ethnicity or geographic location.

Conclusions

This study's findings appear to have confirmed increased pediatric MS risk association with obesity as well as a statistically significantly worse response to current first-line medications interferon beta and glatiramer and greater likelihood of switch to second-line agents in obese patients. The findings do not indicate that obesity promotes greater disease activity, but pharmacokinetic factors are more likely associated with treatment response. This suggestion may have relevant management implications given that a healthy weight may potentially optimize treatment outcomes and reduce disease-related burden and health care costs. These findings also imply that understanding obesity-associated pharmacokinetics of first-line DMTs may increase their value by enabling BMI-adjusted doses.

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