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REVIEW

Role of puberty in multiple sclerosis risk and course

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Abstract Multiple sclerosis (MS) overwhelmingly presents during the reproductive years, and is more common in females than males. The sexual dimorphism observed in post-pubertal cases is absent in pre-pubertal cases, suggesting that puberty is a key risk period for development of disease, particularly in females. Research has identified several risk factors for MS that occur during the adolescent, or post-pubertal reproductive years, which are associated with clinical presentations later in life. These observations necessitate examination of the biological changes associated with puberty, their interactions with MS risk factors, and potential effects on disease immunopathogenesis. Pediatric and adolescent presentations of MS provide a unique opportunity to study the effects of neuroendocrine changes occurring during puberty and its effect on disease development and disease course. Reviewed is the relationship of MS risk factors and puberty, and differences in disease presentation of pre- and post-pubertal children with MS. Further avenues of research are discussed.

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1. Introduction

Multiple sclerosis (MS) overwhelmingly presents during the reproductive years, and is more common in females than males. Pre-pubertal cases of MS are extremely rare, suggesting that the post-pubertal reproductive age period may play a key role in development of disease. Moreover, the sexual dimorphism observed in post-pubertal cases is absent in pre-pubertal cases, suggesting that puberty is a key risk period for development of disease, particularly in females. Research has identified several risk factors for MS that occur during the adolescent, or post-pubertal years, which are associated with clinical presentations later occurring in the 20–40s. These two clinical observations necessitate examination of the biological changes associated with puberty, their interactions with MS risk factors, and potential effects on disease immunopathogenesis. Pediatric and adolescent presentations of MS provide a unique opportunity to study the effects of neuroendocrine changes occurring during puberty and its effect on disease development and disease course. Presented is a review of clinical, neuroendocrine, immunological and central nervous system changes associated with puberty, as well as a discussion of the relationship of MS risk factors and puberty, and differences in disease course of pre- and post-pubertal children with MS.

1.1. Multiple sclerosis overview

Multiple sclerosis (MS) is a disease of the central nervous system characterized by inflammatory cell infiltration, demyelination and axonal damage [1,2]. Clinically, it is characterized by neurological deficits disseminated in time and space. MS is generally considered to be an autoimmune disease, and many of the effective therapies for MS target the immune system.

MS is a major cause of disability in the adult population in North America. The disease is characterized by a varying array of neurological deficits. There are four main disease types, classified on the basis of the clinical disease course: relapsing–remitting (RR), secondary progressive (SP), primary progressive (PP), and progressive relapsing (PR) [3]. RR disease affects 80% of patients and is characterized by onset of neurological deficits that remit over a period of weeks to months. After 15 years, most RR patients go on to have an SP form of disease, in which neurological deficits become fixed and accumulate.

Patients with MS can experience a variety of symptoms including relapses of optic neuritis affecting vision, transverse myelitis affecting spinal cord functions including gait, and brainstem attacks affecting eye movements, coordination or speech or swallowing. Fatigue, depression and bladder and bowel dysfunction are also common symptoms of MS. Magnetic

resonance imaging typically demonstrates hyperintense lesions on T2 imaging and gadolinium-enhancing lesions on T1 imaging and in more advanced disease brain atrophy and T1 black holes and brain atrophy may be present. A diagnosis of MS can be confirmed using the 2010 revised McDonald criteria [4] which require a combination of specific clinical and MRI features disseminated in both space and time. First attacks of MS are typically termed clinically isolated syndromes (CIS), although occasional cases of acute disseminated encephalomyelitis (ADEM) can later develop MS. A related chronic demyelinating condition is neuromyelitis optica [5], which has now been shown to be associated with the Aquaporin-4 antibody or NMO-IgG in approximately 75% of patients [6].

1.2. Age at multiple sclerosis disease onset

Multiple sclerosis (MS) predominantly affects young women, and is less common in men at an overall ratio of 2:1 [7]. The peak age of MS onset is approximately 25 years in men (25 years) and 24 years in women [8], with the majority of cases presenting between the ages of 20 and 40. MS with onset prior to the age of 18, or pediatric MS affects approximately 3–5% of the MS population [9–11], while MS onset after the age of 50, termed late-onset MS occurs in approximately 5% of the population [12]. Over the past 60 years an increasing F:M sex ratio has emerged and continues to grow, reaching 2:1 in the 1980s [13] and approaching [14–16] and even exceeding 3:1 today [17–20].

In pediatric forms of MS, pre-pubertal onset is rare, accounting for 20–30% of pediatric MS cases [21,22], however post-puberty, the incidence rises dramatically [10,21–24]. Sex ratios are generally equal in cases with pre-pubertal onset, however, after puberty sex ratios dramatically increase, favoring females. F:M ratios are 0.9:1 when disease onset occurs prior to age 13 (i.e. puberty) but increases to 2.2:1 F:M when disease onset occurs between the ages of 13 and 18 [10,21,22].

The demographics of MS demonstrate a post-pubertal female preponderance, suggesting that key inciting immune changes occur during or after puberty, which are differential in males and females.

In children with an acute demyelinating syndrome, female sex and older age are significantly associated with a higher risk for MS, although puberty was not specifically evaluated [25]. In general, monophasic demyelinating disorders such as acute disseminated encephalomyelitis [26] and transverse myelitis [27] are more common in the <10 year age groups, and demonstrate equal sex distributions, as opposed to the chronic demyelinating disorders of MS and neuromyelitis optica (NMO) which are predominantly female. This raises the question of whether female pubertal sex hormones predispose to chronic demyelinating disorders, whereas male hormones may have protective effects.

1.3. Age at menarche and MS risk

A question that arises from the preceding demographic data demonstrating a post-pubertal predominance of MS, is whether the age at puberty affects incidence of MS. A recent study from the Canadian Collaborative Project on Genetic Susceptibility in MS which surveyed by phone 5493 MS index cases and 1759 spousal controls, found that females with MS were younger at menarche than controls (12.4 years versus 12.6 years), with a relative risk decrease of 0.9 per year increase in age of puberty [28]. A significant difference was not found between male MS patients and controls, however several mitigating factors including sufficient power and difficulty in the retrospective ascertainment of pubertal onset defined by "voice change". Another population based study from Newfoundland, Canada found that linear regression model demonstrated that the age of first symptoms increased by 1.16 years as the age of menarche increased by one year ($R^2 = 0.69$, $P = 0.04$) [29]. A study of 973 women with MS found no difference in age at menarche between those with a relapsing-onset of MS compared with progressive-onset, however within the progressive-onset group, those with menarche age >13 had a slower progression to EDSS 6 [30]. Several studies have suggested that a lower age at menarche in females is associated with an increased risk of MS, and one has found an association with a more severe disease course, raising the possibility that earlier exposure to pubertal factors may influence disease onset and course.

1.4. Environmental exposures during puberty and MS risk

Several studies have identified exposure to environmental risk factors during or prior to adolescence as associated with the development of MS. In MS, migration studies have demonstrated that migration from a low risk geographic area to a high-risk geographic area prior to the age of 15 increases the risk for MS [31–33]. Clustering studies from Norway suggest that adolescents exposed to common environmental conditions are at increased risk for MS [34,35]. A history of symptomatic infectious mononucleosis during adolescence has been purported as a risk factor for MS (RR 2.3) [36]. Multiple studies in pediatric MS have shown a significant differential in terms of remote EBV exposure in children with MS compared with healthy controls [37–40].

Lack of sunlight exposure is another risk factor associated with an increased MS risk, and several studies have found that lack of exposure during childhood–adolescence is associated with a higher MS risk [41,42]. In army recruits, high Vitamin D levels were associated with a lower risk of MS, and this association was strongest in those sampled prior to the age of 20 [43]. Dietary intake of Vitamin D during adolescence was not associated with increased risk of MS, [44] however serum Vitamin D levels were not assessed. A Canadian nation-wide investigation found that hypovitaminosis D in children with an acute demyelinating syndrome or first attack, is associated with an increased risk of MS [25].

Obesity at the age of 18 has been shown to double the risk of later development of adult-onset MS in a cohort of women enrolled in the Nurses Health Study [45]. In this study, obesity during the adult years was not found to be a risk factor for MS.

A study from Sweden found that obesity ($BMI > 27$) at the age of 20 was a risk factor for MS in both males and females [46]. In a study from Southern California, girls who later developed pediatric-onset MS were twice more likely to be classified as overweight or obese than non-MS girls, whereas this association was not found in boys [47].

Smoking has been identified as a risk factor for MS [48–50], and some studies have found this association in women only [51,52]. Most studies evaluating smoking as a risk factor for MS classify subjects as ever or never smokers, and do not stratify by age at smoke exposure, therefore evaluation of the effect of smoke exposure during the pubertal transition is lacking. However, exposure to parental-smoking has been associated with a two-fold risk of MS in children, and older children who also had longer durations of exposure were at increased risk [53]. Studies examining other risk factors for MS including urbanization, diet, microbial intestinal flora, infection exposure, and sleep disruptions have not specifically examined the interaction with puberty.

Exposure to several risk factors during or prior to the adolescent years is associated with an increased risk of MS. These include infectious mononucleosis, sunlight exposure, hypovitaminosis D and obesity. Further studies are required to identify the precise critical window of exposure. Evaluation of the interaction of these risk factors with biological changes occurring around puberty may shed light on mechanistic events leading to the development of MS.

1.5. Potential role of puberty as a risk factor for MS

Overall, these demographic and clinical studies above indicate that:

1. The onset of puberty is associated with an increasing risk of MS, along with an increased predilection for females, suggesting that this epoch is a key risk period for the sexual dimorphism of MS.
2. Exposure to some risk factors associated with MS occurs in the post-pubertal or adolescent years, suggesting that interaction with endogenous biological factors present during this period may synergize to trigger the development of MS.
3. Earlier onset of puberty is associated with an increasing risk of MS in females, suggesting that either earlier exposure to hormonal changes associated with puberty or common factors leading to both early puberty and autoimmune disease may be present, particularly in females.

These clinical observations necessitate the examination of the biological changes occurring at and after puberty, which may identify key biological changes and points of interaction with exogenous environmental risk factors, that result in irreversible chronic demyelinating disease. Studies examining environmental risk factors in MS should specifically stratify for exposure during the pre- and post-pubertal period in order to identify the critical window for interaction.

2. Differences in MS presentation and course in pre- and post-pubertal children

Effects of the pubertal transition may also be postulated to influence the disease course in children with MS. Although no longitudinal studies have thus far examined the effect of

puberty on clinical or imaging disease measures, several studies have contrasted the clinical and biological presentation of MS between pediatric MS patients with a pre- and post-onset. MS onset prior to age 10 is relatively rare, and occurs in 20–30% of pediatric MS patients. Brain lesions in younger children (age <11 years) are large, with poorly-defined borders and are frequently confluent at disease onset, in comparison with adolescents who demonstrate more well-defined lesion patterns [54] more akin to adult-onset MS. These T2-bright foci seen in younger children may also vanish on repeat scans, unlike that seen in teenagers or adults. This suggests that the developing brain may influence disease processes of MS. Additionally, the CSF profile in childhood-onset MS may vary by age. Children under the age of 11 years can have more neutrophils in the CSF than older children who typically have a lymphocytic predominance [55], similar to adult-onset MS. As well oligoclonal bands in the cerebrospinal fluid appear to be less frequent in younger children (43% versus 63% in adolescents). Serum antibodies to MOG have been preferentially observed in children under the age of 10 years, compared with older children aged 10–18 years [56], however the clinical and biological significance of these are unclear.

Clinically, children have 2–3 times as frequent relapses as adults, however relapse rate was not found to be different in children aged 0–10 versus 10–20 years of age [57]. Studies of disability outcomes including cognitive measures have not specifically focused on differences between pre- and post-pubertal children, possibly because of small sample sizes, and difficulty in comparing cognitive tests specific for each age group.

Overall, these studies suggest that post-pubescent onset of MS more closely resembles the adult counterpart, while pre-pubescent onset has significant differences both clinically and biologically. Immunological, hormonal and CNS maturation during adolescence may affect these phenotypic differences. Studies in pediatric MS may further elucidate the biological factors influencing the transition to a more mature MS phenotype.

3. Clinical markers of the onset of puberty

Puberty results from the awakening of a complex neuroendocrine machinery and is characterized by three key neuroendocrine events, adrenarche, gonadarche and activation of the growth axis [58]. Gonadarche, is a biological process starting with the activation of the hypothalamic–pituitary–gonadal axis and the end is marked by the achievement of reproductive competence. Adrenarche or activation of the hypothalamic–pituitary–adrenal axis often begins at an earlier age than gonadarche, and is characterized by a rise in adrenal androgens, which eventually peak in the early 20s, and contribute to the development of secondary sexual characteristics. The third hormonal event is the activation of the growth axis, with a linear growth spurt that usually occurs approximately 2 years earlier in girls than in boys [59].

Pubertal staging is often measured by Tanner staging, which categorizes breast (B1–5) development in females, genital (G1–5) development in males, and pubic hair development in both sexes (P1–5) [60,61]. In females, the most commonly used markers of the timing of puberty are

thelarche or the first appearance of breast development (Tanner B2) as well as menarche, which occurs approximately 2 years later. In boys, the first sign of pubertal development is an increase in testicular volume above 3 ml, consistent with Tanner G2. The appearance of pubic hair is dependent on testicular androgens in boys and on adrenal androgens in girls. The developmental increase in adrenal androgens (adrenarchia) occurs independently of the pituitary–ovarian maturation in girls.

3.1. Age at puberty

There is a wide range in time to sexual maturation among individuals which may be influenced by factors such as genetic factors, ethnicity, nutrition, environmental exposures and secular trends [62]. The age of onset of puberty in the United States has been evaluated by two recent large studies, the National Health and Nutrition Examination Survey (NHANES) conducted between 1988 and 1994 [63–65], and the Pediatric Research in Office Settings (PROS) conducted between 1992 and 1993 [66,67]. In girls the onset of Tanner B2 was 9.5 years in PROS, and 9.7 years in the NHANES study; onset of menarche was 12.5 years in NHANES. In boys, the mean age at onset of Tanner G2 was 9.9 years in NHANES, and 10.1 years in PROS. A panel assembled in 2008 determined that recent studies support secular trends demonstrating earlier pubertal markers of breast development and menarche in U.S. girls, however insufficient data exists for boys [68]. Similar secular trends to earlier puberty in girls but not in boys are observed in European studies [69–72]. A meta-analysis of European data demonstrates that the age at menarche has dramatically decreased from the late 1800s to 1950s, but appears to have plateaued from 1960 to 2010 [73].

A relationship between younger age at menarche and MS risk has been described in Section 1.4. Therefore, the decreasing age at puberty onset over the past 100 years, particularly in females may contribute to the increased incidence and sexual dimorphism of MS. Potential biological mechanisms of this effect need to be explored, and include early immune maturation (described in Section 3.6), prolonged exposure to higher levels of sex hormones or leptin, or genetic/environmental factors which influence both premature puberty and MS risk (discussed in Sections 3.4 and 3.5).

3.2. Neuroendocrine changes associated with puberty

In general, puberty represents the reactivation (disinhibition) of the CNS suppressed LHRH pulse generator, characteristic of late infancy and childhood, leading to increased amplitude of LHRH pulsatile discharges, and subsequent increased stimulation of the pituitary gonadotropes (FSH and LH). This in turn results in gonadarche, which in girls is characterized by secretion of ovarian androgens from ovarian follicular theca cells and estradiol from granulosa cells before ovulation and secretion of progesterone from the corpus luteum and estradiol after ovulation. In boys, LH initiates the secretion of androgens from testicular Leydig cells [74].

The adipokine leptin acts as a permissive factor for the onset of puberty [75,76], likely through effects on the LHRH secretory neurons of the hypothalamus. Leptin is a highly conserved amino-acid cytokine-like protein produced largely by adipose tissue. The receptor occurs in several isoforms and is expressed in the hypothalamus and other tissues. Leptin also acts as a satiety factor. Leptin deficient ob/ob mice (mutant ob) are obese and also display hypogonadotropic hypogonadism, which first implicated its role in sexual maturation [57]. Administration of leptin to food restricted delayed puberty models partially reversed delay, but administration of leptin does not cause anticipation of puberty [76], supporting its role as a permissive factor for puberty onset. In humans, leptin levels rise just prior to puberty, and rise is associated with the achievement of a threshold of body fat. During puberty, leptin continues to rise in girls, but not in boys, due to effect of testosterone secretion on leptin [77].

In addition to its endocrinological role described above, leptin is an acute phase reactant, and affects both the innate and adaptive immune system. In the innate system, leptin promotes the activation of the monocyte-macrophage lineage, activating phagocytosis and secretion of proinflammatory cytokines and leukotriene B [78]. In the adaptive immune system, leptin promotes proliferation and skewing towards proinflammatory T helper 1 (Th1) responses, with IFN- γ as the principal Th1 cytokine [79]. Leptin deficient mice (ob/ob) are resistant to the induction of experimental autoimmune encephalomyelitis (EAE), the animal model of MS, and administration of leptin shifts the predominant Th2-type response of the ob/ob mice to a Th1-type response [80].

This demonstration that a key pubertal hormone leptin is necessary for the induction of the animal model of MS suggests that its appearance during the peri-pubertal period may enhance susceptibility to MS. The observation that leptin continues to rise in post-pubescent girls, but not boys, suggests that it may play a role in the sexual dimorphism of MS.

3.3. Genetic determinants of puberty

Chromosomal and genetic mutations have been associated with either delayed or precocious puberty. Turner's syndrome (absence of one X chromosome, XO) in girls is characterized by ovarian failure, requiring timed hormonal supplements [81]. Hypothalamic-pituitary deficiency is associated with Kallman's syndrome and other disorders. Klinefelter's syndrome (XXY) causes delayed puberty in males. The G-coupled protein GPR54, and its ligand, kisspeptin, may be involved in the neuronal signaling required for pulsatile LHRH release required for the onset of puberty. An autosomal dominant mutation of the GPR54 receptor has been associated with failure to reach puberty in humans [82], however the precise mechanistic effects are unclear. Other genetic candidates influencing pubertal age have been identified largely in Caucasians [83–85]. Polycystic ovarian syndrome (PCOS) is associated with LH hypersecretion, ovarian abnormalities and dysregulation of fat metabolism, and is associated with premature puberty in some girls, as well as other endocrinological disruptions.

No studies have systematically examined whether genetic risk factors associated with early or precocious puberty are associated with increased MS risk.

3.4. Environmental determinants of puberty

As described above, achievement of sufficient adiposity is required for the onset of puberty. Overall nutrition therefore has an effect on puberty timing, with the consistent finding that food insecurity or malnutrition is associated with delayed menarche [86–88]. The speculative relationship of obesity and precocious puberty is complex and remains to be fully validated, although several studies have found that early life BMI was associated with earlier thelarche [89–91]. Peri-pubertal obesity in girls has been associated with hyperandrogenemia due to increased testosterone production and decreased SHBG, as well as accelerated linear growth associated with decreased GH levels and increased IGF-1, and inflammatory factors, which may influence the extent and timing of growth parameters and secondary sex characteristics [92–94].

Exogenous or environmental factors have also been attributed to alterations in the timing of puberty. Exposure to chemicals which interact with estrogen or androgen receptors, have been shown to have effects on reproductive development in rodents, and in some human studies, however these associations are far weaker. Exposure to organic pollutant, polybrominated biphenyls were associated with earlier menarche in girls exposed in utero [95], while studies in dichlorodiphenyltrichloroethane (DDT) and polychlorinated biphenyl (PCB) have been less conclusive [62]. Lead exposure is associated with delayed puberty in both boys and girls [96,97].

An association with early puberty and MS risk has been suggested as described in the earlier section. Studies are required to explore whether environmental exposures affecting puberty timing also affect MS risk in an independent manner.

3.5. Immunological changes associated with puberty

There are key differences in the pediatric compared with adult immune system, however there is little data specifically describing immune changes which occur with the onset of puberty in humans, however this question is particularly relevant when considering the post-pubertal period as the potential period during which pathogenic immune changes leading to MS take place.

Thymic involution is a key immunological change that starts in puberty and results in a decrease in circulating T cells in adults [98]. Sex hormones, testosterone and estrogen have direct effects on thymic involution through interaction with receptors on either the hematopoietic or the stromal compartments [99,100]. There is a sexual dimorphism in depletion of thymic T cells, as androgen replacement increases CD8⁺ T cells relative to CD4⁺ T cells, while estrogen has the opposite effect, favoring CD4⁺ T cell survival [99,100]. CD4 T cells have been shown to have a central role in MS immunopathogenesis [1], therefore this factor could influence the sexual dimorphism of MS.

Studies examining gene expression in splenic T cells isolated from naive pre- and post-pubertal B6 mice have demonstrated a gender dimorphism in immune gene expression [101]. In contrast, post-pubertal female mice demonstrate an increase in genes associated with an adaptive immune response, whereas post-pubertal males have an increase in genes associated with an innate immune response. Adaptive gene expression increased in post-pubertal females compared with males, including TCR-beta locus, IgG1, IgG2, B cell receptor gene and RING zinc finger protein. Conversely, in post-pubertal males, innate immune response genes including myeloperoxidase, cathepsin G, haptoglobin, MIP-1 gamma, and CCR1 were overexpressed compared with post-pubertal females [101].

Studies evaluating immunological changes in pre- and post-pubertal children have not yet been conducted in humans, however it would be useful to validate these findings, and to explore immune changes potentially relevant to the enhanced post-pubertal risk of MS.

3.6. CNS development and puberty

CNS development must be considered in the discussion of puberty and its relationship to the development of MS. In humans, cortical gray matter increases in volume during childhood, reaches a peak during adolescence, and progressively declines during the adult years [102]. Structural development may be sexually dimorphic at puberty, with observed increases in amygdala volume in males only, and an increase in hippocampal volume in females only [103,104]. In contrast to gray matter, white matter volume increases steadily from childhood into adulthood [105,106], and adolescent males show a steeper age-related increase than females [107]. Magnetization transfer ratio (MTR) decreases with age in adolescent males compared with females, suggesting a relative increase in axonal caliber in males [107,108]. Gene expression of testosterone receptor in adolescence was found to be related to white matter volumes [107,108], suggesting a link between hormone signaling and axonal or glial development.

These observations, demonstrate that the peri-pubertal period may be a pivotal point particularly for CNS development, which may be partially dependent on sex and sex hormone levels. These relationships should be further explored, particularly in the context of pediatric MS and understanding whether hormones influence neuronal reserve and disability outcomes.

4. Conclusions

There is a significant rise in MS in post-pubertal adolescents compared with pre-pubertal children, suggesting a role for puberty-associated neuroendocrine factors in the development of this autoimmune disease. Age-related changes occur in the immune system and central nervous system in during the peri-pubertal years, however their relationship to neuroendocrine changes need to be more fully elucidated. There is an emerging relationship between exposure to risk factors for autoimmune disease during the peri-pubertal years and the later development of disease, necessitating further studies to evaluate this interaction and to elucidate

relationships in disease pathogenesis. Moreover, these relationships may be sexually dimorphic, thereby influencing the observed enhanced development of MS in post-pubertal females. Studies specifically evaluating the interaction of risk factor exposure and biological changes in the peri-pubertal period may lead to the identification of preventative measures for the development of MS.

Conflict of interest statement

The author declares that there are no conflicts of interest.

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