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REVIEW

Sex differences in autoimmune disorders of the central nervous system

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Abstract

Stronger adaptive immune responses in females can be observed in different mammals, resulting in better control of infections compared to males. However, this presumably evolutionary difference likely also drives higher incidence of autoimmune diseases observed in humans. Here, we summarize sex differences in the most common autoimmune diseases of the central nervous system (CNS) and discuss recent advances in the understanding of possible underlying immunological and CNS intrinsic mechanisms. In multiple sclerosis (MS), the most common inflammatory disease of the CNS, but also in rarer conditions, such as neuromyelitis optica spectrum disorders (NMOSD) or neuronal autoantibody–mediated autoimmune encephalitis (AE), sex is one of the top risk factors, with women being more often affected than men. Immunological mechanisms driving the sex bias in autoimmune CNS diseases are complex and include hormonal as well as genetic and epigenetic effects, which could also be exerted indirectly via modulation of the microbiome. Furthermore, CNS intrinsic differences could underlie the sex bias in autoimmunity by differential responses to injury. The strong effects of sex on incidence and possibly also activity and progression of autoimmune CNS disorders suggest that treatments need to be tailored to each sex to optimize efficacy. To date, however, due to a lack of systematic studies on treatment responses in males versus females, evidence in this area is still sparse. We argue that studies taking sex differences into account could pave the way for sex-specific and therefore personalized treatment.

Introduction

It is well-known that women are more frequently affected by a number of autoimmune diseases [1]. Differences in chromosomal composition, reproductive organs, and sex hormones influence immune responses to foreign and self-antigens resulting in more vigorous adaptive immune responses in females such as T cell activity and higher antibody production [2]. This is reflected not only by a better control of infections but also by higher incidences in autoimmune diseases in females, including those affecting the central nervous system (CNS). In this review, we summarize the influence of sex on incidence, activity, and progression in the most frequent CNS autoimmune disease (multiple sclerosis, neuromyelitis optica, and autoimmune encephalitis; Fig. 1) and give possible immunobiological explanations why women compared to men are more prone to autoimmune responses.

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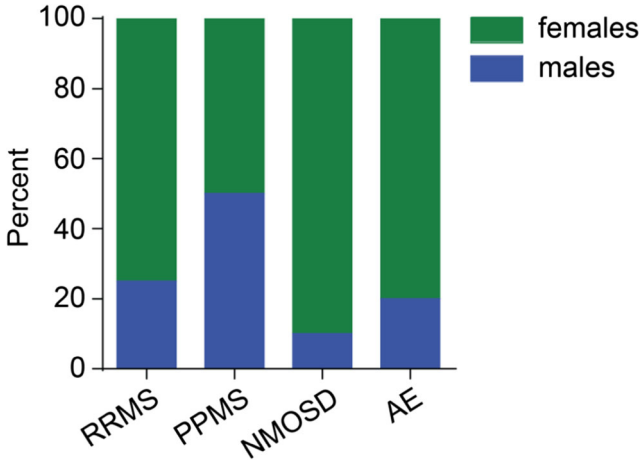

Fig. 1 Female/male ratio of MS subtypes, relapsing-remitting MS (RRMS) and primary progressive MS (PPMS), neuromyelitis optica spectrum disorder (NMOSD), and the most frequent neuronal antibody–mediated encephalitis subtype (anti-*N*-methyl-D-aspartate (NMDA) receptor encephalitis—age group 12–45)

Sex differences in incidence, activity, and progression of CNS autoimmunity

Multiple sclerosis

Sex ratio in multiple sclerosis

Multiple sclerosis is a chronic inflammatory disease of the brain and spinal cord that is a common cause of physical disability in young adults [3]. The average age of disease onset is 30 years, and 25 years after diagnosis, approximately 50% of patients are wheelchair-bound. Approximately 85% of patients are afflicted by relapsing-remitting multiple sclerosis (RRMS), which shows episodes of neurological dysfunction that are followed by remission and clinical recovery. Relapses are caused by bouts of inflammation and demyelination in the central nervous system (CNS). Eventually, disability accumulates and approximately 80% of RRMS patients develop secondary progressive MS (SPMS), which is characterized by a progressive neurological decline. Approximately 10% of MS patients are diagnosed with primary progressive MS (PPMS), which usually starts later at an average age of 40 and shows progressive decline from the outset and absence of relapses [4].

Women are approximately three times more often affected by RRMS than men, making sex one of the top risk factors for developing MS [5]. Intriguingly, PPMS affects men and women equally [6]. In addition, within RRMS, sex ratio quite considerably varies across different ages at onset, with a sharp incline of female preponderance around puberty (reviewed in [7]). Moreover, age at onset of puberty is associated with MS risk in girls but not in boys [8].

One intriguing observation coming from a comparison of epidemiological studies over many decades is that disease incidence of MS appears to be rising in women but not in men, leading to an increase in sex ratio over time [9]. A large study from Denmark covering six decades suggested that from 1950 to 2009, MS incidence rose in women by 114%, whereas the incidence in men rose only by 30%, resulting in a gradually increasing sex ratio. The increase, however, was not consistent across all groups of patients as women aged 50–64 showed the highest relative increase over the study period [10]. A trend towards a widening gender gap was confirmed in another analysis of prevalence rates between 1930 and 1989 comparing sex ratios from different geographical locations [11]. Here, adjusted sex ratios showed a significant increase from the first to the last decade (from 2.35 to 2.73). Intriguingly, this effect differed by latitude with increases in sex ratio limited to northern regions.

However, in more recent periods (i.e., after 2000), the sex ratio in RRMS may have stabilized at around 2.5:1, particularly in regions of high MS prevalence. For example, a large population-based cohort from Canada followed from 1996 to 2009 showed no statistically significant trend in sex ratios and showed some fluctuations in both directions afterwards [12].

Taken together, MS is clearly more prevalent in women than in men in the relapsing-remitting and secondary progressive subtypes. Numerous cohort studies have also suggested that the female to male ratio has increased in the second half of the twentieth century; however, it appears that this phenomenon may now have stabilized, especially in high prevalence geographical locations.

Female multiple sclerosis patients have higher inflammatory activity

In addition to sex difference in incidence and prevalence, MS is also characterized by differences in disease activity and progression between male and female patients.

For example, a recent study demonstrated an 18% higher relapse rate in females compared with males who have RRMS throughout the entire duration of disease and at any age [13]. Also, RRMS patients have a greater female to male ratio when they have at least four relapses per year in the first 5 years of disease, (3.3:1) than patients who experience no relapses in the first 5 years (2.3:1) [13]. Females also have a higher cumulative hazard risk of relapses than males 40 years after disease onset [13].

A potentially higher inflammatory activity in female MS patients is also supported by radiological evidence. Some studies indicated that women with MS have more contrast-enhancing lesions compared to male patients [14, 15], although this was not confirmed in larger studies controlling for age of onset and type of MS [16–18]. Similar to studies showing that responses in females to various immune challenges are stronger than in males [19], this was also reported when comparing autoantigen-specific responses in women versus men with MS [20–22].

Male multiple sclerosis patients have more pronounced neurodegeneration

In contrast to incidence, prevalence, inflammatory activity, and relapses, all of which show a female preponderance, the neurodegenerative component of MS does not seem to be more pronounced in women. The best known indication of this is that PPMS—in contrast to RRMS—is equally prevalent in males versus females. Moreover, some evidence suggests that neurodegeneration may indeed be faster in male versus female MS patients. For example, studies have shown that male sex is among the strongest early predictors of future permanent disability in RRMS (in addition to age of onset and degree of recovery from the first episode) [23]. A natural history study that included both relapsing as well as progressive forms of MS demonstrated that male patients overall reached disability milestones more quickly after disease onset when compared to females [24]. Similar observations, with a shorter time to disability progression in male patients compared to females, were made in cohorts of patients with relapsing disease [25–27]. Several other reports have confirmed this by showing that male sex is associated with more severe disease phenotype characterized by faster accumulation of disability [28] and more rapid progression from disease onset in RRMS [29]. Moreover, male patients may show faster conversion from RRMS to SPMS, according to a natural history study of untreated patients [30]. Finally, a very large registry-based study of over 14,000 patients revealed that male relapse-onset progressive patients accumulated disability faster than female relapse-onset progressive patients [31]. Interestingly, the male bias towards faster neurodegeneration is limited to the relapsing MS subgroup, as male patients with progressive MS do not show significantly faster disease accumulation than women in this subtype [31].

In addition to disability accumulation, neuroimaging parameters such as localized brain atrophy and cognitive dysfunction can provide relevant surrogate measures for neurodegeneration in MS. Also, here, male patients appear to do worse. For example, an early study showed that male MS patients exhibited lower scores on several cognitive subtests as compared to female MS patients matched for important potential confounds such as age, education, and disease severity [32]. Similar results were obtained in a large cohort of MS subjects ($n = 533$) when using clinical cut-offs on a battery of neuropsychological tests with men showing poorer performance than women [25]. Corroborating the clinical results on cognition, a recent study demonstrated smaller regional brain volumes in several deep gray matter structures in male MS patients (− 11%) than in female patients (− 6.3%) when compared to a sex-matched control group. Moreover, male MS patients showed more pronounced cognitive deficits than female patients when compared to male and female control subjects, respectively [33].

Neuromyelitis optica spectrum disorders

Neuromyelitis optica spectrum disorders (NMOSD) are rare autoimmune inflammatory CNS conditions clinically manifesting with attacks of optic neuritis, myelitis, and brainstem encephalitis [34–39]. In addition, burdensome symptoms such as pain, fatigue, and depression are also highly prevalent [40, 41]. In most historic cohorts, disease course was reported to be less favorable than in MS and with higher mortality rates [42]. Depending on the type of immunoassay, up to 80% of patients harbor serum autoantibodies to the astrocyte water channel aquaporin-4 (AQP4) that are not only a diagnostic biomarker but are involved in orchestrating CNS tissue damage [43–46]. Eighty to 90% of patients experience a relapsing course. A monophasic course is more common among seronegative patients [47]. Sex ratio heavily depends on the antibody status; while the female to male ratio is about 9–10:1 in seropositive patients, it is more balanced in seronegative patients with a 2:1 female to male ratio [48]. In a large cohort of 175 Caucasian patients, 83% of females but only 48% of males were seropositive [47], and similar results were reported in Asian populations [49]. The clear female preponderance at least in AQP4 antibody-positive patients has been consistently reported across geographic regions with a proportion of females ranging from 70 to 100% [50]. Variations may be due to differences in seropositivity as well as relapsing versus monophasic disease course. Studies applying the newly devised 2015 diagnostic criteria [51] have confirmed the strong female preponderance (for example, 6.2:1 in a study from Korea with 252 patients [52]). The female to male ratio seems to depend on the age at disease onset; in seropositive patients, the female to male ratios were 3:1, 23:1, and 5:1 for age < 15, 15–40, and above 40, respectively [48]. In this study comprising 186 patients (152 female), women tended to be younger at disease onset (39 ± (SD) 14 versus 44 ± 17 years, $P = 0.075$), and a higher proportion of females was seropositive (92% versus 55% in males). Interestingly, time from onset of symptoms to establishing an NMOSD diagnosis was significantly longer in females (54 months ± (SD) 80) than in males (27 months ± 42), which was related to misdiagnosis of MS particularly in female patients. No differences were reported between females and males with regard to attack frequencies, the distribution of attacks (optic neuritis, myelitis, or other localizations), or the outcome from attacks. Females below the age of 40 had a higher frequency of complete remission from attacks and a better response to high-dose steroids given as relapse treatment than patients over 40 years, which did not hold true for male patients. However, this may have been related to the small sample size of male patients and does not necessarily point to sex differences. Another study comprising 217 female NMOSD patients from multiple centers in the USA and Europe reported a marginally significant association of overuse of systemic hormonal contraceptives with

earlier first symptom onset (39 versus 43 years) [53]. A retrospective study comprising 106 AQP4 antibody-positive NMOSD patients (59 from the UK, 47 from Japan) investigated influence of sex on several disability milestones [54]. Males were more likely than females (hazard ratio 4.9) to attain significant visual impairment (visual acuity in best eye worse than 6/36) whereas no influence of sex on motor disability (unable to walk > 100 m unaided), wheelchair dependence, and death was found.

Recently, serum antibodies to myelin oligodendrocyte glycoprotein (MOG) were described in a subset of patients displaying an NMOSD clinical phenotype who were seronegative for AQP4 antibodies [55–60] and few patients with MS [61]. (Recurrent) optic neuritis was reported to be the most frequent clinical manifestation although myelitis and brainstem involvement are not infrequent [62], and some clinical features associated with anti-MOG autoimmunity such as seizures or muscle involvement are very uncommon in classic NMOSD with AQP4 antibodies [63–65]. Female to male ratios across cohorts from different geographic regions range from 1.1:1 to 1:2.8 [55, 56, 66–71]. In one of the larger studies comprising 50 patients with MOG antibodies [55], a similar proportion of female and male patients experienced a relapsing disease course (84 versus 69%). The issue as to whether anti-MOG autoimmunity represents a disease entity in its own or should be considered as part of the NMO spectrum has not been resolved [72–74], but is indicated by its more evenly balanced female to male ration in comparison to NMOSD or MS.

Autoimmune encephalitis

During recent years, autoimmune encephalitis (AE) has evolved to be used as an umbrella term encompassing encephalitis syndromes of autoimmune origin with and without underlying associated tumors and with or without detectable neuronal autoantibodies [75]. Encephalitis syndromes with detectable neuronal autoantibodies also are often referred to as antibody-mediated encephalitis. AE are much more common than previously considered, surpass the frequency of pathogen-related encephalitis in Western countries [76], and cause significant morbidity, mortality, and direct as well as indirect health care–related costs [77]. Patients usually present with acute or subacute prominent neuropsychiatric syndromes (psychosis, behavioral abnormalities, memory dysfunction) with co-occurring epilepsy, sometimes decrease of consciousness, abnormal movements, and autonomic dysregulation. Other distinct autoimmune syndromes, e.g., autoimmune cerebellitis, stiff-person syndromes, demyelinating syndromes, and systemic autoimmunopathies like systemic lupus erythematosus and sarcoidosis, have to be distinguished from this group of diseases [78].

Many AEs are associated with neuronal autoantibodies which either target superficial synaptic or extrasynaptic proteins involved in signal transduction and synaptic integrity, proteins involved in vesicle trafficking, or intracellular and intranuclear localized neuron-specific proteins [79]. Different neuronal autoantibodies are often associated with distinct clinical syndromes, age spectra, tumor associations (type and frequency), therapy responsiveness, and prognosis [78]. Many of these syndromes have different sex predominance in incidence and sometimes, tumor association and the most common subforms of AE are thus being considered individually in order of their frequency below.

Anti-*N*-methyl-D-aspartate receptor encephalitis

This AE syndrome is responsible for two thirds of all seropositive AE syndromes. It affects patients of all ages but predominantly children and young adults below 45 years of age. It usually manifests with behavioral abnormalities, memory dysfunction, and eventually seizures, loss of consciousness, and orofacial dyskinesias. It mostly responds well to immunotherapy. In a series of 577 patients (81% female), the median age was 21 years; 37% were younger than 18 years and 5% older than 45 [80]. Female preponderance (88%) was especially marked after puberty and before menopause (12–45 years). Sex differences were less obvious in age groups below 12 years (males 39%) and above 45 (males 43%). Of note, tumor association (53%) was highest in women between 12 and 45 years (women < 12 years 6%, > 45 years 25%) whereas in men, tumor association increased with age (< 12 years 0%, 12–45 years 7%, > 45 years 25%). Most tumors were ovarian or extraovarian teratomas (96%) [80]; this in part explains the strong female preponderance in premenopausal women with ovarian teratomas being the most common ovarian tumor in this age group [81]. However, even in non-tumor cases of anti-NMDA receptor encephalitis, women in this age group are significantly more often affected than men (female to male ratio 3.6:1) [80]. No clear sex difference exists concerning response to therapy, relapse rate, and disease severity after exclusion of the confounding effects of teratoma versus non-teratoma cases.

Anti-LGI1 encephalitis and anti-CASPR2 encephalitis

Being considered the second most common AE subform, anti-leucine-rich glioma-inhibited 1-(LGI1) encephalitis is clinically and demographically distinct from the anti-NMDA receptor encephalitis discussed above. It affects older patients (median age 64 years (range 31–84) and does appear to have a slight male preponderance (female:male 1:1.6–1.9) [82, 83]. Recently, another AE subtype associated with detection of antibodies targeting contactin-associated protein-2 (CASPR2) has been identified which shows an even more

striking male preponderance. It usually manifests in older patients (mean age 66 years (range 25–77)) which are in the vast majority male (female:male 1:9) [84]. Its onset is more insidious and clinical signs of limbic encephalitis are often associated with diffuse pain of the extremities, prominent myoclonus, and peripheral nerve hyperexcitability syndromes. Of note, both anti-LGI1 and anti-CASPR2 encephalitis have recently been shown to be associated with the non-complement fixing IgG-isotype IgG4 and have a very strong genetic predisposition being highly associated with distinct HLA class II haplotypes [85, 86]. It is intriguing to speculate that the strong genetic background of these AE might be associated with this male predominance. No clear sex difference exists concerning tumor association, immunotherapy responsiveness, or disease severity in both entities.

Other AE subtypes

Most other AE subtypes have a slight female preponderance or equal gender ratios, however in many of these reported numbers are still too small to draw final conclusion. Anti-α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) encephalitis appears to be more common in women (female:male 2.3:1), anti-γ-aminobutyric acid (GABA) type B receptor (GABABR) encephalitis (female:male 1:1.5), and GABA type A receptor (GABAAR) encephalitis (female:male 1:1) almost equally affect both genders. Some male preponderance has been observed in anti-dipeptidylpeptidase 6 (DPPX) encephalitis (female:male 1:2.3) [78]. A notable exception is the heterogeneous group of patients with limbic encephalitis and detection of glutamate decarboxylase (GAD65) antibodies in CSF and serum. While other autoantibodies might coexist and explain parts of the clinical syndromes, a strong female dominance has been observed in these patients (female:male 9:1) [87, 88].

Immunobiological mechanisms of sex differences in CNS autoimmunity

Sex bias in the immune system

A large body of evidence has implicated a role of sex hormones including testosterone and estrogens in mediating the higher susceptibility to autoimmunity in females versus males. This literature has recently been reviewed elsewhere [89]. In brief, estrogen receptor (ER)α signaling in peripheral immune cells has been shown to be one of the main pathways for protective effects of estrogens in experimental autoimmune encephalomyelitis (EAE), the animal model of MS. More recently, direct effects on the immune system via (ER)β have also been described [90]. Protective effects of androgen treatment in EAE are less well defined. Here, we will thus focus on recent developments in this field.

In a retrospective cohort study, males with gender identity disorders undergoing male-to-female conversion were found to have an increased rate of MS in comparison to females undergoing conversion to male implicating low testosterone or feminizing hormones to increase MS incidence [91]. Corroborating that, in animal studies using SJL mice, a strain showing female preponderance in EAE, mast cells produce IL-33 in response to testosterone in males and thereby lead to a protective type 2 shift in the immune response [92]. Furthermore, there is new evidence that testosterone, despite its ameliorating effects on immune responses when applied early in EAE, can have detrimental effects on neurons when applied during the chronic phase in line with the more pronounced neurodegeneration observed in male MS patients [93]. Sex hormones can also indirectly affect immune function by altering the composition of the microbiome. Sex-specific differences in the microbiome are present in several mouse strains and affected by gonadectomy and hormone treatment [94]. Furthermore, the sex bias in an autoimmune type 1 diabetes model is influenced by sex-specific differences in microbial composition [95], and there is accumulating evidence for a role of gut microbiota in MS pathogenesis [96, 97]. Estrogen treatment in EAE leads to alterations in the composition of the gut microbiome and of immune cells in the mesenteric lymph nodes [98]. Taken together, sex hormones exert complex direct and indirect effects on immune cell functions, which likely contribute to the sex bias in incidence of autoimmune diseases of the CNS.

In addition to hormonal effects, recent evidence has also identified epigenetic pathways that could drive the sex bias in autoimmune disorders. Sex appears to be one of the strongest factors determining the regulome of primary human T cells [99]. Illustrating the clinical relevance of this phenomenon, one human study demonstrated that toll-like receptor 7 (TLR7), which is encoded on the X chromosome, escapes X inactivation in B cells and myeloid cells in females and Klinefelter individuals and might thereby contribute to stronger B cell responses in women [100]. Another potential epigenetic mechanism on sex chromosomes might be paternal imprinting as demonstrated for the FoxP3 gene [101].

Sex differences in CNS response to injury

In addition to immune-mediated effects, sex differences in inflammatory CNS disorders could also be driven by sex effects directly on the CNS. Again, hormonal effects have been well-described and are reviewed elsewhere [89]. An intriguing novel pathway includes genetic influences on the CNS response to injury: in an elegant animal study, mice with a genetically "male" CNS (i.e., bearing an XY genetic background) showed greater EAE disease severity and more

pronounced neurodegeneration compared to mice with a genetically "female" CNS, regardless of the genetic background of the immune system [102]. This phenotype was also linked to increased expression of the X-linked Tlr7 gene in XY neurons compared to XX neurons. Another study demonstrated that XY mice showed impaired functional remyelination in the corpus callosum compared to XX mice. The genetic effect was only observable when the impact of circulating sex hormones was removed [103].

These findings illustrate that the interplay between inflammation and neurodegeneration can be highly complex and that sex could exert differential—and even opposing—effects on various aspects of the pathobiology of human CNS disorders.

Therapeutic implications

A pronounced sex difference in the incidence and prevalence of inflammatory CNS disorders including MS, NMOSD, and AE implies that male and female patients might also differ in their response to treatment for these disorders or even require different therapeutic approaches. In the last section of this review, we will outline the evidence that is available with regard to sex-related factors in the prediction of treatment response as well as briefly highlight efforts that are underway to derive sex-specific treatments in inflammatory CNS disorders. Unfortunately, very little is known to date about the role of sex with regard to treatment response of established disease-modifying therapies.

Sex differences in response to treatment

A recent systematic review analyzed sex differences in the outcome of disease-modifying treatments for MS based on available randomized controlled trials (RCTs) and cohort studies. The authors' main inclusion criteria for any given study were a subgroup analysis by sex was preplanned, a rationale provided, and a statistical test for a sex by treatment interaction provided. Maybe not surprisingly, only 11 RCTs and 11 cohort studies (out of 109 studies identified by a search) met these criteria. Thus, any conclusions from this systematic review need to be interpreted with caution. The authors were able to identify eligible studies of interferon-beta, glatiramer acetate, dimethyl fumarate, natalizumab, fingolimod, and alemtuzumab. Although the presented analyses occasionally showed sex differences for some clinical outcomes or surrogate measures of inflammation and neurodegeneration, no clear picture emerged from the systematic review and methodological considerations severely limited the ability to draw conclusions on the direction or the extent of sex effects [104].

The evidence basis for potential sex differences in response to treatment in NMOSD or autoimmune encephalitis, unfortunately, is even more limited. In part, this may be due to the comparatively much lower prevalence of these disorders, the paucity of large enough clinical trials or observational studies, and the very strong sex bias in incidence, which makes it very difficult to have sufficient sample sizes (and particularly enough male cases) for such comparisons.

Treatment of NMOSD comprises immunosuppressive and B cell–depleting agents such as azathioprine or rituximab while many MS drugs are inefficacious or even harmful and are thus contraindicated (for example, beta interferons, natalizumab, alemtuzumab, glatiramer acetate) [105–113]. To date, there are no studies that have specifically addressed potential differential response to these preventive drugs in female versus male NMO patients. In contrast, a large retrospective multicenter study evaluating treatment response in 871 NMO attacks did not find sex to be an independent predictor of complete remission in a multivariate analysis [114].

Development of sex-specific therapies

In addition to potential sex differences in response to established DMTs, another area where knowledge about sex differences in the pathobiology of these disorders could be translated into clinical practice is the development of sex-specific treatments. In the field of inflammatory CNS disorders, this approach can be illustrated by the efforts to develop hormone-based therapies in MS. So far, clinical phase IIa and IIb trials have been conducted for testosterone in male patients with MS and estrogens in female patients with MS.

The approach to treat male MS patients with testosterone is largely based on the clinical observation that men have a lower risk of developing MS and experimental work in the animal model of MS indicating a therapeutic potential of testosterone and the immune system as well as the CNS (reviewed in [89]). A first pilot phase I/II trial of transdermal testosterone in male MS patients was conducted at UCLA by Voskuhl and colleagues (trial registration clinicaltrials.gov NCT00405353). In this open-label, baseline-to-treatment study [115], patients were monitored for a 6-month period with monthly clinical visits and MRIs followed by a 12-month period of treatment with a testosterone gel (Androgel 100 mg). The treatment increased serum testosterone levels by approximately 50% from the low normal to the high normal range and significantly increased lean body mass (muscle mass). There were no subjective reports of adverse effects and no significant abnormalities in any blood test results. No effects were seen on contrast-enhancing lesions, likely due to the low MRI activity at baseline. However, the authors report a significant effect on a measure of cognition. In addition, a slowing of global brain atrophy rate was detected during the treatment phase, which was later confirmed in a secondary analysis using voxel-based morphometry and localized to gray matter regions in the right frontal cortex [116]. Moreover, testosterone treatment showed significant effects on immune function by decreasing delayed type

hypersensitivity, decreasing CD4+ T cells, and increasing NK cell frequencies, reducing IL-2 production and increasing release of TGF, BDNF, and PDGF by peripheral immune cells [117].

There have also been several phase IIa/b trials of estrogens to treat women with MS, although the rationale for this is provided by the protective effect of pregnancy on disease activity in MS and not sex differences. Some of these trials, particularly those using estriol, have shown therapeutic potential on markers of inflammation as well as relapse rates. A detailed review can be found elsewhere [118].

Conclusions

The clinical evidence reviewed here clearly illustrates a pronounced sex difference in the incidence and prevalence of inflammatory CNS disorders including MS, NMOSD, and AE. Moreover, the course of the disease once established also seems to be different between the sexes, with potentially opposing effects depending on the disease mechanisms as illustrated by inflammatory versus neurodegenerative processes in male and female patients with MS. Taken together, this suggests that the pathobiology of these disorders might not be the same in women versus men. It is also not clear what triggers the pronounced inflammatory response in women. Possible explanations are autoimmune responses to autoantigens but also autoinflammatory responses to CNS-immanent processes could be an explanation. For example, latter is suggested by the absence of female to male bias in PPMS in comparison to RRMS patients. PPMS could be the true underlying cause of MS to which women respond with a vigorous immune response thereby generating inflammatory relapses.

One potential implication of this is that—as a result—male and female patients might also differ in their response to treatment for these disorders or even require different therapeutic approaches. While there is currently a lack of evidence due to insufficient data and stratification, ultimately, new studies need to take these differences into account and thereby could pave the way for developing sex-specific treatment regimen. This could offer a potentially highly attractive way to move the field towards personalized medicine.

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