Overview of Lupus in Women

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Dr Filippa Nyberg, head of Department of Dermatology, Danderyds Sjukhus, Stockholm, held a lecture on Lupus in women in the course "Dermatological Problems in Women" at the Nordic Congress of Dermato-Venereology in Reykjavik.

Abstract

Women are more prone than men to develop autoimmune diseases, especially those diseases with a suspected dominance of T helper type 2 cells (Th2). Systemic lupus erythematosus (SLE) occurs in approximately 31 out of every 100,000 people and affects women nine times more frequently than men. The female:male ratio in subacute LE (SCLE) and chronic cutaneous LE (CCLE) is at least 3:2. Oestrogen can affect the development of lupus, and abnormal metabolism of sex hormones in men and women with SLE has been reported. Approximately 80% of new cases of lupus develop among women during their childbearing years. Women can also be affected during pregnancy by flares in their lupus, by miscarriages in cardiolipin syndrome or by neonatal lupus erythematosus (NLE) in the child. Mothers of babies with NLE are often initially asymptomatic, but eventually most develop symptoms of autoimmune disease. Comorbidities that affect women with lupus are cardiovascular disease, deficiency of vitamin D and human papilloma virus (HPV) disease, notably cancer of the cervix. Recently, adverse drug reactions have been reported to be more common in women. A basic understanding of the pathophysiology behind sex differences in autoimmune diseases and an awareness of gender is necessary for dermatologists investigating and treating cutaneous lupus erythematosus (CLE).

Introduction

Autoimmune diseases affect approximately 8% of the population, and 78% of those affected are women (1–3). For diseases such as Hashimoto's disease, Sjögren's syndrome, systemic lupus erythematosus (SLE) and scleroderma, where a dominance of Th2 is suspected, more than 90% of patients are women (4,5). The reason for the high prevalence in women is unclear. Women are known to respond to infection, vaccination and trauma with increased antibody production and a more Th2-predominant immune response, whereas a Th1 response and inflammation are usually more severe in men. The risk of developing an autoimmune disease increases as the number of autoantibodies increases, and the number of autoantibodies increases as we age. Thus, as an increased antibody response protects women from infections, it also increases the risk of developing an autoimmune disease. In cutaneous lupus erythematosus (CLE) the disfiguring skin lesions, often with permanent scarring and alopecia, will obviously affect both male and female patient's quality of life (QoL). No scientific studies on QoL in CLE have yet been published.

Sex hormones, genetics and SLE

Sex hormones, such as oestrogen, testosterone, and progesterone, are believed to mediate many of the sex-based differences in the immune response and to account for sex differences in the prevalence of autoimmune diseases (5). Patients with SLE demonstrate unique patterns of oestrogen production and metabolism, resulting in a 20-fold increase in the fraction of high-potency to low-potency oestrogens in patients with SLE compared with healthy controls (5). High amounts of biologically potent oestrogens cause patients with SLE to have more circulating self-reactive lymphocytes, imbalanced proportions of lymphocytes favouring humoral responsiveness, and lymphocytes that are primed to react. Immunoreactivity in patients with SLE occurs when lymphocytes are exposed to and stimulated by intracellular "self" components. Exposure of self-antigens in patients with SLE can be the result of errant apoptosis, which in turn is stimulated by oestrogen, which increases Fas ligand expression and increases rates of monocyte apoptosis. Oestrogen also increases the number of B cells that express high-affinity recognition of self-DNA as antigen (5). Prolactin expression is also altered in some patients with SLE, and evidence suggests that its immunostimulatory role contributes to disease pathogenesis.

A large genome-wide scan has recently identified an association for SLE with three genes encoding mediators of innate and adaptive immune responses, including components of the signalling pathways that regulate lymphocyte activation and the cell-surface receptors that generate tissue responses (6).

Epidemiology and lupus

SLE occurs in 25–250 per 100,000 persons, depending on racial and geographic background, being more prevalent in

Asians and blacks. Much less is known about epidemiology in CLE, but it seems that the female predominance Is much less pronounced than in SLE. The female:male ratio in subacute LE (SCLE) and chronic cutaneous LE (CCLE) together has been estimated to 3:2 or 3:1 (7). In a large cohort followed up between 1950 and 1979, there were equal numbers of men and women with discoid lupus erythematosus (DLE), in contrast to the female-predominance seen with SLE (8). However, in our population-based study on epidemiology of SCLE the ratio females:males was 5:1 (9) and in the original cohort it was 4:1 (10). Data on Ro/SSA-positive patients during 1996–2002 (*n*=1323; 85% women) were collected from the three clinical immunology laboratories in which Ro/SSA analysis is performed in Stockholm County, Sweden (1.8 Million inhabitants). The incidence of Ro/SSA-positive SCLE during the study period was estimated to be 0.7 cases per 100,000 persons per year and the prevalence was 6.2–14 cases per 100,000 persons. The age and sex distribution of patients with Ro/SSA antibodies are given in Fig. 1, showing that a majority of the patients were females between 30–80 years of age, with a peak at 51–60 years (9).

A PubMed search on the possible aetiologies underlying the greater prevalence of SLE in females, as well as the differences in the clinical presentation of the disease in both sexes has been performed (11). The authors found that potential causes of the female predilection for SLE included the effects of oestrogen and its hydroxylation, decreased androgen levels, hyperprolactinaemia, and differences in gonadotrophin-releasing hormone (GnRH) signalling. Clinically, females had more frequent relapses, but the incidence of severe relapses was the same in both sexes. Raynaud's phenomenon, arthritis, and leukopaenia were more common in women, whereas skin manifestations, serositis, and renal involvement were more common in men. For neurological manifestations, females with SLE experienced more psychiatric symptoms and headaches, whereas males with SLE experienced more seizures and peripheral neuropathy. Males with SLE also tended to have more severe renal disease and cardiopulmonary involvement. Though less common in men, when it does occur SLE tends to run a more severe course, and the authors conclude that this is an important consideration in the diagnosis and follow-up of male patients with SLE (11).

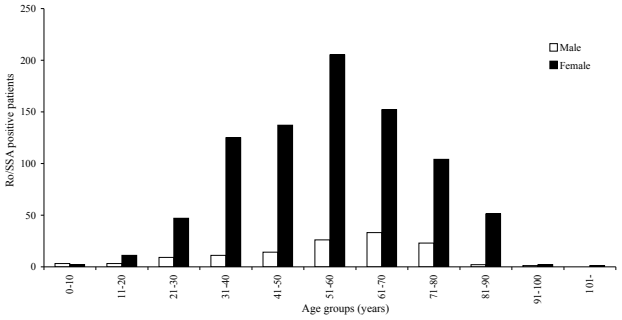

Fig. 1. Demographic data for 1323 Ro/SSA-positive patients in Stockholm county 1996–2002 (10).

In CLE there are no reported sex differences in clinical severity or manifestations.In a recent publication from Helsinki, smoking at the onset of disease was significantly more common in LE (57% for DLE, 35% for SCLE and 34% for SLE) compared with the age-/gender-matched prevalence in the Finnish population, suggesting smoking to be a trigger factor for CLE. The authors found no statistically significant sex differences in age at onset or smoking (12).

Prevention, pregnancy and childbirth

Approximately 80% of new cases of lupus develop among women during their childbearing years. Women can also be affected during pregnancy by flares in their lupus, miscarriages in antiphospholipid syndrome (APS) (13) or by neonatal lupus (NLE) in the child. Mothers of babies with NLE are often initially asymptomatic, but eventually most develop symptoms of autoimmune disease. A common clinical question is whether patients with lupus should receive oestrogen-containing contraceptives. A recent large randomized single-blind trial in 162 women with SLE using combined oral contraceptives, a progestin-only pill, or a copper intrauterine device showed no significant differences in global or maximum disease activity, incidence or probability of flares, or medication use (14). Another trial compared the effects of contraceptives on lupus activity in premenopausal women with stable SLE. Global disease activity, maximum SLEDAI (Systemic Lupus Erythematosus Disease Activity Index score, incidence of flares, time to first flare and incidence of adverse events were similar among women with SLE irrespective of the type of contraceptive they were using. The results indicate that oral contraceptives do not increase the risk of a flare of disease among women with lupus whose condition is stable (15).

Neonatal lupus erythematosus

Neonatal lupus erythematosus (NLE) is an uncommon condition associated with maternal anti-Ro autoantibodies. Findings may include cutaneous lupus lesions, heart block, cardio-myopathy, hepatobiliary disease, and/or thrombocytopaenia or other haematological cytopaenias. It is common for only one organ to be affected, but any combination of organ involvement may occur. The most common severe manifestation of neonatal lupus is third-degree heart block, which usually begins during the second trimester of gestation with an incidence of 1/20,000 live births, but is considered to be the most common cause of congenital heart block (CHB).

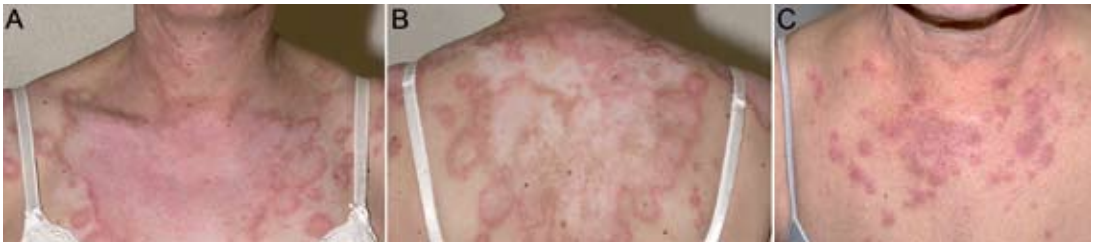

Fig. 2. (A, B) A 39-year-old Ro/SSA-positive woman with systemic lupus erythematosus (SLE) diagnosis and vitiligo, clinically and histologically subacute cutaneous lupus erythematosus (SCLE) lesions which appeared early autumn one month after first intake of proton pump inhibitor and cleared after approximately 3 months. (C) A 63-year-old Ro/SSA-positive woman with SLE diagnosis, previously without skin disease, clinically and histologically SCLE lesions, which appeared early autumn 2 weeks after first intake of methotrexate and cleared after approximately 4 months. *Reproduced after permission from Acta Dermato-Venereologica (23).*

The neonatal lupus disease process is transient, although third-degree heart block, once established, is permanent. Cutaneous lesions tend to resolve completely, but it is possible that affected children have an increased risk to later develop autoimmune diseases. Ro/SSA-antibodies have been found in 1/200 women, and the risk for Ro/SSA-positive women to give birth to a child with NLE is 1%, higher in patients with SLE. Mothers are often asymptomatic at the time of delivery of a baby with neonatal lupus, but can eventually develop autoimmune disease (16).

Comorbidity in lupus

Coronary artery disease is an important cause of death in patients with systemic lupus. In a recent study, electron-beam computed tomography was used to assess coronary-artery calcification in patients with lupus and matched controls. Coronary calcification was more frequent and more extensive and occurred at a younger age in the patients than in the controls. The findings could not be explained by traditional coronary risk factors and the authors conclude that novel approaches to the prevention of vascular disease in patients with lupus are needed and that early detection of atherosclerosis may provide an opportunity for therapeutic intervention (17).

Patients with SLE have been shown to have significantly lower serum levels of vitamin D than control groups, and these patients are at high risk of osteoporosis as they have several risk factors, including chronic inflammation, corticosteroid treatment and vitamin D deficiency. Interestingly, in a study on 27 patients with CLE, none of whom fulfilled the criteria for SLE diagnosis and whose gender was not analysed, 25 patients were shown to have insufficient (n=5) or deficient (n=20) levels of vitamin D (18). The authors conclude that vitamin D should also be monitored in patients with only cutaneous manifestations of lupus.

A recent study from the UK aimed at determination of rates of human papilloma virus (HPV) infections, abnormal cervical smears, and squamous intraepithelial lesions (SIL) among women with SLE. Polymerase chain reaction (PCR) results for viral DNA and HPV-16 sequencing data were correlated with cytology and colposcopic findings in 30 women with SLE, compared with abnormal smears from colposcopy clinics, and community subjects with normal smears. Women with a recent SLE diagnosis had significantly elevated levels of HPV infections (particularly with European HPV-16 variants at a high viral load), abnormal cervical cytology, and SIL (19).

Implications for treatment of lupus

Since hormones are known factors in the pathogenesis of lupus, attempts to modulate sex hormones have been made. Among these, anti-gonadotrophic drugs, oestrogen receptor (ER) antagonists, androgens, and antagonists of prolactin secretion have been tried, especially the adrenal steroidal hormone dehydroepiandrosterone (DHEA). DHEA has both endocrine effects (the ability to be converted peripherally to androgenic and oestrogenic sex steroids) and immunomodulatory effects (the production of the Th(1) cytokines, such as IL-2) The results from a number of clinical trials and observations suggest that 200 mg/day of DHEA for 7–12 months decreases corticosteroid requirement and frequency of disease flares, has an anti-osteoporotic effect and has an overall beneficial effect on SLE disease activity in female patients. A small study suggested benefits for cognitive function in such patients. Side effects acne and hirsutism were found in between 10–35%. DHEA treatment resulted in changes in lipid profile and may have endocrine effects, the consequences of which will need follow-up studies (20). Oestrogen blockade with tamoxifen, in murine models of lupus, improves disease severity. The weaker androgens, danazol and 19-nortestosterone, and bromocriptine have been less well evaluated but may also prove to be beneficial. The dopamine agonist bromocriptine prevents the secretion of prolactin by cells of the anterior pituitary gland. In murine models of SLE, bromocriptine diminishes activation of autoreactive B cells and reduces autoantibody production in direct relationship to the reduction in prolactin levels (20).

Side-effects of drugs

Clinical trials can sometimes show a selection bias towards male patients, but it is possible that women are more prone to develop drug-induced side-effects (21). SCLE was described in 1978 by Gilliam & Sontheimer (10), but recent data have shown that many of the original cases were in fact drug-induced. At least 71 patients have been reported with temporal association of skin lesions and systemic administration of a drug, as reviewed by Sontheimer et al. (22). The mean age of this cohort was 59 years, which was suggested to be older than in previous descriptions of SCLE. Patients had been taking the suspected drug for weeks to years before the onset of SCLE skin lesions and resolution occurred within 2–3 months in many cases. The drug classes were frequently those used for the treatment of cardiovascular disease, especially calcium-channel blockers. In our Swedish cohort of Ro/SSA-positive patients, two previously healthy patients developed SCLE during a short observation time of 2 years, both of these patients were female (23) (Fig. 2). Also, drug reactions other than SCLE seem to be overrepresented in females; in a recent report on 120 patients from the literature including 6 new patients (3 women and 3 men) who developed pustular lesions psoriasis or psoriasiform exanthemata during treatment with tumour necrosis factor (TNF)-alpha inhibitors infliximab, etanercept and adalimubab a majority of reported cases were females (72 women and 36 men, 12 gender not specified). The authors comment that often there are more men in the clinical trials, and the doses are translated without emphasis on different pharmacokinetics, etc. (24).

Conclusion

A basic understanding of the pathophysiology behind sex differences in autoimmune diseases and an awareness of gender is necessary for dermatologists investigating and treating CLE. Also, comorbidities such as atherosclerosis and skin and cervical cancer should be considered and information supplied to the patients. Calcium and vitamin D supplementation as osteoporosis prophylaxis, along with careful control for atherosclerosis should be a part of the clinician's considerations in caring for patients with CLE.

It is possible that new insight into the genetics and pathogenesis of this condition will lead to better treatment possibilities in the future.

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