Close Association of Herpes Zoster Reactivation and Systemic Lupus Erythematosus (SLE) Diagnosis: Case-Control Study of Patients with SLE or Noninflammatory Musculoskeletal Disorders

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ABSTRACT. ***Objective.*** To investigate the prevalence of infections, particularly the frequency of shingles and the timing of varicella zoster virus (VZV) reactivation, and antibiotic use, vaccinations, and joint trauma prior to and at diagnosis of systemic lupus erythematosus (SLE).

Methods. We sent questionnaires to patients with SLE (n = 93) and controls with noninflammatory musculoskeletal disorders (MSK; n = 353) including osteoarthritis, fibromyalgia, and tendonitis. We matched SLE patients to controls for sex (up to 1:3).

Results. The response rate in SLE was 66% and in controls 69% ($p < 0.53$). Four of 61 SLE patients and 12 of 173 controls were men. The mean disease duration in the SLE group was 8 ± 1 years compared to 10 ± 1 years in controls ($p < 0.23$). SLE patients were significantly younger than controls (mean age of SLE patients 49 ± 2 vs 57 ± 1 years for controls; $p < 0.0004$), and results were adjusted for age. A significantly higher proportion of SLE participants had a history of VZV (shingles) (19% vs 7%, respectively; OR 2.98, $p < 0.003$), whereas rubella was reported less in SLE (23% vs 42%; OR 0.43, $p < 0.03$). VZV infections were clustered just prior to or after diagnosis in SLE but were more widely spaced temporally in the controls (1 ± 4.5 years after the diagnosis of SLE vs –14.7 ± 4 years before the diagnosis of noninflammatory MSK disorder; $p < 0.003$). Diagnosis of shingles was observed in 6 of 11 SLE patients within ± 2 years of SLE diagnosis, whereas only 2 of 15 controls had shingles within ± 2 years of diagnosis (OR 7.2, $p < 0.03$). Only 2 patients with SLE were taking immunosuppressive drugs or steroids at time of shingles, so immunosuppressive therapy was not usually concomitant at time of VZV reactivation. Common infections (respiratory, urinary tract, ear, and eye) in the SLE group exceeded controls, but not significantly (23% vs 9%; OR 2.98, $p < 0.06$) and SLE patients were more likely to have been vaccinated since 18 years of age with any type of vaccine (69% vs 51%; OR 2.21, $p < 0.04$). SLE patients were less likely than controls to report joint trauma within one year prior to their diagnosis (25% vs 40%; OR 0.49, $p < 0.04$). There were no differences with respect to streptococcal throat infection ($p < 0.96$), diarrhea/vomiting ($p < 0.84$), rash with fever ($p < 0.07$), parvovirus infection ($p < 0.16$), infection after surgery ($p < 0.58$), respiratory tract infection ($p < 0.71$), or ear ($p < 0.09$) and eye infection ($p < 0.68$) one year prior to diagnosis. A higher proportion of SLE patients had a history of urinary tract infections (46% vs 25%), but this was not significant ($p < 0.17$), nor was it significant one year prior to diagnosis ($p < 0.63$). Overall, the likelihood of having any infection one year prior to diagnosis was not significantly higher in the SLE group ($p < 0.56$). There were no differences one year prior to diagnosis in travel history ($p < 0.69$), hospitalizations ($p < 0.47$), use of antibiotics ($p < 0.54$), history of rheumatic fever, positive TB skin test, or hepatitis A, B or C infection.

Conclusion. Varicella reactivation as shingles is increased in patients with SLE and clusters around diagnosis. Vaccinations are increased in those with SLE compared to controls. Common infections are not significantly increased in SLE patients prior to onset of symptoms. We cannot determine if VZV infections are causally associated with SLE in some people, are from an abnormal immune system response due to the lupus itself or from the use of steroids or other immunosuppressive drugs to control the disease, or are spurious. (J Rheumatol 2004;31:274–9)

Key Indexing Terms:
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Systemic lupus erythematosus (SLE) is a disease of unknown etiology with autoantibodies and immune complexes. There is evidence for genetic disease susceptibility and likely several potential exogenous environmental triggers. We investigated whether patients with SLE had more infections, especially VZV (varicella zoster virus, shingles) one year prior to diagnosis compared to those with noninflammatory musculoskeletal (MSK) conditions.

It has been recognized that certain viruses may act as nonspecific triggers of the immune system, such as cytomegalovirus (CMV)[1,2] and Epstein-Barr virus (EBV)[1,3-5]. Autoantibodies may be generated through molecular mimicry. Haaheim, *et al* reported that the anti-La antigen has sequence similarities to proteins from several common human viruses, especially the herpes viruses[6]. The prevalence of herpes zoster manifesting usually as a reactivation (shingles or disseminated disease) in SLE has been studied by several investigators and is increased compared to controls with a prevalence of 13 to 47%[7-14]. VZV was reported in 56 of 119 Japanese SLE patients (47%), of whom 8% had shingles prior to SLE diagnosis[7]. They found that VZV was not related to steroid dose or renal disease, although others have found these variables to be risk factors. Many did not have a skin reaction to varicella zoster (only 31% of those who had shingles) compared to all controls having positive skin tests. Higher steroid doses were less likely to be associated with positive skin tests to VZV. They also reported that SLE patients had high antibody titers to VZV compared to controls despite the high frequency of negative skin tests[8], and postulated that the increased incidence of VZV in SLE is due to impaired cellular immunity. Pons and colleagues studied 11 people with SLE and 12 controls and reported that cell-mediated cytotoxicity was reduced in SLE for VZV and other viruses (Newcastle and influenza A and B) despite an intact humeral response[15]. Another Japanese study of 58 SLE patients and 42 with scleroderma found VZV in 47% compared to only 10% with scleroderma[14].

The prevalence of shingles in SLE has been reported to be lower in other studies, but higher than would be expected in the general population[9-13]. Eighty-three SLE patients were studied, of whom 21% had VZV, especially those with nephritis who received immunosuppressive drugs with relatively inactive SLE at time of shingles[9]. Similarly, after SLE diagnosis, another study reported 13.5% of 47 SLE patients experienced varicella reactivation[10]. A study of 195 people with SLE and 143 controls reported that shingles occurred more commonly in SLE prior to diagnosis (OR 6.4, 95% CI 1.4–28.0). They did not find an association with other infections[11]. After diagnosis of SLE, 48 of 321 (15%) SLE patients developed shingles, usually self-limited and associated with immunosuppressive treatment and nephritis[12]. In the same year, a Spanish group reported herpes zoster in 13% of 145 SLE patients[13]. There have also been a few cases of SLE described after vaccination, particularly for hepatitis B, although the relationship could have been coincidental[16-19]. It seems likely, therefore, that infectious agents that can polyclonally activate B cells and stimulate T lymphocytes could exacerbate or even induce SLE in a genetically predisposed individual.

We hypothesized that certain infections (in particular, viral) may be increased just prior to the onset of SLE compared to controls with noninflammatory MSK complaints and that shingles would be increased in SLE (as reported by others) and could cluster around time of diagnosis.

MATERIALS AND METHODS

A questionnaire about past infections, vaccinations, antibiotic use, joint trauma, and other insults was sent to patients chosen from the database of patients referred to one rheumatologist (JP) at St. Joseph's Health Care London, an area with a referral base of greater than 1 million. Criteria for inclusion were diagnosis of SLE based on at least 4 of the American College of Rheumatology criteria[20] (n = 93 cases); or diagnosis of noninflammatory rheumatic disorder such as osteoarthritis (OA), tendonitis, or fibromyalgia (n = 353 controls). Patients received a mailed questionnaire, a letter of information, and a stamped, addressed return envelope. Second and third mailings were sent to nonrespondents. Patients were blinded to study hypothesis. The data were collected from the respondents, and SLE participants were matched to controls by sex (approximately 1:3, but there were 10 fewer females in the control group).

Data were analyzed using JMP statistical software, including group differences, means and proportions. Data not normally distributed were analyzed using Wilcoxon rank sum test. Baseline variables such as age and disease duration were determined. Age, a potential confounder, was adjusted for. We studied the "ever risk" of infections defined as the self-reported rate prior to diagnosis and the rate one year prior to diagnosis. Odds ratios (OR) and 95% confidence intervals (CI) were calculated. Multiple comparisons were not adjusted for as we had *a priori* a primary hypothesis that viral infections and in particular VZV would be more frequent in SLE compared to controls. Charts were reviewed to verify reports of viral hepatitis and shingles and to determine the use of concomitant immunosuppressive therapy in the SLE patients.

Ethics approval was obtained prior to the study.

RESULTS

The demographic data of the 2 groups are shown in Table 1. Due to the age difference in the SLE and control groups we adjusted p values for age (Tables 2–4). Statistically significant values for the SLE group compared to controls with

Table 1. Demographic factors in SLE and MSK controls. Cases and controls were matched for sex (3 controls: 1 case).

	SLE	Controls	p
Questionnaires mailed, n	93	353	—
Response rate (%)	61 (66)	243 (69)	0.53
Matched subjects	61	173	—
Age, mean ± SEM	49 ± 2	57 ± 1	0.0004
Sex (%)			
Male	4 (7)	12 (7)	0.92
Female	57 (93)	161 (93)	
Disease duration, yrs, mean ± SEM	8 ± 1	10 ± 1	0.23

Table 2. Events prior to diagnosis of SLE/noninflammatory MSK disorders. Common infections include upper respiratory tract, urinary tract, ear and eye infections.

	SLE, %	Controls, %	p*	OR
Common infections	23	9	0.06	2.98
Rubella	23	42	0.03	0.43
TB skin test positive	7	13	0.83	**
Trauma to joints	25	40	0.04	0.49

* Adjusted for age. ** Unstable estimate or numbers too small to do OR.

Table 3. Events occuring one year prior to diagnosis of SLE/noninflammatory MSK disorders.

	SLE, %	Controls, %	p*	OR
Any infection	45	32	0.56	1.68
Diarrhea/vomiting	14	18	0.84	0.80
Ear infection	11	12	0.65	0.90
Eye infection	8	12	0.13	0.99
Rash with fever	13	7	0.07	2.36
Respiratory tract infection	15	13	0.78	1.54
Streptococcal throat infection	15	11	0.96	1.38
Urinary tract infection	20	16	0.63	1.27
Antibiotic use	34	28	0.54	1.41
Hospitalizations	26	20	0.47	1.42
Travel history	9	13	0.69	0.68

* Adjusted for age.

Table 4. Comparison of ever (before and after diagnosis) having these infections in SLE and the noninflammatory MSK controls.

	SLE, %	Controls, %	p**	OR
Ear infection	23	23	0.09	1.02
Eye infection	23	16	0.68	1.54
Hepatitis A, B, or C*	5	6	0.15	—
HZV	19	7	0.003	2.98
Infection after operation	8	4	0.58	2.12
Parvovirus infection*	5	1	0.16	—
Respiratory tract infection	33	24	0.71	1.57
Urinary tract infection	46	25	0.17	2.49
Vaccination since 18 years of age	69	51	0.04	2.21

* Unstable estimate or numbers too small to do OR; ** adjusted for age. HZV: herpes zoster virus.

noninflammatory MSK problems were found for those (1) with a history of herpes zoster reactivation as defined by shingles ($p < 0.003$); and (2) who had been vaccinated since 18 years of age ($p < 0.04$). Controls were more likely to have had joint trauma ($p < 0.04$) and rubella infection ($p < 0.03$) prior to diagnosis. Virtually all infections were reported more commonly (but not statistically significantly) in SLE except for rubella, eye infections, and respiratory tract infections, which were reduced in SLE compared to controls.

Prior to diagnosis of SLE/noninflammatory MSK disorder. The likelihood of having had a positive TB skin test, rubella, common infections, or joint trauma is presented in Table 2. Forty percent of controls reported they had joint trauma compared to 25% in SLE prior to diagnosis ($p < 0.04$).

One year prior to diagnosis of SLE/noninflammatory MSK disorder. Even though significantly more SLE patients reported a history of urinary tract infections ($p < 0.004$), there was no difference in the occurrence compared to controls one year prior to diagnosis ($p < 0.52$, adjusted for age $p < 0.63$). Overall, the likelihood of having an infection one year prior to diagnosis was not significantly higher in the SLE group ($p < 0.11$, adjusted for age $p < 0.56$). The results comparing the incidence of infections and other insults one year prior to diagnosis are presented in Table 3.

Both prior to and after diagnosis (ever risk). A significantly higher proportion of SLE patients had a history of shingles (19% vs 7%; $p < 0.02$, adjusted for age $p < 0.003$). Eleven of 61 SLE patients had shingles, 6 after and 5 before diagnosis of SLE. In the control group, 7% had a history of shingles, but only one of 15 reported having shingles after diagnosis (one year after diagnosis), one at the time of MSK diagnosis, and 13 patients had shingles before diagnosis. Diagnosis of shingles was observed in 6 of 11 SLE patients within ± 2 years of SLE diagnosis. Only 2 of 15 controls had shingles within ± 2 years of diagnosis ($p < 0.03$, OR 7.2). VZV infection was on average 1 ± 4.5 years after the diagnosis of SLE versus 14.7 ± 4 years before the diagnosis of noninflammatory MSK disorder in controls ($p < 0.003$). The frequency and timing of shingles in relationship to SLE or MSK diagnosis is shown in Figure 1. It is notable that the temporal distribution of shingles reactivation to disease diagnosis was significantly different between the SLE and control populations, whereby the variance was 79.2 in SLE compared to 334.8 in the controls ($p < 0.03$). The chart review revealed that 2 of 6 SLE patients who reported having had shingles after SLE diagnosis met 3 diagnostic criteria of lupus at the time of diagnosis of shingles (and actually just prior to SLE diagnosis). Otherwise all other SLE patients were diagnosed as having 4 or more diagnostic criteria of SLE at the time of shingles diagnosis. Three SLE patients were taking hydroxychloroquine at the time of diagnosis of shingles. One patient was taking high dose prednisone and intravenous gamma globulin at the time of shingles diagnosis and one was taking low dose prednisone. No SLE patient was taking other immunosuppressive agents at the time of shingles diagnosis. The comparison of ever having infections and vaccinations in SLE and noninflammatory MSK controls is presented in Table 4.

Although not all results are statistically significant, the OR of infections was higher in SLE for any infection (1.68), ear infection (1.13), rash with fever (2.36), streptococcal throat infection (1.38), and urinary tract infection (1.27). The OR was lower for SLE patients for eye infection (0.99) and respiratory tract infection (0.65) compared to controls with noninflammatory MSK disease.

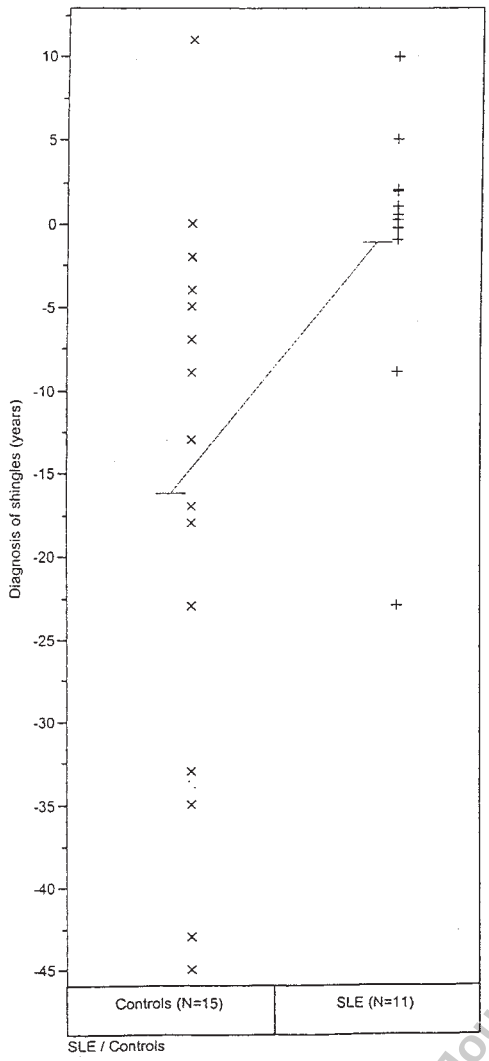

Figure 1. Correlation of timing of VZV reactivation (shingles) and diagnosis of SLE (n = 11) or noninflammatory MSK (n = 15) in years. 0: time of diagnosis of disease in both controls and patients with SLE. Note the clustering around diagnosis of SLE and occurrence of shingles ($p < 0.003$).

DISCUSSION

Our case-control study compares the incidence of infections, vaccinations, and other factors in SLE and noninflammatory MSK disorders using a self-administered questionnaire. Study limitations include a lack of chart review for some patients and the absence of diagnostic or serologic tests or examinations to confirm self-reported infections and vaccinations. Patients with SLE were more likely to self-report certain infections prior to diagnosis compared to controls. It could be that repeated exposure to infectious agents enhances their predilection to autoimmunity; however, certain lupus symptoms (such as fever, rash, lymph node swelling) could be misclassified by SLE patients as infections. It also should be noted that increased infections in SLE patients must be interpreted with care, as many SLE patients may have been diagnosed following years of SLE symptoms, and thus, causality from an infectious trigger cannot be assumed. It may be that the disease itself is immunosuppressive, or steroid and immunosuppressive therapy used in treatment could contribute to an increased risk of infections.

Urinary tract infections were more frequently reported by SLE patients at any given time, but were not more frequent one year prior to diagnosis. The urinary tract has been reported by Zonana-Nacach, *et al* as the most frequent of all infection sites among SLE patients[21]. However, Nived, *et al* did not show an increased number in SLE patients compared to controls[22].

Strom, *et al* described 195 cases of SLE including 18 who reported having had shingles compared to 3 or 143 controls[11]. Both their findings and ours suggest a strong association between herpes zoster infection at or before the diagnosis of SLE. They proposed that lupus be added to a list of possible diseases one considers when a patient presents with shingles (such as cancer)[11]. In our patients, shingles was clustered closely to the time of diagnosis in SLE but not in controls. VZV was found in our study in 19% of patients with SLE, a lower frequency than reported by others (13 to 47%)[7-14], but consistent with studies from North America. Reports of VZV in SLE are higher in Japan[7], but the background rates of shingles may also be higher there. We did not ascertain season at onset of VZV or SLE. Prednisone use could have been an important confounder, but only 2 of our SLE patients were taking prednisone when the shingles occurred (one low dose and the other high dose with intravenous gamma globulin). Strom, *et al* did not find an association between SLE and any other infections or vaccinations[11]. The incidence of shingles might have changed after introduction of the childhood varicella vaccine. We did not find any data in the literature on its possible beneficial effect in adults, and our patients had not received varicella vaccine. In addition, the cell-mediated immunity to VZV in SLE is impaired whereas the antibody titers are often high[7,8,15], so the vaccination may not be effective in preventing varicella reactivation in SLE due to faulty cell-mediated immunity.

Common infections were significantly higher in the SLE group ($p < 0.01$, but not after adjusting for age $p < 0.06$). The SLE group were on average younger than controls and may have been more likely to acquire infections from their younger children. When we looked at the timing of many common infections and SLE diagnosis, 37% reported having them before diagnosis, 14% after, and 48% were not sure. There were no significant demographic differences in those who had infections and those who did not within the SLE patients ($p < 0.23$). We do not know about the medical history, severity of SLE disease, or previous medications of our patients so we are not able to comment on the possible factors that influenced the infection rates. It has been found

that more severe SLE disease such as nephritis, use of immunosuppressive drugs, higher doses of steroids, and history of cancer can increase the risk of shingles in SLE. Most of our patients had mild disease and only 2 were taking prednisone when VZV reactivated.

Rubella infection was increased in the control group. Rubella infection was reported by 13 SLE patients, and as expected from the epidemiology of this disease, 12 patients contracted it before diagnosis (childhood) and one did not indicate the date. Those with SLE were younger, and in the 1960s rubella vaccination became routine, so the difference in infection rate could be related to vaccination differences in the cases and controls due to age. Overall, a significantly higher proportion of SLE participants had been vaccinated since 18 years of age, possibly due to the SLE patients' younger age and thus more vaccination availability. Vaccination data are difficult to interpret as practices have differed over the decades, and other materials in vaccines (adjuvants, stabilizers) could potentially stimulate the immune system. Recall bias may have been present in one or both of the groups, but people with a major life event (such as diagnosis of a disease) remember events around that time vividly and look for causation, so reporting should have occurred similarly in both groups. In the literature, an animal study linked vaccinations and the production of autoantibodies possibly from polyclonal activation[23,24] for which molecular mimicry has been implicated as one of the potential mechanisms behind this phenomenon[24]. There have been reports of SLE symptoms with a temporal relationship to various vaccinations[19] and onset or exacerbation of rheumatic disorders after hepatitis B immunization[16-18], while, in contrast, others found no increase in the incidence of autoimmune disorders following hepatitis B immunization[25-28]. None of our SLE patients reported symptoms after receiving this vaccination, but the sample was too small (n = 4) to make any conclusions. More research on the association of widespread hepatitis B vaccination of children and the later development of autoimmune disorders is warranted.

Parvovirus infection was reported by 3 SLE patients. There have been reports of parvovirus B19 infection as a potential inducing factor of SLE[29-35]. We did not have enough patients who reported parvovirus B19 infection to draw any conclusion, but parvovirus rates of infection were not reported differently between the 2 groups.

Despite the limitations of our case-control study design, it appears that shingles is increased in SLE patients, especially clustering around time of diagnosis (± 2 years). Our SLE patients had more vaccinations overall, which was still the case after adjusting for age (but still may be due to varying recommendations for vaccines in different age cohorts). Whether these associations are causal, spurious, or related due to a faulty immune system in SLE patients remains unclear. However, VZV reactivation is more common in SLE and clusters temporally to diagnosis date.

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