The prevalence and incidence of systemic lupus erythematosus in children and adults: a population-based study in a mountain community in northern Italy

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Abstract

Objective

To estimate prevalence and incidence of systemic lupus erythematosus (SLE) in paediatric and adult populations in Italy.

Methods

The study was carried out in Valtrompia, a valley in northern Italy, where a relatively close community lives, in 2009–2012. The only referral centre for SLE in the area is the Rheumatology Unit of the University Hospital of Brescia. The ascertainment of SLE cases was performed through the integration of three sources: 1) hospital database; 2) database of the Rheumatology laboratory; 3) database of general practitioners and general paediatricians practicing in the area. Each patient was evaluated by a rheumatologist for confirmation of SLE classification based on the presence of at least 4 criteria according to the American College of Rheumatology.

Results

Forty-four SLE patients (39 females, 89%) were identified. The prevalence of SLE at 31st December 2012 was 39.2 (95% C.I. 28.5–52.6) cases per 100,000 individuals in all subjects, and 42.3 (30.5–57.2) and 15.3 (1.8–55.1) in adults and children, respectively. Nine new cases of SLE were diagnosed over the 4 years of the study period, with an annual incidence rate of 2.0 (0.9–3.8) per 100,000 individuals.

Conclusion

This is the first study estimating the prevalence and incidence of SLE in Italy in both adult and paediatric population. Prevalence and incidence rates in line with those reported in other Mediterranean European countries. The accurate assessment of the SLE frequency is supported by the choice of a well-defined area, the integration of multiple data sources and the revision of each case by a rheumatologist.

Key words

systemic lupus erythematosus, epidemiology, prevalence, incidence, childhood-onset lupus

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Introduction

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease with multiple clinical presentations and a multifactorial aetiology. The disease occurs nine times more often in women than men, especially in childbearing age (15 to 35 years of age), and is more common in people of non-European descent. The prevalence and incidence of SLE vary according to the characteristics of each population: epidemiologic studies show that some ethnic groups (Afro-Americans, Asians, Aboriginal) are more susceptible to develop SLE than others (1).

The epidemiological pattern of SLE is of difficult definition. Indeed, the heterogeneity of clinical presentation and the lack of standardised methodology for case ascertainment are great obstacles to estimate the true number of affected individuals. Various studies estimated an incidence from 1 to 31 cases per 100,000 inhabitants and a prevalence from 28 to 207 per 100,000 in European countries, and an incidence from 2 to 11 and a prevalence from 13 to 89 per 100,000 in non-European countries (1).

In Italy, three studies on SLE epidemiology have been carried out in past decades, using either general practitioners' (GPs) databases or hospital discharge data (2-4). In Italy, the National Health System (NHS) covers the entire population. GPs and General Paediatricians (GPeds) provide primary care and most of them keep records of their patients' data using a specific software. The Italian GPs/GPeds electronic archives are considered a valuable source of information for epidemiologic studies, as shown by several studies performed under the "Health Search" project in past decades (5) some of which included both the Italian project and GP archives from other countries for international comparisons (6).

The Italian studies, however, showed inconsistent results regarding the SLE frequency (prevalence estimates ranging from 57.9 to 81 per 100,000), which are possibly due to different methods of retrieving SLE cases, at least partly. In fact, the use of one only source of data, given the relative rarity of the disease and its variable clinical pattern, is the main limit of these studies. Furthermore, none of them evaluated the epidemiology of SLE in the paediatric population.

A precise definition of the epidemiological pattern of SLE in Italy is strongly encouraged by the Italian SLE patients' association as a necessary tool for allocating health resources and planning intervention strategies.

In this study, we aimed to estimate the prevalence and incidence of SLE in the adult and paediatric population in a well-defined geographical region using various sources for patients' identification. As a secondary objective, the clinical characteristics and the damage accrual of SLE patients were also assessed.

Patients and methods

Valtrompia is a 40 kilometers-long prealpine valley located in northern Italy, comprising 18 municipalities (Fig. 1). This valley is a *cul-de-sac* with an only easy access from Brescia, the main city of the province. The public Hospital "Spedali Civili" in Brescia is one of the largest public hospitals in Italy, and also the reference hospital for the local Faculty of Medicine, University of Brescia (University Hospital). It includes the main Paediatric Clinic of the province and the only tertiary, referral Centre of Rheumatology and Clinical Immunology of the area. In recent years, a close collaboration between this Centre and local GPs was established for early referral of patients with suspect of a systemic autoimmune disease. In addition, all the blood samples collected for autoantibody detection in the area are centralised in the Laboratory of the Centre of Rheumatology and Clinical Immunology.

The SLE incidence rate was estimated in the 4-year period from January 1st, 2009 to December 31st, 2012. Prevalence was referred at the end of the period, December 31st, 2012. The population consisted of 112,365 individuals (13,108 under 14 years; 49.5% males) [7]. A total of 70 GPs and 13 GPeds were working in the area in 2012.

In the first phase, patients with clinical diagnosis of SLE were recruited from the following three sources (Fig. 2):

1) source no. 1 (S1): the clinical charts

and electronic databases of the University Hospital, including Rheumatology and Clinical Immunology Unit, Nephrology Unit, Paediatric Rheumatology and Immunology;

2) source no. 2 (S2): the electronic database of the Laboratory of the Unit of Rheumatology and Clinical Immunology, including subjects positive for anti-nuclear antibodies (ANA), anti-dsDNA antibodies, anti-ENA antibodies in 2012;
3) source no. 3 (S3): general Practitioners (GPs) and paediatricians (GPeds); 49 of 70 GPs (70%) and all the 13 GPeds (100%) working in the area collaborated in the study and identified SLE patients through their electronic databases.

In the second phase, SLE diagnosis was assessed and confirmed eventually by the Rheumatologists working at the Centre. For classification purposes, SLE was confirmed on the presence of at least 4 out of 11 American College of Rheumatology (ACR) criteria for SLE (8). The disease damage accrual was evaluated through the SLICC score system (9). The presence of concomitant antiphospholipid syndrome (APS) was defined according to international classification criteria (10).

The 95% confidence intervals (95% Cis) were calculated using the exact method (binomial) for estimating of the prevalence and the Poisson distribution for incidence rates. Prevalence and incidence estimates were expressed as cases per 100,000 individuals. Furthermore, age-standardised prevalences were computed using the direct method with the conventional European population as the standard (11). Prevalences were also computed in native-born and foreign-born separately.

The study was approved by the Ethics Committee of the Local Health Authority (Azienda Sanitaria Locale - ASL - Brescia).

Results

After the record-linkage between the three sources (Fig. 2) a total of 44 SLE patients were identified (39 females, 89%). Two patients were under 14 years of age (both females). Among the 43 patients identified through the Uni-

Fig. 1. Italy: the province of Brescia and area of Valtrompia are highlighted in green and blue, respectively; the red dot represents the University Hospital.

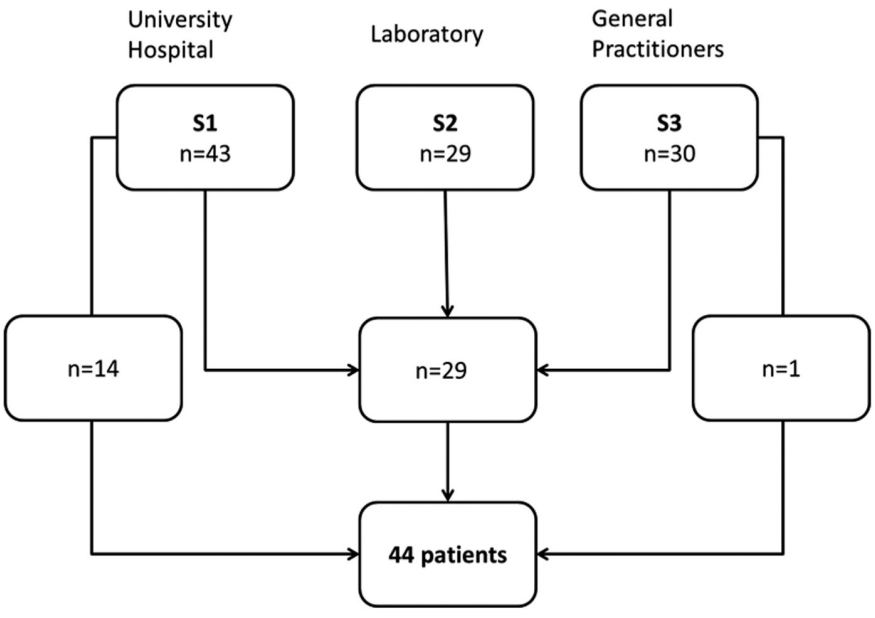

Fig. 2. Flow diagram of the ascertainment and verification of cases of SLE in Valtrompia (prevalent cases). Three sources were used: University Hospital (Units of Adult Rheumatology, Paediatric Rheumatology and Adult Nephrology) (S1), Laboratory of the Rheumatology Unit (S2), and General Practitioners (S3).

Table I. Prevalence at 31st December 2012 and annual incidence rates in 2009–2012 of SLE per 100,000 inhabitants in Valtrompia in adult and paediatric population, by gender. The 95% confidence intervals (CIs) are reported in parenthesis.

	Prevalence		Incidence	
	Number of cases	Prevalence (95% CI) per 100,000	Number of cases	Incidence (95% CI) per 100,000
Overall	44	39.2 (28.5-52.6)	9	2.0 (0.9-3.8)
Males	5	9.0 (2.9-20.9)	0	-
Females	39	68.8 (48.9-94.0)	9	3.9 (1.8-7.5)
Adults	42	42.3 (30.5-57.2)	7	1.8 (0.7-3.6)
Males	5	10.2 (3.3-23.9)	0	-
Females	37	73.4 (51.7-101.1)	7	3.5 (1.4-7.1)
Children	2	15.3 (1.8-55.1)	2	3.8 (0.5-13.8)
Males	0	- 0	-	
Females	2	31.8 (3.9-115.0)	2	7.9 (0.9-28.8)

Table II. Demographic and clinical manifestations of the 44 prevalent cases of SLE.

Demographic and clinical characteristics	
Sex	39 Females (89%), 5 Males (11%)
Race/Ethnicity	38 Caucasians, 3 Africans, 2 Indians, 1 Mixed (Caucasian-African)
Median age (at 31st Dec 2012) (range)	43 (5-91)
Median Follow-up time (at 31st Dec 2012) (range)	11 (0-32)
Age at time of disease diagnosis (range)	33 (3-70)
Juvenile onset of SLE (Below the age of 14)	5 (12%)
Obstetric antiphospholipid syndrome	3 (8%)
Thrombotic antiphospholipid syndrome	2 (4%)
Delay to diagnosis (years between the onset of symptoms and the diagnosis of SLE)	
Less than 1 year	35 (80%)
1 year	5 (11%)
2 years	1 (2%)
3 years	1 (2%)
More than 3 years	2 (5%)
ACR criteria	
Malar rash	17 (39%)
Discoid rash	3 (7%)
Photosensitivity	14 (32%)
Oral ulcers	12 (27%)
Non erosive arthritis	28 (64%)
Pleuritis or pericarditis	5 (11%)
Renal disorder	15 (34%)
Neurologic disorder	3 (7%)
Haematologic disorder	18 (41%)
Immunologic disorder	39 (89%)
Positive antinuclear antibody	44 (100%)
Autoantibodies	
Antinuclear antibodies	44 (100%)
Anti-double stranded DNA	34 (77%)
Anti-SSA/Ro	14 (32%)
Anti-SSB/La	3 (7%)
Treatment (current and/or past)	
Prednisone	40 (91%)
Hydroxychloroquine	30 (68%)
Azathioprine	16 (36%)
Methotrexate	10 (23%)
Mycophenolate Mofetil	6 (14%)
Cyclophosphamide	9 (20%)
Other (plasmaferesis, intravenous immunologlobulins)	2 (4%)

versity Hospital archives, 14 were not retrieved by the other sources. On the other hand, all the 29 patients identified through the laboratory search (S2) were also retrieved by the Hospital (S1) and GPs & GPeds (S3) databases. Among the 30 patients reported by GPs and GPeds, only one was not identified by the other sources (he was followed up in another town).

The prevalence of SLE was 39.2 cases per 100,000 inhabitants, about 7.5-fold higher in females (68.8/100,000) than in males (9.0/100,000), almost all in adults (42.3/100,000) with only 2 cases in children (15.3/100,000) (Table I). Only 9 new incident cases were found in the 4-years period of observation, all of which females, providing an incidence of 3.9/100,000, with only 2 cases in children (adult incidence = 1.8/100,000, paediatric incidence = 3.8/100,000). Age-standardised prevalences using the European population as the standard were 7.7 (0.9–14.5) and 69.5 (46.7–92.2) per 100,000, in males and females, respectively. The population living in the Valtrompia included 101,221 native-born and 11,144 foreign-born in 2012, respectively (7). The corresponding prevalences of SLE were 37.5 (95% CI 26.6–51.5) and 53.8 (19.8–117.1) per 100,000, respectively, with a prevalence ratio of 1.43 (0.50–3.42).

The demographic and clinical characteristics of SLE patients are summarised in Table II. The 2 paediatric patients with SLE were both African girls with first diagnosis in 2011 and 2012 at the age of 3 and 5 years, respectively. Other 3 patients in the cohort had childhood-onset SLE (diagnosis at 3, 12 and 13 years of age, respectively) and had a follow-up of 11, 4 and 5 years, respectively at the time of analysis.

As a measure of disease-related damage accrual, the SLICC score was calculated for each patient. The median follow-up was of 11 years, with some patients followed-up for nearly 30 years. Fifteen patients (35%) had a chronic damage (median SLICC score=1, range 1–5), with damage in multiple organs in 5 patients (12%), who had a longstanding and/or chronic-active disease. Table III shows the damage accrual and time of damage onset according to date of diagnosis. Damage occurred both early and some years after diagnosis (p=0.5 for comparison among the three periods), with no identifiable pattern upon different types of damage. The most commonly damaged organs were eyes (cat-

aract), joints (Jaccoud's arthropathy) and bones (osteoporosis with fractures). We found one only case of malignancy (carcinoma of the Fallopian tube).

Most patients (80%) had early diagnosis of SLE as they had been referred to the rheumatologist less than 1 year from the onset of symptoms, and underwent treatment with low dose steroids in combination with immunosuppressants (data not shown in Table). None of the 5 patients with childhood-onset SLE developed organ damage.

Table III. The damage accrual in 44 SLE patients according to the Systemic Lupus International Collaborating Clinics (SLICC) Damage Index. The onset of damage was categorised upon disease duration (less than 5, 5-10, more than 10 years after the diagnosis). (a): same patient.

SLICC items (type of organ damage)	GLOBAL (overall damage) n° pts	During the first 5 years from diagnosis n° pts	5-10 years from diagnosis n° pts	More than 10 years from diagnosis n° pts
Any cataract ever	8	3	2	3
Major psychosis	1	1	0	0
Cerebral vascular accident	1	0	0	1
Neuropathy	1	0	1	0
Chronic renal insufficiency (a)	1	0	1	0
End-stage renal failure (dialysis) (a)	1	0	0	1
Myocardial infarction	1	0	1	0
Deforming or erosive arthritis	5	4	0	1
Osteoporosis with fracture or vertebral collapse	3	0	1	2
Scarring chronic alopecia	1	1	0	0
Premature gonadal failure	1	0	0	1
Malignancy	1	0	0	1
Total number of pts *Multiple damage in 5 pts	15*/44 (34%)	9/44 (20%)	5/44 (11%)	8/44 (18%)

Discussion

The present study investigated epidemiology of SLE in a well-defined area of northern Italy in 2012. Using a "multiple-source" methodology for the retrieval of SLE cases, instead of the single source used in previous studies, we found a prevalence of SLE of 39.2 /100,000 (95% confidence interval, CI of 28.5-52.6), below the threshold of 50 cases/100,000 used for the definition of a "rare" disease, and an incidence rate of 2/100,000 (0.9-3.8), in 2009-2012.

Our study brings a new insight on the epidemiology of SLE in Italy, since the previous Italian studies (2-4) reported higher prevalence figures (71, 57.9 and 81 per 100,000, respectively). Such discrepancy is probably due to the automatic extraction of SLE cases from electronic databases in those studies, using only disease code for the ascertainment of SLE cases, without checking the selected cases according to standardised criteria for SLE definition. As a consequence, previous Italian studies possibly overestimated the actual number of SLE cases because of classification of cutaneous and non-systemic forms of lupus as SLE. In addition, two of those studies were performed more than 10 years ago, and therefore their data are no longer indicative of present condition, due to relevant changes in the Italian population structure for immigration and to substantial progress in early recognition of SLE cases in last decade.

We are confident that the identification of SLE cases was accurate in our study, for the choice of a relatively closed population, the use of multiple sources for case ascertainment, which were highly concordant among them, and because each single SLE case was also evaluated by an expert rheumatologist who validated the diagnosis using the ACR criteria (8).

The Valtrompia area is suitable for epidemiological studies since it is a narrow alpine valley, though densely populated (112,365 individuals in 2012), with no easy access except from the south. The city of Brescia is located there and the public Hospital "Spedali Civili" offers all types of specialist medical assistance, including Rheumatology Units for both adult and paediatric population. Therefore, patients with rheumatic diseases living in Valtrompia are likely to be diagnosed and followed-up in Brescia, and the Hospital Clinic and Laboratory databases are likely to include most of patients with SLE living in Valtrompia. However, patients with SLE who attend the Hospital may be a selected sample of the total subjects with SLE, as those with a less severe disease may have never been hospitalised or undergone laboratory tests in the 4-year study period. Therefore, we also examined the clinical records provided by the GPs and GPeds operating in Valtrompia. Their participation in the study was rather high (70% of GPs and 100% of GPeds), mainly thanks to a close collaboration between the Hospital and the local practitioners that has been established over last years, which has already allowed us to perform an epidemiological study on Systemic Sclerosis in the area (12). Despite the response rate from GPs was not 100%, the rate of missed patients seems negligible, as all but one patients reported by GPs (1/28, 3.6%) were identified by the other sources.

In our study, there was a good agreement among the three sources of data used (Fig. 2), with a high overlapping between GPs and GPeds archives and the other two sources. For this reason, we could not use the "capture-recapture" method, which is commonly suggested for estimating prevalence and incidence of an event when matching independent data sources, by comparing the magnitude of overlapping cases between two or more sources.

In other European Mediterranean countries, prevalence and incidence of SLE were similar to ours: 39.0 and 1.9, 34.1 and 2.1, 40.0 and 5.0, respectively, in studies carried out in Greece, Spain, and France (13-15), as compared to prevalence and incidence rates of 39.2 and 2/100,000, respectively, in our population. A lower prevalence of SLE was reported in other European countries: 25.4 per 100,000 in Northern Ireland (16), and 15.4 and 55.4 per 100,000 in males and females, respectively, in Germany (17).

Different figures across European countries may of course reflect different study designs and methodologies, but also suggest that genetic and environmental factors may influence the epidemiological pattern of SLE. Indeed, it is well recognised that people of Afro-Caribbean origin are much more affected by SLE than Caucasians (1). However, only 7 out of 43 (16%) patients were non-Caucasian in our study, that is overlapping with the proportion of immigrants in the Brescia province, most of which come from Africa and Asia (18), and therefore ethnic differences do not seem of relevance in this area. On the other hand, the only two cases of paediatric SLE were in immigrants (two females of African origin), in agreement with international data suggesting that childhood-onset SLE is more frequent and severe in nonwhite populations (19).

A secondary objective of our study was to evaluate the damage accrual in our SLE patients. We found that nearly one third of the patients were affected by chronic damage, which occurred both early and some years after diagnosis. The most commonly damaged organs were eyes, joints and bones, with complications mainly related to chronic steroids intake and longstanding disease. In fact, the patients who developed damage had first diagnosis of SLE in the 1980s and early 1990s, when use of steroids (especially at high dosage) was the mainstay of SLE treatment, whereas those who were diagnosed more recently probably got benefit from the early use of immunosuppressive agents and quick tapering of steroids. Furthermore, a causal relationship may be hypothesised between use of cyclophosphamide for glomerulonephritis and premature gonadal failure in one patient. The most severely affected patient was a 42-years-old African lady who developed end-stage renal disease (ESRD) and started peritoneal dialysis (in addition to neuropathy and chronic scarring alopecia). Such a damage accrual in nearly 12 years of follow-up can be related to both a genetic predisposition to a severe disease course and to a poor compliance of the patient to drug treatment and monitoring of her disease. Racial disparities in the burden of SLE have been actually described in two recent, large studies conducted in the United States (US) (20-22). In fact, black patients experienced a 2 to 3-fold increase in SLE incidence and prevalence and increased proportions of renal disease and progression to ESRD as compared to white patients.

On the other hand, the lack of organ damage in majority of patients (65%) during a median follow-up time of 11 years suggests that both early diagnosis of SLE and the prudent use of low-dose steroids in combination with immunosuppressants may have substantially reduced the burden of disease in last decades. This is in agreement with large international SLE cohorts that showed that organ damage is associated with prolonged use of medium-high doses of steroids (23, 24).

This study has various strengths, *i.e.* the high level of completeness and accuracy of case retrieval due to the well-circumscribed geographical area, the use of multiple sources of data, and the further check of all the SLE cases retrieved by any source by an expert rheumatologist. It is also of note that this is the first study reporting data on SLE epidemiology in the Italian paediatric population, although the small number of cases (n=2) does not allow to compute precise estimates. In addition, it should be underlined that both cases were foreign-born children. For these reasons, the estimates of prevalence and incidence in the paediatric population should be taken with caution.

Our study has some weaknesses, too. First, the application of the "classical" ACR criteria for SLE may be questionable, since a new set of criteria has been proposed recently by the SLICC group (25). However, the ACR criteria were more suitable for comparing the results of our study to past research. Giving the lower specificity in favour of a greater sensitivity of the SLICC criteria, their performance in capturing the different spectrum of SLE cases deserves future studies. Second, the investigated population lives in a relatively small mountain area. However, it is a highly industrialised and developed area, not far from the main city of the province, and is similar to the northern Italy general population according to sex (proportion of males 49.6% and 48.6% in Valtrompia and in northern Italy, respectively) and age distribution (Valtrompia *vs.* northern Italy: 18.7% *vs.* 19.8% in age 0–19, 24.3% *vs.* 25.0% in age 20–39, 30.0% *vs.* 29.5% in age 40–59, 21.2% *vs.* 20.5% in age 60–79 and 5.8% *vs.* 5.2% in age ≥80) (7).

In conclusion, our study provides for the first time insight on the epidemiology of both adult and childhood-onset SLE in Italy. The use of highly concordant, multiple sources for the ascertainment of SLE cases assures the accuracy of the study. The long duration of the follow-up allowed us to assess the damage accrual of SLE patients and to show that early diagnosis and wise treatment yielded to a better prognosis for both childhood-onset and adult patients.

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