

Familial Clustering of Systemic Lupus Erythematosus in the Cayman Islands

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ABSTRACT

Objective: To describe the unusual clustering of systemic lupus erythematosus (SLE) in a family from the Cayman Islands.

Method: An observational retrospective study of SLE was done following an index case of mixed connective tissue disease in a 51-year old West Indian woman of African descent. Her two daughters of the same father, who is of Cayman Islands origin, were also diagnosed with SLE. A family tree was subsequently drawn up to 1890 to identify other cases in the same family.

Results: There were 13 cases identified and all occurred between the 6th and the 8th generation. A family tree linked all cases to a man from the Cayman Islands who died in 1890. The nine cases with full medical records showed eight females and one male (8:1). The mean age at diagnosis was 29 years; polyarthrititis occurred in all nine patients (100%), kidney involvement in 6/9 (66.6%), skin rash in 6/9 (66.6%), pleuritis and pericarditis in 6/9 (66.6%) and anaemia in 6/9 (66.6%). The autoantibodies were mainly ANA in all patients (100%) and anti-dsDNA in 8/9 (88.8%).

Conclusion: The unusual extensive familial clustering in this study represents the first to be described in a West Indian population where SLE is most prevalent, and may suggest a genetic predisposition.

Keywords: Familial clustering, systemic lupus erythematosus

Agregación Familiar de Lupus Eritematoso Sistémico en Islas Caimán

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RESUMEN

Objetivo: Describir la agregación inusual de lupus eritematoso sistémico (LES) en una familia de las Islas Caimán.

Método de estudio: Se realizó un estudio retrospectivo observacional de LES a raíz de un caso índice de enfermedad mixta del tejido conectivo en una mujer antillana de 51 años de edad. Sus dos hijas – las dos del mismo padre de origen caimanes – también fueron diagnosticadas con LES. Posteriormente se trazó un árbol genealógico hasta 1890 para identificar otros casos en la misma familia.

Resultados: Se identificaron 13 casos y todos ocurrieron entre la sexta y la octava generación. Un árbol de familia vinculó todos los casos a un hombre de las Islas Caimán que murió en 1890 (Fig. 1). Los nueve casos con historias médicas completas mostraron ocho hembras y un varón (8:1). La edad promedio de diagnóstico fue 29 años. Los nueve pacientes padecían de poliartritis (100%). Asimismo hubo compromiso del riñón 6/9 (66.6%), erupción cutánea en 6/9 (66.6%), pleuritis y pericarditis en 6/9 (66.6%) y anemia en 6 (66.6%). Los autoanticuerpos fueron principalmente ANA en todos los pacientes (100%) y anti-dsDNA en 8/9 (88.8%).

Conclusión: La inusual agregación familiar extensa en este estudio es la primera que se describe en una población antillana donde LES es más frecuente, y puede sugerir una predisposición genética.

Palabras claves: Agregación familiar, lupus eritematoso

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INTRODUCTION

Systemic lupus erythematosus (SLE) is an acquired auto-immune disease characterized by development of autoantibodies against intranuclear antigens, specifically nucleic acids, deoxyribonucleic acid (DNA) and ribonucleic acid (RNA). It presents with widespread inflammation and cellular infiltration of multiple organs, especially joints, kidneys, skin, serous layers, central nervous system and blood elements.

Systemic lupus erythematosus predominantly affects black females with variation in prevalence occurring among different ethnic groups. In the United States of America (USA), the prevalence of SLE is one in 2000 population (50/100 000) with a 9:1 female to male ratio; it is two to four times more frequent in black persons of African ancestry than Caucasians (1).

In a study among women who were recent immigrants in a South London population with diverse ethnicity, the prevalence of SLE was 177/100 000 in Afro-Caribbeans, 110/100 000 in West Africans and 35/100 000 in Europeans (2).

The aetiopathogenesis of SLE is linked to genetic predisposition, environmental exposure and hormonal factors (3).

There are previous studies that described the aggregation of connective tissue diseases in families (4); thus, following a clinical observation, we studied an unusual clustering of SLE in a family from the Cayman Islands, West Indies, as this was not previously described in this region.

SUBJECTS AND METHOD

We did an observational retrospective study of cases of SLE at the Cayman Islands Hospital, Georgetown, Cayman Islands, West Indies, a 125-bed government community hospital serving a diverse ethnic population of 55 000 people. Cayman Islands is made up of Grand Cayman, Cayman Brac and Little Cayman; most of the population lives in Grand Cayman, divided into five districts of Georgetown, East End, North Side, Bodden Town and West Bay.

An index case of mixed connective tissue disease was identified in a 51-year old West Indian woman living in Cayman Islands with three daughters diagnosed with SLE, two of whom had the same father. Based on this observation, an extensive history and interview was done for possible links to other SLE patients seen in the medical unit and specialist clinic of Cayman Islands Hospital. A family tree was subsequently drawn up to 1890 of her two daughters' father's generation (Figure).

The details of history, physical examination and laboratory values of each case were reviewed in paper and electronic records. Clinical information gathered included demographics, initial presentation, complications since diagnosis and autoantibodies.

The medical records of those referred for rheumatologic evaluation in tertiary centres were also reviewed.

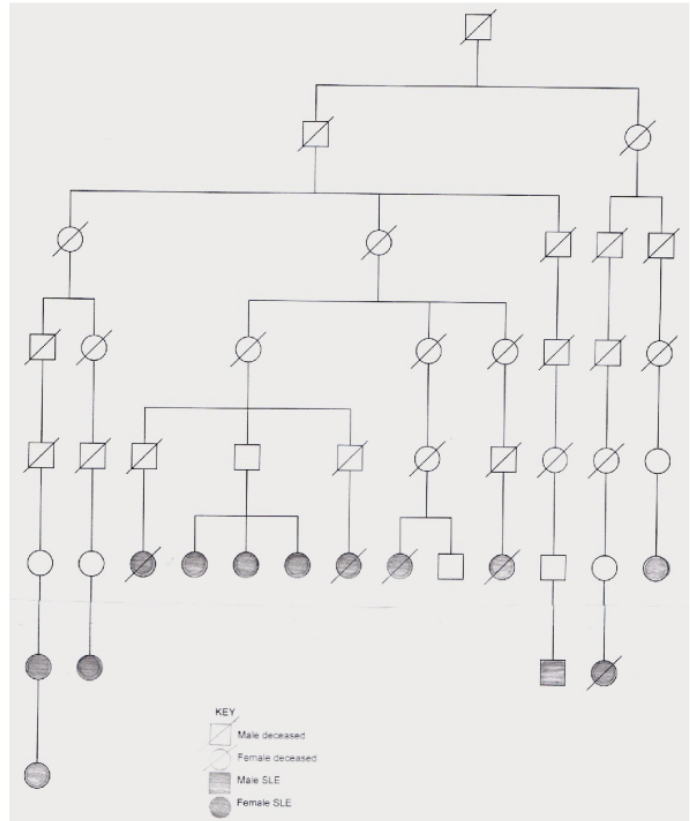


Figure: Family tree illustrating clustering of systemic lupus erythematosus in a single extended family.

Individual interviews were carried out with patients and family members when indicated.

The diagnosis of SLE was made based on the diagnostic criteria of the American Rheumatism Association (5), with the time of fulfilling these criteria considered as age of diagnosis.

RESULTS

There were 13 cases identified; eight are alive and five were dead as at the study period. Full medical records were available for only nine patients and all the cases occurred between the 6th and the 8th generation of this family. A family tree linked all cases to a man that lived in the East End district of Cayman Islands but died in 1890 (Figure). Though the forefathers lived in East End, many of those diagnosed with SLE lived in different districts of the island.

The nine cases reviewed were eight females and one male (8:1). The mean age at diagnosis was 29 years. The most dominant clinical presentation was polyarthritis in all nine patients (100%), kidney involvement ranging from proteinuria, lupus nephritis and end-stage renal disease occurred in 6/9 (66.6%). There was a skin rash in 6/9 (66.6%), mainly photosensitive macula-papular rash, discoid lupus, malar rash, aphthous ulcer and Raynauds changes. Cardio-pulmonary involvement with pleuritis and pericarditis was seen in 6/9 (66.6%), small fibre neuropathy in one

patient, depression in one patient, anaemia in six (66.6%) and thrombocytopenia and leucopenia in one each. The autoantibodies were mainly ANA in all patients (100%) and anti-dsDNA in 8/9 (88.8%).

Of all the nine patients, three were diagnosed with mixed connective tissue disease, had scleroderma features and were more likely to have anti-SSA/SSB, RNP and anti-Sm antibodies.

DISCUSSION

Epidemiologic studies suggest a higher prevalence of SLE in Blacks of African descent. The prevalence of SLE in women aged 15–64 years is three times higher in Blacks of African descent than in the white Caucasian population (2).

The aetiopathogenesis of SLE, though multifactorial, has a strong genetic predisposition. Epidemiologic links showed that familial aggregation of SLE is higher in monozygotic twins than dizygotic twins (6) and generally in families with autoimmune diseases (4). Though the exact mode of inheritance is not known, increased prevalence of SLE was associated with homozygous inheritance of genetic defects that result in deficiency of early compliments C1q, C2 and C4 (7).

Various studies also linked SLE to inheritance of multiple human leukocyte antigen (HLA) *foci* either specific for SLE or in association with multiple autoimmune diseases as the association with single nucleotide polymorphism encoding R620W in the intracellular tyrosine phosphatase gene [PTPN22] (4).

In a review by Flesher *et al*, he described 29 HLA *foci* associated with SLE mostly seen on a region of the short arm of chromosome 6, but the commonest were HLA-DRB1*1501/DQB1*0602 and HLA-DRB1*0301/DQB1*0201 (8). Human leukocyte antigen *foci* on the short arm of chromosome six contain hundreds of genes that regulate inflammation, autoimmune diseases and response to infections.

In an earlier study of HLA haplotypes in Jamaican patients with SLE by Smikle *et al*, the absence of HLA-A9 was significantly observed (9), but in a later study of 70 patients, also in Jamaica, there was association with HLA-DRB3*01/03 and DRB1*13/14 (10).

Our index case is a West Indian woman of African descent married to a man of African descent who is a 5th generation descendant of a man that died in 1890. She had mixed connective tissue disease but her two daughters from the same father, both in the 6th generation, had SLE. Our extensive study of the 6th to 8th generation of the same family showed many first cousins with SLE for a total of 13 cases identified.

The general disease manifestation was consistent with other larger studies, such as the extensive review of 624 patients in the Middle East by Al Arfaj *et al* (11). The female to male distribution was similar. However, our patients presented at an earlier mean age of 29 years compared to 34.3

years in the series by Al Arfaj *et al* (11). Polyarthropathy/polyarthritis was the dominant presentation in all the patients (100%), while kidney involvement as well as pleuritis/pericarditis occurred in 66.6%, unlike 47.9% and 27.4% in the series by Al Arfaj *et al* (11). This may suggest a more aggressive disease in the studied family.

Association with other autoimmune diseases was seen in three patients with anti-SSA/SSB and who had features consistent with scleroderma. A total of five of the patients were dead at the time of study, mostly from end-stage renal failure.

Our cases of SLE did not all live in the same household; hence, they might not have had a common environmental exposure.

There was no HLA haplotype or evaluation for complement deficiency done in our patients, but based on the high incidence of SLE, especially from the 6th generation of this family, we considered that genetic admixture among previous generations may have resulted in genetic changes that predisposed to SLE phenotypes with high penetrance from the 6th generation and a severe disease presentation.

Minor presentations, however, might have occurred in previous generations which were under-diagnosed. The role of genetic admixture in the aetiopathogenesis of SLE was previously studied in a multiethnic community of Northern Trinidad made up 40% African descent, 40% Indian and 15% mixed (12). Using a Bayesian model for population admixture, mixed West African admixture was 0.81 in SLE cases compared with 0.74 in non-SLE controls (12).

Despite established literature on genetic predisposition to SLE and the role of genetic admixture, extensive clustering of SLE in the same family is less described. In an extensive study of clustering of autoimmune diseases in families involving 265 families assembled by the multiple autoimmune disease genetics consortium (MADGC), families had an average of 3.2 other individuals affected, unlike 13 cases that we identified in a single family (4).

Our observational study is the first to describe familial clustering of SLE in the West Indies. Though consistent with other familial clustering previously described worldwide, it appears to be more extensive.

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