A 30-year retrospective study on causes of death in childhood-onset systemic lupus erythematosus in a tertiary care centre in Southern Thailand

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Abstract

Objective

We set out to determine the causes of death in childhood-onset systemic lupus erythematosus (cSLE).

Methods

The medical records of children aged <18 years who were diagnosed with SLE from 1985 to 2016 in the Division of Nephrology, Department of Paediatrics, Faculty of Medicine, Prince of Songkla University, Thailand, were reviewed.

Results

There was a total of 331 patients, 272 girls and 59 boys, of whom 77 (23.3%) died, 28.6% within the first year after diagnosis. Only 29 medical records of the 77 confirmed-death patients were available for evaluation of cause of death; 7 boys and 22 girls, with a mean age at presentation of 10.9±3.1 years. The mean follow-up duration was 4.6±3.7 (range 0.2–12.6) years. The major cause of death was sepsis (n=13 patients with 15 identified organisms, which were Acinetobacter baumannii (9), Escherichia coli (3), Candida albicans (2) and Aspergillosis (1)), followed by acute respiratory distress syndrome (ARDS) (6), severe heart condition (3), acute kidney injury (AKI) (2), chronic kidney disease (CKD) (2) and intracranial haemorrhage (1). Conditions at the time of death were sepsis (25), pneumonia (16), AKI (15), bleeding disorders (11), neurological complications (10), ARDS (10), CKD (4), AKI in addition to CKD (3).

Conclusion

The cause of death in cSLE is usually multi-factorial and it is difficult to assign a single dominant cause. Sepsis was the most common cause of death and, together with sepsis-related organ failure, was the most common condition at the time of death. The most common organism was Acinetobacter baumannii.

Key words

cause of death, childhood-onset, systemic lupus erythematosus, Thai

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Introduction

Systemic lupus erythematosus (SLE) is a rare disease but a common autoimmune disease in children, predominant in females, causing significant morbidity and mortality due to major organ involvement, in worst cases progressing to organ failure and death. SLE patients have an increased immunity against themselves, but SLE itself also decreases their immunity to infection. Immunosuppressive drugs are required to control the auto-immunity, but altogether worsen the patient's immunocompromised status resulting in overwhelming infection and eventually death (1).

In this era of more effective immunosuppressive drugs with fewer side effects, high antibiotic coverage, and advanced palliative care such as renal replacement therapy (RRT) and respiratory support, survival rates in both adult-onset SLE (aSLE) and childhood SLE (cSLE) have improved in the last 10–20 years in both developed and developing countries (2-4).

The causes of SLE-related death need to be understood to guide specific and early treatments in order to improve outcomes. Knowing the preventable causes of death will also improve the survival rate. The causes of death vary depending on organ involvement, activity and duration of disease, and treatment regimens (2). Death in the early stages of disease is usually a consequence of SLE itself due to severe vital organ involvement and/or severe infection. Late deaths may be due to organ damage following chronic inflammation and a consequence of long-term immunosuppressive drug therapy due to side effects (1).

Long-term squeal are also very important. Since survival rates have improved, some problems following chronicity of disease have become more common, for example hyperlipidaemia, chronic hypertension, vascular diseases such as coronary heart disease and cerebrovascular diseases, and malignancy. Improvements in SLE outcomes have also arisen from adjunct therapies such as new anti-hypertensive drugs, and advanced RRT modalities have shown positive results in reducing mortality rates. Angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers (ARB) normally provide good blood pressure control and diminish proteinuria, resulting in the delay of kidney deterioration (5).

cSLE has been reported to be more serious and more fatal than aSLE (2, 6, 7) Due to the scarcity of studies and small sample sizes, differences in the causes of death between cSLE and aSLE are inconclusive. In adults, survival is longer and therefore long-term comorbidities emerge, which ultimately cause death.

The aim of this study was therefore to determine the major causes of death and describe the conditions at the time of death in cSLE at a single tertiary care centre in southern Thailand over a 32-year period.

Methods

The medical records of patients aged <18 years who had been diagnosed with SLE following the American Rheumatism Association criteria between 1985 and 2016, and followed up for at least one year in the Division of Nephrology, Department of Paediatrics, Prince of Songkla University, Thailand, were retrospectively reviewed.

This study was an extension of a study previously published (8). In that study, a consensus of the main cause of death was agreed on by at least two paediatric nephrologists. If the cause was uncertain, the issue was discussed to minimise possible inter-observer error, and the major problem which was obviously uncontrolled and led to death was determined as the main cause of death. In SLE, especially prior to death, patients are usually complicated with several problems altogether leading to death, but also together with various moribund conditions which are more or less under control and less severe than the major cause of death; these conditions were likely contributory to death in the sense that they weakened the overall condition of the patient and made them more susceptible to succumbing to the proximate cause. Both types of complications were documented in this current study.

Acute kidney injury (AKI) was defined on the basis of a sudden increase in serum creatinine concentration to over 177 mole/L (2.0 mg/dL), a serum cre-

Table I. Mean age ± SD at diagnosis and survival time in boys and girls.

	Boys (n=7)	Girls (n=22)	Total (n=29)
Age at diagnosis (yrs) (range)	10.8 ± 2.9 (6.8–14.9)	10.9 ± 3.2 (3.7–14.9)	10.9 ± 3.1 (3.7–14.9)
Survival time (yrs) (range)	2.3 ± 2.0 (0.5–5.9)	5.3 ± 3.8 (0.2–12.6)	4.6 ± 3.7 (0.2–12.6)

Table II. Immunosuppressive treatment in 29 cSLE cases.

Drug	n
Steroid	
Prednisolone	29
Hydrocortisone	24
Methylprednisolone	8
Cyclophosphamide	
Oral	27
Intravenous	11
Azathioprine	26
Mycophenolate mofetil	24

Table III. Major cause of death in 29 cSLE cases.

Cause	n
Sepsis	13
Acute respiratory distress syndrome (ARDS)	6
Congestive heart failure	3
Pneumonia	2
Acute kidney injury (AKI)	2
Chronic kidney disease (CKD)	2
Intracranial haemorrhage	1

atinine concentration that was 2 times the previous or subsequent value and that was also higher than the upper normal value limit for the patient's age (9). The diagnosis of chronic kidney disease (CKD) was based on a serum creatinine concentration that was more than 2-fold higher than the upper normal value limit for the patient's age and which persisted for more than 6 months (6 months was chosen since SLE-induced AKI usually has a longer recovery time than non-SLE induced AKI) (10).

Patients with pre-existing chronic renal impairment, defined as an increase in serum creatinine concentration to over 2.00 mg/dL, with the serum creatinine concentration later returning to the initial level, were deemed to have AKI on top of CKD. End-stage renal disease (ESRD) was defined as CKD stage 5 requiring RRT (11).

Hypertension was defined as a blood pressure greater than the 95th percentile for age and sex (12) or in a patient who was already receiving anti-hypertensive drugs to control their blood pressure.

Statistical analysis was performed using R software, v. 3.4.0 (13). Means and standard deviations (SD) were used to present the results descriptively. The study was approved by the Ethics Committee of the Faculty of Medicine, Prince of Songkla University, Thailand.

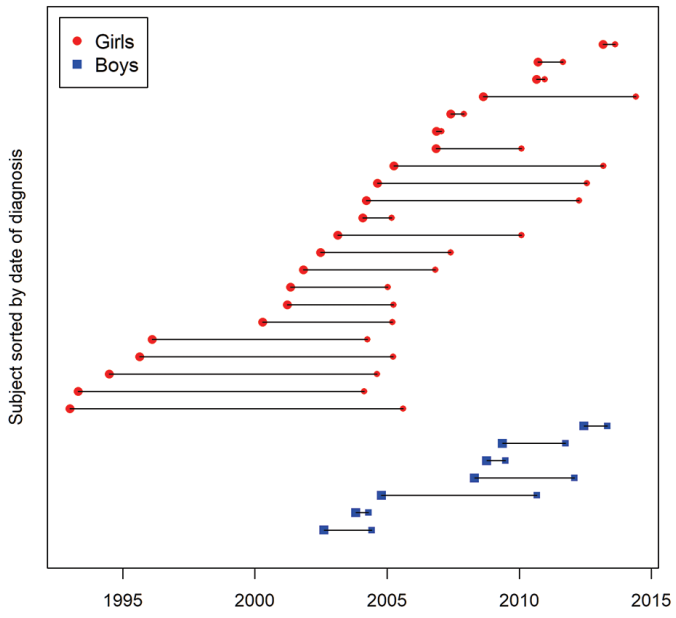

Fig. 1. Survival time of the 29 patients who died stratified by sex. The large symbols represent date of diagnosis; the small symbols represent date of death.

Results

331 children with childhood SLE (cSLE) treated in our institute during the 32-year period were enrolled in the study, 272 girls and 59 boys with a mean age ± SD at presentation to our hospital of 11.5±2.6 years (range 2.3–18.0) (girls 11.7±2.6, boys 11.1±2.6, p=0.13), and with a mean ± SD follow-up duration of 7.0±5.0 years (girls 7.2±5.1, boys 6.0±4.8, p=0.1).

Of the 331 patients, 77 (23.3%) died, 113 were still alive and attending our clinic at the time of review, 36 were lost to follow-up and 105 were referred to adult services after turning 18 (attempts were made to contact these patients without success).

Of those who died, 22 (28.6%) did so within the first year of diagnosis, 8 (10.4%) in the second year, 8 (10.4%) in the third year, and 39 (50.6%) after the 3rd year. The medical records of 48 of the 77 patients who died were not available for evaluation of cause of death because they were either destroyed or because they died in other hospitals or at home. Therefore only 29 medical records of the 77 patients who died (38%) were available for determination of cause of death. Of these, 7 were boys and 22 were girls with a mean age at presentation of 10.9±3.1 years. The mean duration of illness was 4.6±3.7 (Table I).

Table II shows the distribution of chemotherapy drugs prescribed to the 29 children over the course of their disease. Prednisolone was given to all patients but almost all required an additional form of chemotherapy.

As shown in Table III, the major cause of death was sepsis (13) followed by acute respiratory distress syndrome (ARDS) (6), and congestive heart failure (3). Figure 1 shows the survival time (duration between year of SLE diagnosis and death) of all 29 patients, stratified by sex. Girls tended to survive longer than boys.

Table IV shows that the most common moribund conditions at the time of death were sepsis (25), pneumonia (16), and acute kidney injury (15).

Among those who had sepsis at any site, 12 had positive culture from 15 specimens (Table V). *Acinetobacter*

Table IV. Associated moribund conditions at the time of death in 29 cSLE cases†.

Moribund condition	n
Sepsis	25
Pneumonia	16
Acute kidney injury (AKI)	15
Bleeding disorders	11
Neurological complications	10
Acute respiratory distress syndrome (ARDS)	10
Chronic kidney disease (CKD)	4
AKI on top of CKD	3
Miscellaneous	17

†Every patient had more than one condition.

Table V. Distribution of culture results among those with sepsis prior to death.

Organism	n
No growth	10
Acinetobacter. baumannii (once)	4
Acinetobacter baumannii (twice)	2
Acinetobacter baumannii + Candida albicans	1
Escherichia coli	3
Candida albicans	1
Aspergillosis	1

baumannii (*A. baumannii*), was the most common organism (n=9) followed by *Escherichia coli* (n=3), *Candida albicans* (n=2) and Aspergillosis (n=1).

Discussion

The two major causes of cSLE death during the study period were sepsis and ARDS. Often a single specific cause of death was difficult to determine, however we tried our best to reach a consensus. Although our study was conducted in patients with a mean follow-up time of 7.0±5.0 (range 1–28) years, and the survival rates improved dramatically in the last ten years (2007–2016), a useful comparison of the causes of death between the three decades of the study and between genders (there were only 7 boys) could not be made due to the small numbers (8).

In general, immunosuppressive therapy significantly affects infection rates, however, SLE is a multi-organ disease and so therapy was tailored by the clinician depending on the major organ involvement and disease activity (flare). Therefore, a heterogeneity of treatment was given. There was no definitive protocol in terms of drug and duration. Determining the correlation between type of immunosuppressive treatment, treatment duration and infections was not possible since every patient died with sepsis present. Therefore it would be difficult to obtain any significant or meaningful correlation.

When infection occurs in active SLE, balancing the use and/or quantity of immunosuppressive drugs against the risk of infection is a major issue. If less potent immunosuppressive drugs are prescribed, then SLE activity is insufficiently controlled, however, if too aggressive immunosuppressive drugs are prescribed then severe infection can occur and become uncontrolled. In the time immediately prior to death, cSLE patients have usually developed multiple complications. Most fatal conditions originally stem from infection and become complicated with various sepsis-related conditions as well as sepsis in non-SLE patients.

Sepsis was the major cause of death in our study; almost all patients eventually had evidence of sepsis before death, which may be an indication that our treatment using immunosuppressive drugs for cSLE is or has been too aggressive and/or the infections may be poorly controlled.

Whenever patients become critically ill, intubation with an endotracheal tube and respiratory support are required and the association of this treatment with pneumonia or ventilator-associated pneumonia may lead to ARDS, eventually uncontrolled respiratory failure, and death.

Congestive heart failure and renal failure are often concomitant conditions following multi-organ failure, and renal failure was a major cause of death in our study. During the study period, RRT in our institute was limited to patients with ESRD. It is known that RRT can change AKI from a cause of death to a co-morbidity. RRT is actually helpful in renal failure but was not performed often during the study period in our institution due to various limitations. SLE-related AKI and sepsis-related AKI are sometimes indistinguishable, but there is no significant difference in terms of management, including the use of RRT. Half of our patients who died developed AKI during the final stages of disease and the majority of deaths were more likely due to sepsis-induced AKI, rather than SLE-induced AKI, the former usually being found in non-SLE patients.

SLE is a lifelong disease, and a pattern of frequent remissions and relapses is common. Relapse is a warning signal for death either from uncontrolled SLE or from SLE controlled with immunosuppressive drugs, which can lead to infection. Therefore the optimal immunosuppressive drug therapy is a fine balancing act between controlling the disease and the risk of infection. During a remission (inactive) period, patients may be free of medication, or supportive therapies may be required with or without low-dose immunosuppressive drugs for long-standing remission to minimise long-term complications such hyperlipidaemia, hypertension, or CKD.

Two studies in adults, one from North America (124 deaths) (14) and a multicentre study from Europe (68 deaths) (15), showed different proportions of causes of death. In the North American study, infection was the main cause of death (32.3%), followed by thrombosis (16.9%) and active SLE (16.1%). In the study from Europe however, the three main causes of death were approximately equal in proportion: active SLE (26.5%), thrombosis (26.5%), and infection (25.0%).

In a study from Iran the causes of death in cSLE and aSLE were slightly different; lupus nephritis and infection accounted for 90% of all deaths in children, while in adults, they were responsible for only 58% (2). The other causes of death in aSLE were related to vascular disease, particularly alveolar haemorrhage, cerebrovascular accident, and congestive heart failure.

In a study from northern Thailand among 349 aSLE patients, 52 died, 41 (78.8%) within the first year of diagnosis (16). There were 27 (51.9%) infection-related deaths, 18 (34.6%) SLE-related deaths, and 7 (13.4%) died from non-SLE-related conditions. The proportions of causes of death were very different from our cSLE study in southern Thailand, although infection was the major cause of death in both studies.

A study from Taiwan in 1994 among cSLE cases reported only 14 deaths, of which sepsis and pneumonia were the main causes (four each) (17). In a study from Japan in 1997, of 13 children who died, only 11 cases were available for review, and active SLE was the most common cause combined with infection and other causes. Considering the specific causes of death (n=4), infection was reported as the most common cause (18). A more recent study from India in 2016 among cSLE cases reported 24 deaths. Eleven deaths occurred within the first admission and were mostly due to infection and active SLE (90%), while among the later deaths (n=13), infection and/or active SLE were again the major causes of death (53%), with ESRD predominant (31%) (19). Among the 12 infection-induced deaths, surprisingly three had tuberculosis (TB) as the leading contributing factor. However, bacterial sepsis was the leading cause of death (n=7), followed by fungal infection (n=2). (We also reported 3 cSLE patients with TB infection in an earlier study from our institution; the intervals between TB onset and diagnosis were 1, 4 and 6 months due to mimicking symptoms and signs of SLE and TB which resulted in delayed diagnoses; fortunately, no deaths occurred (20)) These three studies in cSLE from Asia are comparable to our Thai study where infection-related deaths predominated.

One important issue to note in cSLE is that improvements in long-term survival rates means that multiple co-morbidities have to be considered at a relatively younger age. The causes of death have changed following the changing of morbidities which are related to adverse effects of therapy and chronic inflammation (21). These include risk of premature atherosclerosis, with a 50-fold increased risk for myocardial infarction in the 3rd and 4th decades of life; osteopenia, osteoporosis and fragility fractures; avascular necrosis of the hip; and recurrent infection secondary to immunosuppressive medications (1). Moreover, SLE also increases the risk of malignancy, particularly lymphoma (22).

Finally, the causes of death in cSLE are different from those in aSLE due to the longer time of disease in adulthood when comorbidities slowly developing over a period of years finally manifest. In our study there were no deaths due to premature arteriosclerosis or malignancy, perhaps because the duration of follow up was not long enough. The main causes of death in the early stages of SLE are infection and SLE-related complications irrespective of age at onset, while in the later stages of aSLE, cardiovascular diseases are more common (1, 3, 23).

The optimal management of SLE is challenging. Based on our years of experience, and the analysis of our current study, we would recommend that infection should be considered whenever an SLE patient does not look well since the symptoms of infection and SLE can be very similar. A septic work-up should be performed and broad spectrum antibiotics should be prescribed immediately without waiting for the fully developed symptoms/signs or confirmation of the culture result. This can avoid treatment delay of actual disease which should improve the chances of survival and result in fewer complications. We also highly recommend that appropriate antibiotics against *A. baumannii* should be given in patients on ventilator support. Striking a balance between aggressive treatment with immunosuppressive drugs and infection control and optimal adjunct therapies is a priority, and ideally, management of SLE should be undertaken by a specialist or at least performed under the supervision of a specialist and tailored to the individual.

Conclusion

The cause of death in cSLE is multifactorial and it is difficult to assign a single dominant cause in most cases. Sepsis remains the most common proximal cause of death, but is also associated with various other complications found in critically ill patients, particularly ARDS which results in respiratory complications, closely followed by infections from endotracheal tube intubation and respiratory support. In the long-term, ESRD is an important cause of death in RRT-limited institutions.

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