MEDICAL PRACTICE

Occasional Survey

Mortality in Systemic Lupus Erythematosus: A 10-Year Review

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British Medical Journal, 1973, 4, 772–774

Summary

During the years 1963-72 33 patients with systemic lupus erythematosus (S.L.E.) died. Of these 30 case records were available for analysis. For the same period 167 patients with S.L.E. were admitted. It was ascertained that of the 30 deaths 22 were directly attributable to the disease itself and 8 were related to complications of therapy. The three commonest causes of death were neurological involvement (11 patients), renal failure (9 patients), and infection (8 patients).

Introduction

In spite of recent advances in the management of systemic lupus erythematosus (S.L.E.) mortality in this disease is still appreciable. In a combined series of 520 cases Dubois and Tuffanelli[1] reported 135 deaths. Similarly Estes and Christian[2] reported 53 deaths among 150 patients. In a local series Tay and Khoo[3] reported a mortality rate of 16%. The commonest cause of death in all these studies was renal. It has been our impression, especially in the past few years, that this pattern is slowly changing, and the present study was undertaken to confirm this impression and to identify other major causes of death.

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Patients and Methods

Death certificates were checked for the years 1963-72. A total of 33 deaths occurred among S.L.E. patients and 30 case records were available for further analysis. For the same period a total of 167 patients with S.L.E. were admitted to the hospital. This is probably an underestimate owing to incomplete record keeping.

All these patients had classical S.L.E. by the criteria laid down by Dubois.[4] Most patients had been followed up for 12 months from the time of diagnosis to death, the mean follow-up period being 19·2 months. All patients received prednisolone 60-30 mg daily. In addition seven patients had cyclophosphamide (Endoxan) 400 mg weekly. Details of therapy were essentially similar to those reported by Seah *et al.*[5]

Clinical manifestations at the time of first admission, response to treatment, events leading to death, and cause of death were studied in detail.

Results

CLINICAL MANIFESTATIONS

The age at onset, initial clinical manifestations, and results of laboratory investigations did not differ significantly from most reported series.[1–3] Altogether 76% of our patients were aged between 15 and 39 years. Fever, rash, and arthritis and arthralgia were the commonest symptom triad. Abnormal urinary findings in the form of significant proteinuria or haematuria or both were present in 50% of the cases. Obvious renal dysfunction as measured by a blood urea of more than 40 mg/100 ml was present in one-third of the cases. Initial neurological manifestations were rare, occurring only in five patients. One patient presented initially with convulsions, one had severe tremor of hands and feet, and three presented with weakness of

lower limbs, one of whom also had urinary retention. These data are summarized in tables I to III.

TABLE I—*Age at Onset of S.L.E. in the 30 Cases*

Age in years ..	10-19	20-29	30-39	40-49	50-59	60-69
No. (%) of cases	7 (23)	10 (33)	6 (20)	5 (17)	1 (3)	1 (3)

TABLE II—*Clinical Manifestations noted on Admission (Percentage of Cases)*

	%		%
Fever	75	Cardiovascular involvement ..	17
Rash	66	Respiratory involvement	17
Arthritis and arthralgia	63	Haematological involvement ..	13
Oedema	33	Neurological involvement ..	17
Nephrotic syndrome ..	17	Alopecia	18

TABLE III—*Results of Laboratory Investigations performed on Admission (Percentage of Cases)*

	%		%
Anaemia < 10 g/100 ml ..	90	R.A. factor	24
Leucoperia < 4,000/mm³ ..	60	Antinuclear factor	92
Thrombocytopenia < 100,000/mm³	43	Blood urea > 40 mg/100 ml	33
E.S.R. > 40 mm in one hour	71	Abnormal urinary findings	50
L.E. cells (criteria for diagnosis)	100		

RESPONSE TO TREATMENT

Response to treatment is difficult to assess accurately in a disease which is so protean in its manifestations and variable in its course. Nevertheless, as a group response was unsatisfactory. Twenty patients required frequent admissions owing to exacerbation of symptoms or complications of therapy. Complete remission was obtained in only one patient. This patient relapsed six months after stopping therapy. Resumption of therapy failed to control the disease. There is some recent evidence to suggest that recurrence of lupus after remission is more malignant and more difficult to treat than the initial episode.[6]

CAUSES OF DEATH

The primary and contributory causes of death in the 30 patients are summarized in table IV. Altogether 22 deaths were directly attributable to the disease process and 8 were related to complications of therapy. The three commonest causes of death were neurological involvement, uraemia, and infection.

TABLE IV—*Primary and Contributory Causes of Death in the 30 Patients with S.L.E.*

	Primary	Contributory
Deaths related to S.L.E. (n = 22)		
Renal failure	9	2
Neurological:		
Generalized convulsions	6	5
Focal lesions/coma	2	1
Subarachnoid haemorrhage	3	
Congestive heart failure	2	3
Severe thrombocytopenia and bleeding ..		2
Deaths related to therapy (n = 8)		
Severe bronchopneumonia	2	2
Miliary tuberculosis	1	1
Septicaemia	2	
Gastroenteritis	2	
Cryptococcal meningitis	1	

Neurological Involvement.—This, in fact, proved the major cause of death in our series. Though only five patients had neurological complaints on their first admission 11 patients excluding those with uraemia had neurological manifestations in their last admission or a short period before death. Disturbance in mentation or consciousness was the commonest feature, occurring in nine patients. A schizophrenic-like picture was seen in three patients, one of whom was admitted to a mental institution and another had attempted suicide because of disturbing hallucinations. Stopping steroid therapy resulted in worsening of the situation. Of the initial five patients two complained of severe tremors of hands and one was treated for Parkinsonism by a general practitioner. Two patients had severe peripheral neuropathy and were confined to bed and one had myelopathy resulting in lower-limb paralysis and urinary retention. Generalized convulsion was the commonest terminal event, occurring in six of these patients. Focal lesions consisting of cranial nerve palsies and hemiparesis occurred in two patients. Three patients died of subarachnoid haemorrhage. Three patients with terminal uraemia and two with bronchopneumonia also had terminal convulsions.

Renal Involvement.—The renal aspect of S.L.E. has been extensively studied.[7-9] In our series of 30 deaths uraemia was the primary cause of death in nine cases and a contributory cause in two. The renal data on these patients at the time of their first admission and shortly before death are given in table V. Analysis of these data show that patients who had a raised urea initially had a poorer prognosis and greater incidence of renal death.

TABLE V—*Renal Data on Patients dying from Various Causes*

Blood Urea (mg/100 ml)		Initial Urinary Findings			Cause of Death
1st Admission	At Death	R.B.C. (/H.P.F.*)	W.B.C. (/H.P.F.*)	Protein	
36	85	2-3	2-3	+	C.N.S. Involvement
34	—	Nil	1-2	Nil	
15	44	Occ.	3-5	+	
24	45	6-10	3-4	0·6 g/l.	
15	68	Occ.	1-2	Nil	
38	42	1-3	2-3	+	
27	40	Occ.	3-5	1 g/l.	
73	20	20-30	20-30	1 g/l.	
27	25	Occ.	2-3	Trace	
39	119	3-4	7-8	+	
18	26	Occ.	Occ.	+	
67	332	20-30	10-15	3·8 g/l.	Uraemia
16	250	Occ.	Occ.	Trace	
180	273	80-100	1-2	+	
63	264	Occ.	3-4	+	
345	350	Occ.	4-6	Trace	
24	345	7-8	2-3	+	
145	465	—	—	—	
122	156	5-10	10-15	+++	
112	165	10-15	2-3	+	
39	60	Occ.	6-8	+	Miliary tuberculosis
31	65	Occ.	10-15	+	Bronchopneumonia
18	91	1-2	6-7	+	Bronchopneumonia
18	70	Nil	2-3	+	Heart failure
23	74	Nil	4-6	Trace	Septicaemia
32	50	80-150	20-30	+	Meningitis
37	88	Nil	1-2	Trace	Septicaemia
66	69	5-6	6-8	+	Gastroenteritis
34	61	Occ.	15-20	+	Gastroenteritis
15	222	Occ.	1-2	Trace	Heart failure

*H.P.F. = High Power Field

Deaths related to Therapy.—In eight patients the fatal outcome seemed related to therapy. Two patients died from bronchopneumonia, two had overwhelming infection, and two died from severe gastroenteritis, dehydration, and electrolyte imbalance. One patient died from miliary tuberculosis and one who died from cryptococcal meningitis also had miliary tuberculosis. The frequent occurrence of severe and often fatal infection in patients with S.L.E. needs further emphasis. This is especially so when powerful drugs like immunosuppressives are used for treatment.

Discussion

Traditionally uraemia has often been quoted as the major cause of death in S.L.E. During the past few years, however, there has been a resurgence of interest in the neurological manifestations

of S.L.E. together with an increasing awareness of their importance. In a recent large prospective study of S.L.E. central nervous involvement including psychosis was seen in 59% of patients and was second only to renal involvement as a cause of death.[2] We were impressed by the high incidence of neurological deaths in our patients. As in neurosyphilis almost any neurological or psychiatric abnormality may occur. Bennett *et al.*[10] reported on a patient in whom psychiatric symptoms preceded other manifestations of S.L.E. for four to five years. Unfortunately a similar clinical picture can occur with advanced renal involvement, hypertension, and therapy with steroids and immunosuppressive drugs. Differentiation between the various groups is often difficult but is essential, since management is different.

Pathogenesis of cerebral lupus is also difficult to explain. Johnson and Richardson,[11] in a recent necropsy study and review of the literature, found that neurological signs could often not be explained by gross or microscopical examination of the brain. They further stated that there was no neuropathological lesion characteristic of S.L.E. and found a true vasculitis in only three of their 24 cases. Atkins *et al.*[12] showed the presence of gammaglobulin deposits in the choroid plexus of two patients with S.L.E. and mental disturbances. Such deposits were not found in the choroid plexus of controls. Immunological and electron microscopical studies suggest that these deposits are immune complexes probably derived from the blood like those deposited in the glomerulus in lupus nephritis. This offers an attractive alternative theory to the pathogenesis of the nervous and mental manifestations of S.L.E., though much work needs to be done.

With regard to diagnosis there is as yet no one test or group of tests that will establish a definite diagnosis of cerebral lupus. Studies on the cerebrospinal fluid from our patients indicated that most of them had raised protein content (>50 mg/100 ml) when compared with lupus patients without neuropsychiatric complaints (see table VI). Pleocytosis has also been reported in the cerebrospinal fluid.[11] Both abnormally low levels of C4 in the spinal fluid of patients with cerebral lupus and increased anti-DNA activity in patients in whom psychosis is the only manifestation of disease activity may prove helpful in the diagnosis and management of cerebral lupus.[13]

Corticosteroids are the mainstay of treatment in cerebral lupus. Dubois[4] advocated massive doses of steroids in its treatment and as much as 2,300 mg of cortisone has been used successfully in treating an acute episode. We have used up to 1,000 mg of hydrocortisone daily in one patient without success. As the renal lesions in S.L.E. become better known and controlled there is an urgent need to apply the same energy to the study of the neurological aspect. It is only then can we hope to reduce further the mortality in S.L.E.

TABLE VI—*C.S.F. Findings in S.L.E. Patients with and without Neurological Involvement*

	Cells (/mm³)	Chloride (mg/100 ml)	Globulin	Glucose (mg/100 ml)	Protein (mg/100 ml)
Neurological involvement	1	680	Trace	75	90
	4	660	+	66	200
	Nil	670	+		140
	8	640	+	50	90
	1	—	+	60	100
	1	750	+	48	180
	1	600	—	47	20
	1	690	—	66	50
No neurological involvement	Nil	745	—	74	40
	Nil	710	—	70	20
	2	670	—	60	30
	1	740	—	68	20
	0	720	—	58	30
	0	680	—	68	30
	0	680	—	82	50

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