Acute Stroke as the first manifestation of Systemic Lupus Erythematosus: A case report and review of the literature

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Summary

Systemic lupus erythematosus (SLE) is an autoimmune, multisystem disease that is characterized by a bewildering array of antibodies. Central nervous system manifestations of SLE are highly diverse and often have major prognostic consequences, accounting for 15% of cases. It is a known cause of 'stroke in the young' especially in the female population. We present the case of a 17-year old female, who presented with acute ischemic stroke as the first presentation of systemic lupus erythematosus. The report is presented to heighten the index of suspicion of SLE, in young patients presenting with acute ischemic stroke, in our environment.

Key words: *Systemic lupus erythematosus, Acute ischemic stroke, Index, Suspicion*.

Introduction

Systemic lupus erythematosus is a chronic, usually lifelong, potentially fatal autoimmune disease characterized by immune dysregulation resulting in the production of antinuclear antibody, generation of circulating immune complexes and activation of the complement system.

SLE is notable for unpredictable exacerbations and remission and a predilection for clinical involvement of the joints, skin, kidneys, brain, serosa, lung, heart and gastrointestinal system. The pathological hallmark of the disease is recurrent widespread and diverse vascular lesions.

SLE is a complex disorder affecting a predominantly young population and shares similarities with human immunodeficiency virus (HIV) infection as regards the propensities for multiple organ involvement, potential life threatening episodes and the need for close monitoring. It is important to note that SLE is not a rare disorder. Although reported at both extremes of life (e.g diagnosed in infants and in the tenth decade of life), it mainly (80%) affects women of childbearing age.

Among children, SLE occurs more commonly in females than in males. In the 60% of SLE patients who experience onset of their disease between puberty and the 4th decade of life, the female to male ratio is 9:1. In addition, women who are exposed to estrogen-containing oral contraceptive pill or hormone replacement therapy have an increased risk. The disorder is more common in blacks (1:250) than in whites (1:1000), however, all ethnic groups are susceptible[1].

In the US, the overall prevalence ranges from 14.6-50.8 cases/100,000. Incidence varies from 1.8-7.6 cases/100,000/year. Internationally, incidence varies with a report of 40 cases/100,000 in northern Europe[1].

The clinical features of SLE are protean and may mimic infectious mononucleosis, lymphoma or other systemic disease. Therefore, the American College of Rheumatology developed criteria to include patients with SLE and exclude those with other disorders[2]. Central nervous system involvement is found in about 15% of cases of SLE[1]. Stroke is among the central nervous system diagnoses in all the large series of patients with SLE[3]. The mean age at the time of stroke is approximately 42 years[4]. Figures on the frequency of stroke in different case series vary from 3% to at least 15%[4]. Stroke was ten times more frequent in 18-44 years old women with SLE than those of similar age without SLE[5]. In the middle age (45-64 years) stroke was approximately two times as frequent and in old age the frequency was slightly below normal [5].

Pathogenetic mechanisms for central nervous system involvement in SLE

The pathogenetic mechanisms can be divided into five categories, each comprising one or several different processes, namely;

Ischemia

The role of ischemia in the causation of disorders of the central nervous system in patients with SLE is undisputable and is generally accepted as prominent. The changes caused by ischemia are in part irreversible and in part reversible or they are entirely reversible. Ischemia is induced by a number of processes leading to transient or permanent narrowing or occlusion of vessels of different type and caliber. Associated factors contributing to ischemia in SLE are as listed below.

(a) Antiphospholipid (APL) antibodies (b) Other antibodies (c) Small vessel vasculopathy (d) Thrombosis of arteries or veins (e) Emboli (f) Atherosclerosis (g) Dissection (h) Vasculitis (i) Vessel spasm (j) Other risk factors present in the general population.

APL antibodies are variously reported to be present in 20-55% or more of patients with SLE[6]. The two classical component of APL antibodies are anticardiolipin antibody (ACL) and lupus anticoagulant (LAC). APL antibodies create a prothrombotic state and there is evidence for the interplay between APL antibodies, thrombin generation and platelet activation[7]. In addition, APL antibodies appear to contribute to the development of atheroma.

Cerebral infarcts in patients with SLE develop significantly more often in LAC-positive than in LAC-negative patients, and also, LAC is a stronger risk factor than immunoglobulin G (IgG) ACL[8]. LAC and ACL are significantly related to arterial (myocardial and cerebral combined) and venous thrombosis in patients with SLE. Screening of other APL components, e.g. anti-beta2-glycoprotein1 did not provide additional information[9]. Protein S levels tend to be decreased in patients with SLE and a relationship with cerebral artery thrombosis and ischemic stroke was not established[10].

There is good evidence of premature atherosclerosis of extracranial or intracranial arteries in SLE and that SLE induces a state of dyslipoproteinemia and is thus likely to contribute to premature atherosclerosis[11]. The risk factors for premature atherosclerosis are as shown below;

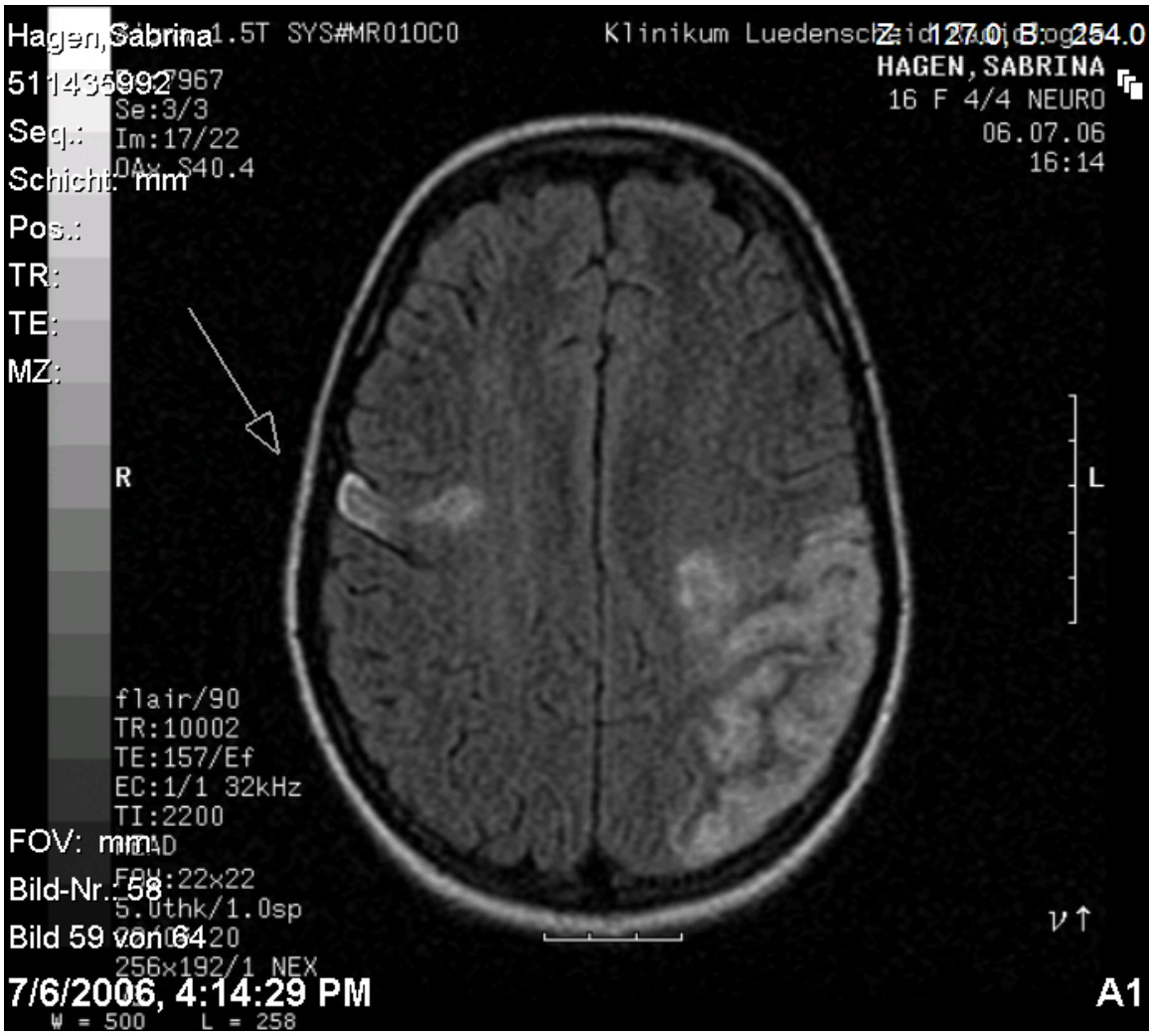
(a) Chronic inflammatory processes and immunological factors including APL (b) Dyslipidemia (c) Renal disease (d) Treatment with corticosteroids (e) Other risk factors for atherosclerosis in the general population.

Other associated ischemic pathogenetic mechanisms include; cerebral small vessel angiopathy, thrombosis of cerebral arteries and veins, cerebral embolism, dissection of arterial wall, cerebral vasculitis and spasm of cerebral arteries. The incidence of various types of intracranial or spinal hemorrhages is also increased in SLE.
Essentially, the causes of stroke in SLE include large artery occlusion, intracerebral hemorrhage and subarachnoid hemorrhage[12]. In two large studies of stroke in SLE, 6 of 27 patients had hemorrhages, three of them had intracerebral hemorrhage and three had subarachnoid hemorrhage[4]. Stroke due to vasculitis is probably rare. The ischemic stroke in SLE is attributed in part to circulating APL antibodies, premature atherosclerosis and other causes. The risk of intracranial hemorrhage is increased by changes in the vessel walls induced by hypertension, corticosteroids or SLE and thrombocytopenia[13].
The incidence of transient ischemic attack in SLE is high and an embolic source is thought to be responsible[4]. Patients with SLE are at increased risk of stroke at a relatively young age[13] and brain stem and cerebellar infarcts are commoner amongst adults and adolescent with SLE compared to non-SLE patients[14].

Case Report

A 17 year-old female who was hitherto enjoying a good state of health until in the early morning hours of 28-06-06, when she developed sudden onset of weakness of the right upper and lower limbs. There was associated deviation of the angle of the mouth to the left side. She also had inability to speak, but there was no headache, no loss of consciousness and no preceding history suggestive of cardiac decompensation. She was not a known migraineur and neither does she take oral contraceptive pill.
Essential findings on examination revealed moderate pallor and marked lethargy. She was afebrile and anicteric. Cardiovascular system examination revealed tachycardia and normal volume, regular pulse. All peripheral pulses were palpable; the jugular venous pressure was not elevated. The precordium was normoactive, only the first and second heart sounds were heard, with no murmur.
Chest and abdominal examinations revealed normal findings.
Central nervous system examination revealed a drowsy patient. Both pupils were of normal and equal sizes with brisk reaction to light. She had expressive dysphasia and right facial nerve paresis, upper motor neuron type. She equally had right spastic hemiparesis with extensor plantar response (positive Babinski sign) on the right. Meningeal signs were absent.
Results of various investigations carried out on her were as shown in table 2.
Plain chest X-ray revealed normal findings in both lung fields. Transoesophageal echocardiography revealed thrombotic vegetations on the mitral valve. Magnetic resonance imaging (figures 1) confirmed left parietal and right temporal ischemic lesions. Her electrocardiographic tracing was normal. She was admitted into the stroke unit and managed (in addition to all other routine management), with intravenous methylprednisolone infusion, intravenous cyclophosphamide, low dose aspirin and anticoagulant heparin. She made steady improvement, becoming fully conscious and the limb paresis progressively got better.

Figure 1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Results of investigations: Table 1

Hematology:	Complete Blood Count	3.7/mm3	(4.5 – 10.1)
	Neutrophils	40%	(41.2 - 75.5)
	Lymphocytes	16%	(25 – 40)
	Haemoglobin	6.6g/dl	(11.2 – 14.8)
	Packed cell volume	0.19	(0.340 – 0.407)
	Reticulocyte count	7.2%	(0.8 – 2.2)
	Platelets count	94/mm3	(185 – 335)
	PT-INR	1.18	(2.5 – 4.5)
	APTT	13.6sec	(30 – 40)
	C-reactive protein	Normal	(<0.5mg/dl)
	Haptoglobulin	<0.06g/L	(0.3 – 2.0)
Biochemistry:	Serum sodium	141mmol/l	(130 – 145)
	Potassium	4.45mmol/l	(3.6 – 4.8)
	Chloride	110mmol/l	(95 – 105)
	Creatinine	1.0mg/dL	(0.5 – 1.0)
	Urea	79mg/dl	(10 – 50)
	AST	26U/L	(10 – 35)
	ALT	9U/L	(5 – 30)
	LDH	440U/L	(135 – 214)
	CK	28U/L	(<167)
	Bilirubin	0.8mg/dl	(<1.1)
	Glucose	107mg/dl	(70 – 110)
	Total cholesterol	153mg/dl	(<200)
	Triglyceride	94mg/dl	(<200)
	LDL	96mg/dl	(<150)
	HDL	38mg/dl	(>45)
	Homocysteine	6.94umol/l	(5 – 15)
Urinary:	Creatinine clearance	52ml/min	(70 – 125)
	Urinary RBC's	235/Ul	
	24-hr urinary protein	2.57g/24hr	(0 – 0.15)
	Urine WBC	Negative	
Serology:	Cardiolipin-IgG	80U/ml	(<7)
	Cardiolipin-IgM	340U/ml	(<4)
	ANA- positive	1:2560	
	Lupus anticoagulant ab	2.20	
	DsDNA-ab	313/ml	(<100)
	Protein C ratio	0.82	(0.8 – 1.8)
Bacteriology:	Blood culture (3 samples)	No growth	

Discussion

The patient presented fulfilled 6 out of the 11 ACR diagnostic criteria[2] for systemic lupus erythematosus namely;

a) Central nervous system manifestations with acute ischemic stroke.
b) Cardiovascular manifestation with non-bacteria thrombotic endocarditis (culture negative).
c) Renal involvement with reduced creatinine clearance of 52ml/min, proteinuria and hematuria.
d) Hematological manifestations such as, leucopenia-neutropenia, thrombocytopenia, hemolytic anemia (elevated LDH, reduced haptoglobulin, anemia).
e) Immunological manifestations such as, presence of APL antibodies, dsDNA, antiSM antibodies, coupled with a very high ANA titer.

Therefore, the diagnosis of systemic lupus erythematosus was firmly established in the patient.

The patient presented with bilateral cerebral infarcts, which agrees with the finding of Futrel and milikan[1], who found multiple cerebral infarcts in 9 (64%) of 14 stroke patients series with SLE studied.

The risk factors for stroke identified in this patient were; cardiac valvular vegetation (non-bacterial endocarditis) and antiphospholipid antibody (presence of ACL antibody and LAC). This also support the findings of Futrell and Millikan[1] who found cardio-embolic embolus or an antibody-mediated hypercoagulable state as the most frequent etiology in their series of stroke in SLE patients. APL antibodies and Libmann sacks endocarditis are associated with occlusive cerebrovascular disease.

In Kitagawa et al series[15], cerebrovascular involvement in SLE was found in 5.6% of cases, out of which cerebral infarct constituted 3.4% of cases, confirming that ischemic stroke is commoner than hemorrhagic stroke in SLE.

Reduced level of protein S and C, which is a prothrombotic state, commonly occurs in SLE patients and this agrees with what we found in our patient; however, a relationship with cerebral artery thrombosis and ischemic stroke has not been established.

The specific treatment modalities for ischemic stroke in SLE are essentially the use of intravenous methyl prednisolone, cytotoxic immunosuppressives, such as intravenous cyclophosphamide, azathioprine, as well as low dose aspirin and anticoagulant.

Although the neurological manifestations have been consistently described, there is an excess of stroke seen in SLE[16], especially, in those cases with anticardiolipin antibodies.

Conclusion

SLE should be sought for in every young especially, female patients that present with acute ischemic stroke. The increasing evidence for the contributing role of other cardiovascular risk factors, including hypertension, hyperlipidemia and inflammatory markers, to the epidemiology of stroke in SLE calls for the full panoply of stroke intervention and prevention strategies as it applies in atherosclerotic stroke.

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