NEUROLOGICAL COMPLICATIONS OF CONNECTIVE TISSUE AND OTHER "COLLAGEN-VASCULAR" DISEASES

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NEUROLOGICAL COMPLICATIONS OF CONNECTIVE TISSUE AND OTHER "COLLAGEN-VASCULAR" DISEASES

I. VASCULITIS

II. CONNECTIVE TISSUE DISEASES

A. Systemic Lupus Erythematosus

B. Rheumatoid Arthritis

C. Polyarteritis Nodosa

D. Progressive Systemic Sclerosis } Nervous System

E. Dermatomyositis and Polymyositis } Rarely Involved

F. Rheumatic Fever

III. GRANULOMATOUS VASCULITIS

A. Wegener's Granulomatosis

B. Granulomatous Angiitis

IV. GIANT CELL ARTERITIS

A. Temporal Arteritis and Polymyalgia Rheumatica

B. Takayasu's Disease

V. BEHCET'S SYNDROME

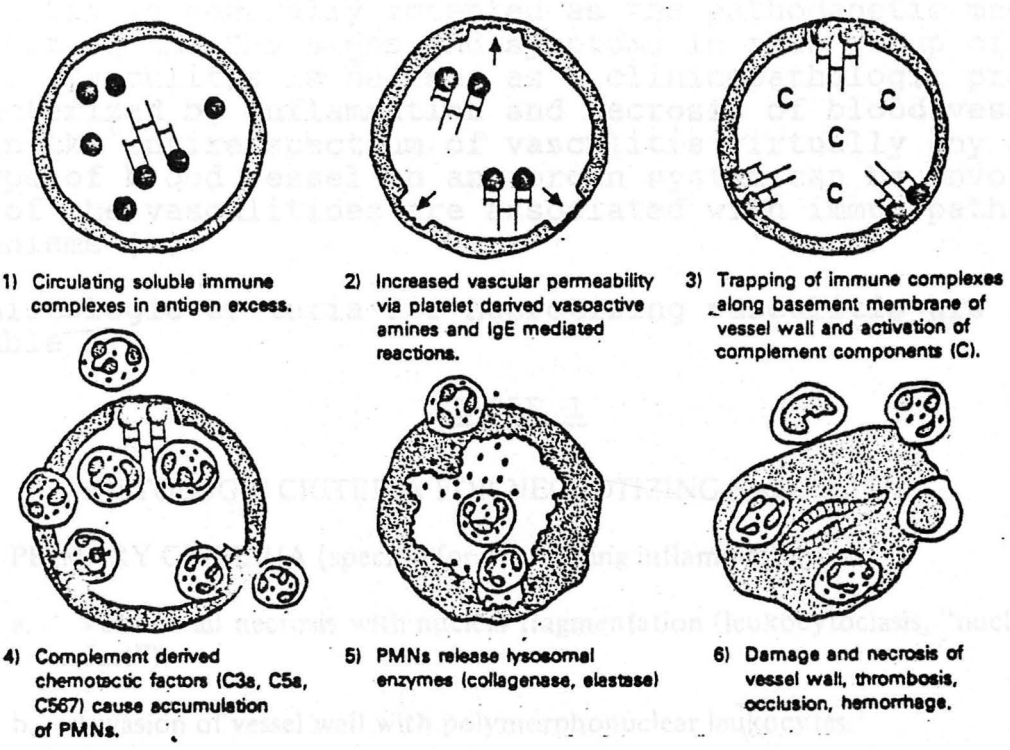
VI. LYMPHOMATOID GRANULOMATOSIS

VII. LEUCOCYTOCLASTIC VASCULITIS

INTRODUCTION

As listed in the outline, a large number of connective tissue diseases and other types of "collagen-vascular" diseases are associated with neurologic complications. With the exception of rheumatoid arthritis, in which many of the manifestations result from nerve compression due to the arthritis or nodules, most of the neurological complications seen in these diseases appear to be related primarily to vasculitis or other types of vascular involvement.

Figure 1



1) Circulating soluble immune complexes in antigen excess.

2) Increased vascular permeability via platelet derived vasoactive amines and IgE mediated reactions.

3) Trapping of immune complexes along basement membrane of vessel wall and activation of complement components (C).

4) Complement derived chemotactic factors (C3a, C5a, C567) cause accumulation of PMNs.

5) PMNs release lysosomal enzymes (collagenase, elastase)

6) Damage and necrosis of vessel wall, thrombosis, occlusion, hemorrhage.

(Ref. 3)

In the immune complex type of vasculitis (Fig. 1), soluble immune complexes formed in antigen excess circulate and are ultimately deposited in blood vessel walls (4) related to increased vascular permeability at the site of deposition. The increased vascular permeability results from the action of vasoactive amines that are derived from platelets and IgE-triggered reactions. The immune complexes are trapped and complement components are activated, some of which are chemotactic for poly-morphonuclear leukocytes (PMNs) that then migrate in and around the vessel wall. These cells then release their lysosomal enzymes that damage the blood vessel wall. Such a mechanism would best explain SLE and RA vasculitis.

The other major immunopathogenic type of vasculitis is shown in Fig. 2.

I. Vasculitis

Vasculitis is generally accepted as the pathogenetic mechanism for most of the CNS signs and symptoms in this group of diseases. Vasculitis is defined as a clinicopathologic process characterized by inflammation and necrosis of blood vessels. Within the entire spectrum of vasculitis virtually any size or type of blood vessel in any organ system can be involved. Most of the vasculitides are associated with immunopathogenic mechanisms (1).

The histologic criteria for necrotizing vasculitis are shown in Table 1.

TABLE 1

HISTOLOGIC CRITERIA FOR NECROTIZING VASCULITIS

I. PRIMARY CRITERIA (specific for necrotizing inflammation)

   a. Vessel wall necrosis with nuclear fragmentation (leukocytoclasis, "nuclear dust").

   b. Invasion of vessel wall with polymorphonuclear leukocytes.

   c. Fibrinoid deposits in or adjacent to the vessel wall.

II. SECONDARY CRITERIA (non-specific vessel injury)

   a. Thrombosis of the vessel.

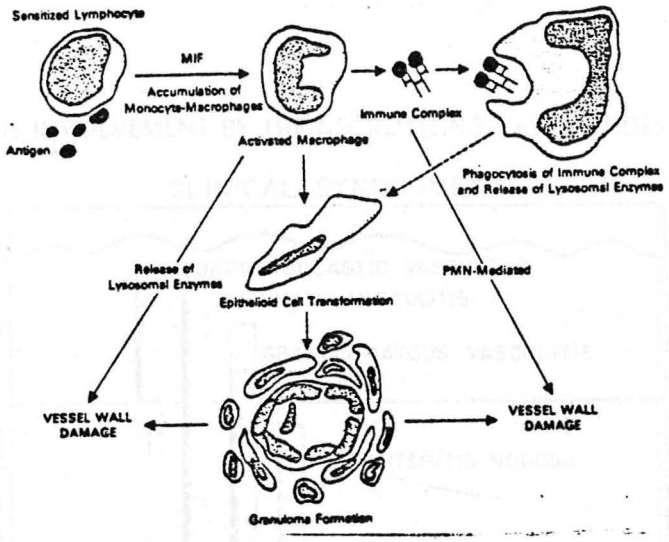
   b. Perivascular hemorrhage.

   c. Chronic granulomatous inflammation and fibrosis in perivascular areas.

(From Reference 2)

Two basic immunopathogenic mechanisms which have been suggested by Fauci et al (3) include (1) immune complex vasculitis. (Fig. 1), and (2) cell-mediated immune reactivity.

Figure 2



Cell-mediated immune mechanisms of vasculitis.

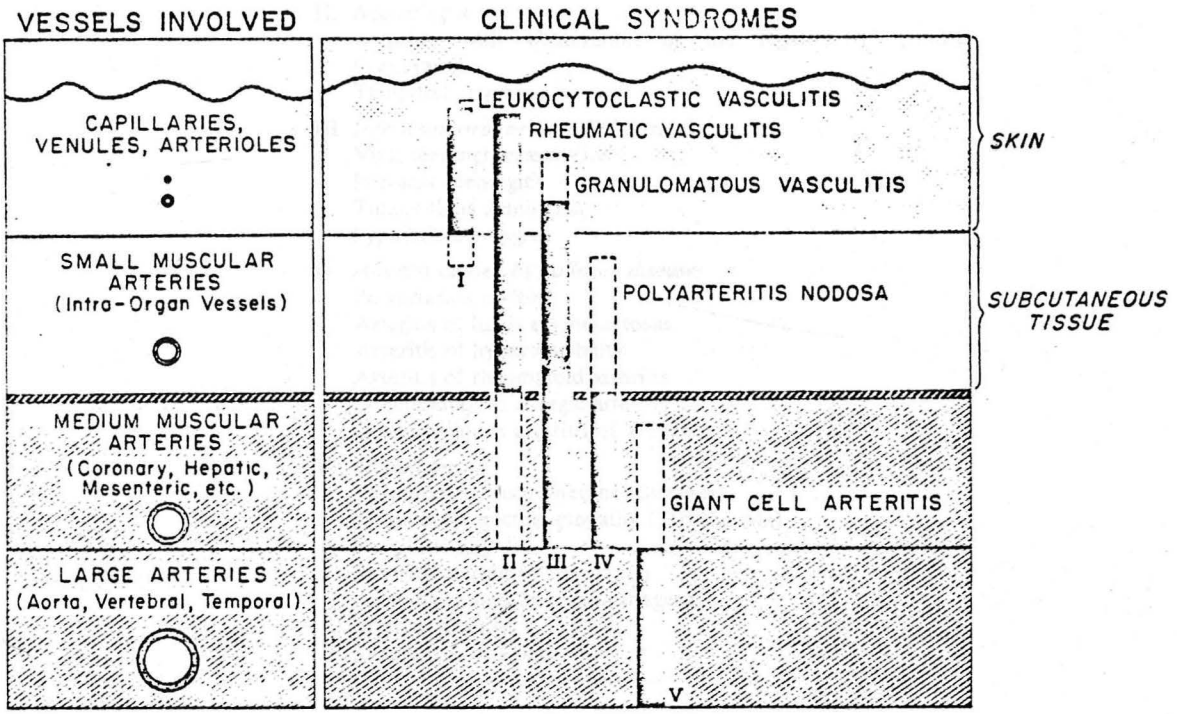
(From Ref. 3)

In this postulated cell-mediated type of vascular injury, sensitized lymphocytes react with antigen and most likely release lymphokines. Some of these soluble products, such as macrophage migration inhibitory factor (MIF), result in the recruitment of monocytes to the immune reaction site. These cells may transform into activated macrophages that can release lysosomal enzymes capable of damaging blood vessel walls. In addition, these cells may further transform into epithelioid cells and ultimately participate in granuloma formation. When this takes place in and around blood vessels, granulomatous vasculitis occurs. It is also possible that macrophages phagocytose or are triggered by immune complexes. Transformation to epithelioid cells may then occur with resulting granuloma formation, or release of lysosomal enzymes (3). Such a mechanism may be of importance in granulomatous vasculitides.

A very helpful diagram which differentiates the different sizes of vessels involved in the various disorders has been published by Drs. Gilliam and Smiley (5,6) (Fig. 3).

Figure 3

THE LEVEL OF CUTANEOUS INVOLVEMENT BY THE NECROTIZING VASCULITIDES



(From Ref. 5)

In this diagram the solid bars represent the size of vessel most commonly involved while the dashed bar represents vessels that occasionally may be involved. Thus leukocytoclastic vasculitis affects primarily capillaries, venules and arterioles. Rheumatic disease-associated conditions, e.g. SLE and RA, affect primarily small arteries as well as capillaries, venules and arterioles. Granulomatous vasculitides and PAN affects small and medium arteries and giant cell arteritis affects primarily the large arteries.

A classification of the various causes of cerebral angiitis (arteritis) has been suggested (Table 2).

TABLE 2

Classification of cerebral angiitis

I. *Arteriopathy and arteritis caused by degeneration*
- Arteriolosclerosis: hyalin, hyperplastic and arteriolonecrosis
- Arteriosclerosis: atheromatosis and atherothrombosis
- Calcifying sclerosis of the tunica media (Mönckeberg)

II. *Necrosing arteritis*
- Arteritis with obliteration of the supra-aortic trunks (Takayasu)
- Temporal arteritis

III. *Infectious viral or bacterial arteritis*
- Viral meningoencephalitis
- Purulent meningitis
- Tuberculous meningitis
- Syphilitic meningitis

IV. *Arteritis caused by collagen diseases*
- Polyarteritis nodosa
- Arteritis of lupus erythematosus
- Arteritis of hypersensibility
- Arteritis of rheumatoid arthritis
- Granulomatous allergic arteritis
- Granulomatous arteritis of Wegener

V. *Miscellaneous*
- Thromboangiitis obliterans (Buerger)
- Thrombotic microangiopathy (Moschowitz)
- Neoplasic angiitis
- Arteritis caused by irradiation
- Arteritis caused by chemical agents
- Mycotic arteritis
- Sarcoidosis of Boeck

(From Ref. 7)

As shown in this Table, a variety of condtions are associated with cerebral vasculitis. For this Grand Rounds, however, only those vasculitides associated with connective tissue diseases and other so-called "collagen-vascular" diseases will be discussed.

References - Vasculitis

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5. Gilliam, J. N. and Smiley, J. D. Cutaneous Necrotizing Vasculitis and Related Disorders. Ann Allerg 37:No. 3, 328-339, 1976.

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II. Connective Tissue Diseases

A. Systemic Lupus Erythematosus

1. Pathologic Findings

The first major discussion of pathology of CNS SLE was attempted by Johnson and Richardson in 1968 (1). They critically reviewed the neuropathological material and attempted a correlation of the clinical and pathological findings. They studied 24 patients whose neurological manifestations are shown in Table 3.

TABLE 3

Neurologic Manifestations in 24 Patients with SLE

	No. Patients	Percent
Seizures	13*	54
Cranial nerve disorders	10	42
Hemiparesis	3	12
Paraparesis	1	4
Peripheral neuropathy	2	8
Mental disorders	8	33

* One case had idiopathic epilepsy.

(From Reference 1)

The highest percentage of manifestations included seizures (54%) and cranial nerve disorders (42%).

A summary of the neurological and neuropathological findings in each of the 24 patients is shown in Table 4.

TABLE 4

Summary of Clinical-Pathological Findings

Case No.	Age and sex	Duration of disease in years	Neurological findings		Neuropathological findings							
			Interval between onset of neurological disease and death	Signs and symptoms (Mode of death in parentheses if non-neurologic)	Gross	Microscopic						
						Vasculitis	Vascular necrosis	Fibrin thrombi	Micro-infarcts	Microhemorrhages	Perivascular microglia	Perivascular infiltrates
1	27F	10	9 yrs.	Numerous transient signs; terminal corticospinal tract signs with death in status epilepticus	Old infarct, left caudatoputaminal junction; many small acute hemorrhages	0	+	+	+	+	+	0[1]
2	49F	6	6 yrs.	Recurrent focal seizures and terminal intracerebral hemorrhage	Fresh hemorrhage, right parietal lobe; old hemorrhage, right parietal-occipital area	+	0	0	0	0	+	+[1,3]
3	23F	8	7 yrs.	Transient left oculomotor nerve palsy (heart failure)	None	0	0	0	0	0	+	0[1]
4	43F	1.5	1 yr.	Paraplegia and psychosis (pulmonary embolus)	Old infarct, genu of left internal capsule. Irregular discoloration of spinal cord	0	0	0	+	0	0	0[1]
5	17M	2	9 mo.	Peripheral neuropathy and psychosis (pneumonia)	Mild dilatation of ventricles	0	0	0	0	0	+	+[1]
6	38F	5	5 yrs.	Single seizure, transient 6th nerve palsy, and episode of hypothermia, bradycardia, and hypotension (pneumonia)	None	0	0	0	+	0	0	0[1]
7	24F	4	2 yrs.	Multiple psychotic episodes, corticospinal tract signs, and transient loss of convergence (septicemia)	None	0	0	0	+	0	+	0[1]
8	34F	4	6 wks.	Severe psychosis and seizures (septicemia)	Thickened leptomeninges	0	0	0	+	0	+	0
9	24F	7	4 days	Deafness followed by coma with ophthalmoplegia and bilateral corticospinal tract signs	Large right frontal intracerebral hemorrhage and many small hemorrhages in corpus callosum	0	+	0	+	+	+	0[2,3]
10	16F	0.6	5 days	Sudden scotomata with retinal hemorrhages and death in status epilepticus	Many 1-3 mm. hemorrhages in lower cortical layers	+	+	+	+	+	0	0[1]
11	18F	2	6 wks.	Recurrent seizures with residual left hyperreflexia. Coma during terminal 3 wks. with papilledema, hemiplegia, and a transient right-sided tremor	Large right fronto-parietal intracerebral hemorrhage	+	0	0	+	0	0	0[4]
12	25F	1.5	12 days	Right internuclear ophthalmoplegia and skew deviation. Terminal seizure. (pericardial effusion and pulmonary edema)	Infarct in left basis pontis	0	0	0	+	0	+	0[5]
13	24F	2	3 wks.	Stupor with dysarthria followed by right supranuclear facial palsy and coma	Multiple hemorrhages in pons extending into midbrain	0	+	+	+	+	+	0[4]

(From Reference 1)

TABLE 4 (Continued)

Case No.	Age and sex	Duration of disease in years	Neurological findings: Interval between onset of neurological disease and death	Neurological findings: Signs and symptoms (Mode of death in parentheses if non-neurologic)	Neuropathological findings: Gross	Neuropathological findings: Microscopic: Vasculitis	Vascular necrosis	Fibrin thrombi	Micro-infarcts	Microhemorrhages	Perivascular microglia	Perivascular infiltrates
14	24F	1	6 wks.	Recurrent Jacksonian seizures, weakness in right leg, and right hyperreflexia (uremia)	Small infarct in left frontal lobe	0	0	0	+	+	+	0
15	34F	2	4 mo.	Schizophrenic reaction unassociated with treatment lasting 3 days (uremia)	None	0	+	0	+	+	+	0
16	23F	2	1 yr.	Single left-sided seizure (heart failure)	None	0	0	0	+	0	0	+
17	21F	0.3	1 day	Two seizures (uremia)	None	0	0	0	+	0	0	0
18	18F	2	1 day	Terminal seizure (pneumonia)	None	0	0	0	+	0	0	0
19	26F	0.2		None (pneumonia)	Recent small subpial hemorrhage	0	0	0	+	0	0	0
20	29F	0.6		None (pneumonia)	None	0	0	0	+	0	0	0
21	33F	1		None (heart failure)	None	0	0	0	0	0	0	0
22	40F	1.5		None (uremia)	None	0	0	0	0	0	0	0
23	23M	2		None (pneumonia)	None	0	0	0	0	0	0	0
24	29F	5		None (constrictive pericarditis and pneumonia)	None	0	0	0	0	0	0	0

[1] Details of clinical disease and pathological findings in text.
[2] Hemorrhages occurred in absence of hypertension or thrombocytopenia.
[3] Typical brain purpura was found in addition to many microinfarcts in cortex, cerebellum, and brainstem.
[4] Vasculitis found in a single vessel in addition to non-inflammatory microinfarcts in cortex, cerebellum, brainstem, and spinal cord.
[5] One area of infarction involved right medial longitudinal fasciculus.
[6] Hemorrhages occurred in presence of hypertension, thrombocytopenia, and uremia, but old microinfarcts were also found in the spinal cord.

(From Reference 1)

Significant gross abnormalities were found in only 10 of the 24 patients in this study. These included 3 cases with large intracerebral hemorrhages, one with multiple pontine hemorrhages, two cases with multiple small fresh hemorrhages, four with small areas of old infarction, and one with a small subpial hemorrhage.

Lesions were far more common microscopically; microinfarcts or increased pericapillary microglia were found in 20 of the 24 cases. Microinfarcts often consisted only of a small cluster of pleomorphic histiocytes, the so-called microglial nodules. The regular occurrence of minute infarcts suggested to these authors that CNS-SLE is, in most cases, a vascular disease involving very small vessels, especially the small arterioles or capillaries.

It is of interest that true vasculitis with inflammatory cells within the vessel wall was found in only 3 of the 24 cases in this study. Polymorphonuclear leukocytes were seen only occasionally within vessel walls. Destructive changes in the walls of small cerebral vessels were frequently found and described as fibrinoid degeneration. The lesions tended to be focal and scattered and varied in age from region to region, rather than appearing to have occurred simultaneously in many localities.

These authors concluded that the localization of vascular changes and resultant microinfarcts in the cerebral cortex and brainstem correlated well with the clinical signs in most cases and that the small size of the infarcts probably accounted for the transient nature of some neurological signs.

A much more recent study has been published by Ellis and Verity (2). The purpose of their study was twofold: (1) to describe the spectrum of pathology in CNS SLE and, (2) to document the changing pattern of neuropathologic disease during the last 20 years. The 57 patients that they studied had been followed for periods of from 1 week to 11 years.

The gross and microscopic lesions seen in these 57 patients were divided into the 5 major pathologic patterns shown in Table 5.

TABLE 5

Incidence of Major Neuropathologic Findings in 57 Autopsied Cases of SLE

Vasculopathy	37 (65%)
Infarction	25 (44%)
Hemorrhage	24 (42%)
Infection	16 (28%)
Miscellaneous	
Transverse myelopathy	1
Progressive multifocal leukoencephalopathy	1
Hodgkin disease	1

(From Reference 2)

Vasculopathy, infarction, hemorrhage and infection comprised the major findings. The types of vascular lesions found are shown in Table 6.

TABLE 6

Incidence and Manifestations of Vascular Lesions in CNS SLE

	1955–1965 (23 Cases)	1966–1976 (34 Cases)	Total (57 Cases)	p
Vascular hyalinization	5 (22%)	26 (76%)	31 (54%)	0.01
Perivascular inflammation (without obvious infection)	6 (26%)	10 (29%)	16 (28%)	—
Endothelial proliferation	3 (13%)	9 (26%)	12 (21%)	—
Thrombosis	1 (4%)	3 (9%)	4 (7%)	—
Vasculitis (without infection)	2 (9%)	2 (6%)	4 (7%)	—
Total (cases)	14 (61%)	26 (76%)	37 (65%)	

(From Reference 2)

Vascular hyalinization, especially of meningeal, subcortical, and cortical arterioles, was common and occurred in 54% of the cases with a significant increase in the period 1966-1976. Perivascular lymphocytosis was found in 28%. Endothelial proliferation was seen in 21%. Thrombosis was uncommon, and, as mentioned in the Johnson-Richardson series, true vasculitis was infrequent (7%).

The incidence of infarction is shown in Table 7.

TABLE 7

Incidence of Infarcts in CNS SLE

	1955–1965 (23 Cases)	1966–1976 (34 Cases)	Total (57 Cases)	p
Microinfarcts	6 (26%)	14 (41%)	20 (35%)	—
Large infarcts	2 (9%)	5 (15%)	7 (12%)	—
Total (cases)	7 (30%)	18 (53%)	25 (44%)	0.01

(From Reference 2)

Both microinfarcts and larger infarcts (greater 1 cm in dimension) increased in incidence from 1955-1965 (30%) to 1966-1976 (53%). Most microinfarcts were in the superficial convexity of the cortex and were seen most commonly in the parietal and temporal pole convexities, within the pons. They were occasionally seen in the brain stem or pallidus. Larger infarcts were usually found in the distribution of the middle cerebral artery.

Prominent hemorrhage was noted in 24 cases (42%) (Table 8).

TABLE 8

Incidence of Hemorrhage in CNS SLE

	1955-1965 (23 Cases)	1966-1976 (34 Cases)	Total (57 Cases)	p
Subarachnoid hemorrhage*	6 (26%)	11 (32%)	17 (30%)	—
Microhemorrhages	5 (22%)	6 (18%)	11 (19%)	—
Intracerebral hemorrhage	2 (9%)	4 (12%)	6 (10%)	—
Subdural hemorrhage	—	2 (6%)	2 (4%)	
Total (cases)	10 (43%)	14 (41%)	24 (42%)	—

* Included are cases showing prominent meningeal hemosiderin depositions.

(From Reference 2)

Subarachnoid hemorrhage was present in 30% of cases. Petechial microhemorrhages were present in 19%. Intracerebral hemorrhage occurred in 6 cases and subdural hemorrhage was present in only 2 cases.

The incidence of CNS infection confirmed at necropsy increased significantly from 1955-1965 (17%) to 1966-1976 (35%). The incidence of meningitis, in particular, also significantly increased from 9% to 26%. (Table 9).

TABLE 9

Manifestation of CNS Infection in CNS SLE

	1955-1965 (23 Cases)	1966-1976 (34 Cases)	Total (57 Cases)	p
Meningitis	2 (9%)	9 (26%)	10 (18%)	0.01
Perivascular inflammation with infection	2 (9%)	6 (17%)	8 (14%)	—
Septic hemorrhages	1 (4%)	2 (6%)	3 (5%)	—
Vasculitis with infection	1 (4%)	2 (6%)	3 (5%)	—
Focal cerebritis	0 (0%)	2 (6%)	2 (3%)	—
Total (cases)	4 (17%)	12 (35%)	16 (28%)	0.03

(From Reference 2)

As shown in Table 10 the increased incidence of meningitis was due primarily to bacterial and mycotic infections.

TABLE 10

Organisms Isolated in Cases of CNS SLE Associated With Autopsy Evidence of Meningitis

	1955-1965	1966-1976
"Aseptic"	1	2
S. aureus	1	1
Candida sp.		3
Cryptococcus		2
Aspergillus		1
Toxoplasma		1
Streptococcus sp.		1
Total cases	2	9

(From Reference 2)

The correlation of the major neuropathologic findings in CNS SLE patients with hemiparesis, seizures, and cranial nerve palsies is shown in Table 11.

TABLE 11

Major Neuropathologic Findings in CNS SLE Patients With Hemiparesis, Seizures, and Cranial Nerve Palsies

	Micro-infarcts	Large Infarcts	Intra-cerebral Hemorrhage	Subarachnoid Hemorrhage	Menin-gitis	Vascu-litis
Hemiparesis (12)	50	33	50	50	25	25
Seizures (11)	63	0	27	54	18	27
Cranial nerve palsies (11)	72	9	0	9	18	9
Total cases (57)	35	12	10	30	18	13

(From Reference 2)

Demonstrable microinfarcts, intracerebral hemorrhage, and/or subarachnoid hemorrhage occurred in one-half the patients with hemiparesis. Patients with a history of seizures had a high incidence of microinfarcts and subarachnoid hemorrhage. Microinfarcts were present in 72% of patients with cranial nerve palsies.

Focal motor seizures were often associated with evidence of chronic subarachnoid hemorrhage while grand mal seizures were associated with a high incidence of cortical infarction.

In contrast to the Johnson-Richardson study (1) who found vasculitis in only 3 of 24 cases, these authors (2) found CNS vasculitis in 3 of 6 patients dying from neurologic causes. They also found an increased incidence of vasculitis in patients autopsied with active CNS disease defined by the presence of progressive clinical neurologic signs during the final

hospital admission. Their data also suggest that vasculitis is pathogenic in many CNS hemorrhages, especially subarachnoid hemorrhage (Table 12).

TABLE 12

Incidence of Hemorrhages in Documented CNS SLE Vasculitis

	Vasculitis* (7 Cases)	No Vasculitis (50 Cases)
Subarachnoid	5 (71%)	12 (24%)
Intracerebral	3 (43%)	3 (6%)
Microhemorrhage	3 (43%)	8 (16%)
Total	6 (86%)	18 (36%)

*The seven cases of vasculitis include those with and without evidence of infection.

(From Reference 2)

It is also suggested that since CNS SLE vasculitis is focal and may be short-lived, the incidence of vasculitis may be greater than previously thought. Thus these authors conclude that the major pathogenetic lesion in CNS SLE is microvascular injury.

Gibson and Myers (3) recently found that 51% of 80 SLE patients had neurological manifestations. Of these, 22 died. The causes of death and the relationship to nervous system involvement are shown in Table 13.

TABLE 13

Causes of death in 22 patients with SLE

Cause	*No. of patients*		
	Nervous system involvement	*No nervous system involvement*	*Total (%)*
Renal failure	7	2	9 (40%)
Neurological	6	–	6 (27%)
Infection	4	–	4 (20%)
Unknown	2	–	2 (9%)
Haemorrhage	–	1	1 (4%)

(From Reference 3)

The pathological findings in the CNS of the 6 patients whose deaths were acribed to nervous system involvement are shown in Table 13.

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TABLE 13

Major pathological findings in the CNS of 6 patients whose deaths were ascribed to nervous system involvement

Case no.	*Age at death (years)*	*Nervous system manifestations*		*Major autopsy findings*
		At death	*Previous*	
7	22	Hemiplegia	–	R middle cerebral artery occlusion; widespread atheroma; old and fresh cerebral infarcts
8	57	Confusional state	Psychosis; convulsions	Isolated haemorrhagic infarcts; plugging of small vessels with hyaline material
9	19	Convulsions; confusional state	Aseptic meningitis; papilloedema; psychosis; convulsions	Small haemorrhagic infarcts; plugging small veins with hyaline material
10	38	Status epilepticus	Psychosis; cranial nerve palsy; hemiplegia; convulsions	Thrombosis superior sagittal sinus; scattered micro-infarcts
11	59	Hemiplegia	Peripheral neuropathy	Diffuse haemorrhagic infarction; vascular and perivascular cell infiltrates
12	23	Convulsions; psychosis	Convulsions; psychosis	Large abscess occipital lobe; scattered small infarcts; hypertrophy walls medium sized arteries

(From Reference 3)

CNS SLE - Pathology

1. Johnson, R. T. and Richardson, E. P. The neurological manifestations of systemic lupus erythematosus. A clinical-pathological study of 24 cases and review of the literature. Medicine 47: 337-369, 1968.

2. Ellis, S. G. and Verity, M. A. Central nervous system involvement in systemic lupus erythematosus: a review of neuropathologic findings in 57 cases, 1955-1977. Semin. Arthr. Rheum. 8: 212-221, 1979.

3. Gibson, T. and Myers, A. R. Nervous system involvement in systemic lupus erythematosus. Ann. Rheum. Dis. 35: 398-406, 1976.

2. Clinical Manifestations

The incidence of neuropsychiatric manifestations in SLE varies considerably depending on the study, as shown in Table 14.

TABLE 14

Incidence of Neuropsychiatric Manifestations in SLE

	This Series (57 Cases)	Johnson and Richardson[6] (24 Cases)
Seizures	24	54
Headache	23	—
Hemiparesis	21	13
Psychosis	14	33
Cranial nerve palsy	19	42
Cerebellar signs	13	—

Incidences are expressed as percentages.

(From Ref. 1)

A number of reviews have been written over the past several years (1-20). In a study of 150 patients with SLE by Estes and Christian (7), 59% were found to have neuropsychiatric manifestations (Table 15).

TABLE 15

Major Clinical Manifestations of SLE in 150 patients

Manifestation	Percent
Musculo-articular	95
Cutaneous	81
Fever	77
Neuropsychiatric	59
Renal	53
Pulmonary	48
Cardiac	38

(From Ref. 7)

The neuropsychiatric manifestations encountered are shown in Table 16.

TABLE 16

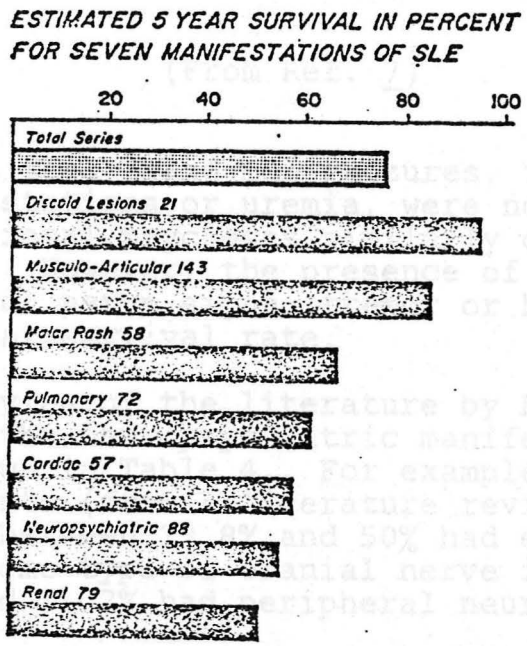
Neuropsychiatric Manifestations of SLE in 150 Patients

Manifestation	Percent
Psychiatric	
Psychoses	
Organic mental syndromes	21
Functional psychoses	16
Neuroses	5
Neurologic	
Seizures	
Without renal disease	17
With renal disease	9
Other central nervous system	
Cranial nerve signs	5
Tremor	5
Hemiparesis	5
Peripheral neuropathy	7

(From Ref. 7)

The 5 year survival for the 88 patients with neuropsychiatric symptoms estimated from the time of appearance of each specific manifestation was approximately 55%, as shown in Figure 4.

Figure 4

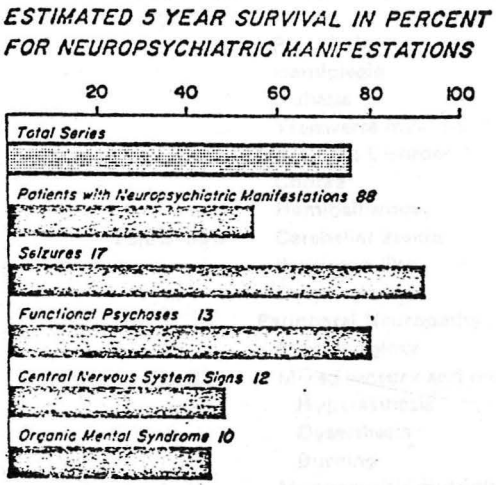


The percentage of five year survival estimated from the time of appearance of each manifestation. The numbers refer to the number of patients who developed each manifestation.

(From Ref. 7)

The estimated 5 year survival for specific neuropsychiatric manifestations is shown in Fig. 5.

Figure 5



The percentage of five year survival for neuropsychiatric manifestations of SLE estimated from time of appearance of each manifestation. The numbers refer to the number of patients who developed each manifestation in the absence of other neuropsychiatric manifestations.

(From Ref. 7)

This data showed that grand mal seizures, in the absence of other CNS manifestations or uremia, were not a grave prognostic sign. Functional psychoses similarly did not adversely affect survival. However, the presence of organic mental syndromes, cranial nerve signs, tremor or hemiparesis sharply lowered the 5 year survival rate.

A more recent review of the literature by Bennahum and Messner (17) summarized the neuropsychiatric manifestations more specifically as shown in Table 4.. For example, an average of 59% of SLE patients (from a literature review) were found to have psychoses, between 13.8% and 50% had epilepsy, between 5% and 33% had some type of cranial nerve involvement, 5% had paralysis and 11.7% had peripheral neuropathy.

TABLE 17

Neurologic Symptoms in Central Nervous System Systemic Lupus Erythematosus

	Totals		Totals
Psychoses	59%	Paralysis	5%
Delerium		Paraplegia	
Schizophrenia		Hemiplegia	
Catatonia		Aphasia	
Paranoia		Transverse myelitis	
Confusion		Movement Disorder	
Hypomania		Chorea	
Progressive dementia		Hemiballismus	
Epilepsy	13.8%-50%	Cerebellar ataxia	
Grand mal		Parkinson-like	
Petit mal		Dysphagia	
Focal		Peripheral Neuropathy	11.7%
Temporal lobe		Stocking glove	
Cranial Nerve	5%-33%	Mixed sensory and motor pain	
Visual defects		Hyperesthesia	
Homonomous hemianopia		Dysesthesia	
Blindness		Burning	
Papilledema		Mononeuritis multiplex	
Extraoccular movement abnormalities		Guillan-Barré type	
Tinnitus and vertigo		Neurogenic bladder	
Pupillary disturbance		Loss of sphincter control	
Nystagmus			
Ptosis			
Optic atrophy			
Facial palsy			

(From Ref. 17)

In their own series of 54 patients with SLE, 57.4% had neurological symptoms and 16.6% had organic psychiatric symptoms (Table 18).

TABLE 18

Neurological and Psychiatric Findings in 54 Patients with SLE at the University of New Mexico Center for the Health Sciences

Patient No.		Percentage
Total	54	100%
Female	48	88.8%
Male	6	11.1%
Neurological symptoms	31	57.4%
Organic psychiatric symptoms	9	16.6%
Functional psychiatric symptoms	29	53.7%
Neurologic and organic psychiatric symptoms combined	38	70%
Death	9	16.6%

(From Ref. 17)

The specific neurological and psychiatric symptoms in these 54 patients are shown in Table 19.

TABLE 19

Clinical Findings in 54 Cases of SLE*

Systemic		Neurological		Psychiatric	
Anemia	35	Convulsions	12	Depression	13
Rash	34	Coma	8	Altered reality testing	11
Arthritis	33	Headache	10	Fatigue	7
Renal disease	21	Hyperesthesia	6	Nervousness	5
Hypertension	18	Decreased vision	8	Emotional lability	5
Cardiac involvement	13	Hemiplegia	7	Confusion	4
Fever	15	Aphasia (expressive)	4	Hallucinations	3
Pleural effusion	11	Burning or itching of face	4	Anxiety	3
Urinary-tract infection	7	Ataxia	3	Staring	2
Family history	4	Retinitis	3	Shaking	2
Weight loss	4	Pain of tongue or mouth	2	Catatonia	2
Alopecia	4	Slurred speech	2	Loss of memory	2
Abdominal pain	3	Opthalmoplegia	1	Somatization	2
Hemoptysis	2	Optic atrophy	1	Dementia	1
Spontaneous abortion	2	Hemiballismus	1	Grinding teeth	1
Dysphagia	2	Chorea	1	Suicide attempt	1
Tracheolaryngeal edema	2	Neurogenic bladder	1	Insomnia	1
Hepatomegally	2	Pain of hands and feet	1		
Splenomegally	2				
Telangiectasia	2				

*A finding is recorded only once for each patient.

(From Ref. 17)

It is apparent that almost any neuropsychiatric symptom may be seen in SLE.

A very thorough study of 140 patients with SLE was performed at Johns Hopkins Hospital by Feinglass and co-workers (18).

In Table 20 it can be seen that only 5 of the 140 patients or 3% presented with a neuropsychiatric manifestation.

TABLE 20

Initial Manifestations in 140 Patients with SLE

Manifestation[1]	Patients (percent)
Arthritis or arthralgias	74 (52)
Skin rash	37 (26)
Fever	25 (17)
Pleurisy/pericarditis	16 (11)
Weight loss	9 (6)
Alopecia	6 (4)
Neuropsychiatric	5 (3)
Nephritis	3 (2)
Thrombocytopenia	3 (2)
Biologic false positive test for syphilis	3 (2)
Raynaud's phenomenon	2 (1)
Anemia	2 (1)
Adenopathy	1 (<1)

[1] When more than one feature presented simultaneously, both were listed separately.

(From Ref. 18)

However, as shown in Table 21, 52 patients or 37% eventually developed neuropsychiatric manifestations (average duration of followup was 9 years from the first manifestation and 6.5 years from the date of diagnosis).

TABLE 21

Clinical Features in 140 Patients with SLE

Manifestation	Patients (percent)
Arthritis or arthralgias	123 (88)
Cutaneous	110 (79)
Fever	98 (70)
Pleurisy/pericarditis	89 (64)
Nephritis	67 (48)
Alopecia	57 (41)
Neuropsychiatric	52 (37)
Vasculitis	39 (28)
Raynaud's phenomenon	32 (23)
Adenopathy	26 (19)
Splenomegaly	24 (17)
Myositis	15 (11)
Myocarditis	12 (9)
Subcutaneous nodules	12 (9)
Cytoid bodies	7 (5)

(From Ref. 18)

The neuropsychiatric manifestations in the 52 patients are shown in Table 22.

TABLE 22

Neuropsychiatric Manifestations in 140 Patients with SLE

Manifestation	Patients
A. SLE Related	52
Psychiatric illness	24
Seizures	17
Long tract signs	16
Cranial nerve abnormalities	16
Peripheral neuropathy	15
Cerebellar signs	5
Scotomata	4
Papilledema (pseudotumor)	2
Chorea	2
Meningitis, myelitis	1
B. Other cause	19*
Psychiatric illness	13
Meningitis	2
Peripheral neuropathy	3
Seizures	1

* In addition to these 19 patients, 7 patients from group A developed other NP abnormalities due to factors not directly related to SLE. See text.

(From Ref. 18)

The types of psychiatric disturbances are shown in Table 23.

TABLE 23

Psychiatric Illness in 140 Patients with SLE

	Patients	
A. SLE Related	24	
Organic[1]		22
Schizophrenic		2
B. Other cause[2]	13	
Organic		3
Schizophrenic		1
Psychoneurotic or personality disorder		9

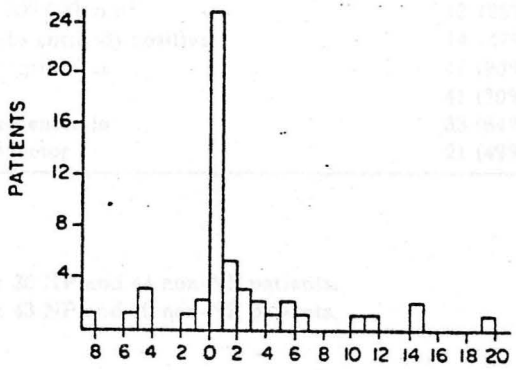
[1] Schizophrenic features were noted in nine and affective features in three of these patients.

[2] In addition to these 13 patients, 5 patients with SLE-related NP disease developed additional psychiatric problems attributable to other causes.

(From Ref. 18)

The temporal relationship between the initial neuropsychiatric events and the diagnosis of SLE is shown in Figure 5.

Figure 5



. Relationship between initial neuropsychiatric event and the diagnosis of SLE.

(From Ref. 18)

It is of interest that in 33 of the 52 patients (63%), neuropsychiatric involvement either preceded the diagnosis or occurred within the first year of diagnosed disease. The

manifestations included seizures, hemiparesis, chorea and papilledema, the latter presenting with a 3 months' history of headaches.

Perhaps the most interesting findings in this study are shown in Table 24.

TABLE 24

Clinical and Laboratory Features of SLE in Patients with and without Neuropsychiatric Involvement

Manifestation	Neuropsychiatric group (52 patients)	Non-Neuropsychiatric group (88 patients)
Arthritis or arthralgias	48 (92%)	75 (85%)
Skin rash	43 (83%)	67 (76%)
Fever	38 (73%)	60 (68%)
Pleurisy/pericarditis	28 (54%)	60 (68%)
Nephritis	29 (56%)	38 (43%)
Vasculitis	24 (46%)	15 (17%)[1]
Raynaud's phenomenon	14 (27%)	18 (20%)
Cytoid bodies	5 (10%)	2 (2%)
Myositis	3 (6%)	12 (14%)
Subcutaneous nodules	3 (6%)	9 (10%)
Anemia	32 (32%)	49 (56%)
Leukopenia	25 (48%)	43 (49%)
Thrombocytopenia		
Less than 150,000/mm³	20 (39%)	12 (14%)[2]
Less than 100,000/mm³	13 (25%)	6 (7%)[3]
Direct Coombs antibody positive	14 (47%)[4]	17 (38%)[4]
Antinuclear antibodies	47 (90%)	82 (92%)
LE cells	41 (79%)	66 (75%)
Hypocomplementemia	33 (64%)	47 (53%)
Rheumatoid factor	21 (49%)[5]	40 (51%)[5]

[1] p .003
[2] p .0006
[3] p .002
[4] Test performed on 30 NP and 44 non-NP patients.
[5] Test performed on 43 NP and 79 non-NP patients.

(From Ref. 18)

As shown in this Table, a comparison was made of the manifestations present in the neuropsychiatric and non-neuropsychiatric groups. Those manifestations which were significantly

different are shown in italics, i.e., vasculitis and thrombocytopenia. Both of these manifestations were significantly higher in the neuropsychiatric group. Cutaneous and visceral sites were the most frequently involved with vasculitis. The authors suggested that the thrombocytopenia might be secondary to widespread vasculitis with subsequent consumption coagulopathy.

Certain clinical syndromes appear to have been reported quite commonly in the literature. These are listed in Table 25.

TABLE 25

Cranial Nerve

- Retinopathy (21, 22)
- Retinal Vein Occlusion (23)
- Retinal Artery Occlusion (24)
- Optic Neuritis (25-27)
- Ophthalmoplegia (28, 29)
- Optic Atrophy (30)
- Trigeminal Neuropathy (31, 32)

Movement Disorders

- Chorea (33-41)
- Cataplexy (42)

Pseudotumor Cerebri (43-46)

Cerebral Disorders of Vision (47) and Migrainous Phenomena (48)

Transverse Myelopathy (49-51)

Multiple Sclerosis-Like Disease (52-54)

Aseptic Meningitis (55-57)

Central hyperventilation and inappropriate ADH secretion has also been reported in a case in which vasculitic lesions were present in the pons and hypothalamus (58). One patient with SLE developed a malignant cerebral lymphoma while receiving corticosteroids and azathioprine (59).

Brandt and co-workers (47) have studied 12 SLE patients with involvement of visual pathways posterior to the optic chiasm (Table 26). Symptoms included hallucinations, visual loss

or both. Patients with loss of vision had scotomas, homonymous field defects, and cortical blindness. The lesion was believed to be in the posterior cerebral artery circulation and presumably caused by cerebral vasculitis.

TABLE 26

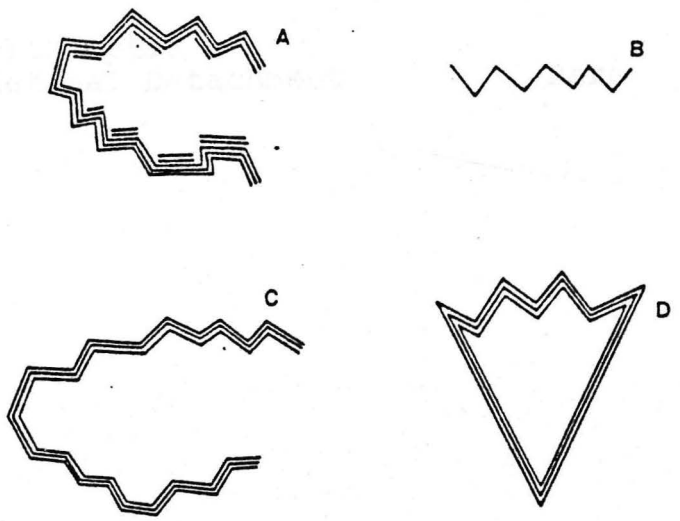
Description and Frequency of Index Events

Patient	Description	Frequency
1	Blurring of upper half of visual fields, lasting several minutes	Single occurrence
	Checkerboard patterns, lasting seconds to minutes	Several times per week within a 2-month period
	Bright lights at periphery of visual fields, lasting minutes	Several times during a 1-month period
	Complete bilateral blindness lasting 1 minute; pupillary light reflexes intact. Fundoscopic examination showed minimal blurring of optic discs	Single occurrence
2	Twinkling lights throughout visual fields with blurring of vision, lasting 20 minutes	Single occurrence
3	White zigzag lines swimming slowly from right to left across visual field, lasting 5 seconds	Three times per week within a 2-month period
	Black and white spots with central blinding "flash bulbs," lasting 10 minutes	Two episodes within a 2-month period
4	Three white lights appearing small initially but growing in size "like approaching headlights" over a 20-minute period before suddenly disappearing	Single occurrence
5	Patchy loss of words on printed page, with bright flashing lights in peripheral visual fields, lasting several hours	Single occurrence
6	Sudden appearance of partial loss of vision persistent after onset; on field testing found to have congruous left homonymous quadrantopia with homonymous right paracentral scotomas	Static
7	"Baseball bats and faces," recognized by patient as inappropriate, lasting 30 minutes	Single occurrence
8	Patchy loss of vision appearing intermittently, lasting minutes to weeks; on field testing found to have congruous homonymous hemianopia	Extremely variable over 1-year period
9	Black spot in front of eyes, lasting 15 minutes	Single occurrence
10	"Alabaster hand and upside-down faces," recognized by patient as inappropriate, lasting 20 to 30 minutes	Twice in 24-hour period
11	Flickering straight single yellow lines moving slowly from right to left across visual field, lasting 5 minutes	Three or four times a day, once or twice monthly for 8 months
12	Complete bilateral visual blackouts, lasting 3 to 5 minutes	Several times during a 4-month period

(From Ref. 47)

Brandt and Lessell (48) also reported migrainous phenomena in SLE patients. These migrainous symptoms were commonly associated with exacerbations of SLE and abated as disease activity subsided. Several of the patients had experienced visual hallucinations typical of the fortification specters (jagged lines that resemble an aerial view of ancient fortifications) that occur with migraine (48,60). (See Fig. 6).

Figure 6



Representation of fortification specters (as drawn by the patient).

(From Ref. 48)

Objective evidence of eye involvement is summarized in Table 27. The cotton wool exudates are most commonly known as cytoid bodies.

TABLE 27

EYE INVOLVEMENT IN SLE

Cotton Wool Exudates	9 - 24%
Flame-shaped Hemorrhages	10%
Retinal Arteritis or Phlebitis leading to Perivascular Sheathing and Fibrosis	
Papilledema with Optic Atrophy and Retinal Detachment	Rare

CNS-SLE - Clinical Manifestations

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3. Pathogenesis

A variety of mechanisms have been suggested as possible pathogenetic factors. (See Table 28) in CNS SLE.

TABLE 28

Possible Pathogenetic Mechanisms in CNS-SLE

Vasculitis of Cerebral Vessels
Deposition of Immune Complexes
in Choroid Plexus
Circulating Brain - Reactive Antibodies

a) Vasculitis and Immune Complexes

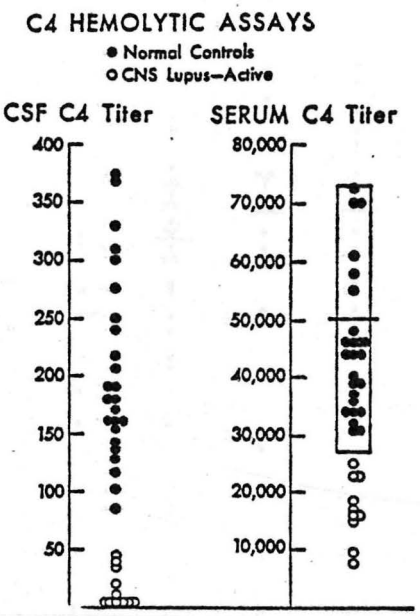
The role of vasculitis in CNS-SLE has been discussed previously (see Pathology section). Additional studies which support this concept include those which have shown hypocomplementemia, associated with antibodies to DNA and DNA: anti-DNA complexes in serum and cerebrospinal fluid from a patient with Lupus Meningitis (1). These authors claimed a striking correlation among the presence of these complexes, activity of disease, and symptomatic improvement from corticosteroids. It should be pointed out, however, that this study deals with only one patient.

Steinman (2) has recently found that persistently circulating DNA occurs specifically in patients with SLE who have vasculitis and CNS involvement. He suggested that the free DNA might bind to basement membranes of blood vessels, allowing for possible subsequent binding of antibody and in situ formation of immune complexes.

Further support for the role of immune complexes is provided by two studies of cerebrospinal fluid complement levels (3,4).

Petz and co-workers (3) first showed that C4 levels were decreased in CSF from SLE patients as compared with normals (Fig. 7) and concluded that this resulted from an immune reaction.

Figure 7

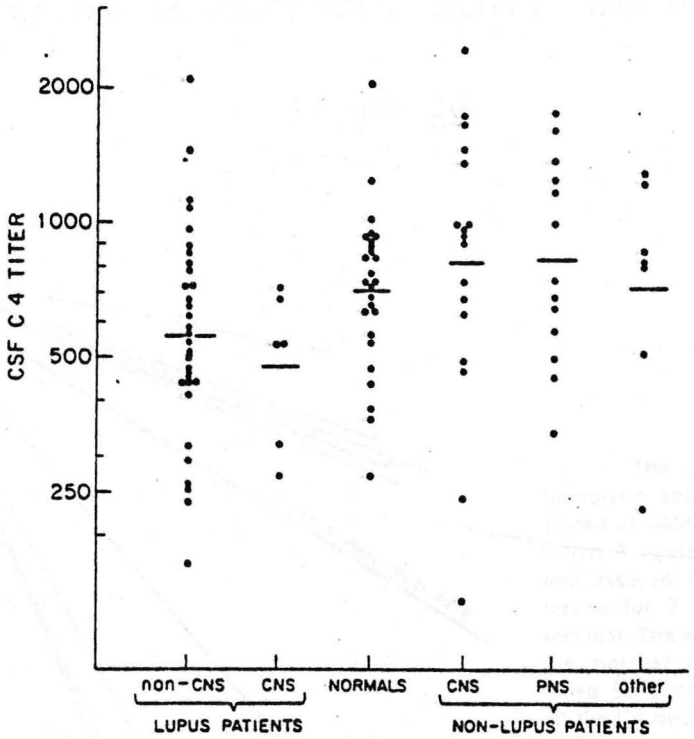


Serum and spinal fluid C4 titers in normal persons and patients with active CNS lupus. The rectangle indicates the normal range for serum C4 and the horizontal line indicates the normal mean.

(From Reference 3)

In a subsequent study by Hadler and co-workers (4), CSF C4 levels were not found to be different from normals (Figure 8) in either CNS-SLE or non-CNS SLE groups.

Figure 8



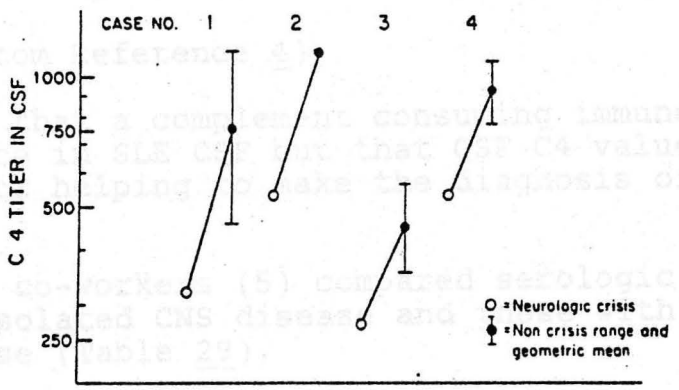
(From Reference 4)

Patients with non-CNS SLE had lower mean CSF C4 values than patients with central (CNS) or peripheral neurologic disorders (PNS) not related to lupus.

They did find, however, that in 4 different individuals with CNS SLE that the C4 values were lower during a neurologic crisis than during remission (Figure 9).

Figure 9

CEREBROSPINAL FLUID C4 IN SLE

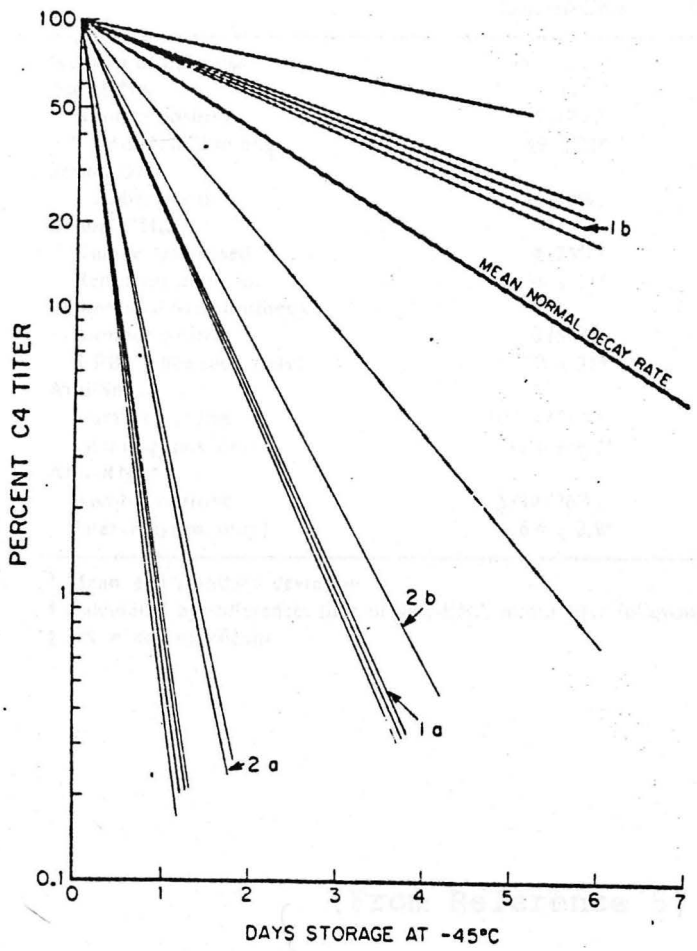


Comparison of the CSF C4 titer at time of acute neurologic involvement with values obtained when the patient was free of such involvement. The case numbers correspond to the numbering in Table 1 and in the Appendix.

(From Reference 4)

They also noted that the CSF C4 levels from active SLE patients decayed in storage at -45°C much faster than did normal CSF CF (Fig. 10).

Figure 10



The rate of loss of CSF C4 hemolytic activity in CSF aliquots stored at -45° C. CSF was aliquoted within 4 hours of lumbar puncture and assayed for C4 at 24-hour intervals for 7 days or until activity was lost. The **shaded area** represents the normal range, i.e., a single-tailed 95% confidence limit, based on the C4 decay data on 20 normal CSF samples. The **lines** are linear regression lines drawn by the method of least squares. **Slopes** represent the rate of decay of C4 for each patient. (Two patients were studied on two occasions each and are noted as 1a, b and 2a, b. See text for discussion.)

(From Reference 4)

These authors concluded that a complement consuming immune reaction was taking place in SLE CSF but that CSF C4 values are of little benefit for helping to make the diagnosis of CNS SLE.

A study by Winfield and co-workers (5) compared serologic data in patients with isolated CNS disease and those with CNS and extra-CNS disease (Table 29).

TABLE 29

Comparison of Serologic Data in Patients With and Without Extra-CNS Disease

	Clinical Group		
	Isolated CNS	CNS + Extra-CNS	
Number of Episodes	16	13	
Anti-DNA			
Number positive	3 (19%)	9 (69%)	
% ^{3}H-nDNA Binding	19 ± 21*	57 ± 39	$P = 0.002$
Serum DNA			
Number positive	2 (13%)	2 (15%)	
Serum $C'H_{50}$			
Number decreased	4 (25%)	8 (62%)	
Hemolytic units/ml	38 ± 11*	25 ± 13	$P = 0.006$
Lymphocytotoxic antibody			
Number positive	8 (50%)	11 (85%)	
% PBL killed (pos. only)	78 ± 31*	54 ± 29	NS‡
Anti-Sm			
Number positive	10/14 (71%)	6/11 (55%)	
Titer (log_2 pos. only)	11.6 ± 6.2*	8.8 ± 5.3	NS
Anti-RNP†			
Number positive	5/14 (36%)	1/11 (9%)	
Titer (log_2 pos. only)	6.4 ± 2.9*	3.0	NS

* Mean ± 1 standard deviation.
† Calculated by difference: titer of anti-ENA minus titer following RNAse digestion.
‡ NS = not significant.

(From Reference 5)

Increased anti-DNA antibody and decreased total hemolytic complement activity were observed only in those patients with associated extra-CNS disease manifestations. Although not shown in the above table, an increased incidence of anti-Sm antibodies was found in the patients with CNS dysfunction relative to that in a large group of patients without neuropsychiatric disease. The incidence of anti-RNP was not increased.

b. Deposition of Immune Complexes in Choroid Plexus

The choroid plexus is composed of vascular membranes of epithelial and endothelial cell types. The choroid plexus and the glomerular basement membrane have striking morphologic and functional similarities (6). They also have similarities in their molecular composition and share common antigenic determinants. Thus it has seemed reasonable to assume that injury to the choroid plexus might result from deposition of circulating antigen-antibody complexes or circulating antibody to glomerular basement membrane.

In the past several years several studies have reported deposits of gamma globulin in the choroid plexus which have tended to correlate with the presence of CNS abnormalities (6-13). The deposits have contained IgG, IgM, C3 and C4.

Studies of acute immune complex disease in the rabbit have shown that immune deposits could be detected in the choroid plexus, as well as the kidney, in a majority of animals (11). Another study has demonstrated that anti-basement membrane, antibody, eluted from the kidney of a patient with Goodpasture's syndrome, cross reacts with the choroid plexus (7).

It has been suggested that because the CSF may reflect injury to the choroid plexus, immunologic injury to the choroid may result in CSF alterations with subsequent behavioral abnormalities (13).

C. Circulating Brain-Reactive Antibodies

Several studies over the past few years have described anti-neuronal antibodies (See Table 30).

TABLE 30
Brain-Reactive Antibodies

Year	Authors	Finding	Ref.
1970	Diederichsen and Pyndt	SLE serum reacted with neuronal cytoplasm as well as nuclei (ANA)	(14)
1972	Quismorio and Friou	Anti-neuronal antibodies reactive with cytoplasm in 41% of SLE patients with active CNS disease, 24% with past history of neurologic disease, 9% of non-CNS SLE and 0.9% of non-SLE controls.	(15)
1976	Bluestein and Zvaifler	Brain-reactive lympho-cytotoxic antibodies in serum of SLE patients with CNS disease.	(16)
1977	Bresnihan, et al	Brain reactive lympho-cytotoxic antibodies (a prospective study), much greater in SLE patients with CNS SLE.	(17)
1978	Bluestein	Neurocytotoxic antibodies in SLE serum. 75% of SLE sera had antineuronal activity mediated by IgM antibody. IgG antineuronal antibody was detected in 17% of SLE sera by antibo-dy-dependent, cell-mediated cytotoxicity (ADCC) assay.	(18)
1979	Wilson, et al	Warm-reactive, brain spe-cific IgG antibodies to neuronal membranes in 82% of CNS SLE patients; absent in non-CNS patients or when focal neurologic deficit or psychosis was the primary manifestation. Cold-reactive IgM anti-bodies cross-reacted with brain and lymphocytes and correlated better with extra-CNS systemic illness.	(19)

Table 31 from the paper of Quismorio and Friou (15) demonstrates that the antineuronal (rabbit brain) cytoplasmic staining was highest in those patients with active CNS disease (41%) or those with a history of CNS disease (24%).

TABLE 31

Percentage distribution of anti-cytoplasmic, anti-DNA protein and anti-DNA antibodies in SLE patients and controls (see text for explanation of the different groups)

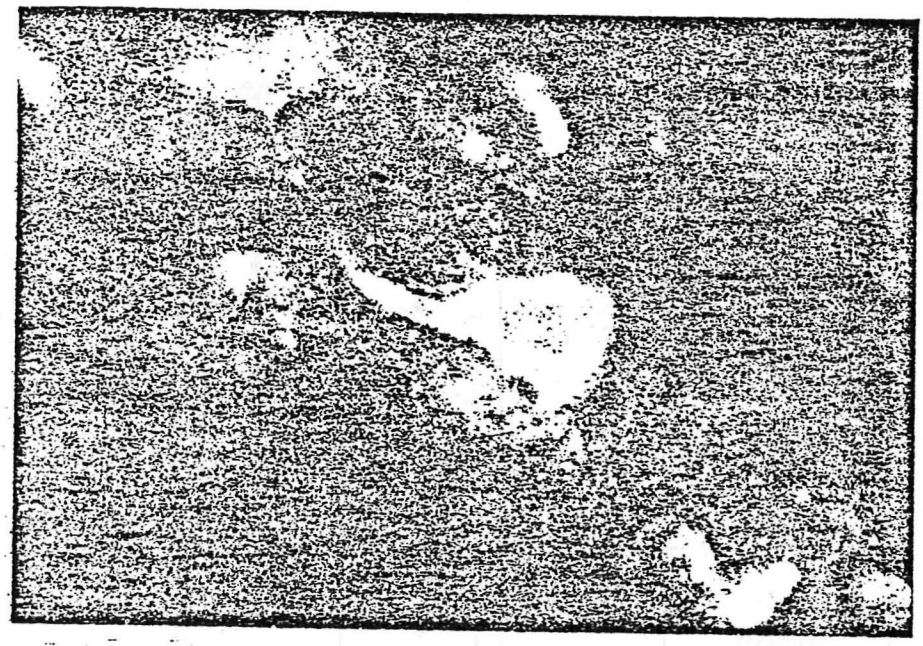
	Number of patients	Number of patients positive (%)		
		anti-cytoplasm	anti-DNA protein	anti-DNA
Active CNS Disease	22	9 (41)	17 (77)	11 (50)
Hx of CNS Disease	25	6 (24)	22 (88)	15 (60)
Non-CNS - SLE	90	8 (9)	74 (82)	50 (55)
Non-SLE Controls	110	1 (0.9)	34 (30)	13 (12)

(From Reference 15)

Figure 11 gives an example of such cytoplasmic staining.

Figure 11

Antibodies Reactive with Neurons in SLE



Antibodies reactive with the cytoplasm of neurons of rabbit brain demonstrated by indirect immunofluorescent test. × 600.

(From Ref. 15)

Both Bluestein and Zvaifler (16) and Bresnihan et al (17) demonstrated the presence of brain reactive lymphocytotoxic antibodies. Figure 12 gives the results from the studies of Bresnihan et al. This demonstrates that lymphocytotoxic antibodies are higher in CNS-SLE patients than in those without CNS disease. It also demonstrates that the cytotoxicity can be absorbed with brain tissue homogenates, but only in those patients with CNS disease. They suggested that subpopulations of lymphocytotoxic antibodies differ in their brain reactivity, and that one population may be causally related to the development of some of the features of cerebral lupus.

Figure 12

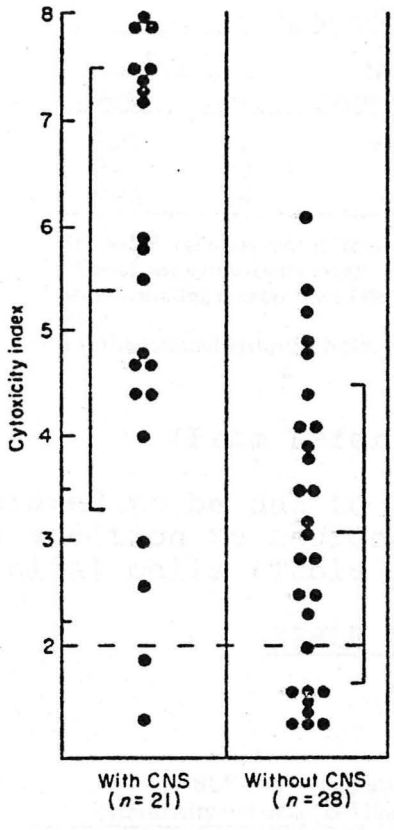


FIG. 1.

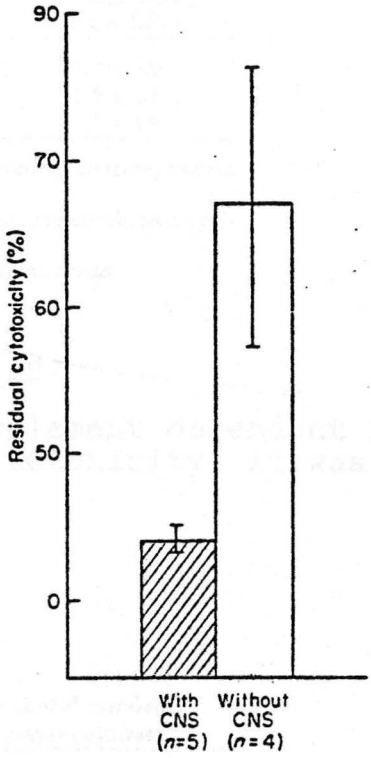


FIG. 2.

FIG. 1. Maximum cytotoxicity indices (with means ± s.d.) of sera from patients with or without cerebral involvement.

FIG. 2. Mean residual cytotoxicity of sera from patients with or without cerebral involvement after incubation with brain homogenates.

(From Reference 17)

In 1978, Bluestein reported that serum from SLE patients was cytotoxic for a human neuronal cell line, SK-N-SH, derived from a metastatic neuroblastoma (Table 32).

TABLE 32

Complement-dependent neurocytotoxicity mediated by serum from patients with SLE*

Sera		No.	% cytotoxicity,
Source‡	No.	cytotoxic†	mean ± SEM
SLE	32	25	31.3 ± 3.9
RA	16	3	8.2 ± 2.8
NHS	15	0	2.7 ± 1.9

* SK-N-SH cells served as targets in a complement-dependent ^{51}Cr-release cytotoxicity assay.
† Sera mediating greater than 14% ^{51}Cr release are considered cytotoxic.
‡ RA, rheumatoid arthritis; NHS, normal human serum.

(From Reference 18)

This factor proved to be due to a complement dependent IgM antibody. In addition to neuronal cytotoxicity, it was also cytotoxic to glial cells (Table 33).

TABLE 33

SLE serum-mediated complement-dependent cytotoxicity to human cell lines in monolayer cultures*

Target cells		% cytotoxicity†	
Line	Type	SLE	NHS
SK-N-SH	Neuronal	38.4 ± 5.9	3.3 ± 1.4
A-172	Glial	26.8 ± 5.3	3.7 ± 1.0
U-118MG	Glial	12.8 ± 2.7	2.0 ± 0.7
594	Fibroblast	5.3 ± 1.6	3.2 ± 1.2

* Sources of the cell lines used as targets in a ^{51}Cr-release cytotoxicity assay are presented in *Methods*.
† The % cytotoxicity was calculated as described in *Methods*. Data are expressed as the mean ± SEM for 20 SLE sera and 15 normal human sera (NHS).

(From Reference 18)

An additional factor was detected which was an IgG antineuronal antibody which was detected by an antibody-dependent, cell-mediated cytotoxicity assay (Table 34).

TABLE 34

Antibody-dependent cell-mediated neurocytotoxicity induced by SLE sera

Sera		% cytotoxicity, mean ± SEM	No. cytotoxic
Source	No.		
SLE	24	11.9 ± 1.0	4
RA	8	6.0 ± 1.1	0
NHS	17	8.6 ± 0.8	0

^{51}Cr-labeled SK-N-SH cells were preincubated with the test sera, the unbound serum was then washed off, and the cells were used as targets in the ADCC assay. Sera were considered to be cytotoxic if they induced greater than 15% cytotoxicity (NHS mean plus 2 standard deviations). RA, rheumatoid arthritis; NHS, normal human serum.

(From Reference 18)

In the most recent study by Wilson et al (19), Tables 35, 36, 37, Sera from 20 patients with systemic lupus erythematosus (SLE) and active central nervous system (CNS) dysfunction were examined by indirect immunofluorescence for antibodies to neuronal membrane determinants. Warm-reactive IgG antibodies were demonstrable in 82% (9/11) of patients with clinical evidence for seizures or diffuse CNS disease, but these antibodies generally were absent in non-CNS SLE sera or when focal neurological deficit or psychosis was the primary CNS manifestation. Cold-reactive antibodies of the IgM class were equally prevalent in patients with or without CNS disease and appeared to be more directly correlated with extra-CNS systemic illness. Absorption experiments with lymphocytes, brain homogenate, and various other tissues suggested a predominant brain-specificity for IgG antibodies and partial lymphocyte cross-reactivity for IgM antibodies.

TABLE 35

Anti-neuroblastoma and lymphocytotoxic antibodies in patients with systemic lupus erythematosus and active central nervous system dysfunction

Patient (date)	Clinical manifestation		Anti-neuroblastoma antibody*		Lymphocytotoxic antibody (% PBL killed)
	CNS†	Extra-CNS	IgG	IgM	
Pc	Seizure	—	+	+	90
Gu (5/76)	Psychosis	—	+	+	90
Gu (9/77)	Encephalopathy	—	+	+	30
Ca (2/78)	Dementia	—	+	+	40
Th	MS-like‡	—	+	−	40
Cr	Seizure	Nephritis	+	+	30
Ta, D	Seizure	Nephritis	+	+	25
Sa	Seizure	Nephritis	+	−	80
Ru	Seizure	Nephritis	+	+	95
Nu	Coma	—	+	−	95
Ca (12/77)	Psychosis	—	−	−	<10
Mo	Psychosis	—	−	+	<10
Ca, F	Hemiparesis	—	−	−	30
Ra	Hemiparesis	—	−	−	<10
Co	Myelopathy	—	−	−	<10
Ki	Myelopahty	—	−	−	<10
Ba	Psychosis	Myositis	−	+	25
Wo	Seizure	Myocarditis	−	−	35
Su	Psychosis	Nephritis	−	+	35
Ta, M	Encephalopathy	Arthritis	−	−	85
Al	Homogeneous hemianopia	Arthritis	−	+	95
Ay	Ptosis	Serositis	−	+	40

* Except for patients Ru, Cr, and Nu who had persistently active CNS disease, sera positive for IgG or IgM antibody were obtained within 4 days of the onset of CNS manifestations.

† CNS = central nervous system.

‡ Multiple sclerosis-like syndrome.

(From Ref. 19)

TABLE 36

Anti-neuroblastoma antibody in patients with SLE, non-SLE neurologic disease, and in normal subjects

Disease state*	Number of patients	Anti-neuroblastoma antibody positive	
		IgG	IgM
SLE with CNS involvement			
Diffuse organic disease	11	9	5
Focal disease	6	0	2
Psychosis	5	1	4
SLE without CNS disease			
Inactive	10	0	2
Active	10	1	7
Non-SLE neurologic disease†	10	3	2
Normal subjects	20	0	0

* CNS = central nervous system.

† Diagnoses included stroke (4), malignancy (3), herpes encephalitis (1), Parkinson's disease (1), and vasculitis (1).

(From Ref. 19)

TABLE 37

. Serial anti-neuroblastoma antibody titers in SLE patients with neuropsychiatric disease

Patient (year)	IgG titers			IgM titers		
	Prior to onset*	Acute stage	After recovery†	Prior to onset	Acute stage	After recovery
Ca	–	1:8	Death	1:2	1:16	
Gu (76)	–	1:4	–	1:4	1:2	1:8
Gu (77)	–	1:2	–	1:8	1:4	–
Ta. D‡		1:2	neat		1:4	1:4
Th	–	1:2	–	–	–	–
Pc	–	neat	1:2	1:8	1:4	1:16
Ay	–	–	–	neat	1:8	1:4
Al	–	–	–	1:4	1:2	1:4

* Sample obtained 6 to 12 months prior to onset of CNS disease. Negative = –; blank indicates no data.

† Samples obtained 4 to 24 months after resolution. Patient Pc had persistent seizures.

‡ Patient presented with seizure disorder.

(From Ref. 19)

References - SLE - Pathogenesis

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4. Diagnostic Procedures

The most commonly used diagnostic procedures and their estimated accuracy are shown in Table 38.

TABLE 38

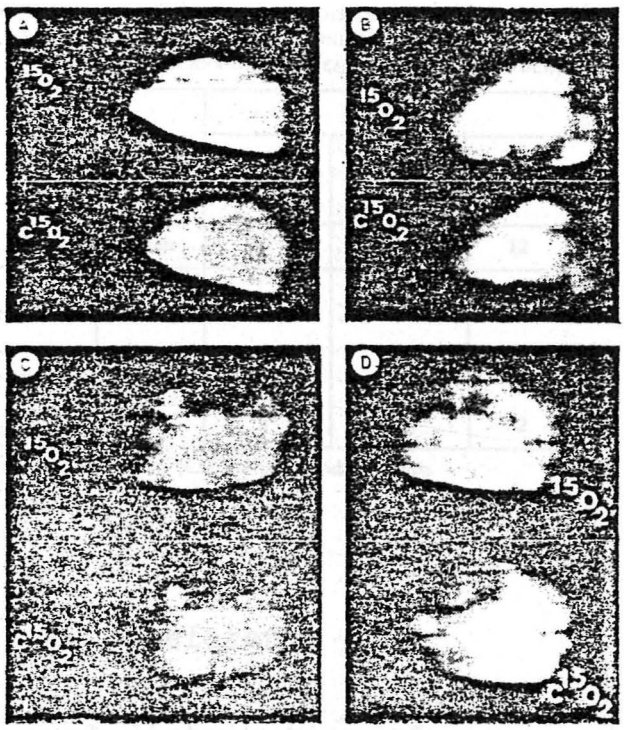
Diagnostic Values of Various Procedures in SLE
(% Accuracy)

Oxygen - 15 Brain Scan	96%
CT Scan	79%
EEG	71% - 84%
Abnormal CSF	25% - 32%
Brain Scan	8% - 100%

1) Oxygen-15 Brain Scan

An ingenious new radionuclide technique was recently described by Pinching, Travers and Hughes (1). $^{15}O_2$, a short-lived gamma-emitting isotope, is inhaled and carried to the tissues of the brain where it is utilized to form radioactive water of metabolism ($H_2\,^{15}O$); the result is a "metabolic image." In addition, $C^{15}O_2$ is inhaled, forms $H_2{}^{15}O$ in the lungs, and provides a brain-scan image that depends on cerebral blood flow. Equilibration occurs after 6 minutes of constant inhalation, and the radioactive signal is recorded over 4 minutes for each gas. The gamma-ray emission from the brain is detected by a gamma camera positioned to view the lateral aspect of the head. Examples of such scans are shown in Fig. 13.

Figure 13



(A) $^{15}O_2$ (metab.)/$C^{15}O_2$ (flow) scan in a normal control (left hemisphere).

(B) 15-year-old female with S.L.E.

Deterioration in school performance and short-term memory; nominal dysphasia. Posterior parietal left hemisphere lesion extending into temporal lobe common to metabolism and flow.

(C) 52-year-old female with S.L.E.

Gross paranoid psychosis. Several large defects in right hemisphere scan affecting metabolism more than flow.

(D) 25-year-old male with S.L.E.

Possible difficulty with recent information recall—clinically suspicious. Left hemisphere scan showing extensive frontal defects, slightly more pronounced on flow scan.

(From Reference 1)

Results of this study are shown in Table 39.

TABLE 39

CORRELATION BETWEEN CLINICAL EVIDENCE OF C.N.S. DISEASE AND OXYGEN-15 SCANS IN FIFTY ONE EPISODES IN 47 PATIENTS (FOLLOW-UP SCANS DURING REMISSION NOT INCLUDED)

		C.N.S		
		Definitely abnormal	Suspicious	Normal
Scan	Totals	24	15	12
Major abnormality	29	19	8	2
Minor abnormality	18	3+1†	6	8
Normal	4	1*	1†	2

*Internal capsule infarct. †Clinically, steroid psychosis.

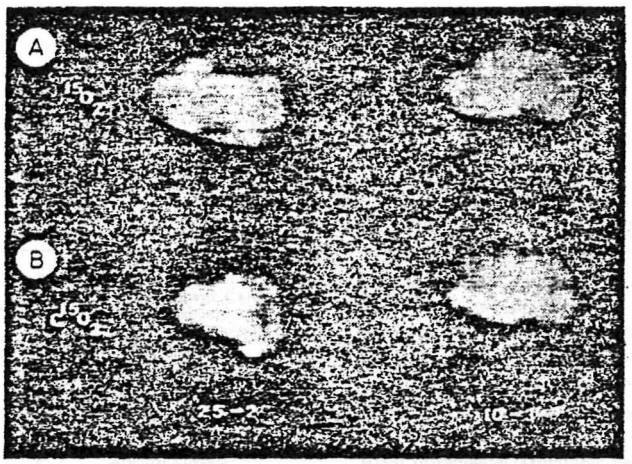
(From Reference 1)

Abnormalities in regional distribution of oxygen utilization and blood flow were seen in 23 out of 24 instances of definite CNS disease, in 14 out of 15 instances of suspected CNS lupus, and in 10 out of 12 instances in which CNS disease was not clinically apparent. The technique also reflected remissions and relapses.

Thus the major potential problems with this technique would appear to be (1) it is positive in almost all patients with SLE and (2) the nearest cyclotron is apparently at College Station, Texas !

Improvement in the CNS disease in association with improvement in the scan is shown in Figure 14.

Figure 14



—(A) 30-year-old femal with mixed connective-tissue disease.
Severe depressive psychosis. Scan shows several defects with right parietal metabolism lesion.
(B) Follow-up scan on same patient.
Considerable resolution after clinical improvement on steroids.

(From Reference 1)

b. Cranial Computed Tomography (CT) Scans

In 1977, Bilaniuk, Patel and Zimmerman (2) described computed tomographic (CT) findings in 14 patients with SLE. Results are shown in Table 40. The authors found that microinfarction (manifested by perisulcal atrophy), large infarcts, and hematomas are the major abnormalities demonstrated by CT.

TABLE 40

Clinical and CT Findings in 14 Patients with SLE*

Patient	Age	Sex	Clinical Findings	CT Findings
D.N.	16	F	Psychosis, Seizures	Unilateral Perisulcal Atrophy
A.L.	16	F	Psychosis	Diffuse Perisulcal Atrophy
C.G.	17	F	Pseudotumor Cerebri	Normal
P.C.	21	F	Abrupt Onset: Left Hemiparesis Hemisensory Defect Psychosis	Right Thalamic Infarct Frontotemporal Perisulcal Atrophy
F.S.	24	F	Psychosis	Left Perisulcal Atrophy
A.K.	27	F	Psychosis	Developing Perisulcal Atrophy over 1 year
M.P.	29	F	Spinal Cord Infarct Paraparesis, Worst Left	Normal
C.H.	44	F	Abrupt Onset: Left Hemiparesis	Right Intracranial Ganglionic Hematoma
E.D.	44	F	Abrupt Onset: Psychosis Left Hemiparesis	Right Parietal Infarct Perisulcal Atrophy
M.D.	47	F	Proximal Myopathy Drop Attacks	Normal
E.J.	48	F	Psychosis Seizures	Left Tentorial Meningioma with Hydrocephalus
J.R.	51	F	Psychosis Polyneuropathy	Normal
F.K.	55	M	Abrupt Onset: Right Hemiparesis Right Homonymous Hemianopsia Right Hemisensory Defect	Intracerebral Hematoma left Posterior Ganglionic and Thalamic
A.S.	77	F	Organic Dementia Sudden Onset	Marked Sulcal Atrophy. Ventricular Enlargement

*The diagnosis of SLE was established by criteria of the American Reheumatism Association.

(From Reference 2)

The CT abnormalities correlated well with the clinical findings.

The authors believe that CT is the first effective method for the in vivo demonstration of the intracranial manifestations of SLE. They state that large areas of infarction may be demonstrated by radionuclide brain scanning or cerebral angiography. They suggest that the isotope brain scan is only positive for recent infarcts. Large hematomas are demonstrated by angiography, but only as an avascular mass, which is a nonspecific finding. They conclude that only CT is sensitive and specific enough to demonstrate relatively small areas of infarction and hemorrhage.

A subsequent study by the same group (3) reviewed CT scans of 29 patients with SLE. Twenty-two patients had a clinical course consistent with CNS involvement. Of these, 20 had abnormal CT studies during the course of their CNS symptoms. The most common finding was sulcal enlargement, and it was prominent in patients with either psychosis or dementia. Infarcts and intracranial hemorrhages were seen as well. Seven CT studies were obtained in SLE patients without a clear diagnosis of CNS involvement. Only one of these was abnormal. The CT findings of this study are shown in Table 41.

TABLE 41

Features of CT Scans in 23 Patients with SLE[a]

CT Findings	Patients with CNS-SLE
Perisulcal atrophy	9
Generalized atrophy	9
Infarct	4
Intracerebral hemorrhage	4

[a]Some of the scans showed more than one diagnostic abnormality. One of the patients was not diagnosed as having CNS SLE.

(From Reference 3)

The authors point out that sulcal enlargement is not specific for CNS-SLE; other causes such as trauma, alcoholism, Alzheimer disease and aging must be considered. They also suggest that perisulcal and generalized atrophy are not reversible processes. They have not seen restoration of a normal pattern on CT scan.

C. Electroencephalography

Gibson and Myers (4) have stressed the point that the value of EEG's is doubtful since although positive in 84% of those patients in whom it was performed, the findings were entirely nonspecific. Johnson and Richardson (5) also stated that they were of little diagnostic or localizing value. They pointed out that even in patients with clear lateralizing signs or seizures diffuse bilateral slowing was the most frequent finding, suggesting widespread cortical disease.

A recent report by Finn and Rudolf (6), however, suggests that the EEG does have an important role in the assessment of the progress of SLE. They compared their EEG results with the $^{15}O_2$ scan results of Pinching et al. The data for both the EEG and the $^{15}O_2$ study are combined in Table 42.

TABLE 42

RELATION BETWEEN E.E.G. FINDINGS (OR OXYGEN-15 SCANS AND CLINICAL EVIDENCE OF CEREBRAL INVOLVEMENT BY S.L.E.

E.E.G. (or scan)	Totals	C.N.S. involvement		
		Probable	Possible	No evidence for
Moderately or very abnormal	33 (29)	22 (19)	9 (8)	2 (2)
Mildly abnormal	16 (18)	5 (4)	5 (6)	6 (8)
Within normal limits	7 (4)	1 (1)	2 (1)	4 (2)
Total	56 (51)	28 (24)	16 (15)	12 (12)

* Figures in parentheses are numbers of scans from data of Pinching et al. The column headings of Pinching et al. were "definitely abnormal", "suspicious", and "normal", and their row headings were "major abnormality", "minor abnormality" and "normal".

(From Reference 6)

As with the $^{15}O_2$ scans, all patients with psychiatric signs or symptoms at the time of the EEG recordings had abnormal EEG's. A summary of results of several studies is given in Table 43.

TABLE 43

Percentage of Abnormal EEG in CNS-SLE

Year	Authors	Results	Ref.
1976	Gibson and Myers	84% of patients with CNS-SLE abnormal	(4)
1976	Feinglass et al	71% of patients with CNS-SLE abnormal	(7)
1978	Tan et al	80% of patients with CNS-SLE abnormal; but 20% with active CNS involvement showed no abnormality.	(8)

d. Cerebrospinal Fluid

The CSF in CNS-SLE shows a mildly raised CSF protein and a mild lymphocytic pleocytosis in about 24% of cases (4,5). A low CSF sugar was found in 4 patients (4), Table 44.

TABLE 44

Details of 4 patients with low CSF sugar

Case no.	*Clinical manifestations*	*CSF*			*Simultaneous blood sugar mmol/l (mg/100ml)*
		Sugar mmol/l (mg/100ml)	*Protein g/l (mg/100ml)*	*WBC $\times 10^9$/l (mm^3)*	
3	Paraplegia	0·55(10)	0·53(53)	0·003(3)	3·5 (64)
4	Convulsions	1·11(20)	1·54(154)	0·022(22)	4·9 (90)
5	(a) Cerebellar ataxia	1·94(35)	0·3 (30)	0	–
	(b) Psychosis	2·49(45)	0·34(34)	0	18·31 (330)
6	Psychosis	1·94(35)	0·24(24)	0	6·66 (120)

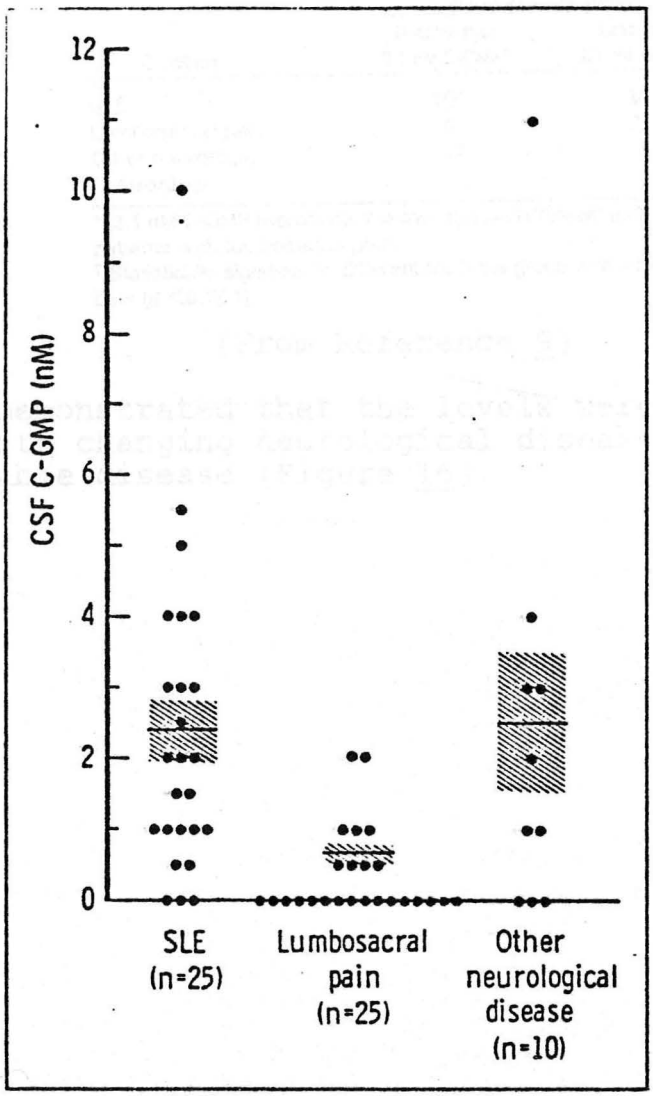
(From Reference 4)

The mechanism is presumed to reflect disturbance of the meningeal transport system between blood and CSF. This is caused by the inflammation. Disturbance of choroid plexus function is another possible explanation.

As mentioned previously (Pathogenesis section), C4 levels are unhelpful because of rapid deterioration of C4, even when frozen.

Kassan and Kagen (9) have shown that cyclic G M P levels in CSF of SLE patients are increased as compared with controls with lumbosacral pain. However, patients with other types of neurological disease including CVA, spinal cord tumor, syringomyelia, craniopharyngioma, etc., also had increased C - G M P levels (Figure 15 and Table 45).

Figure 15



C-GMP concentration in cerebrospinal fluid samples of three patient groups. Line indicates average of each group; hatched area includes ± SE.

(From Reference 9)

TABLE 45

Comparison of C-GMP Concentration in Patients with SLE, Other Neurologic Diseases and Lumbosacral Pain

Condition	No. of Samples With: Greater than 2.1 nM C-GMP*	Less than 2.1 nM C-GMP
SLE	10†	15
Lumbosacral pain	0	25
Other neurologic disorders	4†	6

* 2.1 nM C-GMP represents the average C-GMP level plus 2 SD for patients with lumbosacral pain.
† Statistically significantly different from the group with lumbosacral pain ($p < 0.001$).

(From Reference 9)

They also demonstrated that the levels were higher in CNS-SLE patients with changing neurological disease than in those who had stable disease (Figure 16).

Figure 16

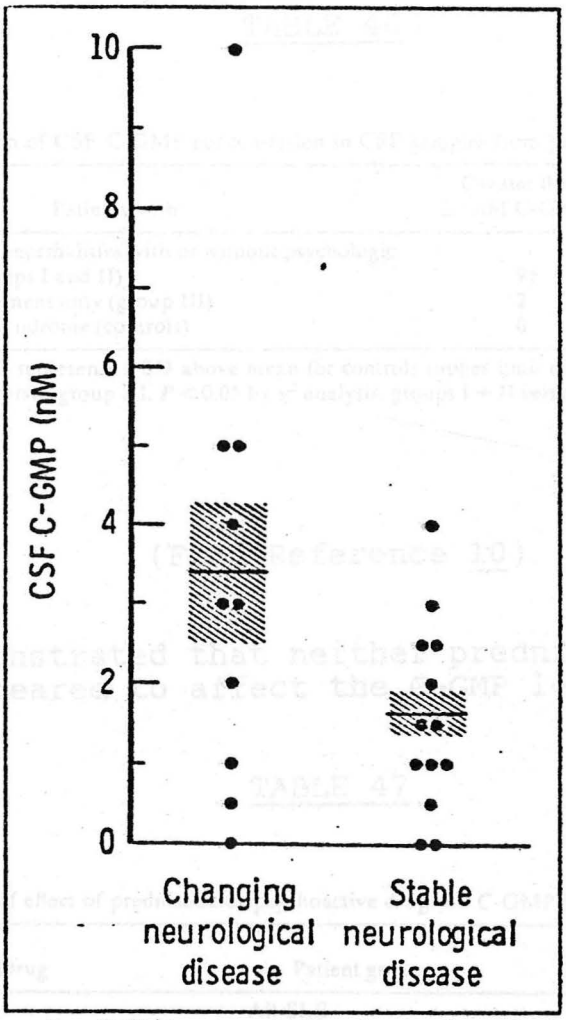


Figure 2. C-GMP concentration in cerebrospinal fluid samples from patients with SLE and either changing or stable neurologic disease. Line indicates average of each group; hatched area includes ± SE.

(From Reference 9)

C-GMP levels in the CSF were higher in patients with neurologic disease than in those with psychologic disease only (Table 46). C-AMP levels were unchanged.

TABLE 46

Comparison of CSF C-GMP concentration in CSF samples from patients with SLE

Patients with:	Greater than 2.1 nM C-GMP*	Less than 2.1 nM C-GMP
Active neurologic abnormalities with or without psychologic involvement (groups I and II)	9†	4
Psychologic involvement only (group III)	2	9
Lumbosacral pain syndrome (controls)	0	25

* 2.1 nM C-GMP represents 2 SD above mean for controls (upper limit of normal).
† Groups I + II versus group III, $P < 0.05$ by χ^2 analysis; groups I + II versus controls, $P < 0.001$ by χ^2 analysis.

(From Reference 10)

They also demonstrated that neither prednisone nor psychoactive drugs appeared to affect the C-GMP levels (Table 47).

TABLE 47

Lack of effect of prednisone or psychoactive drugs on C-GMP levels in CSF of SLE patients

Drug	Patient groups	No.	C-GMP in CSF (nM) (average ± SE)
Prednisone*			
<20 mg per day	All SLE (groups I, II, and III)	13	2.58 ± 0.75
>20 mg per day	All SLE (groups I, II, and III)	11	2.36 ± 0.62
Psychoactive drugs† administered	SLE with psychologic involvement (groups I and III)	8	1.75 ± 0.65
No psychoactive drugs	SLE with psychologic involvement (groups I and III)	8	1.80 ± 0.47

* Dose of prednisone taken within 24 hours prior to removal of CSF.
† Psychoactive drugs included chlorpromazine, thioridazine, amitryptaline, diazepam, and barbiturates.

(From Reference 10)

e. Brain Scan

There is considerable controversy regarding the value of brain scans in diagnosis of CNS-SLE. A summary of the results of several studies is given in Table 48.

TABLE 48

Value of Brain Scan in Various Studies

Year	Authors	Results	Ref
1974	Bennahum and Messner	11/12 with CNS-SLE abnormal, 0/8 without CNS-SLE abnormal	(11)
1975	Stewart and Basten	Suggest caution in interpreting Bennahum and Messner's results- they report 3 similar brain scans; two due to Toxoplasma gondii, the third due to Nocardia asteroides infection.	(12)
1976	Gibson and Myers	4/21 or 19% of cases abnormal	(4)
1976	Feinglass et al	2/26 or 8% of scans (23 patients) abnormal	(7)
1978	Tan et al	25/25 patients with CNS-SLE abnormal. Serial brain scanning found useful in diagnosis of exacerbations and the monitoring of steroid dosage.	(8)

It is difficult to explain such discrepant results in the above studies. There are at least 2 possible explanations: (1) Use of different techniques in brain scanning and (2) only recent infarcts will show up by brain scan.

f. Angiography

While the large vessels are not usually involved in SLE, there are several case reports claiming to show angiographic demonstration of major cerebral vessel occlusion due to SLE (13-16). See Table 49.

TABLE 49

. Angiographically demonstrated cerebral vascular occlusions in systemic lupus erythematosus

Case No.	Age & sex	Artery
1. Bodechtel [2]	49 M	Middle cerebral artery stenosis progressing to occlusion.
2. Silverstein [36]	36 F	Internal carotid artery occlusion.
3.	27 F	Internal carotid artery occlusion.
4. Diederichsen [6]	45 F	Internal carotid artery occlusion.
5. Trevor *et al.*	21 F	Right internal carotid artery occlusion. Three years later, left middle cerebral artery stenosis.
6.	42 F	Right middle cerebral artery stenosis progressing to occlusion in four months.
7.	32 F	Left internal carotid artery occlusion.

(From Reference 16)

Two cases are reported of angiographic demonstration of lupus cerebral phlebitis with communicating hydrocephalus (17).

g. Summary

Several studies have compared various tests in the same patients with CNS-SLE. For example, Table 50 shows the results of Feinglass et al and compares percent abnormalities for EEG, CSF and brain scan. In their hands, the EEG was most often helpful and the brain scan was of little value.

TABLE 50

Diagnostic Laboratory Data

Procedure	Patients	Episodes with study	Abnormal
Electroencephalogram	26	28	20 (71%)
Cerebrospinal fluid	37	44	14 (32%)
Brain scan	23	26	2 (8%)

(From Reference 7)

In striking contrast, the results of Tan et al are shown in Table 51. The brain scan was positive in 100%.

TABLE 51

CNS investigation in 29 episodes of SLE CNS disease

Test	*No. tested*	*No. abnormal*
CSF cell count	20	0
CSF protein	20	10
CSF IgG	13	0
EEG	25	20
Brain scan	29	29

(From Reference 8)

The lab results are shown in Table 52.

TABLE 52

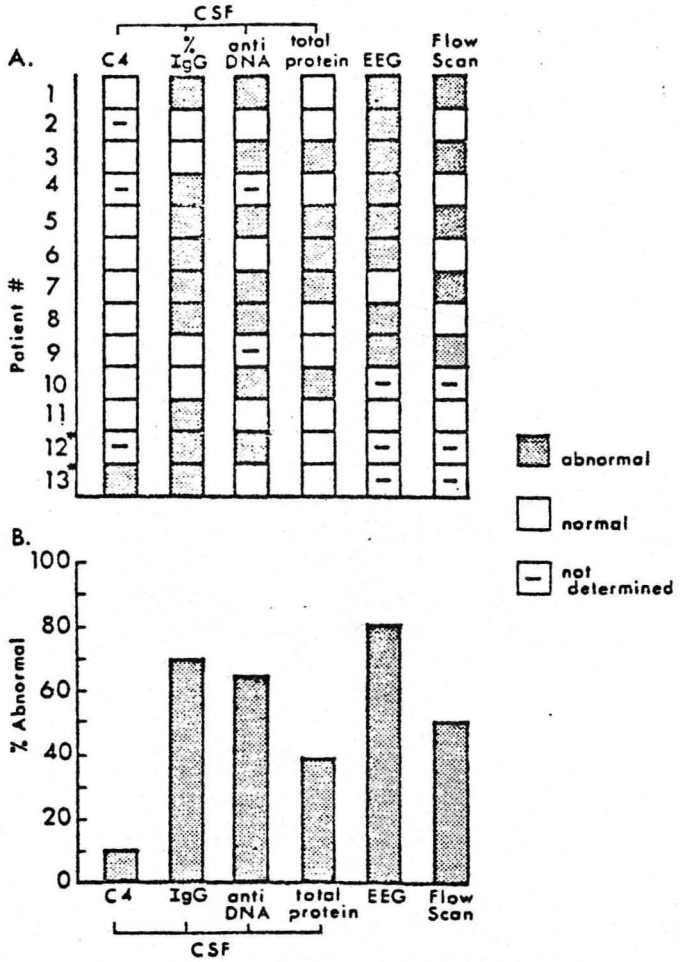
Serology in 29 episodes of SLE CNS disease

Test	*No. abnormal*
ANF	25
LE prep	12
Anti-DNA Ab	18
Low CH_{50}	13
Low B_1C (C3)	21
Low CH_{50} or B_1C	22

(From Reference 8)

In a paper by Small et al (18), the clinical course and so-alled diagnostic profile of 13 patients with CNS-SLE were tabulated. The results are summarized in Figure 17.

Figure 17



Diagnostic profile in 13 patients with CNS-SLE.

(From Reference 18)

The diagnostic yield for each procedure was measured as the percent abnormal: CSF total protein was 38%; increased CSF IgG 69%; decreased CSF hemolytic C4 10%; increased CSF anti-DNA 64%; EEG 80%; flow brain scan 50%; and static brain scan

0%. No single procedure was consistently abnormal, but the battery of tests provided a useful and specific CNS-SLE diagnostic profile.

They concluded that the CSF % IgG, anti-DNA binding, and brain scan flow studies were the most useful markers. They state that when combined with careful clinical observations and a high index of suspicion, this battery of tests has been valuable in the early diagnosis of CNS-SLE.

References -SLE -Diagnostic Procedures

1. Pinching, A. J. et al. Oxygen-15 brain scanning for detection of cerebral involvement in systemic lupus erythematosus. Lancet, 29 Apr. 1978, 898-900.

2. Baliniuk, L. T. et al. Computed tomography of systemic lupus erythematosus. Radiol. 124: 119-121, 1977.

3. Gonzalez-Scarano, F. et al. Cranial computed tomography in the diagnosis of systemic lupus erythematosus. Ann. Neurol. 5: No. 2, 158-165, 1979.

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5. Johnson, R. T. and Richardson, E. P. The neurological manifestations of systemic lupus erythematosus. Med. 47: No. 4. 337-369, 1968.

6. Finn, R. and Rudolf, N de M. The electroencephalogram in systemic lupus erythematosus. Lances 10 Jun. 1978, 1255.

7. Feinglass, E. J. et al. Neuropsychiatric manifestations of systemic lupus erythematosus: Diagnosis, clinical spectrum, and relationship to other features of the disease. Med. 55: No. 4 323-339, 1976.

8. Tan, R. F. et al. Brain scan diagnosis of central nervous system involvement in systemic lupus erythematosus. Ann. Rheum. Dis 37: 357-362, 1978.

9. Kassan, S. S. and Kagen, L. J. Elevated levels of cerebrospinal fluid guanosine 3'5' - cyclic monophosphate (C-GMP) in systemic lupus erythematosus. Am. J. Med. 64: 732-741, 1978.

10. Kassan, S. S. and Kagen, L. J. Central nervous system lupus erythematosus. Measurement of cerebrospinal fluid cyclic GMP and other clinical markers of diseases activity. Arth. Rheum. 22: No. 5, 449-457, 1979.

11. Bennahum, D. A. et al. Brain scan findings in central nervous system involvement by systemic lupus erythematosus. Ann. Int. Med. 81: 763-774, 1974.

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13. Bodechtel, G. Differentialdiagnose neurologisher Krankheitshilder, 229. Stuttgart: Georg Thieme, 1958.

14. Silverstein, A. N. Y. Med. J. 63: 2945, 1963.

15. Diedericksen, H. Ugeskr. Laeg. 127: 1220, 1965.

16. Trevor, R. P. et al. Angiographic demonstration of major cerebral vessel occlusion in systemic lupus erythematosus. Neuroradiol. 4: 202-207, 1972.

17. Kitching, G. B. et al. Angiographic demonstration of lupus cerebral pheblitis with communicating hydrocephalus. Neuroradiology 14: 59-63, 1977.

18. Small, P. et al. Central nervous system involvement in SLE. Diagnostic profile and clinical features. Arth. Rheum. 20: No. 3, 869-878, 1977.

TABLE 54

Manifestations and Course of 67 Episodes of Neuropsychiatric SLE

Manifestation	Course			
	A. Steroid change*		B. No steroid change	
	Improved	Not improved	Improved	Not improved
Psychiatric	17	2	—	—
Psychiatric-seizure	3	1	—	—
Seizure disorder	3	—	5	—
Multifocal disease**	8	3	—	1
Peripheral neuropathy	3	2	—	—
Peripheral and cranial neuropathy	1	1	—	—
Cranial neuropathy	1	—	—	—
Cerebrovascular accident	2	—	2	1
Papilledema	3	—	-	—
Scotomata	2	—	—	—
Meningitis	—	—	1	—
Myelitis and optic neuritis	1	—	—	—
Cerebellar	1	—	—	—
Long tract	1	—	—	—
Chorea	1	—	1	—
Total	47	9	9	2

* Group A includes 24 episodes in which steroids were initiated and 32 in which dosage increments were used. Group B includes seven in which no steroids were given and four in which steroids were continued at previous doses.

** The term refers to three or more NP features occurring with a clinical pattern not explained by a single lesion. Seizures occurred in six.

(From Reference 4)

Only 2 of the 140 patients were felt to have steroid-induced psychoses. It was concluded that steroids appeared to be of benefit in a substantial number of patients although their precise role was difficult to quantitate.

The standard of treatment of CNS-SLE is shown in Table 55.

TABLE 55

Treatment of CNS Lupus

Corticosteroids
- Usual Dose 60-100 mg prednisone/d
- High Dose 200-300 mg prednisone/d

Immunosuppressive Drugs
- Azathioprine 3 mg/kg/d
- Cyclophosphamide 2 mg/kg/d

5. Treatment

Only a few studies have attempted to determine the role of steroids in treatment of CNS-SLE. No double-blind controlled studies have been performed.

The effect of steroid therapy in 28 patients with 52 episodes of neuropsychiatric disease was evaluated (1,2). There was no evidence that therapy with very large doses of steroids was beneficial (100-500 mg prednisone per day). Of the deaths involving the CNS, two were attributable to active CNS disease and 5 were believed due to complications of therapy. Twelve patients had major complications of steroid therapy. Functional psychosis was usually precipitated by steroid therapy and responded to a reduction in steroid dosage and administration of psychoactive drugs.

Gibson and Myers (3) similarly concluded that treatment with massive doses of steroids (>100 mg) was not obviously more effective than treatment with smaller doses. Their data suggests that an intermediate dose (30-100 mg per day) is most beneficial (Table 53).

TABLE 53

Details of 52 separate neurological episodes and response to corticosteroid therapy in various doses

Treatment group (daily prednisone)	*Outcome*	*Convulsions*	*Psychosis*	*Hemiplegia*	*Headache*	*Papilloedema*	*Total*
Massive dose (> 100mg)	Improved	2	5	–	–	2	9 (60%)
	Relapsed	2	2	2	–	–	6 (40%)
Intermediary dose (30-100mg)	Improved	5	5	3	2	–	15 (83%)
	Relapsed	–	–	2	–	1	3 (17%)
Low dose (< 30mg)	Improved	3	3	3	2	1	12 (63%)
	Relapsed	–	4	3	–	–	7 (37%)
Total		12	19	13	4	4	52

(From Reference 3)

Feinglass et al (4) demonstrated that 82% of neuropsychiatric episodes in their series occurred while patients were on no steroids or on low dose therapy (Table 54).

References - CNS-SLE - Treatment

1. Sergent, J. S. et al. Central nervous system disease in systemic lupus erythematosus. Am. J. Med. 58: 644-653, 1975.

2. Sergent, J. S. and Lockshin, M. D. Treatment of central nervous system lupus erythematosus. Ann. Int. Med. 80: 413-414, 1974.

3. Gibson, T. and Myers, A. R. Nervous system involvement in systemic lupus erythematosus. Ann. Rheum. Dis. 35: 398-406, 1976.

4. Feinglass, E. J. et al. Neuropsychiatric manifestations of SLE: diagnosis, clinical spectrum, and relationship to other features of the disease. Medicine 55: 323-339, 1976.

A case in which unusually diffuse involvement of the CNS was present has been described (4). At autopsy this patient had diffuse lymphocytic and plasma cell infiltration of the subarachnoid space and perivascular spaces of the brain associated with focal deposition of granular or hyaline material in the leptomeninges, vascular changes compatible with rheumatoid disease in the pia-arachnoid and in the brain tissue and numerous typical rheumatoid nodules of the leptomeninges, especially over the temporal poles. A second report described meningeal involvement in a patient with chronic rheumatoid arthritis (4). Pachymeningitis involving the entire thoracic region has also been reported (5).

Several cases compatible with cerebral vasculitis have been reported (6-13). Postmortem examination of one patient showed IgM deposit with rheumatoid factor activity in the choroid plexus (7).

Vertebral bodies may also be affected with eventual erosion and collapse (14-16). These lesions may be difficult to differentiate from tumor or infection.

Three other types of cervical spine involvement have been reported. One is rheumatoid discitis (17). In this condition the annulus fibrosus and normal intervertebral disc substance are replaced by rheumatoid pannus, which arises directly in the middle of the neurocentral joints. The second is spinal cord injury and myelopathic disease resulting from thickening and fibrosis of the dura without bone compression (18). The third and most common type of cervical spine involvement is atlantoaxial subluxation with secondary cervical myelopathy. The odontoid process forms two synovial joints, one anteriorly with the atlas and one posteriorly with the transverse ligament of the atlas (Fig. 18).

Figure 18

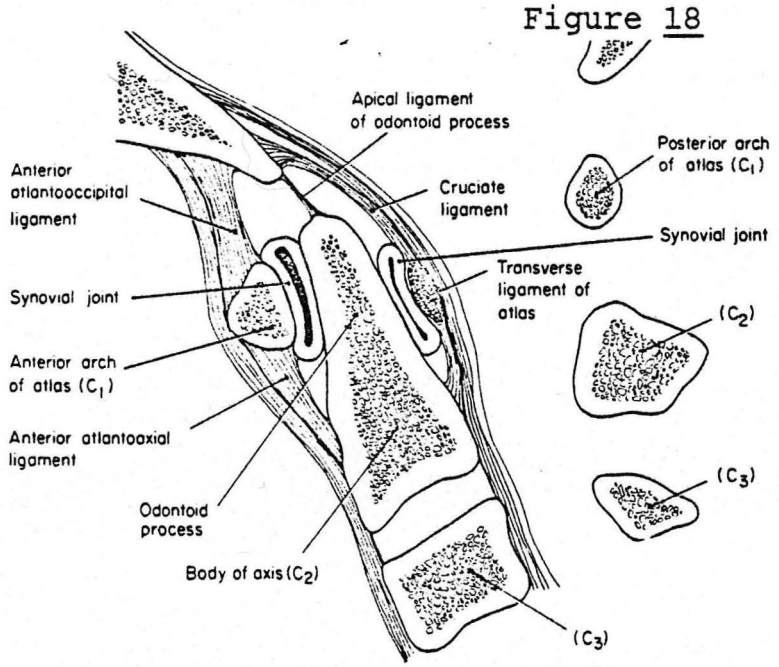

Fig. 2. Anatomic relation of the odontoid process of C2 with synovial joints and with the anterior arch and transverse ligament of the atlas (C), from Boyle and Buchanan.[14]

(From Reference 19)

While the usual dosage of steroids used is approximately 60 to 80 mg per day, some workers apparently use very high doses, e.g., 200-500 mg prednisone per day. Immunosuppressive drugs may be used in instances in which the disease is unresponsive to steroids or there are severe steroid-induced complications.

TABLE 58

Clinical Neurological Findings in 32 Patients with Severe RA and Myelopathy

Neurological Finding	No. of Patients
Weakness	
Upper and lower limbs	27
Legs alone	3
Increased reflexes	
Upper and lower limbs	26
Legs alone	6
Babinski response	25
C2 radicular pain	19
Astereognosis (hands)	18
Altered position sensation (feet)	11
Decreased vibration sense	
Level to clavicle	16
Level to thorax, or legs alone	7
Sensory level (to pinprick)	
Cervical	15
Hemisensory	2
Thoracic	2
Sphincter dysfunction (bladder and/or rectal)	16
Cranial nerve abnormalities	7
Posterior circulation TIAs	6
"Cerebellar" signs	2

(From Reference 26)

Surgical fixation is necessary when there is gross vetebral displacement (27). However, conservative treatment such as attempting to immobilize the neck with a cervical collar is probably the best therapy (19). In fact, surgical therapy has not been ideal, since neurologic complaints frequently return (28). Studies of x-rays of 130 patients showed that over a 5-15 year followup period 46 patients died; 4 developed spinal cord involvement and 6 acquired symptoms of vertebral ischemia. In the 84 survivors, approximately 25% increased their degree of subluxation, less than 50% remained the same, and 25% either improved or recovered completely (29).

B. Rheumatoid Arthritis

The major types of nervous system involvement include nodules in CNS, cerebral vasculitis, cervical myelopathy due to atlantoaxial subluxation, entrapment or compression neuropathy (carpal tunnel syndrome, tarsal tunnel syndrome, ulnar nerve entrapment), and neuropathy due to arteritis. A more complete tabulationn is shown in Table 57.

TABLE 56
NEUROLOGIC INVOLVEMENT

Nodules in CNS

Cervical myelopathy due to Atlanto-Axial Subluxation

Entrapment or Compression Neuropathy
1) Carpal Tunnel Syndrome
2) Tarsal Tunnel Syndrome
3) Ulnar Nerve Entrapment
4) Posterior Interosseous Nerve Entrapment

Neuropathy due to Arteritis

A more complete list is shown in Table .

As with other organ systems, the CNS can be involved with rheumatoid nodules, as infrequently reported.

TABLE 57

Neurologic Manifestations of Rheumatoid Arthritis

Articular-cervical spine disease
Cervical subluxations (four types)
C1 moves anteriorly on C2
C1 moves posteriorly on C2
Vertical subluxation of odontoid
"Staircase" or multiple lower level subluxations
Radiologic findings, often with clinical symptoms
"Double crush" syndrome
Narrowed disc spaces above C5
Radiologic findings without clinical symptoms
Vertebral plate erosion
Apophyseal joint erosion
Basilar impression of the skull
Extraarticular
Peripheral neuropathies
Compression leading to entrapment
Mild sensory neuropathy with a good prognosis
Diffuse sensorimotor neuropathy
Fulminant sensorimotor neuropathy
Vasculitis
Mononeuritis complex
Cerebral vasculitis
Dural rheumatoid nodules causing brain and spinal cord compression

(From Reference 1)

Thus both the odontoid process itself and the transverse ligament are subject to erosion because of their proximity to synovial tissue. Laxity of the transverse ligament also may occur, allowing slippage of the odontoid process posteriorly, causing pressure on the spinal cord. In addition, vertebrobasilar insufficiency may result from torsion of the vertebral arteries caused by the subluxation.

By x-ray of the cervical spine using lateral tomography in flexion, subluxation is probably present if the distance between the posterior aspect of the anterior arch of the atlas and the anterior part of the odontoid process is greater than 2.4 mm in females and 3.0 mm in males. Subluxation can be detected clinically by gently rocking the head. Using the 3-mm x-ray criterion, atlantoaxial subluxation was found in 36 of 100 successive rheumatoid patients (20). Other studies found subluxation in 25% of 76 outpatients studied (21), 19% of hospitalized patients (32), and 71% of rheumatoid patients with neck symptoms (23).

Nakano (1) described four types of cervical subluxation (Table 7): (1) C1 moves anteriorly on C2, which as described above is the most common form; (2) C1 moves posteriorly on C2, resulting from severe erosion or fracture of the odontoid; (3) vertical subluxation of the odontoid and body of C2, which is rare and results from destruction of the lateral atlantoaxial joints or of the bone around the foramen magnum; and (4) "staircase" subluxation or subluxation of one vertebra on another, often being multiple and caused by destruction of the apophyseal joints. It occurs below the level of C2 and is the second most common type of cervical subluxation. The combination of degenerative disease of the cervical spine with variable degrees of spondylosis and the carpal tunnel syndrome occurring in a patient with RA has been termed the "double crush" syndrome. Neurologic involvement consists primarily of cervical cord myelopathy with a pathologic increase in deep tendon reflexes or positive plantar responses. In one study (20), 24 of 36 patients with atlantoaxial subluxation by x-ray had symptoms of cervical cord myelopathy. These symptoms may increase in severity, and death may result from severe compression of the cord, obstruction of the vertebral arteries, or snapping of the weakened odontoid process, which impinges into the foramen magnum (24, 25).

The findings in 32 patients studied by Nakano et al are shown in Table 58.

A more recent study by Nakano et al (26), however, suggested that the preferred approach was use of a halo traction device followed by posterior fusion, with or without laminectomy. Thus once it was clear that neurological signs or symptoms were progressive, little was to be gained by waiting or by nonsurgical therapy (Table 59).

TABLE 59

Modes of Therapy in Patients with Cervical Myelopathy Secondary to RA Cervical Disease

Therapy	No. of Patients	No. Worse after One Year
Nonsurgical (collar, halter traction, medical)	19	7
Surgical	12	1
Posterior laminectomy	3	0
Traction, then laminectomy	3	0
Posterior fusion	4	1
Traction, then fusion	2	0
Halo traction alone	1	0

(From Reference 26)

TABLE 60

Entrapment Syndromes of Rheumatoid Arthritis

Median nerve
- Carpal tunnel syndrome
- "Double crush" syndrome of the median nerve

Ulnar nerve
- Cubital canal syndrome--at elbow
- Canal of Guyon syndrome--at wrist
- "Double crush" syndrome of ulnar nerve

Radial Nerve
- Posterior interosseous syndrome

Sciatic nerve
- Tibial or common peroneal entrapment by a Baker (popliteal) cyst

Common peroneal nerve
- Pressure palsy

Posterior tibial nerve
- Tarsal tunnel syndrome
- Medial plantar syndrome
- Lateral plantar syndrome

(Adapted from reference 30)

Neck trauma should be avoided if at all possible in these patients. Automobile accidents with whiplash injury, intubation, and extreme head positions under anesthesia or even at the hairdresser should all be avoided. [However, in spite of the above considerations and precautions, the experience of the author suggests that the majority of patients with significant subluxation by x-ray do not have cord symptoms].

Entrapment or compression neuropathies may occur in patients with RA (Table 59). (30) These include the carpal tunnel and tarsal tunnel syndromes, ulnar nerve entrapment syndrome, and entrapment of the posterior interosseous branch of the radial nerve.

Median nerve.

The carpal tunnel syndrome is the most common of these entrapment syndromes in RA. In a study of 29 patients (31) and 23 normal control individuals over the age of 40 years, the symptoms of numbness, tingling, and burning in the median nerve distribution were found to be significantly increased in the patients. There was no relationship between symptoms and sex, duration of RA, erythrocyte sedimentation rate, rheumatoid factor, functional class, x-ray stage, limitation of wrist motion, swelling, or wrist tenderness. Symptoms were related to a positive Tinel test. By electromyography, symptomatic rheumatoid patients had significantly slower conduction across the carpal tunnel than the remaining rheumatoid patients. This study concluded that complaints of numbness, tingling, and burning in the median nerve distribution plus a positive Tinel (tapping over median nerve) or Phalen (flexion of wrist to compress median nerve) test suggests the diagnosis of carpal tunnel syndrome.

The diagnosis can be substantiated by electromyography. Approximately two-thirds of patients with verified carpal tunnel syndrome will have prolonged median motor latencies when the nerve is stimulated at the wrist (32, 33). About 85%-95% of affected hands will have prolongation of median distal sensory latencies (beyond 3.5 msec) (34). In a group of 36 patients with early RA, the incidence of electrodiagnostic abnormalities was 5.5%. The incidence of patients with clinically diagnosed carpal tunnel syndrome who underwent electrical tests was 17%, and the overall incidence was 23% (35). Splinting the wrist in slight extension or injecting a corticosteroid preparation into the carpal tunnel provides prompt short-term relief in the majority of cases (34). However, patients with thenar atrophy or progression of numbness and weakness should have surgery (36). Sectioning the transverse carpal ligament will usually relieve the patient's symptoms. The "double crush" syndrome is the combination of cervical spondylosis and carpal tunnel syndrome in a patient with RA.

Ulnar nerve.

Ulnar nerve neuropathy secondary to compression at the cubital fossa occurs uncommonly in the rheumatoid patient. Compression is due to synovitis extending extraarticularly (1). A large olecranon bursa may also compress the ulnar nerve. Decompression and excision of the synovial mass results in alleviation of symptoms. Elbow entrapment causes weakness of the flexor carpi ulnaris, flexor digitorum profundus of the fourth and fifth fingers, and intrinsic muscles. Sensory loss involves the dorsum of the ulnar aspect of the hand. Rarely the synovium within the carpal tunnel can bulge and compress the ulnar nerve proximal to Guyon's canal, resulting in symptoms that simulate ulnar nerve neuropathy at the elbow. If ulnar nerve entrapment and lower cervical spine disease (C8, T1) occur concomitantly, as with the median nerve, it is known as the "double crush" syndrome of the ulnar nerve.

Radial Nerve.

A few patients have been reported with posterior inserosseous nerve paralysis secondary to RA (37-39). Clinically, there is an inability to extend the fingers and thumb. The condition is a compression neuritis of the posterior interosseous nerve secondary to elbow synovitis bulging anteriorly against the overlying supinator muscle. In many patients the diagnosis of extensor tendon rupture has erroneously been made (37). Treatment by injection of corticosteroids may help. Synovectomy with radial head resection may also be of value.

Sciatic nerve.

Occasional patients with RA and synovitis of a knee will develop popliteal (Baker) cysts. They may dissect into the calf and sometimes rupture. When inflamed they may closely simulate thrombophlebitis, including a positive Homan sign. If anticoagulants such as heparin are given, hemorrhage into the cyst may occur. Such a cyst may involve the peroneal or tibial nerves or both (1). If the common peroneal nerve is involved, one will see paresis of the peroneal muscles, tibialis anterior, extensor hallucis longus, extensor digitorum logus, and extensor digitorum brevis. Sensory loss will occur over the lateral leg and dorsum of the foot. When the tibial nerve is involved, there will be weakness of the gastrocnemius, soleus, tibialis posterior, flexor digitorum longus, flexor hallucis longus, and the intrinsic muscles of the foot, including the heel and the posterolateral aspect of the calf.

Aspiration of synovial fluid from the knee joint followed by instillation of corticosteroids may improve symptoms when popliteal or posterior calf cysts communicate with the knee

joint. If the cyst continues to be a problem symptomatically, synovectomy of the knee may be necessary in order to decrease synovial fluid formation. If improvement is not permanent, then careful dissection and ligation of the pedicle of the cyst may be required.

Peroneal nerve.

Pressure palsy of the common deep or superficial peroneal nerve is apparently due more to immobility and a pressure-vulnerable area rather than a true complication of the rheumatoid process (1).

Posterior tibial nerve.

The tarsal tunnel syndrome (40) results from compression of the posterior tibial nerve beneath the flexor retinaculum along the medial malleolus in the foot. It is caused by rheumatoid tenosynovitis affecting the tendon sheaths of the tibialis posterior long foot flexor tendons. Clinically there are paresthesias over the first three toes, and patients may complain of "burning feet", expecially at night, and may have difficulty with the intrinsic toe muscles. As with the carpal tunnel syndrome, local corticosteroid injection may be helpful. A partial tarsal tunnel syndrome involving only the medial or lateral plantar nerves may also be seen. Complaints include weakness or burning of the feet.

Peripheral neuropathy

This is a well-recognized complication of RA (41, 42). A mild distal sensory neuropathy and a severe sensorimotor neuropathy (mononeuritis multiplex) are the two predominant clinical patterns (43). In each, the major etiologic factor is an occlusive arteriopathy (44, 45). According to one study (46), segmental demyelination is the fundamental nerve abnormality in RA. In a study by Dyck et al (47), nerve fiber degeneration was found to be related to sites of vessels occluded due to arteritis. With the distal sensory neuropathy, patients may complain of paresthesias, dysesthesias, or "burning feet." Examination may show decreased touch and pin sensation distally in the toes and feet and decreased vibratory sensation. With the more severe sensorimotor neuropathy, the patient may have symmetric distal weakness of the limbs in addition to diminished touch and vibratory sensations. In a study of five patients with rheumatoid neuropathy of vascular etiology, nerve fibers showed axonal degeneration (48). One patient with acute neuropathy had acute necrotizing arteritis in vessels of the sural nerve with deposits of IgG, IgM, and B_1C present (Table 61).

TABLE 61

Vessel Immunopathology in Sural Nerve Biopsies

Patient	Duration before biopsy (days)		Arteries	
	Neuropatny	Steroid therapy*	Histologic change	Immunofluorescence
1	8	0	Fibrinoid necrosis; PMN and monocell infiltrate	IgG, IgM, & 1C
			Intimal proliferation	Fibrinogen
2	60	25	Intimal proliferation	Fibrinogen
3	48	25	Intimal proliferation; perivascular fibrosis	Fibrinogen
4	53	0	Intimal proliferation	†
5	60	90	Perivascular mononuclear cells	†

*Dosages: Patient 2, prednisone, 100 mg/day; Patient 3, prednisone, 80 mg/day; Patient 4, methylprednisolone in polyethylene glycol, single injection, 40 mg; Patient 5, prednisone, 15 mg/day
†Insufficient vessels for evaluation

(From Reference 48)

Intimal proliferation was present in 4 of the 5 cases, suggesting that sural nerve biopsy may be valuable for diagnosis of peripheral neuropathy. Unfortunately, as shown in Table 62, two patients without clinical evidence of peripheral neuropathy (cases 1 and 7) also had internal proliferation in the arteries supplying the sural nerve.

TABLE 62

Summary of pathological data in rheumatoid patients

Pathological pattern	Case	Anatomical stage	Sural nerve findings			
			Arterial changes	Cellular or C.T. changes	Myelinated fibre population	Teased fibres
Group I	2	II	None	None	Normal	Segmental demyelination, pronounced remyelination
	3	II	None	None	Normal	Segmental demyelination, pronounced remyelination
	4	II	None	Perineural thickening	Normal	Segmental demyelination, pronounced remyelination
	5	II	None	None	Normal	Segmental demyelination, pronounced remyelination
Group II	1	I	Intimal proliferation, partial occlusion	Perineural thickening	Normal	Segmental demyelination, minimal remyelination
	7	III	Intimal proliferation, partial occlusion	None	Normal	Segmental demyelination, minimal remyelination
Group III	6	III	Elastic lamina fragmentation	Perineural thickening, Schwann cells diminished	Patchy loss of large myelinated fibres	Wallerian-type degeneration
	8*	III	Intimal proliferation, total occlusion	Perineural thickening, Schwann cell proliferation	Severe fibre loss	Wallerian-type degeneration
	9**	III	No vessels	Perineural thickening, Schwann cells diminished	No myelinated fibres remain	End-stage Wallerian-type degeneration

Rheumatoid factor (immunofluoresence)—negative in all cases.
* Mild, distal sensory neuropathy.
** Severe, sensorimotor neuropathy.

(From Reference 46)

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C. Polyarteritis Nodosa (PAN)

The major neurological manifestations of polyarteritis nodosa (PAN) are shown in Table 63. (1-8).

TABLE 63

Neurologic Manifestations of Polyarteritis Nodosa

Peripheral Neuropathy - 60-70% of Patients
- Mononeuropathy
- Multiple Mononeuropathy
- Polyneuropathy

Cerebral Manifestations - 40-50% of Patients
- Arteritis of Small and Medium-Sized Arteries with Thromboses and Hemorrhages
- Convulsions, Visual Disturbances, Vertigo, Dizziness, Focal Cerebral Deficits, Coma

Uremia and Acute Hypertensive Crisis

Cranial Nerve Involvement - 15-20% of Patients
- Especially II - VIII

Spinal Cord Involvement - Rare
- Transverse Myelitis

Cogan's Syndrome
- Non-syphilitic Interstitial Keratitis, Mixed-conduction and Nerve Deafness and Labyrinthine Deficits

Pathologically, PAN is characterized by focal, disseminated, inflammatory lesions of small and medium sized arteries. Lesions are segmental, "nodal" and result in scarring, occlusion, small aneurysms or hemorrhage.

In a series of 40 patients with PAN (9), 15 or 38% of patients had peripheral nervous system involvement and 11 or 28% had involvement of the CNS (Table 64).

TABLE 64

Clinical Presentation in 40 Patients with Polyarteritis

System	Number	Per cent
Constitutional symptoms		
Organ system involvement		
Skin	22	55
Muscle	22	55
Gastrointestinal tract	16	40
Peripheral nervous system	15	38
Joints	14	35
Central nervous system	11	28
Hypertension	10	25
Lungs	9	23
Heart	7	18
Ear, nose or throat	6	15
Kidneys	5	13
Peripheral vascular system	4	10
Eye	2	5
Endocrine organs	2	5

(From Reference 9)

An angiographic study of 17 patients was performed by Travers et al (10). Ten (59%) had mononeuritis or polyneuritis and 7 (41%) had CNS involvement. The incidence of CNS involvement was higher in a group with demonstrable aneurysms (Table 65).

TABLE 65

. Clinical Features in PAN

	Aneurysm Group* (10 Patients)	Non-aneurysm Group (7 Patients)	Overall (17 Patients)
Sex	7M:3F	6M:1F	
Age (yr)	15–58 (mean 42)	16–56 (mean 40)	
Duration of disease (mo)	4–20 (mean 8.3)	17 days–24 mo (mean 8.8)	
Weight loss	9 (90%)	3 (43%)	12 (71%)
Fever	8 (80%)	5 (71%)	13 (13%)
Hypertension—mild	2 (20%)	3 (43%)	5 (29%)
—severe	6 (60%)	1 (14%)	7 (41%)
Retinopathy	6 (60%)	2 (28%)	8 (47%)
Renal involvement	8 (80%)	5 (71%)	13 (77%)
Pulmonary involvement	8 (80%)	4 (57%)	12 (71%)
Cardiac involvement	9 (90%)	6 (86%)	15 (89%)
CNS involvement	5 (50%)	2 (29%)	7 (41%)
Mononeuritis/polyneuritis	6 (60%)	4 (57%)	10 (59%)
Abdominal pain/diarrhoea	9 (90%)	2 (29%)	11 (65%)
Liver involvement	6 (60%)	5 (71%)	11 (65%)
RES involvement	5 (50%)	3 (43%)	8 (47%)
Polyarthritis	5 (50%)	4 (57%)	9 (53%)
Skin	5 (50%)	6 (86%)	11 (65%)
ENT symptoms	2 (20%)	3 (43%)	5 (29%)
Muscle involvement	8 (80%)	5 (71%)	13 (77%)

*Divided on the basis of angiographic findings (Table 4).

(From Reference 10)

CNS manifestations included hemiplegia, aphasia or constructional apraxia, subarachnoid hemorrhage due to ruptured aneurysm, nonsteroid related psychosis, and drowsiness and confusion. Cranial nerve involvement was not seen.

Peripheral nerve involvement included 2 patients with a symmetrical polyneuropathy. In 8 patients it took the form of mononeuritis affecting one (3 patients), two (3), 3 (1), or 5 (1) peripheral nerves. The nerves affected included common peroneal (8 patients), sural only (3), lateral cutaneous nerve of thigh (1), radial (1), ulnar (3), and median (1). Thus the nerves affected most often originated from the sacral plexus. (12/17).

A large series by Frohnert and Sheps (11) of 130 cases of PAN demonstrated that 72 (55%) of the patients had nervous system inolvement. 68 of these had mononeuritis multiplex and 4 had CVA's (Table 66).

TABLE 66

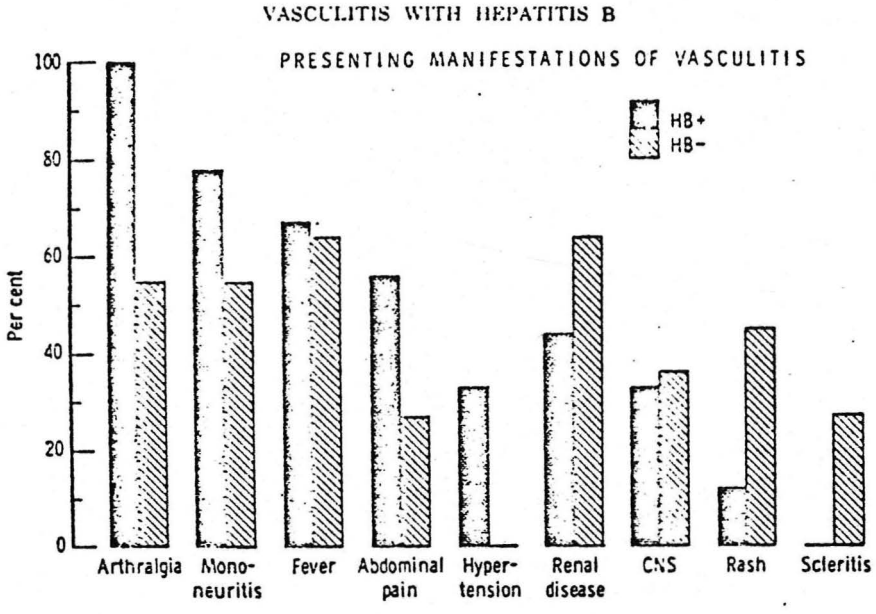
CLINICAL FEATURES IN 130 CASES OF PERIARTERITIS NODOSA

System and Symptom	Cases	
	No.	%
General		
Fever	99	76
Weight loss	92	71
Articular	76	58
Arthralgia	43	
Arthritis	33	
Epidermal	75	58
Rash	37	
Petechiae	36	
Nodules	24	
Ulcerations	8	
Livedo reticularis	6	
Pruritus	3	
Raynaud's phenomenon	2	
Nervous	72	55
Mononeuritis multiplex	68	
Cerebrovascular accident	4	
Respiratory	50	38
Bronchitis	26	
Pneumonia	21	
Asthma	20	
Pleurisy	5	
Hemoptysis	4	
Muscular	39	30
Myalgia	39	
Gastrointestinal	18	14
Duodenal ulcer	11	
Mouth ulcer	4	
Gastric ulcer	4	
Melena	3	
Hematemesis	1	
Jaundice	1	
Small bowel infarction	1	
Cardiac	13	10
Congestive heart failure	8	
Angina pectoris	3	
Pericarditis	2	
Myocardial infarction	1	
Renal	11	8
Flank pain	9	
Hematuria	5	
Vascular	7	5
Phlebitis	4	
Arterial occlusion	2	
Lymphangitis	1	
Genital	3	2
Epididymitis	2	
Orchitis	1	

(From Reference 11)

In the type of PAN associated with Hepatitis B (vasculitis with Hepatitis B antigenemia), long term observations were reported for 9 patients (Figure 20). Mononeuritis multiplex occurred in 7 of the 9 hepatitis B positive patients and CNS involvement occurred in approximately 35%.

Figure 20



(From Reference 12)

In a similar study of 10 patients with diffuse arteritis associated with Hepatitis B antigenemia (13), peripheral neuropathy and CNS disorders occurred in 3 patients each. Three patients developed a stocking-glove sensorimotor neuropathy typical of mononeuritis multiplex characterized by weakness, footdrop, and impairment of pain and sensory perception. Necrotizing vasculitis was present on histologic examination of muscle and/or peripheral nerve.

Stupor, confusion and poor memory, without localizing neurological signs, were features of CNS involvement in one individual. CSF was normal. A second patient had transient global aphasia, motor retardation, and a right seventh nerve paresis associated with a CSF protein of 93 mg/dl. Major motor seizures, headache, nausea and vomiting were recurrent features in a third patient. EEG's in all 3 patients were consistent with a diffuse encephalopathy.

An interesting case was reported by Schimmer and Bloch (14) in which the patient had mixed IgM - IgG cryoglobulinemia and PAN. The patient exhibited non-deforming arthritis, Raynaud's phenomenon, cutaneous vasculitis, and a sensory neuropathy. The patient also developed visual symptoms which were attributed to an alteration in the circulation in the posterior occiptal cortex.

D. Progressive Systemic Sclerosis (Scleroderma)

The nervous system is rarely involved in scleroderma. In a study of 130 patients, 24 were found to have a total of 28 neurologic manisfestations (1). However, none were definitely related to the primary pathological process of scleroderma. This may be due to the lack of collagen in the brain.

Involvement of the peripheral nervous system is also rare, but mild peripheral neuropathy results in paresthesias and sensory lesions. Trigeminal sensory and other neuropathies (2-6) and subacute combined degeneration following vitamin B^{12} deficiency caused by sclerodermal involvement of the small intestine (7) have also been reported.

References - Polyarteritis Nodosa

1. Aita, J. H. Neurologic manifestations of periarteritis nodosa (1972). Neb. Med. J. 57: 362-366, 1972.

2. Kimbrell, O. C. and Whiliss, J. H. Polyarteritis nodosa complicated by bilateral optic neuropathy. J A M A 201 (No. 1): 139-140, 1967.

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E. Dermatomyositis and Polymyositis

According to Pearson (1), pure neurologic symptoms do not occur in this condition, and deep tendon reflexes are normal or depressed in accordance with the associated muscular weakness.

There is a case report of a patient with dermatomyositis and agammaglobulinemia who developed a subarachnoid hemorrhage which was believed to be due to CNS vasculitis (2).

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F. Rheumatic Fever

This disease is an unusual cause of cerebral vasculitis. The most common type of involvement is that of Sydenham's chorea (1).

A comparison of clinical and laboratory features of Sydenham's chorea and chorea preceding SLE is shown in Table 67.

TABLE 67

Table 3.—Comparison of Clinical and Laboratory Features of Sydenham's Chorea and Chorea Preceding Systemic Lupus Erythematosus (SLE)

	Sydenham's Chorea*	Chorea Preceding SLE*
Age at onset, yr		
Range	6-18	7-51
Mean	9-11	17
Median age	Same	15
Sex ratio		
Female:male	2:1	6:1
Duration of chorea		
Range	4 wk-1 yr	1 wk-6 mo
Average	10 wk	12 wk
Frequency of relapse	30%	50%
Laboratory data		
Elevated erythrocyte sedimentation rate	30%	85%
Antistreptolysin O titer ≥ 250 Todd units	63%†	80%

*See also Table 1.
†When more than one determination is performed.

(From Reference 2)

References - Dermatomyositis and Polymyositis

1. Pearson, C. M. In Arthritis and Allied Conditions, D. J. McCarty, Ed., 9th Ed., Lea and Febiger, Phila., 1979, p. 748.

2. Gotoff, S. P., Smith, R. D. and Sugar, O. Dermatomyositis with cerebral vasculitis in a patient with agammaglobulinemia. Am. J. Dis. Child. 123: 53-56, 1972.

III. Granulomatous Vasculitis

A. Wegener's Granulomatosis (WG)

A simplified summary of the most common manifestations of nervous system involvement is shown in Table 68.

TABLE 68

NERVOUS SYSTEM INVOLVEMENT IN WEGENER'S GRANULOMATOSIS

Granulomatous Lesions of CNS

Vasculitis of CNS

Vasculitis of Peripheral Nervous System

Infection of CNS

(From References 1-5)

A more complete outline of the neurological manifestations as suggested by Drachman (6) is shown in Table 69. He suggests 3 basic types of processes: those caused by direct granulomatous invasion by contiguity; those caused by remote granulomatous lesions; and those resulting from vasculitis involving either the CNS or peripheral nervous system.

References - Rheumatic Fever

1. Lessof, M. Sydenham's chorea. Guys Hosp. Rep. 107: 185-206, 1958.

2. Groothuis, J. R. et al. Lupus-associated chorea in childhood. Am. J. Dis. Child. 131: 1131-1134, 1977.

TABLE 69

NEUROLOGICAL MANIFESTATIONS OF WEGENER'S GRANULOMATOSIS

Condition	% of Total Cases
I. Granulomatous invasion by contiguity	26
Exophthalmos	12
Optic nerve or chiasm involvement	7
Pituitary involvement; diabetes insipidus	4
Vestibular involvement; VIIIn. deafness	3
Pathologic involvement of base of brain, meninges	7
Facial neuritis	4
Ophthalmoplegia	3
II. Remote granulomatous lesions	4
Cranial nerve involvement	2
Intracerebral multiple granulomata	1
Granuloma of skull	1
III. Vasculitis of nervous system	28
Mononeuritis multiplex	13
Polyneuritis	8
Intracerebral hemorrhage	3
Subarachnoid hemorrhage	2
Cerebral arterial thrombosis	3
Myopathy	4
Venous thrombosis	1

(From Reference 6)

The incidence of involvement of the various cranial nerves is shown in Table 70.

TABLE 70

CRANIAL NERVE INVOLVEMENT IN WEGENER'S GRANULOMATOSIS

Nerve	No. of Cases Involved
Olfactory	1
Optic	10
Oculomotor	9
Trochlear	7
Trigeminal	7
Abducens	8
Facial	8
Acoustic	8
Glossopharyngeal and Vagus	3
Spinal Accessory	3
Hypoglossal	1

(From Reference 7)

A summary of all neurological cases reported to 1976 is shown in Table 71.

TABLE 71

Neurologic Complications in Wegener Granulomatosis

Year	Author	No. of Cases	No. of Neurologic Complications	Type
1954	Godman and Churg[3]	29	1	Granuloma of dura
1955	Cogan[9]	4	1	Seventh to twelfth nerve palsy
1958	Walton[10]	56	16*	"Neuropathy"
1961	*New England Journal of Medicine*[11]	1	1	Seventh to twelfth nerve palsy
1963	Drachman[8]	105	57†	41% contiguous to nasal lesions 7% remote granulomas 52% vasculitis
1966	Carrington and Liebow[7]	16	1	Peripheral neuropathy
1967	Nielsen[12]	3	1	Eighth nerve deafness
1970	Cassan[13]	4	2	Paresis of ninth to twelfth cranial nerves (Collet-Sicard syndrome) "Meningeal lesions"
1971	Novack[14]	4	3	"Cerebritis," proptosis, orbital destruction Seventh nerve palsy; eighth nerve deafness Third nerve palsy; seventh nerve palsy
1973	Fauci and Wolff[6]	18	5	Peripheral neuritis, cerebral vasculitis, Peripheral neuritis, seventh nerve palsy Optic neuritis Seventh nerve palsy Fifth nerve involvement

* Includes Cogan[9].
† Includes Cogan[9], Case Records.[11]

(From Reference 8)

In a study of 21 patients at the NIH (9), 24% had either mononeuritis multiplex or cranial neuritis (Table 72).

TABLE 72

Typical Clinicopathological Features in 21 Patients with Wegener's Granulomatosis

Organ System Involved	Percent of Patients	Typical Features
Nasopharynx	91	Mucosal ulceration with necrotizing granulomata; saddle-nose deformity
Paranasal sinuses	95	Sinusitis; necrotizing granulomas; secondary bacterial infection
Ears	38	Serous otitis media
Eyes	43	Granulomatous sclerouveitis
Lungs	100	Bilateral nodular and cavitary infiltrates; necrotizing granulomatous vasculitis
Kidneys	81	Focal glomerulitis in early stage; fulminant glomerulonephritis in advanced cases
Heart	29	Coronary vasculitis; pericarditis
Nervous system	24	Mononeuritis multiplex; cranial neuritis
Skin	48	Ulcerations secondary to vasculitis
Joints	57	Fleeting polyarthralgia

(From Reference 9)

A study of 10 patients with WG by Reza et al (10) shows the nervous system involvement in comparison with other sites (Table 73).

TABLE 73

Organ System Involvement in 10 Patients with Wegener's Granulomatosus

Patient	Pharynx	Paranasal Sinuses	Ears	Eyes	Lungs	Kidney	Skin	Joint	Nervous System
1	+	+	+	+−−	+++	+++	−	−	+
2	++	+++	−	++++	+++	+	−	++	+++
3	++	++	++	−	++	−	−	−	+
4	+	−	−	+−−	++	+	−	−	+++
5	++	+++	++	−	+++	+++	−	−	+
6	++	+	++	−	+++	+++	−	−	+++
7	+++	++	−	+	+++	++	+++	++	−
8	+	++	−	−	+++	+	−	−	+++
9	+	++	−	−	+++	+++	−	++	+
10	+++	+++	+++	+	+++	+	−	−	−

\+ = mild.
++ = moderate.
+++ = severe.
++++ = extremely severe.

(From Reference 10)

In all cases cyclophosphamide induced complete remissions.

Haynes and Fauci (11) recently reported a fascinating case of a patient with diabetes insipidus associated with WG which was successfully treated with cyclophosphamide (11, 12). The lab data are shown in Table 74.

TABLE 74

. Laboratory Data before Cyclophosphamide Therapy in a Patient with Wegener's Granulomatosis and Diabetes Insipidus.

Measurement	Serum	Urine
	(mOsm/liter)	
Water-deprivation test:		
0 hr	287	87
3 hr	302	192
After 5 U of vasopressin subcutaneously	*	466
Plasma testosterone	567 ng/dl (normal, 250–1250)	
Plasma luteinizing hormone	23 mIU/ml (normal, 6–26)	
Plasma follicle-stimulating hormone	32 mIU/ml (normal, 5–25)	
Plasma prolactin	47.5 ng/ml (normal, 2–26)	

*Not done.

(From Reference 11)

The most likely pathogenesis was believed to be involvement of the hypothalmus or pituitary stalk by granulomatous infiltration. It was suggested that the granulomatous inflammatory process, either affecting hypothalamic vasculature or causing a mass lesion, led to secretory dysfunction of the supraoptic and paraventricular nuclei.

Optic involvement has been commonly reported (13-16). A recent case of cortical vein thrombosis was also described (17).

B. Granulomatous Angiitis

Granulomatous Angiitis is very similar to Wegener's granulomatosus. A comparison with other types of vasculitis is shown in Table 75.

TABLE 75

—*Differential Diagnosis*

	Principal Affected Vessels	Organ Involvement	Vascular Necrosis	Giant Cells	Eosinophils
Granulomatous angiitis of the CNS	arterioles, venules	principally CNS	+	+	−
Allergic granulomatosis of Churg and Strauss	small arteries and veins; extravascular	many	+	+	+
Cranial arteritis	small and medium-sized arteries	cranial extracerebral vessels	+	+	−
Periarteritis nodosa	small and medium-sized arteries	many	+	−	+
Takayasu's disease	large arteries	great vessels	±	+	−
Sarcoidosis	extravascular	lung, lymph nodes, many others	−	+	−

(From Reference 18)

The neurologic symptoms and signs in 16 cases are shown in Table 76.

TABLE 76

(From Reference 18)

The CSF findings are shown in Table 77.

TABLE 77

—*Granulomatous Angiitis of the CNS: Clinical Features in 16 Cases**

	No. of Patients
Duration	
3 days-6 weeks	8
9½ mo—3¾ yr	8
Symptoms and signs	
Mental changes	12
Headache	11
Hemiparesis	9
Dysphasia	8
Papilledema	6
Seizures	6
Diplopia	5
Impaired vision	4
Paraparesis	3

* Age of patients ranged from 18 to 96 years, with a mean of 50 years.

(From Reference 18)

References Granulomatous Vasculitis

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5. Friedmann, I. and Bauer, F. Wegener's granulomatosis causing deafness. J. Laryn. and Otol. 87: 449-464, 1973.

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9. Wolff, S. M. et al. NIH conference on Wegener's granulomatosis. Ann. Int. Med. 81: 513-525, 1974.

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The disease process pathologically in each of the patients was characterized by a granulomatous inflammatory reaction in the walls of cerebral vessels. Chiefly affected were small arteries and veins with a diameter of less than 200μ. Occasionally, larger vessels, including primary branches of the major cerebral arteries, showed evidence of the disease. In some cases the capillaries were also involved. Veins were frequently more involved than arteries. Serial sections demonstrated that multiple separate, discrete granulomas could be found along the course of a single blood vessel. The vascular lesions bore no constant relationship to bifurcations of vessels, in contradistinction to PAN, in which there appears to be a predilection for bifurcations.

Thus the major findings in this disease are summarized in Table 78 (18, 19).

TABLE 78

Granulomatous Angiitis

Clinical Symptoms and Signs
- Headaches
- Mental Changes
- Dysphasia
- Focal Motor Signs
- Ocular Disturbances

CSF Findings
- Elevated Pressure
- Lymphocytosis
- Increased Protein Levels
- Normal Glucose Values

Pathology
- Nodular, asymmetrical, giant-celled, granulomatous angiitis affecting all sizes and types of blood vessels within the CNS

Steroids are occasionally beneficial (18).

IV. Giant Cell Arteritis

A. Temporal Arteritis (TA) and Polymyalgia Rheumatica (PMR)

The major types of neurologic manifestations in these conditions are shown in Table 79 (1-14).

TABLE 79

Neurologic Manifestations of PMR-Giant Cell Arteritis Syndrome

Hemiparesis

Subarachnoid Hemorrhage

Diffuse Cerebral Dysfunction - Dementia, Confusion, Hallucinations or Coma

Visual Disturbances and Blindness

The typical site of temporal arteritis is shown in Figure 21.

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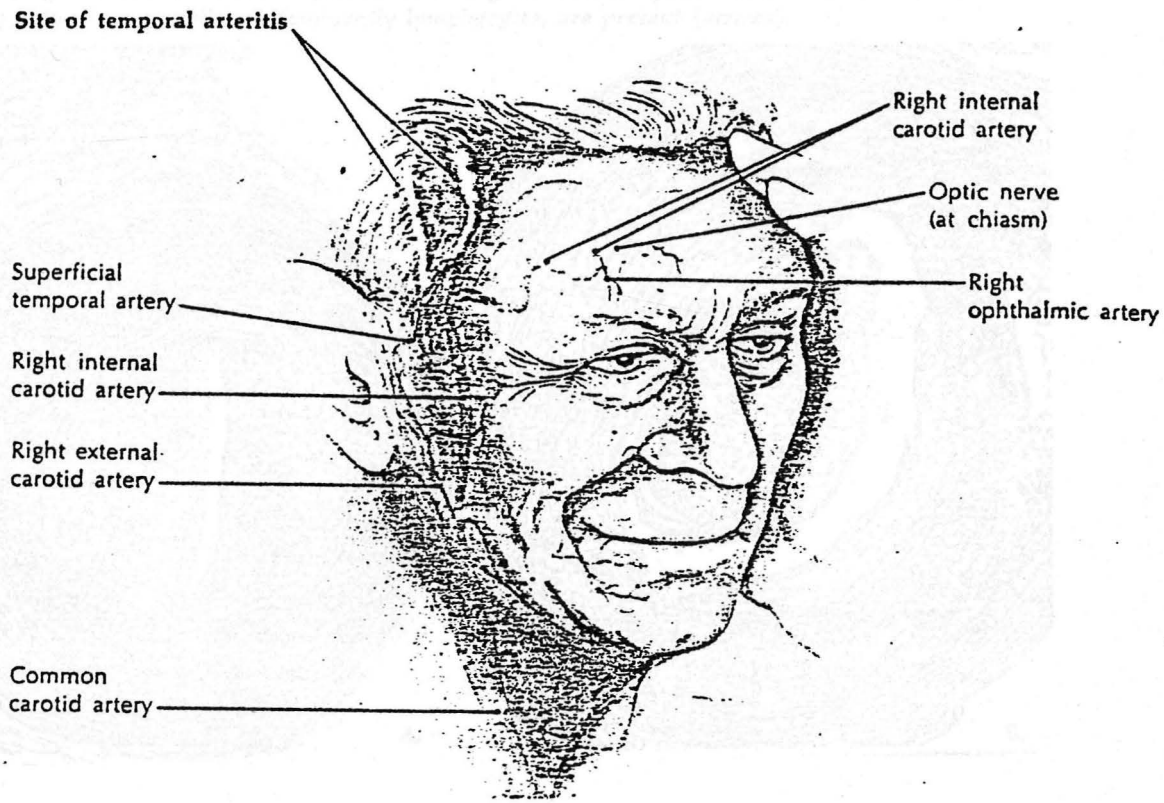
Figure 21

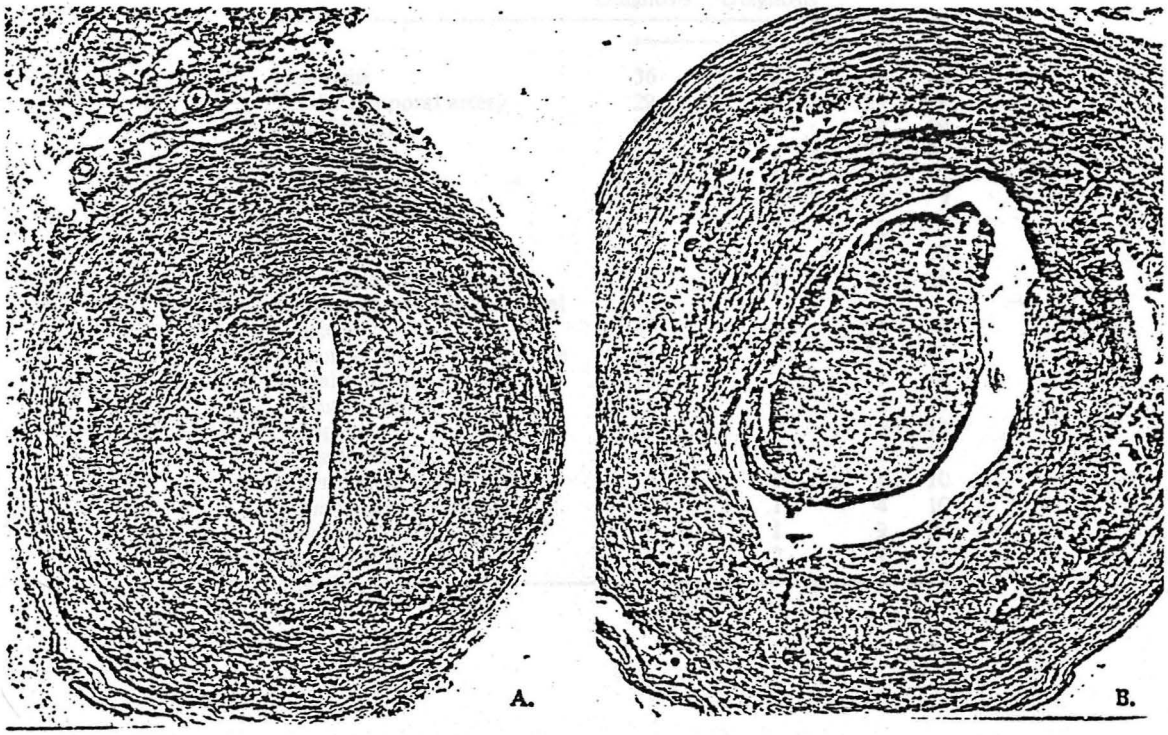


(From Reference 14)

A typical vessel involved by TA is shown in Figure 22, demonstrated marked intimal proliferation. Microscopic sections usually show granulomatous infiltration affecting primarily the media and intima, with mononuclear cells, necrosis, loss of muscle fibers, and multinucleated giant cells.

Figure 22

Photomicrographs of right (A) and left (B) temporal arteries of a 78-year-old man show an excessive proliferation of the intima with almost complete obliteration of vascular lumen. The elastic lamina is fragmented and numerous multinucleated giant cells are found. In the adventitia, a moderate number of inflammatory cells, predominantly lymphocytes, are present (arrows).



(From Reference 14)

Healey and Wilske (15), recently reported their findings in 50 patients with giant cell arteritis (TA) (See Table 80).

TABLE 82

Clinical Features of 42 Patients with Temporal Arteritis in Olmsted County, Minnesota, (1950 to 1974, Inclusive)

Finding	Onset Before Diagnosis	Onset After Diagnosis	Total	
	← no. →			%
Headache	36	2	38	90
Tender temporal artery	29	0	29	69
Claudication	28	1	29	69
Jaw	27	1	28	67
Tongue	3	0	3	7
Deglutition	3	0	3	7
Limb	1	1	2	5
Weight loss	19	4	23	55
Polymyalgia rheumatica	9	11	20	48
Swollen or nodular temporal artery	19	0	19	45
Absent temporal artery pulse	16	1	17	40
Visual symptoms	15	2	17	40
Blurred vision	6	2	8	19
Diplopia	5	0	5	12
Transient loss	5	0	5	12
Permanent partial loss	4	0	4	10
Permanent complete*	3	1	4	10
Fever, >37.7 °C	8	1	9	21
Peripheral joint pain	7	2	9	21

* One or both eyes.

(From Reference 16)

In this series, headache occurred in 90%, tenderness of the temporal artery in 69%, claudication in 69 (mostly jaw), and visual symptoms in 40%.

In another series of 35 patients (Table 83), headache was present in all 35 patients, 7 patients had depression, 5 had diplopia and 4 had mental confusion. There were no overt neurological abnormalities.

TABLE 80

Presenting Complaints of 50 Patients with Giant Cell Arteritis

Polymyalgia rheumatica	16
Symptoms of temporal arteritis	13
Weight loss, malaise, "flu"	8
Fever of undetermined origin	5
Loss of vision	2
Anemia	2
Headache	2
Neck pain	1
Claudication, leg	1

(From Reference 15)

The clinical manifestations are shown in Table 81. Fourteen patients had visual disturbances and 6 had peripheral neuropathy.

TABLE 81

Clinical Manifestations in 50 Patients with Giant Cell Arteritis

Polymyalgia rheumatica	31
Symptoms of temporal arteritis	31
Fever (Temperature > 100°F)	15
Visual manifestations	14
Jaw pain (claudication)	10
Peripheral neuropathy	6
Claudication, leg	4
Rupture of aortic aneurysm	1

(From Reference 15)

A 25-year epidemiologic, clinical, and pathologic study was performed in Olmsted County, Minnesota from 1950 through 1974. The clinical features of the 42 patients with TA are shown in Table 82.

TABLE 84

Neuro-ophthalmic complications (80 cases)

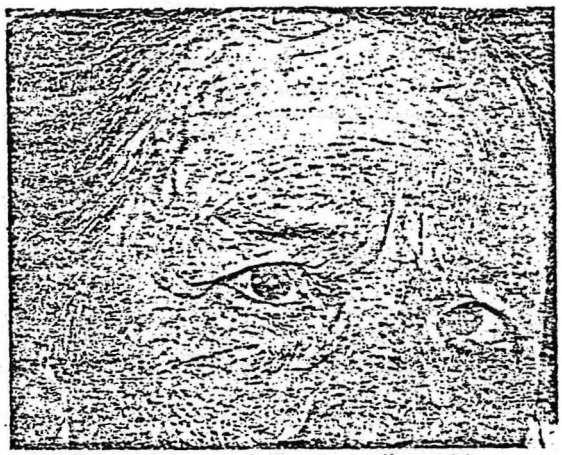
	No. of cases	
Blindness		
Unilateral	18	46 (57·5%)
Bilateral	28	
Ophthalmoplegia		
VI nerve palsy:		12 (15%)
Unilateral	4	
Bilateral	1	
III nerve palsy:		
Unilateral	3	
Bilateral	2	
Diplopia only	2	

3 patients with ophthalmoplegia later developed blindness

(From Reference 23)

external rectus palsy (Figure 23), hallucinations (26) and the combination of miosis, trismus and dysphagia (27).

Figure 23



External rectus palsy in giant cell arteritis

(From Reference 25)

TABLE 83

Clinical Features in 35 Patients with Giant-Cell Arteritis—First Stage (Headache)
(From Russell, R. W. R.: Giant-cell arteritis. A review of 35 cases, *Quart. J. Med.* *28:* 471, 1959.)

Symptoms:	Headache (severe)	33
	Headache (slight)	2
	Tender scalp	34
	General malaise	34
	Loss of weight	25
	Anorexia	24
	Insomnia	21
	Muscular pain	20
	Excessive sweating	15
	Pain on eating	16
	Indigestion	12
	Depression	7
	Vertigo	7
	Sore throat	6
	Diplopia	5
	Mental confusion	4
	Epistaxis	2
Signs:	Tenderness of temporal arteries	32
	Absent pulsation	8
	Diminished pulsation	21
	Fever	29
	Necrosis of scalp	1

(From Reference 17)

Ischemia with infarction of vital areas is the result of arterial insufficiency in TA. Intracranial artery disease may cause delirium or confusion, vertigo, deafness, or strokes (15-17). Other reported manifestations include facial nerve palsy (18), sciatic neuropathy (19, 20), carpal tunnel syndrome (21, 22), ophthalmoplegia (23); (Table 84) pseudotumor of the orbit (24),

References - Temporal Arteritis

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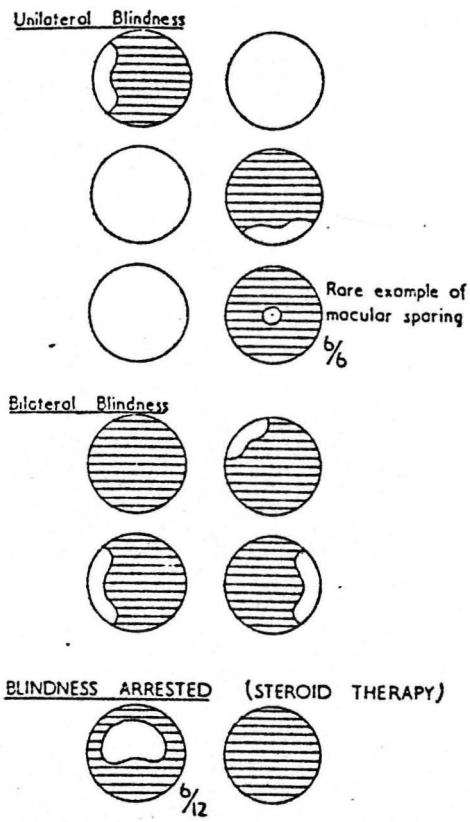
Some examples of the visual field defects which have been reported are shown in Figure 24.

Figure 24



Examples of visual field defects

(From Reference 25)

Temporal arteriography is a sensitive but nonspecific procedure in the diagnosis of TA and must be coupled with biopsy of angiographic abnormalities for confirmation of diagnosis (28).

Treatment with 60-80 mg daily of prednisone is the accepted mode of therapy.

28. Layfer, L. F. et al. Temporal arteriography. Analysis of 21 cases and a review of the literature. Arth. Rheum. 21: No. 7, 780-784, 1978.

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22. Kovarsky, J. et al. Carpal tunnel syndrome in temporal arteritis. J. Rheum. 2: No. 1, 108-112, 1975.

23. Barricks, M. E. et al. Ophthalmoplegia in cranial arteritis. Brain 100: 209-221, 1977.

24. Gibbs, P. Temporal arteritis: onset with pseudotumor orbit or red eye. Pract. 213: 205-211, 1974.

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In addition to the speech impairment caused by the subclavian steal syndrome, the resulting brain stem ischemia may also produce dysphagia, vertigo, hearing deficits, and facial weakness.

Death may result from CVA's, as shown in Table 87, or may present as an acute event. (Table 88).

TABLE 87

Duration, Grouping and Major Factors Related to Death in Eight Cases

Case no	Age (yr)			Classification at the time of diagnosis	Major factors related to death
	Onset	Diagnosis	Death		
9	16	21	23	G IIb: SH	Aortic reconstruction
10	39	42	43	G IIb: SH	CHF
11	21	21	31	G IIa: SH	Cerebrovascular accident
20	27	62	67	G III: SH, AR	Cerebral thrombosis
22	13	19	21	G III: SH, AR	Sudden death, CHF
28	14	23	25	G III: SH, AN	CHF
32	28	46	50	G IIb: TR	Steroid withdrawal shock
45	23	31	34	G III: SH, TR	Cerebral embolism
Av.	22.6	33.1	36.8		

Abbreviations: SH = secondary hypertension; AR = aortic regurgitation; AN = aneurysm; TR = Takayasu's retinopathy; CHF = congestive heart failure.

(From Reference 6)

TABLE 88

Duration, Grouping and Acute Events in Five Cases

Case no	Age (yr)			Classification at the time of diagnosis	Acute events after diagnosis
	Onset	Diagnosis	Occurrence of acute events		
17	17	19	28	G IIa: TR	Cerebral hemorrhage at the 2nd stage of delivery
21	40	44	48	G IIa: AN	Dissecting aneurysm
26	26	40	48	G IIb: SH	Subarachnoid hemorrhage
39	24	40	40	G III: SH, AR	Acute pulmonary edema
41	28	35	36	G IIb: TR	Unilateral blindness
Av.	27.0	35.6	40.0		

(From Reference 6)

B. Takayasu's Arteritis

Morphologically, Takayasu's arteritis is very similar to temporal arteritis. The major features which are considered to be most characteristic of Takayasu's arteritis include (1) the unusual vulnerability of the arch of the aorta, and (2) the equally unusual vulnerability of large elastic arteries, particularly those which arise from the aortic arch (1).

The neurologic manifestations are shown in Table 85 (2-4).

TABLE 85

Neurological Manifestations of Takayasu's Arteritis

Dizziness and Syncope
Headache
Transient Blindness
Diplopia
Hemiparesis and Paraparesis
Cerebellar Symptoms
Seizures
Memory Deficits

Speech defects may be the result of two pathogenetic factors as shown in Table 86.

TABLE 86

Causes of Speech Defects in Takayasu's Arteritis

Lingual Weakness or Atrophy due to Direct Vascular Invasion of the Tongue
Subclavian Steal Syndrome with Vertebrobasilar Artery Insufficiency Causing Speech Impairment

(From Reference 5)

References - Takayasu's Arteritis

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2. Nakao, K. et al. Takayasu's arteritis. Clinical report of eighty-four cases and immunological studies of seven cases. Circ. 35: 1141-1155, 1967.

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C. Differential Features of Temporal Arteritis and Takayasu's Arteritis

The differential charcteristics of the two types of giant cell arteritis are summarized in Table 89.

TABLE 89

Characteristics of the Giant-Cell Arteritides

	Temporal Arteritis	Takayasu's Arteritis
Patients	Disease of the elderly; women more than men	More prevalent in young women; more common in Orient, but neither racially nor geographically restricted
Blood vessels	Characteristically involves branches of carotid artery (temporal artery) but is a systemic arteritis and may involve any medium-sized or large artery	Large- and medium-sized arteries with predeliction for aortic arch and its branches; may involve pulmonary artery
Histopathology	Panarteritis; inflammatory mononuclear cell infiltrates; frequent giant cell formation within vessel wall; fragmentation of internal elastic lamina; proliferation of intima	Panarteritis; inflammatory mononuclear cell infiltrates; intimal proliferation and fibrosis; scarring and vascularization of media; disruption and degeneration of elastic lamina
Manifestations	Classic complex of fever, anemia, high erythrocyte sedimentation rate, muscle aches in an elderly person; headache may be present; strongly associated with polymyalgia rheumatica syndrome	Generalized systemic symptoms; local signs and symptoms related to involved vessels; occlusive phase
Complications	Ocular (sudden blindness)	Related to distribution of involved vessels; death usually occurs from congestive heart failure or cerebrovascular accidents
Diagnosis	Temporal artery biopsy; lesions may be segmental, multiple sections, arteriography, and bilateral biopsy may aid in diagnosis	Arteriography; biopsy of involved vessel
Treatment	Corticosteroids highly effective	Corticosteroids not of proven efficacy; cytotoxic agents untried

(From Reference 7)

In general, temporal arteritis tends to affect older persons, involves branches of the carotid artery (especially temporal artery) and tends to cause sudden blindness. Takayasu's arteritis tends to affect young females, affects the aortic arch and causes death due to CVA or congestive heart failure. There may be considerable overlap, however. Corticosteroids are of proven efficacy in temporal arteritis but of uncertain value in Takayasu's arteritis.

TABLE 91

Diagnostic Criteria of Behçet Syndrome by Behçet Syndrome Research Committee of Japan (1972)

Major Criteria

1. Recurrent aphthous ulceration in the mouth
2. Skin lesions
   a. Erythema nodosum-like eruptions
   b. Subcutaneous thrombophlebitis
   c. Hyperirritability of the skin
3. Eye lesions
   a. Recurrent hypopyon iritis or iridocyclitis
   b. Chorioretinitis
4. Genital ulcerations

Minor Criteria

5. Arthritic symptoms and signs (arthralgia, swelling, redness)
6. Gastrointestinal lesions (appendicitis-like pains, melena, etc.)
7. Epididymitis
8. Vascular lesions (occlusion of blood vessels, aneurysms)
9. Central nervous system involvements
   a. Brain stem syndrome
   b. Meningo-encephalomyelitic syndrome
   c. Confusional type

Types of Behçet Syndrome

1. Complete type: All four major symptoms appear in the clinical course of the patient.
2. Incomplete type:
   a. Three of four major symptoms appear in the clinical course of the patient.
   b. Recurrent hypopyon-iritis or typical chorioretinitis and other one major symptom appear in the clinical course of the patient.

(From Reference 9)

An extensive review was recently published by Shimizu et al (9). The initial CNS symptoms in 12 cases are shown in Table 92.

V. Behcet's Syndrome

The major neurologic and psychiatric manifestations of Behcet's syndrome are shown in Table 90 (1-8).

TABLE 90

Neurologic and Psychiatric Manifestations of Behcet's Syndrome

Brain Stem Lesions

Meningomyelitic Syndrome

Organic Confusional State

Cranial Nerve Palsies

Meningoencephalitis

Hemiparesis

Pseudo-Bulbar Palsy

Epilepsy

Aphasia

Extra-Pyramidal and Cerebellar Disturbances

Depression and Suicidal Tendency

Mortality = 31 - 41%

The incidence of Behcet's syndrome appears to be very high in Japan, especially in the colder regions. The diagnostic criteria used in Japan are shown in Table 91.

TABLE 92

Initial Symptoms of Central Nervous System Involvement in 12 Cases of Neuro-Behçet Disease

Symptom	Number of Cases	Percent
Hemiplegia	4	33
Severe headaches	3	25
Hypesthesia of lower extremity (uni- or bilaterally)	3	25
Paraplegia	3	25
Paresis of bladder and bowel	2	17
Difficulty in speech	2	17
Facial palsy	2	17
Involuntary movements of extremities	2	17
Disturbance of swallowing	1	8
Change of personality	1	8
Coma	1	8

(From Reference 9)

The incidence of neurological symptoms is shown in Table 93.

TABLE 93

Frequency of Occurrence of Neurological Symptoms in 31 Cases of Neuro-Behçet Syndrome

Symptoms	Number of Cases	Percent
Increased tendon reflexes	20	64.5
Spastic paresis	18	58.1
Headache	16	51.8
Sensory impairment	12	38.7
Extensor planter reflexes	11	35.5
Ankle clonus	10	32.3
Absent abdominal reflexes	9	29.0
Dysarthria	9	29.0
Difficulty in urination & defecation	8	25.8
Nystagmus	6	19.4
Diplopia	6	19.4
Facial nerve palsy	5	16.1
Disturbance of coordination	5	16.1
Dysphagia	4	12.9
Focal convulsions in extremities	4	12.9
Vertigo	3	9.7
Impaired visual acuity	3	9.7

(From Reference 9)

The incidence of mental symptoms is shown in Table 94.

TABLE 94

. Frequency of Occurrence of Mental Symptoms in 31 Cases of Neuro-Behçet Syndrome

Symptoms	Number of Cases	Percent
Impairment of memory	15	48.8
Dementia	12	38.7
Depression	12	38.7
Irritability	8	25.8
Hallucination	8	25.8
Clouded consciousness	6	19.4
Euphoria	6	19.4
Apathy	6	19.4
Anxiety	6	19.4
Delusion	5	16.1
Hypochondria	5	16.1
Psychomotor excitement	4	12.9
Insomnia	4	12.9
Suicide attempt	2	6.5

(From Reference 9)

The age incidence at onset is shown in Table 95.

TABLE 95

Age Incidence of Onset of Behçet Syndrome and Neuropsychiatric Signs

Age in Years	Number of Cases With Onset of Behçet Syndrome	Number of Cases With Onset of Neuropsychiatric Signs
Below 19	4	0
20-24	7	5
25-29	8	7
30-34	3	8
35-39	5	3
40-44	2	6
45-49	0	0
Over 50	2	2
Total	31	31

(From Reference 9)

The distribution of focal lesions in the CNS of reported autopsy cases of Neuro-Behcet syndrome is shown in Table 96.

TABLE 96

Distribution of Focal Lesions in the Central Nervous System of Reported Autopsy Cases of Neuro-Behçet Syndrome

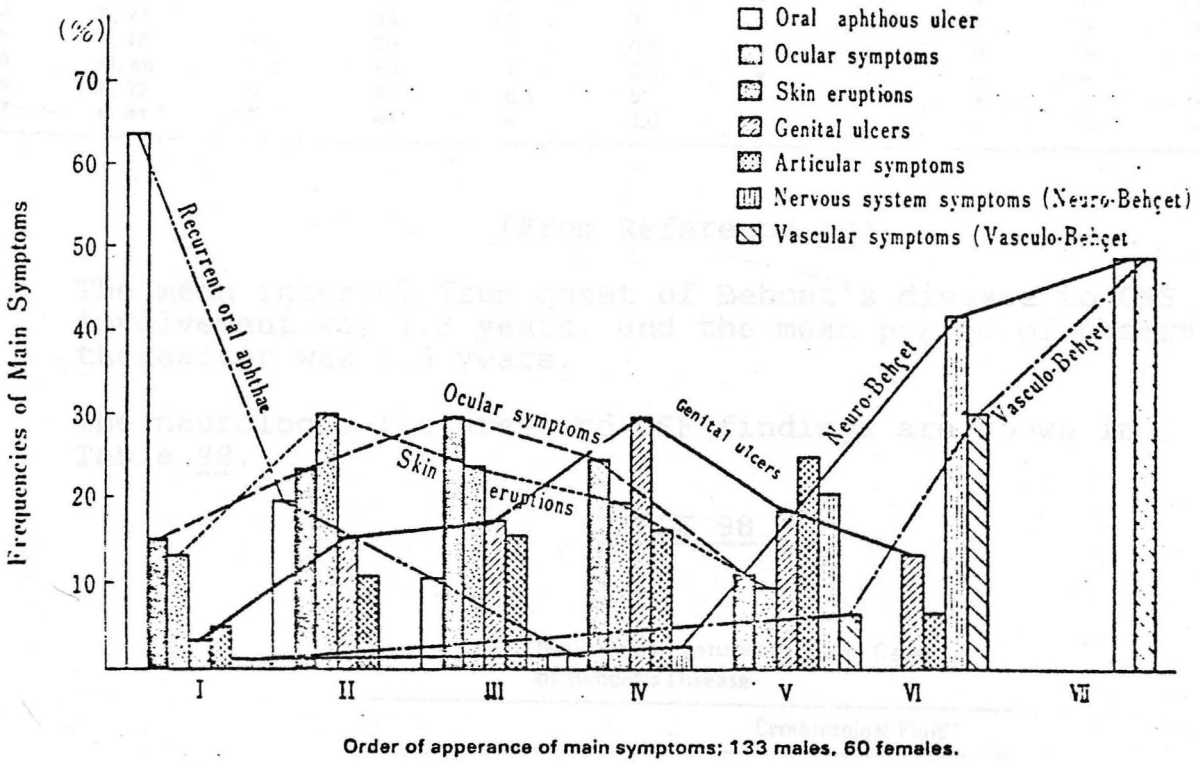
Author	Age and Sex	Localization													
		Cerebral Cortex	Cerebral White Matter	Hippocampic Gyrus	Putamen	Pallidum	Thalamus	Hypothalamus	Optic Tract	Internal Capsule	Midbrain	Pons	Cerebellum	Medulla	Spinal Cord
Berlin (1944)	28 M							+			+				
Silfverskiöd (1951)	19 M								+		+			+	+
Alema and Magni (1952)	34 M					+	+	+		+	+	+			
McMenemey and Lawrence No. 1	29 M	+			+	+		+		+	+	+		+	+
No. 2 (1957)	44 M							+	+	+	+	+		+	+
Kurata et al. (1957)	26 M		+							+		+			
Aksel (1957)	36 M					+	+					+		+	
Suwa et al. (1960)	26 M		+												
Alajouanine et al. (1961)	40 M	+	+					+	+			+		+	
Mitsui (1961)	47 M	+	+		+	+	+			+	+	+		+	
Nakamura and Ikui (1962)	33 M	+									+	+	+	+	
Alemà and Bignami (1962)	45 M					+	+	+		+	+	+		±	±
Rubinstein and Urich (1963)	43 M					+	+		+	+	+	+		+	+
Shimizu et al. (1963)	25 M	+							+		+	+		+	
Strouth and Dyken (1964)	33 M	+		+			+				+	+	+	+	
Ulrich (1964)	49 M									+	+	+	+	+	
Hata et al. (1965)	40 M	+		+		+	+		+		+	+		+	+
Kawakita and Nishimura (1966)	23 F	+							+		+	+			
Hartemann et al. (1966)	44 M		+			+			+	+	+	+			
Hirose et al. (1966)	46 M					+		+		+	+				
Suwa et al. (1966) No. 1	31 M										+	+		+	
No. 2	29 F							+			+	+		+	
Sasaki (1966)	18 M					+			+	+	+	+		+	
Norman and Campbell (1966)	32 M				+	+	+	+	+	+	+	+		+	+
Stefani et al. (1971)	14 M					+		+	+	+	+	+			
Tozuka et al. No. 1 (1964)	26 M					+			+	+	+	+	±	+	+
No. 2 (1968)	39 M			+		+		+	+	+	+	+	+	+	+
No. 3 (1971)	45 M					+		+	+	+	+	+	±	+	±
No. 4 (1971)	36 M			+		+			+	+	+	+	+	+	±

*+, Primary lesion; ±, Secondary lesion.

(From Reference 9)

The order of appearance of various symptoms is shown in Figure 25 and demonstrates that neurologic involvement tended to be later in the course of the disease.

Figure 25



(From Reference 9)

A smaller American study of 7 cases with CNS involvement (of 25 patients with Behcet's syndrome) was performed by O'Duffy and Goldstein (10).

The clinical features are shown in Table 97.

TABLE 97

Clinical Features in Seven Cases of Behçet's Disease

Case	Sex and Age (yr) at Onset	Duration (yr) of Disease to First Visit	Age (yr) When Seen	Duration (yr) Of Disease	Duration (yr) Of Neurologic Involvement	Involvement: Oral	Genital	Eye	Skin	Joint	CNS
1	M, 21	7	28	8.5	7	+	+	–	+	+	+
2	F, 27	3	30	5	3	+	+	+	–	+	+
3	F, 27	7	34	10	7	+	+	+	+	+	+
4	F, 19	1/2	20	1	0.5	+	+	–	–	–	+
5	M, 48	1/2	49	1	0.5	+	+	–	–	–	+
6	F, 22	5	27	6.5	5	+	+	+	+	+	+
7	F, 41	3	44	4	4.0	+	–	–	–	+	+

(From Reference 10)

The mean interval from onset of Behcet's disease to CNS involvement was 1.3 years, and the mean period of observation thereafter was 3.8 years.

The neurologic features and CSF findings are shown in Table 98.

TABLE 98

Neurologic Features in Seven Cases of Behçet's Disease

Case	Findings	Cerebrospinal Fluid*: White Blood Cells (per mm³)	Lymphocytes (%)	Total Protein (mg/dl)
1	Quadriparesis			
	cerebellar	63	100	90
	pseudobulbar	6	100	96
2	Cerebellar	195	60	41
3	Hemiparesis, hemihypesthesia	10	90	31
4	Quadriparesis			
	cerebellar	12	100	44
	pseudobulbar	132	16	50
5	None	52	100	47
6	Hemiparesis	490	15	44
		70	90	35
7	Hemiparesis			
	cerebellar	133	48	
	pseudobulbar	122	100	76

*Values represent single episodes.

(From Reference 10)

Clinical findings included corticospinal tract disease (5 patients), cerebellar ataxia (4 patients), pseudobulbar palsy (3 patients) and transient ocular palsies (3 patients). All patients had headache and fever during or preceding exacerbations of the CNS disease, and all had CSF pleocytosis (WBC counts ranged from 6 to 490/mm^3) with predominant lymphocytosis. The mean CSF protein level was 55 mg/dl, and gamma globulin was less than 15% in 6 patients. Results of CSF fluid, lesional and serologic studies for bacterial, fungal and viral agents were negative (Table 99).

TABLE 99

Microbiologic Studies on Lesions, Cerebrospinal Fluid (CSF) and Serum in Seven Cases of Behçet's Encephalopathy

	Positive	Negative	Not Performed
Bacterial culture (CSF)			
Routine	0	6	1
Mycobacterium	0	5	2
Fungal culture (CSF)	0	5	2
Fungal serology (serum)	0	4	3
Heterophil agglutination	0	3	4
Viral culture			
Lesion	1*	4	2
CSF	0	5	2
Viral antibody			
Herpes simplex (serum)	†	2	3
Herpes simplex (CSF)	0	2	5
Mumps	‡	1	5
Herpes zoster	§	0	6

* Herpes simplex (penis).
† Antibody titer 1:32 in two patients.
‡ Titer 1:8.
§ Titer 1:16.

(From Reference 10)

Corticosteroid therapy was used in 6 patients, cyclophosphamide therapy in two and azathioprine therapy in two (Table 100).

TABLE 100

Treatment of Neurologic Disease in Seven Cases of Behçet's Disease

Case	Treatment	Daily Dose (mg)	Outcome
1	Prednisone	40–60	Died
	Cyclophosphamide	150–200	
2	Prednisone	60–5	Good suppression
	Azathioprine	150–50	
3	Prednisone	15–30	Partial suppression
	Azathioprine	150–50	
4	Prednisolone	32–16	Partial suppression
5	None	...	Died, myocardial infarction
6	Prednisone	60	Died, Pneumocystis pneumonia
	Cyclophosphamide	100	
	Chlorambucil	(?)	
7	Prednisone	20	Persisting episodes

(From Reference 10)

The neurologic manifestations tended to recur when dosages of the drugs were lowered and established CNS damage could not be reversed. These case histories suggested that steroids, when used promptly and in sufficient dosage (up to 60 mg prednisone) were effective in reducing or preventing progression of CNS disease.

Two patients were recently reported in which CNS involvement antedated the other more typical lesions by several months, delaying diagnosis and therapy (11). The serial CSF studies in these 2 patients are shown in Table 101.

TABLE 101

Serial cerebrospinal fluid studies

Date	Total white blood cells (cells/mm^3)	Total polymorpho-nuclears (cells/mm^3)	Protein (mg/dl)	Glucose (mg/dl)
Patient 1				
3/31/73	270	184 (68)*	68	42
4/3/73	35	30 (87)	84	69
2/22/74	45	4 (9)	21	60
2/28/74	24	0 (0)	57	56
3/26/74	6	0 (0)	53	52
5/3/74	750	585 (78)	57	56
5/6/74	320	234 (73)	53	52
1/9/75	14	1 (8)	25	68
Patient 2				
8/20/74	66	13 (20)	109	56
8/30/74	200	152 (76)	65	49
9/5/74	27	3 (10)	92	54

*Percentage of polymorphonuclear cells.

(From Reference 11)

These authors reviewed the literature and summarized the frequency of various neurologic manifestations (Table 102).

TABLE 102

Frequency of neurologic findings in Behcet disease[4, 5, 7, 8, 10-20, 22-24]

Manifestation	Frequency (%)
Hemiparesis or quadriparesis	27
Cranial nerve palsies	12
Cerebellar signs	10
Dementia, organic brain syndrome	10
Meningeal irritation	6
Focal or generalized seizures	5
Pseudobulbar palsy	5
Pseudotumor cerebri	5
Hyperreflexia, pathologic reflexes	4
Hallucinations	4
Extrapyramidal tract signs	3
Spinal cord lesions, cauda equina syndrome	2
Aphasia	2
Encephalitis	1
Coma	1
Peripheral neuropathy	1
Subarachnoid hemorrhage	<1

(From Reference 11)

Hemiparesis or quadriparesis were most common, occurring in 27% of patients with Behcet's disease. Cranial nerve palsies occurred in 12%, cerebellar signs in 10% and dementia in 10%.

Necropsy studies have demonstrated widely scattered foci of necrosis, demyelinization, and scarring throughout the CNS, often in close proximity to small arterioles or venules that are infiltrated with inflammatory cells, i.e., a vasculitis (11-13). The inflammatory cells consist primarily of lymphocytes, plasma cells and macrophages.

It is of interest that a familial incidence, although rare, is recognized in this condition. Fowler et al reported development of CNS Behcet's within 3 weeks of each other in 2 sisters, ages 31 and 34, who lived apart in England (14).

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VI. Lymphomatoid Granulomatosis (LG)

Lymphomatoid granulomatosis is an unusual and peculiar condition with affinities to Wegener's granulomatosis and lymphoma (1-3).

A review of 152 cases of LG revealed that 21.1% had neurological symptoms as their major presenting complaint (Table 103).

TABLE 103

Summary of Ocular Manifestations in Wegener's Granulomatosis and Lymphomatoid Granulomatosis

Manifestations	No.	Per Cent
Wegener's Granulomatosis (342 Cases)		
With ocular disease	131	39
Conjunctivitis, scleritis, episcleritis, corneoscleral ulcer	46	16*
Uveitis	6	2*
Retinal or optic nerve vasculitis	23	8*
Proptosis	52	18*
Dacrocystitis	9	3*
Lymphomatoid Granulomatosis (45 Cases)		
With ocular disease	2	4
Uveitis	1	2
Retinal or optic nerve vasculitis	1	2

* Expressed as per cent of total cases (286) which specified the type of ocular disease. Three series involving an additional 56 cases did not mention the specific type of ocular manifestation.

(From Reference 4)

The overall incidence of neurological signs or symptoms during life are shown in Table 104.

TABLE 104

Extra-Pulmonary Involvement by Lymphomatoid Granulomatosis

Signs/Symptoms during life (152 cases)	No. (percent)	Organ involvement at autopsy (72 cases)	No. (percent)
Skin rash/Nodules	60 (39)	—*	—
Neurological	45 (30)	Brain	19 (26)
CNS signs	29 (19)	—	—
Cranial neuropathy	17 (11)	—*	—
Peripheral neuropathy	11 (7)	—*	—
Splenomegaly	27 (18)	Spleen	12 (17)
Hepatomegaly	18 (12)	Liver	21 (29)
Lymphadenopathy	12 (8)	Lymph nodes (lymphoma)†	16 (22)
—	—	Kidney	23 (32)
—	—	Adrenal	9 (12.5)
—	—	Heart	8 (11)

* Skin, cranial and peripheral nerves were not routinely examined at autopsy.

† This number does not include 2 patients in whom the diagnosis of lymphoma was made during life and who were not autopsied.

(From Reference 4)

CNS signs were present in 19%, cranial neuropathy in 11%, and peripheral neuropathy in 7% of patients. At autopsy, 26% had brain involvement. Adverse prognostic factors included neurologic manifestations, and large numbers of atypical lymphoreticular cells within the pulmonary infiltrate. The atypical cells resemble but are not identical to those seen with lymphoma.

A recent review of the literature by Bone et al (5) summarizes the findings in 12 cases with LG (Table 105).

TABLE 105

Summary of Reported Cases of Central Nervous System Involvement

Case No.	Age (yr) and Sex	Organ System(s)	Autopsy	Brain Scan	EEG	Lumbar Puncture	Therapy	Reference
1	8, F	CNS*, lungs	Alive	L. orbital area uptake	Diffusely enlarged	17 WBC:1 neutrophil, 17 lymphocytes, 4 monocytes; protein 41 mg/100 ml.; glucose 45 mg/100 ml.	Steroids	[1] Case 19
2	...	Lung, kidney, liver, tongue, pancreas, skin	Yes	...	...	...	Prednisone	[1] Case 21
3	40, M	CNS, skin, lung, kidneys, adrenal peripheral nerves	Yes, CNS exam excluded	L. frontal lobe infarct	Abnormal deep midline (brain stem) lesion	No cells, protein:115 mg/ 100 ml. glucose 75 mg/100 ml chloride 118 meq/liter	Prednisone	[1] Case 24
4	...	CNS	No	...	...	"Malignant cells in CSF"	CNS—irradiation prednisone, tetracycline, irradiation to nodes	[1] Case
5	58, F	Skin, CNS lungs	Yes	...	...	...	Prednisone	[1] Case 27
6	34, M	CNS, lungs	No	...	...	...	Prednisone	[1] Case 28
7	...	Lung, lymph node, kidney, CNS, peripheral nervous system	Yes	...	...	...	Prednisone	[1] Case 30
8	...	Lung, CNS kidney, heart skin, prostate	Yes	...	...	...	Cortisone	[1] Case 32
9	67, F	Lung, CNS	No	...	...	...	Prednisone	[1]
10	43, M	Skin, CNS	Alive	...	...	...	Steroids	Case 37
11	33, M	Lung, CNS adrenal, liver	Yes	...	...	No cells, protein 34 mg/ 100 ml., glucose 80 mg/100 ml.	Cyclophosphamide vincristin, prednisone	[1]
12	75, M	Skin, lung, CNS	Limited	...	...	...	Prednisone, cyclophos-phamide	[3]

NOTE: CNS = central nervous system; L = left; WBC = white blood cells; CSF = cerebrospinal fluid.

(From Reference 5)

Israel et al (6) contrasted findings in 35 patients with pulmonary angiitis and granulomatosis; 15 had WG, 11 had benign lymphocytic angiitis and granulomatosis and 9 had LG. As shown in Table 106, the only patients with neurological involvement were 3 patients with LG.

TABLE 106

Anatomic Involvement, Clinical Presentation, Chest Roentgenographic Findings, and Immunologic Studies in Three Disease Entities

	Wegener's Granulomatosis	Benign Lymphocytic Angiitis and Granulomatosis	Lymphomatoid Granulomatosis
Age			
Mean, *yrs*	42	55	43
Range, *yrs*	22-59	31-74	20-68
Male/female	10:5	7:4	5:4
White/black	14:1	9:2	9:0
Anatomic involvement			
Lungs alone	6	10	2
Upper airways	8	0	1
Renal	5	0	0
Cutaneous	0	1	4
Neural	0	0	3
Clinical presentation			
Routine X ray	5	4	0
Cough, fever	8	6	5
Upper airways	1	0	1
Renal	1	0	0
Cutaneous	0	1	2
Neural	0	0	1
Initial chest X ray			
Solitary nodule	4	5	1
Multiple nodules	10	6	8
Cavitation	4	2	1
Immunologic tests before cytotoxic therapy			
Elevated IgG (>1800 mg/dl)	0/8	2/6	0/4
Elevated IgA (>325 mg/dl)	3/8	2/6	0/4
Elevated IgM (>200 mg/dl)	3/8	2/6	0/4
Elevated IgE (>700 mg/dl)	1/7	3/5	0/1
Rheumatoid factor	4/8	0/5	0/4
Tuberculin or candida reactions	6/8	2/5	1/4

(From Reference 6)

A comparison of eye involvement with WG and LG is shown in Table 107.

TABLE 107

Summary of Ocular Manifestations in Wegener's Granulomatosis and Lymphomatoid Granulomatosis

Manifestations	No.	Per Cent
Wegener's Granulomatosis (342 Cases)		
With ocular disease	131	39
Conjunctivitis, scleritis, episcleritis, corneoscleral ulcer	46	16*
Uveitis	6	2*
Retinal or optic nerve vasculitis	23	8*
Proptosis	52	18*
Dacrocystitis	9	3*
Lymphomatoid Granulomatosis (45 Cases)		
With ocular disease	2	4
Uveitis	1	2
Retinal or optic nerve vasculitis	1	2

* Expressed as per cent of total cases (286) which specified the type of ocular disease. Three series involving an additional 56 cases did not mention the specific type of ocular manifestation.

(From Reference 7)

No particular mode of therapy has been shown to be satisfactory for LG, although there is some suggestion that steroids may be useful (4).

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VII. Leucocytoclastic Vasculitis

This category of vasculitides includes Schonlein Henoch Purpura, hypocomplementemic vasculitis, essential mixed cryoglobulinemia and other disease-related dermal vasculitides. The incidence of nervous system involvement ranges from 0 to 64%, depending on the individual study (Table 108) (1-7).

TABLE 108

MANIFESTATIONS OF LEUKOCYTOCLASTIC ANGIITIS

Series	Knowles and Zeek†	O'Duffy et al.†	Winkelmann and Ditto*	McCombs*(*)	Wilkinson*	Avg. (%)
Number of Patients	10	11	36	72	23	
Organ involvement (percent)						
Lungs	40	55	20	30	Δ	36
G.I. Tract	40	55	15	10	22	28
Nervous System	50	64	20	25	0	32
Skin	40	45	100	50	100	67
Joints	20	45	50	50	Δ	41
Kidneys	100	100	60	30	38	66
Heart	10	64	0	0	0	15

(Modified from Braverman, 1970)

†Autopsy study.
*Studied during life.
(*)Seventeen of seventy-two patients had periarteritis nodosa. Organ involvement in two varieties of angiitis not separated in paper.
ΔOrgans affected but frequency not stated.

(From Reference 1)

Peripheral neuropathy has been the most common neurological symptom reported. Neuropathies involving cranial nerves have been noted rarely and bilateral permanent deafness had been reported in one case (2-7).

Other findings include encephalopathies, cerebral thrombosis, headache, diplopia and dysphagia (5).

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SUMMARY

In summary, a wide variety of neurological complications can occur in the various connective tissue and "collagen-vascular" diseases. Most of these complications appear to be due to vasculitis affecting various sites in the central or peripheral nervous system.

While the evidence for definitive vasculitis in SLE is not strong, small vessel damage is commonly present in anatomic sites which correlate well with clinical features.

Although patients with rheumatoid arthritis also may have vasculitis, neurological complications are commonly related to nerve compression by rheumatoid nodules or the arthritic process itself.

Considerable controversy exists regarding the accuracy of various diagnostic tests.

While corticosteroids are the mainstay of therapy for these conditions, there are no definitive studies proving their efficacy.