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Progressive Systemic Sclerosis and Nervous System Involvement

A Review of 14 Cases

R.A. Dierckx[a], *F. Aichner*[a], *F. Gerstenbrand*[a], *P. Fritsch*[b]

[a] University Clinic of Neurology, and [b] University Clinic of Dermatology, Innsbruck, Austria

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Abstract. Nervous system involvement in progressive systemic sclerosis (PSS) has been considered rare compared to other collagen diseases. We present 14 additional cases of PSS with neurological manifestations. Primary involvement of the peripheral nerves could be detected in 4 of the 14 patients and is documented by electromyo- and electroneurographical examinations. Central nervous system (CNS) manifestations directly related to PSS are a rarity, which may reflect the lack of collagen in the brain, histological differences between cerebral and other arteries and the immunological particularity of the brain. There may have been a direct relationship between CNS involvement and PSS in only one patient presenting with an overlap-syndrome.

Introduction

Progressive systemic slerosis (PSS) is a systemic disease of the connective tissue characterized by inflammation, fibrotic and degenerative changes in the skin (scleroderma), synovium, heart, lungs and kidneys [1]. Its protean expression may reflect a spectrum with the CRST syndrome and such overlap syndromes as the mixed connective-tissue disease at the ends [2]. Collagen metabolism disorder, small blood vessel abnormalities and autoimmune mechanisms account for the pathogenesis of PSS, with discussion still about the primum movens [3].

Neurologic manifestations consist of musculoskeletal changes [4–6] and peripheral nervous system involvement with mono- or polyneuropathy [7–16]. Signs of cerebral and spinal cord lesions are seen in advanced cases and the terminal stage of scleroderma is usually marked clinically by

acute cerebral failure in an endotoxic coma [17]. Still, only few reports with clinical descriptions and anatomical and pathological studies of the primary involvement of the central nervous system (CNS) exist [18–21].

We present a series of 14 consecutive patients with PSS and neurological signs and discuss their possible relationship.

Patients and Methods

The patients described are 7 men and 7 women aged 35–77 years, seen between 1978 and 1981. Diagnosis of PSS was settled at the Clinic of Dermatology following the classification by Rodnan [1] (table I).

Nerve conduction velocities were studied in the nervus medianus and nervus peroneus with a concentric needle electrode and consisted of measurements of the motor nerve conduction velocity in each patient and of the sensory nerve conduction velocity in 9 cases. In none of the patients was a biopsy performed.

In order to exclude other causes of peripheral neuropathy an oral glucose tolerance test was performed in all patients, as were determinations of vitamin B_{12}, folic acid, an oscillogram and a screening for porphyria. Furthermore, endotoxic damage was looked for in the biological parameters. Information about exotoxic causes such as alcohol or pharmaca were obtained by interrogation of the patients and their families.

Case history, neurological, physical and psychodiagnostic examination, CAT scan and EEG were used in an attempt to differentiate between primary CNS involvement and iatrogenic or coincidental manifestations of CNS symptoms related to involvement of other organs.

Neuropsychological testing included the Wechsler adult intelligence test, the Benton visual retention test and the Rorschach test. The diagnosis of cerebral atrophy followed the interpretation of the pictures by two independent neurologists experienced in CAT scan. The appearance of a few theta waves with diffuse spreading in the EEG tracings was defined as a slightly abnormal EEG.

Table I. Classification of scleroderma, after Rodnan [1]

PSS
Classic scleroderma
CRST syndrome
'Overlap' syndromes
Eosinophilic fasciitis
Localized forms of scleroderma
Morphea
Single or multiple plaques
Generalized morphea
Linear scleroderma
Scleroderma 'en coup de sabre'

Results

The results are presented in table II. Seven patients manifested a CRST syndrome, six a 'classical' PSS and one an overlap syndrome. Disease had been present for 1–18 years.

The high incidence – from a dermatological point of view – of the classical type of scleroderma within this group of patients may be due to a local policy of following these patients at the Clinic of Dermatology.

Ten patients presented with neurological complaints which consisted of headache, weakness and dysesthesias of the limbs, and in one patient of convulsions.

Neurological examination disclosed a distal paresis (Oxford scale grade IV) in the arms and/or legs and disturbances of the pain perception with a peripheral neuropathy in 8 patients. Clinical and psychodiagnostic examination demonstrated an organic psychosyndrome in 5 patients and an organic dementia in 3 patients.

EEG was normal in 7 patients and showed only diffuse slow theta waves in 3

Table II. Summary of the neurological features, EEG, CAT scan, EMG and ENG in 14 patients with PSS

Case no.	Sex	Age years	Type of PSS Complications	Duration years	Neurological symptoms	Neurological deficit
1	F	35	CRST syndrome	7	none	diffuse muscle atrophy
2	F	55	MCTD, lues, corticother. AV-dissociation	4	focal convulsions status E	organic dementia
3	M	42	classic form, DM, AHT, st.p.hypophyse-adenoma	1	cephalgia	organic psychosyndrome
4	F	37	CRST syndrome	16	progressive leg weakness	organic dementia, diffuse muscle atrophy
5	M	47	classical type	1	none	diffuse muscle atrophy
6	M	48	classical type	4	paresthesia, leg weakness	diffuse muscle atrophy
7	M	55	CRST syndrome	4	cephalgia	organic psychosyndrome
8	F	64	classical type	18	migraine	organic dementia
9	F	48	classical type	8	progr. leg weakness	organic dementia distal paresis
10	F	66	CRST syndrome	12	weakness	diffuse muscle atrophy, organic dementia
11	M	77	classical type	3	none	slight muscle atrophy
12	M	54	CRST syndrome	6	none	organic psychosyndrome
13	F	50	CRST syndrome	3	paresthesia of distal extremities	distal paresis
14	M	44	CRST syndrome ethylism	3	organic psychosyndrome	progressive weakness

EEG	CAT scan	EMG	ENG
normal	normal	chronic neurogenic alterations	reduced
multifocal spikewaves	atrophy	normal	normal
slightly abnormal	sella widened	normal	normal
slightly abnormal	slightly abnormal	chronic neurogenic alteration	normal
normal	normal	chronic neurogenic alteration	normal
normal	normal	chronic neurogenic alteration	reduced
normal	normal	chronic neurogenic alteration	reduced
slightly abnormal	slightly abnormal	myopathy	normal
slightly abnormal	slightly abnormal	chronic neurogenic alteration	reduced
normal	normal	chronic neurogenic alteration	reduced sensory NCV
normal	normal	normal	normal
slightly abnormal	normal	normal	normal
slightly abnormal	normal	normal	normal
normal	normal	chronic neurogenic alteration	slightly reduced

other patients. However, the patients with convulsions showed multifocal spike waves on several occasions. CAT scan of the brain was normal in 10 cases, in 4 cases there was a slight cerebral atrophy.

EMG and ENG demonstrated a peripheral neuropathy in 6 patients, which in 4 out of them was attributed to the PSS. In one patient a myopathic pattern was found. These results have already been described in detail in a former report [16].

Discussion

PSS is a disseminated disease with primary organ involvement of the skin, oesophagus and heart, and less frequent of liver, intestines and kidneys [22]. The classical type of scleroderma progressiva (PSS) is characterized by a symmetrical, often global involvement of the skin and by a steadily and at times very rapidly progressive visceral involvement which may cause death. However, the disease also occurs in a form compatible with long life in which there is limited involvement of the skin – often confined to portions of the fingers and face – and a characteristically prolonged delay before the appearance of distinctive visceral manifestations (CRST syndrome) [1].

In other collagen diseases, such as polyarteritis nodosa and systemic lupus erythematosus, neurologic involvement is common and may be the first or most prominent manifestation [23–25]. On the contrary, neurologic manifestations of PSS are relatively rare [26]. Furthermore, one should differentiate between neurologic phenomena directly related to PSS and those secondary to the involvement of other organs [27].

We will consider separately the central and peripheral nervous system.

The clinical manifestations described, the results of the psychodiagnostic tests, EEG and CAT scan are not specific and do not allow for any correlation with a primary involvement of the CNS in PSS. A secondary manifestation may be discussed, although a clear-cut differentiation with other disorders of the CNS has not always been possible with the examinations used [28–31].

Patients with the CRST syndrome may have a better prognosis associated with the absence of renal complications [32]. Therefore, in these cases neurological symptoms secondary to uremia and hypertension in the treatment of renal failure can be excluded. The preponderance of women in the CRST syndrome group in comparison with the classic PSS still awaits explanation [33].

In this regard the sex ratio of 3 men and 4 women in our patients is not representative.

Mixed connective-tissue disease constitutes an overlap syndrome with elements of PSS, systemic lupus erythematosus and polymyositis in which convulsions may appear [34]. Two years after the first symptoms case 2 showed a focal epilepsia with secondary generalization. A primary involvement in this case seems very likely.

A case reported by Lee and Haynes [20] with a cerebral infarction related to an arteritis localized to a single carotid artery may represent the only primary manifestation of PSS affecting cerebral vessels. We think that other descriptions are neither specific nor proven [21, 35–39].

In neuropathological studies of cerebral vessels no other changes have been found than those resulting from hypertension or atherosclerosis [40–43]. Furthermore, in a controlled study the incidence of brain lesions was similar in the two groups, no specific or characteristic cerebral lesions being observed [44].

Different factors may contribute to this rare primary involvement of the CNS. A unifying hypothesis of the pathogenesis of PSS has recently emerged, which holds a disorder in lymphocyte mechanism responsible for the ignition of the different phenomena [45]. In this respect, it may be noteworthy that only few lymphocytes are found in the brain under normal circumstances [46]. Other factors which may play a role are the particular anatomy of the cerebral vessels and the relative poverty in connective tissue of the brain [26].

Direct peripheral nerve system (PNS) involvement may assume different clinicopathological forms. Cranial-nerve symptoms, especially trigeminal neuropathy, are felt to be primarily due to the microangiopathy of PSS [14]. Furthermore, as the PNS is rich in connective tissue the nerve fibers may become incarcerated in the generalized sclerosing process with thickening of the epineurium and perineurium as described in cases of PSS with polyneuropathy [7, 26].

Remarkably, for a long time a direct involvement of the PNS drew little attention. Zülch [8] described a scleropolyneuropathy with neuropathological findings in 1959. Other clinical and neuropathological case reports followed [9–11]. However, no differentiation between a primary or secondary manifestation was made. A secondary peripheral neuropathy may follow alteration in different organs and malnutrition or malabsorption [17].

In 4 of the 14 cases reported a primary involvement was assumed on the basis of the clinical and electrophysiological examina-

tions, with the reservation that this still awaits histopathologic confirmation [16].

Finally, as no biopsies were made, muscular involvement may have been underestimated. Myositis often runs an asymptomatic course whereas histological evidence shows up in 50% of cases [6].

From the above we may conclude that the apparent rarity of several neurological manifestations in PSS may well be related to the inadequacy in diagnosing it.

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Dr. R. Dierckx,
Department of Neurology,
A.Z.V.U.B.,
Laarbeeklaan 101,
B–1090 Brussels (Belgium)