Sarcoid of the Nervous System

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Sarcoid is a granulomatous disease of undetermined etiology characterized by the presence of epithelioid cell aggregates without caseation which proceeds to conversion to hyaline fibrous tissue or resolution. The sites of nervous system involvement include the meninges, cranial, and peripheral nerves, hypothalamus and pituitary gland, muscles, and, more rarely, brain and spinal cord parenchyma. In nervous system involvement there is usually cerebrospinal fluid lymphocytic pleocytosis and elevated protein but these findings are not specific. When other systems are involved with sarcoid the diagnosis of neurosarcoidosis is obvious. When an unusual neurological symptom complex presents, sarcoid should be considered. The author reviews the literature and presents 22 cases of sarcoid involvement of the nervous system.

Overview

Heerfordt syndrome[1] was the eponym used in the description of patients with enlargement of the parotid gland and other salivary glands, uveitis, and in many cases paresis of the cranial nerves, especially the facial nerve.[2] Sarcoid was the pathological process.

Sarcoidosis is a systemic disorder characterized by granulomatous lesions which may involve almost any organ of the body.[3,4] It has been demonstrated in every tissue of the body except the adrenals.[5-8] It has been classified as infectious but no organism has been consistently and definitely associated with the disease and Koch's postulates remain unfulfilled as regards sarcoidosis.

A routine screening x-ray[9-11] is usually the point of entry for patients classified as having sarcoidosis. Others seek medical advice because of respiratory problems. The prevalence of sarcoidosis varies widely from country to country, among different ethnic groups, and even from area to area within the same country.[12-14] The highest prevalence rate is recorded for Sweden (64/100,000) whereas in Denmark the rate is 10/100,000. In New York City the rate is 30/100,000, while in the area of the city with predominantly black population the rate approaches the Swedish rate.

The sarcoid lesion[15] is characterized by the well-defined appearance of a rounded collection of large epithelioid cells with pale staining nuclei, by a scarcity of lymphocytes located mainly at the periphery, and by the absence of caseation or necrosis. Immune dysfunction is present in patients with sarcoidosis. There is decreased delayed hypersensitivity to variously encountered allergens. The literature indicates that there is a decreased number of circulating cells capable of forming spontaneous sheep cell rosettes. On the other hand, B-cell function is thought to be hyperactive in most patients. There is a hypergammaglobulinemia and high circulating antibody titers to a wide range of specific antigens. High levels of angiotensin-converting enzyme have reported in patients with sarcoidosis.

Neurosarcoidosis

Most patients with neurosarcoidosis are those with previously diagnosed systemic sarcoidosis who develop signs of neurologic involvement in the course of their illness. Rarely is neurologic involvement the initial sign. Neurosarcoidosis[16-35] was once thought to be a rare complication of sarcoidosis but is being reported with increasing frequency as the syndromes of neurosarcoidosis are being recognized. Of 108 cases of sarcoidosis, 22 patients at the Brooklyn VA Medical Center also had neurological involvement. These findings compared favorably with other reported series (Table 1).

The frequency of neurologic involvement varies from one to twenty percent (Table 1). No part of the nervous system is immune to sarcoidosis though some divisions are more frequently demonstrated clinically or pathologically to be the site of involvement.[36-39] Intracranial involvement may present in many ways reflecting involvement of various segments of the intracranial (Table 2) contents. Abnormal mental states have been described[22,26,33] and two of the patients studied had spent time in psychiatric institutions. The determination as to whether the mental syndrome is due to sarcoidosis is frequently difficult. Metabolic dysfunction in sarcoidosis is frequently the result of derangements of kidney, liver, and lung. In addition to direct hypothalamic (Table 3) and pituitary involvement,[16,30,40] encephalopathic syndromes in patients with sarcoidosis can frequently be the result of steroid therapy. Steroid therapy may also allow the development of meningitis as a result of "opportunistic" infectious agents. This may present as a sarcoid meningitic syndrome. The syndrome of hypopituitarism is seen as a result of direct invasion of the hypothalamus and pituitary gland. Sarcoid can mimic a space-occupying lesion.[41-43] One of the cases was diagnosed as meningioma on plaque following studies and craniotomy. Focal seizures can occur as a result of infiltration or granuloma and extrapyramidal manifestations[17,18,24] have been observed in sarcoidosis. Richardson[44] has reported a case of multifocal leucoencephalopathy in a patient with sarcoid. Rare involvement of the brain stem and cerebellum[17,34] with diplopia, cranial nerve palsies, bulbar palsy, quadri-

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Table 1. Incidence of Neurologic Manifestations in Sarcoidosis

Author	Location	Number Patients	Intra-crainal	Hypo-thalamic Pituitary	Myelo-pathy	Peri-pheral Neuro-pathy	Cranial Neuro-pathy	Percent of Neurological Involve-ment
Longcope [35] 1941	Baltimore	31	2	1	1	—	—	13
Gravesen[22] 1942	Scandinavia	150	—	1	—	—	5	4
Reisner[39] 1944	New York	35	—	—	1	—	1	6
Fisher[6] 1947	Baltimore	94	—	1	2	—	6	10
Ricker and Clark[7] 1949	Washington, DC	195	3	—	—	—	—	1.5
Riley[31] 1950	New York	52	1	—	—	1	1	6
Longcope[5] 1952 and Freiman[5] 1952	Baltimore and Boston	90 70	— 1	1 —	— —	1 —	3 —	6 1.4
Gendel et al[37] 1952	Memphis	24	—	1	1	—	4	25
Nitter[9] 1953	Oslo	90	—	—	—	—	3	3
Cowdell[65] 1954	Oxford	90	1	3	—	1	—	5.5
Israel and Sones[36] 1958	Philadelphia	160	2	2	—	—	3	4
James and Thompson[62] 1959	London	200	2	—	—	—	4	3
Goodson[20] 1960	Nashville	63	1	—	—	1	2	6
Douglas[13] 1961	Scotland	100	—	2	—	—	6	8
Barharacih[4] 1961	Denver	111	1	—	—	—	—	1
Rudberg-Ross[64] 1962	Sweden	296	4	1	—	4	4	4
Mayock et al[28] 1963	Philadelphia	145	10	—	2	10	3	17
Silverstein et al[33] 1965	New York	450	5	—	1	4	3	4
Wiederholt and Siekert[34] 1965	Minnesota	807	7	3	3	3	13	3.6
James and Sharna[23] 1967	England	261	—	—	3	—	—	1
James et al[12] 1976	Worldwide	3,676	(134 cases with neurological involvement)*					4
Present Series	Brooklyn	108	5	3	2	7	5	20

*Includes 134 cases not localized to specific neurologic area

paresis, ataxia, nystagmus, papilledema, and other brain stem signs have been described. Brain stem involvement seems to be associated with poor prognosis.[18] A diagnosis of intracranial pathology related to sarcoidosis may be reached by many avenues. Some centers report a positive score of 77 percent for computerized axial tomography (CAT) scans. The indications for air studies are limited to those cases in which the CAT scans are negative as the pneumoencephalogram (PEG) may show small mass lesions or incomplete filling of the basal cisterns. Since sarcoid masses are avascular, angiography is useful in excluding tumors with pathological circulation.

Cranial Nerve Involvement

Cranial nerves are involved in many ways and the symptoms are related to the cranial nerve(s) involved.[10] Basal infiltration of the meninges is the most common finding, with frequent multiple cranial nerve involvement. Optic nerve defects[45-48] are common (Table 4) and the seventh cranial nerve is the cranial nerve most frequently involved. The disability of the facial nerve is often transient, making differentiation from Bell palsy difficult. Dysphagia, hoarseness, vocal cord paralysis, and absent gag reflexes are often concomitants of ninth and tenth nerve involvement. The response of cranial nerve involvement due to sarcoid to steroid therapy is usually favorable.

Spinal Cord Involvement

Spinal cord involvement is also uncommonly seen.[49-51] Day and Sypert[52] reviewed the literature and reported 15 cases and added two of their own. The signs and symptoms may vary from none to paresis, lessened sensory levels, and Brown-Séquard syndrome. Although multiple levels rather than a single level is the rule, the thoracic level is often involved. Cord syndromes indicate that the cord may be involved by intramedullary granuloma or meningeal infiltration causing arachnoiditis, both of which cause

Table 2. Cerebral Signs and Symptoms

Headache
Acute and chronic brain syndromes
Focal seizures
Hemiparesis
Papilledema
Extrapyramidal signs
Nuchal rigidity
Signs of space-occupying lesion
Episodic dyslexia

Table 3. Hypothalamic-Pituitary Involvement

Abnormalities of water metabolism
Impotence
Amenorrhea
Diabetes Insipidus
Somnolence
Obesity
Extreme variations in temperature
Personality changes
Froelich's Syndrome
Pituitary Dwarfism
Infantilism
Hyperglycemia
Deficiencies in TSH, ACTH, and gonadotropins

Table 4. Cranial Nerve Involvement

Nerve	Frequency
I	Rare
II	Common
III, IV, VI	Rare
VII	Common
VIII	Infrequent
IX, X	Common
XI	Rare
XIII	Rare

nonspecific myelographic abnormalities.[25] Granuloma tends to be perivascular, may extend in the adventia and media, and may present problems in differential diagnosis. Thrombosis may occur. Meninges of the spinal cord, while seldom involved, may cause root pain. Spinal fluid protein is usually elevated as is the cell count. Prognosis seems poor in spinal cord sarcoidosis. Peripheral nerves are often involved in sarcoidosis.[17-23] Actual infiltration is difficult to demonstrate. The clinical picture is dependent upon the site of involvement. Mononeuropathy,[17] polyneuropathy, and Guillian-Barré syndrome[20] have been reported. Sarcoid has also been listed as a cause of intercostal neuralgia. The neuropathic symptoms involving peripheral nerves are transient but less so than in cranial nerve involvement. The response to steroids is usually good.

Myopathic Sarcoid

Myopathic sarcoidosis (Table 5) was described by Licharew in 1908.[53] It has been divided into symptomatic and asymptomatic by Silverstein and Siltzbach.[54] Hinterbuchner and Hinterbuchner described a myopathic syndrome in muscular sarcoidosis in 1962.[55] The asymptomatic type is most common, the diagnosis being made by muscle biopsy. These are clinically silent lesions and are frequent during the first two years of the disease. It must be remembered that this granuloma is not specific for sarcoid.[23] In the symptomatic type, nodules are more frequent.[56-58]

Acute myopathy due to sarcoid occurs more frequently in women and is rare. Chronic myopathy is the more common type and the onset is gradual over a period of months to years. Response to steroids is unpredictable. Involvement of muscle may thus produce myopathy[59-60] in some and acute myositis in others, while in most it may remain asymptomatic.

Therapy

The treatment of sarcoidosis of the nervous system is that of sarcoid in general.[61-67] Steroids are the most frequently used therapy. They should be reserved for the symptomatic stages as there are possible side reactions as well as refractoriness to the therapy. A course may last from four to six months with two to three additional months for tapering. Relapses are common. When steroids are contraindicated, alternative drugs are oxyphenbutazone, chloroquine,[68] hydrochloroquine paraaminobenzoate, and Imuran. It should be remembered that spontaneous remissions do occur.[69]

Conclusion

The combinations of neurologic manifestations are manifold and there is no definite syndrome of neurosarcoidosis. When the neurological signs are the only manifestation of sarcoid, the diagnosis becomes a herculean task. The differentiation of sarcoid and giant cell arteritis occasionally presents a problem (Table 6). The question of healed lesions of neurosarcoidosis remains, as does the impression that sarcoidosis involving the central nervous system is a progressive condition with exacerbations and remissions, but ultimately heralds a fatal outcome.

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Table 5. Sarcoid Myopathy
Diffuse, symmetrical polymyositis with atrophy
Muscle biopsy definitive role in diagnosis
Widespread muscle involvement histologically
Proximal muscle most frequently involved clinically
Neuropathy may coexist
May simulate muscluar dystrophy or progressive muscular atrophy
Onset usually middle age or later
May or may not be evidence of sarcoidosis elsewhere
Muscle fibers usually not invaded by granuloma

Table 6. Meningovascular Sarcoidosis and Granulomatous Angitis

	Sarcoid	Angitis
Vessel	Small eccentric granuloma Wall eroded	Small and large concentric Granuloma wall normal
Elastica	Focal destruction	Preserved
Lumen	Often obliterated	Patent
Giant Cells	Large and many	Smaller and fewer

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