Neuro-ophthalmic sarcoidosis

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Purpose of review

Almost 100 years after its original description, sarcoidosis remains an enigmatic disease with unclear etiology and capricious symptomology, as well as a diagnostic challenge. This review coalesces current literature on the neuro-ophthalmic manifestations of sarcoidosis and discusses the epidemiology, etiology, clinical presentation, diagnosis, and management of this disease.

Recent findings

Recent investigations strongly identify a genetic component as well as a host of candidate antigenic triggers. Certain human leukocyte antigen polymorphisms may influence not only the susceptibility of individuals to sarcoidosis but also the course of the disease. Diagnostic advances include the finding of two additional potential biomarkers of sarcoidosis as well as the use of positron emission tomography technology in localization of disease sites for biopsy. In addition to the concomitant and alternative use of immunosuppressive agents to steroid therapy, disease remission in refractory neuro-ophthalmic sarcoidosis with tumor necrosis factor alpha inhibitors has also been reported.

Summary

Sarcoidosis can affect any part of the visual system; the most common neuro-ophthalmic presentation is optic neuropathy. Diagnosing the disease is problematic as the clinical presentation is nonspecific which may be associated with many other pathologies and no diagnostic finding is pathognomonic. In recent years, progress has been made in identifying new biomarkers and developing imaging techniques. Although corticosteroids remain the mainstay of therapy, many new pharmacological agents have been added to the treatment arsenal.

Keywords

neuro-ophthalmology, optic neuropathy, sarcoidosis

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Introduction

Sarcoidosis is a multisystem inflammatory disease of unclear etiology characterized by the hallmark histologic finding of noncaseating epithelioid granulomas. In the USA, the incidence of sarcoidosis has been estimated to be 40 per 100 000 and varies among geographic regions as well as with ethnicity [1]. Ophthalmic disease occurs in 22–60% of sarcoidosis patients and can involve any part of the eye [2–5]. Neurological involvement is less frequent with a prevalence of 5–15% of sarcoidosis cases [6,7], although one study found the prevalence to be as high as 26% [8]. Neuro-ophthalmic sarcoidosis concerns disease affecting the afferent or efferent visual pathways including involvement of the optic nerve and its axonal processes, ocular motor, trochlear, abducens and facial nerves, pupillary and extraocular muscle function. Diagnosis of neuro-ophthalmic sarcoidosis is difficult owing to the surreptitious nature of the disease and its nonspecific and extensive symptomatology. The finding of noncaseating granulomas on biopsy strongly substantiates the diagnosis of sarcoidosis; however, brain or intraocular tissue is rarely amenable to surgical investigation; therefore in the absence of pulmonary or other systemic findings, histological confirmation of sarcoidosis may not be achieved. Recent positron emission tomography (PET) technology may provide improvement in localization of disease sites in the brain for biopsy [9]. In this review, we discuss current literature on epidemiology, etiology, clinical presentation, and latest advances on diagnostic measures and management of neuro-ophthalmic sarcoidosis.

Epidemiology

Sarcoidosis occurs worldwide with greater prevalence in Scandinavia and in African–American women in the USA [10]. Typically, sarcoidosis presents during the second to fourth decades of life [11]. In northern Europe and Japan, a second peak in incidence occurs in women aged 50 and

older [12,13]. In the USA, the overall age-adjusted incidence of sarcoidosis is reported to be three-fold higher in Blacks (35.5 per 100 000) compared with Whites (10.9 per 100 000), with the highest incidence of 109 per 100 000 in Black females [14]. The reason for this racial predilection is unclear and may be due to genetic predisposition or environmental exposure. Neuro-ophthalmic involvement may occur more frequently in Blacks as well [2,15]. One retrospective US series found that the overwhelming majority of neuro-ophthalmic sarcoidosis cases involved Black women [2]. In contrast, a recent retrospective neuro-ophthalmic sarcoidosis study conducted in the USA found most of the patients to be White females [16]. The difference in epidemiological findings may be due to the differences in racial distribution or referral patterns in their respective geographic locations.

Immunopathology

Sarcoid inflammation is characterized by the formation of noncaseating granulomas in an apparent resultant exaggerated localized immune response to an inciting antigen. A number of studies demonstrate a preferential expression of type 1 helper T cells (Th)-1, cytokines, including interleukin (IL)-2, and interferon-γ, at sites of disease in sarcoidosis [17,18]. Additionally, macrophage-derived cytokines IL-1β, IL-6, and tumor necrosis factor (TNF)-α, known to be important for initiation of inflammatory response and pivotal for granuloma formation, are expressed at higher levels in patients with active sarcoidosis [19–22]. Increased levels of TNF-α have, moreover, been reported to correlate with a prolonged disease course in sarcoidosis [23,24].

Sarcoidosis may spontaneously resolve or progress into a chronic disease with a risk for fibrosis [10]. This difference in sarcoidosis outcome has been associated with an imbalance in the expression of Th-1 and Th-2 cytokines [23,25]. A subset of immunoregulatory T cells has been implicated in the pathogenesis of sarcoidosis [22,26–28]. Natural killer T (NKT) cells, which produce both Th-1 and Th-2 cytokines, are found at reduced levels in sarcoidosis patients [27,28]. Downregulation of NKT may be involved in the exaggerated T cell response in sarcoidosis.

Etiology

The search for a causative antigenic trigger is still ongoing. Current theory suggests that environmental exposure in genetically susceptible hosts may be the pathogenetic mechanism in formation of sarcoid granuloma [10].

Environmental irritants and certain occupations have been reported to have a positive association with sarcoidosis [29–35]. Izbicki *et al.* [36] reported an increased incidence of New York City firefighters developing sarcoidosis in the aftermath of the World Trade Center bombing in 2001.

Many putative infectious organisms have been implicated as potential antigenic trigger of sarcoidosis, although recent attention has been focused on *Mycobacterium* and *Propionibacterium*. Propionibacterial genome (*Propionibacterium acnes*, *Propionibacterium granulosum*) have been isolated in lymph node biopsies of sarcoidosis patients [37,38], and recently, Ichikawa *et al.* [39] reported that the amount of *P. acnes* DNA in bronchoalveolar lavage fluid (BALF) of patients with sarcoidosis was significantly higher than that in patients with other pulmonary diseases. A number of investigations have reported specific immune cellular recognition in serum as well as BALF of sarcoidosis patients to mycobacterial antigens, early secreted antigenic protein (ESAT-6) and catalase–peroxidase (katG) [40•,41–44]. *Mycobacterium tuberculosis* heat shock protein (hsp) and antigen 85A both induce Th-1 immune activity and both have been implicated in systemic sarcoidosis [45,46]. Interestingly, a recent study by Chen *et al.* [47•] reports that Amyloid A may be involved in the pathogenesis of sarcoid inflammation through regulation of Toll-like receptor-2.

Genetic predisposition has long been considered to be a factor in the development of sarcoidosis [48]. An association between human leukocyte antigens (HLAs) and sarcoidosis was early recognized in the 1970s [49,50]. Since that time, a wealth of genetic research has ensued, identifying specific polymorphisms in predisposed individuals. HLA-DRB1 and -DQB1 alleles have been implicated in sarcoidosis by a number of reports [51–53]. Grunewald *et al.* [54] found HLA-DRB1*03 to be strongly associated with disease resolution, whereas HLA-DRB1*15 associated with disease persistence; these findings are supported by others [55].

Clinical presentation

Neurosarcoidosis has been called 'the great mimicker' as those affected with the disease can present with nonspecific and variable symptoms that can be associated with a constellation of many other pathologies [56]. The clinical spectrum of neurosarcoidosis includes encephalopathy, vasculopathy, psychiatric symptoms, seizure, aseptic meningitis, space occupying brain lesions, hydrocephalus, hypothalamic and pituitary involvement, myopathy, spinal cord involvement, and peripheral neuropathy [57–60].

Cranial neuropathy is the most frequent neurological manifestation, identified in 50–70% of patients with neurosarcoidosis [60,61]. Involvement of almost every

cranial nerve has been reported with the facial nerve followed by the optic nerve being the most commonly affected [57,62,63]; however, one study found optic nerve involvement in 38% of cases compared with only 19% in facial nerve palsy [62]. Cranial nerve lesions may be unilateral or bilateral and may be caused by direct granulomatous intrusion on nerves, or indirectly via increased intracranial pressure or granulomatous basal meningitis [60].

Involvement of the optic nerve, chiasm, and tract in neurosarcoidosis occurs in 1–5% of cases [64]. Optic neuropathy is the predominant neuro-ophthalmic sarcoidosis manifestation, occurring in 33–70% of cases [2,7,15,16,65]. A selected series of anterior visual pathway neurosarcoidosis by Frohman *et al.* [64] revealed optic disc pallor to be the most common finding, seen in 55% of involved eyes, followed by optic disc edema (29%), periphlebitis (14%), and optic disc granulomas (10%), whereas classic fundus findings of optic granuloma and vitreous snowballs were less frequently appreciated. This may in part also reflect referral patterns. Vision loss associated with neuro-ophthalmic sarcoidosis may be acute or chronic and may be painful or painless. Optic nerve disease is typically severe, with profound impairment of visual acuity. In a follow-up study of neurosarcoidosis patients with impaired vision receiving corticosteroid therapy, less than half had appreciable visual recovery after 18 months [62].

Sarcoid granulomas can affect any part of eye and visual system. Anterior uveitis (30–70%) is the most frequent ophthalmologic manifestation of sarcoidosis [3,66,67]. About 10% of sarcoid uveitis patients develop unilateral or bilateral vision loss mainly due to cystoid macular edema [3]. Granulomatous infiltration of the periorbital or lacrimal tissue may result in keratoconjunctivitis sicca [3].

Diagnostic measures

Compatible clinical, laboratory, and radiologic findings, supported by histologic evidence of non-necrotizing granulomas, are the usual criteria to establish the diagnosis of sarcoidosis.

Sarcoid granuloma produces both angiotensin-converting enzyme (ACE) and lysozyme [68]. Serum ACE levels are significantly elevated in patients with sarcoidosis; however, this test has poor sensitivity as it is found to be elevated in only 40–60% of sarcoidosis patients [68,69]. Serum ACE levels may be influenced by polymorphisms in the ACE I/D gene where homozygous individuals express either the highest or lowest ACE levels [70]. The standard use of a single reference interval instead of genotype corrected ACE I/D-corrected reference intervals for ACE activity can result in an imprecise measurement [70].

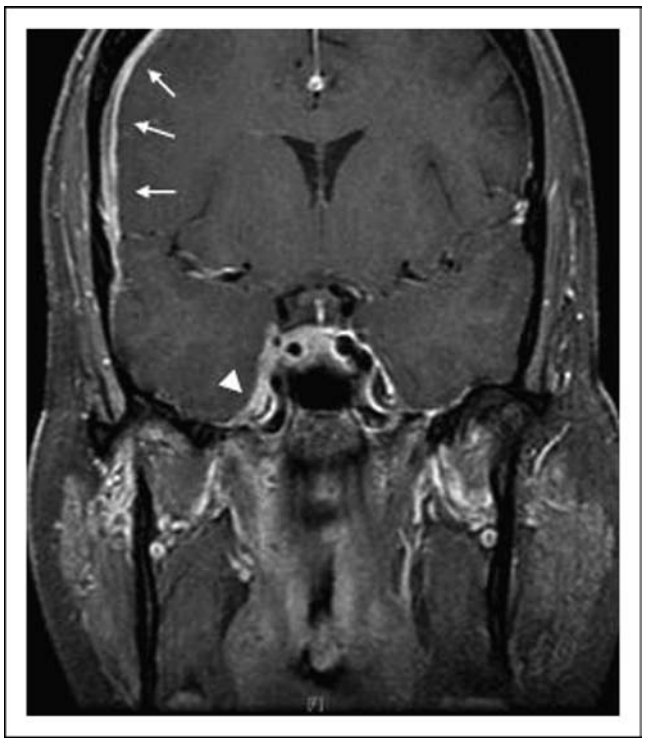
Serum lysozyme has been shown to be a more sensitive marker of sarcoidosis activity [71]; although, the lower specificity for sarcoidosis compared to ACE limits its diagnostic value [71,72]. However, in a study of ocular sarcoidosis, serum lysozyme levels were shown to have equal specificity (0.953) but better sensitivity (0.789), positive predictive value (0.918), and negative predictive value (0.872) than ACE (0.583, 0.897, and 0.766, respectively) [67], suggesting a role for serum lysozyme as a parameter in diagnosis as well as in disease activity monitoring in known sarcoidosis.

Two additional potential biomarkers of sarcoidosis disease activity have been identified. Both chitotriosidase and CCL 18 are produced by activated macrophages and have previously been used as measures of Gaucher disease [73]. Patients with sarcoidosis have significantly increased serum chitotriosidase concentrations which correlated with increased serum ACE [74,75]. Grosso *et al.* [74] found higher serum chitotriosidase concentrations in chronic sarcoidosis patients than in normal subjects as well as a significant correlation between chitotriosidase levels and the four radiographic stages of the disease, suggesting a prognostic role for chitotriosidase in sarcoidosis. Another study report average increases of 13.7-fold in plasma chitotriosidase concentrations and a 3.5-fold in CCL18 of sarcoidosis patients [76•]. Steroid treatment resulted in reduction of chitotriosidase and CCL18 but disease relapse was preceded by increases in both markers [76•]. The value of these biomarkers in the clinical management of sarcoidosis needs to be further evaluated.

BALF analysis showing elevated total cell count, predominantly lymphocytes, together with a nearly normal percentage of eosinophils and polymorphonuclear neutrophils and the absence of plasma cells characterizes a pattern consistent with sarcoidosis [77]. Some studies indicate that BALF analysis of ACE levels reflect pulmonary sarcoid activity better than serum testing [78]. Sarcoidosis is frequently associated with high CD4/CD8 ratio in BALF analysis; however, measurements of BALF CD4/CD8 are highly variable and its diagnostic role is still up for debate [79,80]. Recently, elevated levels of BALF transferrin have been reported in sarcoidosis patients, which is correlated with elevated BALF lymphocytosis and ACE levels; however, serum transferrin concentrations remained low [81•].

MRI of the brain and/or orbit with gadolinium contrast enhancement is the preferred imaging modality in evaluating neuro-ophthalmic sarcoidosis [62]. Typical MRI findings of cranial nerve lesions are thickening and

Figure 1 T1-weighted gadolinium-enhanced coronal MRI



MRI shows enhancement of the dura along the right frontal and temporal convexity (arrows) and right Meckel's cave and V3 distribution of the right trigeminal nerve (arrowhead).

enhancement on T1-weighted scans postcontrast. Figure 1 shows abnormal dural enhancement along the right frontal and temporal lobe convexity as well as enhancement of Meckel's cave and right trigeminal nerve V3. Although the facial nerve is usually the most common clinically affected cranial nerve in sarcoidosis, the optic nerve is most frequently involved radiographically [62].

A complete ophthalmological examination should be performed in the neurosarcoidosis evaluation because the optic nerve is commonly affected, second only to the facial nerve. Fluorescein and indocyanine green angiography may demonstrate posterior segment activity such as choroidopathy, periphlebitis, and cystoid macular edema [3,82,83]. Studies using visual evoked potentials (VEPs) report abnormalities of the VEPs in sarcoid patients without ocular or neurologic symptoms, suggesting the value of VEPs in revealing subclinical involvement which can also help in the early diagnosis of neuro-ophthalmic sarcoidosis [84–86].

The gold standard in establishing a diagnosis of sarcoidosis is through biopsy of lesions. Ophthalmic and neurologic manifestations of sarcoidosis are generally not sites amenable for surgical investigation [87,88]. In many cases of occult sarcoidosis with isolated optic neuropathy, biopsies of the optic nerve were performed which obviated the chances of visual recovery [64]. Recently, several reports suggested that whole-body ^{18}F-fluorodeoxyglucose (18F-FDG) PET, which is a nonspecific measure of tissue hypometabolic or hypermetabolic activity, may be useful in sarcoidosis to identify possible diagnostic biopsy sites as well as assess the extent of organ involvement [9,89]. In one study, the sensitivity of 18F-FDG PET/CT in detecting active sarcoidosis localizations in the thoracic, sinonasal, and pharyngolaryngeal areas were 100, 100, and 80%, respectively [90]. Combined PET scanning of the brain with F18-FDG and C-11 methionine was reported to improve localization of CNS biopsy sites in neurosarcoidosis [9].

Management

There is no standardized pharmacological therapeutic regimen for the treatment of neurosarcoidosis, and the disease course ranges from a self-limited disease to chronic progressive fibrotic course [10,63]. The mainstay of initial therapy remains the use of systemic corticosteroids. The dosing regimen varies depending on clinical presentation, and many reports advocate the initial use of high-dose glucocorticoids. Patients are usually maintained on 40–80 mg of prednisone per day for 4–8 weeks with slow taper [91]. In another report, the daily prednisone treatment regimen was 0.5–1 mg/kg for up to 6 weeks followed by taper that is maintained for about a year [92]. Doses of prednisolone of less than 20–25 mg/day have been reported to increase the likelihood of recurrence [62]. Neurosarcoidosis typically responds quickly to steroid treatment, usually within days to weeks of initiating therapy [91,93]. Patients responding to this medical treatment have a good prognosis with 55% reported showing complete recovery [94]. Unfortunately, the incidence of steroid-related side-effects, including glucose intolerance, osteoporosis, and obesity, is high due to the prolonged course of high-dose steroid use.

Adjunctive immunomodulatory agents such as methotrexate, mycophenolate mofetil, cyclophosphamide, azathioprine, cyclosporine, chlorambucil, chloroquine, and hydroxychloroquine have all been reported to be effective in refractory neurosarcoidosis without adequate corticosteroid response [91,95]. Concomitant use of these immunomodulatory agents may minimize steroid requirement. Methotrexate has been used as a first-line steroid-sparing agent in sarcoidosis and was demonstrated to have a better response rate (61%) compared with corticosteroid therapy (29%) [96,97]. Mycophenolate mofetil, previously used in systemic sarcoidosis, has been efficacious and well tolerated in neurosarcoidosis [98,99]. Disease remission in refractory neuro-ophthalmic sarcoidosis with TNF-α inhibitors, thalidomide and infliximab,

has also been reported [100–103]. Salama *et al.* [103] reported successful remission with infliximab in a case of sarcoid optic neuropathy, refractory to corticosteroid, azathioprine and methotrexate, in which the patient had vision recovery.

Conclusion

Neuro-ophthalmic sarcoidosis is an uncommon disease with variable manifestations that mimic a myriad of other diagnostic possibilities. Due to the lack of standardized universal diagnostic criteria and specific testing, early recognition of the disease is challenging, thereby delaying treatment. In recent years, much progress has been made in the development and refinement of biomarkers and radiographical techniques. Although the etiology of sarcoidosis remains elusive, there is greater understanding of genetic and environmental contributions. Although corticosteroids remain the mainstay of therapy, many new pharmacological agents have been added to the treatment arsenal. However, to date, there is still no large-scale randomized controlled study to standardize optimal therapy.

Neuro-ophthalmic symptoms may present early, even before a known diagnosis of systemic sarcoidosis, and is therefore important for the ophthalmologist or neurologist to recognize the clinical signs and employ the appropriate diagnostic measures so that a diagnosis can be achieved and thereby treatment initiated as soon as possible.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

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- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 496).

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