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Ocular Sarcoidosis – Review

Oczna postać sarkoidozy – przegląd piśmiennictwa

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Abstract: Sarcoidosis is a systemic granulomatous disease of unknown aetiology, which may affect every organ. Ocular manifestation of sarcoidosis may be diagnosed in as many as 70% of patients. The objective of this work was to describe the ophthalmological and neuro-ophthalmological symptoms, which may occur in this disease, with a detailed division into eye structures. For this purpose, a search was conducted in the Pubmed, MEDline and Google Scholar databases to find the appropriate articles, which described investigation of sarcoidosis, ocular symptoms rate in sarcoidosis and were written in English. According to the literature the most frequent ocular manifestation of sarcoidosis is granulomatous anterior uveitis. Only early diagnosis and proper treatment may protect patients from late complications, leading to permanent damage to eyesight and complications in other organs.

Key words: ocular sarcoidosis, neurosarcoidosis, granulomas.

Abstrakt: Sarkoidoza jest wielosystemową, ziarniniakową chorobą o nieznanej etiologii, która może objąć procesem zapalnym każdy narząd człowieka. Postać oczna sarkoidozy może wystąpić nawet u 70% chorych. Celem pracy jest opis objawów okulistycznych oraz neurookulistycznych mogących wystąpić w tej jednostce chorobowej ze szczegółowym podziałem na możliwe zaangażowanie poszczególnych struktur ocznych. W tym celu przejrzano artykuły w języku angielskim, posługując się bazą danych Pubmed, MEDline, Google Scholar. Według piśmiennictwa do najczęstszych objawów okulistycznych, które mogą wystąpić w przebiegu sarkoidozy, należy ziarniniakowe zapalenie przedniego odcinka błony naczyniowej. Wczesne rozpoznanie i włączenie odpowiedniego leczenia mogą uchronić pacjentów przed wystąpieniem późnych powikłań w postaci trwałego uszkodzenia wzroku oraz powikłań ze strony innych narządów.

Słowa kluczowe: sarkoidoza oczna, neurosarkoidoza, ziarniniaki.

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Introduction

Sarcoidosis is a systemic granulomatous disease, in which the earliest symptoms often include eye tissue inflammation. The eye is the organ second most often affected by the disease after the lungs. This location poses a problem in performing a biopsy of affected tissue, which is a gold standard in diagnostics of the disease (1). In the year 2009, international criteria for the diagnosis of ocular sarcoidosis were developed (by the International Workshop on Ocular Sarcoidosis – IWOS), taking into account indicative clinical signs and appropriate laboratory investigations that may indicate sarcoidosis (2). Despite the convenience offered by these criteria, none of the symptoms or their number generated a statistically significant prognostic value for a positive biopsy of the affected tissue The course of the disease may vary, from mild to severe and even fatal. This is correlated with race and demographic factors. It is known that in black patients, the course is more severe in comparison with white patients. Nevertheless, mortality rates are the same. Such factors as: black race, late diagnosis of the disease, duration of more than 6 months, involvement of three or more organs and the 3rd stage of pulmonary sarcoidosis, are associated with a less favourable prognosis (3). The disease attacks mainly the lungs, pectoral lymph nodes, the skin and the eyes. In about one half of all patients, the disease is limited, and remission takes place within 3 years. In about one third of all patients, the disease is chronic, requiring long-term immunosuppression.

Material and Methods

A search was performed in Pubmed, MEDline and Google Scholar databases, selecting 23 articles published in English in the years 2000-2017, describing ophthalmological symptoms, which may be present in sarcoidosis. These articles were analysed with regard to application of current diagnostic methods, demographic data and selection of statistical methods.

Orbital cellulitis

Sarcoidosis should be taken into account in differential diagnostics of orbital tumours, in particular, in elderly and female patients (4). Tumours may be tender on palpation or result in generalised orbital pain. However, a poorly delineated inflammatory infiltration in the form of a chronic unilateral palpebral oedema, resulting in such symptoms as diplopia, deteriorated

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visual acuity, conjunctival hyperaemia with limited eyeball mobility and exophthalmos may be an early symptom of orbital sarcoidosis. Lesions may also appear in the orbital bone, and in the case of coexistence of deteriorated visual acuity, disturbed pupillary reflex, visual field defects and lack of pathologies found in an examination of the fundus of the eye, it is necessary to take into account the possibility of location in the posterior part of the orbit. Eyeball mobility disorders in the course of sarcoidosis occur very rarely. They are accompanied by soft tissue oedema, dropping of the upper eyelid and double vision. In such cases, it is necessary to analyse two possibilities: motor nerves of extraocular muscles having been attacked by sarcoidosis, or inflammation of the muscles themselves. An magnetic resonance imaging (MRI) of the head and orbits indicates oedema and the presence of hyperintense nodules, consistent with granuloma formation. However, it is not pathognostic of sarcoidosis (5).

Lacrimal gland

The lacrimal gland involvement, often bilateral, is observed in even as many as 30% of patients, and it leads to dry eye syndrome and dry keratitis. It occurs when the disease attacks the main lacrimal gland, as well as in situations, in which it affects the additional lacrimal glands, located in the eyelids and in the conjunctiva (6). Patients report painless oedema of the upper lid, similar to allergic or contact dermatitis. After turning the eyelid, the swollen and reddened eyelid lobe of the lacrimal gland becomes visible (6, 7). Palpation of the upper eyelid reveals compact masses in the projection of the lacrimal gland. Affecting the salivary glands may be observed, accompanying the inflammation of the lacrimal gland, in the form of a „panda sign" in scans during scintigraphy after administration of radioactive gallium-67, particularly in the case of extrapulmonary sarcoidosis (7). Non-caseating granulomas may also be located within the boundaries of the lacrimal sac, leading to recurrent inflammations and tearing. Poor response to treatment in such cases suggests the need for histopathological examination of lesions in this area (7).

Eyelids

Nodules, which are granulomas associated with sarcoidosis, may also appear on the eyelids. There have been several reports of inflammatory infiltrates of both the anterior and the posterior eyelid lamellae, leading to their scarring and extensive anatomical changes (8). Affecting of the eyelids is associated with lesions appearing on the edges, manifested by eyelash loss or improper growth and entropion. Obliteration of the Meibomian gland ducts is probably one of the causes of dry eye syndrome in these patients. The nodules may also appear in old scars of the eyelids, causing skin lesions in this area (8).

Ocular surface inflammation

The episclera and the conjunctiva

Sarcoidosis may involve the episclera and the conjunctiva (9). Lesions may take the form of a subconjunctival haemorrhage, conjunctivitis, scarring of the conjunctiva, formation of adhesions or nodular episcleritis. The most common are nodules of the conjunctiva, which may appear in patients with uveitis symptoms and constitute a diagnostic indication of this disease. Thus, searching for these nodules should be a part of the ophthalmological examination in these patients. These nodules may be located in the corneal limbus, and they may be bilateral and multiple (9). A much less often encountered form of this disease is hypertrophy of the conjunctiva in the area of the corneal limbus. In such cases, sarcoidosis should be taken into account in differential diagnostics along with conjunctival neoplasia, lymphoma, as well as allergic conjunctivitis (10).

The sclera

Affecting the sclera has not been described frequently in literature, particularly in situations, in which other tissues of the eye have not been affected. It may take the form of painless nodules, which, upon histopathological examination, turn out to be equivalent to non-caseating granulomas. Correct diagnosis may be facilitated by the presence of facial skin lesions, which sometimes coexist with the disease, consisting of decolouring, irritation and hard, raised plaques (11).

The cornea

Sarcoidosis in the form of parenchymal or nummular keratitis is rare. Similarly, coexistence of corneal infiltrations with anterior uveitis and lesions in the ocular fundus has been described in literature only once, by Gungor et al. Aetiology of bilateral corneal infiltrations, similar to subepithelial viral opacity, although larger and deeper, was suspected due to their occurrence simultaneously with uveitis, and a similar response to treatment (12). Marginal ulceration of the cornea, leading to its perforation, may also be caused by sarcoidosis if there are no other localised or systemic inflammatory or infectious diseases. Dry keratitis and conjunctivitis occurs in even more than 30% of patients with ocular sarcoidosis, and it is the second most frequent ocular symptom of this disease after anterior uveitis. It may be associated with inflammation of the lacrimal gland or not. It is probable that in these cases, inflammation of the lacrimal gland is too mild to cause its swelling, but it is severe enough to give symptoms of dry eye syndrome. It is diagnosed more frequently in women (13).

Uveitis

a. Anterior uveitis

Sarcoidosis is the cause of anterior uveitis even in 22% of patients (14). Uveitis is the most frequently encountered manifestation of the ocular disease. Its most common type is anterior uveitis, the second most frequently occurring – posterior uveitis, the third – intermediate uveitis, and the least common is panuveitis. Anterior uveitis occurs more frequently in black patients, who also tend to suffer from it at a younger age. The characteristic symptoms, listed among the IWOS criteria, include mutton-fat keratic precipitates in the corneal endothelium and nodules in the pupillary margin (Koeppe nodules) and in the stroma of the iris (Busacca nodules). Similar granulomas (Berlin's nodules) with tent-like adhesions may affect the trabecular meshwork of the angle. This symptom occurs more frequently, although not with statistical significance, in patients with a po-

sitive biopsy result (13). White granulomas are visible in the slit lamp along the edge of the cornea and the iris, but they become much more apparent in gonioscopy. They may cause obliteration of the Schlemm's canal and lead to increase in intraocular pressure. Acute iritis may occur even in 26.5–42% of patients suffering from inflammation in the course of ocular sarcoidosis (14, 15). Acute iritis and inflammation of the ciliary body is observed in Lofgren syndrome and Heerfordt syndrome, which are easily diagnosed thanks to other systemic symptoms (9). Chronic or acute symptoms may depend upon earlier anti-inflammatory treatment. Affecting of the anterior section may be accompanied by intermediate and posterior uveitis; as a result, examination of the ocular fundus in such patients is obligatory.

b. Intermediate uveitis

According to the literature on the subject, intermediate uveitis in sarcoidosis is less frequent than anterior uveitis; however, it may be the first symptom of the developing disease. Intermediate uveitis occurs more often in white patients in comparison with black patients (16). It affects the vitreous humour and the pars plana of the ciliary body. Usually, it is accompanied by exudate in the vitreous cavity or inflamed masses, resembling "snowballs" or "strings of pearls". Patients complain about blurred vision and floaters before their eyes. These symptoms are not specific to sarcoidosis, as they may appear in other granulomatous diseases and in multiple sclerosis.

c. Posterior uveitis

Posterior uveitis occurs in about 28% of patients with ocular sarcoidosis. It is observed more often in white patients (14). It is associated with lesions in the retina, often combined with chorioretinitis – however, these two structures can also be occupied separately. Posterior uveitis is usually bilateral, although the symptoms may be asymmetrical. A symptom of posterior uveitis, which is characteristic of sarcoidosis, is perivenous inflammation. It results in the emergence of sheaths around vessels or exudates in venous blood vessels, which result in a characteristic symptom of "candle wax dripping". According to available literature, these are visible in 70% of patients, whose posterior uvea has been affected, during ophthalmological examination (15). In subclinical form, they are not observed during the examination using the slit lamp, but only in fluorescein angiography. Single- or multifocal granulomas of the chorion may appear, usually located along the perimeter of the retina. According to literature, these occur in 5 to 12% of patients with ocular sarcoidosis (9). Most often, these are white, raised masses. They may differ in terms of size, from small structures, similar to Dalen-Fuchs nodules, to large ones, which can be differentiated from tumours of the chorion. Active lesions are usually white. When granulomas disappear, they usually leave a trace in the form of an area of hypopigmentation and scarring, and the lesion becomes yellowish-grey, with clearly indicated boundaries (9). Lesions located along the perimeter rarely cause blurring of vision; a problem emerges, when they are located in the posterior part (17) (Fig. 1).

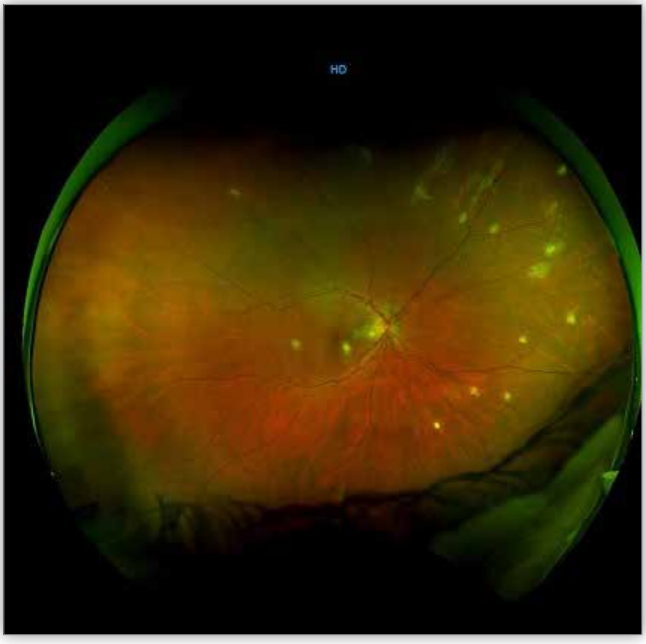

Fig. 1. Picture of 60-year-old female patient with multifocal choroiditis secondary to sarcoidosis demonstrates multiple, round, creamy subretinal lesions.

Ryc. 1. Zdjęcie przedstawiające wieloogniskowe zapalenie naczyniówki u 60-letniej kobiety, z kremowymi ogniskami zapalnymi umiejscowionymi pod siatkówką.

d. Panuveitis

Panuveitis may occur in 9–30% of cases of ocular sarcoidosis (9). Inflammation of these structures may give no symptoms – it is the so-called "clinically silent" disease, and it may precede signals from various organs.

The most frequent complications in posterior uveitis are macular oedema (76%), cataract (49%), glaucoma (36%), ischaemia of the retina (16%), and subretinal and intraretinal neovascularization, as well as neovascularization of the optic disc (11%).

Other symptoms associated with the disease affecting the posterior uvea

Neovascularization of the optic disc or peripheral retinal neovascularization may lead to haemorrhage into the vitreous cavity (2). Other less common symptoms of posterior uveitis may include serous retinal detachment, mainly in patients with large granulomas of the chorion. Closing of the central vein of the retina or its branches is not a common phenomenon in the course of sarcoidosis. Macroaneurysms, which are present sometimes, coexisting with multi-focal lesions along the perimeter of the retina, are observed mainly in elderly women, suffering from sarcoidosis and coronary heart disease (18, 19).

Cataract and glaucoma

Glaucoma may develop in the course of ocular sarcoidosis as a result of accumulation of inflammatory cells within the boundaries of trabeculation due to long-term anterior uveitis or a steroid therapy applied. Gonioscopy conducted in the Japanese population revealed trabeculation nodules in 61% of the population and tent-like anterior adhesions in 55% of the population (19). Anterior adhesions may lead to closing of the filtration angle. Among patients suffering from secondary glaucoma, the percentage of unsuccessful filtration treatments is high. As

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a result of chronic inflammation and the application of steroid therapy, cataract develops more frequently and at a faster pace (9).

Neurosarcoidosis

Sarcoidosis also affects the central and peripheral nervous system, and it may cause various symptoms, depending on the location of the granulomas. Neurosarcoidosis, which, according to literature, may be diagnosed in 5–16% of all patients, may be associated with blurred vision as the optic nerve or the optic tract is affected, as well as oedema of the optic disc, secondary to increased intracranial pressure, eyeball mobility disorders, visual hallucinations or disorders of the structure and functioning of the pupils (20). Cranial neuropathy is the most often encountered symptom of neurosarcoidosis. In most cases, the facial nerve and the optic nerve are affected (20). Attacking of the optic nerve is usually unilateral and may be isolated, without any dysfunctions of other organs. According to Frauhamn et al., the most frequently encountered manifestations of the optic nerve being attacked include atrophy (55%), swelling of the optic disc (29%), perivenous inflammation (14%), granulomas of the optic nerve (10%) (21). If swelling of the optic disc, accompanied by facial nerve paralysis, occurs in young women of reproductive age, it may strongly suggest sarcoidosis. Swelling of the optic disc may be due to increased intercranial pressure or posterior uveitis. In more than half of all patients suffering from optic nerve symptoms, irreversible deterioration of visual acuity takes place. Cranial neuropathy is a part of the Heerfordt syndrome, which also includes uveitis, fever and swelling of the parotid gland. Other symptoms of neurosarcoidosis have also been reported, including Horner syndrome, Adie's tonic pupil or Argyll Robertson pupil (20).

Attacking of the motor neuron of the facial nerve is associated with ophthalmic consequences, including lagophthalmos, excessive tearing, keratopathy, ectropion. Severe disorders of the ocular surface lead to ulceration of the cornea.

Affecting of the central nervous system may lead to nystagmus or hallucinations. All symptoms may be due to damage to the optical tract due to inflammation, pressure or granulating infiltration.

Ocular sarcoidosis in children

Sarcoidosis in children is rare; however, when it occurs, it commonly affects the eyes. In this age group, the most frequently encountered manifestation of ocular sarcoidosis is anterior uveitis – according to literature, diagnosed in 58–90% of children with sarcoidosis (22). Anterior uveitis may be accompanied by mutton-fat keratic precipitates in the corneal limbus or an inflammatory ring (23). Unlike juvenile idiopathic arthritis, in which the inflammatory infiltrations are located rather centrally and less delineated, in sarcoidosis, their location is peripheral, and delineation is stronger. The second most frequent lesion are conjunctival nodules. Affecting of the vitreous body and the associated presence of snowballs, optic neuritis or granulomas of the retina and the choroid occur less frequently. Perivenous inflammation of the retina is virtually absent in children suffering from sarcoidosis. Other rare symptoms that may emerge include interstitial keratitis, band keratopathy, dacryocystitis, swelling of the lacrimal gland or infiltration of the orbit, which may result in exophthalmos (22, 23).

Summary

Sarcoidosis may affect many organs – quite frequently including the eye. It should be kept in mind that as the ocular symptoms listed in this study appear, it is necessary to conduct diagnostics towards sarcoidosis, as neuro-ophthalmological symptoms may be the earliest manifestation of the disease. A quick diagnosis and introduction of proper treatment may prevent multi-organ complications.

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