Ocular Manifestations of Systemic Autoimmune Diseases

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Abstract

Ocular manifestations may be the initial, presenting features of various neuro-immune and neuro-degenerative diseases. Ophthalmic involvement may present as orbital, intraocular or adnexal inflammation or as discrete lesions involving different components of the eye and may serve as the barometer for the severity of the underlying systemic diseases. Often, the lesions may present as an ophthalmic emergency, requiring aggressive therapy before the diagnosis can be confirmed. The clinician scientist must be vigilant and maintain a high level of suspicion in order to diagnose the condition early and institute prompt therapy. The ocular signs and symptoms may be associated with a constellation of neurological complaints. Therefore, an integrated approach with close collaboration among ophthalmologists, neurologists, internists and pathologists is required to ensure optimal patient care, preserving not only the vision but also the lives of the patients.

Keywords

Adamantiades-Behçet's disease • Cornea • Optic nerve • Retina • Uveitis • Vogt-Koyanagi-Harada disease

36.1 Introduction

The eye has been recognized as an immune-privileged organ due to the presence of non-permeable blood-ocular barriers. However, over the years, a number of systemic disorders have been associated with characteristic ophthalmologic manifestations, which may often lead to severe visual morbidity. Recognition of such pathological changes in the eye may provide valuable clues leading to the diagnosis of the associated systemic immunologic dysfunction. Typically, systemic immunologic conditions affect musculoskeletal, gastrointestinal, renal and neurological systems. Identification of the constellation of ocular and systemic signs may allow the clinician to consider a definitive diagnosis and plan appropriate management.

Intraocular inflammation of the uvea (uveitis) is the hallmark of ophthalmic involvement associated with systemic autoimmune diseases. In addition, there may be concomitant involvement of extraocular structures and the periorbita. Pathological changes such as inflammation of the retinal and/or choroidal vasculature, optic nerve swelling, macular edema, exudative retinal detachment, corneal ulceration and granulomatous inflammation of the uveal tissue are common causes of visual loss in these patients (Vodopivec et al. 2014).

Autoimmune diseases may also present initially only with ophthalmologic manifestations. The diagnosis of the underlying systemic disease, which may be life-threatening, may be delayed, unless the clinician scientist maintains a high level of suspicion. With appropriate screening, comprehensive examination and laboratory evaluation, the underlying

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systemic immunologic dysfunction can be identified and treated to prevent further ophthalmic, neurologic and systemic morbidity. Similarly, detailed evaluation of ocular symptoms and periodic, routine eye examination of patients with autoimmune diseases may allow early detection, treatment and prevention of significant visual loss.

36.2 Pathophysiological Basis of Ocular Disease

The immune privilege of the eye is maintained due to interplay of several complex mechanisms that include both innate and adaptive arms of immunity and by contribution of both, local and systemic factors that decrease inflammatory responses (Stein-Streilein and Caspi 2014). Anatomical barriers in the eye, such as the blood-ocular-barrier, avascularity of structures such as the cornea and sclera, lack of lymphatic channels, blood-retinal-barrier and highly-regulated production and maintenance of aqueous and vitreous humor contribute towards immune-tolerance of eye-derived antigens (Caspi 2014).

The ocular tissues have characteristic differences compared to other tissues with regards to their immunologic make-up. The ocular milieu has lower expression of major histocompatibility factors, soluble cell-surface receptors, growth factors and pro-inflammatory cytokines. This results in a decreased T- and B-cell response in the eye and production of non-complement fixing antibodies *(anterior chamber-associated immune deviation - ACAID)*. The biochemical microenvironment of the eye actively decreases the response of the immune system. Thus, ordinarily, systemic immune response to non-ocular antigens does not illicit damage to the eye (Taylor and Kaplan 2010).

However, various systemic autoimmune diseases are characterized by ocular manifestations that may precede systemic symptoms. These conditions are associated with breakdown of immune-privilege mechanisms of the eye, and frequently of the brain, as well. Various antigens that incite an inflammatory response are found both in the eye and the nervous system. Immune response against such antigens (e.g. Vogt-Koyanagi-Harada syndrome) results in disease manifestations that affect both organ systems.

36.3 Clinical Features of Select Autoimmune Diseases

36.3.1 Vogt-Koyanagi-Harada Disease

Vogt-Koyanagi-Harada (VKH) disease is characterized by diffuse, non-necrotizing granulomatous inflammation of the uveal tissue along with involvement of the central nervous system, auditory system and the integumentary system. VKH consists of two entities: Harada's disease and Vogt-Koyanagi syndrome. Harada's disease (first reported by Einosuke Harada in 1926) is characterized by bilateral exudative retinal detachment along with cerebrospinal fluid (CSF) pleocytosis. Vogt-Koyanagi syndrome is associated with anterior segment inflammation (chronic anterior uveitis) along with alopecia, vitiligo and poliosis (described in 1906 by a Swiss resident in Ophthalmology—Alfred Vogt). These findings were brought together below one umbrella term, VKH, by Babel in 1932 (Herbort and Mochizuki 2007). Presently, the International Workshop on Vogt-Koyanagi-Harada Syndrome and Sympathetic Ophthalmia provides the guidelines for diagnosis, investigations, imaging interpretation and management of VKH.

36.3.1.1 Epidemiology

There is a wide geographic and ethnic variation in the incidence of VKH, with higher proportion of Japanese, Asian, Hispanic and Native Americans diagnosed with the disease. In the US, VKH disease accounts for less than 5 % of all the uveitis clinic referrals. The incidence is higher in Japan, where VKH disease accounts for approximately 7 % of all the uveitis referrals. Higher incidence of the disease among individuals with dark pigmented skin may be linked to the pathogenesis of the disease. Women may be more commonly affected. The most common age group for the occurrence of the disease is between the second to the fifth decade of life (Ohno et al. 1977).

36.3.1.2 Etiology and Pathogenesis

The etiology of VKH appears to be granulomatous inflammatory response to antigens located in the ocular, auditory and central nervous systems. Electron microscopic analysis of uveal tissues has revealed predominance of T-cell population in close association with melanocytes (Yamaki et al. 2000). In addition, histopathological and immunohistochemical findings suggest that VKH occurs as a result of altered T-cell response against yet undiscovered ligands of the melanocytic proteins (Sugita et al. 1996). Tyrosine-related proteins (Hayakawa et al. 2004), molecular mimicry (Sugita et al. 2007) and immunologic cross-reactivity with various external antigenic stimuli such as those caused by cytomegalovirus infection have also been shown to play a role in the etiology of VKH.

Derangement in cytokines and inflammatory mediators, such as increased levels of IL-17, IL-1β (Li et al. 2010), IL-6 and tumor necrosis factor (TNF)-α and decreased levels IL-25 (Xu et al. 2014) has also been linked to the pathogenesis of VKH. Interleukin (IL) -21 may promote secretion of IL-17 resulting in pleiotropic effects on the immune system (Li et al. 2010). In addition, role of decreased IL-25 and increased release of IL-1β, IL-6 and tumor necrosis factor (TNF)-α by peripheral blood mononuclear cells may play a role in the pathogenesis of the disease (Xu et al. 2014).

VKH disease has a strong immunologic basis with higher prevalence of the disease among individuals with HLA-DR1 and DR4 as compared to controls (Weisz et al. 1995). The predominant alleles associated with VKH include HLA-DRB1*0405 and HLA-DRB1*0410 (Shindo et al. 1994). The relative risk of developing VKH is higher with HLA-DR1 as compared to HLA-DR4 (4.11 versus 1.96) (Arellanes-Garcia et al. 1998; Tiercy et al. 2010). Thus, various population-based studies indicate that specific Human Leukocyte Antigen (HLA) genes may confer increased susceptibility for the development of VKH disease.

The demographic, immunologic and laboratory features of VKH disease closely resemble those of sympathetic ophthalmia (Rao 1997). This may explain the similarities in the morphological manifestations of both the diseases.

36.3.1.3 Clinical Features

Ocular features of VKH disease are divided into various stages including prodromal, acute, chronic and convalescent/recurrent stage. The disease may present initially with a viral-like illness. The patient may complain of malaise, headache, fever, orbital pain, meningisms and nausea. CSF analysis at this stage may indicate presence of pleocytosis in 80% patients. This stage is followed by the acute uveitic stage characterized by *bilateral exudative panuveitis* that is usually symmetric (Fig. 36.1). There is anterior segment inflammation, vitritis, bilateral exudative retinal detachment (which may be multifocal and bullous), hyperemia and edema of the optic nerve head and retinochoroidal thickening detectable by ultrasound B-scan. Mutton-fat keratic precipitates and iris nodules may be visualized. Fundus fluorescein angiography reveals an impressive picture with multiple hypofluorescent dots initially followed by multiple, focal areas of hyperfluorescence (Fig. 36.1). Choroidal vessel leakage and hyperfluorescence can be detected using Indocyanine green angiography (ICGA) (Sakata et al. 2014; Cunningham et al. 2014).

This stage is followed by the stage of chronic uveitis heralded by integumentary signs such as vitiligo, poliosis and choroidal depigmentation. *Suguira's sign*, which is perilimbal vitiligo, may be observed at this stage. Depigmentation of the choroid gives an appearance of *sunset-glow fundus*. Retinal pigment epithelium (RPE) may show a moth-eaten appearance. Along with disc pallor, focal areas of yellow, well-circumscribed chorioretinal atrophy, especially in the inferior mid-periphery (earlier referred to as Dalen-Fuch's nodules), may be seen. Approximately two-third of the patients may have recurrent disease resulting in complications

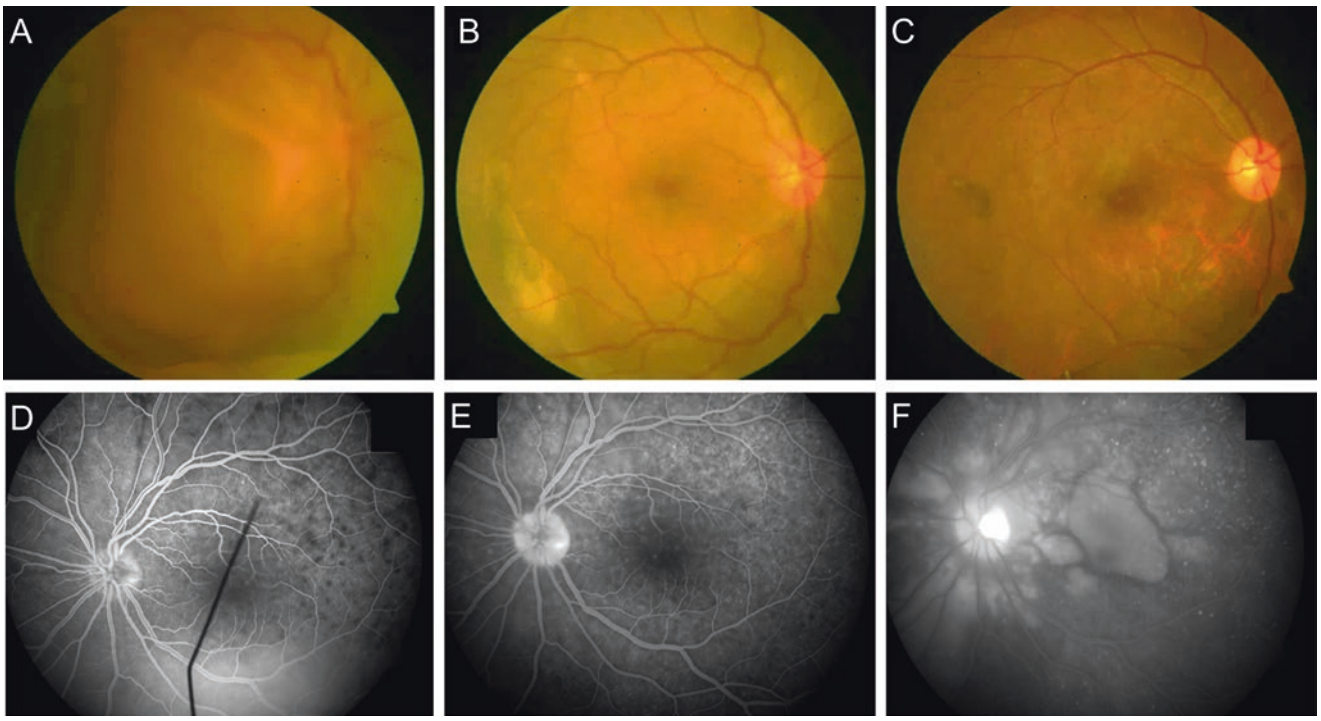

Fig. 36.1 Fundus photographs (right eye) of a 19-year-old girl diagnosed with Vogt-Koyanagi-Harada Syndrome. (**a**) shows the fundus photograph at presentation, with vitreous cells, optic nerve head edema and exudative retinal detachment. (**b**) shows improvement in the media clarity, decreased vitreous haze and exudation after 5 days of intravenous methylprednisolone (1 g/day). At 2 months (**c**), the media clarity has much improved with resolution of the exudative retinal detachment. The patient received a course of oral prednisone and azathioprine. (**d**)–(**f**) show the fluorescein angiography at baseline (left eye) of the same patient. In the early phase (**d**), there are focal areas of hypofluorescence (temporal to fovea), which become progressively hyperfluorescent (**e** and **f**) along with pooling of the dye due to exudative retinal detachment

Table 36.1 Revised diagnostic criteria of Vogt-Koyanagi-Harada disease proposed by the first international workshop (Read et al. 2001)

I. Complete disease (*criteria 1 to 5 must be present*)		
	1. No history of penetrating ocular trauma or surgery preceding the initial diagnosis of uveitis	
	2. No clinical or laboratory evidence suggestive of other ocular disease	
	3. Bilateral ocular involvement (a or b criteria must be met, depending upon the stage of the disease at which the patient is examined)	
		(a) Early manifestations of the disease
		– *Diffuse choroiditis (focal areas of subretinal fluid; bullous serous retinal detachments), OR* – *Characteristic fluorescein angiography AND echography evidence of diffuse choroidal thickening*
		(b) Late manifestations of the disease
		– *History suggestive of prior uveitis with the above described characteristics AND ocular depigmentation (sunset glow fundus, Suguira's sign)* – *AND other ocular signs (nummular chorioretinal depigmented scars, retinal pigment epithelium clumping and/or migration, or recurrent/chronic anterior uveitis)*
	4. Neurological/auditory findings	
	– *Meningismus OR tinnitus, OR cerebrospinal fluid pleocytosis*	
	5. Integumentary findings (*NOT* preceding the onset of central nervous system or ocular disease)	
	– *Alopecia, OR poliosis, OR vitiligo*	
II. Incomplete disease (*criteria 1 to 3 and either 4 or 5 must be present*)		
III. Probable disease (*isolated ocular disease; criteria 1 to 3 must be present*)		

Table 36.2 Clinical findings predictive of Vogt-Koyanagi-Harada disease (Rao et al. 2010)

Acute stage	Chronic stage
Bullous retinal detachment[a]	Sunset glow fundus[a]
Choroidal thickening[a]	Suguira's sign[a]
Subretinal fluid[a]	Vitiligo[a]
Alopecia[a]	Choroidal thickening
Hearing loss	Nummular choroidal scars
Vitiligo	Retinal pigment epithelium clumps/migration
	Hearing loss

The clinical findings with ≥50 % positive predictive value (PPV) and negative predictive value (NPV) have been listed in the table

[a]Indicates clinical findings associated with ≥75 % PPV and NPV

such as subretinal fibrosis, neovascular glaucoma, cataract and painful blind eye (Rao et al. 2010).

The diagnosis of VKH may be challenging since patients may presented with a limited ocular disease without systemic manifestations. The international workshop on VKH has divided the disease into complete, incomplete and probable disease (Table 36.1).

Involvement of other melanin-containing organs presents with dermatological features (vitiligo over the head, trunk, eyelids; poliosis of the eyebrows; alopecia), neurological features (headache, meningo-encephalitis and/or focal neurological deficits) and auditory involvement (sensorineural hearing loss, tinnitus and vertigo). The frequency of distinguishing features and findings most predictive of VKH disease obtained from a cohort of 1147 patients has been summarized in Table 36.2 (Rao et al. 2010).

36.3.2 Adamantiades-Behçet's Disease

Adamantiades-Behçet's disease (ABD) is a multi-system inflammatory vasculitis characterized by autoimmune ulceration of mucous membranes, involvement of ocular, central nervous system, and articular and renal systems. Majority of the patients may present with isolated mucous membrane or ocular involvement, making the diagnosis challenging.

ABD is named after two eminent clinicians, a Greek ophthalmologist, Benedictos Adamantiades and a Turkish dermatologist, Hulusi Behçet. The disease is more prevalent in the Middle East and the Mediterranean region, or the silk route of Europe. The description of association of ocular signs and other systemic involvement dates back to the writings of Hippocrates (Zouboulis and Keitel 2003). However, due to the growing recognition of the potential visual-

blinding complications of this condition despite aggressive therapy, an International Workshop on Granulomatous Uveitis and Ocular Behçet's Disease has proposed criteria for the diagnosis and classification of ABD.

ABD is characterized by non-necrotizing uveitis along with necrotizing obliterative retinal vasculitis. It affects many organs and tends to recur every 1–2 months without therapy. Data from large population based studies from countries such as Japan, Turkey, Germany and USA suggest that the aggressive disease course may lead to legal blindness within 4 years in the absence of immunosuppression (Evereklioglu 2005).

36.3.2.1 Epidemiology

The highest prevalence of ABD has been reported from Turkey, with as many as 420 cases per 100,000 in Istanbul. The prevalence in US and Europe ranges from 0.12 to 7.5 cases per 100,000 population. The incidence of ABD is ≤20 % among all uveitis in Japan, Taiwan, Israel, Saudi Arabia, Australia and China. Thus, the disease may be associated with HLA alleles more common in certain ethnic groups. Dissemination of genetic information across gene pools may be responsible for spread of the disease to the Asian and Western population (Zouboulis and Keitel 2003).

The disease usually affects younger individuals between the second and third decades of life. Recently, ABD has been recognized as an important cause of pediatric uveitis with cases reported in patients as young as 2 months of age (Hatemi et al. 2014).

Population-based studies from the Middle East have shown that the male:female ratio of the disease is approximately 2.3:1 and it is believed to have worse prognosis in males as compared to females, who may present with less organ involvement. The rates of ocular involvement vary from 28 to 50 % cases depending upon the sampled cohort.

Tables 36.3 and 36.4 provide the diagnostic criteria for ABD as per the International Team for the Revision of the International Criteria for Behçet's disease (ITR-ICBD) (2014) and the International Uveitis Study Group on Behçet's disease (1990).

36.3.2.2 Etiology and Pathogenesis

The exact etiology of ABD is unknown. The disease is multifactorial and it is accepted that ABD occurs in immunologically and genetically susceptible population, triggered by environmental agents or infections. Bacterial cross-reactivity with human antigens, cytokines and circulating immune-complexes are also implicated in the pathogenesis of this condition (Park et al. 2014).

Although classical Mendelian inheritance pattern has not been described for ABD, strong association with specific HLA genotypes has been shown. Subjects with HLA-B51/B5 have an increased risk of developing ABD. The prevalence of HLA-B51 allele among Japanese, Greek, Iranian, Italian and Saudi Arabian patients varies between 60 and 77 %. The most common allele associated with ABD is HLA B*5101. Apart from HLA B51, there are several other genes located in close proximity that may be implicated in the pathogenesis of ABD (Wallace 2014).

A large number of infectious agents have been linked to the pathogenesis of ABD. Among these, the most common associations have been found with herpes simplex virus (HSV-1), *streptococcus* spp and *mycoplasma fermentas* based on oral, salivary and respiratory tract cultures. Streptococcal antigens may increase the T-lymphocyte cell-mediated IL-6 and interferon (IFN) –γ release. Various antigens such as heat shock proteins, cytotoxins of *Helicobacter pylori* may play a role in the vascular damage typical of ABD (Hatemi and Yazici 2011).

Pathological immune dysfunction involving both the innate and adaptive immunity may occur in ABD. Low levels of mannose binding lectins, altered expression of toll-like receptors in monocytes and activation of adenosine deaminase may contribute towards increased T-cell expression in patients with ABD. Increased levels of TNF-α, IL-6, IL-8, IL-10 and IL-12 may increase leucocyte migration, activation of neutrophils, fibroblast proliferation and synthesis of prostaglandins. In ABD, both Th1 and Th2 cells seem to be involved in the pathogenesis. In addition to the T-cells, B cell population also plays an important role by presenting the antigens to the T-cell population (Park et al. 2014).

Table 36.3 International criteria for Behçet's disease (ICBD) by the international team for the revision of the international criteria for Behçet's disease (ITR-ICBD) (2014) (Davatchi et al. 2014)

Sign/symptom	Points
Ocular lesions	2
Genital aphthosis	2
Oral aphthosis	2
Skin lesions	1
Neurological manifestations	1
Vascular manifestations	1
Positive pathergy test[a]	1

Score of ≥4 indicates Behçet's disease

[a]Pathergy test is optional and primary scoring system does not include the test

Table 36.4 International study group for Behçet's disease diagnostic criteria (1990) (IUSG 1990)

Mandatory: Recurrent oral ulceration (*minor aphthous, major aphthous, or herpetiform ulceration observed by a physician or patient, which recurred at least three times in 1–12 month period*)
Plus two of the following criteria:
Recurrent genital ulceration (*aphthous ulceration or scarring, observed by physician or patient*)
Eye lesions (*anterior uveitis, posterior uveitis, or cells in the vitreous, or retinal vasculitis observed by ophthalmologist*)
Skin lesions (*erythema nodosum observed by physician or patient, pseudofolliculitis, or papulopustular lesions, or acneiform nodules observed by physician in post-adolescent patients not on corticosteroid treatment*)
Positive pathergy test (*read by physician at 24–48 hours*)

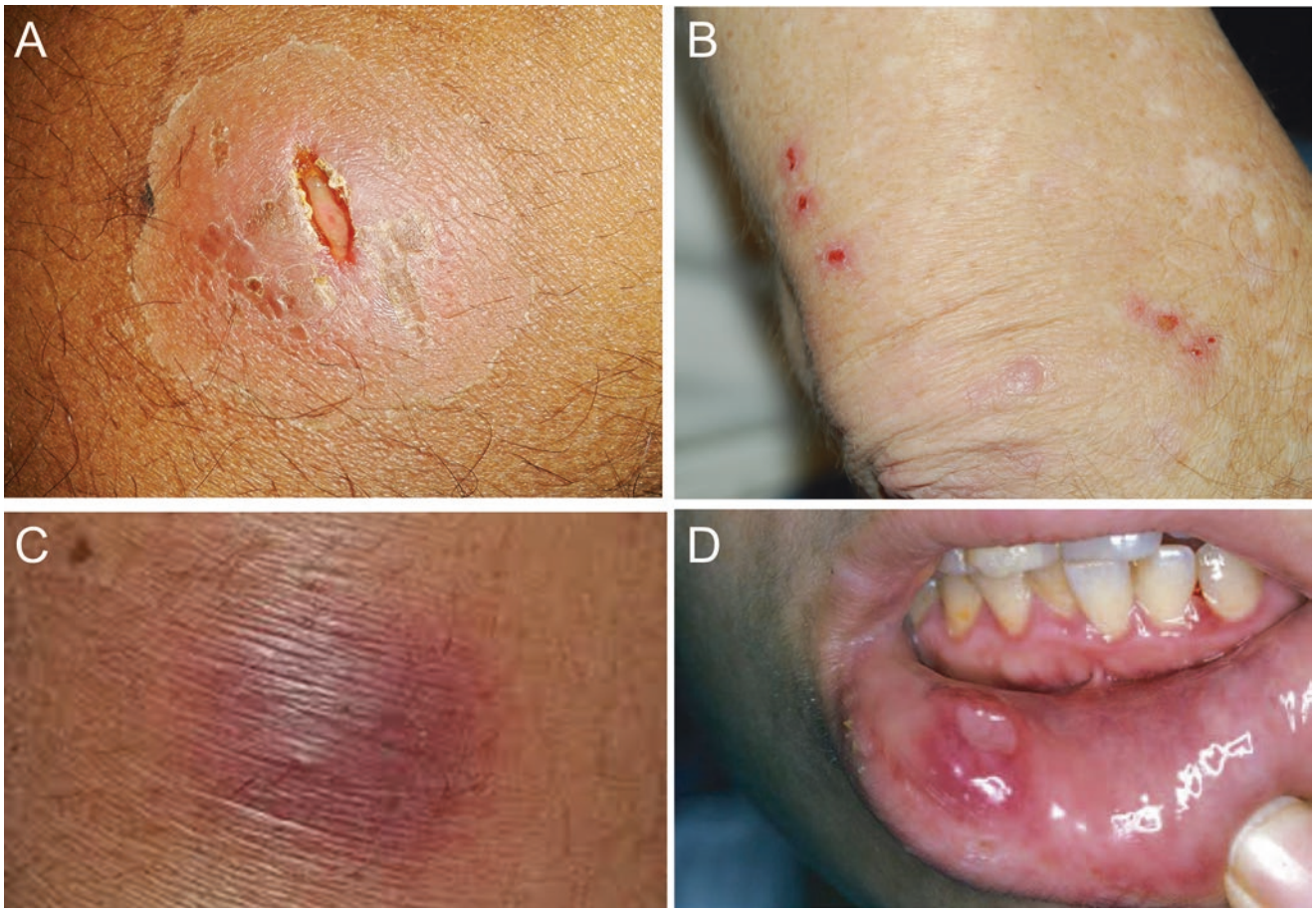

Fig. 36.2 Various skin and mucous membrane lesions in Adamantiades-Behçet's disease (ABD). (**a**) shows a large, pustulo-nodular lesion with central ulceration in the thigh of a young male patient. (**b**) shows multiple erythematous, acneiform lesions at the elbow in another Caucasian patient with ABD. (**c**) shows a dark, plaque-like lesion during the active stage of the disease. (**d**) shows a large, oral aphthous ulcer on the buccal mucosa of a patient with ABD

Vascular thrombosis in ABD is associated with increased levels of nitric oxide, plasma metabolites, low concentration of Protein C, increased platelet activation and lower plasma levels of tissue plasminogen activator. These may occur as a result of endothelial dysfunction leading to a generalized state of hypercoagulability, especially in cases with neuro-Behçet's disease. Plasma and cerebrospinal fluid concentrations of vascular endothelial growth factor have been shown to increase in patients with neurological complaints in ABD (Evereklioglu 2005; Hatemi et al. 2014).

36.3.2.3 Clinical Features

The most frequent, disease-defining clinical feature of ABD is painful oral *aphthae* and mucocutaneous ulcers. These are more common in males and appear round-bottomed, yellowish-white surrounded by an erythematous halo. Major ulcers (more than 1 cm in diameter) may leave behind residual scarring. Genital ulcers are less common and not mandatory for the diagnosis of ABD. They usually involve the scrotum or vulva. Epididymitis and salpingitis are rarer complications of the disease. Acneiform skin lesions, erythema

nodosum and pyoderma gangrenosum-like lesions are other dermatological manifestations of ABD (Fig. 36.2).

Vascular involvement may lead to aneurysms, cardiovascular events, hemoptysis, dyspnea and gastrointestinal manifestations due to Budd-Chiari syndrome. Aches and pains due to asymmetric, non-erosive, non-deforming arthritis are common in ABD (Mat et al. 2014).

Central nervous system involvement may occur due to thrombosis of dural venous sinuses. Neurological involvement usually occurs after 5 years of the diagnosis and affects 5% patients with ABD. There may be small vessel vasculitis (*vascular-Behçet*), focal neurological deficits, headache, pyramidal, cerebellar or cognitive defects, memory loss, aseptic meningitis, extrapyramidal symptoms, euphoria and disinhibition, or magnetic resonance imaging (MRI) abnormalities but absence of symptoms (*silent-Behçet*). Neuromuscular involvement may present with multiple mononeuritis or myositis (Siva and Saip 2009; Saip et al. 2014).

Ocular manifestations may occur in as many as 83–95% males and 67–73% females with ABD. Ocular symptoms usually follow mucocutaneous lesions and recurrence is common. All the structures of the eye m ay be involved in ABD, leading to severe debilitating visual loss. The classical finding in the anterior segment is presence of iridocyclitis with *mobile hypopyon*, which may be seen in less than one-third cases. Anterior chamber may show cells, flare, fibrin and endothelial dusting suggestive of non-granulomatous inflammation. There may be evidence of episcleritis or conjunctival ulcers. Posterior segment may show vitritis and retinal vasculitis involving both arteries and veins. Perivascular sheathing and hemorrhages may be observed. Vascular thrombosis may lead to branch or central retinal vein/artery occlusion. Papillitis and papilledema may occur that may progress to optic atrophy. Retinitis may be seen in as many as 52% patients with ocular involvement. Larger lesions of retinitis may lead to scarring resembling viral retinitis. Exudative retinal detachment may also occur (Khairallah et al. 2009; Bonfioli and Orefice 2005) (Fig. 36.3).

Fluorescein angiography may reveal vascular tortuosity, occlusion, staining of vessel walls and capillary leakage (Fig. 36.4). Shunt vessels and neovascularization may develop due to widespread ischemia. ICGA may reveal irregular filling of choriocapillaris and other choroidal perfusion defects (Durrani et al. 2007).

36.3.3 Sarcoidosis

Sarcoidosis is a multi-system chronic inflammatory disease characterized by presence of non-caseating granulomas most commonly affecting the respiratory system, lymph nodes, central nervous system, skin and the eyes. This condition was first recognized by Hutchinson in 1869 and the term '*sarkoid*' was coined by a Norwegian dermatologist, Caeser Boeck in 1899 to describe the skin lesions. Association of sarcoidosis with uveitis was first described in early twentieth century as a combination of facial nerve palsy and uveoparotid fever (Heerfordt's syndrome). Acute systemic inflammation may present as Löfgren's syndrome (fever, polyarthritis and erythema nodosum). In the last few decades, there has been a great increase in knowledge regarding the pathogenesis and manifestations of the disease.

Ocular disease may occur in up to one-third patients with the disease at any time during the natural history of the condition. Uveitis is the most common ocular manifestation and is usually bilateral. Granulomas may involve the periorbita, lacrimal gland, extraocular muscles and adnexa (conjunctiva and lid). The spectrum of disease manifestations is very wide; neuro-ophthalmologic signs such as optic neuropathy or Horner's syndrome may also occur in sarcoidosis.

The diagnosis of sarcoidosis is often challenging due to variable manifestations, which may often appear to overlap with other clinical entities. Since most of the patients have a chronic progressive disease, early recognition and treatment can prevent ocular complications and systemic sequelae of sarcoidosis. The diagnostic criteria for ocular sarcoidosis by the first International Workshop on Sarcoidosis (IWOS) is provided in Table 36.5.

36.3.3.1 Epidemiology

Sarcoidosis accounts for nearly 5% of all the adult uveitis cases and 1% of the pediatric cases (Hoover et al. 1986). Ocular involvement in sarcoidosis may be in up to 40% cases. The incidence of sarcoidosis is higher among African Americans as compared to Caucasians, with an incidence of 35.5 per 100,000 individuals versus 10.9 per 100,000 individuals respectively. The African American population is more likely to have a chronic, progressive course with higher number of patients developing ocular manifestations. Thus, blinding complications are also more common in this ethnic group. The incidence of sarcoidosis peaks between the age groups of 20–39 years. The incidence of the disease is higher among women across all racial and ethnic groups. Overall, the highest annual incidence is seen in northern European countries (Iannuzzi et al. 2007).

36.3.3.2 Etiology and Pathogenesis

The etiology of Sarcoidosis remains unknown. Due to multisystem involvement, environmental causes and occupational influences such as irritants, inorganic particulate matter and metals in furnaces, have been evaluated as possible causative agents. Investigators have also reported mycobacterial DNA in the sarcoidal tissue. A number of ubiquitous environmental influences may play a role in the alteration of immune response in sarcoidosis.

The most common HLA associated with sarcoidosis is HLA B8. Genetic factors located in the HLA class II region,

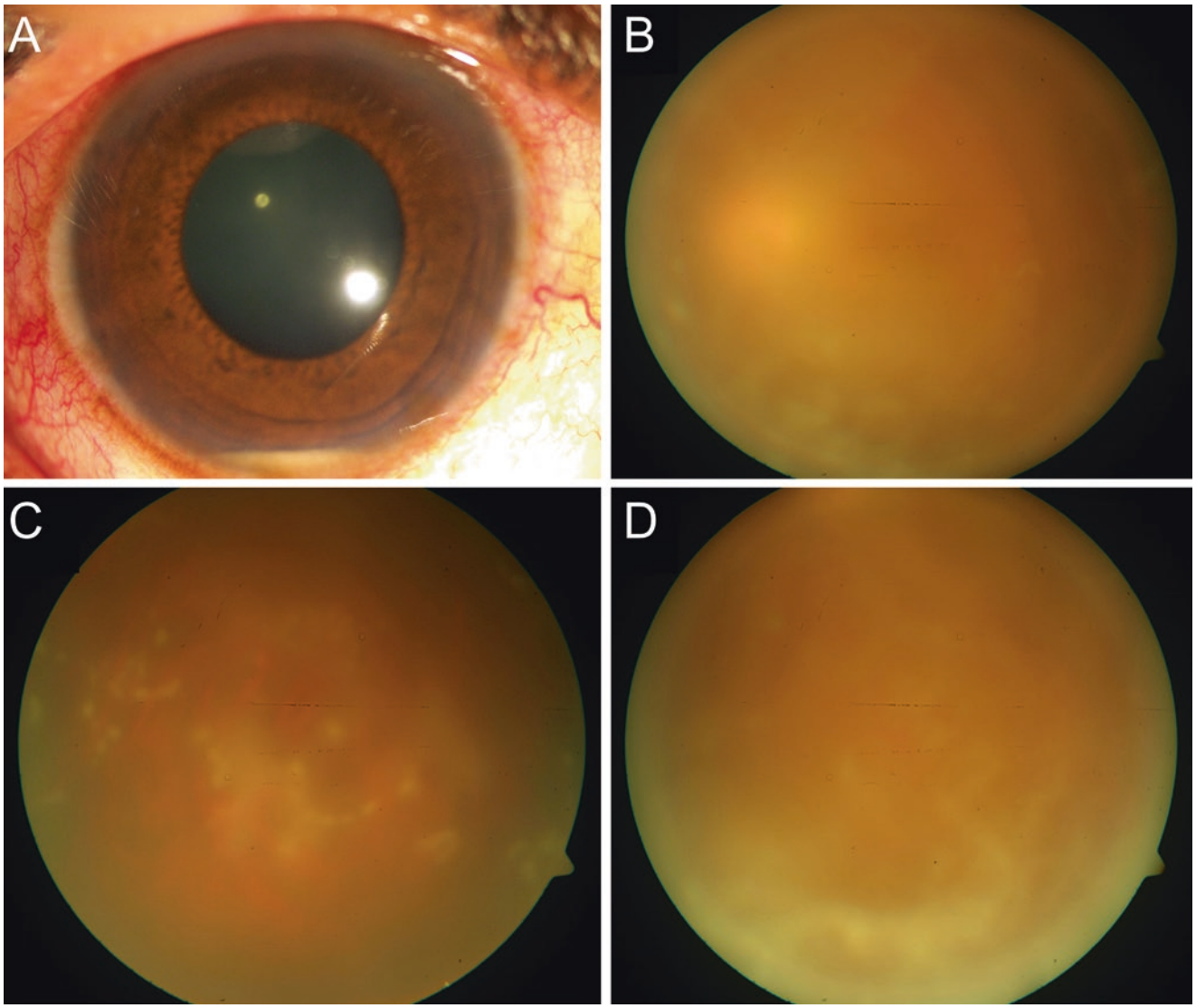

Fig. 36.3 Fundus photographs of an 18-year-old male diagnosed with Adamantiades-Behçet's disease. Slit-lamp photography of the anterior segment (**a**) shows ciliary congestion, cells in the anterior chamber and a hypopyon. Posterior segment examination revealed dense vitritis (**b**), multiple exudates in the vitreous cavity (**c**), forming posterior hypopyon (**d**)

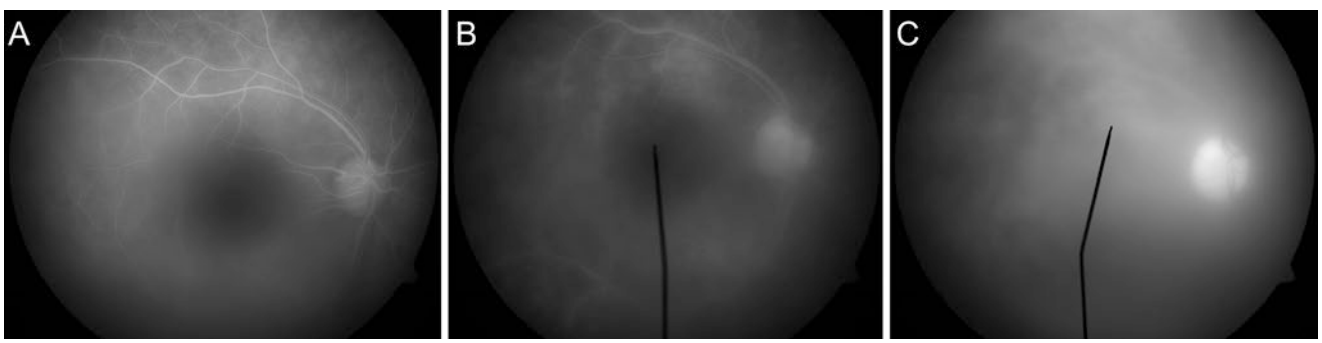

Fig. 36.4 Fluorescein angiography of the same patient as in Fig. 36.3 shows media haze in the early frame (**a**), diffuse hyperfluorescence in the mid-phase (**b**), optic disc leakage and vascular staining in the late phase (**c**), suggestive of active vasculitis and optic neuritis in a case of Adamantiades Behçet's disease

Table 36.5 Diagnostic criteria[a] for ocular sarcoidosis by the first international workshop on ocular sarcoidosis (IWOS) (2009) (Herbort et al. 2009)

Definite ocular[b] sarcoidosis	Biopsy-supported diagnosis with a compatible uveitis
Presumed ocular[b] sarcoidosis	Biopsy not done; presence of BHL with a compatible uveitis
Probable ocular[b] sarcoidosis	Biopsy not done; negative BHL; presence of three suggestive intraocular signs and two positive investigational tests
Possible ocular[b] sarcoidosis	Biopsy negative; four suggestive intraocular signs positive; two positive investigational tests

BHL bilateral hilar lymphadenopathy
[a]All other causes of uveitis, especially tuberculosis must be ruled out in all cases
[b]The term 'ocular' is used for both intraocular inflammatory lesions in patients with systemic disease and in patients with disease seemingly limited to the eye without any clinically detectable involvement of any systemic organ

i.e. DRB1 and DQB1 have been also implicated in the pathogenesis. HLA DQB1*0201 and DRB1*0301 have been associated with a better prognosis. In addition, familial pattern of disease occurrence has also been described. Sarcoidosis is also noted to occur after organ transplantation (Iannuzzi et al. 2007; Umur et al. 2012).

CD4 T helper cell population that interacts with antigen presenting B cells may play a central role in the pathology of sarcoidosis. Th1 cells produce IL-2, IFN-γ and TNF-α resulting in formation of multisystem granulomas. Hyperglobinemia and hypercalcemia are other laboratory abnormalities in sarcoidosis (Boyd et al. 2001).

36.3.3.3 Clinical Features

Sarcoidosis most commonly presents with anterior uveitis. Posterior uveitis, retinal vasculitis, vitritis, choroidal granulomas and papillitis are other manifestations of the disease. The disease may involve the lacrimal gland resulting in enlargement, orbital inflammatory disease (*pseudotumor*), myositis, scleritis, keratitis and cranial nerve palsies. Uveitis can precede systemic involvement in 30 % cases of sarcoidosis *(limited ocular sarcoid)*.

Anterior uveitis may be non-granulomatous or chronic granulomatous (more common) with large mutton-fat keratic precipitates, iridocyclitis and attacks of glaucoma. Interstitial keratitis and conjunctival nodules may be noted.

Posterior segment disease may present with vitreous snowballs and debris. The classical perivascular sheathing in sarcoidosis is termed as *'candle wax drippings' (taches de bougie).* There may be multiple, round, punched-out choroidal lesions associated with macular edema (Fig. 36.5). Choroidal granulomas are observed as whitish elevated mass. Optic nerve leakage may be seen on fluorescein angiography. There may be papillitis, optociliary shunt vessels and macro-aneurysms. Clinical signs suggestive of ocular sarcoidosis are provided in Table 36.6.

Neurological manifestations associated with sarcoidosis *(neurosarcoid)* include encephalopathy, hypothalamic dysfunction, cranial nerve palsies, and pituitary disorders. Chiasmal syndromes and motility disorders may occur. Direct infiltration of the sarcoid mass can affect the optic nerve, leading to optic atrophy (Fig. 36.5). Facial nerve palsy may be associated with significant corneal sequelae due to exposure keratopathy (Umur et al. 2012; Jamilloux et al. 2014).

36.3.4 Multiple Sclerosis

Multiple sclerosis (MS) is a chronic, relapsing demyelinating disease involving the central nervous system and the eye. Ocular and neuro-ophthalmic manifestations of the condition are diverse and the disease may affect virtually any anatomical structure including the components of the visual pathway. MS is one of the most common diseases of the central nervous system and its discovery dates back to the anatomical drawings from autopsies in the early nineteenth century. MS was recognized as a clinical entity in 1873 by Dr. Walter Moxon in England and Dr. Edward Seguin in 1878 in the US. Since then, efforts were made by scientists worldwide to establish the etiopathogenesis of the disease (Murray 2009).

Optic neuritis and uveitis are the two main clinical manifestations of MS in the eye. The association between MS and uveitis was first described in 1910. However, despite decades of intensive research and multicenter clinical trials, much needs to be learnt about the pathology of ocular disease in MS.

36.3.4.1 Epidemiology

MS affects individuals of all ages and race. The disease prevalence varies greatly and the incidence is higher in North America as compared to Asia. The typical onset of MS is between the second and the fifth decade of life. However, MS can occur in childhood as well as old age. Women are more commonly affected. Data from two large uveitis centers in the US and Germany showed that more than 90 % patients presenting with uveitis associated with MS were females. The mean age of presentation in this cohort was 40.6 years (Toosy et al. 2014).

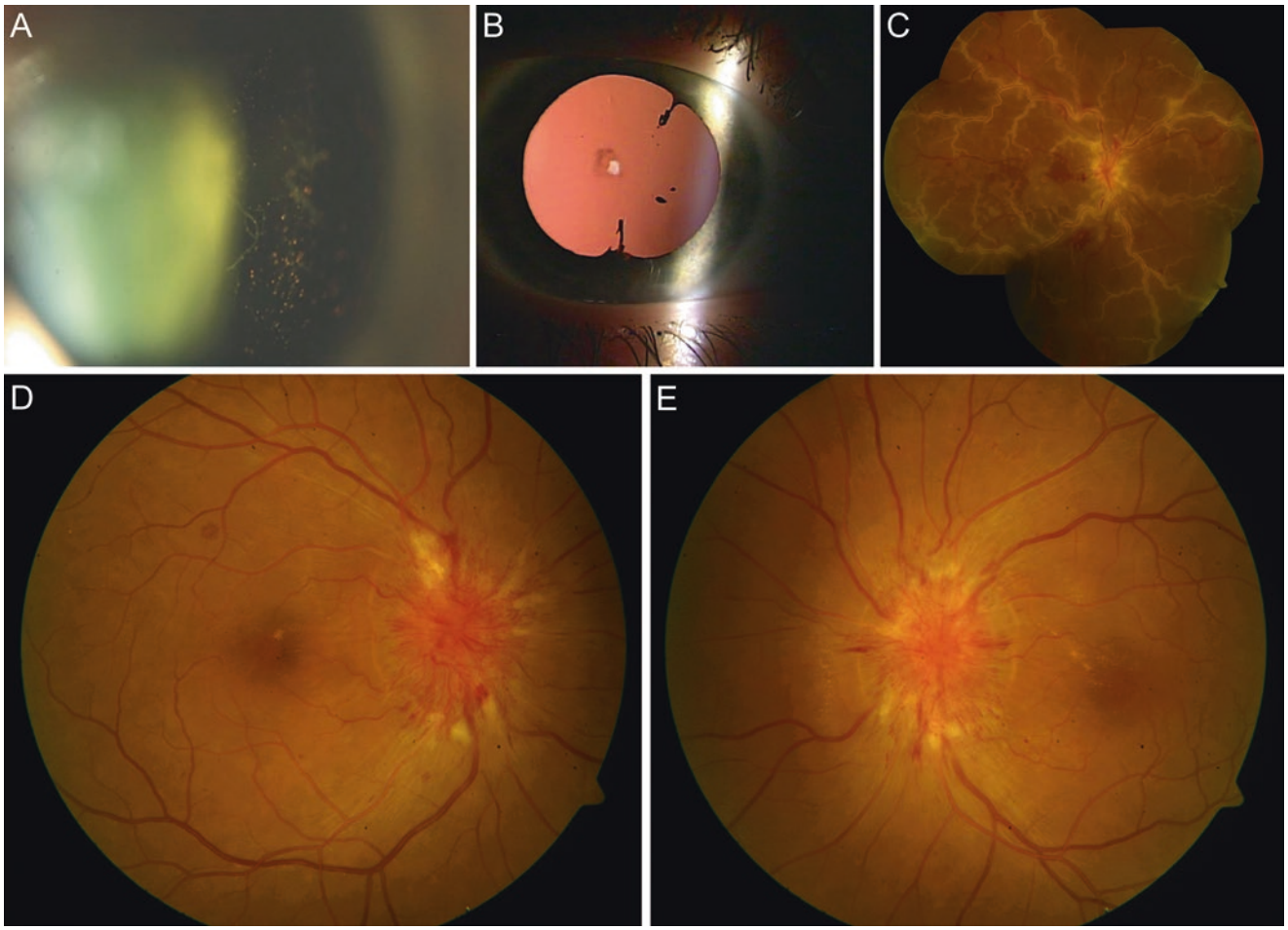

Fig. 36.5 Dense vitritis in a patient diagnosed with ocular sarcoidosis (**a**). (**b**) demonstrates tent-like posterior synechiae, observed in retro-illumination anterior segment slit-lamp photograph of a patient diagnosed with sarcoidosis. (**c**) shows diffuse vasculitis (termed as frosted branch angiitis) in another patient with sarcoidosis. (**d**) and (**e**) show fundus photographs of a patient diagnosed with neuro-sarcoidosis. The optic nerve heads in both eyes show direct infiltration with the sarcoid mass

Table 36.6 Ocular signs predictive of sarcoidosis as per the international workshop on ocular sarcoidosis (IWOS) (Herbort et al. 2009)

1.	Mutton-fat keratic precipitates (large/small) and/or iris nodules at pupillary margin (Koeppe) or in stroma (Bussacca).
2.	Trabecular meshwork nodules and/or tent-shaped peripheral anterior synechiae
3.	Snow-balls/string of pearls vitreous opacities
4.	Multiple chorioretinal peripheral lesions (active and atrophic)
5.	Nodular and/or segmental periphlebitis (± candle wax drippings), and/or macro-aneurysm in the inflamed eye
6.	Optic disc nodule(s)/granulomas(s) and/or solitary choroidal nodule
7.	Bilaterality (assessed by clinical examination or investigational tests showing subclinical inflammation)

36.3.4.2 Optic Neuritis and Multiple Sclerosis

Optic neuritis may be the presenting symptom of MS in 25 % of the cases *(MS-associated optic neuritis)*. About 70 % patients with MS may develop optic neuritis during the disease course, usually in the relapsing-remitting stage. MRI studies have revealed disseminated white matter lesions suggestive of demyelinating disease in more than 50 % patients with optic neuritis. As many as 72 % patients with MRI abnormalities convert to MS within 15 years *(clinically silent MRI lesions)*. Bilateral simultaneous optic neuritis is rare, but sequential involvement of the fellow eye is common (Toosy et al. 2014).

Optic neuritis is usually preceded by periorbital or ocular pain in a majority of the patients. The pain may be

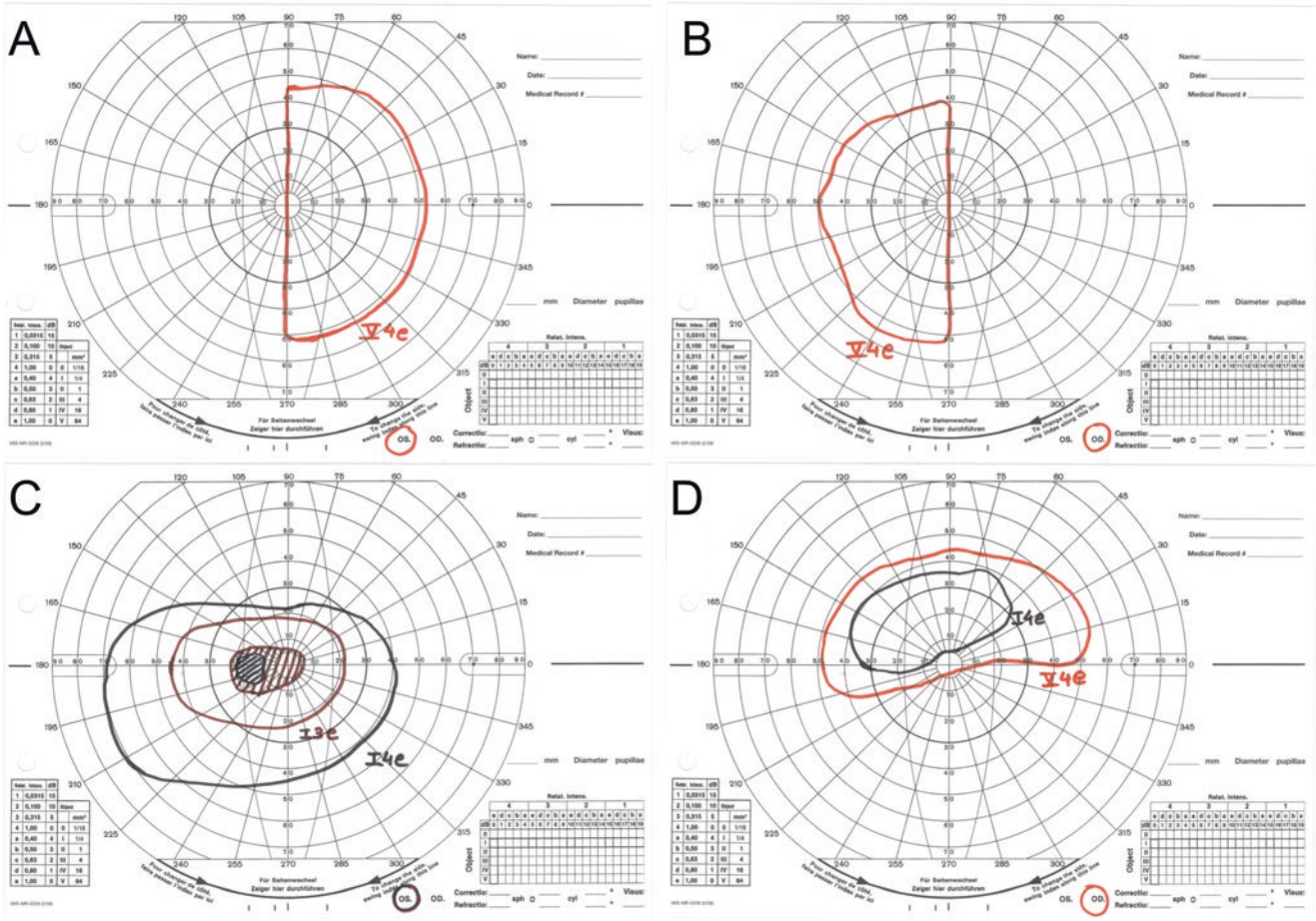

Fig. 36.6 Various visual field defects that can be observed in patients with optic neuritis secondary to multiple sclerosis using Goldman Visual Fields (GVF). (**a**) and (**b**) demonstrate bitemporal hemianopia. (**c**) shows a patient with cecocentral scotoma. Panel (**d**) demonstrates altitudinal defect in a patient with optic neuritis

Table 36.7 Visual phenomena in optic neuritis associated with multiple sclerosis (Toosy et al. 2014)

Phosphenes	Bright fleeting, flashes of light that tend to be connected to eye movement
Uhthoff's phenomenon	Worsening of vision provoked by small increases in body temperature attributed to exercise, hot baths or showers, or hot weather conditions
Pulfrich's phenomenon	Anomalous stereoscopic perception of objects in motion due to asymmetrical conduction between the optic nerves

increased with extraocular movements and usually lasts several days. Optic neuritis usually presents with acute monocular vision loss, the severity of which may vary from mild visual field defects to no light perception. The peak usually reaches in about 2 weeks. Visual field defects include diffuse loss, central scotoma, arcuate and nasal-step scotomas, and altitudinal defects (Fig. 36.6). Visual field mapping with short wavelength automated perimetry may be more sensitive than conventional perimetry in detecting these losses. Color vision and contrast sensitivity may be impaired in more than 75 % patients. The disease course is characterized by foggy vision, dyschromatopsia (blue-yellow or red-green), phosphenes, *Uhthoff's phenomenon* and *Pulfrich's effect* (Brodsky et al. 2008) (Table 36.7).

Clinical examination reveals relative afferent pupillary defect (Marcus Gunn pupil) in the affected eye. The appearance of the optic disc may be normal initially. However, later stages of the disease are characterized by swelling of the optic nerve head, peripapillary flame-shaped hemorrhages, and loss of spontaneous pulsations (Fig. 36.7). About two-third of patients may show normal appearance of the optic disc *(retrobulbar optic neuritis)*. Retinal periphlebitis may occur but retinal exudates forming macular star, or vitreous cells should arouse a suspicion of an alternate diagnosis (Jacobs and Galetta 2004; Kaur and Bennett 2007).

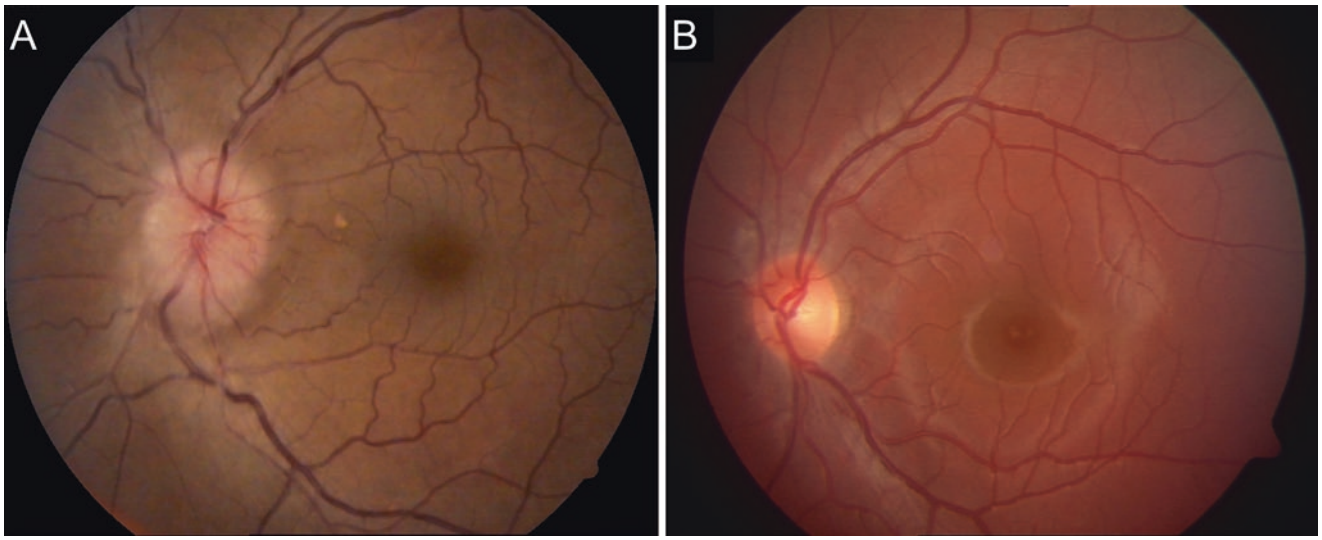

Fig. 36.7 Fundus photographs of two patients diagnosed with optic neuritis. (**a**) shows a patient diagnosed with papillitis with blurring of the disc margins, hyperemia of the optic nerve head and retinal nerve fiber layer edema. (**b**) shows a normal appearing optic nerve head of a patient diagnosed with retrobulbar optic neuritis

Visual improvement in optic neuritis associated with MS correlates poorly with initial loss. Visual recovery is generally good with ≥90 % patients achieving visual acuity of 20/40 or better. However, the incidence of persistent defects such as color vision, contrast sensitivity, pupillary reactions and motion perception (indicating damage to the magnocellular pathway) are high (Beck et al. 1994).

36.3.4.3 Uveitis Associated with Multiple Sclerosis

The incidence of uveitis ranges from 0.4 to 26.9 % among patients diagnosed with MS; however, it is infrequently recognized as an important association with the disease. Uveitis is 10 times more common in patients with MS as compared to the general population. Most cases are bilateral and present with intermediate uveitis that affects the vitreous, peripheral retina and the pars plana. Macular involvement with cystoid macular edema is the most important prognostic factor for visual outcome. The incidence of MS among patients with intermediate uveitis is 16 % and is higher among individuals with HLA DR15 allele.

Intermediate uveitis is characterized by inflammation of the pars plana and the peripheral retina. There are vitreous cells, usually in the anterior vitreous. Pars plana exudates can result in formation of a snow-bank. The complications of this condition may lead to formation of cataract, glaucoma and epiretinal membrane.

Uveitis in MS may present as an isolated granulomatous anterior uveitis with mutton-fat keratic precipitates, similar to VKH or sarcoidosis. Since the clinical findings of anterior uveitis are not pathognomic for any condition, a high level of suspicion is necessary to rule out MS (Kaya et al. 2014; Messenger et al. 2015).

36.3.4.4 Neuro-Ophthalmic Manifestations of Multiple Sclerosis

MS may be associated with a diverse range of ocular motor defects and nerve palsies. Isolated cranial nerve palsies most commonly affect the abducens nerve. Oculomotor and trochlear nerves are less commonly involved. This may lead to development of gaze palsies and deficits in pursuit, saccades and vestibular eye movement. Saccades, ocular flutter, opsoclonus and saccadic oscillations may also occur.

Lesions in the dorsal mid-brain may result in convergence retraction nystagmus, pupillary light-near dissociations. Nystagmus can be vertical, vestibular, pendular or periodic alternating. *Internuclear ophthalmoplegia* (INO) is the commonest form of nystagmus in patients with MS and occurs in up to 40 % patients with the disease. INO is characterized by limitation of adduction of the ipsilateral eye and rapid nystagmus during abduction of the contralateral eye due to lesions in the medial longitudinal fasciculus. MS is associated with an increased risk of bilateral INO.

The other neuro-ophthalmic manifestations of MS include diplopia, skew deviation, oscillopsia and blurring of vision. These manifestations may greatly reduce the quality of vision among patients with MS (Kaur and Bennett 2007). The rarer manifestations of MS include Charles Bonnet Syndrome, characterized by complex visual hallucinations in a person with partial or complete blindness (Pula and Reder 2009).

36.3.5 Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease with protean ocular and neuro-ophthalmic manifestations. The presentations are diverse and the disease may have a life-threatening course. Formation of autoantibodies and presence of circulating immune complexes resulting in tissue damage are the hallmark of this condition. The altered immune response in SLE is associated with inflammatory and thrombotic effects. Anti-phospholipid syndrome is a component of SLE characterized by formation of autoantibodies against plasma proteins resulting in venous and arterial thrombosis (Tsokos 2011).

36.3.5.1 Epidemiology

Approximately 90 % patients with SLE are females. The peak of the disease occurs between late teens to the fourth decade of life. The prevalence of the disease varies from 40/100,000 individuals in North Europe to more than 200/100,000 among African Americans (Tsokos 2011).

36.3.5.2 Etiology and Pathogenesis

Since the prevalence of the disease is higher among women, a role of female sex hormones has been described in the pathogenesis of SLE. Lupus can be drug-induced or may follow an antecedent viral-like illness. Other environmental factors linked with SLE include exposure to ultraviolet radiation (Mak and Tay 2014).

Genetic factors have also been implicated in the pathogenesis of SLE. The concordance rate is 25 % among monozygotic twins and 2 % among dizygotic twins. The pathogenesis of the disease has also been linked to HLA haplotypes such as HLA A1, B8 and DR3. The HLA subtype may be associated with enhanced response of the T cells to antigenic stimuli. In addition, genetic influences leading to deficiency of early complement factors such as C1q or C2 have also been linked to SLE.

Autoantibodies play a key role in the pathogenesis of SLE. Activation of T- and B lymphocytes occurs via various cellular pathways along with tissue injury due to formation of circulating immune complexes. Antibodies associated with SLE include anti-RO, anti-LA, anti-C1q, anti-Sm, anti-nucleosome and anti-α actinin, among several others (Tsokos 2011).

36.3.5.3 Clinical Features

Ocular manifestations may occur in more than one-third of patients diagnosed with SLE. SLE can occur at almost any anatomical location in the eye and the visual pathway. The most common finding of SLE is dry eye or keratoconjunctivitis sicca. SLE may be associated with secondary Sjǒgren's syndrome. Slit-lamp examination may reveal diffuse or localized corneal epitheliopathy and reduced tear production. Severe corneal involvement may present with peripheral ulcerative keratitis, interstitial keratitis and corneal melt/ulceration. SLE may be associated with conjunctivitis, episcleritis and scleritis (Read 2004).

Anterior segment involvement can present with anterior uveitis. Lupus associated retinopathy may occur in 3–29 % patients with the disease. SLE-associated retinopathy is secondary to microangiopathy caused by immune-complex mediated damage to retinal vascular endothelium. It is characterized by cotton wool spots, intraretinal hemorrhages, arteriolar narrowing, retinal edema and exudation. Severe vaso-occlusive disease is rare but can present with sight-threatening complications. Large vessel (central or branch retinal arteriolar/venular) occlusions may be observed. Patients with diffuse retinal vascular damage are at high risk for visual loss. Frosted branch angiitis and extensive macular exudation has also been reported in association with SLE (Palejwala et al. 2012). Although less known than retinopathy, lupus choroidopathy may be more common than what is generally appreciated. It usually serves as a sensitive indicator of lupus activity. The presence of SLE choroidopathy is generally indicative of coexistent (although sometimes occult) nephropathy, central nervous system (CNS) vasculitis, and other SLE visceral lesions (Nguyen et al. 2000).

Approximately 30–40 % patients may present with involvement of the central nervous system *(neuropsychiatric lupus)*. This condition is characterized by psychosis, neurological deficits resulting from thrombosis, limbic encephalitis, mononeuritis complex and polyneuropathy (Hanly 2014). Optic neuritis in association with SLE is rare (Lin et al. 2009).

36.3.6 Systemic Vasculitides Associated with Ophthalmic Manifestations

Systemic vasculitis is caused by an autoimmune process and is characterized by leucocytic infiltration of the vascular wall and necrosis. Rarely, systemic vasculitis may be associated with concomitant ophthalmic manifestations, including inflammation of the ocular vasculature. This is distinguished from retinal vasculitis, which is a term used to describe inflammatory involvement of retinal arterioles or venules. Retinal vasculitis usually occurs as an isolated, idiopathic disease.

Systemic vasculitis can have protean ophthalmic manifestations and these may precede systemic involvement, making the diagnosis challenging. Central nervous system involvement may result in neuro-ophthalmologic symptoms in addition to ocular inflammation. Among systemic vasculitis, granulomatosis with polyangiitis (GPA; previously known as Wegener's granulomatosis), polyarteritis nodosa (PAN) and giant cell arteritis (GCA) are common entities with ophthalmic manifestations (Abu El-Asrar et al. 2005).

36.3.6.1 Granulomatosis with Polyangiitis

GPA is a rare, systemic autoimmune disease associated with anti-neutrophil cytoplasmic antibody (ANCA)-mediated vasculitis and predilection to involve the respiratory tract and kidneys. Ocular involvement is known to occur in 28–59 % patients with GPA. On the other hand, neurological manifestations may occur in 10–45 % patients. The disease is most common in the Caucasian population and the peak incidence is observed in the fifth decade of life (Tarabishy et al. 2010).

The most common ocular manifestation seen in GPA is necrotizing scleritis, which may occur in more than 50 % patients with ocular GPA. Thinning of the sclera may result in perforation. GPA may also be associated with episcleritis and tarso-conjunctival disease resulting in formation of fibrosis, granulomas and eyelid abnormalities such as trichiasis and entropion. Orbital inflammatory disease (pseudotumor) may present with pain, epiphora, proptosis, lacrimation and movement disorders (Isse et al. 2013). Paranasal granulomas in GPA may result in *bony erosion* and secondarily involve the orbit and adnexa (Jiang et al. 2013). Optic nerve dysfunction may occur, either due to compression or direct invasion with granuloma formation. Ensuing fibrosis may result in orbital socket compression and enophthalmos (Tan et al. 2014).

Corneal involvement may present with peripheral ulcerative keratitis, interstitial keratitis or it may be associated with scleritis *(sclerokeratitis)* (Florine et al. 1993). Retinal disease results in severe visual morbidity. Retinal involvement may present with chorioretinitis, macular edema, exudative retinal detachment or retinal necrosis. Associated retinal vasculitis may result in central or branch retinal artery or vein occlusion.

36.3.6.2 Polyarteritis Nodosa

PAN is a multisystem necrotizing vasculitis affecting small and medium-sized arteries in the heart, kidneys, central nervous system and gastrointestinal system. Ocular involvement in PAN is seen in 10–20 % of the cases. The incidence of PAN is higher among males between the age-groups 40 and 60. The most common ophthalmic association is *choroidal ischemia*, which is usually recognized at autopsy (Vodopivec et al. 2014).

The ocular manifestations of PAN include retinal vascular diseases such as retinal vasculitis, hemorrhage, edema and central or branch retinal artery occlusion. Vascular supply of the optic nerve may be affected resulting in anterior or posterior ischemic optic neuropathy (Emad et al. 2007). Similar to GPA, PAN may be associated with scleritis, episcleritis, keratitis, non-granulomatous iritis and exudative retinal detachment.

Neurological disease may manifest with papillitis, Extraocular muscle palsies, amaurosis fugax, homonymous hemianopia and rarely, nystagmus. Mononeuropathy multiplex is among the most common findings in patients with PAN (Paula De Carvalho Panzeri Carlotti et al. 2004).

36.3.6.3 Giant Cell Arteritis

GCA is the most common form of granulomatous medium-to-large vessel vasculitis. The most common vessels affected include aorta, extradural cranial vessels, ophthalmic artery, posterior ciliary arteries, superficial temporal artery and occasionally, the central retinal artery. The disease is most common above 50 years of age and the incidence increases with age. Individuals of Scandinavian or North European origin have the highest incidence of the disease. Familial clustering of the disease is noted along with HLA DRB1*04, DRB1*01 and DW6 associations (McAlinden et al. 2014).

Visual loss in GCA was first described by Jennings in 1938. Ophthalmic involvement in GCA presents as sudden-onset visual loss and is considered to be an *ophthalmic emergency*. The diagnosis of the condition is confirmed by biopsy of the temporal artery, which presents as nodular granulomatous infiltration of the vessel wall. However, the treatment with high-dose glucocorticosteroids is initiated prior to the biopsy results due to the high risk of blinding complications and fellow eye involvement. The involvement of the fellow eye can occur within 14 days in one-third of the untreated cases (Kale and Eggenberger 2010).

The most common ocular manifestation of GCA is arteritic anterior ischemic optic neuropathy (AAION), which can result in acute visual loss in 60 % patients. Up to 21 % patients may have no light perception. AAION manifests with a chalky white optic disc edema. Posterior ischemic optic neuropathy usually presents with a normal appearing optic nerve head. Central retinal artery occlusion can occur in up to 10 % patients with GCA (Kale and Eggenberger 2010).

Neuro-ophthalmic manifestations of GCA include extraocular muscle ischemia resulting in paresis/palsies, Horner's syndrome, anterior segment ischemia, hypotony and diplopia. Uveitis is an uncommon manifestation of GCA. Temporal or occipital headache, scalp tenderness, *jaw claudication* and constitutional symptoms such as fever, malaise, anorexia and myalgia are important clues to the diagnosis of this condition (Chew et al. 2009).

36.3.7 Systemic Arthritides Associated with Ophthalmic Manifestations

36.3.7.1 Rheumatoid Arthritis

Rheumatoid arthritis (RA) is the most common systemic autoimmune condition affecting 1 % of the population. The principle target of the inflammatory damage in RA is the

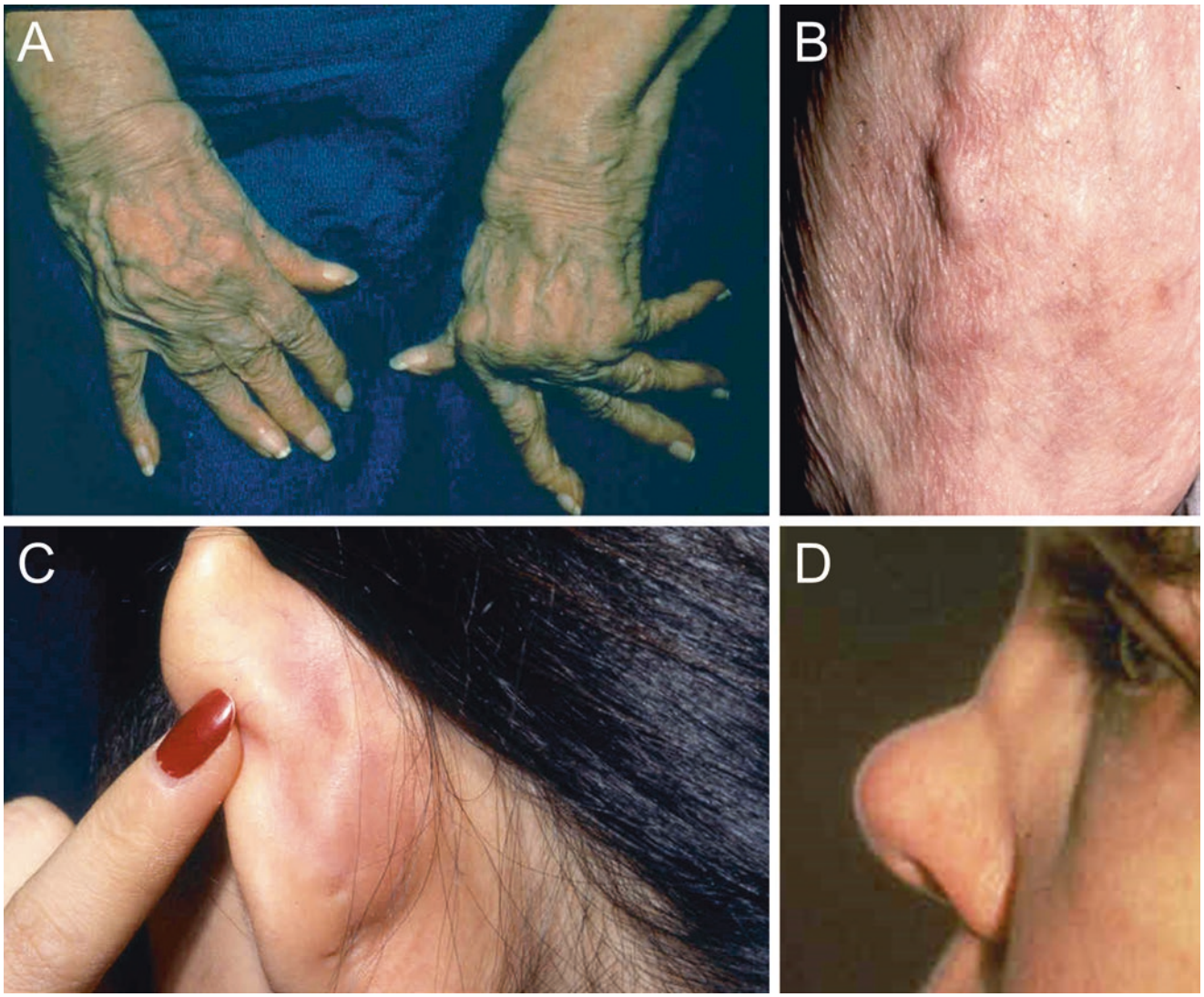

Fig. 36.8 Systemic deformities seen in patients with rheumatoid arthritis (RA) and relapsing polychondritis (RP). (**a**) shows characteristic ulnar drift, swelling of metacarpal joints and rheumatoid nodules in an elderly patient. (**b**) shows appearance of an inflamed vessel in a patient with RA. (**c**) shows inflammation and destruction of the auricular cartilage in a patient with RP. (**d**) shows the characteristic saddle nose deformity due to cartilage destruction in a patient with RP. Figures A-D are couresty of Professor C. Stephen Foster (Walham, MA, USA)

synovial tissue and cartilage (Fig. 36.8). However, RA may be associated with a number of extra-articular systemic manifestations including ophthalmic involvement. Autoimmune damage affecting other visceral organs in RA can be life-threatening.

The most frequent ophthalmic involvement in patients with RA is the damage to the ocular surface, resulting in dry eyes. The involvement of ocular surface in patients with RA has immunologic similarities to the joint disease, with evidence to suggest a heightened state of both, adaptive and innate immune system responsiveness. *Keratoconjunctivitis sicca* is characterized by increased number of antigen-presenting cells, and decreased anti-inflammatory cytokines such as IL-13 and decreased suppressor T cells (T_{reg}) (Tong et al. 2014). Dry eye may be complicated with chronic keratitis, ulceration and corneal melt due to poor tear-film. Frequency of dry eye syndrome may be as high as 45–71 % in patients with RA.

Patients with RA may develop *peripheral ulcerative keratitis (PUK)*, an inflammatory thinning of the peripheral cornea that may lead to perforation. PUK occurs in approximately 3 % patients with RA and is bilateral in 40 % patients. Usually, PUK appears as a crescent-shaped peripheral corneal infiltration associated with scleritis. RA is the most common cause of scleritis and is associated with 20 % of the cases. In 10 % cases, the diagnosis of scleritis may precede the diagnosis of RA. Necrotizing scleritis is an extra-articular condition associated with an increased risk of death in patients with RA. Scleritis may be complicated by scleral perforation *(scleromalacia perforans)*. Other ocular mani-

festations in patients with RA include conjunctivitis and episcleritis (Artifoni et al. 2014; Galor and Thorne 2007).

36.3.7.2 Sero-Negative Spondyloarthropathies

Sero-negative spondyloarthropathies (SSpAs) are a group of chronic inflammatory conditions affecting the axial skeleton, characterized by a negative serum rheumatoid factor. SSpAs are strongly associated with HLA B27 positivity. SSpAs include ankylosing spondylitis, reactive arthritis, psoriatic arthritis and arthritis associated with inflammatory bowel disease (Crohn's disease and ulcerative colitis), among other entities. Inflammatory eye disease is the most common extra-ocular manifestation of SSpAs with incidence of 25 % in patients with ankylosing spondylitis and 10 % with psoriatic arthritis (Zagora and McCluskey 2014; Zochling and Smith 2010).

The hallmark manifestation of SSpA is anterior uveitis, occurring in up to 40 % cases. Anterior uveitis is typically acute, unilateral or alternating between the two eyes. Epidemiological data suggests that there may be a mean of 5 attacks of uveitis during the course of the disease (Monnet et al. 2004). Ankylosing spondylitis may be associated with *hypopyon uveitis*. Episcleritis, scleritis and conjunctivitis may occur with SSpAs. Involvement of the posterior segment is less common. Infrequently, posterior or panuveitis may develop in patients with inflammatory bowel disease (Zagora and McCluskey 2014).

36.3.7.3 Relapsing Polychondritis

Relapsing polychondritis (RP), first coined by Pearson et al., is a multisystem chronic inflammatory disease primarily affecting the musculoskeletal system. The disease spectrum may vary from mild intermittent episodes of auricular and nasal cartilage pain to life-threatening airway disease. The peak age of onset of the disease is in the fifth decade of life and it is thought to be more common among women. The etiology of RP remains unknown thus far. Circulating antibodies against collagen II, IX and XI, as well as immune-complex deposition have been implicated in the pathogenesis of the condition (Sharma et al. 2013).

Most patients with RP present with auricular chondritis sparing the ear lobule. Progressive destruction and deformities may also involve the nasal cartilage in more than 80 % patients, resulting in *saddle nose deformity* (Fig. 36.8). Approximately 33 % patients may present with joint pain. The most common cause of death in these patients is due to laryngotracheal involvement leading to destruction, dislocation and stricture formation (Puechal et al. 2014; Sharma et al. 2013).

Ocular disease is seen in approximately 50 % patients with RP. Common ocular manifestations include scleritis, episcleritis and conjunctivitis (Rucker and Ferguson 1965). There may be associated corneal thinning. Uveitis is seen in 25 % patients and usually presents as sclerouveitis or iridocyclitis. Retinal involvement may present with exudates, hemorrhages and retinal vascular occlusion (Isaak et al. 1986). Orbital involvement manifests as proptosis, periorbital edema or extraocular muscle palsy (Yoo et al. 2011).

36.3.8 Myasthenia Gravis

Myasthenia gravis (MG) is a systemic autoimmune disease affecting the neuro-muscular junction and presenting with a wide variety of ophthalmic manifestations. Ocular MG is a localized form of the disease characterized by involvement of extraocular muscles, levator palpebrae superioris and orbicularis muscles with sparing of the pupillary muscles. This condition can easily masquerade cranial nerve palsies and INO due to nystagmus and limitation of movements. A history of weakness with diurnal variation and fatigue should raise a suspicion of ocular MG (Weinberg et al. 1994).

36.3.8.1 Epidemiology

Ocular MG may affect any age group and there is no racial or geographic predilection. The onset of the disease is rare in the first decade and after the seventh decade of life. Overall, women are affected more than men. However, the incidence of the disease is higher in men above the age of 50 years. Among individuals with pure ocular MG, the incidence is higher among men (Vaphiades et al. 2012).

36.3.8.2 Clinical Features

Among patients presenting with ocular disease, about 50–80 % progress to a generalized disease. Extraocular muscles are frequently affected in ocular MG as they are composed of fast-twitch muscle fibers and have a higher rate of synaptic firing. The tonic fibers, which are responsible for gaze, may be affected resulting in gaze paresis. Ptosis and diplopia are initial signs of the disease in over 50 % patients with MG. The ptosis worsens under stress such as prolonged upward gaze. Lifting of eyelid may result in enhancement of ptosis of the contralateral side. Ice-pack applied to the eyelid may result in improvement in the degree of ptosis. Ptosis can be unilateral or bilateral and is usually asymmetric (Elrod and Weinberg 2004).

Small amplitude upward movement of the eyelid *(hopping)* during lateral gaze is referred to as the *Cogan lid twitch sign*. Reverse Cogan lid twitch sign is the downward movement of the eyelid elicited by saccade to primary position from upgaze. Lid retraction and orbicularis weakness are other eyelid signs of MG. *Peek sign* is the increased visibility of the sclera due to drifting apart of the eyelid without forceful opening (Barton and Fouladvand 2000).

Extraocular muscle weakness in MG may mimic cranial nerve palsies or INO *(pseudo-INO)*. However, gaze-evoked

vertical nystagmus, classical feature of INO, is absent in ocular MG. Medial rectus is the most commonly affected muscle. Ocular MG may thus, mimic incomitant strabismus. Saccadic movements and nystagmus is also common in MG (Vaphiades et al. 2012; Nair et al. 2014).

Various clinical tests such as the ice pack test, edrophonium (Tensilon) test or sleep test, and laboratory evaluations such as repetitive nerve stimulation or single-fiber electromyography may help in the diagnosis of this condition (Nair et al. 2014).

36.3.9 Graves' Disease

Graves' ophthalmopathy (GO), also known as thyroid eye disease, is an autoimmune thyroid disease with orbital manifestations. While more than 25 % patients with Graves' disease manifest with GO, subclinical disease can be found in over 70 % patients using imaging techniques such as orbital MRI. Unless treated appropriately, patients with severe GO may develop sight-threatening sequelae with a high risk of permanent blindness (Wiersinga and Bartalena 2002).

36.3.9.1 Epidemiology

The incidence of GO is approximately 16 per 100,000 in females and 2.9 per 100,000 in males in the United States. The estimated prevalence of the disease is 0.25 %, ranging from 0.1 to 0.3 % world over. The disease is more common in women with female to male ratio ranging from 9.3 to 1.4 depending upon the severity of the disease. Men are more commonly affected with severe forms of the disease with a female to male ratio of 1:4. The disease has bimodal age distribution with peaks in the 40s and late 60s. GO is rare in children with an incidence of <0.1 per 100,000 (before puberty). A number of racial, anatomical and environmental factors play a role in the epidemiology of GO. Cigarette smoking plays an important role in the development and occurrence of GO and adversely affects the severity of the disease. More than 80 % patients with GO have hyperthyroidism at the onset of the disease. Approximately 50 % patients with euthyroid Graves' disease develop hyperthyroidism within 2 years of the disease onset (Carter and Utiger 1992; McAlinden 2014).

36.3.9.2 Clinical Features

The most common presenting feature of GO are eye lid signs such as lid retraction and lid swelling. There may be widened palpebral fissure with decreased blink rate *(frightened face).* The patients may develop lid lag in downgaze *(von Graefe's sign),* and loss of eyebrows in the extreme third of the lid *(Hertoge's sign).* Hyperpigmentation of the superior eye lid folds is known as *Jellinek's sign.* Upper eye lid retraction resulting in excessive scleral show is known as *Stellwag's sign.* Due to an increase in the orbital fat volume and infiltration by inflammatory cells, there is proptosis and enlargement of extraocular muscles (sparing the tendons) resulting in diplopia. If left untreated, the muscles may lose the ability to contract and become rigid, resulting in increased intraocular pressure in the up-gaze *(Sattler's sign).* Eventually, patients may develop paralytic strabismus and permanent lid lag. Lack of convergence of the eye balls is known as *Moebius's sign.* Patients may develop limitation of abduction and rotation of eyeball *(Jendrassik's sign).* Horizontal nystagmus or complete ophthalmoplegia may develop.

Complications such as exposure keratopathy may occur resulting in staining of the corneal surface. Neglected cases may develop corneal ulceration that may progress to perforation. Due to excessive mechanical stretch, the optic nerve may develop edema and atrophy *(dysthyroid optic neuropathy)*, which may develop in approximately 3–7 % patients with GO. Corneal and optic nerve complications may lead to permanent visual loss among patients with GO (Saraci and Treta 2011; Yeatts 1995).

36.4 Miscellaneous Neuroimmune Diseases with Ophthalmic Involvement

36.4.1 Susac's Syndrome

Susac's syndrome (SS) is a rare, autoimmune microangiopathy characterized by infarcts in the brain, retina and cochlea. The classical triad of SS includes neurological dysfunction (*encephalopathy*), multiple branched retinal arteriolar occlusions (*BRAOs*) and sensorineural hearing loss. The disease typically occurs in young women and is often misdiagnosed as MS. Fluorescein angiography may detect presence of multiple BRAOs that may result in variable visual field loss. In addition to BRAOs, SS may be associated with retinal vasculitis (Greco et al. 2014). Unusual neurological manifestations, such as cauda equine syndrome, may occur in patients with SS (Allmendinger et al. 2014).

36.4.2 Cogan's Syndrome

Cogan's syndrome is characterized by non-syphilitic interstitial keratitis and bilateral audio-vestibular defects secondary to an autoimmune process. The autoantibodies may be directed against antigenic peptides expressed in epithelial cells in the inner ear. Corneal involvement presents with granular, irregular corneal infiltrate affecting the posterior stroma and endothelium. Ocular inflammation may manifest as scleritis, episcleritis, conjunctivitis, retinal vasculitis or papillitis. More than 90 % patients have associated systemic

symptoms. Neurological disease includes aseptic meningitis, hemiparesis or hemiplegia, pyramidal syndrome, vigilance disorders or trigeminal neuralgia. One-fourth patients may also present with cardiovascular, gastrointestinal or musculoskeletal disease (Kessel et al. 2014; Azami et al. 2014).

36.4.3 Reactive Arthritis

Reactive arthritis is a multi-system autoimmune seronegative disease that develops 1 to 3 weeks after gastrointestinal or genitourinary infection. Antigens from gram negative intracellular bacteria may trigger an inflammatory cascade with CD4 T Helper cell and CD8 response following mucosal invasion (Stavropoulos et al. 2015). While there are no diagnostic criteria established for reactive arthritis, the condition primarily affects the joints resulting in arthritis similar to psoriasis and is associated with urethritis and conjunctivitis/uveitis. Some forms of reactive arthritis developing the triad were previously referred to as 'Reiter's syndrome'. However, the term reactive arthritis encompasses a broader category of the disease (Selmi and Gershwin 2014). Ocular manifestations are often frequent in this condition, with more than 50% men experiencing conjunctivitis or acute anterior uveitis. Patients may also develop genital lesions and other visceral involvement, including cardiac valvular abnormalities and conduction defects.

36.4.4 Primary Sjǒgren's Syndrome

Sjǒgren's syndrome is a multisystem autoimmune condition with lymphocytic infiltration of the exocrine glands, such as the salivary and lacrimal glands. In addition, the disease can affect the nervous system in about 20% cases resulting in *sensory ganglionopathy* or transverse myelitis. Other visceral manifestations include interstitial lung or kidney disease, autoimmune hepatitis or pancreatitis. Ocular manifestations include dry eye, corneal haze/scarring, *sterile corneal melt* and papillary or cicatrizing conjunctivitis. Sjǒgren's may be associated with scleritis, episcleritis or uveitis (Akpek et al. 2015). Cases with optic neuritis and retinal vasculitis have been reported in literature (Tang and Wei 2013).

36.4.5 Dermatomyositis

Dermatomyositis is an inflammatory myopathy characterized by cutaneous manifestations that occur in the presence of minimal muscle involvement. Other features of the disease may include multiple systemic involvement and/or underlying malignancies. The typical rash of dermatomyositis is described as heliotrope rash (face), Gottron's papules (hands and elbows), and trunk (shawl and 'V' sign). The disease has two distinct forms—adult and juvenile (Luo and Mastaglia 2015). In a large series of 108 patients with juvenile dermatomyositis, eye lid manifestations (supraciliary heliotrope line with or without telangiectatic vessels, lid scarring, or pox-like lesions) were the most common manifestations. Other ocular manifestations include cataract (posterior subcapsular variety), retinal hemorrhages, and retinal vasculitis that may manifest as frosted branch angiitis (Lee et al. 2011).

36.5 Review Questions

1. The following clinical features are seen during the acute stages of Vogt-Koyanagi-Harada disease except:
   a. Exudative retinal detachment
   b. Subretinal fluid
   c. Choroidal thickening
   d. *Sun-set glow fundus*
2. The pathogenesis and clinical features of Vogt-Koyanagi-Harada disease is most closely related to which of the following condition:
   a. Serpiginous choroiditis
   b. Sarcoidosis
   c. *Sympathetic Ophthalmia*
   d. Graves' disease
3. Choroidal manifestations in Vogt-Koyanagi-Harada disease include all of the following except:
   a. *Choroidal excavation*
   b. Choroidal thickening
   c. Choroiditis
   d. Nummular choroidal scars
4. Most common Human Leucocyte Antigen (HLA) associated with Adamantiades-Behçet's disease includes:
   a. HLA B-27
   b. *HLA B51/5*
   c. HLA A29
   d. HLA DRB1
5. Which of the following is the most common systemic manifestation of Adamantiades-Behçet's disease?
   a. Central nervous system vasculitis
   b. Genital ulcers
   c. *Oral ulcers*
   d. Uveitis
6. According to recent estimates, which of the following individuals are at an increased risk of developing sarcoidosis?
   a. Caucasian males
   b. Hispanic females
   c. Caucasian females
   d. *African-American females*
7. Which of the following cells play a central role in the pathogenesis of sarcoidosis:
   a. *CD4 -T Helper cells*
   b. Cytotoxic CD8 cells

c. Eosinophils
d. Natural Killer cells

8. Worsening of vision provoked by small increases in body temperature attributed to exercise, hot baths or showers, or hot weather conditions among patients with Multiple Sclerosis is described as:
   a. Sugiura's sign
   b. *Uhthoff's phenomenon*
   c. Pulfrich's phenomenon
   d. Von Graefe's sign
9. Among patients with rheumatoid arthritis, the most common ocular involvement includes:
   a. *Dry eye syndrome*
   b. Optic neuritis
   c. Choroiditis
   d. Subretinal fluid
10. Susac's syndrome is characterized by presence of:
   a. Central retinal artery occlusion
   b. Branch retinal vein occlusion
   c. Cilio-retinal artery occlusion
   d. *Branch retinal artery occlusion*
11. Cogan Lid Twitch sign is described as:
   a. *Small amplitude upward movement of the eyelid during lateral gaze*
   b. Nystagoid movements of the eyes
   c. Presence of internuclear ophthalmoplegia
   d. Ptosis

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