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Autoimmune Retinopathy

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Abstract

Autoimmune retinopathy encompasses a spectrum of rare autoimmune diseases that primarily affect retinal photoreceptor function, and include cancer-associated retinopathy (CAR), melanoma-associated retinopathy (MAR) and presumed non-paraneoplastic autoimmune retinopathy (npAIR). Autoimmune retinopathy typically presents in the fifth and sixth decades with rapidly progressive, bilateral, painless visual deterioration but an unremarkable fundus examination. CAR, MAR and npAIR have an overlapping clinical phenotype, and extensive investigation is required to exclude other causes of retinopathy, and to identify any occult malignancy, before a presumptive diagnosis can be made. Delayed diagnosis, and treatment initiation relatively late in the disease course, may contribute to the poor visual prognosis. Various treatments have been attempted, including systemic immunosuppression with steroid and steroid-sparing agents, intravenous immunoglobulin, and plasmapheresis, but these lack an evidence base. A variety of antiretinal antibodies have been identified in patients with autoimmune retinopathy, including antibodies to recoverin, α-enolase and transducin-α, but seronegative disease is also common. Clinical access to specialised serological investigation is very limited internationally, and this exacerbates the management challenge presented by patients with suspected autoimmune retinopathy. Several decades of experimental research have resulted in very considerable advances in our understanding of the pathophysiological mechanisms that may underlie autoimmune retinopathy. However, the precise triggers which result in loss of ocular immune privilege and sudden autoimmune attack on retinal cells have yet to be elucidated. This review summarizes the classification, investigation and management of autoimmune retinopathy, and considers the evolving concepts about its immunological aetiology.

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Introduction

Autoimmune retinopathy encompasses a spectrum of rare autoimmune diseases, including cancer-associated retinopathy (CAR), melanoma-associated retinopathy (MAR) and presumed non-paraneoplastic autoimmune retinopathy (npAIR). Conventionally, and for the purposes of this review, paraneoplastic disorders that predominantly involve the retinal pigment epithelium (such as bilateral diffuse uveal melanocytic proliferation) and the optic nerve are not included. The autoimmune retinopathy syndromes have an overlapping clinical and immunological phenotype characterized by rapidly progressive, bilateral, painless visual deterioration. They

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present a clinical management challenge on account of their rare incidence, the frequent dissociation between symptoms and signs, the difficulty accessing investigations to support the diagnosis, and the absence of an evidence-based treatment strategy. Various hypotheses about the aetiology and pathophysiology of these diseases are being advanced through experimental research, and autoantibodies against an array of retinal antigens have been identified in affected individuals. The available data give novel insight into the interaction between the eye and immune system, but also highlight how much remains poorly understood. The aim of this review is to summarize the classification, investigation and management of autoimmune retinopathy, and to consider the evolving concepts about its immunological aetiology.

History and Classification

The first cases of a degenerative retinopathy presenting as a remote effect of cancer were reported in 1976 [1]. A decade later, the clinical phenotype was associated with the presence of antibodies in blood serum that recognized an antigen of molecular weight 23 kDa [2], subsequently identified as recoverin [3]. A related clinical phenotype was reported in patients with cutaneous malignant melanoma in 1988 [4], who were found to have autoantibodies to an unknown antigen on bipolar cells [5]. These paraneoplastic diseases were termed 'cancer-associated retinopathy' (CAR) and 'melanoma-associated retinopathy' (MAR), and since their discovery, hundreds of cases have been reported in the literature [6, 7]. Subsequently, a non-paraneoplastic autoimmune retinopathy, of uncertain aetiology, similar in phenotype and electrophysiology to CAR, has also been reported [8]. The term 'autoimmune retinopathy' has been proposed to encompass CAR, MAR and presumed npAIR [9]. Over the past two decades, further autoantibodies to novel retinal antigens have been characterized, including antibodies to α-enolase [10], transducin-β [11] and transducin-α [12]. The identification of multiple retinal autoantibodies has led to the concept that they may serve as molecular biomarkers for clinical phenotypes, including antirecoverin, anti-α-enolase and antitransducin retinopathies [12, 13]. However, the frequent finding of multiple serum autoantibodies in a single patient leads to a lack of clarity as to which, if any, of the detected antibodies are disease causing. The challenge of obtaining detailed immunological investigations in clinical practice limits the reliability and validity of this approach to classification at present.

Clinical Phenotypes

CAR typically presents with bilateral, sometimes asymmetric, progressive vision loss, which may result in blindness over days to years [14]. Predominant cone dysfunction is suggested by worsening acuity and colour vision, symptoms of photosensitivity, glare, flickering or shimmering lights and central scotoma, whilst impaired dark adaptation, night blindness, ring scotoma and peripheral field defects indicate predominant rod dysfunction [14, 15]. Simultaneous rod and cone involvement is common, especially in association with antirecoverin antibodies, but the phenotype is heterogeneous [7, 14]. Symptoms are typically worse than the clinical signs, and the fundus frequently appears normal [14]. Retinal arteriole attenuation and waxy optic disc pallor develop later in some cases [14], and iritis and vitritis have also been reported in a few patients [16]. Diagnosis involves the exclusion of genetic retinal dystrophies or any medical cause for the retinopathy (pseudo-retinitis pigmentosa and drug toxicity). The clinical phenotype of npAIR is very similar to CAR, with similar heterogeneity [8, 14], but onset has been reported at a younger age than in CAR [12, 17]. Patients often have a family or medical history of autoimmune disease, but no other disease associations or risk factors have been identified.

MAR typically presents with night blindness, photopsia and visual field defects. Though less heterogeneous in presentation than CAR, atypical presentations have been reported [18]. In a case series and review of the literature including 62 patients with MAR, the presenting visual acuity was 6/18 or better in 82% patients and central and paracentral scotomas were common [6]. The fundus appeared normal in some patients, whilst in others optic nerve pallor, vessel attenuation, retinal pigment epithelial changes and vitreous cells were seen [6]. Limited follow-up data suggested that around half the patients had moderate to severe vision loss in one or both eyes at last follow-up [6].

Initial Investigation

All patients with suspected autoimmune retinopathy without a past medical history of cancer need to be thoroughly investigated for occult malignancy before a diagnosis of npAIR can be considered. Ophthalmic work-up should include perimetry, fundus autofluorescence [19], and fluorescein angiography, which help to exclude other causes of retinopathy. Perimetry may detect peripheral

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losses, scotomas, enlargement of the blind spot and pericentral losses that although non-specific are contributory to establishing the diagnosis. A recent case series suggested that ocular coherence tomography (OCT) allows for identification of outer retinal pathology and may aid selection of patients with suspected autoimmune retinopathy for further specialized investigation [20]. Outer retinal abnormalities, in the form of loss of the photoreceptor layer or disruption of the photoreceptor outer and inner segment junction, were seen in 7 out of 8 patients with autoimmune retinopathy [20]. The increasing availability of spectral domain OCT in clinical practice, which offers higher spatial resolution than time domain OCT, may yield further insights into the cytoarchitectural integrity of affected eyes.

Electrophysiology

Electrophysiological tests are a valuable diagnostic aid in suspected autoimmune retinopathy, allowing objective measurement of the electrical activity generated by the eye, the optic pathways and visual cortex [21]. Different electroretinographic patterns help to differentiate between diseases affecting different retinal layers and cell types. Associations may exist between different electroretinographic patterns and the clinical entities of CAR, npAIR and MAR, or different antiretinal antibodies. However, there are few studies including detailed electrophysiological data for patients with autoimmune retinopathy in the literature, and insufficient data to draw firm conclusions. The available case reports and small studies suggest considerable heterogeneity, and no pathognomonic electrophysiological features have emerged.

The full-field electroretinogram (ERG), measured under different conditions, provides information about activity in the rod and cone systems and other neural elements, and the multifocal ERG indicates the topographical location of disease within the retina, whilst the electro-oculogram (EOG) gives a measure of the integrity of the retinal pigment epithelium layer [21]. The leading edge of the full-field ERG a-wave response to a bright flash stimulus is thought to indicate the relatively isolated response of the photoreceptors [21]. The b-wave is composed of contributions from numerous neural elements, with a primary contribution from bipolar cells [21]. The scotopic, rod-driven b-wave primarily reflects activity of on-bipolar cells, whereas the photopic, cone-driven b-wave reflects a mix of activity from on- and off-bipolar cells [21]. Diseases targeting the photoreceptors affect both the a- and b-waves, whilst diseases targeting the bipolar cells result in an absent b-wave and an a-wave that appears as a negative deflection, which slowly returns to the baseline but does not rise above it [21]. Oscillatory potentials (OPs) are thought to represent activity in a complex feedback circuit including the bipolar, amacrine and interplexiform cells [21].

In one case series of 4 patients with CAR, one patient had reduced OPs, a second had a reduced amplitude, delayed b-wave and reduced OPs, a third had reduced amplitudes of both a- and b-waves and reduced OPs, and a fourth had reduced b-waves and an electronegative ERG, and their EOGs were normal [22]. In another case series of 2 patients with npAIR, the full-field ERG was extinguished in one patient, and selective b-wave loss with reduced OPs was seen in the other [8]. In a larger case series of patients with MAR, more homogeneous ERG patterns were seen, with the majority of patients having a markedly reduced b-wave, but a normal dark-adapted a-wave (negative ERG appearance), indicating compromised bipolar cell function but normal photoreceptor cell function [6]. This pattern was seen in 54 out of 56 patients, and was bilateral in 53 patients, with diffuse loss of the a-wave and b-wave seen in both eyes of the other 2 patients [6]. However, this 'electronegative' ERG is not pathognomonic and is found in numerous other disorders of the inner retina, including congenital stationary night blindness, which need to be excluded before a diagnosis is reached [23]. In a case series of 10 patients with antirecoverin-associated CAR, similar loss of rod and cone amplitudes and normal or prolonged implicit times were seen [24]. In a case series of 39 patients with antirod transducin-α associated npAIR and CAR, electroretinography was reported for two thirds of cases and was abnormal in all except 1 patient, with heterogeneous patterns. These included reduced scotopic responses and abnormal photopic cone and 30-Hz flicker responses, with prolonged rod and cone implicit times, and an extinguished ERG in several eyes, indicating global retinal damage [12]. A case series of 12 patients with anti-α-enolase-associated retinopathy, 4 of whom had cancer, identified more frequent central or global cone dysfunction than rod dysfunction [14].

Epidemiology

There are no population-based epidemiological data on CAR, MAR or npAIR, and these diseases are assumed to be rare, even though other paraneoplastic syndromes

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are thought to occur in 10–15% of cancer patients, most frequently in association with small-cell lung cancer and carcinoma of the breast and ovary [25]. A review of 209 patients with CAR and MAR determined a mean age at diagnosis of 65 years (range 24–85 years), with twice as many women than men affected [7]. The major cancer associations included breast (16%), lung (16%), melanoma (16%), haematological (15%, including lymphomas, leukaemias and myelomas), gynaecological (9%), prostate (7%), and colon (6%) [7]. In this case series, fewer than 4% of patients presented with autoimmune retinopathy prior to a diagnosis of cancer. The latency from cancer diagnosis to onset of retinopathy in patients ultimately diagnosed with CAR varied, from weeks to months, in patients with lymphomas and lung cancers, to years in patients with breast and prostate cancers [7]. A shorter latency between cancer diagnosis and onset of retinopathy was associated with more rapidly progressive visual loss [7]. Some patients presenting with CAR had antirecoverin, anti-α-enolase, anti-carbonic anhydrase II (anti-CAII), and antitransducin-α autoantibodies months to years prior to cancer diagnosis [7]. In another case series of patients with MAR, the mean age of onset was 57.5 years (range 30–78 years), and it most often developed after the diagnosis of malignant melanoma, with a mean latency of 3.6 years (range 2 months–19 years) [6]. It also frequently developed following metastatic disease, with a latency of 1.9 years (range 1 month–15 years). Less often, it was the first presentation of an occult malignant melanoma, with or without metastasis, and occasionally preceded a diagnosis of malignant melanoma, by as much as 2 years [6]. Unlike malignant melanoma, which occurs in men and women with similar frequency, the majority of patients in this case series of MAR were male [6]. One large case series of 141 patients with npAIR reported a younger mean age at presentation (55.9 years) than has been reported elsewhere for patients with MAR and CAR [17].

Specialized Investigation

Diagnostic testing for serum autoantibodies is hampered by (1) the lack of methodological standardization and (2) the unknown predictive value of a positive test

Various techniques are available to investigate the presence of serum autoantibodies to components of retina including immunohistochemistry, Western blotting, ELISA, cytotoxicity assays and multiplex assays. When several tests are combined to investigate a single patient, they yield considerable immunological information, but each has a number of limitations [17], and access to these investigations remains limited.

In immunohistochemistry, serial dilutions of patient sera are incubated on normal, non-human retinal tissue sections followed by an antihuman immunoglobulin antibody. The binding of the latter is localized using either a colorimetric or fluorescent secondary antibody [17]. This technique allows cellular localization of antiretinal antibody binding, and comparison of staining intensity across multiple serum samples indicates relative antibody titres. Limitations of this approach include an inability to distinguish reactions to specific proteins and variations in staining intensity due to the tissue processing/fixation method employed [26].

In Western blotting, retinal extract or purified retinal proteins are separated by gel electrophoresis into discreet bands based on differing molecular weight. The protein bands are transferred to a nitrocellulose membrane and incubated with serial dilutions of patient sera. After the addition of a secondary antihuman immunoglobulin antibody, a chemoluminescent reaction highlights the presence of bound antiretinal antibodies from the patient sera [17]. Interpretation of Western blots depends on the intensity of protein bands visualized on the film, which can be influenced by the adequacy of protein transfer to the nitrocellulose membrane, exposure time to primary and secondary antibodies, the length of colorimetric development and film exposure time [26]. Western blotting differentiates proteins by weight but does not identify the protein. For example, recoverin is 23 kDa, but immunoassay or proteomic identification is required to differentiate recoverin from other retinal proteins of the same weight [27].

In enzyme-linked immunosorbent assay (ELISA) serial dilutions of patient sera are added to small wells coated with specific retinal protein, such as recoverin or α-enolase, and binding of the specific antibody is detected with a secondary antihuman immunoglobulin antibody [17]. The amount of binding is determined by spectrophotometry [26]. Standard curves help to determine the titre of the antibody of interest in relation to the measured absorbance and replicated samples allow well-to-well variation in the reaction to be checked [26]. In a cytotoxicity assay, purified serum IgG antibodies from patients and controls are cultured in wells containing retinal cells at a density of 10^4 cells per well. The viability of cells is measured after 24–48 h by various approaches, for example by a colorimetric MTT (thiazolyl blue) cytotoxicity assay [28]. Multiplex assay systems enable high-

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throughput detection and measurement of up to 100 antibodies in one sample [29]. There are various commercially available bead-based multiplex assays. For example, in the Luminex system, dual-laser flow cytometry is used to detect and quantify the amount of bound antibody after patient serum has been added to antigens coupled to fluorescent beads and a fluorochrome-coupled secondary antibody [29]. In the line immunoassay, computer-assisted imaging and densitometry are used to quantify the relative amount of bound autoantibody resulting from the application of several antigens to a solid matrix in a similar fashion to conventional immunoblotting [29]. In the luciferase immunoprecipitation system, patient serum is added to mammalian cell lines that have been engineered to express a luciferase-tagged fusion protein. The resulting immunoglobulin-antigen complexes are captured by Protein A/G, washed, and antibody-bound luciferase is measured by light production [29]. Other multiplex technologies including autoantigen microarrays, nanotechnology formats and microfluidics are in development. These may serve as novel tools for detecting and quantifying antiretinal antibodies, but will need internal validation and standardization before they can be employed in clinical practice [29].

Forooghian et al. [26] have highlighted the absence of validated, reproducible, standardized assays internationally. Interlaboratory variation in methodological approach, and handling of potential sources of bias and measurement error, makes the interpretation and comparison of the available data challenging [26]. Many studies have not included adequate positive and negative controls, such as purified protein and antibody samples, and serum from patients with well-characterized disease and healthy subjects. Without these, it is not possible to determine the sensitivity, specificity, positive and negative predictive values of the assays [26]. Masking of laboratory personnel to patient diagnosis has not been consistently reported. Different labs have varied in the species origin of the retinal protein extracts, the methods of protein extraction and their definition of positive reactivity [30]. Studies have frequently used bovine, rodent and monkey tissue in assays on account of the difficulty of obtaining fresh cadaveric human retinal tissue samples. The generation of human recombinant proteins for purified antigen samples may help to overcome this. Independent testing and verification of the same masked samples by multiple laboratories will be needed to reach consensus on the standardization of antiretinal antibody testing [31].

Antigens and Antibodies

Not all patients fitting the clinical phenotype consistent with MAR, CAR and npAIR have identifiable autoantibodies to retinal antigens in their serum. In one case series of 209 patients with CAR and MAR, 65% were seropositive for antiretinal antibodies [7]. In another case series of 141 patients with npAIR, 41% had autoantibodies [17], and in another case series of 87 patients, most of whom had npAIR, 43% had antiretinal antibodies [14]. Amongst the patients who do, approximately 15 different target retinal antigens have been identified so far. Whilst this reflects a degree of heterogeneity in the autoimmune response, the antigens represent a small proportion of all the potential target antigens in the retina [17]. Some autoantibodies appear to be associated with different clinical phenotypes within the antiretinal antibody syndrome spectrum, but whether any are specific or sensitive has yet to be determined.

For example, in the largest case series including seropositive CAR patients, 10% patients had antirecoverin antibodies, 30% had α-enolase antibodies, 17% had anti-transducin antibodies and 14% had anti-CAII antibodies [7]. Recoverin is a 23-kDa calcium-binding protein expressed in photoreceptors, which is involved in regulating rhodopsin phosphorylation during dark and light adaptation [3]. In humans, antirecoverin antibodies bind to rods, cones, off bipolar cells [32], and cone-opsin-positive cells in the ganglion cell layer [33]. Recoverin is expressed by numerous tumours [5], and antirecoverin retinopathy has been associated with various cancers including small-cell lung [34], cervical [35] and endometrial carcinomas [36], uterine sarcoma [37] and mixed Mullerian tumour [38]. The clinical phenotype most frequently reported with antirecoverin-associated CAR is that of aggressive, severe rod and cone dysfunction and marked vision loss, to no perception of light in some cases [16, 34, 39]. Antirecoverin antibodies were once thought to be sensitive [16] and specific [13] to CAR, and have not been identified in npAIR [13], but were recently found in 5 out of 521 patients with retinitis pigmentosa [27].

Another autoantibody identified in both CAR and npAIR patients with similar frequencies is directed against α-enolase [17]. This 46-kDa glycolytic enzyme protein is ubiquitously expressed, but highly expressed in neoplasms, and may escape during tumour cell turnover or resection [7, 10]. It is located in the cytoplasm and on the cell membranes [40] of retinal ganglion cells, Müller cells, cones and rods [14]. Epitope mapping has revealed that three binding regions are common to the autoanti-

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bodies, and an additional binding region has been identified which is associated with cytotoxic activity [28]. The clinical phenotype associated with some cases of anti-enolase retinopathy is one of predominant cone dysfunction, often asymmetric or unilateral in onset, with subacute or chronic acuity and colour vision deterioration, but a visual acuity seldom worse than 20/300 [14]. Anti-α-enolase-associated CAR has been reported months to years after the development of lung, breast, bladder, uterine, prostate, salivary gland, and gastro-intestinal tract carcinomas and chronic lymphocytic leukaemia [10, 28]. Anti-α-enolase does not appear to be specific to the antiretinal antibody syndrome as it has also been described in various systemic autoimmune diseases [41], and anti-enolase antibodies are found in 10% of healthy subjects [10]. However, these antibodies appear to target different epitopes on enolase and do not induce apoptosis, in comparison to those found in the sera of patients with CAR and npAIR, which are cytotoxic and induce apoptosis [28].

Antibodies to rod transducin-α have been identified in patients with CAR, MAR and npAIR [12]. Transducin is a 3-subunit guanine nucleotide-binding protein that stimulates the coupling of cGMP-phosphodiesterase to rhodopsin and results in the phototransduction cascade and hyperpolarization of the photoreceptor [12]. The transducin α-subunits in rods and cones are encoded by separate genes; GNAT1 in rods and GNAT2 in cones [42], and GNAT1 mutations have been associated with congenital stationary night blindness [43, 44]. The antigen is aberrantly expressed in cancer cells, and inactivation by autoantibodies is hypothesized to reduce signalling and lead to changes in intracellular calcium with resulting apoptosis [12]. In a case series of 39 patients with antirod transducin-α-associated CAR (25%) and npAIR (75%), twice as many patients were female as male and the average age at presentation was 56 ± 6 years. The presenting acuity was 20/20–20/40, with symptoms including photopsias, photophobia, and blurred or dimmed vision. Sudden, progressive, bilateral vision deterioration and field loss developed over weeks to months in all patients with central scotomas [12].

Other retinal antigens targeted by autoantibodies in CAR and npAIR include CAII, a 30-kDa enzyme whose expression is increased during carcinogenesis [7, 45], and heat shock cognate protein 70 (hsc 70), a 65-kDa protein that acts as a chaperone to assist in various cellular processes including translocation into organelles, folding and rearrangement of proteins, protein degradation and protein aggregate dissolution [46].

Melanomas express rhodopsin, transducin, recoverin, arrestin and other phototransduction proteins [47]. Some patients with MAR have been found to express a variety of autoantibodies against various proteins including transducin-β [11], rhodopsin [47], arrestin [48], a 35-kDa protein in Müller glial cells, a 22-kDa neuronal antigen, mitofilin, titin and COX [49]. Mitofilin is a mitochondrial protein anchored in the inner mitochondrial membrane, presumed to influence the morphological structure and function of mitochondria [49]. Titin is a 4,200-kDa protein that forms the third myofilament of the striated muscle expressed in heart and skeletal muscle, and was not previously known to exist in the retina, where its function is unknown [49]. Cytochrome c oxidase autoantibodies have been found in patients with melanoma both with and without MAR [49]. It is an important enzyme in the mitochondrial respiratory chain that is exclusively encoded by mitochondrial DNA.

Antiretinal antibodies have also been found in the serum of healthy controls. A recent study on 92 samples of laboratory 'normal control' human sera revealed that 62% of serum samples had antiretinal IgG immunoreactivity to solubilized human retinal proteins [30]. Western blot analysis detected reactivity against a few retinal protein bands in 33%, and against 5 or more retinal protein bands in 22%, ranging in weight from 13 to 148 kDa [30]. Autoantibodies have been found in numerous other retinal and systemic diseases, and in patients with cancer but no visual symptoms [50, 51]. For example, various antiretinal antibodies have been identified in 10% of patients with retinitis pigmentosa [27], and in a case series of 30 patients with retinitis pigmentosa and cystoid macular oedema, antiretinal antibodies were found in 90% of cases [52]. Six out of ten patients with cystoid macular oedema resulting from other disease processes were found to have anti-CAII and anti-enolase antibodies [53]. Antibodies to the outer segments of photoreceptors and Müller cells have been identified in some patients with Vogt-Koyanagi-Harada, Behçet's and sympathetic ophthalmia [54]. Antiphotoreceptor antibodies have also been identified in significantly more patients with *Toxoplasma retinochoroiditis* than in controls [55]. Numerous antiretinal antibodies have been identified in both dry and exudative age-related macular degeneration patients compared to controls, including one of molecular weight between 28 and 32 kDa [56–58]. In onchocerciasis, more cases than controls have autoantibodies to cell surface molecules in the inner retina nerve fibre layer, ganglion cells, Müller cells, and outer segment photoreceptors [59, 60]. Multiple retinal autoantibodies are present in the serum of pa-

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tients with diabetic retinopathy compared to controls, including anti-aldolase [61]. Antiretinal antibodies have also been identified in patients with idiopathic retinal vasculitis [62], and idiopathic uveitis [63].

It is interesting to note that not all the retinal antigens characterized to date are located on the cell surface, raising questions about the role of the humoural versus cell-mediated immune response in these diseases. It remains unclear whether all of the autoantibodies play a direct pathophysiological role, or whether some appear as bystanders in the disease process [49].

Pathophysiology

Hypotheses about the pathophysiology of antiretinal antibody syndrome are slowly evolving from experimental study data including animal models and in vitro cell culture experiments. Whilst the picture remains incomplete, considerable insight into the interaction between the eye and immune system has been advanced, and the mechanism by which antirecoverin antibody might result in CAR has been particularly intensively studied in the past few decades.

In antirecoverin antibody-associated CAR, the initial event has been hypothesized to be novel autoantigen expression outside the eye by malignant cells following germ line mutation. The recoverin gene has been located close to the p53 tumour suppressor gene on chromosome 17 in a patient with small-cell lung cancer and CAR [64]. It is thought to be expressed by more than 50% of a variety of cancer cells and may play an important role in cellular proliferation [65]. Aberrant expression of recoverin stimulates a systemic immunological response, which may induce a degree of tumour immunity and be associated with a more favourable prognosis for the primary cancer [66]. However, in a very small number of patients, for reasons that are not understood, the serum antirecoverin antibodies cross-react with retinal rod and cone photoreceptors, resulting in widespread retinal dysfunction [16, 34, 67]. Immunization of both rabbits and Lewis rats with recoverin has resulted in uveitis and retinal degeneration [68, 69]. However, intravenous injection of polyclonal monospecific antibody to recoverin has not caused retinal damage in rabbits or mice [69, 70], and the mechanism by which endogenous antirecoverin antibodies traverse the blood-retinal barrier to exert pathological effects has yet to be determined. After co-injection of antirecoverin and anti-hsc 70 antibodies into the vitreous of Lewis rats, penetration into the outer nuclear layer and outer segments was evident within 12–24 h, and the retinal antibody titre declined over several days [71]. Antibody uptake occurred via endocytosis, and was detected in vitro by immunofluorescence at 24 h [72]. Once within the cell, antirecoverin antibodies had a modulatory and enhancing effect on rhodopsin phosphorylation. They induced expression of various proteins, including bcl-x(s) and bax, decreased the expression of others, including bcl-x(L), stimulated cytochrome c release, and the deregulation of apaf-1 protein. These various intracellular actions resulted in sequential activation of caspase 9 and caspase 3, degradation of the caspase substrate PARP and the fragmentation of DNA, thus inducing intracellular calcium influx and apoptosis via the mitochondrial pathway involving the caspase enzymes [73, 74]. Cells undergoing apoptosis have been identified through a variety of approaches, including terminal transferase-mediated dUTP nick-end labelling (TUNEL), electron microscopy [75], the cell death detection ELISA and the terminal deoxyuridine triphosphate nick-end labelling assay [76]. Antirecoverin IgG has been found to cause apoptosis of rod but not amacrine cells in rat retinal cell cultures, although IgG was taken up by almost all cells [76]. Antirecoverin antibodies produced cell destruction in a time- and dose-dependent manner [72]. Histopathology has revealed significant atrophy of the outer and inner nuclear layers in rat eyes receiving intravitreal antirecoverin antibody compared to control eyes, and TdT-dUTP terminal nick-end labelling has identified apoptotic cells throughout the outer and inner nuclear layers [71].

Co-injection of caspase inhibitors and antirecoverin antibody significantly suppressed the enhancement of rhodopsin phosphorylation, and inhibited the ERG impairment otherwise seen in rats [74]. Nifedipine, a calcium-channel blocker, inhibited the entry of calcium into cells and was protective in vitro against antirecoverin antibody-mediated apoptosis [77]. The ERG abnormalities seen in rat eyes co-administered with antirecoverin and anti-hsc-70 antibodies improved following administration of corticosteroid or cyclosporin A [71]. Peripheral activation of recoverin-specific cytotoxic T lymphocytes is likely to contribute to the favourable prognosis of CAR-positive cancer patients, providing natural immunotherapy against the underlying malignancy [78, 79]. Strengthening negative cytotoxic T cell signalling may lessen the retinal damage, but it is unclear whether this might have unintended consequences on cancer prognosis.

Interestingly, none of the serum autoantigens identified in patients with MAR to date are located on the cell

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surface. For example, mitofilin, titin and COX are cytoplasmic and nuclear antigens, which must be released from an antigen-expressing cell by secretion, shedding or lysis in order to be captured by antigen-specific immunoglobulins on B cells. B cells develop into antibody-secreting plasma cells with T cell help. This questions the pathogenic role of antiretina antibodies in MAR [49].

The pathophysiology of npAIR is still relatively poorly understood, but it is possible that a proportion of npAIR results from aberrant tumour retinal antigen expression, where the tumour is controlled by immune surveillance and never manifests clinically. It has also been proposed that a subgroup of npAIR may develop as a secondary complication of other retinal diseases, including retinitis pigmentosa with cystoid macular oedema and acute zonal occult outer retinopathy (AZOOR), because serum antiretinal antibodies have been identified in a few patients with these diseases [9]. However, experimental studies demonstrate that serum antiretinal antibodies develop in rabbits which have laser-induced retinal damage, without triggering autoimmune retinopathy [80], so cause and effect have yet to be determined.

The eye has evolved immune privilege to protect the delicate tissues of the visual axis from the damaging effects of inflammation, and the ocular microenvironment is profoundly immunosuppressive [81]. The mechanisms of ocular immune privilege are still incompletely understood, but it is apparent that the phenomenon is not absolute. Retina-specific T cells primed for effector function before entering the eye have recently been demonstrated to resist conversion to suppressive T regulatory cells, and can overcome the immunosuppressive ocular microenvironment to cause inflammatory tissue damage [81, 82]. It is thus possible that the primary step in immune attack on the eye is mediated by cytotoxic t-cells rather than the humoral response, which could be an epiphenomenon or by-product without a significant role in pathogenesis [49].

Prognosis

Data from the available case series suggest that the visual prognosis is poor in the majority of cases with antiretinal antibody syndrome, and that no significant, spontaneous visual improvement occurs. There is some suggestion that the final visual outcome may be associated, in some cases, with the antiretinal antibody type. The vision loss associated with CAR and npAIR is seldom worse than 20/300 in patients with anti-enolase-associated retinopathy, but may progress to no perception of light in patients with antirecoverin antibodies [14]. Patients with CAR and MAR have a high mortality rate on account of the underlying malignancy. Interestingly, several studies suggest that patients with CAR who are seropositive for antirecoverin antibody may have improved survival compared to those who are seronegative [79, 83]. It has been hypothesized that this results from peripheral activation of recoverin-specific antitumour cytotoxic T-lymphocytes [79]. It is not known whether immunosuppression therapy negatively impacts life expectancy in these patients. Reduction of the tumour load by various methods is thought to reduce the immunogenic drive of the melanoma underling MAR, and result in improved visual function. This has been reported in several patients with MAR following cycloreductive surgery with adjuvant immunotherapy [6].

Treatment

There is no established treatment protocol for CAR, MAR or presumed npAIR, and the evidence base for therapeutic intervention includes only a small number of retrospective case series and case reports. Many clinicians aim to modulate the immune system and reduce the autoimmune attack on the retina before irreversible damage occurs. For example, one small case series reported some visual improvement in 5 out of 6 patients with CAR, and 8 out of 16 with npAIR following treatment with a variety of immunosuppressive treatments [9]. Chronic immunosuppression was required in this cohort to stabilize visual function, and some visual field improvement was typically seen after 4 months treatment. However, there have been other case reports and case series of patients with CAR and npAIR reporting progressive decline in vision function despite immunosuppression with high-dose oral steroids, azathioprine and cyclosporine [13, 14]. Vision loss in MAR has also been treated with intravenous corticosteroid, intravenous immunoglobulin and plasmapheresis, but these have, with a few exceptions, been largely ineffective [6]. Occasional reports of treatment with plasmapheresis have described more significant visual gains when commenced prior to significant vision loss. For example, 1 patient with small-cell lung cancer and CAR, who had antibodies to a 60-kDa retinal protein, had a sustained improvement from counting fingers to 20/200 in one eye, and from 20/40 to 20/25 in the other eye following treatment with steroids and plasmapheresis [84]. Another patient with metastatic

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cancer and rapidly progressive vision loss from CAR treated with intravenous immunoglobulin 400 mg/kg/day for 5 days had a sustained improvement in visual acuity from hand movements to 20/40 over 3 days, and by 2 weeks, the visual field had also markedly improved [35]. A second patient with metastatic cancer and CAR, who had perception of light only at presentation, had no gain with the same treatment [35].

The effectiveness of these various approaches is difficult to ascertain from the available reports, for a number of reasons. Firstly, the sample sizes discussing treatment are very small and the cases, clinically and immunologically heterogeneous. Secondly, the diagnosis is frequently delayed and reached after extensive investigation and exclusion of other possible causes, by which time the baseline visual function is often significantly impaired. Given the rare incidence of the antiretinal antibody syndrome, and the absence of an evidence-based treatment, a prospective, multicenter, double-masked, randomized controlled trial would be valuable to inform future practice.

Experimental studies have explored various potentially efficacious novel therapies in animal models, including calcium channel blockers [77, 85], caspase inhibitors [74], and resveratrol, a plant-derived phenol [86]. However, efficacy in humans has not yet been assessed.

In recent years, cellular therapy has become a realistic proposition for the treatment of degenerative retinal diseases such as age-related macular degeneration and retinitis pigmentosa, with potential donor cell sources ranging from human fetal and adult retina to pluripotent human stem cells [87–90]. While this approach is unlikely to be beneficial to patients suffering from CAR, MAR and npAIR, the work reviewed above highlights a problem that could potentially arise from transplanting large numbers of retinal-antigen-laden cells into the diseased eye of patients with age-related macular degeneration or retinitis pigmentosa. That is, because large numbers of cells are known to die immediately following subretinal engraftment [87, 90], a sudden surge in the release of retinal photoreceptor antigens (such as recoverin and transducin-α) could conceivably serve to potentiate an autoimmune retinopathy-type response. Indeed, there is experimental evidence indicating that in animal models of outer retinal degeneration the blood-retinal barrier becomes progressively compromised [91], with a chronic T cell-mediated rejection of non-autologous mouse photoreceptor transplants [92]. While pigment epithelial cells can operate specialized immune modulatory mechanisms in the subretinal space akin to those seen in the phenomenon of anterior chamber-associated immune deviation [93], it is not known whether these would afford sufficient immune protection to photoreceptor progenitor cells transplanted into the subretinal space.

Conclusion

Autoimmune retinopathy encompasses a group of rare diseases which present a diagnostic and management challenge. The typically rapid onset of vision loss and the extensive investigation required to reach a presumptive diagnosis result in delay in trials of treatment and a poor visual prognosis. The clinical, electrophysiological and immunological heterogeneity apparent in the limited literature on CAR, MAR and presumed npAIR exacerbates the difficulty in diagnosing and classifying these diseases, and treatments remain without an evidence base. Progress towards faster and more accurate diagnosis and classification of autoimmune retinopathy is hampered by the lack of clinical availability of specialized serological investigations. As services develop, it will be essential to reach international consensus on a standardized laboratory methodology to ensure results are valid, reliable and comparable.

Several decades of experimental research have resulted in very considerable advances in our understanding of the pathophysiological mechanisms that may underlie autoimmune retinopathy. However, the precise triggers which result in loss of ocular immune privilege and sudden autoimmune attack on retinal cells have yet to be elucidated. The available evidence to date suggests the trigger factors are peripheral to the eye in CAR and MAR, but they have yet to be determined in npAIR. Given the apparent rarity of autoimmune retinopathy, it is likely that disease initiation is a multistep process, modulated and prevented in the majority of patients with cancer and autoimmune disease by as yet unidentified systemic and ocular factors. The frequency of seronegative disease in various case series has challenged hypotheses on the pathogenic role of the humoural immune response in autoimmune retinopathy. Ongoing experimental work and clinical studies will hopefully clarify the pathophysiology and lead to earlier investigation, diagnosis and treatment for patients with this devastating ocular disease.

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