Review Article

Updates on Diagnosis, Clinical Presentation, and Management of Ocular Cicatricial

Hyder O.Mirghani[1], Aedah A. Alqrid[2], Hadeel M. Albalawi[3], Saud Q. Alshabab[4], Dana F. Aljezany[3] ,Hamdan S. Alghamdi[3], Khalid B. Aljohani[3],Mohammed S. Almousa[4], Ali M. Alshehri[4] , Zeyad S. Alahmri[5] ,Sara E. Alsaidalani[6], Abdullah A. Alshahrani[4], Salman A. Alshamrani[3].

[1]Prof. of Internal Medicine and Endocrine, Department of Internal Medicine, Faculty of Medicine, University of Tabuk, KSA. [2]Medical intern, Faculty of Medicine in Tabuk University, Tabuk, KSA. [3]Student, Faculty of Medicine in Tabuk University, Tabuk, KSA. [4]College of medicine, king khalid university, Abha, KSA. [5]College of pharmacy, King Khalid University, Abha, KSA. [6]Student, Faculty of Medicine in king Abdulaziz University, Rabigh, KSA.

ABSTRACT

This study systematically searched literature on the diagnosis, clinical presentation, and management of ocular chronic pain (OCP), including eight studies with 168 patients. The most reliable method of diagnosis was biopsy, with inflammatory markers detected in a small proportion of patients. Some patients had systemic or oral involvement and associated Sjogren's syndrome. Common immune-suppressives were MFF and steroids. Cyclophosphamide is a good choice in severe cases. Methotrexate and Rituximab were used as a maintenance therapy. OCP is characterized by ocular involvement that progresses to fibrosis and scarring. Diagnostic hurdles and inconclusive results make a comprehensive examination and clinical suspicion crucial.

Keyword: Ocular cicatricial pemphigoid; Diagnosis; Management; Systematic review.

Introduction

Pemphigoid with optical cicatrix, or OCP, stays an unusual chronic inflammatory condition that mostly affects the eye surface. Acute conjunctivitis episodes that recur are its hallmark, and the condition may ultimately lead to cicatrisation, or scarring, of the eye's surface, which might result in blindness [1]. Slimy casing pemphigoid (MMP) stays a form of autoimmune sub-epithelial blistering disorders that affect the mucosal membranes of the mouth, throat, pharynx, esophagus, eyes, nasal cavity, and genitals.

OCP is one of these conditions. The epithelial basement membrane's linear immunoglobulin deposition against particular antigens is a characteristic shared by this group of disorders [2]. Ocular cicatricial pemphigoid is a kind of mucous membrane pemphigoid, CP, or cicatricial pemphigoid, mostly affects the ocular surface [1]. OCP is often thought to be an illness that affects the elderly and typically manifests in the seventh decade of life [3, 4]. There have been instances reported involving patients as young as their twenties despite the fact that they are incredibly uncommon [3].

Access this article online	
Quick Response Code:	Website: www.smh-j.com
	DOI: 10.54293/smhj.v4i2.106

Address for correspondence: Hyder Osman Mirghani, Prof. of Internal Medicine and Endocrine, Department of Internal Medicine, Faculty of Medicine, University of Tabuk, KSA.
E-mail: h.mirghani@ut.edu.sa

Received: 9 Mar 2024 **Accepted:** 6 Apr 2024

Please cite this article as: Osman Mirghani H, Alqrid A, Albalawi H, Alshabab S, Aljezany D, Alghamdi H, Aljohani K, Almousa M, Alshehri A, Alahmri Z, Alsaidalani S, Alshahrani A, Alshamrani S. Updates on Diagnosis, Clinical Presentation, and Management of Ocular Cicatricial Pemphigoid (OCP): A Systematic Review. SMHJ [Internet]. 2024;4(2):89-96.

According to the description, Ocular cicatricial pemphigoid is a chronic illness in which the conjunctiva progressively decreases until it completely disappears. These can also take the form of an acute-on-chronic progression, where the process is accelerated by sporadic assaults [4]. It is believed that 66% of MMP patients have ocular involvement [3]. The initial sign of mucous membrane pemphigoid involvement of the eye is usually unilateral conjunctivitis, which can progress to a chronic illness. Blindness may result as a result of further development and eventual scarring [1, 3, 4]. Because OCP has a systemic autoimmune origin, systemic therapy is necessary. Topical medications are used as a supplement to reduce the complications associated with ocular surface fibrosis. They have not proven to be successful in stopping the disease's progression. Systemic immunosuppression is therefore the cornerstone of care for these patients. This calls for a coordinated, multidisciplinary strategy that frequently involves rheumatology, ophthalmology, and other medical disciplines [5]. Strict cooperation with the patient is necessary because therapy optimization and relapse prevention depend on close follow-up, which is typically needed for life [1]. This review's primary objective is to study the recent literature on diagnosis, clinical presentation, and management of OCP.

Methods

This systematic review was done in compliance with PRISMA principles. [6].

Study Design and Duration: January 2024 marks the beginning of this comprehensive review.

Search strategy: To find relevant material, a comprehensive exploration remained performed crosswise four major databases: PubMed, SCOPUS, Web of Discipline, and Science Direct. We focused our exploration on English and took taking into account the specific needs of each database.The following keywords were converted into PubMed Mesh terms and used to find the pertinent studies;" Ocular cicatricial pemphigoid," "analysis," "diagnostic work-up," "manifestations," "treatment," and "management." The essential keywords were matched using the Boolean operators "OR" and "AND". The search results showed publications in entire English, freely available articles, and human trials.

Selection standards

We investigated the subsequent criteria in our review:

- Summarized studies on the diagnosis, clinical presentation, and treatment of OCP.
- Studies conducted between 2019 and 2024 were included.
- Limited studies to human beings.
- Proficiency in English required.
- Articles are freely available.

Data extraction: Rayyan validated the search technique result twice (QCRI) [7]. The academics evaluated the bearing of the titles and summaries by applying inclusion/prohibiting standards to the combined exploration results. The reviewers thoroughly assessed each paper that satisfied the presence criteria. The writers discussed many ways to conflict settlement. The allowed study was submitted using a previously created data extraction form. The authors collected data on research titles, authors, study years, countries, participants, genders, follow-up periods, diagnoses, clinical symptoms, and treatments. A second spreadsheet was created to assess the risk of bias.

Data Synthesis Strategy:

Summary tables were prepared based on data from relevant studies to provide a qualitative overview of the research components and conclusions. After gathering data for the systematic review, the most effective method for utilizing the information from the included study articles was determined.

Assessing the risk of bias: The superiority of the comprised studies was assessed using the ROBINS-I risk of bias valuation approach for non-randomized hearings of treatments [8]. The seven subjects examined were confusing, research participant selection, and involvement classification, deviation from intended interventions, missing data, result assessment, and optimal of reported result.

Results

Search results: The thorough search revealed 302 study articles, 88 of which were identified as duplicates. A total of 214 manuscripts were evaluated for title and abstract, and 185 were rejected. Twenty nine reports were sought for recovery, and four items were discovered. Finally, 25 publications were chosen for full-text examination; seven were deleted owing to inaccurate study findings, eight due to improper population type, and two were letters to the editors. The systematic review included eight eligible study papers. A summary of the study selection approach is shown in (Figure 1).

Characteristics of the included studies: (Table 1) summarizes the sociodemographic features of the education articles comprised. Our findings comprised eight trials with 168 patients, 99 of whom (58.9%) were female. Seven studies were retrospective [9, 11-16], One research was a case-control study [10]. (Table 2) shows the clinical features. Biopsy was the most accurate approach for diagnosing OCP [9, 12, 15]. Inflammatory markers such as CRP, ESR, or polyclonal antibodies were detected in a small portion of the patients [10]. Some patients had systemic or oral involvement [9] and associated sjogren's syndrome [10]. MFF and steroids were most commonly used as immunosuppressives for OCP cases with no

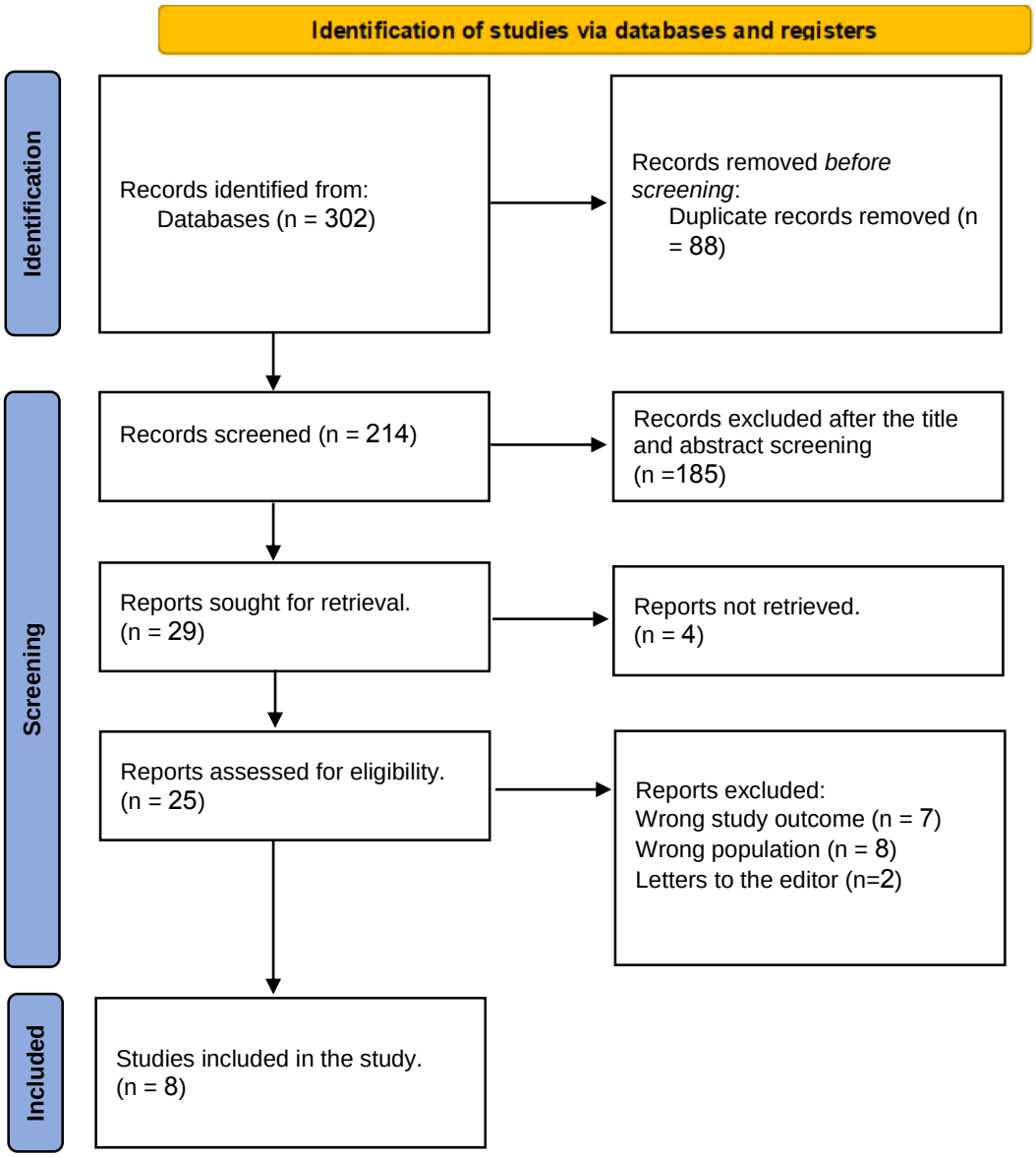

Figure 1: PRISMA flowchart summarizes the study selection process.

Table 1: Sociodemographic characteristics of the included participants.

Study	Study design	City	Participants	Mean age	Gender (Males)
Çiftçi et al., 2023 [9]	Retrospective	Turkey	11	14±5.76	8 (72.3)
Smichowski et al., 2022 [10]	Case-control	Argentina	27	66-76 (range)	17 (63)
He et al., 2022 [11]	Retrospective	China	13	NM	9 (64.29)
Alkeraye et al., 2021 [12]	Retrospective	Saudi Arabia	60	69.6	37 (66.7)
Bevans et al., 2021 [13]	Retrospective	USA	13	NM	10 (76.9)
Khan et al., 2022 [14]	Retrospective	Canada	10	79 (median)	5 (50)
Fremont et al., 2019 [15]	Retrospective	France	17	75.6 ± 11	6 (35)
Ma et al., 2019 [16]	Retrospective	USA	17	60.7	7 (41.2)

Table 2: Clinical characteristics and outcomes of the included studies.

Study	Follow-up (months)	Population type	Main outcomes	ROBIN-I
Çiftçi et al., 2023 [9]	14 ± 5.76	Of the nine individuals who had a biopsy, six (66.66%) had the diagnosis confirmed. Of the patients, 45.45% (5/11) had	It was recommended to take MFF in addition to corticosteroids. Four (66.66%) of the six patients who received steroid treatment in addition to	

		systemic involvement, with oral mucosal involvement accounting for most cases (18.18%).	MFF demonstrated partial or complete clinical remission even though treatment responses prior to MFF administration could not be well assessed due to loss of follow-up. There were no significant adverse effects or signs of drug withdrawal.	High
Smichowski et al., 2022 [10]	4-35	Sjogren's syndrome was identified in 5 individuals (18.5%), and it is noteworthy that 4 of them required a combination or rotation of therapies. Less than half of the patients had polyclonal antibodies, positive reactive C protein, and increased erythrocyte sedimentation rates in laboratory testing.	Early initiation of immunosuppressive therapy is crucial; in our experience, methotrexate is a good starting alternative. Treatment must be escalated in accordance with the course of the disease.	
He et al., 2022 [11]	60.6±35.6	NM	At the start of their treatments, all patients took oral immunosuppressive medications. Of them, seven patients (87.5%) took oral methotrexate, and one patient (12.5%) received oral cyclophosphamide. There was little chance of disease activity following surgical trauma in OCP patients receiving systemic steroids and immunosuppressants once active conjunctival inflammation had been successfully eliminated.	High
Alkeraye et al., 2021 [12]	49.9	Conjunctival biopsies were taken in 16 cases (26.6%) for direct immunofluorescence, although only 3 patients in the true OMMP group and 4 patients in the pseudo-OMMP group had positive results.	Twelve of the thirteen (21.7%) individuals who underwent systematic immunotherapy were determined to have genuine OMMP. MFF is the most often utilized agent in systemic immunotherapy, with prednisolone coming in second.	Moderate

Bevans et al., 2021 [13]	4.3	NM	Rituximab may be considered a maintenance or rescue therapy for OCP patients. This could lead to an earlier arrest of the disease's course, preserving the patient's vision, and allowing for the tapering of adjuvant IMT.	Moderate
Khan et al., 2022 [14]	24.9 ± 29.1	NM	Of the OcMMP patients, half needed subsequent corrective surgery, and only one patient kept a deep fornix. Three patients underwent evisceration or enucleation procedures after their visual acuity decreased by an average of 1.75 ± 1.09 logMAR. All except one of the patients experienced a recurrence of trichiasis. At the time of surgery, eight patients were receiving systemic immunosuppressive medication; nevertheless, there was no difference in the success rate of instances that were treated medically versus those that were not.	Moderate
Fremont et al., 2019 [15]	12	The diagnosis can be verified by biopsy and immunohistochemical analysis; however, in the event of a clear clinical picture, therapy should not be postponed due to a negative biopsy result. When treating patients, it is crucial to use a clinical staging method to identify mild, moderate, and severe forms.	For mild to moderate forms, dapsone is recommended; however, MMF seems to be a good and well-tolerated substitute. For severe instances, cyclophosphamide can still be used, whereas rituximab is a promising substitute. Using a sample of eyes treated with rituximab, this retrospective analysis found that the overall efficacy of immunosuppressive drugs in treating OCP was 83.9%.	High
Ma et al., 2019 [16]	12-140	NM	For individuals with resistant OCP, imipenem monotherapy is a safe and effective treatment option. OCP relapse may be linked to ocular surgery.	Moderate

Documented side effects [9, 12], and cyclophosphamide was a good choice for severe cases [15]. Methotrexate was also a good alternative [10, 11], and Rituximab was used as a maintenance therapy [13].

Discussion

This study included a total of 168 OCP patients with slight female predominance (58.9%). The ratio of females to males is considered to be approximately 1.6:1, and numerous studies have demonstrated that this condition is more common in females [3]. There have been no reports of racial or geographic preferences [4]. This study also found that biopsy was the most reliable method of diagnosis for OCP [9, 12, 15]. Inflammatory markers such as CRP, ESR, or polyclonal antibodies were detected in a small portion of the patients [10]. A conjunctival biopsy that uses immunofluorescence or immunoperoxidase methods is the gold standard for diagnosing OCP. OCP can be diagnosed by looking for Immunoreactants (IgG, IgA, IgM, and complement 3 component, or C3) are deposited in the basement membrane zone of an inflamed conjunctiva in a consistent linear pattern. The literature [17] indicates a variety of positive biopsimal rates; from 20 to 67%. A negative biopsy result does not rule out OCP; depending on the level of clinical suspicion, more testing and a second biopsy may be necessary. For a repeat biopsy, use a more sensitive immunoperoxidase staining method using avidin-biotin complex (ABC) [3,17]. Tauber [18] and colleagues reported in 1991 that when immunoperoxidase testing was added to routine immunofluorescent tests, the sensitivity of conjunctival samples increased from 52 to 83%. Standard hematoxylin and eosin-stained sections show some highly suggestive features, but conventional histologic evaluation is insufficient to diagnose OCP. Subepithelial inflammation is seen in the conjunctiva, where T-cells, neutrophils, and histiocytes predominate. Supporting evidence includes fewer goblet cells and a total artificial separation of the epithelium from the highly inflamed substantia propria [19, 20]. Treatment for general mucous membrane pemphigoid without ocular involvement is somewhat different from that for ocular cicatricial pemphigoid. Nonetheless, a national consensus reached in 2002 stated that because blindness is a possibility, MMP patients with ocular disease are considered to be "high-risk" patients [20]. As a result, stricter measures must be taken to help restrict this possibility. The diagnosis stage, the location, the severity, and the rate of illness development all play major roles in the therapeutic agent selection. Decision-making is also influenced by drug tolerability and response to treatment. More intensive care is needed for severe diseases in order to slow their progression. Cyclophosphamide (1-2 mg/kg/day) with systemic prednisone (1-2 mg/kg/day), are widely regarded as the first-line treatment for individuals with advanced or quickly advancing illness, according to professional opinion and the research that are currently available [20]. We found that MFF and steroids were most commonly used as immunosuppressives for OCP cases with no documented side effects [9, 12], and cyclophosphamide was a good choice for severe cases [15]. Methotrexate was also a good alternative [10, 11], and Rituximab was used as a maintenance therapy [13]. Because operating on inflamed eyes carries a significant risk of complications and poor outcomes, surgical intervention is a challenge for patients with OCP. Prior to any planned treatments, the patient must attain a stable disease or remission state on medicinal therapy; otherwise, there is a risk of surgical failure or even worsening of the condition. Surgical operations may result in complications such as conjunctivalization, creation of symblephara, epithelial abnormalities, and ulcerations. Other treatments, In addition to surgical restoration, procedures like amniotic membrane transplantation can help target inflammation and promote ocular surface regeneration [21].

Conclusion

OCP is an autoimmune systemic disease called ischaracterized by ocular involvement that progresses to fibrosis and scarring. Doctors face a significant diagnostic hurdle because of its vague early symptoms and overlap with other autoimmune illnesses. Furthermore, available testing frequently yields inconclusive results. Therefore, making a diagnosis and delivering a timely and successful solution depends heavily on a comprehensive examination and clinical suspicion. It is advised to use systemic immunosuppression as soon as the diagnosis is highly suspected or confirmed to reduce the inflammation causing the tissue damage.

Conflict of Interest

None

Funding

None

References

1. Ruan Y, Jiang S, Musayeva A, Pfeiffer N, Gericke A. Corneal Epithelial Stem Cells–Physiology, Pathophysiology and Therapeutic Options. Cells. 2021 Sep 3;10 (09): 2302.

2. Patzelt S, Schmidt E. Autoimmunity against laminin 332. Frontiers in Immunology. 2023 Aug 10;14:1250115.
3. Georgoudis P, Sabatino F, Szentmary N, Palioura S, Fodor E, Hamada S, et al. Ocular mucous membrane pemphigoid: current state of pathophysiology, diagnostics and treatment. Ophthalmology and therapy. 2019 Mar; 8 : 5-17.
4. Bonnet C, Roberts JS, Deng SX. Limbal stem cell diseases. Experimental eye research. 2021 Apr 1; 205:108437.
5. Jovanovic N, Russell WW, Heisel CJ, Hood CT, Kahana A. Direct injection of 5-fluorouracil improves outcomes in cicatrizing conjunctival disorders secondary to systemic disease. Ophthalmic Plastic & Reconstructive Surgery. 2021 Mar 1;37 (2):145-53.
6. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. Bmj. 2021 Mar 29; 372.
7. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan—a web and mobile app for systematic reviews. Systematic reviews. 2016 Dec;5: 1-0.
8. Jüni P, Loke Y, Pigott T, Ramsay C, Regidor D, Rothstein H, et al. Risk of bias in non-randomized studies of interventions (ROBINS-I): detailed guidance. Br Med J. 2016; 355:i4919.
9. Çiftçi MD, Korkmaz İ, Palamar M, Yaman B, Eğrilmez S, Yağcı A, et al. Clinical approach to ocular cicatricial pemphigoid. Turkish journal of ophthalmology. 2023 Apr; 53(2):79.
10. Smichowski AM, Caputo VD, Romeo C, Rivero E, Morales NS, Casado G. Ocular cicatricial pemphigoid: Methotrexate as an initial treatment. Reumatología Clínica (English Edition). 2022 Jan 1;18 (1):30-2.
11. He Y, Quan Z, Zhang R, Ji Z, Jia J, Liu H, et al. Perioperative Management and Long-Term Outcomes in Ocular Cicatricial Pemphigoid Patients Undergoing Cataract Surgery. Oxidative Medicine and Cellular Longevity. 2022 Apr 30; 2022.
12. Alkeraye S. The Clinical Characteristics of Patients with Ocular Cicatricial Pemphigoid in a Tertiary Eye Hospital in Riyadh, Saudi Arabia. EC Ophthalmology. 2021; 12:03 - 9.
13. Bevans SL, Parker J, Ivey JM, Pavlidakey P, Sami N. Rituximab as an adjuvant rescue treatment for ocular cicatricial pemphigoid. Cornea. 2021 Nov 1;40 (11):1440-4.
14. Khan HM, Wirth M, Dolman PJ, Yeung S, Iovieno A. Long-term Outcomes of Rehabilitative Surgery in Ocular Cicatricial Pemphigoid and Drug-induced Pseudo-Pemphigoid. Investigative Ophthalmology & Visual Science. 2022 Jun 1;63 (7):3989-A0269.
15. Fremont F, Pelissier-Suarez C, Fournié P, Porterie M, Thevenin A, et al. Clinical characteristics and outcomes of ocular cicatricial pemphigoid: a cohort study and literature review. Cornea. 2019 Nov 1;38 (11):1406-11.
16. Ma L, You C, Hernandez M, Maleki A, Lasave A, Schmidt A, et al. Management of ocular cicatricial pemphigoid with intravenous immunoglobulin monotherapy. Ocular Immunology and Inflammation. 2019 May 19; 27 (4):636-42.
17. Ahmed M, Zein G, Khawaja F, Foster CS. Ocular cicatricial pemphigoid: pathogenesis, diagnosis and treatment. Progress in retinal and eye research. 2004 Nov 1;23 (6):579-92.
18. Tauber J, de la Maza MS, Foster CS. Systemic chemotherapy for ocular cicatricial pemphigoid. Cornea. 1991 May 1;10 (3):185-95.
19. Ahuero AE, Jakobiec FA, Bhat P, Ciralsky JB, Papaliodis GN. Paraneoplastic conjunctival cicatrization: two different pathogenic types. Ophthalmology. 2010 Apr 1;117 (4):659-64.
20. Bedell AJ. Ocular pemphigus: a clinical presentation of kodachromes. Transactions of the American Ophthalmological Society. 1964; 62:109.
21. Kirzhner M, Jakobiec FA. Ocular cicatricial pemphigoid: a review of clinical features, immunopathology, differential diagnosis, and current management. InSeminars in ophthalmology. 2011 Sep 1;26 (4-5):270-277.