Progress in etiology, diagnosis, and treatment of idiopathic orbital inflammatory diseases

Ward Rogier Bijlsma

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Progress in etiology, diagnosis, and treatment of idiopathic orbital inflammatory diseases

Vorderingen in etiologie, diagnose en behandeling van idiopathische orbitale ontstekingsziekten
(met een samenvatting in het Nederlands)

proefschrift

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Voor Rhodé,
voor je steun en
je vertrouwen

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Chapter 1

General introduction and aims of the study

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Introduction

Definition

In 1905 Birch-Hirchfield described the first patients with an orbital mass in whom on orbital biopsy a mixed inflammatory infiltrate was found without any signs of tumor growth.[1] Because of the clinical resemblance to an orbital tumor the term orbital *pseudotumor* was coined. This term led to confusion on the nature of the disease for both patients and doctors. A more descriptive term of idiopathic orbital inflammation (IOI) was proposed by Kennerdell and Dresner to describe this heterogeneous group of orbital inflammatory lesions.[2]

Impact

IOI can have a major impact on quality of life due to disfiguring facial appearance, intractable pain, reduced visual function, diplopia, and side effects of treatment. Often, long-standing treatment with systemic corticosteroids is needed to control symptoms and signs. Although rare, IOI may result in blindness, especially in patients with sclerosing inflammation (19%).[3]

Epidemiology

Idiopathic orbital inflammation is an uncommon disease from a population perspective, with no true incidence published. However, in a tertiary orbital referral center, IOI is seen rather commonly. Rootman found that IOI makes up 6.5% of orbital diseases at the University of British Columbia orbital clinic, coming next after Graves' ophthalmopathy that makes up 51.7% of orbital disease.[4] Yuen found an IOI incidence of 6% in another tertiary clinic in Boston.[5] Arguably, orbital lymphoma is currently taking this second place of most frequently encountered orbital diseases.[6] IOI develops mostly in adults with pediatric cases accounting for only 11%.[4] IOI is equally common in men and in women. The average age at onset is 47 years.[7] Co-occurrence has been described between IOI and autoimmune diseases such as reumatoid arthritis, lupus, and inflammatory bowel disease.[8]

Presentation

Depending on the localisation, IOI presents with one or more of the classic symptoms and signs of inflammation: rubor, dolor, calor, tumor, and functio laesa. Common presenting symptoms are pain and diplopia.[5] Common presenting signs are periorbital swelling and redness, proptosis, and motility dysfunction. In most cases one orbit is affected but the disease may present bilateral concurrently in 8%,

or subsequently in 14%.[5;7] The presentation is acute over days in a third, or subacute or chronic in the remainder.[7]

Diagnosis

IOI is a diagnosis of exclusion after other identifiable local or systemic causes have been eliminated.[5] The diagnostic work-up to exclude identifiable causes consists of history taking, orbital imaging, laboratory testing, and in selected cases orbital biopsy.

Imaging

Computed tomography (CT), magnetic resonance imaging (MRI), and ultrasonograpy (US) have all been described as imaging modalities for IOI.[5] In the majority of cases CT imaging is used to show the localization and extent of inflammation. CT will show inflammatory changes in various orbital structures such as sclera, lacrimal gland, extraocular muscles, orbital fat, and optic nerve.[9] Variable enhancement is seen after administration of contrast. MRI imaging is advocated in suspected involvement of the cavernous sinus.[10]

Laboratory testing

No single laboratory test is available to diagnose IOI, but rather laboratory testing is used to exclude other, more specific diagnoses such as Graves ophthalmopathy, infection, sarcoidosis, and Wegener's granulomatosis. Gordon suggests the following diagnostic panel for IOI: complete blood cell count, erythrocyte sedimentation rate, C-reactive protein, anti-nuclear antibody screen, anti-neutrophil cytoplasmic antibody, rheumatoid factor, serum protein electrophoresis, angiotensin-converting enzyme, thyroid function studies, and anti-thyroid antibodies.[11]

Biopsy

The place of orbital biopsy in the diagnostic work-up of IOI has been controversial. Biopsy rates of IOI range widely from 29% to 73% reflecting this controversy about biopsy.[5;7] Early reports describe exacerbation of the condition and biopsy-related complications of ptosis, extraocular muscle paresis, and vision loss.[7;12;13] These complications have not been reconfirmed in the last decades.[14;15] As in all medical decisions, a judgment should be made on the risks and possible benefits of orbital biopsy. Probably, only apical or optic nerve lesions should be left unbiopsied.[16]

Fine-needle aspiration biopsy is performed in IOI but mainly to make a distinction between malignant and non-malignant lesions.[17;18] In IOI, the number of cells obtained by needle aspiration is often insufficient to allow for histological typing.

Pathology

The classical histologic pattern of IOI is a chronic inflammatory infiltrate with small, well-differentiated mature lymphocytes, admixed with plasma cells, neutrophilic, and eosinophilic granulocytes, and occasional histiocytes and macrohpages.[19] Non-classical patterns show disproportional interstitial connective tissue (called sclerosing inflammation), granulomatous inflammation, vasculitis, or predominant eosinophilia.

Differential diagnosis

Diagnostic work-up of patients suspected of having IOI is targeted at excluding other orbital inflammatory, infectious or neoplastic causes. Rootman divides orbital inflammatory conditions in specific and nonspecific, where a specific orbital inflammatory condition is well described.[4] The group of specific orbital inflammations include Graves' ophthalmopahty, sarcoidosis, Sjögren's syndrome, systemic lupus, Wegener's granulomatosis, Melkersson-Rosenthal syndrome, and adult xanthogranulomatous disease. Rootman includes idiopathic sclerosing inflammation in this category because of its distinct clinicopathologic entity.[3] The distinction between specific and nonspecific idiopathic orbital inflammation is important because for the former more specific treatment protocols exist. The most common neoplastic lesions affecting the orbit are lymphomas. Reactive lymphoid hyperplasia and atypical lymphoid hyperplasia are in many respects similar to lymphoma but can be differentiated from IOI with immunophenotypic and molecular-genetic analyses.[2;20]

Treatment

Various treatment modalities are in use with varying success rates. Only a minority of patients do well *without treatment*.[5;7] The main treatment of IOI consists of a trial of high-dose *oral corticosteroids* (1 mg/kg prednisone) with a two month taper.[5;7;21] The effect of corticosteroids is variable with initial response in two-thirds, but with recurrences in half of patients and long-term steroid dependence in some. Infrequently, corticosteroids have been used as local therapy and intravenously.[22;23] Other treatment options that can be given as monotherapy or in addition to corticosteroids are immunosuppressives, radiotherapy, and surgical

excision.
Immunosuppressives used are non-steroidal anti-inflammatory drugs[24], methotrexate[25;26], azathioprine[27], cyclosporin[28;29], cyclophosphamide[30], mycophenolate mofetil[31], and the newer biologicals adalimumab[32], infliximab[33], and rituximab.[34] No specific preference for any of these immunosuppressives exists.
Radiotherapy is mainly used in recurrent inflammation or when corticosteroids fail. In a subset of patients in whom corticosteroids had failed, the response to radiotherapy was about 75%.[35;36]
Surgical excision is mainly used in lacrimal gland inflammation[37] or intractable pain.[46]

Prognosis
Treatment results in complete symptom relief in 63% of patients.[5] However, 35% of patients experience only partial relief and are left with persistent motility dysfunction, pain, or visual loss. In 2% of patients treatment is ineffective. Of patients who experience relief, one-third have recurrence of disease at the same or a different location.[8]

Challenges
Many challenges about IOI remain:
- Do infectious triggers initiate IOI?
- Does the diagnosis of Graves' ophthalmopathy exclude the diagnosis of IOI?
- How do we differentiate between IOI and Wegener's granulomatosis?
- Can we classify the mixed group of IOI in specific subtypes that are helpful for therapy or research?
- Are intravenous steroids effective in treating severe IOI?
- Why do one in three patients not respond to corticosteroids?
- Why does IOI recur in half of patients after withdrawal of systemic steroids?
- Is a combination of prednisone and an immunosuppressive effective in treating patients with severe orbital inflammation?

Outline of the thesis

This thesis tries to solve some of the aforementioned challenges of IOI.

Etiology

As the term idiopathic in the name IOI implies, little is known about the origin of the disease. Research has not helped in solving this question for the majority of orbital inflammations. Case reports describe environmental factors that could attribute to the development of IOI.[39-42] Associations have been described between IOI and other systemic autoimmune diseases that may point us to a common autoimmune etiology.[19;43] Infectious triggers have been reported that may initiate the disease.[44-47] The unrestricted growth of some orbital lesions suggests a neoplastic origin.[48]

Risk factors involved in the development of IOI were studied in a case control study. Sixty nine patients and 269 controls from 3 academic orbital centers responded to a six-page questionnaire. The Odds ratio for a variety of risk factors was calculated and repeated with an imputed dataset to obtain more precise values (Chapter 2).

The possibility of an infectious trigger as initiator for IOI was researched by obtaining fresh biopsy specimens from IOI patients. These specimens were tested for remnants of infectious entities using PCR. Twenty one biopsies of IOI patients and 22 of control patients were tested and compared(Chapter 3).

Clinically, it was observed that IOI and Graves' disease occur both in some patients. The definition of IOI being a diagnosis after exclusion of other local or systemic diseases was challenged. In our institution, four patients could be identified that were both diagnosed with IOI and Graves'. The clinical course of these patients was described (Chapter 4).

Diagnosis

Diagnostic challenges arise from the current definition of IOI as an orbital inflammatory lesion after exclusion of identifiable causes. No consensus exists on the diagnostic approach and the extent one should go to exclude identifiable causes. A stepwise algorithm to diagnose IOI in clinical practice is presented. This algorithm was evaluated using retrospective data of 117 patients with an orbital inflammation for whom a diagnostic problem existed. The role of orbital biopsy in the diagnosis of IOI was evaluated (Chapter 5).

Orbital Wegener's granulomatosis can have a devastating clinical course that can only be prevented by appropriate, aggressive therapy. Therefore, it is important to differentiate this specific orbital inflammation from IOI. The diagnostic process of 15 orbital Wegener's, 6 sarcoidosis, and 11 IOI patients was evaluated and a diagnostic approach was recommended (Chapter 6).

Heterogeneity of the IOI group has impeded research on etiology, treatment

effectiveness, and prognosis of IOI. By classifying IOI into more homogenous subtypes, research is expected to provide more consequent results. To determine a best practice classification system, a systematic literature search was performed for existing classification systems and a new multidimensional classification system was proposed. Next this new classification system was tested for reliability, feasibility, face validity, content validity, and distinction using clinical data of 84 IOI patients (Chapter 7).

Therapy

Treatment of IOI with oral prednisone is still unsatisfactory because of persistent symptoms and the high recurrence rate after discontinuation. Especially in this time of targeted medical therapy, the universal treatment of IOI with high-dose oral prednisone seems coarse. Over the past years, a trend was noted of using intravenous methylprednisolone pulse (IVMP) therapy for severe IOI. The rationale for pulse therapy is an overall reduction in treatment duration. To research if this purported effect of IVMP is realized in IOI, a retrospective study was conducted. A group of prednisone treated IOI patients was divided into mild and severe cases. In the group of severe disease 12 patients had been treated with IVMP and 15 patients with only oral prednisone. These patients were compared for treatment duration, outcome, and side-effects (Chapter 8).

Some IOI patients need prolonged immunosuppressive therapy. Prednisone is known for its long-term side effects and other agents are preferred in such cases. Immunosuppressive therapy was evaluated for 13 patients with adult periocular and orbital xanthogranulomatous disease, a severe orbital inflammatory condition. Specific attention was given to the combination of prednisone and azathioprine treatment (Chapter 9).

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Chapter 2

Risk factors for idiopathic orbital inflammation: a case-control study

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Abstract

Objective: To identify risk factors involved in the development of idiopathic orbital inflammation (IOI).

Methods: Case–control study of 69 adults who had had a first episode of IOI and 296 adult controls with rhegmatogenous retinal detachment (RD) selected from three orbital centres in The Netherlands between 2000 and 2006. Participants filled out a questionnaire on demographic factors, medical history, health status and exposures for the two years prior to disease presentation. In addition, women were questioned about previous or current pregnancies and their hormonal status. Odds ratios (ORs) and accompanying 95% CIs for IOI in relation to potential risk factors such as body mass index (BMI), bisphosphonates and autoimmune disease were estimated. ORs were adjusted for age, sex, socio-economic status, smoking and blunt orbital trauma using logistic regression. Analyses were carried out both with and without multiple imputation of missing values.

Results: The risk of IOI was increased in participants who had a higher BMI (third vs first tertile: OR, 2.88; 95% CI 1.32 to 6.32) and in participants who used bisphosphonates (OR 8.68; 95% CI 1.16 to 65.0). The risk was decreased in participants with a higher socio-economic status (third vs first tertile: OR 0.38; 95% CI 0.17 to 0.84) and in women who were older at first childbirth (third vs first tertile: OR 0.14; 95% CI 0.03 to 0.64). An almost significant association was found for IOI and autoimmune disease (OR 2.56; 95% CI 0.93 to 7.05).

Conclusions: IOI is associated with lower socio-economic status, higher BMI and use of oral bisphosphonates. In women, IOI is also associated with younger age at first childbirth.

Introduction

Idiopathic orbital inflammation (IOI) is among the most frequent orbital diseases encountered by ophthalmologists.[1] IOI is a non-infectious inflammation of the orbital soft tissues for which no cause is found after local and systemic evaluation.[2] The term IOI refers to a collection of different entities, including idiopathic sclerosing orbital inflammation,[3] idiopathic granulomatous orbital inflammation,[4] dacryoadenitis[5] and orbital myositis,[6] which makes patients with IOI an inhomogeneous patient population.

IOI presents with various signs and symptoms of inflammation, most frequently pain, eyeball motility disturbances and proptosis.[2] Due to the orbital soft tissue swelling, IOI may mimic a neoplasm ('orbital pseudotumour' is the historical term for IOI). The clinical course of IOI ranges from mild and self-limiting to devastating orbital sclerosis with blindness.[2]

IOI, as is indicated by the word 'idiopathic' in the disease name, is of unknown etiology. Many case reports and series have highlighted possible etiological factors for IOI, including autoimmune diseases[7] and medications such as bisphosphonates,[8] lithium[9] and chemotherapeutics.[10] Retroperitoneal fibrosis is a systemic disease entity that is similar in many respects to IOI.[11] Ergot derivatives,[12;13] asbestos[14] and a genetic predisposition[15] have been reported as risk factors for retroperitoneal fibrosis.

To our knowledge, systematic research of the risk factors for IOI has not been previously conducted. In this case–control study, we explore associations between a number of risk factors and IOI.

Methods

This study was designed as a case–control study.

Our patients came from three orbital clinics in The Netherlands between 2000 and 2006. Patients with IOI were identified by searching the hospital diagnosis database for ICD-9 code 376.1. ICD-9 code 376.0, which was primarily used for orbital infection, was excluded.

Patient records were reviewed, and patients with all of the following three criteria were included in the study: (1) a clinical picture of orbital inflammation with either no improvement after antibiotic therapy and prompt improvement after systemic prednisone, or non-specific inflammation after an orbital tissue biopsy; (2) no local or systemic identifiable cause of the inflammation; and (3) age 18 or older and residing in The Netherlands. For example, sarcoidosis, lupus and Wegener

granulomatosis were excluded as causes of IOI. Only patients who had had a first episode of IOI were included in the study. The localisation of IOI was determined by reviewing radiology images and was categorised as localised myositis, localised dacryoadenitis or diffuse inflammation. Histology reports, when available, were reviewed and classified as classic, sclerosing or granulomatous inflammation.[7] Laterality and corticosteroid treatment were recorded.

For the controls, adults who had had a first episode of a rhegmatogenous retinal detachment (RD) were identified using the hospital surgical database. For each patient with IOI, we randomly selected four controls who had been diagnosed as having RD in the same hospital and in the same year and month as the patient. Hospital-based controls were chosen for availability, similar geographic area, high response rate and similar recollection of information. These controls were considered to be a good representation of the study base. Moreover, rhegmatogenous RD was considered to be of mechanical aetiology and expected to share none or few aetiological factors with IOI.

Institutional review board approval was given for this study, which adhered to the tenets of the Declaration of Helsinki.

A six-page questionnaire was sent to all patients and controls. The questionnaire collected information on sex, age at diagnosis, body mass index (BMI) at diagnosis, smoking status (current, former, never), pack years of smoking, diabetes (yes/no) and average number of days with flu or colds per year. Socio-economic status was determined by the highest educational level of the participant (primary school, secondary school, professional education, higher education) and, when the information was available, by the highest educational level of the participant's partner. To determine whether an autoimmune disease was or had been present, participants were asked to describe prior inflammation of the orbit, muscles, joints, skin, connective tissue, neural tissue, intestines, kidneys, lungs and/or thyroid up to the time of the questionnaire. An immunologist determined whether the self-reported inflammation was consistent with autoimmune disease.

The following questions were asked about the two years preceding the diagnosis of RD or IOI, all defined as yes/no variables: any occurrence of blunt trauma to the orbit; any surgery of the orbit, sinuses or facial bones; any use of bisphosphonates, ergot derivatives, lithium, chemotherapy or thyroid hormones; any exposure to asbestos or lysergic acid diethylamide (LSD); or any reported physical or emotional distress. In addition, participants were asked if any siblings, parents or grandparents had ever had any orbital inflammatory disease, lupus, thyroiditis, myasthenia gravis, uveitis or diabetes mellitus. Women were asked about the number of pregnancies, age at birth of their first child, use of oral contraceptives or hormone-replacement therapy during the 2 years preceding diagnosis, menopausal

status at disease development and age at menopause, if applicable. A time period of 2 years before the onset of the disease was chosen for adequate recall and to look at relative short-term effects of potential aetiological factors.
One reminder was sent to participants who did not respond to the first request. The response forms were checked for sex and age to identify forms that were not filled out by the intended individual. Nonmatching forms were excluded. Response forms were entered into a database and analysed using statistical software (SPSS for Windows 15.0 (SPSS, Chicago, Illinois) and R 2.6.0 for Windows, R Development). Characteristics of responders and non-responders were compared. Continuous variables were categorised into tertiles. Using complete case analysis, ORs and accompanying 95% CIs were computed to describe the associations between risk factors and the occurrence of IOI. Multivariate analysis was performed using binary logistic regression to adjust relationships for age (continuous), sex, tertiles of socio-economic status, pack-year tertiles of smoking and blunt orbital trauma because adjustment for these variables changed the ORs more than 10%.
Multivariate analysis was repeated on a multiple imputed dataset to obtain more precise and valid measures of association for variables with missing values.[16] Multiple imputation was chosen because of its wide applicability to almost any statistical situation.[17] The pattern of missing values was evaluated and considered missing at random. For each missing value, 10 imputations were performed using between six and 19 best-correlated variables, including the outcome.[18] Imputation was carried out in R (with the aregImpute function in library 'Hmisc').

Results

Questionnaires were sent by mail to 103 patients and 410 controls. Two questionnaires to controls under the age of 18 were not sent because of their age. Sixty-nine patients (67%) and 295 controls (72%) returned the questionnaires after two mailings. Of the non-responders, 16 (all controls) had died, and 16 (four patients; 12 controls) had moved without providing a new address. Patients who responded were somewhat older than patients who did not respond (average age, 52.6 years vs 49.0 years) (table 1.1). Response rates of patients and controls differed somewhat between clinics (patients from clinic B responded less) and between years of diagnosis (controls diagnosed between 2002 and 2003 responded less).

The patients with IOI were categorised as follows: 17 with isolated myositis, 19 with isolated dacryoadenitis and 33 with diffuse inflammation. Biopsies showed

Table 1.1. Characteristics of responders and non-responders among patients and controls

	Patients					**Controls**				
	Responders (n=69)		**Nonresponders** (n=34)		*P* -Value*	**Responders** (n=295)		**Nonresponders** (n=115)		*P*-Value*
Age, mean (SD), y	52.6	(13.4)	49.0	(14.6)	.224	59.6	(11.8)	60.7	(15.6)	.465
Male sex	29	(42%)	13	(38%)	.832	190	(64%)	73	(64%)	.909
Orbital clinic					.116					.204
A	12	(17%)	8	(24%)		53	(18%)	26	(23%)	
B	24	(35%)	17	(50%)		125	(42%)	38	(33%)	
C	33	(48%)	9	(26%)		117	(40%)	51	(44%)	
Years of diagnosis					.676					.005
2000-2001	8	(12%)	3	(9%)		30	(10%)	14	(12%)	
2002-2003	16	(23%)	7	(21%)		54	(18%)	38	(33%)	
2004-2005	23	(33%)	9	(26%)		102	(35%)	26	(23%)	
2006-2007	22	(32%)	15	(44%)		109	(37%)	37	(32%)	

**P*- values calculated by $\chi 2$ test.
SD standard deviation, y year

classic inflammation in 21, sclerosing in eight and granulomatous in two patients. Five patients had bilateral orbital involvement. Fifty-one patients were treated with corticosteroids.

The mean (SD) age at diagnosis of the patients with IOI was 52.6 (13.4) years. For controls with RD, the mean (SD) age was 59.6 (11.8) years. The male-to-female ratio was 2:3 in patients with IOI and 7:4 in controls with RD.

Potential risk factors for IOI are described for patients and for controls in table 1.2. Patients with IOI were younger, more often female and of lower socio-economic status. In the multivariate analysis, we adjusted the effect of other potential risk factors for the confounding effect of age (continuous variable), sex and socio-economic status (tertiles). In addition, we adjusted for pack years (tertiles) of smoking and for blunt trauma to the orbit.

The risk of IOI was lower for those with higher socio-economic status (third vs first tertile: adjusted OR, 0.36; 95% CI 0.16 to 0.81). The risk increased with higher BMI (third vs first tertile: adjusted OR 2.88; 95% CI 1.32 to 6.32). Use of bisphosphonates was associated with IOI (adjusted OR 8.68; 95% CI 1.16 to 65.0) with imprecision due to low absolute numbers of bisphosphonate users. The association between bisphosphonate use and IOI persisted in the stratum of postmenopausal females (adjusted OR 9.29; 95% CI 1.98 to 72.0), after additional adjustment for female hormone supplements (adjusted OR 9.35; 95% CI 1.21 to 72.5). A trend for association between IOI and autoimmune disease was found, although it was not statistically significant (adjusted OR 2.56; 95% CI 0.93 to 7.05). Female patients were more often premenopausal at diagnosis than female controls, but this association disappeared after adjustment for age, socio-economic status, smoking and trauma (adjusted OR 1.07; 95% CI 0.22 to 5.19). For women who had given birth, a higher age at first childbirth was associated with a lower risk of IOI (third vs first tertile: adjusted OR 0.15; 95% CI 0.03 to 0.72). The other variables in table 1.1 did not show a clear relationship with IOI. Little seasonal variation of IOI presentation was found, with 26% presenting in winter, 22% in spring, 25% in summer and 28% in autumn.

Multiple imputation changed the association measures on average by 16.5% to a weaker association in 23 variables and a stronger association in 12 variables.

Discussion

In this study, risk factors for the development of IOI are evaluated by comparing patients with IOI to controls with RD. We found a significant association between

Table 1.2. Risk factors for patients with idiopathic orbital inflammation and controls with retinal detachment

	Cases (n=69)		**Controls** (n=295)			**adjusted OR***		**adjusted, multiple imputed OR***	
Variable	N observed	%	N observed	%	*P*-value**	OR	95% CI	OR	95% CI
Demographics									
Male sex	28	40.6	189	63.9	0.001	0.33	0.18-0.63	0.31	0.17-0.57
Age at diagnosis, y					<0.001				
21-54	35	50.7	93	31.4		1.00	[Reference]	1.00	[Reference]
55-64	24	34.8	99	33.4		0.54	0.27-1.08	0.52	0.27-0.99
65-88	10	14.5	104	35.1		0.20	0.08-0.48	0.17	0.08-0.40
Socioeconomic status***					0.091				
Tertile #1	22	31.9	84	28.7		1.00	[Reference]	1.00	[Reference]
Tertile #2	25	36.2	76	25.9		0.87	0.39-1.94	0.89	0.42-1.87
Tertile #3	22	31.9	133	45.4		0.36	0.16-0.81	0.37	0.17-0.79
Body mass index[#]					0.090				
Tertile #1	17	24.6	104	35.9		1.00	[Reference]	1.00	[Reference]
Tertile #2	22	31.9	97	33.4		1.86	0.83-4.17	1.66	0.78-3.54
Tertile #3	30	43.5	89	30.7		2.88	1.32-6.32	2.49	1.21-5.16
Exposures									
Smoking[##]					0.461				
never	23	34.3	105	35.8		1.00	[Reference][#]	1.00	[Reference][#]
former	25	37.3	125	42.7		1.59	0.80-3.18	1.61	0.80-3.21
current	19	28.4	63	21.5		1.40	0.65-3.01	1.38	0.64-2.97

Table 1.2. (Continued)

	Cases (n=69)		**Controls** (n=295)			**adjusted OR***		**adjusted, multiple imputed OR***	
Variable	N observed	%	N observed	%	*P*-value**	OR	95% CI	OR	95% CI
Pack years of cigarette smoking					0.782				
0	23	38.3	106	43.1		1.00	[Reference]	1.00	[Reference]
1-15	16	26.7	59	24.0		1.67	0.77-3.66	1.67	0.76-3.71
16-110	21	35.0	81	32.9		1.74	0.83-3.65	1.71	0.78-3.72
Medication use									
bisphosphonates	6	8.8	4	1.4	0.004	8.68	1.16-65.0	9.23	1.93-44.2
ergot derivatives	1	1.5	4	1.4	0.653	1.57	0.14-17.7	1.60	0.14-17.7
lithium	0	0.0	4	1.4	0.430				
chemotherapy	1	1.5	3	1.0	0.566	2.05	0.08-54.5	0.80	0.06-10.4
thyroid hormones	2	2.9	7	2.4	0.533	1.52	0.28-8.32	1.47	0.27-7.96
Environmental exposure									
asbestos (any)	7	10.3	42	14.5	0.437	1.36	0.49-3.82	1.22	0.47-3.16
LSD	0	0.0	0	0.0	1.000				
physical or emotional distress	19	27.5	75	25.9	0.763	0.86	0.43-1.72	0.93	0.48-1.79
Health status									
Past medical history									
autoimmune disease	8	12.3	16	5.5	0.058	2.56	0.93-7.05	2.48	0.90-6.85
diabetes	5	7.7	28	9.7	0.814	1.10	0.37-3.28	1.01	0.34-2.95
blunt trauma to orbit	2	2.9	17	5.8	0.547	0.34	0.07-1.67	0.32	0.07-1.56

Table 1.2. (Continued)

	Cases (n=69)		**Controls** (n=295)			**adjusted OR***		**adjusted, multiple imputed OR***	
Variable	N observed	%	N observed	%	*P*-value**	OR	95% CI	OR	95% CI
surgery of orbit, sinuses or facial bones	2	2.9	4	1.4	0.324	2.90	0.32-26.4	2.58	0.33-20.3
Family history (first-third degree relatives)									
orbital inflammatory disease	2	3.6	9	4.2	1.000	0.85	0.16-4.58	0.70	0.14-3.60
lupus	3	5.4	8	3.7	0.703	1.64	0.39-6.97	1.87	0.43-8.07
thyroiditis	7	12.5	16	7.5	0.280	1.58	0.55-4.55	1.50	0.53-4.24
myasthenia	2	3.6	10	4.7	1.000	0.62	0.12-3.37	0.70	0.13-3.91
uveitis	0	0.0	3	1.4	0.607				
diabetes	29	51.8	92	43.0	0.291	1.49	0.75-2.96	1.22	0.67-2.21
Flu or cold days per year					0.984				
0-4	25	40.3	112	38.6		1.00	[Reference]	1.00	[Reference]
5-8	18	29.0	84	29.0		0.95	0.43-2.07	0.81	0.39-1.70
9-200	19	30.6	94	32.4		0.91	0.42-1.98	0.85	0.41-1.75
For women									
Pregnancies (number)					0.235				
0	6	14.6	13	12.4		1.00	[Reference]	1.00	[Reference]
1-2	24	58.5	48	45.7		0.93	0.20-4.32	1.59	0.43-5.91
3-12	11	26.8	44	41.9		0.44	0.09-2.26	0.72	0.17-2.97
Female hormone supplement	13	33.3	21	19.8	0.121	0.67	0.20-2.21	0.83	0.27-2.51
Postmenopausal	24	58.5	92	86.8	<0.001	1.07	0.22-5.19	0.92	0.22-3.88

Table 1.2. (Continued)

	Cases (n=69)		**Controls** (n=295)			**adjusted OR***		**adjusted, multiple imputed OR***	
Variable	N observed	%	N observed	%	*P*-value**	OR	95% CI	OR	95% CI
For postmenopausal women									
Age at menopause , y					0.195				
27-46	4	19.0	29	40.3		1.00	[Reference]	1.00	[Reference]
47-51	10	47.6	25	34.7		4.85	0.94-24.9	3.15	0.79-12.5
52-58	7	33.3	18	25.0		3.35	0.69-16.8	2.12	0.49-9.11
For women with children									
Age at birth first child, y					0.141				
14-24	26	63.4	49	46.2		1.00	[Reference]	1.00	[Reference]
25-27	9	22.0	28	26.4		0.79	0.23-2.71	0.72	0.24-2.23
28-36	6	14.6	29	27.4		0.15	0.03-0.72	0.26	0.07-0.96

BMI body mass index; CI, confidence interval; IOI, idiopathic orbital inflammation; LSD, lysergic acid diethylamide; OR, odds ratio; RD, retinal detachment

* adjusted for gender, age (continuous), social economic status, packyears of smoking, and blunt trauma to the orbit; however, gender, age, social economic status, packyears, and blunt trauma to the orbit are adjusted for 4 of 5 variables

** *P*-values calculated using Chi-square test

*** Tertile 1 Education < age 16 years, Tertile 2 Education age 17-18 years, Tertile 3 Education > age 18 years

[#] Tertile 1 BMI < 23.7, Tertile 2 23.7≤ BMI < 26.6, Tertile 3 BMI ≥ 26.6

[##] smoking is not adjusted for packyears because of high correlation between the variables

IOI and sex (female), age (younger), socio-economic status (lower), BMI (higher), use of bisphosphonates and age at birth of first child (younger). The association between autoimmune disease and IOI was almost statistically significant.
In the IOI group, there were relatively more females (61%) than in the RD group (39%), and the patients with IOI were, on average, 7 years younger than the controls with RD (mean age 53 and 60 years, respectively). These differences highlight the different demographic features of IOI and RD, where RD is associated with male sex and older age.[19]
We used the highest level of education of the patient and of their partner as a surrogate variable for socio-economic status. RD has been associated with a lower education level (education beyond age 16 years: OR 0.6; 95% CI 0.3 to 1.1).[19] This association may be explained by ocular trauma as a cause of RD (10% in a large survey of RD[20]; it was 6% in our study), and a higher risk of ocular trauma in craftsmen. However, in our study, we found lower educational levels to be associated with IOI as well, even after adjusting for ocular trauma.
As is known from clinical practice, a higher BMI was associated with IOI. The BMI was calculated from height and weight at diagnosis of IOI and, therefore, should not have been affected by the use of corticosteroids. The relation between metabolic regulation and the immune system has been of interest in recent research. Obesity is associated with a chronic inflammatory response. In obesity, the inflammatory response appears to be triggered and reside predominantly in adipose tissue. The high orbital fat content in obese patients may explain why inflammatory diseases occur in the orbit.[21] Leptin is thought to be central to the link between obesity and autoimmunity because leptin is secreted by adipocytes and can trigger the production of proinflammatory and pathogenic cytokines.[22]
The cases of three patients who developed IOI after administration of intravenous bisphosphonates have been reported.[8;23] The proposed mechanism of action is the release of the inflammatory cytokines IL-1 and IL-6 triggered by bisphosphonates. The prevalence of bisphosphonate use in the population is low (it was 2.8% in our study). Therefore, the association between bisphophonate use and IOI will not have major clinical consequences.
We decided to look at the role of female hormones in IOI because of the intimate relationship between hormones and the immune system. Oestrogens are implicated as enhancers of humoural immunity, and androgens and progesterone are natural immune suppressors.[24;25] We looked for higher oestrogen levels in patients with IOI, which is suggested by a small female predilection and higher age at menopause.[24] However, the observation of a lower number of pregnancies in patients with IOI, when oestrogens are high, does not support an aetiological role of high oestrogens in IOI. The statistically significant association between the lower

age at first childbirth and IOI suggests that female hormones play a role in IOI, but it is not clear how this relates to oestrogens and progesterone. Lower age at first childbirth may also be a risk indicator of risk factor clustering, as occurs with breast cancer.[26]

An association between IOI and autoimmune diseases was postulated by Mombaerts and Koornneef,[27] who found that 10% of patients with IOI had a concurrent autoimmune disease. We found concurrent autoimmune diseases in 12% of patients with IOI (OR 2.56; 95% CI 0.93 to 7.05). Although the association was not statistically significant, it is suggestive of an autoimmune pathogenesis in IOI. A genetic predisposition, or a disregulated immune system with autoantibodies against multiple self-antigens could explain the high co-occurrence of IOI with autoimmune diseases.

Of the proposed possible risk factors, we did not find an association between IOI and ergot derivatives, lithium, LSD, chemotherapy, asbestos, trauma or family history. The equal number of days patients with IOI and controls with RD had flu or colds suggests that they had similar immune system functioning.

A case–control study is implicitly limited in that only associations can be described, but no causality inferred. The quality of such a study is highly dependent on the selection of controls. In this study, it is not possible to draw conclusions about common risk factors between IOI and RD. Because RD is caused by posterior vitreous detachment, we thought RD unlikely to be associated with risk factors other than age, sex and ocular trauma. We did not use a control group of healthy volunteers because we expected an unacceptable low response rate. A cohort design was considered inefficient because of the long inclusion time of 7 years.

By selecting all patients with IOI (some who were not histologically confirmed), we have selected a heterogeneous group of diseases. This will likely dilute associations of risk factors that are specific for subgroups like dacryoadenitis and myositis. However, the sample size is too low for subgroup analysis. Limiting the study to histologically confirmed patients would have introduced a selection bias and would have yielded a lower number of cases.

Recall bias due to the retrospective nature of this study was considered to have influenced both patients and controls in equal amounts. The effect of missing values was evaluated by using multiple imputation. Multiple imputations caused the associations to attenuate in a majority of variables. A group of variables that was largely affected by multiple imputations were variables measured only on females, which is probably due to the lower number of observations. Multiple imputations did not alter the conclusions but might have resulted in more valid and precise effect estimates.[16]

In conclusion, this study describes the first systematic search for risk factors for IOI.

Novel and statistically significant associations with IOI are found between lower socio-economic status, higher BMI, use of oral bisphosphonates and a lower age at first childbirth in women. An important and almost statistically significant association has been found between autoimmune diseases and IOI.

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Chapter 3

Detection of infectious entities in idiopathic orbital inflammation biopsies

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Abstract

Purpose: to determine whether infectious agents are involved in the development of idiopathic orbital inflammation (IOI).

Study design: experimental study.

Methods: orbital biopsies from 21 IOI patients and 22 controls were collected and analysed using polymerase chain reaction (PCR) for a panel of 3 bacteria, 7 DNA viruses and 10 RNA viruses. IOI patients were classified as dacryoadenitis (13), diffuse (7), and myositis (1).

Results: Epstein-Barr virus (EBV) was found in 4 IOI and 2 control patients, Human Herpesvirus-6 (HHV6) in 4 IOI and no controls, and Parvovirus B19 was found in 10 IOI and 10 control patients. In 3 patients 2 viruses were found. There was no correlation between any of these viruses and a specific IOI subtype. Overall, viruses were more often demonstrated in IOI (17/21) than in control (11/22) patients (P =.028, chi-square).

Conclusions: an association between the presence of a viral entity and IOI was found. Positive tests for EBV, HHV6, and Parvovirus B19 suggest that they may be involved in the development of IOI.

Introduction

Idiopathic orbital inflammation (IOI) is a poorly understood disease that can cause symptoms of pain, proptosis, and diplopia .[1] The condition is considered of non-infectious origin and a diagnosis is only made after exclusion of a neoplasm, primary infection, and systemic disorders. However, a recent history of upper respiratory tract infection prior to development of IOI is not uncommon.[2;3] Histological examination of IOI biopsies shows a mixed inflammatory infiltrate, but the origin of this infiltrate is still unclear.[4] It has been postulated that IOI is caused by an auto-immune response that develops after an infectious trigger.[5] This was supported by the demonstration of cell wall-deficient bacteria in leukocytes of patients with chronic IOI,[6] the close time-relationship between upper respiratory tract infection and the myositis subtype of IOI,[7-9] and an association between herpes zoster ophthalmicus and IOI.[10;11] Moreover, idiopathic inflammation in other organ systems has been associated with Epstein-Barr virus (EBV),[12] *Mycoplasma pneumoniae,*[13] *Actinomyces,*[14] *Pseudomonas,*[15] and human herpesvirus-8.[16]

Here we investigated whether IOI may have an infectious origin, using molecular techniques to demonstrate genetic material of a panel of viruses and bacteria in tissue biopsies of patients with IOI and controls. The identification of infectious agents would not only be interesting from an etiological point of view, but may also have therapeutic implications.

Methods

Subjects

Biopsy tissue remains were collected from patients with a presumed diagnosis of IOI who were biopsied to confirm the diagnosis. Biopsies were taken by direct surgical excision through either anterior or lateral orbitotomy. Tissue was flash frozen in liquid nitrogen and stored at -80 degrees Celsius until PCR analysis. Only patients with confirmation of the diagnosis IOI by nonspecific inflammation on histology were included for further research. Controls were patients without IOI who underwent a surgical procedure where orbital tissue was excised that was otherwise discarded. Surgical procedures included orbital decompression for Graves' ophthalmopathy, orbital exenteration for neoplasms, and eyelid surgery with opening of the orbital septum. All patients were informed on the study and consented with use of their tissue. Approval for this study was given by the institutional review board of the University Medical Center Utrecht and the study

adhered to the tenets of the Declaration of Helsinki.

Detection of viruses and bacteria by PCR analysis

The IOI biopsies were analyzed for the presence of *Mycobacterium tuberculosis*, *Mycobacterium genus species*, *Mycoplasma pneumonia*, *Chlamydia pneumonia*, Herpes simplex virus, Varicella zoster virus, Cytomegalovirus, EBV, Human herpes virus 6 (HHV6), Adenoviruses, Parvovirus B19, and the RNA viruses human Coronaviruses OC43, 229E and NL63, Enteroviruses, Influenza viruses A and B, human Metapneumovirus, Parainfluenzaviruses 1 to 4, human Parechovirus, Respiratory Syncytial virus, Rhinoviruses and Rubella virus. Nucleic acid was purified using the MagNA Pure LC DNA Isolation kit III (Bacteria, Fungi) (Roche,Mannheim, Germany) with minor modifications. From the frozen biopsies a section of approximately 2 cubic millimeter was cut, added to 300 ul of Bacteria Lysis buffer and shaken for 1 minute at 6500 rpm in a MagNA Lyser (Roche, Mannheim, Germany). Subsequently, nucleic acid was extracted from a total of 200 ul of pretreated biopsy material using the MagNA Pure LC DNA Isolation kit III according to the instructions. To monitor the quality of the extraction and the subsequent amplification procedure a standard dose of Phocine Herpesvirus type 1 (PhHV-1) and Encephalomyocarditis virus (EMCV) was added to each sample as an internal control prior to extraction. Nucleic acid was collected in a total volume of 400 ul. For detection of RNA viruses, 60 ul of extract was added to 90 ul of reverse transcriptase mix to produce copy DNA (Taqman, reverse transcription reagents, Applied Biosystems, Foster City, CA, USA). The mixture was incubated for 10 minutes at 25ºC and 30 minutes at 48ºC. The cDNA synthesis reaction was stopped by incubating for 5 minutes at 95ºC. Per amplification reaction 10 ul of extracted nucleic acid (for DNA detection) or 10 ul of copy DNA (for RNA detection) was used. Real-time PCR assays were performed as described previously on an ABI Prism 7900 sequence detection system (Applied Biosystems, Branchburg, NJ, USA).[17] Primers and probes have been described previously.[17] In addition, *Mycobacterium tuberculosis* was detected using forward primer 5' GGGTAGCAGACCTCACCTATGT 3' , reverse primer 5' AGCGTAGGCGTCGGTGAC 3' and probe 5' FAM-TCGCCTACGTGGCCTTT-MGBNFQ-TAMRA 3'. For *Mycobaterium genus* species detection a mix of forward primers 5'AGGTACTCGAGTGGCGAACG 3', 5'GGGGTACTCGAGTGGCGAA 3' and 5' GAGATACTCGAGTGGCGAACG 3', reverse primer 5'CGGGCCCATCCCACAC 3 and probe 5' FAM-TATTAGACCCAGTTTCCCA-MGBNFQ-tamra 3' were used. Rubella virus was detected with forward primer 5' GGGAAGTGCGCGATGTTG 3', reverse primer 5' CGTGGAGTGCTGGGTGATC 3' and

probe 5'FAM-AAGCGGGCCATCG-MGBFNQ-TAMRA 3'.

Results

Between 2007 and 2010, biopsy specimens of 21 IOI patients and 22 controls were collected at orbital clinics in Amsterdam, Maastricht, Rotterdam, and Utrecht in the Netherlands. Forty-eight percent of IOI patients and 41% of controls were male. The lacrimal gland was biopsied in 10 IOI patients and 2 controls, and the extraocular muscle in 1 myositis IOI patient. Orbital connective tissue was biopsied in the other patients. The average age was 49 (range 19-67) for the IOI patients and 56 (range 18-88) for the controls. Sixty-two percent of IOI patients were classified as dacryoadenitis (12 with classical histology, 1 sclerosing), 33% as diffuse IOI (6 with classical histology, 1 sclerosing), and 5% as myositis (1 with classical histology). The diagnoses of control patients included 9 Graves' ophthalmopathy, 9 eyelid malposition , 3 neoplasm, and 1 Wegener's granulomatosis.
The results of PCR detection of viruses and bacteria in orbital biopsies of patients with IOI and controls are shown in the table. Overall, in 17 of 21 IOI patients and in 11 of 22 controls viruses could be found (*P*=.028, Chi-square test). No bacteria were found in the biopsies. Parvovirus B19 was found in equal proportions of IOI and control patients (10/21 versus 10/22 respectively). HHV6 was only found in 4 IOI patients and EBV was detected more often in IOI patients (4 versus 2 controls). One control patient was both positive for EBV and Parvovirus B19. Two IOI patients were positive for both HHV6 and Parvovirus B19.

Table 3.1. Viruses found in orbital biopsies of 21 IOI and 22 control patients

Group	Diagnosis		N	EBV	HHV6	Parvo B19	Negative
IOI		total	21	4	4	10	5
	Dacryoadenitis		13	3	1	6	3
	Diffuse		7	1	3	3	2
	Myositis		1			1	
Controls		total	22	2		10	11
	Eyelid malposition		9			6	3
	Graves'		9			3	6
	Wegener's		1	1		1	
	Neoplasm		3	1			2

IOI idiopathic orbital inflammation; EBV Epstein-Barr virus; HHV6 Human Herpesvirus 6

Discussion

The aim of this study was to investigate whether infectious agents may be a trigger for the development of IOI. In tissue biopsies of IOI patients genetic material of a mixed panel of predominantly respiratory viruses and bacteria was detected using the PCR technique. Viruses were significantly more frequently found in orbital biopsies of IOI patients (17 of 21) than of controls (11 of 22). Three theories may explain the association between viruses and autoimmune disease: molecular mimicry, bystander activation, and viral persistence.[18] In molecular mimicry a shared immunologic epitope exists between the microbe and host. In bystander activation a viral infection activates antigen presenting cells to upregulate preprimed autoreactive T cells. In viral persistence viral antigens continuously drive the immune response. Multiple autoimmune diseases have been linked with viral persistence in tissue: giant cell arthritis,[19] systemic lupus erythematosis,[20] myocarditis,[21] and reumatoid arthritis.[22] However, these associations are controversial because high viral prevalence is also found in healthy controls.[23;24] Moreover, the prevalence of viruses differs largely between studies and might be related to the quality of the specimens and the efficiency of DNA/RNA extraction.[22;25]

The most common virus encountered in our IOI biopsies was Parvovirus B19. This is a small DNA virus that causes erythema infectiosum, hydrops fetalis, and transient aplastic crisis.[26] Seroprevalence of Parvovirus B19 exceeds 80%.[27] Classically it was thought that after viral infection humans clear the virus. However, persistence of Parvovirus B19 was demonstrated in bone marrow, skin, synovium, and myocardium.[23] B19 virus has been implicated as a causative agent in reumatoid arthritis because of its high presence in B and T cells of synovia of patients compared to controls.[28] In myocardial biopsies of dilated cardiomyopathy B19 virus was demonstrated to reside in interstitial tissue, endothelial cells, and myocytes.[29] One case report describes a child with rheumatoid arthritis and Parvovirus infection who subsequently developed unilateral orbital pseudotumor.[30] Although the theories on association between Parvovirus B19 and autoimmune disease are plausible, the high prevalence in our control biopsies prohibits us to associate IOI with this virus. Corcioli et al. found a high prevalence of Parvovirus B19 in solid tissue samples of asymptomatic controls.[31] and postulated that in these patients the virus persists without replication at sub-immunogenic levels. Parvovirus detection by our PCR techniques does not allow us to differentiate between sub-immunogenic and immunogenic levels.

Epstein-Barr virus was found in 4 IOI patients and 2 controls. EBV, a gamma-herpesvirus, causes infectious mononucleosis but the infection is asymptomatic in

the majority of cases. In the general population, seroprevalence for EBV is even higher than for Parvovirus B19.[32] EBV has not only been associated with autoimmune diseases,[33] but also with neoplasms.[34] EBV has also been shown to persist in synovial tissue of rheumatoid arthritis patients.[35] In Rosai Dorfman disease, a histiocytic disorder that can cause orbital inflammation and inflammatory pseudotumors of other organ systems, EBV has been implicated in the pathogenesis.[12;36] Recently, EBV infection has been associated with acute dacryoadenitis[37] and orbital myositis.[38] However, the clinical picture of patients with acute viral dacryoadenitis is different from our IOI patients. Acute EBV dacryoadenitis presents within one month with lymphadenopathy and more generalized symptoms of upper respiratory tract infection and conjunctivitis.[37] In Rhem et al.'s series only one patient without systemic signs experienced motility restriction. This patient, who had a clinical presentation similar to our patients, was diagnosed with orbital pseudotumor.

Human Herpesvirus-6 was found in 4 patients who had IOI. HHV-6 causes mild fever, sometimes with roseola in childhood (exanthema subitum). It is a beta-herpesvirus and omnipresent with seroprevalences of more than 80%.[39] HHV6 has been found in cardiomyopathy along with Parvovirus B19.[40] The virus has also been implicated in Rosai Dorfman disease.[41] Whether there is an association between HHV6 and autoimmune disease is less clear.[42] and a relationship between HHV6 and IOI has not been reported yet.

So far, no studies have been published that describe PCR identification of bacteria and viruses in biopsies of IOI. Leibovitch reviewed 91 IOI patients for paranasal sinus inflammation and found signs of inflammation by computed tomography or magnetic resonance imaging in 6 patients (4 myositis, 2 diffuse inflammation).[43] The authors concluded that a possible association exists between paranasal sinus inflammation and IOI. A similar association was also postulated by others.[44]

The demonstration of viruses in biopsies of IOI may have therapeutic implications. In 3 patients with Parvovirus B19 infection unresponsive to corticosteroids and cyclophosphamide, intravenous immunoglobulin resulted in rapid improvement of vasculitis, clearance of the infection, and no recurrence.[45] Also, the clinical response to immunosuppressive agents may be modulated by viral presence. This has been demonstrated in reumatoid arthritis where EBV-positive patients experienced a superior improvement of disease activity after rituximab treatment compared to EBV negative patients.[46] The theory is that rituximab selectively removes CD20-positive B-cells that harbor EBV, resulting in concomitant clearance of EBV. Because in patients with reumatoid arthritis a higher viral EBV load was found, it was concluded that the RA patients'immune system resonds less efficiently to EBV. Such an altered immune response was postulated as one of the

multifactorial causes of RA.

No bacteria could be detected using our PCR techniques. This could be explained by the limited sample size, but more likely by a different pathogenesis of bacteria-triggered IOI. Case reports that postulate a relationship between a bacterial infection and IOI, describe the development of IOI after a streptococcal pharyngitis.[8;9] We hypothesize that in these patients bacteria-induced auto-antigens had a distant effect on orbital tissue. The positive anti-streptolysin-o, as also found in acute rheumatic fever, and the non-response of the orbital disease to antibiotics in one patient support this hypothesis. This distant bacteria-induced auto-antigen effect could explain the absence of bacteria in orbital tissue.

This study has several limitations. No serum was available to link systemic viral activity to the presence of virus in orbital biopsies. However, most humans are infected by Parvovirus B19, EBV, and HHV6 in early childhood whereas our patients were adults. Furthermore, in other studies on viral persistence and autoimmune disease no active viral infection was found.[21] Therefore it is unlikely that analysis of peripheral blood of our patients would have shown active viral infection. Another limitation of this study is that a heterogenous group of IOI patients is included which makes it more difficult to find an etiology for one subtype of IOI. Also, tissue sources of the biopsy specimens were different between IOI patients and controls, and the patients's biopsies were more often from lacrimal gland tissue. The low number of lacrimal gland control biopsies is related to ethical concerns to remove lacrimal gland-tissue from control patients. The lacrimal gland has an immune function in secreting antibodies and therefore may contain different pathogens than orbital connective tissue. However, when comparing viruses in lacrimal tissue (9/12) versus connective tissue (18/31) no significant differences were found (*P*=.30, Chi-square test). Also, the demonstration of Graves' ophthalmopathy and IOI to occur in the same patients in a recent case series may indicate a common etiology and might have made Graves' patients less suitable as controls.[47] However, this co-occurrence is uncommon and in this study no patients were included with both IOI and Graves' ophthalmopathy.

In conclusion, in orbital biopsies of IOI patients a significantly higher number of viruses was found compared to controls. This finding supports a role of viral agents in the development of IOI. However, not one specific virus could be appointed to be directly related to IOI, and other etiologies may be involved as well, suggesting the pathogenesis of IOI to be multifactorial. It is possible that other, as yet unidentified viruses are involved. Future research should be aimed at determining the role of oribit-resident viruses in the pathogenesis of IOI.

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Chapter 4

Idiopathic orbital inflammation and Graves ophthalmopathy

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Archives of Ophthalmology 2010; 128:131-2.

Introduction

Idiopathic orbital inflammation (IOI) is a poorly understood disease entity in which an orbital inflammatory process is found with, by definition, no identifiable local or systemic cause.[1] Graves ophthalmopathy (GO) is often mentioned as a disease to exclude in the diagnosis of IOI.[2] In the Orbital Clinic of the University Medical Center Utrecht, we have encountered 4 patients in whom diagnoses of both IOI and GO were made at different times. In this case series, we describe the clinical and diagnostic features of these patients, show that both IOI and GO can occur at different times in the same patient, and demonstrate the ways the diseases can be differentiated.

Report of Cases

Case 1

A 47-year-old woman with autoimmune hypothyroidism, had slowly progressive painless proptosis of the left eye. Computed tomography (CT) showed an orbital mass located in the posterior superior orbit (Figure 4A). A biopsy specimen showed lymphoid cells without indication of lymphoid hyperplasia on flow cytometry, and a diagnosis of IOI was made. Treatment with oral prednisone resulted in complete resolution of the condition. Eleven months later the patient was diagnosed as having diffuse retrobulbar IOI on the right side and treated with oral prednisone. At the age of 52 years, she developed right-sided eyelid retraction and proptosis. The extraocular muscles on both sides were enlarged on CT (Figure 4B), and thyroid antibodies were found in her blood serum. A diagnosis of GO was made. After resolution of inflammatory symptoms, the eyelid retraction was surgically corrected.

Case 2

A 35-year-old woman with primary hypothyroidism, had subacute eyelid swelling, proptosis, eyeball motility restriction, and pain. On CT, the right lacrimal gland appeared enlarged; biopsy of the gland revealed lymphoid cells. She was treated for IOI (dacryoadenitis) with intravenous, high-dose methylprednisolone sodium succinate. Four years later she was treated for dacryoadenitis on the left side (Figure, 4C) with intravenous steroids.

Four months after that treatment, she had developed diplopia and left upper eyelid retraction. Computed tomography revealed left-sided extraocular muscle

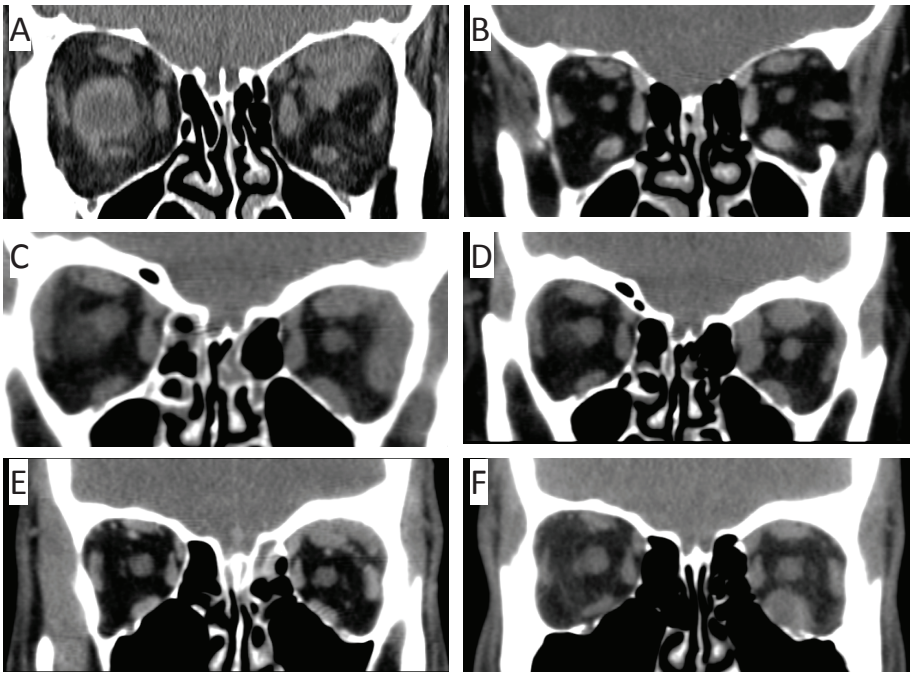

Figure 4. Computed tomographic coronal scans of the study patients. A, Patient 1: idiopathic orbital inflammation (IOI) of the left posterior superior orbit. B, Patient 1: 5 years later, bilateral extraocular muscle enlargement in Graves ophthalmopathy (GO). The mass in the left orbit has disappeared. C, Patient 2: dacryoadenitis of the left orbit. D, Patient 2: 4 months later, left-sided extraocular muscle enlargement in GO. The dacryoadenitis has resolved itself. E, Patient 4: IOI of the left superior orbit. F, Patient 4: 5 years later, extraocular muscle enlargement in GO. The mass in the left superior orbit has disappeared.

enlargement (Figure, 4D). Thyroid antibodies were found in her blood serum, and she was diagnosed as having unilateral GO. To improve eyeball motility, she was treated with radiotherapy.

Case 3

A 30-year-old man with diabetes mellitus, Crohn disease, and hyperthyroidism, had bilateral painless proptosis, eyeball motility disturbances, and upper eyelid retraction. The extraocular muscles appeared enlarged on CT, and thyroid antibodies were found in his blood serum, which yielded a diagnosis of GO. The disease resolved itself without therapy.

At the age of 39 years, the patient developed proptosis on the left side with eyeball

motility disturbances. Two months later the right side had become involved as well. Computed tomography revealed lacrimal gland enlargement, and a biopsy specimen showed chronic inflammation. A diagnosis of IOI (dacryoadenitis) was made, and the patient was treated with oral prednisone.

Case 4

A 22-year-old man, had left-sided proptosis, eyeball motility disturbances, and pain. Computed tomography revealed a mass in the medial superior orbit (Figure, 4E). The lesion was biopsied twice, which revealed fibrosis with some lymphocytes. He was diagnosed as having IOI and treated with radiotherapy and oral prednisone. At the age of 27 years, he developed progressive proptosis of the left eye and extraocular muscle enlargement on radiologic imaging (Figure, 4F). Antithyroid antibodies were found in his blood serum, but thyroid function test results were normal. A diagnosis of euthyroid GO was made. After resolution of inflammatory signs, his left orbit was surgically decompressed.

Discussion

In this article, 4 patients with both GO and IOI separated in time of onset and localization in the orbit are described. Both GO and IOI share characteristics of proptosis and motility disturbances, thus they are considered orbital inflammatory diseases. However, some features differentiate GO from IOI. Upper eyelid retraction and enlargement of the bellies of the extraocular muscles are considered pathognomonic for GO. Furthermore, in Graves disease, thyroid dysfunction and antibodies against the thyroid are often, but not necessarily, found. Idiopathic orbital inflammation can manifest itself with inflammation of any orbital structure and often with pain. In the patients described in this report, the localization of orbital inflammation that does not involve the muscles distinguished IOI from GO. Idiopathic orbital inflammation of extraocular muscles, a condition known as myositis, is different from GO in that it also affects the muscular tendon and not only the belly of the muscle, as is found in GO. However, this distinction can be difficult to make on radiologic images, especially in the case of pure eye muscle GO.[3]

In 3 of the 4 patients, multiple autoimmune diseases were found. The finding of both GO and IOI in the same patients could be explained by the tendency of autoimmune diseases to occur together, but given the low incidence rate of GO and IOI, it is more likely that both diseases share a yet-unknown common pathogenesis. Remarkably, 2 of the 4 patients had hypothyroidism compared with

the general population with GO, most of whom have hyperthyroidism. This observation may point to a thyrotropin-binding inhibitory antibody in the pathogenesis.

Cankurtaran et al[4] described a patient with thyroid dysfunction and IOI that occurred together as part of Riedel thyroiditis. However, their patient did not show signs of GO. To the best of our knowledge, this is the first report to describe GO and IOI that occurred in the same patients.

In summary, we have described 4 patients with both IOI and GO separated in both time of onset and orbital localization. Idiopathic orbital inflammation and GO can be differentiated by upper eyelid retraction, pain, and orbital localization inside or outside the extraocular muscles. Therefore, the theory that GO automatically rules out IOI is not necessarily true.

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Chapter 5

Evaluation of a Diagnostic Algorithm for Idiopathic orbital inflammation

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submitted

Abstract

Purpose: To evaluate a clinical algorithm to diagnose idiopathic orbital inflammation (IOI) within a cohort of patients with signs and symptoms of orbital inflammation.

Methods: Steps of the diagnostic algorithm included: 1. history and physical examination; 2. imaging and laboratory testing; 3. either biopsy or a therapeutic trial of corticosteroids; and 4. consultation with medical specialist. This algorithm was evaluated on 117 patients.

Results: The most common diagnoses were Graves' ophthalmopathy (33%), IOI (24%), and neoplasm (16%). The diagnostic algorithm was efficient in making a diagnosis after three steps in 93% of patients and after four steps in all patients. No patients with a malignancy were inadvertently treated with corticosteroids. One patient underwent subsequent biopsy after a therapeutic trial of corticosteroids.

Discussion: This study presents an algorithm that uses a therapeutic trial of corticosteroids only in patients with low suspicion of malignancy with muscular and apical mass localisations, or with optic nerve compression. The algorithm was demonstrated to be safe in not delaying diagnosis of malignancies and efficient in providing a diagnosis within four steps.

Introduction

Idiopathic orbital inflammation (IOI) is a benign, noninfectious, inflammatory condition that is only diagnosed after exclusion of identifiable local or systemic causes.[1] IOI being a diagnosis of exclusion makes the diagnostic process difficult to define. Yuen proposed a stepwise algorithm to diagnose IOI in clinical practice, but did not evaluate the algorithm on the target patient population.[1]

In a diagnostic process, tests are performed to make a diagnosis either more likely or less likely.[2] A diagnosis is made when more information does not change the decision to act as if a patient has the disease. A diagnosis is ruled out when more information does not change the decision to act as if a patient does not have the disease. As long as one is not sufficiently certain of a diagnosis, additional testing is performed.[3] In deciding upon additional testing, the risk and benefit of treatment and the risk and benefit of testing are considered.

Traditionally, diagnostic studies have focused on sensitivity and specificity of tests applied to a group of patients with the disease and an equal-sized group of patients without the disease.[4] To translate the findings of such studies to a physician's patient population infers an unlikely disease prevalence of 0.5 in a patient population.[5] In addition, such research focuses only on one test, whereas in reality multiple tests are performed. Therefore, it is advised that a diagnostic study should include patients who are suspected of having the disease and for whom a diagnostic problem exists. Patients in whom a diagnosis is self evident should be excluded. Ideally, presence of disease should be tested using a reference standard. When no reference standard is available, expert group consensus or clinical follow-up can be used to make a final diagnosis. Tests evaluated in such a diagnostic study should reflect tests commonly performed in clinical practice. Likewise, the stepwise approach used in clinical practice should be reflected in the study's diagnostic algorithm. This paper evaluates a clinical algorithm designed to diagnose IOI within a cohort of patients with signs and symptoms of orbital inflammation.

Materials and methods

Patients

Patients who presented with suspected orbital inflammation at the orbital clinic of the University Medical Center Utrecht in 2006 and 2007 were selected, and their charts were reviewed. IOI was suspected if two or more signs of orbital inflammation were present: periorbital redness, periorbital swelling, proptosis, and/or orbital pain.[6] Patients in whom a diagnosis was self evident (e.g., referral

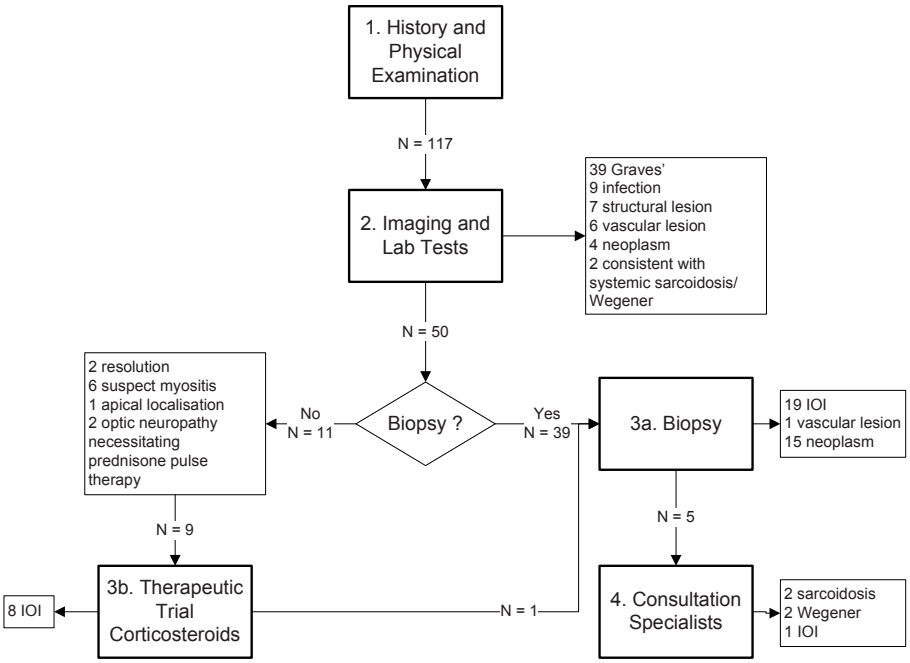

Figure 5. Stepwise diagnostic algorithm of 117 patients suspected of idiopathic orbital inflammation (IOI).

for therapeutic intervention of Graves' ophthalmopathy) were excluded. The reference standard for diagnosis was the final diagnosis at the end of follow-up. This study was performed in accordance with the ethical standards of the 1964 Declaration of Helsinki and adheres to Dutch law regarding studies on human subjects.

Diagnostic algorithm for IOI (figure 5)

The first step is history and physical examination. Second, patients undergo imaging (either CT or MRI) and laboratory testing. When a diagnosis is confirmed, the diagnostic process is stopped. Third, orbital biopsies are considered. Patients with suspected active IOI who do not undergo biopsy are given a therapeutic trial of corticosteroids. For patients in whom biopsy specimens suggest a systemic autoimmune disease, consultation with a specialist is sought.

Diagnostic laboratory tests (second step).

The tests performed are imaging (either CT or MRI) and laboratory tests: complete blood count=CBC, C-reactive protein=CRP, and culture for infection; free thyroxine

(fT4), thyroid-stimulating hormone (TSH), thyroid-stimulating immunoglobulin (TSI), and anti-thyroid peroxidase (anti-TPO) for Graves' ophthalmopathy.

Results

Diagnostic algorithm

In 2006 and 2007, 682 patients were seen with an orbital disease. In 117 patients with signs and symptoms of orbital inflammation, no diagnosis was made after history and physical examination; for these patients a diagnostic problem existed. Of these 117 patients, 24% were finally diagnosed as IOI, 33% as Graves' ophthalmopathy, 16% as nonvascular neoplasm, 8% as infection, 6% as vascular lesion , 6% as structural lesion, 3% as Wegener's granulomatosis, and 3% as sarcoidosis (table 5). In 2 patients, the disease resolved before the diagnostic process was finished. For comparison, a total of 281 patients of 682 patients were diagnosed as Graves' ophthalmopathy.

A diagnosis could be made in 67 of the 117 patients with history, physical examination, imaging, and laboratory tests. In 40 patients, orbital lesions were biopsied, resulting in a final diagnosis in 34. In 5 patients, a rheumatologist, pulmonologist, or otolaryngologist was consulted to confirm or exclude systemic inflammation. Nine patients were subjected to a therapeutic trial of corticosteroids without biopsy: to avoid muscular damage in 6 cases with high suspicion of myositis and to avoid optic nerve damage in 1 case with apical lesion suggestive of IOI; in 2 patients with optic nerve edema and loss of visual acuity, biopsy was deferred to give intravenous methylprednisolone pulse treatment. In all but one patient given a therapeutic trial of corticosteroids prompt response was seen. These patients were considered to have IOI and none were demonstrated to have another diagnosis during follow-up. One patient on therapeutic trial of corticosteroids responded insufficiently and underwent biopsy that showed an IOI. In a few patients, biopsy results were inconsistent with the most probable pre-biopsy diagnosis. One patient was thought to have an infectious dacryoadenitis, but when there was no response to antibiotics, the lacrimal gland was biopsied and patient was diagnosed with noninfectious dacryoadenitis. Seven patients were biopsied because of suspicion of malignancy, but were found to have IOI (3 myositis, 4 diffuse IOI). Two patients with lacrimal gland swelling were found to have pleomorphic adenoma. One patient thought to have lymphangioma was demonstrated to have rhabdomyosarcoma. One major complication was encountered after biopsy of a tumor adjacent to optic nerve: a retro bulbar

Table 5. Final diagnosis of 117 patients suspected of idiopathic orbital inflammation

Diagnosis	No	Diagnosis	No
Idiopathic orbital inflammation		vascular lesion	
myositis	9	fistula	4
dacryoadenitis	10	hemangioma	2
diffuse	9	lymphangioma	1
Graves' ophthalmopathy	39	structural lesion	
nonvascular neoplasm		dermoid cyst	4
lymphoma	6	staphyloma	1
meningioma	4	anatomical variation	1
metastasis	3	cholesterol granuloma	1
pleomorphic adenoma	2	infection	9
rhabdomyosarcoma	2	Wegener's granulomatosis	3
retinoblastoma	1	sarcoidosis	3
osteoma	1	resolved before making diagnosis	2

hemorrhage that resulted in vision loss to hand motion.

Diagnostic tests

In step 2 of the diagnostic algorithm, imaging and lab tests were performed. In this step, the diagnosis was based on imaging (computed tomography (CT) or magnetic resonance imaging (MRI)) in 17 patients with neoplasms, structural lesions, and vascular lesions. Diagnosis was based on laboratory tests (complete blood count (CBC), C-reactive protein (CRP), and microbiological culture) in 4 cases of infection, whereas in the remainder of cases diagnosis was based on combination of imaging and lab tests (free thyroxine (fT4), thyroid-stimulating hormone (TSH), thyroid-stimulating immunoglobulin (TSI), and anti-thyroid peroxidase (anti-TPO)). In thethird diagnostic step, biopsies were taken. With fine-needle aspiration biopsy, a diagnosis could be made in 3 patients (metastasis, lymphoma, and dacryoadenitis), and in 9 patients the sample provided insufficient information and patients were subjected to incisional biopsy. In the patients with Wegener antineutrophilic cytoplasmic antibodies (ANCA), testing was found to be positive in 2 of 4. Of the 2 tested patients with sarcoidosis, 1 had positive lysosyme and neither had positive angiotensin-converting enzyme (ACE).

Discussion

This study evaluated a clinical algorithm to diagnose IOI within a cohort of patients with signs and symptoms of orbital inflammation. This algorithm was efficient in making a final diagnosis in 57% of patients in two steps, and in 93% in three steps. No patient needed more than four steps to make a diagnosis. The main diagnoses found were Graves' ophthalmopathy, IOI, and neoplasm.

The proposed diagnostic algorithm closely follows medical practice. At first consultation with ophthalmologists, after history and physical examination, patients suspected of having IOI are offered noninvasive diagnostic tests consisting of imaging and laboratory tests. At a second consultation, in more than half of patients, a diagnosis can be made based on the imaging and laboratory test results. In this diagnostic step, mainly patients with Graves' ophthalmopathy, infection, and structural lesions are diagnosed. Next, for patients without a definitive diagnosis, the decision is made to either biopsy or give a therapeutic trial of corticosteroids. In this decision the risks and benefits of both options are considered. In 9 patients the decision was made for a therapeutic trial of corticosteroids, whereas in 39 patients the decision was made to biopsy. Indications for a therapeutic trial of corticosteroids in patients with low suspicion of malignancy were to benefit from the decongestive effects of corticosteroids in patients with optic nerve compression, and to avoid risk of muscular and optic nerve damage. Only one patient responded insufficiently to corticosteroids and was subjected to biopsy that was consistent with IOI. Furthermore, because in none of these patients did diagnosis change during follow-up, the choice for a therapeutic trial of corticosteroids was safe. Of the patients being biopsied in step 3, 38% were diagnosed with a neoplasm, of which 73% were malignant (metastasis, lymphoma, and rhabdomyosarcoma). The majority of the other patients were diagnosed with IOI. The question remains as to whether or not these patients with a final diagnosis of IOI would have been better off without biopsy. One patient with an IOI adjacent to the optic nerve was harmed by a biopsy-related complication and lost vision. Perhaps the localisation close to the optic nerve would have affected vision anyway, but more likely, proper treatment of IOI would have prevented vision loss.[7] If all patients would have first received a therapeutic trial of corticosteroids, the neoplasms would have been treated. Probably the 6 lymphomas would have been steroid responsive delaying diagnosis of a malignant process.[8] It can be expected that about half of the patients would have proceeded to biopsy due to unresponsiveness to corticosteroids. Irrespective of the potential harm of unnecessary corticosteroid treatment, the approach of a therapeutic trial of corticosteroids would have made the algorithm less efficient, resulting in an

estimated final diagnosis in three steps in about 82% of patients (versus 93% in the current algorithm).
Therefore, the proposed algorithm is demonstrated to be both efficient and safe. The following guidelines for biopsy can be deduced: 1. Biopsy all lesions with a suspicion for malignancy; 2. Biopsy easily accessible lesions such as in anterior orbit and lacrimal gland; 3. Defer biopsy until after a therapeutic trial of corticosteroids in muscular and apical localisations, and in optic nerve compression. The rationale for criterion 1 is the high rate of malignancies (28% of biopsies); for criterion 2 the low risk/benefit ratio in easily accessible lesions; and for criterion 3, the risk avoidance of deferring biopsy without compromising the diagnostic process.
The final step, consultation with a medical specialist, was added to look for systemic inflammation in patients with a biopsy suggestive of a specific orbital inflammation due to granulomas, vasculitis, or necrosis. Specialists consulted were rheumatologists, pulmonologists, and otolaryngologists.
This study evaluated diagnostic tests for patients suspected of having IOI. Not all tests were applied in all patients, but rather tailored to the diagnoses highest in the differential diagnosis. The most useful tests performed were imaging (either CT or MRI), laboratory (CBC, CRP, and culture for infection; TSH, fT4, TSI, and anti-TPO for Graves' ophthalmopathy), and incisional biopsy. FNAB was helpful in making a diagnosis in only 25% of cases and therefore has a limited role in diagnosing IOI.[9] The high false negative rate has limited the role of ACE, lysosyme and ANCA testing diagnosing orbital sarcoidosis and Wegener's granulomatosis.[10;11]
Yuen described a stepwise diagnostic and therapeutic approach for IOI tailored to the highest suspected diagnosis.[1] Yuen's approach is similar in performing laboratory and imaging testing after history and physical examination. However, in the next step Yuen advises treatment of IOI and biopsy only in cases of persistent or recurrent episodes refractory to systemic steroids.[1] In our institution, we make a decision to biopsy or to give a therapeutic trial of corticosteroids, and we tend more often to biopsy. The biopsy approach has shown to be very efficient in the majority of patients.
This diagnostic study researched the diagnostic process in clinical practice in contrast to historical diagnostic studies that look at sensitivity and specificity testing of single tests. The algorithm is based on combinations of diagnostic tests ordered per patient visit and moves initially from least invasive to more invasive.
This was a mono-center retrospective study on one patient population. Ideally, the diagnostic algorithm should be tested in other institutions to gauge how well these findings can be extrapolated.
In summary, this study evaluated a diagnostic algorithm for IOI in patients suspected of having orbital inflammation. This algorithm, using a therapeutic trial

of corticosteroids only in patients with low suspicion of malignancy with muscular and apical localisations or with optic nerve compression, was demonstrated to be safe in not delaying diagnosis of malignancies and efficient in providing a diagnosis within four steps.

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Chapter 6

Orbital mass as manifestation of Wegener's granulomatosis: an opthalmologic diagnostic approach

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Abstract

Objective: Orbital manifestation of Wegener's granulomatosis is diverse and diagnosis is often difficult. This study aims to improve the diagnostic strategy in orbital Wegener.

Methods: A review of the diagnostic process in patients in whom a diagnosis of orbital WG was considered.

Results: Thirty-three patients were analysed, consisting of 15 patients with orbital WG, 11 with idiopathic orbital inflammation, 6 with orbital sarcoidosis and one with aspergillosis. Diagnostic findings indicating orbital WG were ear/nose/throat involvement, multiple organ system involvement, a positive ANCA, and one histology vasculitis, whereas granulomatous inflammation without signs of vasculitis was more indicative of another orbital disease.

Conclusion: The diagnostic process of orbital WG should include CT scanning of the orbit and sinuses, ANCA blood testing, consultation of a rheumatologist, an ophthalmologist, and an ear-nose-throat specialist, and biopsy of an easily accessible, active inflammatory lesion.

Introduction

To diagnose orbital Wegener's granulomatosis (WG) is a challenge. WG is a relapsing multi-organ disease most often affecting the kidneys and respiratory tract. If untreated, the disease can result in renal failure and death[1-3]. Ophthalmic involvement is quite diverse as it may include scleritis, corneal melting, uveitis, lacrimal duct obstruction and orbital mass[4].
The diagnostic process in orbital WG is complicated by negative and aspecific findings in blood tests[5;6], imaging[7] and biopsy[8-12]. As a result, the diagnostic process takes longer. This may harm the patient as inflammation continues, causing irreversible damage. To improve our diagnostic strategy, we reviewed patients with an orbital mass in whom WG was in the differential diagnosis. Our aim is to shorten the diagnostic process in WG by identifying diagnostic features that differentiate orbital WG from other orbital inflammatory diseases.

Materials and methods

At the University Medical Centre Utrecht, the Netherlands, patients were collected with a new orbital mass in which WG was in the differential diagnosis between 1992 and 2007. These patients had been referred to the orbital clinic either by other ophthalmologists or rheumatologists. Patients were identified searching the diagnosis, radiology and pathology databases for orbital masses in which Wegener was in the differential diagnosis. A history of systemic WG was not an exclusion criterion.
Information was collected on sex, age at diagnosis, race, final diagnosis, organ system inflammation reported by other physicians, ocular involvement, past medical history, symptoms at presentation to the orbital clinic, laboratory findings, radiologic imaging, and biopsy of orbital inflammation. The data used for analysis included only information gathered during the diagnostic process and not thereafter. ANCA was considered positive when before or during the diagnostic process an elevated C- or PANCA level was found using immunofluorescence, mostly with confirmation of PR3- or MPO- ANCA using ELISA.
The final diagnoses of the orbital lesions were: WG, idiopathic orbital inflammation (IOI), sarcoidosis and aspergillosis. The diagnosis WG was made according to the American College of Rheumatology (ACR) criteria[13] and two or more of the following criteria 1) nasal or oral inflammation, 2) abnormal chest radiograph showing nodules, fixed infiltrates, or cavities, 3) abnormal urinary sediment, and 4) granulomatous inflammation on biopsy of an artery or perivascular area.

Sarcoidosis was diagnosed after work-up by a pulmonologist. A diagnosis of idiopathic orbital inflammation was made, after exclusion of other diseases and biopsy showing non-specific orbital inflammation. Aspergillosis was diagnosed by fungus stain and culture.
Statistical analysis was performed using SPSS 15.0 for Windows. Diagnostic features were compared between WG and the combined group of IOI, sarcoidosis, and

Table 6.1. Characteristics of 32 patients in whom a diagnosis of orbital Wegener's granulomatosis (WG) was considered

	Orbital WG (N=15)		**Idiopathic orbital inflammation** (N=11)		**Sarcoidosis** (N=6)		**Aspergillosis** (N=1)
Variable	N observed	%	N observed	%	N observed	%	N observed
Demographics							
Sex male	8	53	4	36	3	50	0
Race Caucasian	15	100	11	100	5	83	0
Age mean in years (min-max)	47	12-70	39	1-61	45	22-72	25
Organ inflammation							
Kidneys	3	20	0	0	0	0	0
Lungs	5	33	0	0	2	33	0
Skin	1	7	0	0	0	0	0
Joints	3	20	0	0	0	0	0
Ear, nose throat*	11	73	1 **	9	0	0	1
Nervous system	3	20	1 **	9	0	0	0
Gastro intestinal	1	7	0	0	0	0	0
Median number of organs involved (min-max)*	3	1-5	1	1-2	1	1-2	1
Ocular involvement							
Intraocular	1	7	1	9	0	0	0
Sclera	4	27	1	9	0	0	0
Cornea	1	7	0	0	0	0	0
Orbit	15	100	11	100	6	100	1
Lacrimal duct	3	20	0	0	0	0	1
Median number of eye structures involved (min-max)	1	1-3	1	1-3	1	1-1	2

* significantly deviating between Wegener's granulomatosis and the group of other diagnoses at the *p*=0.05 level
** by extension from orbit

aspergillosis. Student's t-test was used for normal distributed, continuous data, Mann-Whitney test for non-parametric distributed data, and chi-square tests for frequencies. This study has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

Results

Thirty-three patients were identified in whom a diagnosis of orbital WG had been seriously considered. The final diagnoses were: WG in 15 cases, idiopathic orbital inflammation in 11, orbital sarcoidosis in 6, and aspergillosis in 1. In the patients with orbital WG, 5 had systemic involvement and 8 were limited to the respiratory tract. Another two patients did not fulfil the ACR criteria, but were considered WG and treated as such. Of these two, one patient was considered ocular limited WG because of a biopsy showing granulomatous vasculitis and a history of recurrent sinus disease, but with a negative sinus mucosa biopsy[14-16]. The other presumed WG had a positive ANCA, necrosis on biopsy, and arthralgias and skin lesions suggestive of WG.

In Table 6.1 'patient characteristics' shows that patients with WG have more often other organ system inflammation (median number of organs involved in WG 3 versus 1 for the other diagnoses $p<0.001$). Especially ear/nose and throat symptoms were more frequently encountered in orbital WG patients (11/15 in WG versus 2/18 in other diagnoses $p<0.001$). Table 6.2 "diagnostic data" shows that ANCA testing was found to be positive only in WG (10/11 $p<0.001$). Biopsy sites for the orbital WG group were eyelid 1, lacrimal gland 2, orbit 8, and paranasal sinus 2; for the IOI group extraocular muscle 2 and orbit 9; for the sarcoidosis group lacrimal gland 2 and orbit 4; for the aspergillosis patient the paranasal sinus. Granuloma on biopsy was found in many patients, but mostly in sarcoidosis, whereas vasculitis was found more in WG (5/10 in WG versus 1/18 in other diagnoses $p=0.013$). Granuloma without vasculitis was found less in WG (1/10 in WG versus 13/18 in other diagnoses $p=0.004$).

Nine patients had already been diagnosed as WG of another organ system at first presentation to the orbital clinic. The group with and without prior WG diagnosis were similar in most aspects. The group without prior WG diagnosis presented more often with periorbital swelling (5/6 versus 3/9 $p=0.084$) but had fewer ocular structures involved (median number structures involved 1 versus 2 in prior WG diagnosis $p=0.088$).

In Table 6.3, "treatments and clinical course", highlights the serious course of orbital WG with more aggressive therapies applied and poorer outcome compared

Table 6.2. Diagnostic data of symptoms, signs, laboratory, imaging, and biopsy

	Orbital WG		**Idiopathic orbital inflammation**		**Sarcoidosis**		**Aspergillosis**
	N observed/ N total	%	N observed/ N total	%	N observed/ N total	%	N observed/ N total
Symptoms							
Vision loss	4 / 15	27	1 / 11	9	0 / 6	0	1/1
Swelling	8 / 15	53	5 / 11	45	6 / 6	100	1/1
Proptosis	4 / 15	27	1 / 11	9	0 / 6	0	1/1
Eye motility disturbances	1 / 15	7	2 / 11	18	0 / 6	0	1/1
Diplopia	3 / 15	20	5 / 11	45	1 / 6	17	1/1
Median duration of symptoms in days (min-max)	73	10-600	60	7-700	105	15-360	14
Past medical history							
Wegener's granulomatosis	9 / 15	60	0 / 11	0	0 / 6	0	0/1
Other autoimmune diseases	0 / 15	0	1 / 11	9	0 / 6	0	0/1
Signs							
Mass	7 / 14	50	2 / 11	18	4 / 6	67	1/1
Proptosis	8 / 14	57	5 / 11	45	3 / 6	50	1/1
Limited eye movements	5 / 15	33	7 / 11	64	1 / 6	17	1/1
Bilateral	2 / 15	13	2 / 11	18	0 / 6	0	0/1
Laboratory							
Thyroid dysfunction	0 / 3	0	0 / 8	0	0 / 3	0	0/0
ACE raised	2 / 6	33	0 / 6	0	2 / 6	33	0/0
ANCA*	10 / 11	91	0 / 5	0	0 / 2	0	0/0
Radiologic imaging							
Anterior orbit involved	8 / 14	57	7 / 11	64	3 / 5	60	1/1
Intermediate orbit involved	9 / 14	64	5 / 11	45	2 / 5	40	0/1
Apex involved	3 / 14	21	2 / 11	18	0 / 5	0	0/1
Extraocular muscle involved	8 / 11	73	7 / 9	78	1 / 4	25	0/1
Lacrimal gland involved	5 / 11	45	3 / 9	33	2 / 4	50	0/1
Bone erosion	5 / 11	45	2 / 7	29	0 / 2	0	1/1
Discrete mass	1 / 11	9	0 / 5	0	1 / 3	33	0/1

Table 6.2. (Continued)

	Orbital WG		**Idiopathic orbital inflammation**		**Sarcoidosis**		**Aspergillosis**
	N observed/ N total	%	N observed/ N total	%	N observed/ N total	%	N observed/ N total
Mucosal swelling in sinusses	10 / 13	77	6 / 6	100	2 / 3	67	1/1
Biopsy							
Inflammation	8 / 10	80	9 / 11	82	6 / 6	100	1/1
Granuloma*	3 / 10	30	6 / 11	55	6 / 6	100	1/1
Vasculitis*	5 / 10	50	1 / 11	9	0 / 6	0	0/1
Necrosis	3 / 10	30	0 / 11	0	3 / 6	50	0/1
Granuloma without vasculitis*	1 / 10	10	6 / 11	55	6 / 6	100	1/1

* significantly deviating between Wegener's granulomatosis and the group of other diagnoses at the *p*=0.05 level
WG Wegener's granulomatosis

Table 6.3. Treatment and clinical course of 15 orbital Wegener, 11 idiopathic orbital inflammation and 6 sarcoidosis patients

	Orbital Wegener's		**Idiopathic orbital inflammation**		**Sarcoidosis**	
	N observed/ N total	%	N observed/ N total	%	N observed/ N total	%
Treatment						
None	1 / 15	7	3 / 11	27	4 / 6	67
Corticosteroids	14 / 15	93	7 / 11	64	2 / 6	33
Cyclophosphamide or azathioprine	14 / 15	93	0 / 11	0	0 / 6	0
Radiotherapy	2 / 15	13	1 / 11	9	0 / 6	0
Surgery	3 / 15	20	1 / 11	9	0 / 6	0
Maintenance therapy	12 / 15	80	0 / 11	0	0 / 6	0
Course						
Regression	2 / 15	13	6 / 11	55	6 / 6	100
Stabilisation	6 / 15	40	4 / 11	36	0 / 6	0
Progression	7 / 15	47	1 / 11	9	0 / 6	0
Outcome						
Visual acuity loss	6 / 15	40	1 / 11	9	0 / 6	0
Persistent eyeball motility disturbances	6 / 15	40	4 / 11	36	0 / 6	0
Visual field loss	4 / 15	27	1 / 11	9	0 / 6	0
Loss of eye	2 / 15	13	0 / 11	0	0 / 6	0
Median follow-up in years (min-max)	3	1-13	4	0-7	2	0-4

to idiopathic orbital inflammation, and sarcoidosis.

Discussion

This study was aimed to shorten the diagnostic process in orbital WG by identifying diagnostic features that differentiate WG from other orbital inflammatory diseases. Of all considered diagnostic features, ear/nose/throat involvement, a positive ANCA, multiple organ system involvement and vasculitis are most indicative of WG, whereas granulomatous inflammation without signs of vasculitis is more suggestive of sarcoidosis, IOI or aspergillosis.

In WG, ninety percent of active, generalised diseases are ANCA positive[17]. However, ANCA is less often present in limited WG and can become negative after treatment[15;18]. A positive ANCA has been reported by Woo and Perry in about 2 out of 3 cases of orbital WG[8;9]. Absence of ANCA does not rule out WG, but was a strong predictor of Orbital WG in this study. Current evidence suggests a pathogenetic role for ANCA in the development of vasculitides including Wegener[19].

As the name implies, Wegener's granulomatosis is a granulomatous disease and "granulomatous inflammation on biopsy of an artery or perivascular area" is one of the ACR criteria for WG. However, on orbital biopsy granulomatous inflammation is a nonspecific finding and in the absence of vasculitis more indicative of sarcoidosis, idiopathic orbital inflammation, or aspergillosis. This implies that orbital biopsy often does not make the diagnosis of WG, but can be helpful in ruling out other diseases. The difficult interpretation of orbital biopsy in suspected WG has been pointed out by others. WG lesions are thought to evolve from extravascular granuloma to granulomatous vasculitis to systemic vasculitis, making the findings on biopsy dependent on the timing of biopsy in the clinical course of the disease[20]. The classic triad of necrosis, granuloma and vasculitis is only present in a minority of cases, and more often one or two features are present, with vasculitis reported most frequently[8-12]. It is known that biopsy of an active site gives the best di agnostic yield in WG. Therefore, biopsy of other sites of involvement should be included in the diagnostic work-up. Because the upper respiratory tract is often involved and is easy accessible, this can be a good site for biopsy by the ear/nose/throat (ENT) specialist. WG of the orbit often occurs together with WG of the nose and paranasal sinuses. Orbital manifestations mostly occur in limited WG. This high co-occurrence of ocular and nasal/sinusoidal WG, and the combination of limited WG with ocular disease were also found by others[8-10].

Radiologic imaging, although helpful for localising the orbital mass, did not help to differentiate the nature of the inflammatory process in this study. Tarabishy et al.

have shown that magnetic resonance imaging with gadolinium is able to differentiate between orbital WG, Graves', IOI, and lymhoma based on different T1 and T2 intensities[21]. In selected patients with an established diagnosis of systemic WG, a radiologic scan highly suggestive of orbital WG may yield an orbital biopsy unnecessary. Bone erosion and sinus lesions are frequently reported in WG[7-9]. In this series, these lesions were found in both WG and other inflammatory diseases. In summary: ear/nose/throat involvement, a positive ANCA, multiple organ system involvement and vasculitis are most indicative of WG, whereas granulomatous inflammation without signs of vasculitis is more suggestive of another orbital inflammatory disease. In an orbital lesion where WG is in the differential diagnosis, we recommend a CT/MRI scan of the orbit and sinuses, ANCA testing, systemic evaluation by a rheumatologist, consultation of an experienced ENT specialist with biopsy of inflammatory nasal lesions, and biopsy of easy accessible active orbital lesions. If the aforementioned workup does not make a diagnosis, less accessible or nonactive orbital lesions should be biopsied.

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Chapter 7

Evaluation of Classification Systems for Nonspecific Idiopathic orbital inflammation

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submitted

Abstract

Purpose: To systematically analyze existing classification systems for idiopathic orbital inflammation (IOI) and propose and test a new best-practice classification system.

Methods: A systematic literature search was conducted to find all studies that described and applied a classification system for IOI. Classification categories used in more than two studies were extracted, and criteria for these categories were defined using common descriptors. Using patient data, these newly defined classification systems were evaluated. Reliability was tested by inter- and intrarater agreement of two raters and distinction tested by evaluating clinical differences among classification categories. Feasibility, face validity, and content validity were qualitatively tested.

Results: The most frequently encountered IOI classification systems were based on onset (acute, chronic), histopathology (classic, granulomatous, sclerosing), or localization (diffuse, extraocular muscle, lacrimal gland, sclera, optic nerve). Systems based on histopathology and localization showed good reliability (kappa values range 0.74 – 0.89), were easy to apply (feasibility), and described the biologic process (face validity). Because of static sampling, histopathology-based systems had moderate content validity and moderate distinction between classification categories. Being a static measure, localization had moderate content validity, but good distinction. It was found that content validity was improved by combining histopathology and localization into a two-dimensional classification system.

Conclusions: This combined histopathology and localization based classification system provides a repeatable, easy to use, plausible, and complete classification system that can be used to further advance the research of IOI.

Introduction

Idiopathic orbital inflammation (IOI) is the term used to describe a heterogeneous patient group with signs and symptoms of an orbital mass without apparent cause after local and systemic evaluation.[1]Heterogeneity of the IOI patient group has impeded research on IOI etiology, treatment effectiveness, and prognosis. For example, effectiveness of a therapy in one IOI subtype is diluted by noneffectiveness in other IOI subtypes when all types are included in one study. Moreover, a good prognosis in one IOI subtype may not be apparent when intermixed with modest and poor prognosis of other subtypes. To further our knowledge of IOI, homogenous patient groups should be researched. A good classification system is crucial in forming such groups.

Diagnostic systems are used to clinically evaluate the presence of disease in individuals.[2] Classification systems are more complex and serve to group patients with similar clinical entities for clinical trials and epidemiologic studies.[3;4] The development of a classification system is a process that ideally should include the selection of potential criteria, application of these criteria to a sample, identifying best distinguishing criteria, and testing of this new set of criteria on a new sample.[2] Characteristics important for a classification systems include reliability, feasibility, face validity, content validity, and distinction.[3;4] Reliability relates to inter- and intrarater reproducibility. Feasibility refers to ease of applying a criteria set. Face validity is being biologically plausible. Content validity evaluates whether all relevant aspects of the disease have been presented. Distinction is about being able to differentiate between disease and nondisease or between different disease subgroups. For example, when we look at the Glasgow Coma scale (GCS) performed by a medical professional to classify traumatic brain injury, the scale is reproducible because different observers will give similar scores. The GCS is feasible because it is easy to apply in an emergency situation without the need for special equipment. The GCS has face validity because eye opening, speech, and limb movement are easily recognized expressions of brain functioning. The GCS has moderate content validity because only a limited number of brain functions are tested.[5] The GCS is good at distinguishing comatose from alert patients, but is less reliable in distinguishing different levels of severity of brain injury.

Multiple IOI classification systems have previously been proposed in the literature. However, none of these systems have been evaluated for reliability, feasibility, face validity, content validity, and distinction. The purpose of this paper is to evaluate current IOI classification systems and define a new best-practice classification system that can be used to group patients with similar clinical entities to advance future research on IOI.

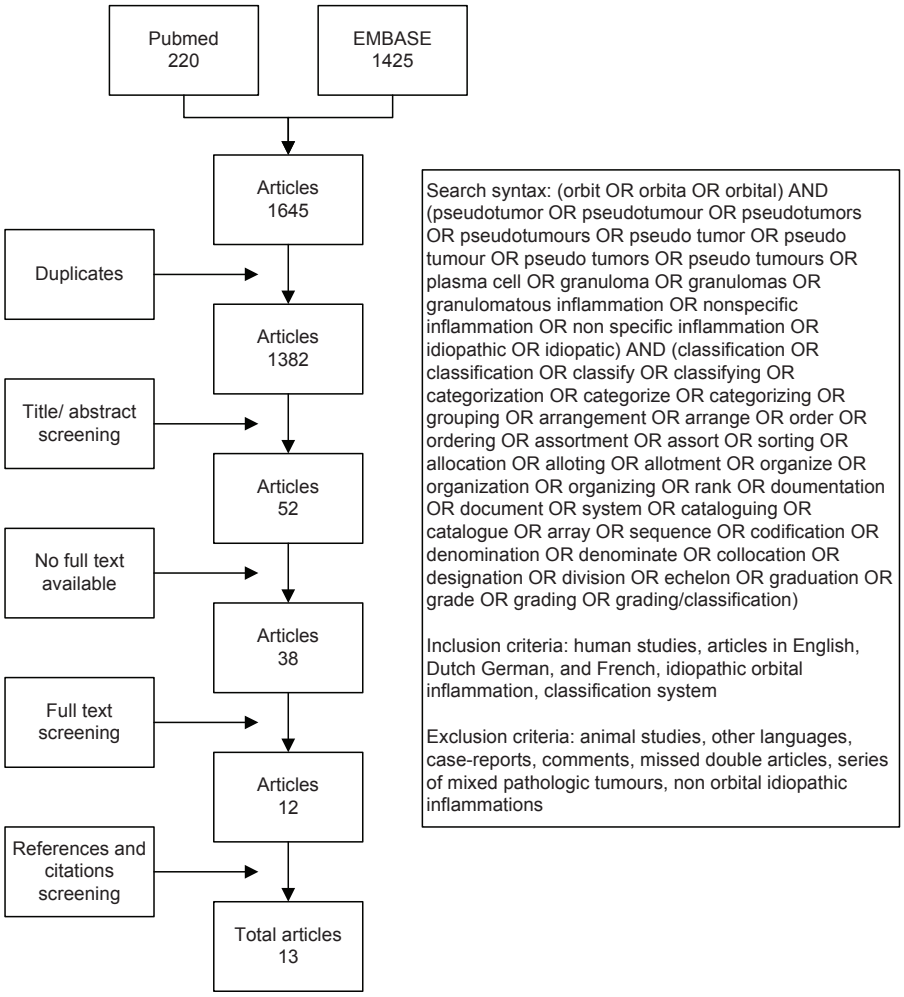

Figure 7.1. Systematic Literature Search

Materials and methods

A systematic literature search on IOI classification systems was conducted on March 1, 2010 using Pubmed and EMBASE databases with an update on December 1, 2010 (Figure 7.1). The search was performed on title and abstract fields for various synonyms of “idiopathic orbital inflammation” and on all fields for various synonyms for “classification systems.” Papers were screened by title and abstract by two authors (WB and FH). References of selected papers were checked using ISI

Web of Science for additional relevant publications. Studies that described and applied an IOI classification system were selected. Classification systems were categorized based on onset of symptoms, histopathology, or orbital localization. Classification systems that used response to therapy for classification were excluded because such a post-hoc measure cannot be used as the inclusion criterion for clinical studies.

For each classification system, categories were selected that had been used in more than two studies and that were mutually exclusive. Category descriptions found in the different studies were combined, and categories were defined to be as specific as possible. These newly defined classification systems were then evaluated for reliability, feasibility, face validity, content validity, and distinction.

To test the classification systems, a sample population was extracted from the patient database of the University Medical Center Utrecht by selecting patients who had received a clinical diagnosis of IOI between 2000 and 2010. Reliability of histopathology reports, radiology reports, and radiology images were tested by having two trained raters (WB and FH) each apply the classification criteria twice, at a two-week interval, calculating inter- and intrarater agreement. For histopathology, full detailed reports were interpreted. Both radiology reports and radiology images were tested separately for reliability. Raters repeated the rating two weeks later and were masked to prior ratings. Duration of onset was based on history recorded in the patient chart and not tested for reliability.

Feasibility, face validity, and content validity were qualitatively tested. Using patient data, distinction was tested for each classification system by evaluating clinical differences in demographics, presentation, treatment, and outcome for all classification categories. Each patient was assigned to one classification category after consensus was reached between the researchers. Age was defined as age at presentation of disease. Soft tissue swelling was defined as any swelling of eyelids, conjunctiva, and/or proptosis. Motility restriction was defined as any restriction in primary or secondary gaze. Optic nerve dysfunction was defined as visual acuity ≤0.3, optic disc swelling or pallor, or visual field defect. Recurrence was defined as new symptoms and signs after a symptom-free period of more than one month. Treatment was categorized as “no” when no treatment was initiated or only treatment with nonsteroidal anti-inflammatory drugs.

Statistical analyses were performed using SPSS for Windows 17.0. To determine consistency within and between raters, Kappa statistics were performed. Clinical differences between classification categories were tested using Chi-square for proportions and ANOVA for means. This research adhered to the Declaration of Helsinki.

Table 7.1. Classification Systems With Classification Categories Applied in Clinical Studies on Idiopathic Orbital Inflammation

Author	Year	Study size	**Subtypes** (number of patients)				
Classification Based on Onset							
Nugent[6]	1981	16	Acute (16)				
Rootman[7]	1982	23	Acute (17)	Chronic (6)			
Sekhar[8]	1993	6	Acute (2)	Chronic (4)			
Gunalp[9]	1996	132	Acute (48)	Chronic (84)			
Total patients (relative frequency)		*177*	*83 (47%)*	*94 (53%)*			
Classification Based on Histopathology							
Blodi[16]	1968	138	Lymphocytic (70)	Dense collagen (13)	Granuloma (11)	Vasculitis (2)	Other (42)
Heersink[10]	1977	27	Lymphocytic (23)			Angiitis (4)	
Fuji[18]	1985	43	Lymphoid (25)	Sclerosing (8)	Granulomatous (10)		
Constantinidis[15]	2000	12	Lymphoid (3)	Sclerosing (3)	Granulomatous (6)		
Yan[11]	2006	20	Diffuse infiltrative (9)	Fibrotic (3)			Other (8)
Swamy[17]	2007	24	Classical (9)	Sclerosing (13)	Granulomatous (1)	Vasculitic (1)	
Total patients (relative frequency)		*264*	*139 (53%)*	*40 (15%)*	*28 (11%)*	*7 (3%)*	*50 (19%)*

Table 7.1. (Continued)

Author	Year	Study size	**Subtypes** (number of patients)						
Classification Based on Localization									
Heersink[10]	1977	26							Other (26)
Nugent[6]	1981	16	Lacrimal (6)	Diffuse (2)	Myositic (2)				Other (6)
Rootman[7]	1982	17	Lacrimal (6)	Diffuse (2)	Myositic (2)				Other (7)
Hara[19]	1983	22							Other (22)
George[20]	1989	21	Dacryoadenitis (3)	Diffuse (7)	Myositis (9)	Orbital apex syndrome (2)			
Sekhar[8]	1993	20	Dacryoadenitis (2)	Diffuse (6)	Myositis (8)		Perineuritis (2)	Periscleritis (2)	
Gunalp[9]	1996	84	Dacryoadenitis (14)	Diffuse (40)	Myositis (21)	Tolosa-Hunt (2)	Perineuritis (1)	Periscleritis (1)	
Yuen[1]	2003	65	Dacryoadenitis (21)		Myositis (19)	Orbital apex (6)			
Yan[11]	2006	205	Dacryoadenitis (66)	Diffuse (21)	Myositis (16)		Perineuritis (5)	Periscleritis (4)	
Total patients (relative frequency)		*476*	*118 (25%)*	*78 (16%)*	*77 (16%)*	*10 (2%)*	*8 (2%)*	*7 (1%)*	*61 (13%)*

Figure 7.2. Composite Classification Criteria for Idiopathic orbital inflammation

Category	Definition
Histopathology references 10;11;13;15-18	
Classic	Chronic inflammatory infiltrate with small well-differentiated mature lymphocytes, admixed with plasma cells, neutrophil and eosinophil granulocytes, occasionally with histiocytes and macrophages.
Granulomatous	Various cellular response, mainly histiocytic infiltration and multinucleated giant cells, sometimes with well-formed noncaseating granulomas .
Sclerosing	Interstitial connective tissue is disproportionately great and inflammatory infiltrate is paucicellular. Includes fibrosis (loosely attached immature collagen bundles with multiple fibroblasts) and sclerosis (more hyalinized connective tissue with few fibroblasts).
NOS	Not otherwise specified. Impossible to classify elsewhere.
Localization references 1;6-11;19-22	
Diffuse	Nonlocalized enhancing mass obscuring orbital structures in variable extent, possibly expanding from the apex to the posterior margin of the globe or appearing to mold itself along fascial planes, the globe or the orbital bones.
Extraocular muscle	Relatively diffuse enlargement of one or more extraocular muscles (with or without the involvement of the associated tendons) accompanied by some spillover of the inflammatory process into orbital fat bordering the muscle, blurring the margin of the muscle.
Lacrimal gland	Diffuse, oblong enlargement of the lacrimal gland with preservation of the shape of the gland that may be accompanied by an inflammatory reaction in the periglandular tissue, blurring the gland margin.
Optic nerve	Enlargement and enhancement of the optic nerve sheath, without nerve fiber involvement, and possible streaky inflammatory densities in the contiguous orbital fat.[196]
Sclera	Enlargement of the scleral uveal rim may be associated with edema extending into Tenon's space. Including periscleritis and sclerotenonitis.[197;198]
NOS	Not otherwise specified. Impossible to classify elsewhere.

Results

Selection of classification systems

The systematic literature search resulted in 1382 unique papers. A total of 13 papers were finally selected using our defined selection criteria. Table 7.1 shows the classification systems either based on onset, histopathology, or localization with their classification categories. Six studies used two dimensions of IOI to classify patients.[6-11]

Figure 7.2 shows the final category definitions that were extracted from the

different classification systems. Acute IOI was defined as onset within days to weeks, and chronic as onset within weeks to months.[6-9] This description was translated to a quantitative cutoff value of 14 days in line with other definitions of acute disease.[12]

For histopathology, the predominant categories were lymphoid, granulomatous, and sclerosing. The vasculitic/angiitis category was excluded because of inadequate distinction from orbital Wegener's granulomatosis,[13] which is a specific orbital inflammation. A category of "not otherwise specified" (NOS) was added for histopathology that could not be classified elsewhere (eg, predominant eosinophilic specimens). Localization was assessed using radiology studies. The most common localization categories were diffuse, extraocular muscle, lacrimal gland, optic nerve, and sclera. An NOS category was added for localizations that could not be classified elsewhere (eg, eyelid-only localizations).

Evaluation of classification systems

Reliability: Eighty-four patients with a clinical diagnosis of IOI were selected. One patient was included twice because of two episodes of IOI on different sides and at different times. The raters rated 41 histopathology reports, 67 radiology reports, and 46 computed tomography and magnetic resonance imaging scans. Kappa statistics were good to very good (range 0.74 – 0.89) for inter- and intrarater agreement applying the Figure 2 criteria definitions for IOI (Table 7.2). Both histopathology and localization were scored as good reliability. The combined histology-localization classification system showed good reliability (range 0.81-0.85).

Table 7.2. Kappa Statistics Describing Inter and Intrarater Agreement for Histopathology Report, Radiology Report, and Radiology Scan Using Figure 7.2 Classification Criteria

	Kappa	95% confidence interval
Pathology round 1, interrater	0.75	0.57-0.93
Pathology round 2, interrater	0.76	0.57-0.94
Radiology report round 1, interrater	0.89	0.90-0.97
Radiology report round 2, interrater	0.79	0.68-0.90
Radiology scan round 1, interrater	0.74	0.59-0.89
Radiology scan round 2, interrater	0.85	0.73-0.97
Pathology observer 1, intrarater	0.79	0.62-0.96
Pathology observer 2, intrarater	0.76	0.62-0.96
Radiology report observer 1, intrarater	0.87	0.78-0.96
Radiology report observer 2, intrarater	0.83	0.72-0.93
Radiology scan observer 1, intrarater	0.75	0.60-0.89
Radiology scan observer 2, intrarater	0.82	0.69-0.95

Table 7.3. Distinctive Properties of IOI Classification Systems by Comparing Demographics, Presentation, Treatment, and Outcome Between Classification Categories for Onset, Histology, and Localization Based Classification Systems

	Onset			**Histopathology**				**Localization**				
	Acute (n=16)	Chronic (n=57)	*P*-value	Classic (n=28)	Granulomatous (n=2)	Sclerosing (n=4)	*P*-value	Diffuse (n=22)	Muscle (n=19)	Lacrimal (n=16)	NOS (n=8)	*P*-value
Male %	38	40	0.96	43	100	25	0.21	33	22	22	22	0.20
Age mean (SD)	45 (20)	49 (17)	0.43	46 (15)	72 (10)	50 (11)	0.08	52 (20)	40 (11)	44 (16)	48 (25)	0.17
Soft tissue swelling %	88	95	0.18	96	100	100	0.91	34	25	29	13	0.47
Motility restriction %	67	52	0.37	44	100	67	0.26	38	34	13	16	0.04
Optic nerve dysfunction %	13	10	0.86	11	0	33	0.45	100	0	0	0	0.10
Bilateral %	13	5	0.16	7.1	0	25	0.45	0	60	40	0	0.19
Treatment %			0.56				0.46					0.90
No*	13			25	50	0		42	17	33	8.3	
Only oral prednisone	50			29	50	67		30	26	26	17	
Other	38			46	0	33		33	33	22	11	
Symptom-free outcome %	71	80	0.45	79	100	67	0.77	32	24	29	15	0.15
Recurrence %	0	29	0.03	23	100	0	0.15	36	50	14	0	0.17
Average distinction			0.44				0.42					0.27

*No treatment or treatment with nonsteroidal anti-inflammatory drugs only.

Feasibility: Onset criteria were easy to apply to patient history data. Most ophthalmologists are not trained to be pathologists and therefore rely on pathology reports to classify IOI patients. The histopathology classification criteria were easy to apply to pathology reports. The radiology reports varied in the detail of description of orbital involvement in IOI and were less informative for classification purposes than the radiology images. Only in cases of extraorbital extension did the radiology reports add valuable insight regarding localization ofthe IOI mass. Onset, histopathology, localization, and combined histopathology-localization were scored as good feasibility.

Face validity: It was not clear how the onset criteria with a cutoff of 14 days should translate to a different biologic mechanism, and therefore it was scored as poor in face validity. Histopathology describes the biologic process. Localization may describe different biological processes such as those affecting the lacrimal gland or extraocular muscle tissues. Histopathology, localization, and combined histopathogy-localization were scored as good in face validity.

Content validity: Onset is part of the domain clinical presentation of IOI, but because it only describes part of a domain, it was rated as poor content validity. Histopathology was rated as moderate content validity because by describing all cells involved in the inflammation, it describes a full domain, but is still dependent on tissue sampling. Localization was rated as moderate for content validity because by describing the extent of the disease, it describes a full domain, but is still only a static measure. Because the combined histopathology-localization describes multiple domains, it was rated as good for content validity.

Distinction: In Table 7.3, patient classification systems for onset, histopathology, and localization are applied and patient characteristics given. Good distinction of a classification system should translate into groups within that system having distinctive patient characteristics.

Using the onset classification criteria, 16 patients could be classified as acute and 57 as chronic (left columns). Using the histopathology classification criteria, 34 patients could be classified as classic (28), granulomatous (2), or sclerosing (4) (middle columns). No patients were classified as NOS. Using the radiology classification criteria, 65 patients could be classified as diffuse (22), extraocular muscle (19), lacrimal gland (16), or NOS (8) (right columns). The NOS category included only cases of extraorbital extension including eyelid involvement (n=4), bone erosion (n=3), and intracranial extension (n=1). In four patients, the optic nerve showed enhancement, but did not meet the optic nerve category criteria because of extensive orbital fat involvement. One patient was classified as scleral, but this patient was not shown in the table because patient chart data was missing. One patient showed scleral enhancement but was not classified as scleral because

of extensive orbital fat involvement. The classification system based on localization showed best distinction between patient categories with an average *P*-value of 0.27. The onset and histopathology based classification systems were equally distinctive with *P*-values of 0.44 and 0.42, respectively. The combined histology-localization classification system showed good distinction (*P*-value 0.24).

Table 7.4. Evaluation of Classification Systems for IOI Based on Onset, Histopathology, and Localization

	Onset	**Histopathology**	**Localization**	**Combined Histopathology and Localization**
Reliability		+	+	+
Feasibility	+	+	+	+
Face validity	-	+	+	+
Content validity	-	0	0	+
Distinction	0	0	+	+

IOI idiopathic orbital inflammation; + = fully satisfying criterion, 0 = partially satisfying criterion, - = not satisfying criterion

Table 7.4 summarizes the evaluation of classification systems based on onset, histopathology, and localization.

Discussion

This study systematically analyzed classification systems for idiopathic orbital inflammation, evaluated them on 84 patients, and proposed a new two-dimensional classification system. The systematic approach resulted in a reproducible literature search with only one additional paper found by hand searching references. The classification systems based on histopathology and localization showed good reliability, feasibility, and face validity. Only the localization-based classification system showed good distinction. Apparently histology findings do not necessarily reflect distinct clinical courses. Content validity of systems based on histopathology and localization was considered moderate because histopathology provides only a sample of the process and radiology provides a static measure. By using a combined classification system based on both histopathology and radiology, more elements of the orbital inflammation can be described, and content validity of the classification system increases. This study proposes the combined histopathology-radiology classification system as a new best-practice classification system for nonspecific IOI. The combined classification system uses readily available data and does not require

extra testing or expertise. Moreover, the system is easy to apply and can be performed by the ophthalmologist or a trained rater.

The onset-based classification system did not score well on face validity, content validity, or distinction. Onset as a measure of days until presentation is not only a disease characteristic, but also dependent on accessibility of an ophthalmologist. This study shows that onset is not a good base for IOI classification. Classification systems that used response to therapy for classification were excluded because such systems cannot be used for grouping patients for clinical trials.[14]

A combined classification system using both histopathology and localization would imply biopsy for all cases of IOI for research settings. However, 16 patients in this study were not treated or treated only with nonsteroidal anti-inflammatory drugs, and to biopsy these patients would be an unnecessary burden.

The most frequently encountered categories of IOI using a combined classification system based on histopathology and localization are classic-diffuse, classic-extraocular muscle, and classic-lacrimal gland. Therefore, these subtypes should be the main focus for research on etiology, diagnosis, treatment, and prognosis. The NOS categories are by definition heterogeneous groups and thus unsuitable for research. Even though the sclera and optic nerve were found to be involved in a number of cases, few patients entered the sclera and optic nerve localization categories because of additional orbital fat involvement.

This study looked at localization both by using radiology reports and by looking at the actual scan images, because the differing viewpoints of radiologists and ophthalmologists may result in different interpretation of scans. The actual scan images were more informative for classification purposes. However, in areas outside the orbit, where the ophthalmologist is less familiar with normal anatomy, the radiologist reports were of additional value. Therefore, we propose using a combination of looking at both the images and reports for classifying localization.

This study has some limitations. The filter used in the literature search based on languages and databases may have excluded relevant publications. Inclusion of only categories used in more than two studies is arbitrary and has resulted in exclusion of some categories (eg, Tolosa-Hunt subtype[9;15] that is now classified under NOS). This is a retrospective study based on existing literature that did not describe immunohistological and cytogenetic analyses. Such techniques may prove to be valuable bases for categorization in the future.

In summary, a combined classification system based on histopathology and localization provides a two-dimensional, repeatable, easy, plausible, and complete classification system for IOI. Such a classification system is crucial in furthering our understanding of nonspecific idiopathic orbital inflammatory diseases through research.

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Chapter 8

Treatment of severe idiopathic orbital inflammation with intravenous methylprednisolone

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Abstract

Background: Prednisone pulse therapy is used to treat active non-infectious orbital inflammatory disease to attain faster clinical improvement and to shorten the duration of prednisone treatment. This study addresses the use of intravenous methylprednisolone (IVMP) pulse therapy, in addition to oral prednisone (OP), in the treatment of severe idiopathic orbital inflammation (IOI).

Methods: This was a multicentre retrospective cohort study. Patients with severe IOI treated with IVMP pulse and OP therapy (IVMP+OP) were compared with patients with IOI who were treated only with OP. Main outcome measures were duration of prednisone treatment, symptom-free outcome and complications.

Results: Between 2000 and 2007, 12 patients with severe IOI were treated with IVMP+OP and 15 patients were treated with OP only. The median treatment duration was 160 (range 34–680) days in the IVMP+OP group and 110 (range 27–730) days in the OP-only group. In patients who had severe IOI, 73% in the IVMP+OP group and 87% in the OP-only group were symptom-free after treatment. No patients developed complications related to prednisone therapy.

Conclusion: In our study there was no advantage of treating patients with severe IOI with IVMP+OP in terms of shortened treatment duration, lower cumulative dose or decrease in persistent symptoms. We suggest that the indication of IVMP in the treatment of severe IOI is limited to speeding symptom relief and recovery from optic nerve dysfunction.

Introduction

Non-infectious orbital inflammation is frequently treated with glucocorticoids. There is a trend to use intravenous methylprednisolone (IVMP) pulse therapy, in addition to the usual treatment of oral prednisone (OP), to treat severe and active orbital inflammatory disease.[1;2] The rationale for using IVMP pulse therapy is that high doses treat the disease aggressively and quickly, resulting in a shorter duration of prednisone administration with fewer side effects.[3] The effectiveness of using very high doses of glucocorticoids is related to an additional inhibition of the excessive immune response on top of the genomic effects mediated by cytosolic glucocorticoid receptors.[4] IVMP pulse therapy in addition to OP (IVMP+OP) has been shown to be superior to OP-only in clinical response and side effects in the treatment of Graves' ophthalmopathy.[5] However, the superiority of IVMP+OP over OP-only therapy has not been studied in the treatment of other orbital inflammatory diseases.[6] This study addresses the use of IVMP pulse therapy, in addition to OP, in the treatment of severe idiopathic orbital inflammation (IOI).

Methods

Patients diagnosed with IOI were selected from the databases of two orbital clinics in the Netherlands between 2000 and 2007. Patient records were reviewed. Patients with all of the following criteria were included in the study: (1) a clinical picture of orbital inflammation with non-specific inflammation on orbital tissue biopsy, or with no improvement on antibiotic therapy but prompt improvement on systemic prednisone, or both; (2) no identifiable local or systemic cause; and (3) treatment with glucocorticoids.

Patient records were reviewed for demographics, history of IOI and systemic autoimmune diseases, symptoms and signs (pain, periorbital soft tissue swelling, proptosis ≥2 mm, optic nerve dysfunction (visual acuity ≤0.3, optic disc swelling or pallor, or visual field defect), diplopia and laterality), duration of symptoms, applied treatments, treatment complications and outcome. Radiology reports, when available, were reviewed for localisation of orbital inflammation and categorised as isolated myositis, isolated dacryoadenitis and diffuse.[7] Histology reports, when available, were reviewed and categorised as indicating typical inflammation or sclerosing inflammation (disproportionately affecting interstitial connective tissue with paucicellular inflammatory infiltrate), and the remaining were classified as 'other'.[8]

Prednisone dose was recorded for each day of treatment to calculate median dose,

cumulative dose, cumulative dose excluding IVMP, and number of prednisone treatment days differentiated for any dose (low dose (<10 mg), medium dose (10–30 mg), high dose (>30 mg) and intravenous dose).[4] To calculate cumulative dose, maintenance prednisone therapy given beyond 2 years was not included in the cumulative dose. Methylprednisolone dose was converted to prednisone dose by multiplying by 1.25. Duration of prednisone treatment reflects the clinical situation upon which the physician acted at the time of disease. Therefore duration of prednisone treatment is considered both a clinically relevant and objective outcome for this retrospective study.[9] If IOI relapsed within 2 months after prednisone treatment was stopped we considered the treatment to be incomplete—and the subsequent period of corticosteroid treatment was included in the treatment duration. Recurrence was defined as new disease activity more than 6 months after stopping prednisone therapy, and for which prednisone was reinitiated. Patients were considered symptom-free when there was no persistent pain, diplopia or optic nerve dysfunction after the cessation of therapy. Each patient was included only once for analysis irrespective of disease relapse or new disease on the contralateral side. To prevent prednisone side effects, all patients on extended prednisone therapy (>3 months) were treated with calcium, vitamin D3, a bisphosphonate and an H2-receptor antagonist. Only major prednisone-related complications were registered (corticosteroid-induced diabetes, aseptic necrosis, congestive heart failure, Addison crisis, gastrointestinal bleeding and fracture related to osteoporosis).

Data were analysed using statistical software (SPSS for Windows 17.0). Using the propensity score method, patients were stratified into those having mild or severe disease.[10] This method uses a binary logistic regression model with outcome pulse treatment and covariates relating to demographics, history, symptoms, signs, localisation and histology to calculate a score for severity. Patients with an above-average score were considered to have severe disease. Patients with mild IOI were excluded from further analysis. Patients with severe IOI treated with IVMP+OP were compared with patients with severe IOI treated with OP only. The primary outcome was days of prednisone treatment. Secondary outcomes were cumulative prednisone dose, being symptom-free after cessation of therapy and treatment-related complications.

Results

Table 8. Patients with severe idiopathic orbital inflammation (IOI) treated with intravenous methylprednisolone and oral prednisone (IVMP+OP) versus patients treated with OP only

Characteristics	**OP Only** (n=15)		**IVMP+OP** (n=12)		
	N observed	%	N observed	%	***P*-value** [a]
Male, %	3	20	3	25	1.0
Age, mean (SD), years	49	19	47	13	.80
Clinic A[b], %	9	60	8	67	1.0
History, %					
IOI	2	13	0	0	.49
Autoimmune	2	13	1	8.3	1.0
Median days with symptoms (range)	35	5-180	14	2-370	.14
Presentation, %					
Pain	11	73	9	75	1.0
Soft tissue swelling	13	87	12	100	.49
Proptosis	10	67	8	67	1.0
Optic nerve dysfunction	1	6.7	1	8.3	1.0
Diplopia	12	80	10	83	1.0
Bilateral	2	13	3	25	.63
Localization, %					.53
Dacryoadenitis	2	14	3	30	
Myositis	5	36	4	40	
Other	7	50	3	30	
Histology, %					.57
Typical	5	83	4	67	
Sclerosing	1	17	1	17	
Other	0	0	1	17	
Prednisone treatment					
Median dose, mean (SD), mg	18	13	15	8.3	.44
Median cumulative (range), mg	2300	600-10000	5100	2400-18000	.011
Median cumulative exclusive IVMP (range), mg			2100	640-15000	.81
Median days (range)	110	27-730	160	34-680	.24
Median days <10 mg (range)	21	0-540	42	0-420	.38
Median days 10-30 mg (range)	84	11-620	85	21-330	.32

Table 8. (Continued)

Characteristics	**OP Only** (n=15)		**IVMP+OP** (n=12)		
	N observed	%	N observed	%	***P*-value** [a]
Median days >30 mg (range)	15	0-75	8.5	3-150	.94
Median days IVMP (range)	. . .		3	3-7	
Maintenance, %	2	13	0	0	.49
Other treatment, %					
Radiotherapy	0	0	3	25	.075
Immunosuppressives	2	13	2	17	1.0
Surgery	1	6.7	1	8.3	1.0
Outcome					
Median follow-up days (range)	750	350-1700	430	14-2200	.064
Recurrence, %	4	27	2	17	.66
Major prednisone complications, %	0	0	0	0	1.0
Symptom-free, %	13	87	8	73	.62

To calculate percentages, cases with missing information on variables were excluded.
[a] Fisher exact test was used for two proportions, χ2 test for multiple proportions, t test for means, and Mann-Whitney test for medians.
[b] This study was performorded at two centres, clinic A and clinic B.

Between 2000 and 2007, 95 patients were treated for IOI in the Rotterdam Eye Hospital and University Medical Center Utrecht. Forty patients did not receive prednisone and were excluded from further analysis. Twenty-seven patients were included in the group with mild IOI and were further excluded. Of the remaining patients with severe IOI, 15 patients had been treated with OP-only and 12 patients had been treated with IVMP+OP. The severe patients differed statistically significantly from the mild patients in being more often female (54% vs 22%) and bilateral (19% vs 0%), and having more pain (74% vs 29%). Other non-statistically significant differences were found in having a history of autoimmune disease (11% vs 7.1%), not having a history of prior IOI (7.4% vs 18%), more proptosis (67% vs 46%), soft-tissue swelling (93% vs 82%) and receiving more additional radiotherapy (11% vs 3.6%).
When comparing patients with severe IOI treated with IVMP+OP with patients with severe IOI treated with OP only (table 1), patients treated with IVMP+OP had a shorter duration of symptoms, received more radiotherapy and had shorter follow-up time. However, the differences were not significant. No differences in clinical presentation could be identified that could explain the choice of therapeutic

regimen. Patients treated with IVMP+OP received larger cumulative doses, but this difference disappeared when subtracting the pulse dose. Patients with severe IOI treated with IVMP+OP used prednisone, on average, 50 days more than patients with severe IOI treated with OP only (p=0.24). After exclusion of the three IVMP+OP patients that had also been treated with radiotherapy, the IVMP+OP group used prednisone for 20 days more than the OP-only group. With regard to treatment outcome, no significant differences were seen. Patients who were not symptom-free had diplopia (64%), pain (18%), or both (18%), but had no permanent optic nerve dysfunction.
IVMP was administered in doses of 500 mg (in eight patients) or 1000 mg (in four patients) for three consecutive days, or 500 mg every other day for a total of four administrations (in one patient). IVMP therapy was always followed by OP therapy. A second course of IVMP was not initiated until 2 weeks after pulse therapy (four patients).
Two patients in the OP-only group were kept on maintenance prednisone treatment because of chronic IOI in one and rheumatoid arthritis in the other. Patients in this group of severe IOI did not develop any major prednisone-related complications. One patient in the group with mild IOI developed corticosteroid-induced diabetes.

Discussion

In this study, we hypothesised that IVMP+OP would result in a shorter duration of prednisone treatment due to aggressive attack of the inflammatory process. However, within the group with severe IOI, IVMP+OP did not result in a shorter duration of prednisone therapy or a difference in symptom-free outcome or recurrence rate compared to OP-only treatment.
This study was not an experiment, but we believe it provides valuable information because of proper adjustment for treatment bias using the propensity score method. A good balance was found in pre-treatment patient variables between the IVMP+OP and OP-only groups. No differences in clinical presentation could be identified that could explain the choice of therapeutic regimen and we conclude that treatment allocation can be regarded as random. One could argue that the application of radiotherapy to three patients in the IVMP+OP group and none in the OP-only group is an indication of residual treatment bias. However, after exclusion of the three patients in the IVMP+OP group that had also been treated with radiotherapy, the IVMP+OP group still used prednisone for 20 more days. Therefore, the difference in radiotherapy treatment did not affect the outcome of

this study.

Is there a place for IVMP in addition to OP treatment in severe IOI? This study could not find an advantage of using IVMP+OP in terms of treatment duration. It is possible that the short-term positive effect of using IVMP+OP in the treatment of IOI is cancelled out because of the often prolonged duration of prednisone treatment due to the chronicity of the disease. In our clinical experience, IVMP is effective in severe IOI in treating serious pain refractory to OP. However, pain is a subjective outcome and could not be accurately studied retrospectively. Moreover, in patients with optic nerve dysfunction treatment with IVMP should be considered to speed recovery.

In our study, all patients treated with IVMP also received OP. IVMP was expected to attack only the peak of the inflammatory process. Subsequent OP therapy was thought to prevent rebound symptoms of inflammation and provide long-term immunosuppression. Different IVMP regimens were used in this study. These differences both reflect the changing trends and lack of knowledge of the optimal prednisone dose and scheme.[11] No difference in cumulative prednisone dose could be found between patients with severe IOI treated with IVMP+OP and patients treated with OP-only when the intravenous dose was excluded. The rationale behind exclusion of the intravenous dose is that the effect is mostly non-genomic, and it is unlikely that intravenous doses have a sustained effect.[4] The IVMP+OP group had fewer days on high doses (>30 mg) of prednisone. However, this is not a clinical advantage because the cumulative dose was similar between the groups, and because the cumulative dose has been found to be associated with prednisone-related complications.[12] Only prednisone doses of less than 10 mg have been shown to have few side effects.[4] None of the patients in both groups experienced prednisone-related complications.

The effect of IVMP versus OP has been studied in other diseases. In a randomised clinical trial of 27 patients with giant cell arteritis, patients treated for 3 days with IVMP+OP versus OP-only used a lower median daily dose of prednisone at 78 weeks (0.5 vs 7 mg), used a lower median cumulative dose of OP (5.6 vs 7.9 g), had a higher number of sustained remissions (86% vs 33%)[3] and had fewer major prednisone-related complications (14% vs 46%). In a randomised clinical trial of 70 patients with Graves' ophthalmopathy, the patients treated once weekly with high-dose IVMP for 12 weeks versus OP therapy had a greater proportion of treatment response at 3 months (77% vs 51%)[13] with fewer major prednisone complications (0% vs 6%).

Unlike our study, the aforementioned randomised controlled trials clearly demonstrate a benefit of IVMP over OP. These studies differ from our study in being randomised trials that, by design, eliminate treatment bias. A strict protocol

was followed using IVMP+OP in the treatment of giant cell arteritis only as a one-time induction therapy and in Graves' ophthalmopathy without OP therapy. In our study, some patients were treated with IVMP+OP after first being treated with high-dose OP. In some patients, pulse therapy was repeated, and all patients received OP therapy. Furthermore, giant cell arteritis and Graves' ophthalmopathy are more homogeneous disease populations than IOI in which myositis, dacryoadenitis, sclerosing pseudotumor and diffuse inflammation are grouped. IOI differs from Graves' ophthalmopathy in that Graves' ophthalmopathy is a self-limiting disease, whereas many patients with severe IOI show recurrences and chronic disease. IVMP may be less effective in recurrent and chronic diseases.
The use of OP in a subgroup of 32 patients with IOI has been evaluated by Mombaerts et al.[14] Based on a low cure rate of 37% after a single course of prednisone and a high recurrence rate of 52%, the authors doubted the effectiveness of prednisone in the treatment of IOI, but valued prednisone for treatment of optic neuropathy because of prompt restoration of vision upon treatment. In our study, prednisone treatment resulted in 79% of patients being symptom-free. We believe that prednisone is effective in the treatment of IOI, although, to be effective, it sometimes has to be administered for years.
In conclusion, our study demonstrated that there was no advantage of treating patients with severe IOI with IVMP+OP in terms of shortened treatment duration, lower cumulative dose or decrease in persistent symptoms. Therefore we suggest that the indication of IVMP in the treatment of severe IOI is limited to speeding symptom relief and recovery from optic nerve dysfunction.

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Chapter 9

Azathioprine and prednisone combination treatment for adult periocular and orbital xanthogranulomatous disease

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Abstract

Purpose: To report the authors' experience with azathioprine and prednisone combination for adult periocular and orbital xanthogranulomatous disease.

Methods: We identified 13 adults with histology-proven periocular or orbital xanthogranuloma in two tertiary referral orbital centres from 1984 to 2008. Patient records were reviewed and data collected on orbital localization, immune dysfunction, applied treatment and outcome.

Results: Five patients with periocular or orbital xanthogranulomatous disease were fully treated with prednisone and azathioprine combination, which resulted in stabilization in two and regression in three. Two other patients had to discontinue azathioprine because of side-effects. Of the non-fully treated prednisone/azathioprine patients, four out of eight progressed.

Conclusion: In adult periocular and orbital xanthogranuloma, combined treatment with prednisone and azathioprine yields adequate immunosuppression, often for a prolonged period of time.

Introduction

Orbital xanthogranuloma is a rare disease. The clinical presentation in adults consists of uni- or bilateral orbital mass lesions or periocular yellow-brown infiltrates that may mimic xanthelasmata. These abnormalities tend to progress, causing eyelid disfigurement, eyeball displacement, eyeball motility disturbances and – rarely – optic neuropathy. Periocular and orbital xanthogranulomatous disease is now considered to constitute a spectrum of four entities that comprise adult-onset orbital xanthogranuloma (AOX), adult-onset asthma and periocular xanthogranuloma (AAPOX)[1], necrobiotic xanthogranuloma (NBX)[2;3] and Erdheim–Chester disease (ECD)[4].

Various treatments have been applied for periocular and orbital xanthogranulomas including surgical debulking,[5;6] radiotherapy,[7;8] immunosuppression[9-15] and observation. Best treatment results are gained with a combination of prednisone and an immunosuppressive.[16] However, there is no consensus on the best choice of immunosuppressive drug. In this article, the authors report on their good results with combined azathioprine and prednisone treatment in orbtial xanthogranulomatous disease.

Methods

We analysed the records of 13 consecutive patients of adult periocular and orbital xanthogranulomas: 10 from the Rotterdam Eye Hospital and three from the University Medical Centre Utrecht. Diagnostic features of three patients (patients 1, 2 and 4) have been reported previously.[8] From the case records we collected data on demographics, presence and extent of orbital involvement, ophthalmic signs, systemic immune function, treatment modalities and outcome in terms of regression of lesions and functional deficit. Patients were categorized to suffer from ECD in the event of systemic involvement of retroperitoneal structures and/or long bones, from NBX in the event of marked necrobiosis on histology specimens, and from AAPOX when adult-onset asthma was present. When lesions were isolated to the periocular structures and/or orbit the patient was categorized as having AOX.

Regression was defined as reduction in orbital and adnexal tissue involvement and resolution of inflammatory signs. Stabilization was defined as persistent structural changes of orbital and adnexal tissues. Progression was defined as an increase in orbital or adnexal tissue involvement. The extent of orbital involvement was determined radiographically.

Table 9.1. Characteristics of 13 adult periocular and orbital xanthogranuloma patients

Patient	Age*	Sex	Structures involved	Periocular skin findings	Other ocular signs and associations
1 AOX	34	M	Bilateral lacrimal gland regions	Bilateral eyelid swelling	Motility disturbance
2 AOX	40	F	Left lacrimal gland region, bilateral extraocular muscles, left fossa temporalis	Bilateral xanthomatous lesions	Motility disturbance, xanthogranuloma of oral cavity (sublingual)
3 AAPOX	75	F	Right lacrimal gland region and extraocular muscles	Bilateral eyelid swelling, xanthomatous lesions	Psoriasis, asthma
4 ECD	43	M	Bilateral: lacrimal gland regions, extraocular muscles, intraconal, apical, cavernous sinus, hypophysis	Bilateral xanthomatous lesions	Bilateral: motility disturbance, optic neuropathy; retroperitoneal fibrosis,long bones and skull involvement
5 NBX	43	M	Preseptal eyelid	Xanthomatous lesions	Multiple myeloma, granuloma annulare
6 AAPOX	60	F	Bilateral lacrimal gland regions, extraocular muscles	Xanthomatous lesions	Motility disturbances, asthma, autoimmune thyroiditis
7 AOX	30	M	Lacrimal gland region, extraocular muscles, apex, fossa pterygopalatina	–	Motility disturbance, optic neuropathy, hypesthesia supraorbital nerve
8 AOX	62	F	Preseptal eyelid	Brown xanthomatous lesions	Motility disturbance
9 AOX	60	M	Preseptal eyelid and conjunctiva	Xanthomatous lesions	–
10 AAPOX	78	F	Bilateral lacrimal gland regions	Eyelid swelling	Cheek swelling, asthma
11 AOX	44	M	Lacrimal gland regions, extraconal upper temporal quadrant	–	Motility disturbance
12 NBX	58	M	Lacrimal gland regions	Bilateral xanthomatous lesions	Idiopathic thrombotic thrombocytopenic purpura,lymphadenopathy
13 NBX	47	M	Preseptal eyelid	Xanthomatous lesions	Chronic lymphocytic leukaemia

AOX, orbital xanthogranuloma; NBX, necrobiotic xanthogranuloma; AAPOX, adult-onset asthma and periocular xanthogranuloma; ECD, Erdheim–Chester disease. *Age at diagnosis.

This study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and institutional review board approval was not required.

Results

Patient characteristics are summarized in Table 9.1. Diagnosis of xanthogranuloma was based on biopsy of orbital tissue in patients 7 and 11, of lacrimal gland in patients 4 and 6 and of eyelid tissue in all others. Six patients suffered from AOX, three from NBX, three from AAPOX and one from ECD. There were eight men and five women. The age at presentation ranged from 30 to 78 years (median 47). The most commonly involved orbital structures were the lacrimal gland, with diffusion into adjacent structures (9/13) and the extraocular muscles (5/13). Superficial eyelid lesions were present in nine patients.

Table 9.2 summarizes the applied treatment and outcome. The median follow-up is 2 years (range 0.5 to 17 years). The mainstay of medical treatment consisted of oral prednisone with azathioprine combined (8/13). Of the eight patients with prednison and azathioprine combination, two had to discontinue treatment because of nausea or gastrointestinal upset, and one refused further medical treatment for years. Of the five patients who had been fully treated with combination azathioprine and prednisone, two stabilized and three regressed. Of the patients who discontinued azathioprine because of its side-effects, one progressed slowly under ciclosporin with prednisone and one regressed under cyclophosphamide with prednisone. The patient who refused azathioprine and other medical treatment progressed slowly.

Two patients with lymphoproliferative disease were treated with chemotherapy, of whom one stabilized and one died because of pulmonary complications after bone-marrow transplantation and the development of graft-versus-host disease. One patient was treated with prednisone alone and progressed slowly. Two patients were not treated medically, of whom one progressed slowly and one regressed spontaneously.

Overall, the patients treated fully with combined prednisone and azathioprine seemed to have better outcomes: five of five patients stabilized or regressed, compared with three of the eight patients who were treated differently ($p = 0.075$, Fisher's exact test).

The combined prednisone–azathioprine treatment regimen consisted of high-dose prednisone at 0.5–1 mg/kg/day and azathioprine 1–2 mg/kg/day. Upon clinical resolution of inflammatory signs, the prednisone was first tapered to 10 mg/day or

Table 9.2. Treatments and outcomes of 13 patients with adult periocular and orbital xanthogranuloma

Patient	Treatment	Treatment complications	Follow-up, y	Outcome
1 AOX	Prednison, debulking 3 ×	Ectropion	17	Slowly progressive, lost to follow-up
2 AOX	Blepharoplasty 7 ×		16	Slowly progressive, lost to follow-up
3 AOX	Prednison, azathioprine, ciclosporin	Azathioprine stopped (nausea)	11	Slowly progressive
4 ECD	Prednison, ciclosporin, octreotide, cyclophosphamide, etanercept, gammaglobulin, azathioprine (maintenance), decompression, debulking, radiotherapy 36 Gy, 177Lu-DOTA-Tyr3-octreotate	Systemic herpes infection	12	Stable, mild optic nerve dysfunction, moderate motility disturbances
5 NBX	Chemotherapy for multiple myeloma, radiotherapy to systemic lesions, bone-marrow transplantation	Pulmonary fibrosis	1	Died of pulmonary complications
6 AAPOX	Prednison, azathioprine, decompression (diagnosis of Graves' orbitopathy was presumed), debulking, blepharoplasty 2 ×		9	Slowly progressive, refused medical treatment for 2 years, regression after restarting prednison
7 AOX	Prednison, azathioprine (maintenance)	–	2	Regression with persistent hypesthesia and minor optic nerve dysfunction
8 AOX	Prednison, azathioprine, debulking	Eyelid retraction	2	Regression
9 AOX	Prednison, azathioprine, debulking	–	1	Regression
10 AOX	–	–	0.5	Spontaneous resolution
11 AOX	Prednison, azathioprine, cyclophosphamide	Weight loss and abdominal discomfort resolved after discontinuation azathioprine	3	Regression
12 NBX	Prednison, azathioprine (maintenance)	–	2	Stable
13 NBX	Chemotherapy for leukaemia	–	2	Stable

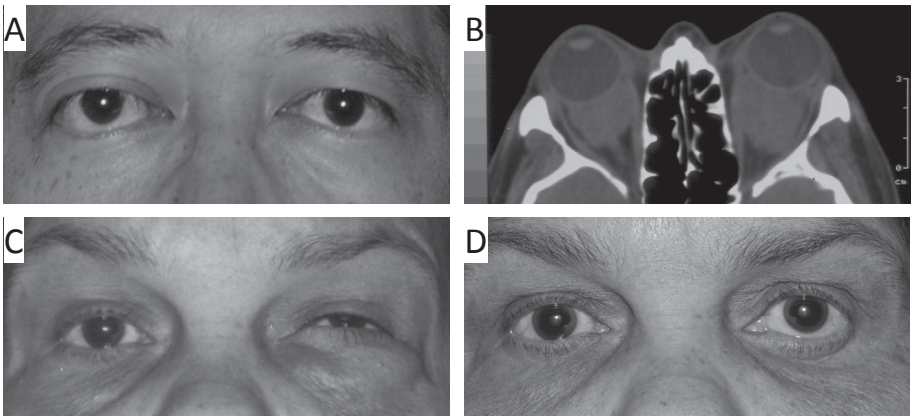

Figure 9. Results with combined prednisone and azathioprine treatment. A, B, case 4 Erdheim-Chester Disease. A, before eyelid lesions appeared. B, extensive, but stable involvement of retrobulbar spaces left more than right. Stabilization was achieved by maintenance therapy with azathioprine and prednisone. C, D, case 8 Adult onset Orbital Xanthogranuloma. C, brown xanthomatous lesions of the lower left eyelid. D, eyelid lesions disappeared after treatment with azathioprine and prednisone.

less. Secondly, the azathioprine was tapered to the lowest effective dose (patients 4 and 7) or discontinued after an average administration duration of 1 year. Figure 9 shows pre- and post-treatment images of patients treated with both prednisone

Table 9.3. Treatment effects of various therapeutic regimens for orbital and adnexal xanthogranuloma.

	Oral corticosteroids	**Local corticosteroids**	**Corticosteroids with other immuno-suppressives**	**External beam radio-therapy**	**Surgery**
	N improved/ treated	N improved/ treated	N improved/ treated	N improved / treated	N improved / treated
Cruz[243]		5/6			
Hayden[244]			2/3 MTX		
Karcioglu[245]	0/3			1/4	4/6
Ugurlu[246]		2/9	10/17 CHL or MEL	2/5	
present series	0/1		5/5 AZT		0/1
Total (%)	*0/4 (0)*	*7/15 (47)*	*17/25 (68)*	*3/9 (33)*	*4/7 (57)*

MTX, metotrexate; CHL, chlorambucil; MEL, melphalan; AZT, azathioprine.

and azathioprine. Table 9.3 compares the treatment effects of various therapeutic regimens for orbital and adnexal xanthogranuloma; it demonstrates that corticosteroids combined with other immunosuppressives, particularly azathioprine, are most effective.

Discussion

In this series of 13 patients, good treatment results of combined azathioprine and prednisone are shown in adult periocular and orbital xanthogranulomas. Regression and stabilization of orbital disease occurred in all five patients treated fully with both azathioprine and prednisone. In contrast, progression after cessation of azathioprine treatment occurred in two out of three patients who were treated with azathioprine and prednisone, two of whom had to discontinue azathioprine because of gastrointestinal upset or nausea and one of whom refused medical treatment. Of the patients never treated with azathioprine/prednisone, three showed progression. Interestingly, the patient with Erdheim–Chester disease, a disease known to be a recalcitrant fibrosclerosis of the orbit and internal organs, had been treated with numerous different immunosuppressive agents, but finally stabilized under maintenance treatment with prednisone and azathioprine.
The effectiveness of corticosteroids combined with immunosuppressives in adult periocular and orbital xanthogranulomatous disease is consistent with literature findings, as is shown in Table 3. Of these combined treatments, chlorambucil, melphalan and metotrexate appear to be less effective than azathioprine.
Azathioprine is a purine antagonist belonging to the group of antimetabolites and causes disruption of nucleic acids. Lymphocytes rely on de novo synthesis of purines. Azathioprine is thought to be relatively specific to lymphocytes, i.e. more specific for T-cells than for B-cells.[17] Azathioprine is a widely used immunsuppressive agent in rheumatic and dermatological diseases.[17]
The association between orbital xanthogranuloma and other autoimmune diseases is interesting. In our patient series the co-occurrence of asthma, psoriasis, granuloma annulare and idiopathic thrombocytopenic purpura is noted. These conditions are considered to be related to T-cell dysfunction, and to be more specific as a CD4+ T-helper cell derangement. Recent findings suggest orbital xanthogranuloma to be CD8+ cytotocix T-cell-related.[8] However, there is evidence for a B-cell-related pathogenesis by immunohistochemistry of a necrobiotic xanthogranuloma showing strong CD20 (B-cell-related),[18] a monocyte-related pathogenesis, in a patient with ECD;[9] there is also evidence of a link with Borrelia burgdorferi in six NBX patients.[19] In view of these findings, treatment of adult

periocular and orbital xanthogranulomatous disease should be directed at T-cells and, preferably, also against B-cells. Azathioprine is one of the immunosuppressive agents that has both T- and B-cell effects.

A substantial number of NBX patients are seen by dermatologists when there is solitary or additional involvement of skin of the trunk or extremitie.[20;21] Dermatologists tend to treat NBX with more aggressive cytotoxic drugs such as cyclophosphamide, chloroambucil and melphalan. Because immunosuppression with the least toxic drug is preferable, azathioprine is proposed as a good alternative.[8;10;13;22;24]

Two of the nine patients treated with azathioprine had to discontinue medication because of side-effects. Among the side-effects of azathioprine, leucopaenia and bone-marrow depression are encountered most frequently, necessitating frequent blood counts. Nausea, gastrointestinal upset and thrombocytopenia occur in about one in 10 patients. When the drug is tolerated, people can often stay on azathioprine for years, as shown by patients 4 and 12. In others, after regression had been observed, the immunsuppressive agents were phased out and discontinued.

This study is limited by its observational nature. To fully demonstrate azathioprine with prednisone treatment to be superior to other treatments in adult periocular and orbital xanthogranulomas, a randomized controlled clinical trial would be necessary. However, because of the low incidence of the disease, this would not be feasible.

In conclusion, because of the good outcome of combined treatment with prednisone and azathioprine in our patients, supported by a positive statistical trend, we recommend this regimen as initial treatment for periocular and orbital xanthogranulomatous disease.

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Chapter 10

Discussion

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The aim of this thesis was to further our understanding of etiology, diagnosis and treatment of IOI. This thesis has provided some new insights into IOI that will be discussed below.

Progress

What progress has been made in the etiology of IOI?
So far, IOI has been hypothesized to be a disease with autoimmune, infectious or neoplastic origin. This study demonstrated an association between IOI and the risk factors BMI and use of bisphosphonates. BMI has been associated with autoimmune disease through the protein leptin. Both leptin and bisphosphonates have been shown to influence the immune system through the release of cytokines. Furthermore, an almost significant association between IOI and the risk factor history of autoimmune disease was found. In addition, a close link between IOI and the orbital autoimmune disease Graves' ophthalmopathy was established. Another key-finding in the etiology of IOI was the demonstration of viral persistence in patients with IOI. Viral persistence has been associated with autoimmune disease by continual stimulation of the immune system, by a shared antigen between self and a virus, or by bystander activation of immune cells. Taken together, a multitude of autoimmune related factors can be pointed out to play a role in IOI development. These findings make us believe that IOI is an autoimmune disease with a multifactorial etiology.

What progress has been made in the diagnosis of IOI?
Biopsies in IOI have been controversial. Proponents of biopsies in IOI plea for biopsy in almost all IOI patients. Others claim that a good clinical response to a therapeutic trial of corticosteroids is sufficient to demonstrate IOI. This thesis analyzed the diagnostic process of a group of patients suspected of IOI and a group of patients suspected of orbital Wegener's granulomatosis, a specific orbital inflammatory disease. It was demonstrated that a biopsy is pivotal in the diagnosis of both IOI and Wegener's granulomatosis. Another study on the diagnostic process of IOI suggests biopsy in all IOI suspected patients except for patients with low suspicion of malignancy with muscular and apical orbital mass localizations. Furthermore, a new classification system is proposed that combines histology and localization information to create more homogenous patient groups for research purposes, such as a randomized controlled clinical trial for treatment of severe IOI. This classification system asks for biopsy samples to fill in one of the classification

dimensions.
These results suggest that biopsies should be performed in IOI with fewer restraints.

What progress has been made in treatment of IOI?
The mainstay of treatment for IOI has been with oral corticosteroids. However, oral corticosteroids have been unsuccessful in providing long-term remission in many patients with IOI. These unsatisfactory results have prompted search for better treatment modalities. In some autoimmune diseases, intravenous methylprednisolone has been shown to be superior to oral prednisone treatment, but this superiority could not be demonstrated in severe IOI. In case of prolonged corticosteroid treatment, the use of steroid sparing drugs has been advocated. The combination of corticosteroids and steroid sparing agents may be even more potent as has been demonstrated in the successful treatment of some patients with severe orbital inflammatory disease with the combination azathioprine and prednisone.

Consequences for clinical practice

This thesis has some implications on how we diagnose and treat patients with IOI. Patients with IOI are often treated with prednisone for an extended period. One is inclined to prevent osteoporosis in these patients by using bisphosphonates. Because bisphosphonates have been found to be a risk factor for IOI, one should be cautious in prescribing bisphosphonates to IOI patients. It is recommended to withhold bisphosphonates until decrease in bone mineral density has been demonstrated. This is in line with recent evidence of osteonecrosis and poor fracture healing in steroid-treated patients on long-term bisphosphonate therapy.[1]
We recommend calcium and vitamin D3, along with bone mineral density measurement in all patients that are treated for more than three months with corticosteroids.
The association between higher BMI and development of IOI has suggested aiming at weight loss in obese patients as part of the therapeutic strategy.
The demonstration of co-occurrence of Graves' ophthalmopathy and IOI has prompted us to use Graves' not as an exclusion criterion for IOI. However, in active Graves ophthalmopathy a simultaneous diagnosis of IOI still seems unlikely.
A low threshold for biopsy should be used for patients suspected of IOI because of the advantages of histological- confirmation and classification. The only exceptions are patients with low suspicion of malignancy with muscular and apical mass

localizations, or with optic nerve compression. In these patients biopsy is postponed until after the result of a therapeutic trial of corticosteroids. Intravenous methylprednisolone in IOI is not administered with the intention to decrease treatment duration, but rather in some patients for more rapid clinical improvement. In more aggressive types of IOI the combination treatment with prednisone and other immunosuppressives is considered a potent treatment strategy.

Limitations of studies presented

Most studies in this thesis used retrospective patient data. Ideally, all studies would have been designed prospectively with accurate and extensive data recording on subtypes of IOI as classified according to the chapter 7 criteria. However, because of the low incidence of IOI such designs would have prolonged the research project. The population that was researched in this thesis consisted of Dutch, mostly Caucasian patients. Also, only patients at specialized orbital clinics were included. It is not known how many IOI patients are treated by their general ophthalmologist and in what way these patients differ from our population. No subtypes of IOI were studied because study sizes were too small to warrant subgroup analyses. Studies should be repeated in other populations with different racial constitutions before results can be generalized.
In the study on infectious triggers and IOI only a limited number of bacteria and viruses were tested and no microorganism was identified to be directly related to IOI. It is possible that another, non-tested, microorganism is responsible for the development of IOI, but one would expect a higher number of case reports to describe a link between the systemic infection caused by such an organism and orbital inflammation.
In chapter 7 a new best-practice IOI classification system is presented. This system was only developed at the end of the research project. As a result, the classification system was not used in other studies presented in this thesis. Only in future studies can we gain experience with this new classification system.
A problem still unsolved is that we have very limited extraocular muscle biopsies of patients with myositis. As a result, orbital myositis can be studied less adequately. Another problem is the lack of criteria that differentiates non-severe from severe IOI. Without such criteria it is hard to start clinical trials to test aggressive therapies for severe IOI.

Suggestions for future research

This research has solved some questions about the etiology, diagnosis and treatment of Idiopathic orbital inflammation. As can be expected, many questions have evolved that can be elaborated on.
A promising road to follow is the association with BMI that highlights a possible role for leptin or the fat cell in the etiology of IOI. Bisphosphonates can be associated with IOI through their action on inflammatory cytokines. Cytokines can be studied in biopsies and animal models to unravel the pathogenesis. Possibly, the plea to lower the biopsy threshold in IOI will result in more biopsy remnants to be available for research.
The diagnostic process of IOI as it was laid out can be further improved when more specific diagnostic tests become available, such as immunohistopathology, molecular-, and genomic techniques. Also, new etiologic factors in IOI should be followed by the development of new diagnostic tests.
Ideally, as our understanding about IOI evolves, the number of patients who are diagnosed as non-specific IOI should decrease because more specific orbital inflammations can be diagnosed. IgG4 associated orbital disease is a good example of the coining of specific entities.
The causes for the high recurrence rate of IOI after discontinuation of corticosteroids and the high rate of persistent symptoms after IOI are still unknown and should be prioritized for future research. The classification system of IOI will enable selection of appropriate patients for future therapeutic studies, preferably with more targeted therapy. Currently, IOI seems to have a multifactorial etiology suggesting that treatment can be targeted at multiple aspects of the disease. To obtain enough patients for such further research, collaboration between centers should be continued. This study has shown that collaboration within the Netherlands is possible, but international cooperation would lead to larger study groups and faster and more conclusive results. A focus group of the European Society of Plastic and Reconstructive Surgery would be an ideal start.

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Chapter 11

Summary and conclusions

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Idiopathic orbital inflammation (IOI) is a disease with signs and symptoms of an orbital inflammatory lesion with after local and systemic evaluation no apparent cause. As the term idiopathic implies, little is known about the etiology of the disease. This study aimed to answer three questions: a) what etiologic factors are involved in the pathogenesis of IOI, b) what diagnostic approach should be taken to diagnose IOI and how can IOI be classified into subtypes, and c) what therapies are effective in treating IOI.

In **chapter 1** Idiopathic orbital inflammation was defined and current challenges in IOI were formulated. The epidemiology, clinical presentation, diagnostic studies, treatments, and outcomes of IOI were described. Gaps in our knowledge of IOI were identified that have prompted the conduction of the current studies.

Etiology

What etiologic factors can be identified in the pathogenesis of IOI?
Chapter 2 described the first systematic search for risk factors in IOI using a case-control study. Sixty nine adults with a first episode of IOI were compared to 296 adults with rhegmatogenous retinal detachment. Risk factors considered were demographic factors, medical history, health status, and exposures in the two years prior to disease presentation. Women were questioned about previous or current pregnancies, and their hormonal status. Odds ratios were calculated adjusted for age, sex, socio-economic status, smoking, and blunt orbital trauma.
The outcome was that the risk of IOI was increased in participants who had a higher BMI or who used bisphosphonates. The risk was decreased in participants with a higher socio-economic status and in women older at first childbirth. An almost significant association was found between IOI and autoimmune disease.

Do infectious triggers initiate the disease IOI?
A high rate of co-occurrence between IOI and sinus inflammation has led to the hypothesis that an uncontrolled immunologic response to a microorganism can result in IOI. This hypothesis was tested in **chapter 3** by testing IOI biopsy specimens for remnants of microorganisms. Using quantitative PCR techniques, the following microorganisms have been tested: Mycobacterium tuberculosis, Mycobacterium genus species, Mycoplasma pneumonia, Chlamydia pneumonia, Herpes simplex virus, Varicella zoster virus, Cytomegalovirus, EBV, Human herpes virus 6 (HHV6), Adenoviruses, Parvovirus B19, human Coronaviruses OC43, 229E

and NL63, Enteroviruses, Influenza viruses A and B, human Metapneumovirus, Parainfluenzaviruses 1 to 4, human Parechovirus, Respiratory Syncytial virus, Rhinoviruses and Rubella virus. An equal number of specimens of control patients was tested.
The results showed that no remnants of bacteria were detected. Viral presence was statistically significant more often present in orbital biopsies of IOI patients compared to controls. The most common virus encountered in our IOI biopsies was Parvo-B19, but with equal prevalence among controls. However, Epstein-Barr virus and Human Herpesvirus-6 was found more often in patients than in controls. These results support a role of viral persistence in the development of IOI.

Does the diagnosis of Graves' ophthalmopathy exclude the diagnosis of IOI?
Chapter 4 questioned the current definition of IOI that claims that a diagnosis can only be made after exclusion of systemic causes like Graves ophthalmopathy. Four cases were presented in whom diagnoses of both Graves and IOI were made in the same patient, at different times.
The results demonstrated that Graves' disease should not by default be an exclusion criterion for IOI. Also, a possible common etiology between these two orbital inflammatory diseases was suggested.

Diagnosis

What is the best diagnostic approach for patients suspected of IOI?
Because IOI is a diagnosis of exclusion, the diagnostic process is per definition difficult to define. In **chapter 5** the first effort was presented of testing a stepwise, clinical algorithm to diagnose IOI within a cohort of 117 patients with signs and symptoms of orbital inflammation. Steps of the diagnostic algorithm included: 1. history and physical examination; 2. imaging and laboratory testing; 3. either biopsy or a therapeutic trial of corticosteroids; and 4. consultation with medical specialist.
The results showed that this algorithm was efficient in making a diagnosis after three steps in 93%. The algorithm was demonstrated to be safe in that sense that no patients with a malignancy were inadvertently treated with corticosteroids. The study advocates the reservation of a therapeutic trial of corticosteroids for patients with low suspicion of malignancy with muscular and apical mass localizations, or with optic nerve compression.

How do we differentiate between IOI and Wegener's granulomatosis?
Chapter 6 tackled the difficult differentiation between IOI and orbital Wegener's granulomatosis (WG). Both IOI and Wegener can show granulomas on orbital biopsy. Because of the devastating nature of Wegener's granulomatosis, not only for the orbit but also for other organs, it is important to make the correct diagnosis of Wegener. This study looked at 33 patients in whom a diagnosis of Wegener was considered and looked at what factors made the final distinction between Wegener, and IOI.
The results showed that diagnostic findings indicating orbital WG were ear/nose/throat involvement, multiple organ system involvement, a positive ANCA, and vasculitis on histology, whereas granulomatous inflammation without signs of vasculitis was more indicative of other orbital disease. Histopathology is therefore important for the diagnosis of WG.

Can we classify the mixed group of IOI in specific subtypes that are helpful for therapy or research?
Heterogeneity of the IOI patient group has impeded research on etiology, treatment effectiveness, and prognosis of IOI. **Chapter 7** described the evaluation of existing IO classification systems, the extraction of a new multidimensional classification system, and the testing of the new classification system for reliability, feasibility, face validity, content validity, and distinction.
A combined histopathology and localization-based classification system was shown to provide a repeatable, easy to apply, plausible, and complete IOI classification system. Such a classification system is crucial in furthering our understanding of non-specific idiopathic orbital inflammatory diseases through research.

Treatment

Are intravenous steroids effective in treating severe IOI?
Chapter 8 evaluated the use of intravenous methylprednisolone in the treatment of severe IOI. In many autoimmune diseases, intravenous methylprednisolone is advocated because of its ability to knock down disease activity aggressively resulting in shorter prednisone treatment duration. A sub selection of severe IOI patients was made in a cohort of IOI patients. In this group of severe IOI 15 patients had been treated with oral prednisone and 12 patients had been additionally treated with intravenous methylprednisolone.
The group of intravenously treated patients did not show shorter treatment

duration, nor any significant differences in symptom-free outcome and treatment-related complications. These results suggest that the benefit of additional intravenous methylprednisolone to oral prednisone in IOI is limited. The chronic and recurrent nature of IOI is thought to limit effectiveness of intravenous methylprednisolone.

What is the effect of prednisone and an immunosuppressive treatment combination for adult periocular and orbital xanthogranulomatous disease?
Chapter 9 described treatment of adult periocular and orbital xanthogranulomatous disease with azathioprine and prednisone combination. Adult periocular and orbital xanthogranulomatous disease is a spectrum of aggressive diseases with xanthogranulomas in biopsy specimens.
Five patients were treated with combination of prednisone and azathioprine, which resulted in stabilization in two and regression of the disease in three. These results suggest prednisone with azathioprine combination to be a good treatment regimen in aggressive orbital inflammation.

Conclusions

In **chapter 10** the progress that has been made in etiology, diagnosis, and treatment of IOI was discussed. It was concluded that IOI is likely a multifactorial autoimmune disease, that biopsies have a pivotal role in the diagnosis and classification of IOI, and that treatment of severe IOI is still unsatisfactory. Furthermore, the consequences for clinical practice, the limitations of the studies, and suggestions for future research were highlighted.

Samenvatting en conclusies

Idiopatische orbitale inflammatie (IOI) is een ziekte met klachten en bevindingen van een orbitale ontsteking zonder aanwijsbare oorzaak na lokaal en systemisch onderzoek. Zoals de naam idiopatisch aangeeft, is er weinig bekend over het ontstaan van de ziekte. Dit proefschrift was er op gericht drie vragen te beantwoorden: a) welke factoren zijn betrokken bij het ontwikkelen van IOI, b) welke benadering kan het beste gekozen worden om de diagnose IOI te stellen en hoe kan IOI onderverdeeld worden in subtypes, en c) welke behandelingen zijn effectief voor IOI.

In **hoofdstuk 1** werd de ziekte idiopatische orbitale ontsteking omschreven. De epidemiologie, klinische presentatie, diagnostische onderzoeken, behandelingen en uitkomsten van IOI werden beschreven. Hiaten werden geïdentificeerd in onze kennis over IOI die hebben geleid tot de in dit proefschrift beschreven studies.

Etiologie

Welke factoren kunnen worden aangewezen die leiden tot het ontstaan van IOI?
In **hoofdstuk 2** werd het eerste systematische onderzoek beschreven naar risicofactoren voor IOI middels een case-control studie. Negenenzestig volwassenen met een eerste episode van IOI werden vergeleken met 296 volwassenen met een rhegmatogene netvliesloslating. Onderzocht als mogelijke risicofactor werden demografische factoren, medische voorgeschiedenis, gezondheidstatus en blootstellingen in de twee jaren voorafgaand aan de ziektepresentatie. Vrouwen werden bevraagd naar voorgaande of huidige zwangerschappen en de hormoonstatus. Odds ratios werden berekend gecorrigeerd voor leeftijd, geslacht, sociaal-economische status, roken en stomp oogkastrauma.
Deze studie toonde aan dat het risico op IOI groter is voor mensen met een hogere body mass index en voor mensen die bisfosfonaten gebruikten. Het risico op IOI was lager bij mensen met een hogere sociaal-economische status en bij vrouwen die ouder waren op de leeftijd van de geboorte van het eerste kind. Een bijna significante associatie werd gevonden tussen IOI en auto-immuun ziekte.

Zijn infectieuze triggers betrokken bij het ontstaan van IOI?
Het veelvuldig samen voorkomen van IOI en bijholteontsteking heeft tot de hypothese geleid dat een ongecontroleerde immunologische reactie op een micro-organisme een IOI kan veroorzaken. Deze hypothese werd getest in **hoofdstuk 3**

door bioptweefsel van IOI patiënten te onderzoeken op micro-organismen. Met kwantitatieve polymerase chain reaction technieken werden de volgende micro-organismen getest: Mycobacterium tuberculosis, Mycobacterium genus species, Mycoplasma pneumonia, Chlamydia pneumonia, Herpes simplex virus, Varicella zoster virus, Cytomegalovirus, Epstein-Barr virus, Humaan herpes virus 6 (HHV6), Adenovirussen, Parvovirus B19, humane Coronavirussen OC43, 229E en NL63, Enterovirussen, Influenza virussen A en B, humaan Metapneumovirus, Parainfluenzavirussen 1 tot en met 4, humaan Parechovirus, Respiratory Syncytial virus, Rhinovirussen en Rubella virus. Een zelfde aantal biopten van controle patiënten werd getest.
Er werden geen bacteriën aangetoond. Virussen kwamen significant vaker voor in orbitale biopten van IOI patiënten in vergelijking met controle patiënten. Het meest aangetoonde virus in onze IOI biopten was Parvo-B19, maar dit kwam even vaak voor bij de controles. Daarentegen kwamen Epstein-Barr virus en Humaan Herpesvirus-6 vaker voor bij IOI patiënten dan bij controles. Deze resultaten ondersteunen een rol voor virale persistentie bij het ontstaan van IOI.

Sluit de diagnose Graves' oogziekte de diagnose IOI uit?
In **hoofdstuk 4** werd de huidige definitie van IOI in twijfel getrokken waarbij de diagnose alleen kan worden gesteld na het uitsluiten van lokale of systemische oorzaken zoals Graves' orbitopathie. Vier patiënten werden beschreven bij wie zowel de diagnose Graves en IOI werden gesteld op verschillende momenten in de tijd.
De beschrijving van deze patiënten toonde aan dat Graves' orbitopathie niet per definitie een exclusie criterium is voor IOI. Een mogelijke gemeenschappelijke oorzaak van deze twee oogkasziektes werd gesuggereerd.

Diagnose

Wat is de beste diagnostische benadering voor patiënten verdacht van IOI?
Omdat IOI een diagnose is die bij exclusie van meer specifieke diagnoses wordt gesteld, is het diagnostisch proces lastig te omschrijven. In **hoofdstuk 5** werd een stapsgewijs algoritme om IOI te diagnosticeren getest bij een cohort van 117 patiënten met tekenen en symptomen van oogkasontsteking. Stappen van het algoritme zijn: 1) anamnese en lichamelijk onderzoek, 2) beeldvorming en laboratorium testen, 3) of een biopt of een proefbehandeling met corticosteroïden, 4) consult bij een medisch specialist.

Dit algoritme was efficiënt in het stellen van een diagnose in 93% van de patiënten bij de derde stap. Het algoritme was veilig in de zin dat geen patiënten met een maligniteit onjuist werden behandeld met corticosteroïden. De studie adviseert om proefbehandeling met corticosteroïden te beperken tot patiënten met een lage verdenking op een maligniteit met in de spier of in de apex van de oogkas gelokaliseerde massa's en tot patiënten met compressie van de oogzenuw.

Hoe maken we het onderscheid tussen IOI en de ziekte van Wegener?
In **hoofdstuk 6** werd het moeilijke onderscheid tussen IOI en de ziekte van Wegener besproken. Zowel IOI als Wegener kunnen in het biopt een granulomateuze ontsteking tonen. In verband met de verwoestende aard van de ziekte van Wegener, niet alleen in de oogkas, maar ook elders in het lichaam, is het belangrijk tijdig de diagnose te stellen. Deze studie onderzocht 33 patiënten die verdacht werden van de ziekte van Wegener en keek naar welke factoren het uiteindelijke onderscheid tussen Wegener en IOI maakten.
De belangrijkste diagnostische bevindingen passend bij orbitale Wegener waren betrokkenheid van de keel/neus/oren, betrokkenheid van andere orgaansystemen, een positieve ANCA test, en vasculitis in het biopt. Daarentegen wezen granulomateuze ontsteking zonder tekenen van vasculitis eerder op een andere oogkasziekte. Daarom werd gesteld dat weefselonderzoek belangrijk is om de diagnose Wegener te stellen.

Kunnen we de gemengde groep van IOI patiënten in meer specifieke subgroepen onderscheiden die zinvol zijn voor behandeling of wetenschappelijk onderzoek?
Doordat IOI een heterogene patiëntengroep is ,wordt onderzoek bemoeilijkt naar het ontstaan, de effectiviteit van therapie en de prognose. **Hoofdstuk 7** beschreef de evaluatie van bestaande IOI classificatiesystemen, het extraheren van een nieuw multidimensionaal classificatiesysteem, en het testen van dit nieuwe classificatiesysteem op betrouwbaarheid, doenlijkheid, indruksvaliditiet, inhoudsvaliditeit en onderscheidingsvermogen.
Een gecombineerd weefsel en lokalisatie classificatiesysteem bleek te voldoen aan de eisen voor betrouwbaarheid, doenlijkheid, indruksvaliditiet, inhoudsvaliditeit en onderscheidingsvermogen. Dit classificatiesysteem is cruciaal om verder te komen in het ontrafelen van IOI door wetenschappelijk onderzoek.

Behandeling

Zijn intraveneuze corticosteroïden effectief in de behandeling van ernstige IOI?
In **hoofdstuk 8** wordt het gebruik van intraveneuze methylprednisolon voor de behandeling van ernstige IOI beschreven. Bij veel auto-immuun ziektes wordt intraveneus methylprednisolon geadviseerd omdat deze toediening in staat is de ontsteking de kop in te drukken en daardoor de totale behandelingsduur te bekorten. Uit een cohort IOI patiënten werden patiënten met ernstige IOI geselecteerd. Binnen deze groep bleken 15 patiënten met alleen oraal prednison behandeld te zijn en 12 met oraal en intraveneus methylprednisolon.
Na analyse bleek additionele behandeling met intraveneus methylprednisolon geen kortere behandelduur te geven. Ook wat betreft klachtenvrije uitkomst en behandelingsgerelateerde complicaties, bleek er geen verschil te bestaan in de groep met en zonder intraveneus methylprednisolon. Deze resultaten suggereren dat de voordelen van additioneel methylprednisolon in aanvulling op oraal prednison beperkt zijn. De chronische en recidiverende aard van IOI dragen waarschijnlijk bij aan deze beperkte effectiviteit van intraveneus methylprednisolon.

Wat is het effect van prednison gecombineerd met een immunosuppressivum op de behandeling van perioculaire en orbitale xanthogranulomatose bij volwassenen?
In **hoofdstuk 9** werd de behandeling beschreven van perioculaire en orbitale xanthogranulomatose bij volwassenen met de combinatie prednison en azathioprine.
Vijf patiënten waren behandeld met de combinatie prednison en azathioprine, met als resultaat stabilisatie bij 2 en regressie bij 3 patiënten. Deze resultaten suggereren dat de combinatie prednison met azathioprine een goede behandeling is voor agressieve oogkas ontstekingen.

Conclusies

In **hoofdstuk 10** werden de in dit proefschrift gemaakte vorderingen besproken in etiologie, diagnose en behandeling van IOI. Geconcludeerd werd dat IOI waarschijnlijk een auto-immuun ziekte is met een multifactoriële oorzaak, dat biopten een belangrijke plaats hebben in de diagnose en classificatie van IOI en dat de behandelingsmogelijkheden van ernstige IOI nog steeds onvoldoende zijn. Daarnaast werden de consequenties van de in dit proefschrift beschreven studies

voor de dagelijkse praktijk beschreven evenals de methodologische tekortkomingen. Suggesties voor verder onderzoek naar IOI werden gedaan.

Postscriptum

De drijvende motor achter dit proefschrift waren de patiënten met een idiopatische orbitale ontsteking. Het gebruik van de alternatieve naam 'pseudotumor' wekt bij veel patiënten angst op door de associatie met kanker. Om die angst vervolgens weer weg te nemen leggen we uit dat er geen sprake is van kanker en dat er een ander proces speelt, maar wat precies kunnen we niet vertellen omdat de wetenschap daarover tekort schiet. Deze constatering vormde de eerste aanzet tot nader onderzoek naar idiopathische orbitale ontsteking. Een andere initiatior van dit onderzoek was de onduidelijkheid over het te lopen diagnostisch traject inclusief de discussie over wel of niet biopteren. Ook speelde mee de discrepantie tussen waarom sommige patiënten met een snufje prednison volledig genezen en bij anderen grammen prednison aangevuld met andere ontstekingsremmers het ziektebeeld niet kunnen stoppen. Nu vier jaar en acht studies verder kan ik patiënten met een idiopathische orbitale ontsteking wat beter informeren, diagnosticeren en helpen, maar er blijft nog steeds veel onbekend en te onderzoeken.

Vanaf het moment dat ik besloot geen promotietraject te volgen voor aanvang van mijn opleiding tot oogarts, spoorde professor Jan Stilma mij aan om wel op een later moment te gaan promoveren. Geïnspireerd en geïntrigeerd door het contact met de idiopathische orbitale ontsteking patiënten, werkte ik met Rachel Kalmann en Maarten Mourits openliggende vragen uit tot onderzoeksvoorstel. Jan Stilma hielp bij het verkrijgen van financiering door de F.P. Fischer stichting en was bereid de rol van promotor op zich te nemen. Anderhalf jaar werd besteed aan het verkrijgen van toestemming bij de medisch ethische toetsingscommissie. Op de valreep van het afsluiten van de opleiding tot specialist, werd na methodologische hulp van Carla van Gils groen licht gegeven voor het onderzoek.

Het eerste jaar van het promotietraject stond in het teken van de Master Clinical Epidemiology waarvoor ik met veel plezier weer plaatsnam in de schoolbanken en samen met lotgenoten me door de statistiek heen worstelde. In de tussentijd was mijn echtgenote Rhodé Bijlsma – van Leeuwen door de zwangerschapshormonen beïnvloed en wist zij het project Merellaan 1 aan mij te verkopen. Op 30 september 2007 werd onze dochter Annelie geboren. Ik kon geen woord meer uitbrengen. Een allerliefst klein mensje lag daar in de armen van mijn vrouw die net een topprestatie had geleverd. Ik werd er acuut nederig van en wist dat werk en carrière maar relatieve begrippen waren als je zoiets moois bezat. Een maand later ging de sloophamer in het pand aan de Merellaan 1 waar ik vanaf dat moment niet meer uit kwam, behalve dan voor onderwijs, werk, slapen of een gaslekkage. Toen we in januari dan eindelijk in het huis trokken, was er weer meer tijd voor onderzoek en werden de eerste studies opgestart . Met hulp van Dion Paridaens, Roel Kloos en Maarten Mourits werden van patiënten met idiopathische orbitale

ontsteking biopten verzameld, waarvoor Jolanda de Groot – Mijnes de analyses verzorgde. Het echte epidemiologische werk leerde ik van Carla van Gils toen ik de risicofactoren studie opzette, analyseerde en uitwerkte. Ook Simone Schotgerrits en Rikkert van der Valk stonden mij later bij met aanvullende epidemiologische vragen.
Het tweede jaar waren de meeste epidemiologie vakken afgerond en stortte ik me meer op de klinische taken. In ruil voor cappuccino, leidde Rachel Kalmann mij verder op tot orbitachirurg. Op 23 november 2008 leverde Rhodé een tweede wereldprestatie en werd onze zoon Laurens geboren. Hoe veel je van je kinderen houdt en hoe kwetsbaar dat je maakt werd na drie weken duidelijk toen Laurens met hersenvliesontsteking in het ziekenhuis werd opgenomen. Gelukkig hield hij er geen schade aan over en ontwikkelde hij zich tot een allervrolijkst mannetje dat elke dag een glimlach op mijn gezicht weet te toveren. In de periode daarna was het schipperen om naast de patiëntenzorg en nieuw aangenomen managementtaken, de tijd te vinden om het onderzoek voort te zetten. Dit ging door op een lager pitje wat niet eens slecht uitkwam door vertraagde patiënteninclusie. Ondersteuning door Marja Wilmans, Birgit Wilms, Petra Fernhout en Suzan van het Zadelhof scheelde enorm in het rond krijgen van alle taken en maakte dat er tijd geoormerkt bleef voor onderzoek.
Ook het derde en vierde jaar stonden vooral in het teken van patiëntenzorg. Tijdens de opkomst van allerlei nieuwe speerpunten op de afdeling oogheelkunde streden Rachel en ik in een team van orthoptisten, balie-geel medewerkers en Petra Kreukniet om de orbita in stand te houden. Op het moment dat de orbita met naam genoemd werd als belangrijke topklinische zorg in de oratie van Saskia Imhof, wisten we zeker dat we een plekje in het hart hadden veroverd van ons medisch afdelingshoofd. In de wat betreft patiëntenzorg wat rustiger zomer van 2010 doken Fleur van ’t Hullenaar en Niels Engelberts mee de diepte in op zoek naar diagnostiek en classificatie van de idiopathische orbitale ontsteking. In het najaar, toen de eerdere frustraties met de medisch ethische toetsingcommissie net een beetje waren weggeëbd wisten ze het einde van mijn promotie even lastig te maken als de opzet ervan. Het resultaat was een verdere verlenging van het promotietraject, maar gelukkig wist de inrichting van het elektronisch oogheelkundig dossier de vrijgekomen tijd zinvol op te eisen.
Nu aan het eind van dit promotietraject ben ik blij dat ik het heb ondernomen omdat ik er met veel plezier aan heb gewerkt en veel van heb geleerd. Aan de andere kant kijk ik er naar uit om mijn tijd weer meer vrijelijk te kunnen besteden. Misschien was dit proefschrift er wel nooit gekomen als mijn vader niet als voorbeeld had gediend en met een half woord had gezegd dat een promotie er wel bij hoort. Aan mijn moeder heb ik mijn eeuwige energie te danken die maakt dat ik

alle taken heb weten te combineren. Mijn kinderen Annelie en Laurens doen mijn werk vergeten en maken mij trots. Mijn familie en vrienden hebben gezorgd voor voldoende afleiding om de geest scherp te houden. De medewerkers van de afdeling oogheelkunde en OK hebben er voor gezorgd dat ik elke dag met veel plezier naar mijn werk kwam. Eelco Hendriks en Joppe Bijlsma – mijn paranimfen – hebben eerlijk opgebiecht dat ze geen snars van de inhoud van dit proefschrift begrijpen, maar dat ze me graag bijstaan op 29 november.

Iedereen die een bijdrage heeft geleverd aan het tot stand komen van dit proefschrift en in het bijzonder Rhodé voor haar onvoorwaardelijke steun en vertrouwen dank ik zeer hartelijk.

Ward R. Bijlsma, september 2011

Curriculum vitae

Ward Rogier Bijlsma was born on January 30th 1977 in Biharamulo Tanzania, where his parents worked as developmental medical doctors. At age two he moved to Utrecht, the Netherlands. He graduated from secondary school Stedelijk Gymnasium in Utrecht in 1995. He went on to study medicine at Utrecht University and fell in love with ophthalmology. In 1999 he performed a six month research project at the Schepens Eye Institute of Harvard Medical School, Boston MA, USA (Prof.dr. D.A. Sullivan). He graduated from medical school in 2002 and started his residency in ophthalmology at the University Medical Center Utrecht (Prof.dr. W.F. Treffers and Prof.dr. J.S. Stilma). Inspired by Prof.dr. M.P. Mourits and dr. R. Kalmann he started to write a research proposal on idiopathic orbital inflammation for the dr. F.P. Fischer foundation in 2006. After he finished his residency in 2007, he started a combined job as PhD researcher and ophthalmologist specialized in orbit, eyelid, and lacrimal surgery at the University Medical Center Utrecht. As part of his PhD project, he obtained his Master of Clinical Epidemiology in 2009 at Utrecht University. Subsequently he obtained a Master of Business Administration at the University of Phoenix (Arizona, United States of America). Ward is married to Rhodé M. van Leeuwen and has two children (Annelie 2007, Laurens 2008).

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