



Spectrum of orbital inflammatory Disorders

Dr. Hadi M Khazaei ^{1*}, Dr. G. Seethapathy ²

1 Division of OculoFacial Reconstructive and Oculoplastic Surgery, Oregon Health Science University, Portland, Oregon, United States

2 Consultant Ophthalmic Plastic and Orbital Surgeon, Manipal Hospital, Salem, India

* Corresponding Author: **Dr. Hadi M Khazaei**

E-mail :- khazaei@ohsu.edu

Article Info

ISSN (online): 2582-8940

Volume: 03

Issue: 02

April-June 2022

Received: 05-05-2022;

Accepted: 25-05-2022

Page No: 35-38

DOI: <https://doi.org/10.54660/Ijmabhr.2022.3.2.3>

Abstract

Knowledge of the incidence and distribution of inflammatory responses can help clinicians understand orbital disorders, and establish standard protocols for appropriate treatments, including those conditions that warrant immediate attention ¹. The orbital compartment contains a variety of tissues arranged in a fashion reminiscent of Pandora's box. These tissues can be independently involved in a plethora of disorders which can impose a number of sight-threatening risks. Many prior studies of these matters have laid a foundation for understanding the approximate incidence of various orbital pathologies ¹⁻¹⁵.

Keywords: Spectrum, orbital, Disorders

Introduction

The fields of specialization in medicine have progressed at an astounding rate in the last few decades, but due to the rarity of orbital problems and insufficient exposure to orbital pathology the information pertaining to the occurrence of orbital conditions remains obscure.

The current literature describing the incidence of orbital inflammatory diseases contains reports from various sources, including general ophthalmology practices ^[2], sub specialty practice¹ in orbit or oncology ^[3-5], and pathology specimen reviews ^[5-8].

A comprehensive literature search was performed to ascertain the previously reported incidences of various type of orbital disease ^[1]. Pathological and clinical classification was then tabulated and incorporated to compare different data using various sources.

A multiple-case series compilation of orbital disorders done by Wilson and Grossniklaus ^[6] and later on by Shields *et al* ^[7] (1984) were based on review of biopsy specimens, whereas the Henderson ^[4], Kennedy ^[2], Rootman ^[3], and Shields ^[9] (2004) studies were based on clinical practice. Of all the studies conducted on this subject and tabulated, Rootman³ evaluation of 1409 cases from a 10-year retrospective study may provide a more comprehensive paradigm of the incidence of orbital disorders.

Feasibility and Preliminary Data

This study follows the Preferred Reporting Items for systemic reviews and Meta-Analysis (PRISMA) ^[16] checklist. Given these varying criteria, we decided to compare the 5-series compilation with our data -" A retrospective review of 6328 consecutive patients with orbital disease in south India" ^[1]. We included all comprehensive description and review of orbital disorders, checked for duplication based on overlapping authorship, study description, number of participants and participant characteristics.

The main outcome measured was incidence¹ of orbital diseases in south Indian population, as determined by

clinical and pathological criteria. (Table 1).

Table 1: Summary of orbital lesions. Usha R. Kim, Hadi Khazaei, William B. Stewart, Akash D. Shah. Spectrum of Orbital Disease in South India. *Ophthal Plast Reconstr Surg* 2010; 26:315-322

	Shields ⁸	Kennedy ¹	Henderson ³	Rootman ²	Wilson ⁵	Aravind
Systemic	—	54 (6.6)	52 (3.8)	682 (49)	10 (3.2)	1965 (31.0)
Inflammatory	132 (20.5)	142 (17.3)	61 (4.4)	129 (9.2)	45 (14.5)	2161 (34.1)
Trauma	—	107 (3.0)	—	76 (5.4)	13 (4.1)	308 (4.8)
Congenital	194 (30.1)	69 (8.4)	39 (2.8)	101 (7.1)	23 (7.3)	600 (9.4)
Vascular	4 (0.6)	26 (2.2)	65 (4.7)	40 (2.8)	7 (2.2)	17 (0.2)
Primary neoplasia						
Epithelial	21 (3.3)	18 (2.2)	68 (4.9)	15 (1.0)	5 (1.2)	68 (1.0)
Fibrous	11 (1.7)	2 (0.2)	20 (1.4)	13 (0.9)	2 (0.6)	40 (0.6)
Fibro-osseous	8 (1.2)	28 (3.4)	31 (2.2)	21 (1.5)	3 (0.9)	37 (0.6)
Cartilagenous	2 (0.3)	1 (0.1)	7 (5.1)	2 (0.1)	—	7 (0.1)
Adipose	2 (0.3)	—	7 (5.1)	—	3 (0.9)	46 (0.7)
Vascular	38 (6.0)	51 (6.2)	125 (9.0)	56 (4.0)	16 (5.1)	369 (5.8)
Neural	23 (3.6)	67 (8.2)	225 (16.3)	71 (5.0)	16 (5.1)	336 (5.3)
Striated muscle	8 (1.2)	8 (0.9)	38 (2.7)	5 (0.3)	12 (3.4)	23 (0.3)
Lymphocytic/leukemic	73 (11.6)	107 (13.0)	126 (9.1)	55 (4.0)	16 (5.1)	131 (2.0)
Langerhans cell	1 (0.1)	3 (0.3)	11 (0.8)	4 (0.3)	3 (0.9)	21 (0.3)
Other	2 (0.3)	—	4 (0.3)	2 (0.1)	—	78 (1.2)
Secondary neoplasia	70 (11.1)	51 (6.2)	269 (19.5)	44 (3.1)	90 (28.7)	82 (1.3)
Metastases	16 (2.5)	27 (3.3)	111 (8.0)	38 (2.7)	15 (4.8)	39 (0.6)
Total	645	821	1376	1409	312	6328

Research Design and Methodology

This is a comparison of multiple retrospectives, observational case series study to correlate incidence of orbital disorders as determined by clinical and pathological criteria. The study protocol was approved by the Institutional Review Board.

All tabulated charts were reviewed by investigators to determine the clinical diagnosis made for patients presenting with orbital pathology. While considering all orbital and preorbital lesions, we have included thyroid-related orbitopathy, idiopathic orbital inflammation and other inflammatory conditions involving head and neck area including orbit and pre orbital regions.

Inflammation of the orbit is not a specific diagnosis but a physiological end response to multiple disease processes. Several systemic, immune-mediated diseases can involve the orbit (17). Entities that cause orbital inflammation include infections that may be bacterial, viral or fungal in etiology, systemic autoimmune diseases such as Graves' disease (thyroid eye disease, TED) (18), sarcoidosis (19), systemic lupus, IgG4 disease (20), granulomatosis with polyangiitis (GPA) (21), neoplastic diseases, and as a diagnosis of exclusion, non-specific orbital inflammation (NSOI; idiopathic orbital inflammation, orbital pseudotumor). (22, 23)

Each of these disease processes can present in varying severities. When there is impending vision loss from optic nerve compression, vascular compromise with the risk of infarction from vasculitis or orbital apex or cavernous sinus involvement, or significant disability due to pain, intractable diplopia or ocular surface damage from exposure, there is a great impetus to quickly and accurately diagnose and treat these diseases.

The differential diagnosis of orbital inflammation can be narrowed using epidemiologic data on age distribution and the probability of diseases. For example, the most common causes of orbital inflammation are infection and thyroid eye disease. According to a recent review, the thyroid gland is the most common organ affected by autoimmunity. (24) Graves' disease affects about 1% of the US population, half of whom have ophthalmopathy, although the eye disease is markedly symptomatic in only about 10% of those affected. (25)

Given these criteria, it is logical that some differences are encountered when reviewing and comparing the existing data. Despite the unavoidable biases in each study, it is useful to compare the reported incidences to establish a better understanding of orbital disorders worldwide.

We had compared the data in the tabulated chart (Table 1) and analyze the outcome using appropriate statistical tests (t-test correlation and linear regression). The outcome measurements include mean, range, standard deviations, odd ratio and hazard ratio, incidental ratio and incidental rate. The final effect estimate is just a weighted average of all the individual study estimates. The weights are determined by the precision of the study level estimates and sample size. In our study, weights are proportional to sample size.

The main outcome measured was the incidence of orbital diseases as determined by clinical and pathological criteria. In this study of 6328 patients, 34.1% had inflammatory orbital disease with 2161 patients including 1473 idiopathic orbital inflammation, 270 infection, 126 dacryoadenitis, and 292 other etiologies. Among the 1965(31%) patients presenting with systemic diseases involving the orbit, 1938 were diagnosed with thyroid orbitopathy (1).

Table 1: Summary of orbital lesions. Kim UR, Khazaei H, Stewart WB, Shah AD. Spectrum of orbital disease in South India: an Aravind study of 6328 consecutive patients. *Ophthalmic Plast Reconstr Surg.* 2010; 26(5):315-22.

	Shields	Kennedy	Henderson	Rootman	Wilson	Aravind
Systemic	-	54 (6.6)	52 (3.8)	682 (49)	10 (3.2)	1965 (31.0)
Inflammatory	132 (20.5)	142 (17.3)	61 (4.4)	129 (9.2)	45 (14.5)	2161 (34.1)
Trauma	-	107 (3.0)	-	76 (5.4)	13 (4.1)	308 (4.8)
Congenital	194 (30.1)	69 (8.4)	39 (2.8)	101(7.1)	23 (7.3)	600 (9.4)
Vascular	4 (06)	26 (2.2)	65 (4.7)	40 (2.8)	7 (2.2)	17 (0.2)
Primary neoplasia	229(35.5)	345(42)	779(56,6)	299(21,2)	109(34,9)	1155(18,2)
Secondary neoplasia	70(11.1)	51 (6.2)	269 (19.5)	44(3.1)	90 (28.7)	82 (1.3)
Metastases	16 (2.5)	27 (3.3)	111 (8.0)	38 (2.7)	15 (4.8)	39 (0.6)
Total	645	821	1376	1409	312	6328

The adherence to a strict criterion is important to boost the understanding of the pathophysiology of eye disease and to lead the initiation of new preventive and therapeutic modalities.

Clinically useful biomarkers in orbital inflammatory diseases (OID) are rare. An ideal molecular biomarker would be minimally invasively obtained allowing for repeat testing, specific to the disease with high sensitivity, with quantitative measurements, and inexpensive. Potential biofluids to test include blood, urine, or tears. Geographically, tears are the closest to the location of disease in OID with theoretically the highest concentration of potential biomarkers. Most proteins in tears originate from the lacrimal gland, but they may also be released from epithelial cells that are shed or leaked from blood vessels during inflammation, injury, or irritation.

They are also the most readily accessible body fluid and much less complex than blood or urine. With technological advancements, the ability to identify subtle differences increases the chance to find such a biomarker.

Tear proteomics in OID allows us to monitor patients longitudinally, clarify disease pathogenesis, develop new therapeutic targets, predict response and optimal timing of therapy, as well as determine which patients will go on to develop sight threatening disease. Thyroid eye disease (TED) is the most prevalent OID leading itself to research. To our knowledge, there are no tear studies in other OID. (26) Studying OID together will allow for selection of unique disease specific biomarkers and determine possible existence of shared pathogenesis, which may lead to therapeutic expansion.

Potential pitfalls and alternative strategies

The limitation of this study could be the differences in geographic distribution of orbital disorders around the world. The diversity of orbital diseases and varying sources leads to inherent biases. Our review suggests a higher incidence of inflammatory diseases affecting the orbit in South India, with comparable incidences of systemic diseases, neoplasms, and congenital diseases in Western world. Researchers become interested in the treatment response of a specific subgroup of patients. We already know that subgroup analyses are inherently under powered and notorious for providing spurious findings. We can combine these subgroup results from multiple similar studies which may be able to obtain a large enough sample size to produce more trustworthy results. We assume that incidence varies somewhat from study to study, and we instead try to estimate the average effect. This study may be the only report describing the incidence of orbital lesions worldwide.

This data will facilitate diagnosis capabilities, increase

precision of results by combining Data and thereby increase the therapeutic expertise for orbital conditions.

Acknowledgment

I like to thank Dr. Usha R. Kim. Dr. Wiliam B. Stewart and Dr. Shah and Aravind Eye Hospital and all my patients who had contributed in this study.

HK drafted the manuscript. All the authors edited the manuscript jointly and approved the final manuscript. The authors thank Dr. Kaneez Abbas for critical feedback and helping to develop the search strategy and proof reading.

References

1. Usha R Kim, Hadi Khazaei, William B Stewart, Akash D Shah. Spectrum of Orbital Disease in South India. *Ophthal Plast Reconstr Surg.* 2010; 26:315-322.
2. Kennedy RE. An evaluation of 829 orbital cases. *Trans Am Ophthalmol Soc.* 1984; 82:134-55.
3. Rootman J. *Orbital Surgery in Disease of the Orbit.* Philadelphia, PA: JB Lippincott, 1988:1-612.
4. Henderson J. *Orbital Tumors.* 3rd ed. New York, Brian C. Decker, 1994, 43-51.
5. Shields JA, Bakewell B, Augsburger JJ, *et al.* Space-occupying orbital masses in children. A review of 250 consecutive biopsies. *Ophthalmology.* 1986; 93:379-84.
6. Wilson MW, Grossniklaus HE. Orbital disease in North America. *Ophthalmol Clin North Am* 1966; 9:539-47.
7. Shields JA, Bakewell B, Augsburger JJ, Flanagan JC. Classification and incidence of space-occupying lesions of the orbit. A survey of 645 biopsies. *Arch Ophthalmol* 1984;102:1606-11.
8. Bekibele Co, Oluwasola AO. A clinicopathological study of ocular diseases in Ibadan between. 1991-1999. *Afr J Med Sci.* 2003; 3:197-202.
9. Shields JA, Shields CA, Scartozzi R. Survey of 1264 patients with orbital tumors and simulating lesions: the 2002 Montgomery Lecture, part 1. *Ophthalmology.* 2004; 111:997-1008.
10. Grossniklaus HE, Yanoff M. *Foundations of Clinical Ophthalmology.* Philadelphia. PA; JB Lippincott, 1994, 1-36.
11. Jakobiec FA, Jones IS. *Diseases of the orbit.* Hagerstown, MD. Harper and Row Publishers Inc, 1979, 17-30.
12. Hou PK, Garg MP. Tumors of the orbit, a report of 193 consecutive case. *Current Concepts in Ophthalmology.* St, Louis, MO; CV Mosby, 1972, 176-85.
13. Crawford JS. *Diseases of the orbit. The Eye in Childhood.* Chicago, IL: Year Book Medical Publishers, 1967, 331-64.

14. Illif WJ, Green WR. Orbital Tumors in children. In: Jakobiec FA, ed. Ocular and Adnexal Tumors. Birmingham, AL: Aesculpius, 1978, 669-84.
15. Duke-Elder S. System of Ophthalmology, Vol XIII, Part II: Lacrimal, Orbital and Para-Orbital Disease, St. Louis, MO: Cy Mosey, 1974, 669-84.
16. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Annals of internal medicine*. 2009; 151(4):264-269.
17. Sharma SM, Choi D, Planck SR, Harrington CA, Austin CR, Lewis JA, et al. Insights in to the pathogenesis of axial spondyloarthritis based on gene expression profiles. *Arthritis Res Ther*. 2009; 11(6):R168.
18. Bahn RS. Graves' Ophthalmopathy. *New Engl J Med*. 2010; 362(8):726-38.
19. Rosenbaum JT, Choi D, Wilson DJ, Grossniklaus HE, Harrington CA, Sibley CH, et al. Parallel Gene Expression Changes in Sarcoidosis Involving the Lacrimal Gland, Orbital Tissue, or Blood. *JAMA Ophthalmol*. 2015; 133(7):770-7.
20. Wong AJ, Planck SR, Choi D, Harrington CA, Troxell ML, Houghton DC, et al. IgG4 immunostaining and its implications in orbital inflammatory disease. *PLoS One*. 2014; 9(10):e109847.
21. Rosenbaum JT, Choi D, Wilson DJ, Grossniklaus HE, Harrington CA, Sibley CH, et al. Orbital pseudotumor can be a localized form of granulomatosis with polyangiitis as revealed by gene expression profiling. *Exp Mol Pathol*. 2015; 99(2):271-8.
22. Rosenbaum JT, Sibley CH, Choi D, Harrington CA, Planck SR. Molecular Diagnosis: Implications for Ophthalmology. *Progress in retinal and eye research in review*, 2015.
23. McAleer JP, Nguyen NL, Chen K, Kumar P, Ricks DM, Binnie M, et al. Pulmonary Th17 Antifungal Immunity Is Regulated by the Gut Microbiome. *J Immunol*. 2016; 197(1):97-107.
24. Sharma S, Wheelan S, Marchionni L, Harrington CA, Choi D, Planck SR, et al. Identification of a gene expression profile specific to non-infectious uveitis using high throughput microarray data and a novel pipeline of in-silico methods. *Invest Ophthalmol Vis Sci Invest. ARVO Abstract*, 2015; 56(7):1719.
25. Van Elburg RM, Uil JJ, Mulder CJ, Heymans HS. Intestinal permeability in patients with coeliac disease and relatives of patients with coeliac disease. *Gut*. 1993; 34(3):354-7.
26. Hadi Khazaei, Danesh Khazaei, Rohan Verma, John Ng, Phillip A Wilmarth, Larry L David, et al. The potential of tear proteomics for diagnosis and management of orbital inflammatory disorders including Graves' ophthalmopathy, *Experimental Eye Research*. 2021; 213:108813. ISSN 0014-4835, <https://doi.org/10.1016/j.exer.2021.108813>.