ORIGINAL ARTICLE

Serum IgE Levels: An Effective Diagnostic Tool for Evaluation and Monitoring of Orbital Fungal Granuloma

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Abstract

Objective: To determine the changes in IgE levels in diagnosis and postoperative monitoring of orbital fungal granuloma.
Study Design: Descriptive analytical study.
Place and Duration of Study: Al-Shifa Trust Eye Hospital, Rawalpindi, Pakistan, from July 2012 to June 2013.
Methodology: Cases with clinically high index of suspicion for orbital fungal granuloma and 50 healthy volunteers were inducted as control subjects. Patients with recurrent cases of orbital fungal granuloma, previous orbital surgery, and those with very low clinical suspicion of fungal granuloma were excluded. Total serum IgE level (IU/ml), eosinophil counts and skin prick test were performed in all subjects. Independent t-test was used for comparison of healthy volunteers and patients with biopsy proven orbital fungal granuloma. Repeated measures ANOVA was used for comparing the pre-operative and postoperative total serum IgE level of patients with biopsy proven fungal granuloma.
Results: The mean total serum IgE level for the healthy volunteers was 208.82 ± 41.43 IU/ml. The mean pre-operative IgE value of histologically confirmed cases of fungal granuloma was 1613.72 ± 282.83 IU/ml. The total serum IgE level gradually declined after surgery and anti-fungal treatment. The mean serum IgE level 3, 6 and 9 months postoperatively were 1039.48 ± 308.40, 568.77 ± 162.01 and 224.92 ± 51.55 IU/ml respectively. These tests showed that the drop in IgE level in cases of fungal granuloma with treatment was statistically significant ($p < 0.001$).
Conclusion: Total serum IgE level can be used as a reliable diagnostic and postoperative monitoring tool in orbital fungal granuloma.

Key Words: *Fungal granuloma serum. Immunoglobulin E. Orbit. Diagnosis. Postoperative monitoring.*

INTRODUCTION

Fungal granuloma of the orbit constitutes a rare subtype of orbital tumors worldwide. In immuno-competent individuals, orbital aspergillosis is a rare entity. Infrequent case reports have been reported in literature.[1] Mody *et al*. reported only 35 cases of orbital aspergillosis in immuno-competent individuals over a period of 15 years.[1] Moreover, Trief *et al*. analyzed the invasive fungal disease of the orbit and sinonasal cavity over a period of 20 years in a single institute and came across just 14 patients who had invasive fungal disease along with orbital involvement.[2]

Diagnostic radiology, biopsy with microbiological and histopathological work-up is mandatory for diagnosis.[1] Surgical debridement, antifungal therapy and reversal of immuno-suppression, when possible should be considered.[2]

The pathogenesis of fungal granuloma in orbit can be linked to chronic Allergic Fungal Sinusitis (AFS). AFS can cause noninvasive pansinusitis and is an immunological reaction to the fungal deposits.[3] IgE mediated hypersensitivity reactions (type 1 hypersensitivity) play a pivotal role in the pathogenesis of AFS.[4] The total serum IgE level can reveal the atopic characteristics of the patients with AFS.[5]

The IgE levels are likely to be raised in patients with orbital fungal granuloma due to supposed relation with AFS. This has not been studied and remains unexplored. The goal of the current study, therefore, was to determine Immunoglobulin E (IgE) as a new diagnostic tool as well as a monitoring tool for follow-up of fungal granuloma in the orbit.

METHODOLOGY

The study was conducted in the Orbit and Oculoplastics Department of Al-Shifa Trust Eye Hospital, Rawalpindi, Pakistan, from 1st July 2012 to 30th June 2013. A descriptive analytical study of 103 participants was carried out. The sampling technique was non-randomized convenience sampling. Fifty three patients were cases with clinically high index of suspicion for orbital fungal granuloma while 50 were healthy volunteers as control subjects. The study was approved by the Institutional Ethical and Research Committee on March 10th, 2012. A written informed consent was taken from all the participants of the study.

A patient was considered to have clinically high index of suspicion for fungal granuloma of orbit on the basis of

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relatively younger age group, chronic/acute sinonasal symptoms, a firm well defined mass palpable on superficial or deep palpation along the medial, inferomedial or superomedial orbit and well defined mass in the medial/superomedial/inferomedial orbit with or without sinonasal involvement visible on CT scan of orbit. Patients with recurrent cases of orbital fungal granuloma, history of previous orbital surgery, patients with very low or no clinical suspicion of fungal granuloma- like mass in the lateral half of the orbit and patients with high clinical index of suspicion of fungal granuloma but unwilling to undergo surgery were excluded.

All patients underwent standard orbitotomy with or without sinonasal surgery followed by treatment with oral 200 mg of itraconazole daily for a period of about 9 months. Cases (before and after treatment) and controls were tested for total serum IgE by using ELISA kit method, eosinophil count and skin prick test. Total serum IgE level was repeated postoperatively at intervals of 3, 6 and 9 months for each patient with biopsy proven orbital fungal granuloma. For statistical analysis and results interpretation, only total serum IgE level was discussed.

Statistical analysis was performed by using SPSS version 17.0. A value of $p < 0.05$ was taken to indicate statistical significance. Independent t-test was used to compare healthy volunteers and patients with biopsy proven orbital fungal granuloma. The mean IgE level in cases of fungal granuloma pre-operatively and 3, 6, 9 months postoperatively were compared using repeated measures ANOVA with post hoc Bonferroni's test. Sphericity was not assumed and Green-house Geisser correction was used.

RESULTS

The mean age of the healthy volunteers in the control group was 32.22 ± 5.08 years. The mean age of the patients with high clinical index of suspicion for fungal granuloma was 34.75 ± 3.94 years. Amongst the healthy volunteers, 74% (n=37) were males and 26% (n=13) were females whereas 75.5% (n=40) were males and 24.5% (n=13) were females amongst the patients with high clinical index of suspicion for fungal granuloma.

In patients with high clinical index of suspicion for orbital fungal granuloma, CT scan showed isolated orbital involvement in 45.3% (n=24) of cases, sino-orbital involvement in 39.6% (n=21) and orbito-cranial involvement in 15.1% (n=8). Forty eight (90.6%) cases had unilateral involvement whereas 9.4% (n=5) had bilateral involvement. Only 15.1% (n=8) of cases had prior history of asthma, pulmonary/extra pulmonary tuberculosis and nasal polyps. Orbital fungal granuloma was confirmed by histopathology in 94.3% (n=50) of the patients with high clinical index of suspicion for fungal granuloma in the orbit. It was not confirmed in 5.7% (n=3) of the cases giving a 94.3% accuracy for clinical suspicion.

The mean total serum IgE level for the healthy volunteers was 208.82 ± 41.43 IU/ml. Total serum IgE was raised in 100% (53 patients) of patients with high clinical index of suspicion for orbital fungal granuloma before treatment. In about 94.3% (n=50) of patients with raised total serum IgE level pre-operatively, the total serum IgE level gradually declined after surgery and all these cases had histologically confirmed fungal granuloma. However, in about 5.7% (n=3) of patients who did not have the histopathological confirmation of fungal granuloma, the pre-operative total serum IgE level did not change upon removal of tumor by surgery.

The mean pre-operative IgE value of histologically confirmed cases of fungal granuloma was 1613.72 ± 282.83 IU/ml (range 965.70 - 2123.52 IU/ml). The total serum IgE level gradually declined after surgery and the mean serum IgE level 3, 6 and 9 months postoperatively were 1039.48 ± 308.40, 568.77 ± 162.01 and 224.92 ± 51.55 IU/ml respectively (Table I). These tests showed that the drop in IgE level in cases of fungal granuloma was statistically significant ($p < 0.001$, $F = 708.21$, $df = 1.94, 95.20$, Table II).

Pair-wise comparison of pre-operative and 3, 6, 9 months postoperative IgE level in cases of fungal granuloma is shown in Table III.

Table I: IgE level (IU/ml) in control group (n=50) and in cases of fungal granuloma (n=50) before and after surgical excision.

IgE level (IU/ml)	Mean ± S.D	Minimum	Maximum
Cases			
Pre-op	1613.72 ± 282.83	965.70	2123.52
3 month post op	1039.48 ± 308.40	490.79	1700.90
6 month post op	568.77 ± 162.01	309.54	990.78
9 month post op	224.92 ± 51.55	119.70	358.32
Control	208.82 ± 41.43	118.02	319.00

Table II: IgE levels (IU/ml) in cases of fungal granuloma (n=50) (repeated measures ANOVA test).

IgE levels	Mean ± S.D	95% Confidence Interval		df 1	df 2	F-value	p-value
		Lower Bound	Upper Bound				
Pre op	1613.72 ± 282.83	1533.34	1694.10	1.94	95.20	708.21	<0.001
3 month post op	1039.48 ± 308.40	951.83	1127.13				
6 month post op	568.77 ± 162.01	522.73	614.82				
9 month post op	224.92 ± 51.55	210.27	239.57				

Table III: Pair wise comparisons of mean IgE level (IU/ml) in patients with fungal granuloma (n=50) before and 3,6,9 months after granuloma removal.

Pair wise comparisons		Difference Mean ± S.D (pair wise comparisons)	p-value
Pre op	3-month post op	574.24 ± 201.82	<0.001
Pre op	6-month post op	1044.94 ± 221.81	<0.001
Pre op	9-month post op	1388.80 ± 266.09	<0.001

The mean pre- and postoperative IgE level of cases of fungal granuloma were compared with IgE level of healthy volunteers using independent sample t-test. The IgE level in cases of fungal granuloma pre-operatively was significantly raised as compared to healthy controls. The IgE level dropped postoperatively but after 3 and 6 months difference was significant. Nine months post-operatively there was no significant difference (p=0.089) in IgE level of cases and controls.

The eosinophil count, however, was raised in only 30.18% (n=16) of the patients with high clinical index of suspicion for orbital fungal granuloma and none of the controls. Fifty three patients and 8 healthy volunteers tested positive for skin prick test. These two parameters were not statistically analyzed.

DISCUSSION

Space occupying lesions are infrequently found in the orbit. As fungal infection of the orbit is a rare entity, treatment is aimed at limiting the progression of the disease.[1] Literature in ophthalmology is very sparse on the fungal granuloma of the orbit, however, ENT literature refers to the involvement of orbit in Allergic Fungal Sinusitis (AFS).[6] The current study lays emphasis on the introduction of total serum IgE level as a time-efficient marker for the diagnosis and postoperative follow-up of fungal granuloma of the orbit.

Fungal infection of the orbit can be primarily orbital, or sino-orbital with or without intracranial involvement. It can be caused either by invasive or non-invasive forms of the fungi.[7] In immuno-competent individuals, orbital aspergillosis has a much higher survival rate.[1] Orbital involvement in invasive fungal sinusitis is fraught with serious complications and fatal outcome as compared to invasive fungal sinusitis without orbital involvement (78.6% vs. 20% respectively).[2]

Patients with fungal infections of the orbit can present with strabismus, nasolacrimal duct obstruction, isolated orbital mass, optic neuropathy or even CRAO.[2,8] The most common presenting feature in the study conducted by Mody and colleagues was chronic progressive proptosis. Periocular swelling, pain, restrictive ocular motility, papilloedema, raised intraocular pressure; ptosis and choroidal folds were other presenting features in immuno-competent patients with orbital fungal infections.[1] Wang *et al*. showed that nasal obstruction and hyposmia were the most common presentations in AFS.[9] These complaints along with proptosis were seen in almost all the patients in the current study with orbital fungal granuloma. A small number of patients also had pain, ptosis, diplopia, and decreased visual acuity. No history of bronchial asthma, nasal polyps, pulmonary and extra pulmonary tuberculosis was reported in almost 85% of the patients with biopsy proven orbital fungal granuloma.

As fungal infections of the orbit are rare and can masquerade as non-infectious inflammatory conditions, misdiagnosis is commonly reported in literature.[10] The differential diagnosis of orbital fungal infection includes Non-Specific Orbital Inflammatory Disease (NSOID), paranasal sinus malignancy, lymphoma, orbital cellulitis and Giant Cell Temporal Arteritis (GCTA).[1]

Diagnostic radiology, biopsy with microbiological and histopathological work-up is mandatory for diagnosis. Ultrasonography (USG) and CT scan imaging play a pivotal role in supporting the diagnosis and extent of orbital fungal granuloma.[1] On CT scan, orbital fungal granuloma appears as a heterogeneous, irregular lesion, isodense to extra ocular muscles, showing bony erosion and affecting the paranasal sinuses.[11] Some authors have suggested the role of Fine Needle Aspiration Cytology (FNAC) in the diagnosis of orbital fungal granuloma.[12] The present experience shows that radiological imaging and biopsy with adequate tissue sample for microbiological and histopathological examination is a preferred way for diagnosis.

Fungal granuloma has been reported in immuno-competent individuals of Pakistan, Sudan and India. They are usually not seen in the western world.[13] There are more than 185 different species of *Aspergillus* and any form can lead to an aggressive disease.[14] Orbital involvement and intracranial spread are serious complications of AFS. Orbital erosion is more common than erosion of the skull base.[15] Orbital involvement occurs by the contiguous spread of the disease from paranasal sinuses, micro-invasion, expansion, fungal tissue invasion or bony erosion due to the pressure effects. It worsens the prognosis of AFS and leads to the development of fungal granuloma in the orbit. Fungal granuloma, through superior orbital fissure and optic canal, can lead to intracranial complications as well.[16]

Total serum IgE level has been proposed as a useful indicator of AFS and allergic bronchopulmonary fungal disease's clinical activity. Healthy, non-allergic individuals have a total serum IgE concentration of about 120 IU/ml.[17] Total serum IgE level is raised to more than 1000 IU/ml in AFS.[15] The current study discusses the role of total serum IgE level in the pre-operative diagnosis and monitoring the postoperative follow-up of fungal granuloma in the orbit for the first time.

In the current study, the authors measured the total serum IgE level in patients with high clinical index of suspicion for orbital fungal granuloma pre-operatively and healthy volunteers. The suspected patients were later confirmed for orbital fungal granuloma by histopathology and the total serum IgE level was assessed again at an interval of 3, 6 and 9 months postoperatively. The patients with biopsy proven fungal granuloma of the orbit had pre-operative total serum IgE level more than 10 times than that of healthy volunteers.

A significant decrease in the level of total serum IgE in patients with biopsy proven fungal granuloma of the orbit after treatment over a period of 9 months shows an association between total serum IgE level and fungal granuloma of the orbit. Total serum IgE level is, therefore, a unique, non-invasive niche of diagnostic ophthalmology in patients with fungal granuloma of the orbit.

The clinical profile of patients with orbital fungal granuloma in the current study is exactly similar to that of AFS patients in general with respect to dwelling conditions, climate and history of sinusitis, causative fungi and immuno-competence. An association of AFS with Allergic Bronchopulmonary Aspergillosis (ABPA) has been reported in literature.[18] This study shows an association of AFS and orbital fungal granuloma.

Surgical debridement in sino-orbital fungal infections leads to decrease in morbidity. It removes the devitalized tissue, results in debulking of infected tissue, facilitates rapid action of antifungal agents and provision of specimen for culture and histopathology to confirm the etiological diagnosis. The role of hyperbaric oxygen and steroids in the management of orbital fungal infections is controversial.[1,2]

CONCLUSION

Fungal granuloma of the orbit in Pakistan results from Allergic Fungal Sinusitis (AFS). Fungal granuloma of the orbit can lead to morbidity and mortality. Because of the convenience, utility, reliability and availability, total serum IgE level is a time-efficient marker for the diagnosis of orbital fungal granuloma. Total serum IgE level, being non-invasive and simple, can also be used to monitor the follow-up of the disease.

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