Pediatric Idiopathic Orbital Inflammation: Clinical Features of 30 Cases

Jordan Spindle, M.D.*, Sunny X. Tang, M.D.*, Brett Davies, M.D.†, Edward J. Wladis, M.D.‡, Elena Piozzi, M.D.§, Marco Pellegrini, M.D.§, Sara E. Lally, M.D.¶, Carol Shields, M.D.§, and Roman Shinder, M.D.*

*Department of Ophthalmology, SUNY Downstate Medical Center, Brooklyn, New York; †Department of Ophthalmology, The University of Colorado, Denver, Colorado; ‡Lions Eye Institute, Albany Medical College, Albany, New York; §A.O. Ospedale Niguarda Ca’Granda, Milan, Italy; ¶Eye Clinic, Department of Biomedical and Clinical Science, Luigi Sacco Hospital, University of Milan, Milan, Italy; and ¶Ocular Oncology Service, Wills Eye Hospital, Philadelphia, Pennsylvania, U.S.A.

Purpose: Pediatric idiopathic orbital inflammation (IOI) is a rare entity with little known about the clinical presentation and natural history. The authors report the demographics, clinical presentations, radiographic and histopathologic characteristics, and treatment outcome of 30 children with IOI.

Methods: Retrospective chart review of 30 patients 18 years and younger diagnosed with IOI and statistical analysis using analysis of variance and Fisher's exact test. This study was reviewed and approved by the Institutional Review Board of SUNY Downstate Medical Center.

Results: There were 9 males (30%) and 21 females (70%) with pediatric IOI who presented at a median age of 11 years (range 2–18 years). Primary IOI was found in 19 patients (63%) and recurrent IOI in 11 patients (37%). Overall, 26 patients (87%) had unilateral IOI while 4 patients (13%) had bilateral disease at presentation. There were 12 patients (40%) with systemic constitutional signs. The most common ophthalmic findings included periorbital edema (n = 20, 67%) and blepharoptosis (n = 17, 57%). All patients had orbital radiography with common findings of dacryoadenitis (n = 12, 40%), orbital mass (n = 12, 40%), or myositis (n = 10, 33%). The presence of a radiographic orbital mass was significantly related to the clinical presence of blepharoptosis (p = 0.03). The most common treatment was oral glucocorticoids in 24 patients (80%). Over mean follow up of 19 months (range 6–64 months), females were more likely to display recurrent disease (p = 0.01).

Conclusions: Idiopathic orbital inflammation is an uncommon but important cause of acute orbital syndrome in children, manifesting as a bilateral condition in 13% and with constitutional signs and symptoms in 40%. Posttreatment recurrence is found in 37% of cases.

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Address correspondence and reprint requests to Roman Shinder, M.D., Department of Ophthalmology, SUNY Downstate Medical Center, 541 Clarkson Ave, E bldg, 8th Fl, Suite C, Brooklyn, NY 11203. E-mail: shinder.roman@gmail.com

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Methods

The authors report the demographics, clinical presentation, radiographic and histopathologic characteristics, and treatment outcome of patients 18 years or younger diagnosed with IOI. Records of 30 patients were reviewed from January 2005 to July 2013 from 6 institutions in the United States and Italy. Diagnosis of IOI was made based on the following clinical criteria: acute, benign, noninfectious, inflammatory disorder of the orbit without local or systemic cause.

Data were collected regarding patient age, race, sex, primary versus recurrent disease, past medical history, laterality. The data regarding eye findings included visual acuity, intraocular pressure, pupil size and reactivity, extraocular muscle movements, external examination, slit lamp examination, and fundus examination.

Idiopathic orbital inflammation (IOI) was first described in 1905 by Birch-Hirschfield who termed the condition orbital pseudotumor.1 This term was used to describe orbital disease with an idiopathic cause, spontaneous resolution, and non-granulomatous changes on histopathology.1 Idiopathic orbital inflammation is currently understood to be a benign, noninfectious, space-occupying lesion typically presenting in the third to sixth decade of life. It accounts for 6% to 16% of all orbital lesions and is a common entity requiring orbital biopsy.2–5

Idiopathic orbital inflammation is the third most common cause of unilateral proptosis in adults after thyroid eye disease and lymphoproliferative disease.6–8 It typically presents with acute orbital signs and symptoms, such as pain, proptosis, ocular injection, limited ductions with diplopia, periorbital edema, chemosis, and less commonly vision loss.2,4,5 Idiopathic orbital inflammation has historically shown no sex or racial predilection. However, recent studies have shown a middle aged female predominance.6

While IOI is well described among adults, it has a very low incidence in the pediatric population with approximately 70 reported prior cases,1 and therefore little is known about the clinical presentation and spectrum of disease. It is reported to differ from IOI in adults in that affected children more often have bilateral disease, as well as constitutional signs and symptoms, such as headache, fever, malaise, emesis, anorexia, lethargy, abdominal pain, and weight loss.2,6,10 The most frequent idiopathic orbital clinical findings are palpable mass, decreased ocular motility, eyelid swelling, pain, proptosis, and increased intraocular pressure.2 Reportedly, pediatric cases are more commonly associated with iritis, eosinophilia, and optic disk edema.10,11

The authors herein review pediatric IOI through the collaborative experience in 30 consecutive patients.
All patients received a rheumatologic evaluation and an extensive serologic workup that included a complete blood count, comprehensive metabolic panel, angiotensin converting enzyme, lysozyme, antinuclear antibody, rheumatoid factor, thyroid function testing and thyroid-stimulating hormone receptor antibodies, antineutrophil cytoplasmic antibody, Sjögren’s syndrome antibodies, and rapid plasma reagin. Immunoglobulin G-4 was checked in all patients who presented subsequent to 2008. Orbital radiography was obtained on all patients, and biopsy was offered in each case to parents except those children who presented with a primary isolated myositis or optic perineuritis. This study was reviewed and approved by the Institutional Review Board of SUNY Downstate Medical Center. The research adhered to the tenets of the Declaration of Helsinki, and the Health Insurance Portability and Accountability Act.

Statistical analyses were conducted using Stata v.12.0. Comparisons among categorical variables (sex, race, clinical variables) were analyzed using the Fisher’s exact test. Age was compared across other categories using analysis of variance.

RESULTS

Demographic and Clinical Characteristics

Table 1. Demographics and constitutional signs

<table>
<thead>
<tr>
<th>Features</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years) (n = 30 patients; median, range)</td>
<td>11 (12, 2–18)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>21 (70)</td>
</tr>
<tr>
<td>Male</td>
<td>9 (30)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>14 (47)</td>
</tr>
<tr>
<td>African American</td>
<td>11 (37)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>5 (17)</td>
</tr>
<tr>
<td>Laterality</td>
<td></td>
</tr>
<tr>
<td>Unilateral</td>
<td>26 (87)</td>
</tr>
<tr>
<td>Bilateral</td>
<td>4 (13)</td>
</tr>
<tr>
<td>Constitutional signs</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>6 (20)</td>
</tr>
<tr>
<td>Fever</td>
<td>3 (10)</td>
</tr>
<tr>
<td>Malaise</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Nausea/Emesis</td>
<td>1 (3)</td>
</tr>
</tbody>
</table>

Ophthalmic findings are listed in Table 2 and included periorbital edema (67%), blepharoptosis (57%), pain (40%), and decreased extraocular movements (37%) most commonly. Pain was more common in older children (mean age 13 years) compared with those without pain (mean age 10 years; p = 0.05).

The correct diagnosis of IOI by first health care provider occurred in 10 (33%) of the patients, with 20 (67%) misdiagnoses including orbital or preseptal cellulitis (n = 10, 50%), conjunctivitis (n = 4, 20%), malignancy (n = 3, 15%), chalazion (n = 1, 5%), allergic reaction (n = 1, 5%), and migraine headache (n = 1, 5%). Initial health care providers ranged from pediatricians, emergency room physicians, ophthalmologists, nurse practitioners, and general ophthalmologists.

Imaging and Biopsy

Radiographic findings are shown in Table 3. All patients had orbital radiography with 10 patients (33%) having computed tomography, 14 patients (47%) having magnetic resonance imaging, and 6 patients (20%) having both modalities. Age, sex, and race did not differ when considering the radiographic findings. The presence of an orbital mass was significantly related to the clinical presence of blepharoptosis (p = 0.03). There was no relation between the presence of an orbital mass and either the presence of proptosis or limitation of extraocular movements. Biopsy was performed in 16 patients (53%), which were all consistent with the classic histopathologic features of IOI including mixed inflammatory infiltrates of lymphocytes, plasma cells, eosinophils, and the presence of fibrosis without neoplastic cells, granulomatous disease, or vasculitis. Immunohistochemistry ruled out orbital IgG4 in each case. Ten children (33%), who presented with either primary myositis of 1 rectus muscle or optic perineuritis were not biopsied. In addition, the parents of 4 (13%) children deferred biopsy when suggested.

Treatment and Response

Treatment algorithms were based on patient age, severity and extent of clinical and radiographic findings, initial versus recurrent disease, past treatments and responses, recurrence during tapering or completion of primary therapy, rheumatologist and pediatrician suggestions, and parent preferences. Treatments included oral corticosteroids (n = 24, 80%), steroid sparing immunosuppressive therapy (n = 2, 7%), oral corticosteroids followed by chemoradiation (n = 1, 3%), intravenous corticosteroids followed by oral corticosteroids, rituximab and intravenous immunoglobulin (IVIG, n = 1, 3%), and observation (n = 3, 10%). When oral steroids were given the tapering dose began at 1 mg/kg/day. Mean follow-up time was 14.1 months (range 3–54 months) with clinical improvement noted in all patients when compared with presentation. At last follow up, 25 patients (83%) had complete resolution, 2 patients
Representative Cases

Case 1
A 10-year-old female with no past medical or ocular history presented with 1 week of painful right superior periorbital edema and complete mechanical blepharoptosis (Fig. 1A). Constitutional symptoms included malaise and headache. She was diagnosed with preseptal cellulitis by an outside physician and started on an oral antibiotic. On ophthalmic examination the patient was afebrile, and the periorbital edema and ptosis were noted. Visual acuity, pupil response to light, confrontational visual field, globe position, and fundus exam were normal. Extensive serologic workup was negative, and orbital computed tomography disclosed an enlarged left lacrimal gland with involvement of the lateral rectus muscle (Fig. 2A, B). The child was afebrile, and visual acuity, pupil response to light, confrontational visual field, and fundus exam were normal. Extensive serologic workup was negative, and orbital computed tomography disclosed an enlarged left lacrimal gland with involvement of the lateral rectus muscle (Fig. 2C). Incisional biopsy of the lacrimal gland was consistent with IOI. The patient was started on oral corticosteroids at 1 mg/kg/day. There was rapid clinical resolution within 3 days, and the steroids were tapered over 6 weeks. At last follow up 15 months after presentation the child remained asymptomatic without recurrence.

Case 2
A 12-year-old male with no past medical or ocular history presented to the emergency room with a 4-day history of a painless left red eye. On ophthalmic examination, there was tender edema centered in the left lacrimal fossa, inferonasal globe dystopia, limited left abduction with binocular horizontal diplopia in left gaze, injection of the temporal bulbar conjunctiva and palpebral lobe of the lacrimal gland (Fig. 2A, B). The child was afebrile, and visual acuity, pupil response to light, confrontational visual field, and fundus exam were normal. Extensive serologic workup was negative, and orbital computed tomography disclosed an enlarged left lacrimal gland with involvement of the lateral rectus muscle (Fig. 2C). Incisional biopsy of the lacrimal gland was consistent with IOI. The patient was started on oral corticosteroids at 1 mg/kg/day. There was rapid clinical resolution within 3 days, and the steroids were tapered over 6 weeks. At last follow up 15 months after presentation the child remained asymptomatic without recurrence.

DISCUSSION

Idiopathic orbital inflammation is uncommon in the pediatric age group. Many of the same clinical and radiographical findings seen in adults with IOI are also noted in children afflicted with this disease. Idiopathic orbital inflammation can involve any of the orbital soft tissues with the rectus muscles (myositis) and the lacrimal gland (dacryoadenitis) being the most commonly involved sites. Clinical improvement can occur spontaneously over time; however, corticosteroids have been shown to hasten resolution and decrease risk of flare ups or recurrence when tapered gradually over several weeks to months. Mo et al. studied 29 cases of pediatric IOI, which they defined as disease in a patient ≤20 years of age. The most common ophthalmic findings in their series were periorbital edema (93%), pain (69%), and blepharoptosis (42%). The cohort displayed less periorbital edema (67%) and pain (40%), with similar rate of blepharoptosis (57%). The smaller proportion of patients with periorbital edema and pain in this study should be noted as to not exclude IOI from the differential diagnosis in children with orbital syndromes lacking these findings. Mo et al. also found that children who underwent biopsies (55%) for diagnostic confirmation were more likely to suffer residual from their disease, which was not found in this study. In 6 cases, they

TABLE 3. Radiographic findings

<table>
<thead>
<tr>
<th>Radiographic finding</th>
<th>n (%)</th>
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<tbody>
<tr>
<td>Dacryoadenitis</td>
<td>12 (40)</td>
</tr>
<tr>
<td>Orbital mass</td>
<td>12 (40)</td>
</tr>
<tr>
<td>Myositis</td>
<td>10 (33)</td>
</tr>
<tr>
<td>Diffuse orbital inflammation</td>
<td>4 (13)</td>
</tr>
<tr>
<td>Bone remodeling</td>
<td>3 (10)</td>
</tr>
<tr>
<td>Scleral enhancement</td>
<td>3 (10)</td>
</tr>
<tr>
<td>Optic nerve sheath enhancement</td>
<td>1 (3)</td>
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(7%) had residual mechanical blepharoptosis from periorbital edema, 2 patients (7%) had residual proptosis, and 1 patient (3%) was being treated for uveitis.

Four patients in this study were initially treated with steroids (oral prednisone or prednisolone 1 mg/kg), and later switched to a steroid sparing therapy. One patient, a 9-year-old African American female suffered multiple bilateral recurrences as well as weight gain and glucose intolerance on oral corticosteroid therapy. She was given IV corticosteroids, IVIG, and rituximab as an inpatient and then discharged on methotrexate with full resolution on last follow up of 24 months. An 18-year-old Caucasian male had a recurrence of orbital signs while on an oral corticosteroid taper and was switched to methotrexate with clinical improvement noted at last follow up of 15 months. A 15-year-old African American female originally diagnosed at age 10 years and treated with oral corticosteroids was treated with chemoradiation on recurrence with full resolution on last follow up of 27 months. Another 11-year-old Hispanic female originally diagnosed at age 10 years was switched to a steroid sparing agent on recurrence due to concerns of growth suppression. She obtained full resolution without recurrence at last follow up of 24 months.

noted permanent reduction in visual acuity, persistent proptosis, chil/or extraocular muscle limitation.11 Of the patients, most of the biopsies were performed before the availability of computed tomography to help in diagnostic evaluation and disease localization. Besides this potential iatrogenic explanation, another possibility is a selection bias if the authors performed biopsies on the more advanced cases that may have suffered persistent ophthalmic signs and symptoms regardless of biopsy. There were 16 patients (53%) in this study, who underwent biopsy, of which were patients with recurrent disease. Biopsy was universally recommended to parents except in cases of isolated primary myositis or perineuritis. There was no increased risk of recurrence or other ophthalmic sequelae noted in the patients that underwent biopsy in this study. It is the belief that biopsy should be offered to all patients excluding those with primary myositis or optic nerve perineuritis to rule out malignancy or other infectious or inflammatory disorders.

Yan et al.2 compared IOI among 185 adults and 24 children (defined as ≤20 years of age). They found blepharoptosis to be more prevalent and proptosis to be less prevalent in children than adults.2 The most frequent presenting signs in children they studied were palpable mass (58%), motility limitation (46%), and swollen eyelid (42%).2 Periocular pain was only seen in 17% of studied children, as opposed to previous studies of adults with IOI that report pain in up to 75%.2,6 This was consistent with the cohort where less than half of children presented with pain.

Additional studies have found the medial and lateral rectus muscles to be the most commonly affected extraocular muscles in IOI with no difference noted between adult and pediatric cases.8,16,17 In this study, most of the patients were found to have multiple tissues involved at presentation including lacrimal gland, extraocular muscle, and orbital fat. Isolated involvement of tissues, such as purine myositis or dacracoenititis represented the minority of cases. Constitutional signs, such as headache, emesis, anorexia, malaise, abdominal pain, and weight loss have also been reported in approximately 50% of pediatric cases,24 which is consistent with the study population in whom these signs were noted in 40% of children.

Approximately, one third of pediatric cases are reported to present with bilateral disease;11 however, this study showed only 13% of cases to be bilateral. Bilateral involvement is reported to be more predominant in children but 1 report showed that 3 of the children with presumed bilateral IOI were ultimately diagnosed with a systemic cause of disease.6 Bilateral involvement is much more common in thyroid eye disease, sarcoidosis, and granulomatosis with polyangiitis which should be ruled out in any patient presenting with suspected bilateral IOI.4 This has led to the suggestion that workup with a pediatric rheumatologist may be helpful in these cases. In this study, there was a significant interaction between race and laterality as all patients with bilateral disease were African American (p = 0.02).

Recurrence rates in the pediatric population are reported as high as 76%.11 Historically, the patients most likely to recur are those with bilateral disease at presentation or iritis.11 Eleven patients (37%) in this study had recurrences with all 4 bilateral cases being recurrent. One patient in this study that had recurrent unilateral disease also had iritis on initial presentation. In recent series, most of the patients with IOI were female; however, the sex of the patients with bilateral and/or recurrent disease is not described. Of note, all patients with recurrent disease in this study were female, as were all bilateral cases. This may point toward a potential autoimmune etiology for IOI, as females are known to have a higher prevalence of autoimmune diseases. Additional studies are needed to elucidate this finding.

The etiology of IOI remains unknown, although several theories have been described including autoimmune disorders, upper respiratory infections, viral illnesses, and aberrant wound healing.9,12,16,18–20 Idiopathic orbital inflammation is a diagnosis of exclusion and it is therefore paramount to approach the evaluation with a thorough differential diagnosis. In the pediatric population, this should include orbital cellulitis, rhadomyosarcoma, neuroblastoma, leukemia, thyroid eye disease, Langerhans cell histiocytosis, paranasal sinus mucocele, lymphangioma, ruptured dermoid cyst, infectious dacryoadenitis, among others. A thorough evaluation for a systemic cause, such as sarcoidosis, thyroid eye disease, granulomatosis with polyangiitis, and Langerhans cell histiocytosis should be performed especially in patients with bilateral disease.6,21–24 The diagnostic workup should also include a computed tomography and/or magnetic resonance imaging which may show a focal or diffuse process that usually enhances with iodinated contrast or gadolinium.5,23–25 Despite being a benign entity, IOI may cause vision loss, ocular motor dysfunction, and other ocular sequelae.6,15

Steroid therapy has been the mainstay of treatment; however, in the pediatric population adverse effects may limit long-term use of this modality especially in the setting of multiple recurrences. Localized steroid injections and intravenous rituximab have been used in adults with success. Additional studies are needed to help elucidate their usefulness in children. Immunosuppressive therapy, chemotherapy, radiation, and intravenous immunoglobulin have been reported treatment modalities8,9,23,26–28 and may be beneficial in this population to prevent long-term consequences.

Although this study is limited by its retrospective design, referral bias to academic and tertiary care centers, and limited number of patients, it nevertheless represents the largest series of pediatric IOI cases to date. The authors also acknowledge that when evaluating pediatric patients with orbital inflammation, workup and treatment algorithms often differ among physicians. Each patient in this study underwent exhaustive clinical, serological, radiographic, and in some cases histopathologic workup to rule out systemic causes. Although biopsy was suggested in all cases excluding isolated primary myositis and perineuritis, it
was deferred by parents in 4 (13%) of the cohort. The authors did not choose to exclude these patients as the authors thought they added important data to the study, and presented and responded to treatment as would be expected with IOI. Past published series on this topic also included patients without a histologic confirmation, and underscores the reality that some parents are unwilling to consent to orbital incisional biopsy for their children and the inherent risks thereof. It is imperative to include a multidisciplinary team of physicians including ophthalmologists, pediatricians, rheumatologists, endocrinologists, and radiologists to diagnose and treat these patients in a timely and effective manner.

REFERENCES