When an Orbital Infection Isn’t Infectious at All: A Review of Orbital Inflammatory Syndrome

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ABSTRACT

Orbital inflammatory syndrome (OIS) includes a wide range of clinical manifestations and may initially be misdiagnosed as orbital cellulitis due similar symptoms of fever, periorbital swelling, and pain with eye movements. A diagnosis of OIS requires evaluation for underlying systemic disorders including autoimmune disorders and thyroid disease. Symptoms typically improve rapidly after initiation of steroid therapy, although recurrence can occur. This article presents an illustrative case of a 13-year-old girl with OIS. [Pediatr Ann. 2017;46(11):e433-e436.]

Orbital inflammatory syndrome (OIS) is an uncommon entity in pediatrics, and its initial symptoms can mimic that of orbital cellulitis; therefore, early recognition and intervention are vital for managing symptoms and decreasing morbidity.

ILLUSTRATIVE CASE

A 13-year-old girl with no significant medical history presented to the emergency department with 5 to 6 days of headache, 3 days of vomiting, and 1 day of neck pain, fever, and photophobia. Her medical history was negative for previous hospitalizations, travel, or unusual environmental exposures. Her immunizations were up to date.

Due to initial concern for meningitis, a lumbar puncture was completed. Initial cerebrospinal fluid (CSF) studies (protein, glucose, cell count, and gram stain) were normal. An ultrasound of her neck performed to evaluate for Lemiere’s disease showed no deep vein thrombosis or clot. Subsequently, the decision was made to admit the patient to the hospital for treatment with intravenous (IV) ceftriaxone and observation while awaiting CSF culture results, which ultimately were negative. In the 24 hours after admission, the patient developed blurred vision, diplopia, right-sided periorbital swelling, and pain with and limitation of extraocular movements. Brain and cervical spine magnetic resonance images were obtained on hospital day 2 and were notable for post-septal edema on the right side greater than on the left without any sinus disease evident. Antibiotics were switched to IV ampicillin-sulbactam for coverage of presumed orbital cellulitis.

The patient was seen by the ophthalmology service on hospital day three. Based on the clinical characteristics of fever, headache, nausea, and photophobia as well as bilateral orbital inflammation on magnetic resonance imaging (Figure 1) and no underlying sinus disease, an alternate diagnosis of orbital inflammatory syndrome (OIS) was suggested. Additional evaluations, including anti-neutrophil cytoplasmic antibodies (ANCA), thyroid function tests, thyroperoxidase antibodies, and chest X-ray, were negative. After several days of antibiotics, the patient had not shown clinical improvement and continued to have severe eye pain. On hospital day four, the patient was started on oral prednisone at a dose of 1 mg/kg per day. Her symptoms rapidly improved and she was discharged the next day.

The patient was followed closely by the ophthalmology service as an outpatient. Steroids were tapered over 6 weeks with complete resolution of all symptoms; a slower taper was initially planned but was later accelerated due to adverse effects of mood changes, appetite changes, and fatigue.
OIS, initially characterized in 1905 by Birch-Hirschfeld under the name orbital pseudotumor and also known as idiopathic orbital inflammatory disease and idiopathic orbital inflammation, is defined as a “benign, noninfective clinical syndrome characterized by features of nonspecific inflammatory conditions of the orbit without identifiable local or systemic causes.” The initial nomenclature of “pseudotumor” described an orbital mass similar to a neoplasm on presentation but determined to be histologically inflammatory. Our understanding of orbital inflammation has broadened significantly since that description and now encompasses a wide range of clinical manifestations. Peak incidence is between the fourth and fifth decade of life, but children comprise 6% to 15% of patients in published case series.

OIS remains a diagnosis of exclusion, and consideration of this entity should prompt investigation for underlying causes. Orbital inflammation can be caused by ANCA-related vasculitis (either as an additional part of the systemic disease or as the primary presentation), thyroid eye disease, sarcoidosis, and infection. Less common associations include systemic lupus erythematosus, Crohn’s disease, and rheumatoid arthritis. Other important entities for consideration include malignancy, vascular malformation, and cavernous sinus thrombosis.

**CLINICAL PRESENTATION**

Symptoms of orbital inflammation depend on involved structures, which can include the lacrimal gland, extraocular muscles, sclera, fat, and optic nerve. In adult case series, the most commonly reported symptoms at presentation are pain and periorbital swelling. In pediatric case series, proptosis is typically mild or moderate, visual acuity loss is common, and periorbital swelling tends to be worse in the morning and improve throughout the day. Bilateral involvement is present in approximately 25% of adult patients but in 45% of children. Approximately one-half of affected children also report systemic symptoms, including headache, vomiting, sore throat, or fever. Patients commonly report preceding upper respiratory symptoms or flu-like illness. Signs can also include uveitis, optic nerve swelling, and lacrimal gland enlargement. Pediatric cases show higher rates of uveitis, disc edema, and eosinophilia than their adult counterparts.

Presentation may be similar to orbital cellulitis, including acute onset of symptoms over hours to days. Features that suggest OIS rather than the more common infectious entity include ptosis, chemosis, conjunctival injection, and bilateral presentation, as well as lack of underlying sinus disease on imaging. Other differential considerations are malignancies, including rhabdomyosarcoma (the most common orbital tumor of childhood), retinoblastoma, neuroblastoma, and lymphoma. These malignant lesions should not cause the iritis or chemosis typically present in OIS.

Figure 1. Transverse view of gadolinium-enhanced, fat-saturated magnetic resonance image of orbits showing mild right-sided proptosis, right preseptal soft tissue enhancement (blue arrow), and bilateral enhancement of the retrobulbar fat (white arrows) (greater on the right side than on the left).
PATHOGENESIS
An autoimmune mechanism is thought to underlie OIS, although the frequent unilateral presentation is not fully consistent with this assumption. Specific circulating antibodies have not been found associated with the condition.

The tissues surrounding the orbit are susceptible to inflammation from many conditions. Inflammatory cytokines such as interleukin-1 are known to be increased in OIS. Immunohistochemical staining of tissue samples from affected patients demonstrates the presence of toll-like receptors not found in unaffected samples, suggesting an abnormal innate immune response may be responsible.

Recently, an association with other sclerosing immunoglobulin (Ig) G4-related diseases has been proposed, as there is a subset of OIS patients with elevated serum IgG4 levels. Those patients thought to have IgG4-related ocular disease have more frequent systemic symptoms, less conjunctival involvement, and more commonly develop sclerosing than other patients with OIS. They are less likely to respond adequately to steroid therapy alone. Pediatric cases have been reported.

EVALUATION
A thorough history and physical examination are necessary for all patients with evidence of orbital inflammation, in particular searching for any signs of systemic illness such as infection, thyroid disease, autoimmune disease, or malignancy. A full ophthalmologic examination should be completed. Initial laboratory evaluation may include a complete blood count, electrolytes, thyroid function studies, erythrocyte sedimentation rate, antinuclear antibodies, and ANCA.s although ANCA testing may be negative in cases of granulomatosis with polyangiitis limited to the orbit.

Additional laboratory evaluation to consider includes angiotensin-converting enzyme and rheumatoid factor. Orbital imaging is appropriate for all patients suspected to have orbital inflammation, as characteristic imaging findings may help differentiate idiopathic inflammation, thyroid, infectious, and oncologic causes. Imaging findings in OIS will be dependent on the structures involved. One distinguishing feature of extraocular muscle involvement in OIS is thickening of the entire muscle from origin to insertion, whereas thyroid eye disease classically spares the tendons.

Orbital cellulitis, a common diagnostic consideration, is accompanied by evidence of underlying sinus infection on imaging in 75% of cases. Rhabdomyosarcoma, which is important to rule out in pediatric patients, is typically accompanied by bony changes that are not present in OIS.

A biopsy is generally not performed as part of the initial evaluation but may be appropriate for atypical cases or those refractory to initial management. When a biopsy is obtained, a variety of histological findings may be present in OIS, including granulomatous inflammation, diffuse infiltrate, tissue eosinophilia, and sclerosis.

TREATMENT
First-line treatment for OIS is systemic steroid therapy starting at oral doses of 1 to 1.5 mg/kg daily with a slow taper over 4 to 8 weeks. Response is typically rapid, with dramatic symptom improvement within 24 to 48 hours. A small number of cases will spontaneously resolve. Nonsteroidal anti-inflammatory medication may be used in conjunction with steroid therapy, or as monotherapy in mild cases. Recurrence is more likely with bilateral disease.

Rapid response to steroid therapy supports the diagnosis of OIS. Although steroid therapy could cause some improvement if eye findings were due to an underlying thyroid disorder, autoimmune disorder, or malignancy, resolution should not be as rapid or complete in those cases.

Adult cases series have reported up to 37% of patients not showing adequate resolution of disease with steroid therapy alone, and there are no clear protocols for these patients. Various clinicians have reported successful outcomes using a wide range of interventions in adults not adequately responding to steroids, including cyclophosphamide, methotrexate, intravenous immunoglobulin, cyclosporine, biologic agents including rituximab and infliximab, radiation, and surgical debulking. Consultation with a rheumatologist is appropriate at any point in the evaluation of pediatric patients with OIS and should be strongly considered for those who fail first-line therapy.

OUTCOMES
Patients with a single unilateral episode typically recover fully without any long-term sequelae. Recurrence rate of OIS in pediatric patients has not been well characterized, although one of the earliest pediatric case series noted at least one recurrence in 75% of patients.

Age and gender do not seem to be predictive of response to therapy. Iritis is associated with recurrent disease and residual impairment.

Severe disease, bilateral involvement, and/or recurrent disease may lead to permanent loss of visual acuity along with residual proptosis or strabismus. Over time, sclerosis may cause destruction of orbital tissue or lead to optic nerve compression and damage. For those patients who undergo biopsy of affected areas, the presence of sclerosis is associated with a more severe disease course. Severe acute complications such as orbital compart-
ment syndrome, in which increased intraorbital pressure compromises blood flow to the optic nerve, may occur.\textsuperscript{12}

REFERENCES