• Clinical Research •

Guidelines for the standardized diagnosis and treatment of non-specific orbital inflammation (2024)

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Abstract

● Non-specific orbital inflammation (NSOI) is a non-infectious orbital inflammation. Although it is often considered the most common diagnosis in orbital biopsies, it is an exclusionary diagnosis that requires ruling out systemic disease or other possible causes. Its characteristics include acute orbital signs and symptoms, including pain, proptosis, periorbital edema, chemosis, diplopia, and visual impairment. The clinical manifestations and histological findings of NSOI are heterogeneous, without specific diagnostic criteria or treatment guidelines, which poses significant challenges for diagnosis and treatment. This guideline provides a detailed description of the definition, classification, diagnosis, and treatment of NSOI.

● **KEYWORDS:** non-specific orbital inflammation; clinical manifestation; diagnosis; treatment

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Background and Methods for the Development of the Guidelines for the Standardized Diagnosis and Treatment of Non-Specific Orbital Inflammation

Non-specific orbital inflammation (NSOI), referred to orbital pseudotumor, was initially introduced in 1905 by Birch-Herschfield[1]. This term was coined to describe cases in which patients exhibited protruding eyeballs resembling orbital tumors, yet surgical exploratory biopsies revealed inflammatory tissue rather than neoplastic growths. The term has persisted for over a century. However, since the end of the last century, scholars have raised concerns regarding the designation of "pseudotumor" due to its focus on what it is not, rather than what it is[2]. With advancements in diagnostic technology, various alternative nomenclatures have been suggested to better describe these diseases in accordance with their etiology, clinical features, and histopathologic characteristics. Emerging terminologies suggesting inflammatory reactions of unknown etiology in diseases include "nonspecific orbital inflammation", "idiopathic orbital inflammation", "primary non-granulomatous orbital inflammation", "idiopathic orbital inflammatory disease", and "idiopathic orbital inflammatory

syndrome", but the term "orbital pseudotumor" remains prevalent in clinical practice[3-5]. The diagnosis of NOSI poses a challenge due to diverse clinical presentations and the uncertain etiology, which relies heavily on the expertise and intuition of the clinician. Currently, there are no established laboratory assays for diagnosing NSOI, and no standardized diagnostic criteria or guidelines exist.

In response to challenges encountered in the diagnosing and treating of NSOI, the Ocular Oncology Committee of the Ophthalmology Branch of China Medical Doctors' Association, in collaboration with the Ophthalmic Imaging and Intelligent Medicine Branch of China Medical Education Association, convened a panel of ophthalmic clinical experts and ophthalmic clinical imaging experts to set up a writing group of "Guidelines for the Diagnosis and Treatment of Non-Specific Orbital Inflammatory (2024)" (the "Guidelines"). This Guidelines included a comprehensive survey on orbital diseases in China, conducted on December 5, 2022. The group conducted a comprehensive analysis of the most recent clinical insights on NSOI as outlined by the Casey Institute in Oregon, USA. They also identified and organized the diagnostic and treatment challenges associated with NSOI in various disciplines, as well as the obstacles encountered in the clinical application of related technologies. Drawing upon a thorough review of both of domestic and international NSOI research, the expert panel convened offline and online meetings to thoroughly discuss and validate the collected NSOI problems. The initial version of the Guide was authored by the members of the penning team. Following the formation of the first draft, the document was reviewed individually by all the experts through email and WeChat, who proposed modifications that were subsequently presented to the core members of the Guide writing team. These modifications were deliberated, discussed, and summarized through various communication channels including WeChat, email, and virtual meetings. During the revision period, the Guidelines incorporated the suggestions and guidance provided by participating experts, culminating in the final draft after a duration exceeding one year. The primary objective of this article is to improve the diagnosis and treatment of NSOI among healthcare professionals, as well as to provide dependable treatment guidelines for patients with ocular diseases.

Definition of Non-Specific Orbital Inflammation

The precise definition of NSOI remains elusive, as It is currently perceived as a non-specific inflammatory disease of the orbit lacking obvious local or systemic etiology[6]. Common clinical features include acute or subacute proptosis, periorbital swelling and erythema, pain, diplopia, visual impairments, and effective treatment with oral corticosteroids[7].

Epidemiological

NSOI is estimated to account for approximately 8%-11% of all orbital tumors[8], with another study estimated the prevalence range of 6%-16% is more commonly observed in adults, particularly middle-aged women, with the lacrimal gland being the most frequently affected site. This condition is more prevalent in adults, particularly middle-aged women, with the lacrimal gland being the most frequently affected site. Bilateral involvement is rare in adults but more common in children[9]. The recurrence rate of NSOI after remission ranges from 33%-58%[10], with pediatric patients experiencing a higher rate of up to 76%. The association between bilaterality and recurrence in patients remains unclear.

Classification of Non-Specific Orbital Inflammation

Classification based on speed of symptom onset Based on the speed at which symptoms appear, NSOIs typically are categorized into two main groups. Acute NSOI, with onset occurring days to weeks, and Chronic NSOI, with onset occurring weeks to months[5]. In a recent study, Young *et al*[11] recently proposed a further classification of NSOIs into 3 categories: acute, subacute, and chronic NSOI. In our clinical experience, many NSOIs present as recurrent conditions, leading us to suggest a classification encompassing 4 categories, including acute, subacute, chronic, and recurrent NSOIs, which is helpful for clinicians to judge the condition.

Classification based on anatomical location The most commonly used classification is based on the specific orbital anatomy affected by the lesion. There are three main categories: part of a specific orbital tissue, present in multiple orbital structures and spreading throughout the entire orbit. Specific subtypes of NSOI include lacrimal gland type (lacrimal gland, LG), myxoid type (extraocular muscle, EOM), anterior (sclera, uvea, tendon sheath capsule), posterior (orbital aponeurosis), and diffuse[12], in addition to bone-destroying type, which is rarer and is often misdiagnosed as a malignant tumor without a histologic basis. The clinical manifestations and radiological characteristics of various subtypes exhibit significant variability, as shown in Figure 1.

Classification based on histopathology This classification is based on the pathological characteristics of the disease. The fundamental pathological alterations distinctive of NSOI include an infiltration of inflammatory cells, such as lymphocytes, plasma cells, eosinophils, and macrophages, as well as varying degrees of fibrous connective tissue proliferation. On the basis of exclusion of other lesions, the pathohistological manifestations differ among the various subtypes, including classical, granulomatous, vascular, eosinophilic, and sclerosing NSOI[13]. Classical NSOI also known as lymphoid NSOI, is characterized by a predominantly lymphocytic infiltrate with varying degrees of fibrosis and

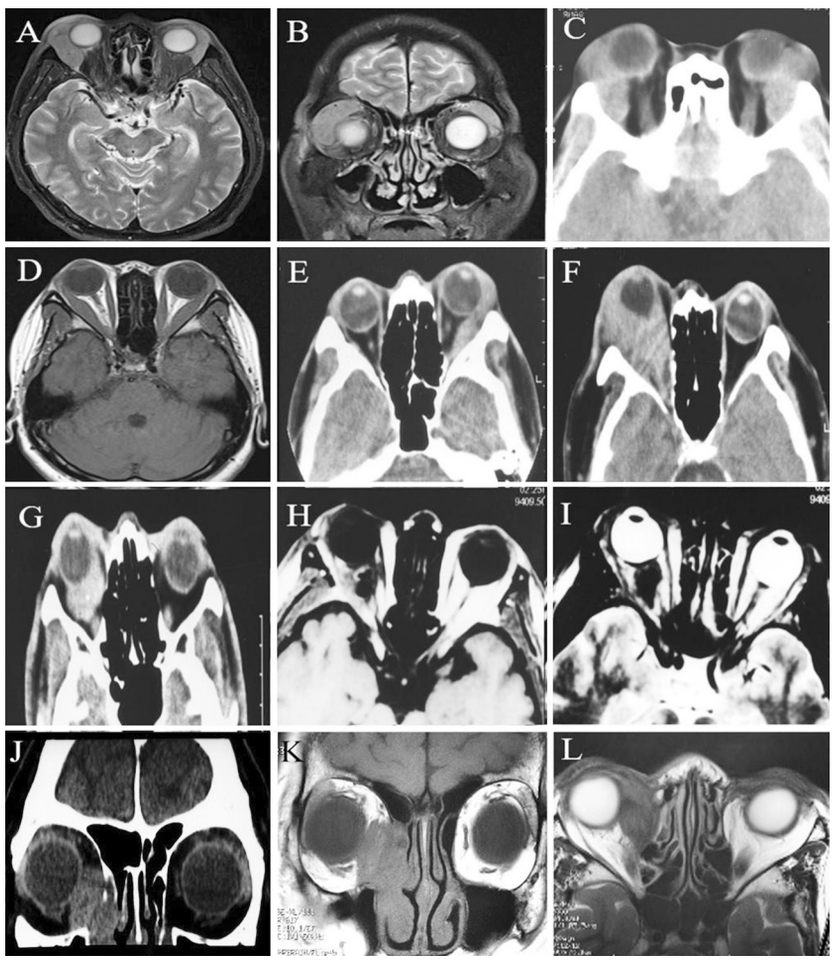

Figure 1 CT and MRI images of different subtypes of pathologically confirmed NSOI A, B, C: MRI (diffuse enlargement of the lacrimal gland, isotropic T1 and short T2 signals, well-defined fat suppression borders, prominent enhancement on enhancement imaging, neighboring extraocular muscles can be involved or displaced) and CT images (amygdaloid enlargement of the lacrimal gland with homogeneous increase in density, partial infiltration of the surrounding tissues, and absence of bone destruction) of lacrimal gland type NSOI. D, E: MRI (thickening of the tendon and muscle belly of the lesion muscle, isotropic T1, short T2 signal, moderate enhancement on enhancement imaging) and CT images (thickening of the tendon and muscle belly at the same time, blurred borders, and no bony destruction) of the myotropic type of NSOI. F, G: CT images of the diffuse type of NSOI (the lesion is more extensive, characterized by thickening of the extraocular muscles, lack of clear demarcation of the extraocular muscles from the lesion, enlarging of the lacrimal gland, thickening of the ocular ring, and enlargement of the optic nerve. The ocular ring exhibits thickening, potentially encircling the optic nerve, which demonstrates enhancement without affecting the optic nerve. Typically, intraorbital low-density fat shadow is replaced by soft tissue density shadow. H, I: MRI images of posterior (orbital apical) NSOI (isometric TI signal, long T2 signal, moderate-significant enhancement on enhancement scan. J, K, L: Images of bone-destroying type NSOI (CT and MRI: soft tissue density shadow visible in the orbital septum, with a relatively homogeneous density, generally without calcification, limited destruction of the orbital bone in the inner and lower walls is missing, and the lesion involves extra-orbital tissues. MRI: Isotropic T1 signal, inhomogeneous short T2 signal. NSOI: Nonspecific orbital inflammation; MRI: Magnetic resonance imaging; CT: Computed tomography.

edema[14]. Granulomatous NSOI is distinguished by histiocytic infiltration and multinucleated giant cell infiltration[15]. Vascular changes are a defining feature of Vascularity NSOI[16]. Eosinophilic NSOI is characterized by a significant presence of eosinophils in the lesion tissue without evidence of vasculitis[17]. Sclerosis NSOI is distinguished by a notable increase in fibrous connective tissue at the site of the lesion, showing marked sclerosis and mild mixed inflammation[18]. From a clinical perspective, ophthalmologists can categorize NSOI into 3 types: lymphocytic infiltrating NSOI, fibroproliferative NSOI, and mixed NSOI, according to the predominant pathohistologic changes. NSOI characterized by predominantly inflammatory cell infiltration typically responds more sensitive to glucocorticoid therapy, whereas NSOI characterized by fibrous connective tissue proliferation does not. Therefore, pathohistological typing plays a crucial role in guiding treatment decisions for NSOI, as shown in Figure 2.

Other Each of the aforementioned NSOI classification systems presents both advantages and disadvantages. Classification based on the rapidity of symptom onset is

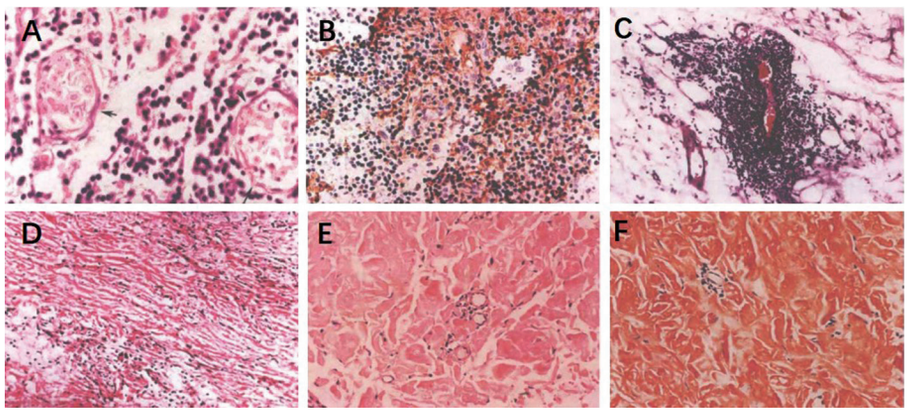

Figure 2 Pathohistologic changes of NSOI A: Inflammatory cell infiltration of intraorbital tissues and nerves (arrows), HE ×400; B: Positive staining for CD20 and CD3, IHC ×200; C: Pathologic tissue of vascular NSOI, with dilated blood vessels and inflammatory cell infiltration seen within the orbital fat, HE ×200; D: Large amount of fibrous connective tissue hyperplasia accompanied by inflammatory cell infiltration within the lesion of sclerosing NSOI, HE ×200; E: Amyloidosis pathologic tissue (eosinophilic inflammation), a large amount of amyloid amorphous material is seen to be deposited within the lesion, mostly along the perivascular area, HE ×100; F: Amyloidosis pathologic tissue (eosinophilic inflammation) with positive Congo red staining, Congo red staining ×200. NSOI: Nonspecific orbital inflammation; HE: Hematoxylin-eosin; IHC: Immunohistochemistry.

straightforward and does not necessitate supplementary laboratory tests. However, the onset of symptoms is relatively subjective and dependent on patient statements, poses challenges in establishing a clear distinction between acute and chronic NSOI. The anatomical structure-based classification method is widely utilized, yet it relies on imaging techniques. Histopathology-based classification approaches are vulnerable to the precision of biopsies. Recent research has confirmed the validity of NSOI classification systems based on lesion localization and histopathology, as well as proposed a two-dimensional joint classification system incorporating both factors with good reliability and feasibility[19].

Diagnosis of Non-Specific Orbital Inflammation

Ophthalmologic assessment The ophthalmologic examination includes eyelid assessment (eyelid swelling, congestion, ptosis, recession, delayed eyelid movement), orbital assessment (proptosis, palpable mass, tenderness, orbital pressure), ocular motility, the eye itself (conjunctival congestion, edema, intraocular inflammation, retinal anomalies), and assessment of visual function (visual acuity, visual fields, color vision, and relative afferent pupillary deficits)[20]. These examination aim to elucidate reveal the characteristics, anatomical site, severity, and functional impairment of the inflammation, providing valuable clues and guiding diagnosis strategies.

Laboratory tests Laboratory tests encompass a comprehensive blood count, basal metabolic assessments, and inflammatory marker analyses (*e.g.*, sedimentation rate or C-reactive protein). Previous studies have shown that NSOI could serve as a potential precursor to systemic inflammatory disease. Therefore, it is critical to perform a comprehensive systemic inflammation assessment[17]. Thyroid function and thyroid autoantibody tests are essential for the diagnosis of thyroid eye disease (TED), which is a common orbital inflammatory condition associated with systemic disease[21-22]. A serum IgG4 level of ≥135 mg/dL is one of the diagnostic criteria for IgG4-related disease (IgG4-RD), but it lacks specificity or sensitivity[23]. When dry syndrome (Sjögren's syndrome; SJS) is suspected, screening can be done by measuring the levels of antinuclear antibodies, rheumatoid factor, erythrocyte sedimentation rate, total serum IgG, and Ro antibodies[24].

These inflammatory marker tests are chosen based on clinical history and a thorough physical examination findings. However, serologic tests play a limited role in the diagnosis of NSOI. There are no definitive diagnostic indicators or alternative markers for NSOI (tests are not used to diagnose NSOI, but are used to rule out other possible diseases). In addition, most serologic tests for NOSI have limited sensitivity and may give false-negative results in mildly case or when lesions are confined to the orbit[25].

The role of imaging Orbital imaging, such as CT and MRI, is essential for evaluating orbital diseases. CT scanning is effective, rapid, with good resolution and contrast[26], which is especially suitable for the detection of lesions such as calcified lesions and bone tissue involvement; MRI is particularly effective in detecting soft-tissue lesions, and outperforming CT in evaluating optic nerves, optic nerve sheaths, and extra-orbital extensions of the lesions[27]. It excels in diagnosing inflammatory activity, especially with enhanced imaging. MRI imaging performance varies based on the anatomical location and histopathologic features of the lesion. With the advancement of MRI technology, many solutions aimed

at improving the diagnostic accuracy of MRI for orbital inflammation have been generated. Diffusion weighted imaging (DWI) with an apparent diffusion coefficient (ADC) map is a valuable tool for imaging orbital lesions, and helping to distinguish between NSOI on orbital lymphoma[28].

Treatment of Non-Specific Orbital Inflammation

Mild NSOI can sometimes resolve on its own[29], but prompt and adequate treatment can shorten the duration, reduce the risk of recurrence, and prevent orbital fibrosis[30]. Treatment options for NSOI include corticosteroids, immunomodulators, biologic agents, radiation therapy, and surgical resection[31]. Most patients with NSOI respond well to corticosteroid therapy. Immunomodulators and biologics are gaining prominence. Some studies have reported cases of reduced inflammation with radiation therapy. However, overall, it is difficult to systematically compare the efficacy of each treatment modality due to the large individualization of patients, the lack of standardized and uniform treatment protocols and criteria for assessing efficacy.

Corticosteroids Oral corticosteroids are the predominant treatment for the disease, with glucocorticoids being the first-line clinical option[32]. Typically, an initial dose of 1 mg/kg of prednisolone or prednisone per day is recommended. These medications rapid improvement in symptoms within 24-48h. The drug typically show rapid improvement in signs and symptoms[33]. Following the initial high-dose treatment, corticosteroids should be gradually tapered to prevent disease relapse and minimize side effects. Corticosteroid tapering typically takes place over weeks to months, with no set regimen or timeline[34].

Immunosuppressive drugs Methotrexate (MTX) is a widely used medication for treating orbital inflammation[35]. Studies have indicated positive therapeutic outcomes in 64% of patients when administered at a dose of 15-20 mg per week. It is typically prescribed when patients are unable to taper off corticosteroid treatment dose or when corticosteroid therapy is ineffective. Common side effects of MTX include fatigue, gastrointestinal disturbances, alopecia, and elevated liver enzymes[36]. To mitigate these effects, patients are advised to supplement their diet with folic acid and undergo regular liver function monitoring[36]. Mycophenolate mofetil (MMF) is an immunomodulatory drug which has been widely used to prevent organ transplant rejection[37]. Studies have shown that MMF has demonstrated a high degree of effectiveness in the long-term treatment of orbital inflammation with relatively few side effects. Common side effects include gastrointestinal disturbances, nausea, rash, myalgia, headache, and rarely bone marrow suppression[38]. Cyclosporin A (CsA) inhibits interleukin-2 production, resulting in decreased T-cell activity and major side effects such as renal insufficiency, immunosuppression, and hypertension. Monitoring of renal function is necessary during treatment. Additional symptoms such as gingival hyperplasia, hair growth, and myalgia are also commonly seen with treatment. However, there are relatively few treatment cases for reducing orbital inflammation with CsA[39]. Azathioprine, an analog of mercaptopurine, disrupts purine bases into DNA and RNA[40], inhibiting relevant enzymes involved in purine metabolism. There have been limited reports of azathioprine being used to treat NSOI[41].

Biological agents Recently, monoclonal antibodies targeting inflammatory cytokines, mediators or their receptors have been recognized as a novel type of immunomodulator. These biologic drugs act in a specific way and are considered more effective and safer than traditional immunosuppressive drugs. Rituximab, is a chimeric monoclonal antibody, targets the B-cell surface antigen CD20 to clear B-cells and inhibit their interaction with T-cells. The drug has been widely used in a variety of non-infectious inflammatory diseases of the orbit[42]. Infliximab is a chimeric monoclonal antibody that inhibits tumor necrosis factor (TNFα). It binds to soluble and membrane-bound TNF, neutralizing its biological activity. Infliximab has been used successfully in the treatment of various types of uveitis[43].

Radiation therapy Traditionally, radiation therapy has been considered an effective treatment for patients with persistent or recurrent NSOI or those who cannot use corticosteroids[44]. Low-dose radiation therapy averaging 15-20 Gray is usually used, delivered in 10 sessions over 2-3wk. Common complications include blepharitis, dry eye, cataracts, and retinopathy, but these are usually mild and well-tolerated by patients. Treatment success rates range from 62%-90%[45].

Surgical treatment Surgery is also a common method for managing NSOI, with the main goal of clarifying the diagnosis. Due to the lack of specificity of the clinical manifestations of NSOI, it is often necessary to make differential diagnosis with many diseases. Clinical manifestations and imaging results alone are insufficient for differential diagnosis with other diseases. Currently, a definitive diagnosis can only be attained the pathological and histological examinations for NSOI with localized lesions or when confined to specific orbital tissues, surgical excision of the lesions is feasible and glucocorticoid treatment can often achieve the goal of cure after surgery. Careful consideration of surgical indications is crucial to minimize complications during NSOI surgery. In the specific implementation of NSOI surgery, careful consideration of surgical indications is crucial to minimize complications during NSOI surgery[46].

Risk Factors for Relapse

Standardized treatment guidelines or protocols for NSOI complicates the accurate determination of recurrence rates. The absence of standardized treatment guidelines or protocols

for NSOI makes it difficult to accurately determination recurrence rates. Analyzing previous studies indicates that recurrence occurs 38%-52%[3]. Regarding the risk factors for recurrence, some researchers have proposed that site-specific histopathologic features may contribute to recurrence, but it is still controversial whether they are risk factors for recurrence. Recent studies have compared CT and clinical indicators in patients with single and multiple recurrences of NSOI. These studies have identified several potential risk factors for multiple recurrences, including: underage patients, binocular onset, optic disc edema, poor initial response to steroid treatment, sclerosing NSOI, overly rapid tapering of steroid dosage, and a family history of autoimmune disorders; Furthermore, in patients with recurrent NSOI, the duration between the initial episode and the interval between the first relapse may serve as a prognostic indicator for the likelihood of further relapses[10].

Current Treatment Options

Current treatment protocols are guided by the physician's preference, the patient's medical history, and the severity of the condition. Typically, oral corticosteroids are initiated at doses agreed upon by the physician and patient, the objective of resolving inflammation within a two to three months period from of commencement of treatment. During treatment, calcium and vitamin D are frequently administered to mitigate bone loss, while blood glucose, weight, mood and blood pressure are closely monitored during corticosteroid therapy. In patients experiencing recurrent disease, clinicians may need to initiate non-steroidal medications shortly after the commencement of glucocorticoid therapy, contingent upon the specific clinical context. Based on cost, convenience of weekly dosing, and clinical accumulated experience, methotrexate, typically at a dosage of 20 mg/wk administered subcutaneously, in conjunction with 1 mg/d of folic acid is generally selected. During the course of treatment, it is imperative to inform patients about potential complications such as immunosuppression, oral ulcers, fatigue, hepatic impairment, infections, rare forms of pneumonia, alopecia, and cytopenias. In special cases, the attending physician may collaborate with other specialists, such as rheumatologists experienced in immunosuppression, to ensure the feasibility and safety of the therapeutic regimen. If the patient remain asymptomatic for approximately one year, a discussion may be initiated regarding the gradual reduction or tapering of immunosuppressive therapy. In cases where the patient exhibits intolerance to methotrexate or presents with contraindications, oral azathioprine at a dosage of 1.5 mg/kg serves as a viable alternative. It is recommended that the physician assess the patient's thiopurine methyltransferase level before initiating azathioprine therapy, as decreased enzyme levels may be associated with increased risk of side effects. Additionally, it is crucial to note that azathioprine should not be co-administered with allopurinol. Clinicians should be aware that azathioprine can occasionally induce flu-like symptoms, which may be mistakenly attributed to an infectious process rather than recognized as a potential drug-related side effect. Drawing on prior clinical experience, rituximab emerges as the most effective biologic treatment for patients who have not responded to antimetabolite therapy. Localized corticosteroid injections can be given to patients with less severe disease; radiation therapy is indicated for those who are either refractory or resistant to corticosteroids, or for whom corticosteroid therapy is contraindicated.

Complications (Undesired Side-Effect of Medical Procedure)

Inflammation associated with NSOI can spread to adjacent anatomical structures such as the periorbital region, optic nerve, and intracranial areas. If an NSOI remains untreated or if the treatment is ineffective, there is a risk of permanent vision loss and severe motoneuron dysfunction. Multiple cranial nerves may be affected, leading to both sensory and motor deficits. In severe cases, secondary glaucoma may develop. Progressive ocular protrusion can result in exposure keratitis and ulcer formation.

Summarize

NSOIs encompass a spectrum of diseases characterized by variability in anatomical locations, diagnostic manifestations, and therapeutic responses[47]. Undoubtedly, with the improvement and standardization of molecular diagnostic accuracy, it is expected that NSOIs will be further classified by more precise techniques. These emerging technologies are expected to provide enhanced insights into pathogenesis and prognosis.

Although future research on NSOI remains fraught with uncertainty, experts are confident about five significant changes that are likely to occur within next decade. Firstly, the comprehension of pathogenesis will progress rapidly. The implementation of molecular diagnostics represents a crucial advancement in the field, facilitating more extensive and profound research endeavors. Secondly, there will be ongoing advancements in imaging technology. Data from large databases can enhance the precision of imaging, allowing radiologists to determine disease activity with greater accuracy than clinicians. Improved MRI scanning technology may contribute significantly to it. The third is that the fibrosis associated with NSOI remains a significant impediment to current drug therapy. However, emerging treatments for fibrotic diseases of the organ may also be applicable to orbital fibrosis[48]. The fourth is that tear studies are a relatively untapped resource for orbital disease. Tear studies have been reported for use in the diagnosis and management of thyroid eye disease[49]. In NSOI, tear fluid can contain inflammatory

markers, offering valuable biochemical data for diagnosis, disease activity monitoring, and prognosis assessment. Finally, NSOI therapy will advance. A deeper comprehension of pathogenesis is expected to facilitate the development of novel treatments and "precision" medicine approaches. The purpose of this guideline is to provide clinicians and researchers with a systematic overview of NSOI, thereby assisting ophthalmologists in selecting more efficacious NSOI treatment options, optimizing diagnostic accuracy and treatment efficacy, and furthering the progress of research in the field of NSOI disease.

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Guidance Statement: All the experts involved in the development of this guideline declare that they adhere to an objective position, based on professional knowledge, research data and clinical experience, and that this guideline is formed after full discussion and unanimous agreement of all the experts. This guideline is drafted by some experts from the Ophthalmic Imaging and Intelligent Medicine Branch of the Chinese Association for Medical Education and the Ophthalmology Specialty Committee of the International Society for Translational Medicine.

Disclaimer: The contents of this guideline represent only the guidance of the experts involved in the development of this guideline for the reference of clinicians. Despite extensive consultation and discussion among experts, there are incomplete points. The recommendations provided in this guideline are not mandatory, and practices that are inconsistent with this guideline do not imply error or inappropriateness. There are still many issues to be explored in clinical practice, and ongoing and future clinical trials will provide further evidence. With the accumulation of clinical experience and the emergence of new treatments, this guideline will need to be revised and updated periodically in the future to bring more clinical benefits to the subjects.

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