

Nasal manifestations of systemic diseases

Objawy nosowe w chorobach ogólnoustrojowych

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Otolaryngol Pol 2009;
63 (3): 228-235

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– Chirurgów Głowy i Szyi
Otrzymano/Received:
25.03.2009
Zaakceptowano do druku/Accepted:
05.04.2009
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Introduction

The nasal airway may be the initial target of a spectrum of systemic diseases. Recognition of these signs may permit earlier and more effective management of the underlying condition. Systemic diseases affecting the nasal airway can produce pathologic changes in three general ways. First, the general pathophysiology of the disease may affect the tissues of the nose as in recurrent or severe epistaxis secondary to a coagulopathy. Second, the unique mucosal histology of the nose may make an otherwise minor pathologic process more severe and apparent as seen in hereditary hemorrhagic telangiectasia. In this particular disease, telangiectasia in the skin cause few symptoms whereas in the superficial, easily traumatized vessels of the nasal mucosa, severe epistaxis may occur. Third, a systemic disease may affect the tissues of the nose as part of a symptom complex as seen in Wegener's granulomatosis.

Granulomatous disease

Several granulomatous diseases have a predilection to involve tissue in the airways. These include Wegener's granulomatosis, Churg-Strauss syndrome, and sarcoidosis. These diseases are often characterized by local inflammatory response in the airways, particularly in the upper nasal passages. Wegener's granulomatosis is perhaps the most common granulomatous disease to affect the upper airway and the nasal airway in particular. Sarcoidosis and Churg-Strauss vasculitis, although much less frequently found to involve the nasal airway, also have characteristic findings.

Wegener's Granulomatosis

Friedrich Wegener first clearly defined WG as a systemic disease in 1939 characterized by necrotizing granulomas with vasculitis of the upper and lower respiratory tract, systemic vasculitis, and focal necrotizing or proliferative glomerulonephritis [1]. The classic triad of WG includes the following organ systems: the upper respiratory tract, lungs, and kidneys. Formerly, WG was often confused with several other entities causing midline granulomas or midface destruction including lymphomas, carcinomas and infectious processes. WG can now be easily separated with more precise nasal biopsies, histopathologic examination and the cytoplasmic antineutrophilic cytoplasmic antibody (c-ANCA) test.

The prevalence of WG is estimated to be 3 cases per 100,000 while the mean age at diagnosis is 55 years [2]. Males and females are similarly affected and more than 90% of all WG patients are white per recent studies. The remaining 1-4% of cases are comprised of African-Americans, Hispanics, and Asians [3].

Rhinologic symptoms of patients with WG may include nasal congestion, rhinorrhea and, anosmia. These symptoms may progress to rhinitis, sinusitis, septal perforation and/or nasal airway stenosis. Nasal endoscopy typically reveals mucosal cobblestoning, edema, and crusting [4].

Clinical features of WG can be divided into three categories. Type 1 patients present with a limited form of the disease characterized by upper airway symptoms and few systemic findings. They typically present with several weeks of symptoms reminiscent to an upper respiratory tract infection which are unresponsive to antibiotics. There is often associated nasal pain and serosanguinous rhinorrhea and crusting.

Type 2 patients have systemic features, but their initial presentation is similar to type 1. There is a characteristic prolonged upper respiratory tract infection with a continued nasal discharge which progresses to nasal pain, tenderness, serosanguinous discharge, ulceration, and crusting. Pulmonary involvement is often present and associated with a cough, hemoptysis and cavitory lesions on chest x-ray.

Type 3 is a widely disseminated form of the systemic disease with upper and lower airway involvement, cutaneous lesions, and progressive renal involvement. Systemic features are more profound and again nasal ulcerations and symptoms are present.

Diagnosis

The clinical diagnosis of WG is suggested by the history and characteristic nasal findings. Laboratory values which are often abnormal in WG include the erythrocyte sedimentation rate (ESR), hemoglobin, serum creatinine and c-ANCA. These serologic findings in conjunction with nasal biopsy can provide a definitive diagnosis of WG.

Immunofluorescence is a study which distinguishes anti-PR3 antibodies from antimyeloperoxidase antibodies by the pattern of staining: cytoplasmic ANCA for anti-PR3, versus perinuclear ANCA for antimyeloperoxidase [5]. The characteristic pattern of coarse granular staining of c-ANCA is caused by antibodies against proteinase 3 and neutral serine protease present in the azurophilic granules of neutrophils. The c-ANCA is highly sensitive for WG but a negative c-ANCA does not exclude the diagnosis of WG. The specificity of c-ANCA for WG has been confirmed in large studies and may in some cases preclude the need for biopsy [6,7,8]. The c-ANCA titer may be used to monitor disease activity as rise in the titer may be predictive of a relapse of disease although this concept remains controversial. However, it is clinically appropriate to interpret an increase in c-ANCA titer as an indicator to closely monitor the patient for signs of relapse.

Nasal biopsy may provide supportive evidence for the diagnosis. It is important to remove all visible nasal crusts followed by liberal removal of tissue from the septum, nasal floor, and turbinates in order to provide ample tissue for stains and culture [8]. Culture is necessary to rule out granulomatous infectious agents such as fungi and mycobacteria.

Because of the non specific nature of many of the symptoms of WG, diagnosis and treatment may be delayed.

Pathology

The histopathologic features of WG include vasculitis of medium and small vessels with intramural eccentric

necrotizing granulomatous lesions. Typically arteries, arterioles, capillaries, venules, and veins are involved. Large vessels are rarely affected. There may also be microabscesses that enlarge and coalesce into larger necrotic areas.

Treatment

Treatment algorithms are often based on disease severity and the organ system affected [9]. Patients are typically treated with immunosuppression in order to first induce remission and then adjusted to maintain the state of remission. The main agents used to induce remission are cyclophosphamide, methotrexate and/or glucocorticoids.

Cyclophosphamide is an alkylating agent which impairs DNA replication and transcription. The current standard regimen for treatment of WG with cyclophosphamide is oral administration of 2mg/kg per day with a maximum dose of 200mg/day. It is typically continued for 6 months to 1 year and then tapered gradually after the disappearance of symptoms.

Methotrexate is an alternative to cyclophosphamide in patients with limited forms of WG such as found in Type 1 patients. It acts as an antimetabolite and inhibits dihydrofolate reductase in order to impair folate metabolism. The standard dose begins at 0.25mg/kg/week which can be increased to 25mg/week. It is typically continued for 1 year and may be continued indefinitely or tapered or stopped abruptly.

Glucocorticoids are given concurrently whether cyclophosphamide or methotrexate is used. The recommended starting dose is prednisone 0.5-1.0 mg/kg/day up to a maximum of 80mg/day [9]. Tapering may begin after 1 month with the goal to discontinue completely within 6-9 months.

After the symptoms are stabilized WG may be effectively maintained on a regime of trimethoprim-sulfamethoxazole [10]. Although the mechanism of action of this drug is not known with certainty, it had been shown to prevent relapses, and has minimal side effects.

New therapeutic agents have been shown to be promising in resistant cases. Rituximab a chimeric monoclonal antibody has been reported to be effective in treating resistant WG [11].

Surgical reconstruction may be used to restore function once the disease is in remission. This includes correction of saddle nose deformity and septal perforation repair. Functional endoscopic sinus surgery may benefit select patients with chronic nasal crusting. Saline irrigations with or without antibiotics are essential to management although nasal debridement may be helpful with mucosal sparing techniques and frequent post-operative care to minimize scar formation.

Sarcoidosis

Sarcoidosis is a chronic systemic granulomatous disease capable of involving almost any organ in the body. It frequently involves the lymphatic system, lungs, liver, spleen, and bones. Although involvement of the epithelium of the upper respiratory tract is comparatively infrequent, nasal symptoms may be the first manifestation of this disease.

The etiology of sarcoidosis is unknown, but etiologic claims have been made for various infective agents, chemicals (including beryllium and zirconium), pine pollen, and peanut dust [12]. It has also been associated with cell-mediated and humoral immune abnormalities.

The clinical course in most cases is benign with spontaneous resolution within 2 years although 10% may progress to pulmonary fibrosis. The lung is the primary organ affected by sarcoidosis. Ninety percent of patients will have evidence of thoracic involvement, either enlarged intrathoracic lymph nodes or pulmonary parenchymal infiltrates. Approximately 40% of patients with sarcoidosis will have granulomatous changes in extrapulmonary organs.

The involvement of the nose and paranasal sinuses by sarcoidosis is relatively infrequent and most reports are anecdotal, so the true incidence of nasal involvement is not known with certainty. The observed incidence of histologically confirmed nasal involvement in large populations of patients with sarcoidosis has ranged between 1% and 6% [13, 14]. The most frequent symptom of nasal involvement is nasal obstruction, but, epistaxis, dyspnea, nasal pain, epiphora, and anosmia may also occur.

Nasal sarcoidosis commonly affects the mucosa of the septum and inferior turbinate. The nasal mucosa is usually dry and friable with crusting [15]. Submucosal nodules with a characteristic yellow color may be noted. These nodules are the macroscopic presentation of intramucosal granulomas which can be identified in mucosal biopsies. In more advanced disease, irregular polypoid mucosa is seen, which is friable and bleeds readily.

Paranasal sinus involvement in sarcoidosis often accompanies nasal mucosal involvement. Mucous membrane thickening or opacification of paranasal sinuses occurs. Some patients with nasal sarcoidosis will have bony lesions of the nasal bones. The lesions may appear as scattered regions of osteoporosis or zones of frank destruction. These lesions are a response to granulomas within the bone. The suture lines may disappear, but no periosteal reaction is seen [16].

Diagnosis

The diagnosis of sarcoidosis is based on a combination of histologic, radiographic, immunologic, and

biochemical data. The diagnosis of sarcoidosis of the nose and paranasal sinuses is based on the clinical findings of crusting friable nasal mucosa with either polypoid changes or characteristic yellowish submucosal nodularity. Sinus CT and x-ray will be abnormal in most cases of nasal sarcoidosis. Pulmonary findings of either hilar lymphadenopathy or pulmonary fibrosis are commonly found. Laboratory findings that may support a presumptive diagnosis of sarcoidosis are elevated serum or urinary calcium. Radiogallium uptake may be increased in the nasal mucosa in sarcoidosis [17]. The diagnosis is confirmed by the presence of noncaseating granulomas in the nasal mucosa.

Angiotensin-converting enzyme (ACE) elevations occur in 83% of patients with active sarcoidosis. At the present time, this test has become very useful for the diagnosis of sarcoidosis as well as monitoring for relapse. It must be remembered that ACE levels can also be elevated in tuberculosis, lymphoma, leprosy, and Gaucher's disease.

Pathology

Multiple noncaseating granulomas are the characteristic histology feature of sarcoidosis. The sarcoid granuloma consists of a central area of tightly packed epithelioid cells surrounded by lymphocytes and fibroblasts. Multinucleated giant cells up to 150 μm in diameter are frequently found within granulomas. There is no specific histologic feature of sarcoidosis, and similar granulomas occur in tuberculosis, berylliosis, leprosy, hypersensitivity pneumonitis, fungal disease, and chronic inflammatory processes [18, 19].

Treatment

Most cases of stage I sarcoidosis will undergo spontaneous remission within 2 years without specific treatment. Sarcoidosis beyond stage I with elevated ACE levels or extrapulmonary involvement will usually require treatment. This includes most cases of nasal sarcoidosis.

The mainstay of treatment is systemic corticosteroids. The majority of patients' symptoms can be controlled with oral prednisone in doses of 10-40 mg daily [20]. If nasal symptoms relapse while a patient is taking relatively high systemic doses of corticosteroid, local treatment with intranasal steroids may be used to allow reduction in the oral dosage.

Methotrexate has been used to treat nasal sarcoidosis successfully at a dose of 30mg weekly [21]. The use of methotrexate should only be considered if there are contraindications to the use of systemic corticosteroids, since its effectiveness in sarcoidosis has not been extensively tested.

Churg-Strauss Syndrome

Churg-Strauss syndrome (CSS) is also known as allergic granulomatous angiitis and affects small to medium sized vessels. It is a granulomatous vasculitis which is characterized by three phases: Phase 1. a prodromal phase with allergic rhinitis and asthma; Phase 2. an eosinophilic infiltrative phase with chronic eosinophilic pneumonia or gastroenteritis; and Phase 3. a systemic, life-threatening vasculitis with granulomatous inflammation. CSS is associated with nasal crusting and polyposis and may be distinguished from WG by the presence of both nasal polyps and asthma in CSS. C-ANCA will also be negative in CSS while p-ANCA is positive in 70% of patients. CSS may be distinguished from sarcoidosis by the presence of asthma, eosinophilia, and vasculitis with necrotizing granulomas all of which are absent in sarcoidosis [22].

Pathology

Histopathologically, CSS is characterized by necrotizing vasculitis of small and medium sized vessels. Necrotizing extravascular granulomas may also be present. There is prominent eosinophilia of the vessels and perivascular tissue.

Treatment

Glucocorticoids continue to be standard treatment for CSS. Cyclophosphamide may be helpful in life threatening cases or in patients with poor prognostic factors [23].

Neoplastic diseases

The most notable neoplastic, systemic disease with nasal manifestations is nasal T-cell lymphoma. Leukemia and B-cell lymphomas may also have nasal presentations. B-cell lymphomas may cause unilateral nasal obstruction by an enlarged nasal or nasopharyngeal mass. Acute leukemia may produce symptoms of an upper respiratory infection or cause epistaxis secondary to friable mucosa in the anterior nose.

T-Cell Lymphoma

Previously known as midline malignant reticulosis or polymorphic reticulosis, nasal T-cell lymphoma is a rare disease that can be difficult to diagnose. Long term remission is only 50% in patients with this disease and 50% will die from distant extranodal spread or from relapses outside of the treatment field [24, 25]. Nasal T-cell lymphomas differ phenotypically from lymphomas of the paranasal sinuses and in Waldeyer's ring which tend to be of B-cell origin.

Diagnosis

Clinical manifestations of nasal T-cell lymphoma usually start with nasal obstruction followed by purulent rhinorrhea and serosanguinous discharge. As symptoms progress, usually unilateral mucosal ulceration with extension into the palate, maxillary sinus and upper lip help distinguish lymphoma from WG which is associated with diffuse nasal mucosal ulceration. Mucosa is often pale, friable and extensive crusting is often present. Oronasal fistulas often occur as well as nasal septal perforations which have been reported in 40% of cases of nasal T-cell lymphoma [26]. Typically, there is an explosive unilateral involvement of one side of the nose, face, palate, and/or orbit. Systemic symptoms are more notable in advanced cases and include malaise, night sweats, febrile episodes and arthralgias [27].

Laboratory workup is similar to that for Wegener's granulomatosis. However, it is important to include HIV testing. A nasal biopsy may benefit diagnosis if there is adequate sampling of both abnormal and adjacent normal tissue.

Pathology

T-cell lymphomas have a polymorphic lymphoid infiltrate made up of mature, immature and atypical lymphocytes, plasma cells, histiocytes, eosinophils, and macrophages. The infiltrate is characterized by angiocentricity and angioinvasion and can lead to vessel occlusion and local tissue infarction. This may lead to the rapid tissue necrosis and ischemia seen with nasal T-cell lymphoma. Immunohistochemical studies of biopsy specimens typically demonstrate the presence of T-cell associated markers CD2, CD7, CD45RO, CD43 and natural-killer marker CD57 [28].

The association of Epstein-Barr virus (EBV) and nasal T-cell lymphoma has frequently been reported. Various studies report the detection of EBV DNA and RNA in tumor cells associated with high titers of EBV antibodies in patients with T-cell lymphoma [25, 29, 30]. The causative role of EBV in the pathogenesis of T-cell lymphoma has been strongly suggested but remains to be definitively determined. Treatment

Localized disease responds well to radiation therapy. Chemotherapy may benefit patients with disseminated disease or relapses. A 2004 study suggested that high dose chemotherapy as well as autologous peripheral blood stem cell transplant may be an effective treatment option for relapsed nasal T-cell lymphoma [24]. Currently, multiple agent chemotherapy in addition to radiation therapy is the initial treatment recommendation for nasal T-cell lymphoma [25].

Immunodeficiency diseases

Immunodeficiency is of special importance in the nasal manifestations of acquired immune deficiency syndrome and the infectious consequences of iatrogenic immunodeficiencies resulting from chemotherapy for neoplastic and hematologic diseases. These two forms of immunodeficiency create difficult problems of diagnosis and treatment of infectious diseases of the nose, which will become an increasing component of the practice of rhinology.

Sinusitis in the immunocompromised patient

Rhinitis and sinusitis in immunocompromised patients is usually due to the same pathogens affecting the general population. There may be more subtle signs of bacterial infection but treatment is similar including antibiotics and/or surgery. Complications including periorbital or orbital abscess may be more subtle and open surgical treatment may be instituted prior to full demonstration of an abscess on CT scan.

Fungal sinusitis appears rarely in immunocompromised patients but is extremely important to the otolaryngologist in terms of diagnosis and treatment. *Aspergillus sp.* and *Mucor sp.* are the most commonly involved fungi. Patients present with bloody nasal discharge, facial pain and swelling, fever, and edema. The disease often progresses rapidly in an invasive manner to cause facial cellulitis, gangrenous mucosal changes in the nose and paranasal sinuses, obtundation, cranial nerve palsies, vision loss, and proptosis [31].

Diagnosis is established via physical exam findings of pale or gray mucosa of the nasal cavity or palate or the classic black middle turbinate [32]. Decreased pain and sensitivity of the nasal cavity is a suspicious sign. Small tissue biopsies should be taken of the nasal lesions and sent for culture and microscopic examination including GMS stain. CT scan of the sinuses may demonstrate a destructive bony lesion but can often understate the clinical problem in a severely immunocompromised patient.

Treatment includes standard treatment for febrile neutropenia if present, blood glucose control in diabetics as well as medical therapy for biopsy or culture confirmed *Mucor* or *Aspergillus*. Current antifungal therapies include amphotericin B systemically and nasal irrigations, voriconazole and posaconazole. Aggressive surgical debridement is strongly advocated if the patient can tolerate surgical intervention. Surgical interventions range from endoscopic debridement to total maxillectomy with orbital exenteration and craniofacial resection.

Acquired Immunodeficiency and the nasal airway

The acquired immunodeficiency syndrome (AIDS) is a syndrome characterized by the presence of one or more opportunistic diseases that indicate an underlying cellular immunodeficiency, without any other known cause of immunodeficiency [33]. It is well known that the condition is caused by the human immunodeficiency virus which attacks T-helper cells.

The most common nasal manifestation of AIDS is chronic rhinitis. Patients present with drying, crusting, nasal congestion, partial obstruction and pain or discomfort. Purulent rhinitis may be seen secondary to cytomegalovirus. Other causative agents of rhinosinusitis reported in the literature include *Strep. Pneumoniae*, *Haemophilus influenzae*, *Legionella pneumophilia*, *Alternaria*, *Cryptococcus neoformans*, and *Acanthamoeba castellanii*. Treatment of rhinosinusitis in HIV/AIDS patients according to Lucente and Meitels includes a trial of antibiotics and decongestants initially. Failure of this trial should be followed by antral lavage and culture with directed treatment. If there is inadequate response, surgical intervention should be undertaken [34].

Benign and malignant neoplasms are also present in the patient with AIDS. Patients may complain of nasal obstruction and hearing loss or foul-smelling nasal discharge. Reported findings upon examination and biopsy of the nasal cavity and nasopharynx include benign lymphoid hypertrophy and nasal lymphomas. Kaposi sarcoma has also been documented in the nasal skin, vestibule, cavity, septum, and nasopharynx in patients with AIDS [34]. Symptoms can present as nasal obstruction, drainage and epistaxis. Physical exam may reveal nodular violaceous lesions. Treatment of these neoplasms ranges from supportive care to chemotherapy and radiation if warranted.

Cutaneous diseases

Nasal findings associated with selected autoimmune or collagen-vascular disorders are uncommon. However, there are a few major disorders with nasal manifestations which may cause significant morbidity and are worthy of mention. They include pemphigus, pemphigoid, scleroderma, and Behcet's disease.

Pemphigus vulgaris

Pemphigus vulgaris is a common mucocutaneous bullous disorder characterized by non-scarring bullous dermatitis of presumed autoimmune origin [35]. The oral cavity is the most common site involved in the head and neck region and only 10% of all patients will have involvement of the nasal mucosa. Desquamative

ulcerative lesions can be seen and ulceration of the nasal septum with anterior perforation has also been reported. The external nose is more likely to be affected. Steroids are the mainstay of treatment and may have to be combined with other immunosuppressants.

Pemphigoid

Pemphigoid is an uncommon disease characterized by blisters and scar formation and has a presumed auto-immune etiology. It can be divided into two categories: bullous and cicatricial. Cicatricial pemphigoid is more likely to affect the mucosa while bullous pemphigoid is confined to skin. Nasal findings occur in 25-50% of affected patients [36]. The usual site of involvement is the anterior nasal region which is found to be painful, ulcerative crusting. Scar formation is usually found in the nasal valve area but can also affect the nasopharynx. Scarring may be bilateral and lead to partial or total nasal obstruction [37]. Treatment is usually managed by a dermatologist and includes dapsone and/or immunosuppressive agents.

Scleroderma

Scleroderma is a systemic disorder of unknown etiology. Its characteristics include symmetrical stiffness of the skin and vascular insufficiency. Head and neck manifestations are very common and mostly affect the skin and oral cavity. Nasal findings involve telangiectasias of the mucosa leading to epistaxis. Treatment is symptomatic.

Behcet's Disease

Behcet's disease is characterized by the following triad: oral ulceration, genital ulceration, and ocular inflammation. The typical aphthous ulceration found in the oral cavity in this disease can also be found in the nasal mucosa. These lesions typically heal without scarring but can cause rhinorrhea and pain. Treatment includes symptomatic care as well as immunosuppressive agents.

Mucociliary diseases

A major defense mechanism of the nose and paranasal sinuses against infection is the mucociliary system. The physiology of this system has only recently come under close scrutiny. Its role in the prevention of sinusitis is apparent by noting the effects of mucociliary deficiencies in dysfunctional cilia syndrome and cystic fibrosis. New techniques for evaluating cilia function have permitted better diagnosis of these conditions, whose detrimental consequences can be controlled by early treatment.

Normal mucociliary function in the nose is toward the nasopharynx in all parts except for the very anterior end of the septum. The direction of mucociliary transport is independent of the position of the body in reference to gravity. Mucociliary transport can be bridged at areas lacking ciliated epithelium by the traction exerted by the viscous mucous layer [38].

Primary Ciliary Dyskinesia

Primary ciliary dyskinesia was first described in association with Kartagener's syndrome. The dyskinesia is characterized by chronic respiratory tract disease beginning in childhood leading to a constellation of symptoms including chronic rhinitis, sinusitis, bronchiectasis, chronic cough, otitis media, and sterility [38]. The incidence of primary ciliary dyskinesia is 1 in 15,000 to 1 in 30,000 and it is suspected to be an autosomal recessive disease [39].

Primary ciliary dyskinesia can be diagnosed by the saccharin test which is performed by placing a tablet of sodium saccharinate just behind the anterior aspect of the inferior turbinate. The transit time is recorded for the patient to notice a sweet taste after the tablet is placed. The maximum normal time is typically 30 minutes. This test may be influenced by many variables and does not itself identify a specific etiology of symptoms. Morphologic studies of the ciliated epithelium can confirm the diagnosis, but care must be taken to exclude secondary changes due to bacterial or viral infections. Management of primary ciliary dyskinesia includes antibiotics and nasal irrigations. Surgery is indicated for chronic or recurrent infections in order to establish a dependent drainage pattern. But even with appropriate surgical drainage chronic use of antibiotic and nasal irrigations will be necessary to control symptoms.

Cystic Fibrosis

Cystic fibrosis is the most common fatal inherited disease among Caucasians and is autosomal recessive. It affects 1 in 2000 live births and is associated with a mutation on chromosome 7q31-32 [40]. Cystic fibrosis is a disease affecting the mucous component of mucociliary transport rather than the cilia themselves as is the case in ciliary dyskinesia. The disease is characterized as an exocrinopathy with clinical features of chronic lung disease, chronic sinusitis, and pancreatic insufficiency [40].

Diagnosis is confirmed by sweat chloride test. Specific nasal symptoms include intermittent nasal obstruction with clear but thick rhinorrhea and nasal polyps. Patients with cystic fibrosis will often have grayish-green puttylike material in their sinuses and the most common bacteria affecting these sinuses are

Pseudomonas aeruginosa and *Staphylococcus aureus* Radiology demonstrates underdevelopment of the sinuses, especially of the frontal sinus.

Treatment of the nasal symptoms of cystic fibrosis is important to maintain a patent nasal airway and prevent infection. Long term antibiotics may be needed and nasal irrigations are often beneficial. Nasal polyp and/or sinus surgery may be indicated in cases of failed medical management and depends upon the degree of nasal obstruction, the severity of sinusitis symptoms, and the motivation of the patient and family. Much debate and controversy remains surrounding the exact role of surgical intervention in these patients.

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