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Risk factors for allergic *Aspergillus* sinusitis

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Allergic *Aspergillus* sinusitis is a type of allergic fungal sinusitis (AFS), a form of chronic rhinosinusitis with pathological findings similar to those seen in allergic bronchopulmonary aspergillosis (ABPA). There are no evidence-based criteria for diagnosis or management, and the pathogenesis is unknown. Known risk factors are underlying chronic rhinitis, exposure to *Aspergillus fumigatus*, and the ability to make an IgE-mediated allergic response to that organism. While many individuals meet these conditions, it is not known why only some go on to develop allergic *Aspergillus* sinusitis. Speculative risk factors are unknown conditions permitting fungal growth, concomitant superantigen responses, and HLA associations.

Keywords Aspergillus, sinusitis, risk factors

Introduction

Fungi are known triggers of allergic rhinitis and allergic asthma in sensitized individuals. Some patients with asthma develop a peculiar IgE-mediated, Th2 inflammatory response to *Aspergillus fumigatus*, resulting in allergic bronchopulmonary aspergillosis (ABPA). Allergic *Aspergillus* sinusitis is another IgE-mediated allergic disease with many clinical and pathologic similarities to ABPA. In 1981, Millar and colleagues coined the term 'allergic aspergillosis of the paranasal sinuses' in reporting five patients with chronic maxillary sinusitis and skin test reactivity to *Aspergillus fumigatus* [1]. One patient had pre-existing ABPA. Katzenstein and coworkers [2] described the sinus contents of nine patients as containing necrotic eosinophils, Charcot-Leyden crystals, other cellular debris including sloughed respiratory epithelium, and (in seven patients) fungal hyphae morphologically resembling *Aspergillus* sp. Because of the presence of eosinophils, they used the term 'allergic mucin' to describe these findings. They noted that these histologic findings are identical to those seen in the bronchial mucoid impaction of ABPA. All seven patients had chronic sinusitis and nasal polyps; one patient was skin-test positive to *Aspergillus fumigatus*, and two patients had *A. fumigatus* specific IgE. They used the term 'allergic *Aspergillus* sinusitis'.

Subsequent papers from around the world identified patients with chronic sinusitis and 'allergic mucin'. These studies did not normatively examine sinus contents microscopically for fungal hyphae, but instead relied on cultures of sinus contents or the nasal passages themselves. Cultures implicated a variety of fungi, particularly of the dematiaceous pigmented group, especially *Bipolaris spicifera*. Fungal identification was usually performed by hospital laboratory personnel, perhaps without training and experience in identifying and speciating organisms usually regarded as contaminants. Reporting results of allergy testing was complicated by the fact that testing extracts are available for only a few of the implicated fungi, and that typical patients are sensitized to many apparently unrelated fungi, as well as other inhalants. The condition has become more broadly known as 'allergic fungal sinusitis' (AFS). The focus of this discussion, however, is allergic *Aspergillus* sinusitis.

Clinical features

Typical patients are atopic adolescents or young adults with a history of chronic rhinitis that has become progressively more severe and unresponsive to standard therapies for rhinitis and sinusitis. Nasal blockage increases as intranasal polyps develop. Patients often complain of expelling brown rubbery plugs from the nose. The expanding fungal mass can cause facial pain and deformities, proptosis with diplopia and other

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vision disturbances, cranial base erosion, and cranial nerve palsies. There are reports of associated asthma, and also associated ABPA, Patients are uniformly immunocompetent. There is typically no family history of the disease, and the condition does not occur in family clusters. Sinus imaging shows multisinus involvement often with unilateral predominance, and serpiginous areas of increased attenuation. There is often bone erosion and remodeling. The allergic mucin is often described as greenish-brown with peanut butter-like consistency. It consists of sloughed respiratory epithelium, prominent eosinophilia with Charcot-Leyden crystals, and fungal hyphae without tissue invasion. On skin testing, typical patients are sensitized to multiple aeroallergens, including multiple fungi. Some patients have peripheral eosinophilia, and some have an elevated serum total IgE level.

Allergenic fungi in allergic fungal sinusitis

Many fungi have been implicated in the disease on the basis of cultures of sinus contents or nasal cultures. In many reports, fungal identification has been performed by hospital microbiology laboratories that may not have expertise in identification and speciation of environmental fungi. The literature is further confused by variations in fungal nomenclature. Organisms most commonly cultured are *(Dematiacieae) Alternaria* sp., *Dreschlera* sp., *Curvularia* sp., *Bipolaris* sp., *Exserohilum* sp., *Cladosporium* sp., *Stemphylium* sp.; and *(Moniliaceae) Aspergillus* sp., *Fusarium* sp., *Penicillium* sp., *Cephalosporium* sp. Other organisms have been reported sporadically.

Diagnostic criteria

Clinical reports of AFS have used varying degrees of stringency in making the diagnosis of AFS; in fact, some individuals have stated that all forms of sinusitis are caused by fungi and that results of allergy testing are irrelevant. There are no evidence-based criteria for the diagnosis. In an attempt to bring some clarity to our own study of this condition, we adopted a rather strict case definition, requiring patients to have five of the following six criteria to be considered as having 'definite AFS': (1) history and physical examination do not suggest another etiology; (2) characteristic computed tomographic findings such as increased attenuation patterns; (3) typical allergic mucin with eosinophils, Charcot-Leyden crystals, and tenacious consistency; (4) fungus detected in allergic mucin (histology or culture); (5) presence of fungal specific IgE by skin testing or measurement of specific IgE in the serum; (6) elevated total IgE level (>150 IU/ml). We also required that there be no histologic evidence of tissue invasion [3]. Patients with 'probable' AFS met fewer criteria.

Aspergillus fumigatus allergens

In our own work, we assumed that sera from AFS patients ought to be able to identify fungal allergens contained in the allergic mucin obtained at surgery [4]. This effort was not particularly successful, causing us to question whether the fungi cultured from the sinuses play an etiologic role in disease pathogenesis, or are environmental contaminants. In a subsequent study, we asked a pathologist with expertise in visual identification of fungi *in situ* to review slides of allergic mucin from the patients whom we had seen [5]. Of 18 patients with 'definitive' AFS, surgical specimens could be found for 17 patients. Of these, 10 had fungal hyphae morphologically resembling *Aspergillus* sp. or *Fusarium* sp. Slides were available for 10 patients with 'probable' AFS; one case had hyphae resembling *Aspergillus* sp. Sera were available for all 18 'definitive' AFS patients. Specific IgE immunoassay (IgE ImmunoCAP, Pharmacia Diagnostics, Uppsala, Sweden) was positive for *Aspergillus fumigatus* in 17/18 samples. Furthermore, 11/18 patients had IgE specific for one or more of the intracellular *A. fumigatus* allergens (rAsp f 2, rAsp f 4, and rAsp f 6) that have been considered specific for ABPA [6]. This led us to question whether *A. fumigatus* is more important in the pathogenesis of AFS than is commonly thought, whether *A. fumigatus* is present in allergic mucin but in a non-viable state, whether *A. fumigatus* allergens could be identified in allergic mucin, and whether studies of AFS ought to parallel lines of thought in studies of ABPA.

Risk factors

Exposure

Exposure to *Aspergillus fumigatus* is essentially universal, but allergic *Aspergillus* sinusitis and ABPA are uncommon conditions.

Underlying rhinosinusitis

Patients with allergic *Aspergillus* sinusitis usually present with a history of classic allergic rhinitis that has become progressively severe. Similarly, patients with ABPA typically have a long history of pre-existing asthma. However, only a few individuals with allergic rhinitis or allergic asthma go on to have allergic *Aspergillus* sinusitis or ABPA.

Th2 (IgE) immunologic response

Aspergillus fumigatus is a commonly encountered aeroallergen, implicated in allergic rhinitis and allergic asthma. Yet, not all sensitized individuals develop allergic *Aspergillus* sinusitis and ABPA.

Fungal growth in situ

Patients with allergic rhinitis and allergic asthma do not apparently have *in situ* fungal growth, yet patients with allergic *Aspergillus* sinusitis and ABPA do. It is not known whether this is due to a host factor that permits fungal growth in patients with allergic *Aspergillus* sinusitis and ABPA, or a host factor that prevents fungal growth in non-affected allergic patients. As noted above, it is known that some patients with allergic *Aspergillus* sinusitis and ABPA are sensitized to intracellular *A. fumigatus* allergens (Hemmann).

Other risk factors

Superantigens are implicated in the pathogenesis of chronic sinusitis in some individuals. Schubert has proposed a role for superantigens in the pathogenesis of ABPA and AFS, but this has not been proven [7]. HLA associations are important risk factors in the pathogenesis of many diseases. Some genotypes appear to confer disease susceptibility, others give protection. In ABPA, DRB1*1503, DRB1*1501, DRB1*1104 have been associated with disease; a DQ2 allele may be protective [8]. In AFS, DQB1*0301, DQB1*0302 appear to be disease-associated; allergic *Aspergillus* sinusitis has not specifically been studied [9]. It is not clear whether the reported HLA associations are related to the pathogenesis of the underlying respiratory disease (rhinosinusitis or asthma) or to the nature of the IgE and IgG immune response to *A. fumigatus*.

Conclusion

Specific risk factors for allergic *Aspergillus* sinusitis, or more broadly AFS, are not known. Studies of risk factors for allergic *Aspergillus* sinusitis should parallel those of ABPA since the nature of the immune response in the two conditions is apparently similar. The role of *A. fumigatus* in the pathogenesis of allergic fungal sinusitis warrants detailed study.

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