

## Central compartment atopic disease: the missing link in the allergy and chronic rhinosinusitis with nasal polyps saga

There has been a long-standing debate on the relationship between allergy and chronic rhinosinusitis (CRS). Multiple studies have been published with mixed results for both CRS without nasal polyps (CRSsNP) and CRS with nasal polyps (CRSwNP). In an evidence-based review of the relationship between CRS and allergy, Wilson et al.<sup>1</sup> found no consistent association between allergy and CRSsNP and CRSwNP. For CRSwNP, 10 articles showed an association whereas 7 showed no association, with 1 being equivocal. This yielded an aggregate level of evidence grade D. A weakness of this review and the studies included is that CRSwNP is viewed as a single entity, despite the fact that there are multiple subtypes, such as allergic fungal rhinosinusitis (AFRS), aspirin-exacerbated respiratory disease (AERD), and CRSwNP not otherwise specified (CRSwNP NoS). It is likely that these individual subtypes have different degrees of association with allergy.<sup>2</sup>

Some clarity to the issue of whether or not there is a relationship between allergy and CRSwNP has been provided in recent years. Our group first reported a clear association between allergy and nasal polyps in 2014, with 16 of 16 patients with isolated middle turbinate polyps or polypoid edema having positive allergy testing.<sup>3</sup> In 2016, Hamizan et al.,<sup>4</sup> in a retrospective review, found a strong association between middle turbinate edema/polyps and allergy. Brunner et al.<sup>5</sup> reported that patients with isolated middle turbinate polyps are a distinct group compared to patients with diffuse sinonasal polyps, with younger age (35 vs 53 years), less CRS (10% vs 100%), lower Lund-Mackay scores, and significantly more allergy (83% vs 34%), respectively.

In 2017 we first described central compartment atopic disease (CCAD), a nasal inflammatory subtype of CRSwNP that involves polypoid changes of the central compartment of the nasal cavity, which includes the posterosuperior nasal septum, middle turbinate, and/or superior turbinate.<sup>6</sup> In this series, 15 patients with central compartment polyps were positive on allergy testing. The disease process, similar to middle turbinate polyps, only involves the sinuses secondarily by lateralization or polypoid changes of the middle turbinates causing secondary obstruction of the sinuses. This tends to be absent in early CCAD but more

common in advanced stages of the disease process. This is reflected in the computed tomography (CT) findings in CCAD. The Lund-Mackay score is low in early CCAD due to the paucity of sinus involvement, and the majority of the changes are seen in the nasal cavity. Sinus involvement starts in the medial parts of the ethmoid and maxillary sinuses with peripheral clearing. The “central” radiologic findings were found to correlate with allergy status in a paper by Hamizan et al.<sup>7</sup> Additional radiologic findings that can distinguish CCAD from other subtypes of CRSwNP include nasal septal thickening and obliquely positioned middle turbinates, due to the central compartment polyps.<sup>8</sup>

With advanced stages of CCAD, increasing postobstructive changes in the sinuses can lead to higher Lund-Mackay scores, and more radiologic difficulty distinguishing advanced CCAD from other forms of CRSwNP subtypes.

Polypoid changes of the central compartment structures are related to normal nasal airflow. Computational fluid dynamics (CFD) shows that inhaled air travels in an arc that begins at the leading edge of the inferior turbinate, travels superiorly between the nasal septum and middle and superior turbinates, and descends into the nasopharynx, crossing the tail of the inferior turbinate. During this arc, the velocity of inspired air slows at the central compartment structures. This likely results in deposition of the contents of inspired area on the mucosa of the central compartment structures.<sup>9</sup> Our group has developed a CFD model of allergen deposition that shows that allergens preferentially deposit of the middle turbinate and nasal septum, whereas the sinuses and nasopharynx are protected. Also, the distribution from side to side is different depending on anatomic factors such as nasal septal deviation. This can account for the asymmetric involvement that we frequently see in patients with CCAD. Resection of the middle turbinate results in increased deposition of allergen on the nasal septum and in the sinuses and nasopharynx. (DelGaudio et al., unpublished data) This an important consideration in CCAD patients. Surgically opening the sinuses should be performed when the sinuses are involved primarily or secondarily, but this will allow subsequent deposition of inhaled allergens to allergen-naïve sinus mucosa. At a minimum, aggressive management with allergy control and topical steroids is recommended.

We have also noticed that although patients with CCAD have a high incidence of allergy, there is a low incidence of asthma, similar to AFRS, but lower than other CRSwNP subtypes. In a retrospective review, Marcus et al.<sup>2</sup> found the incidence of clinical allergic rhinitis (AR) to be 100% for AFRS, 97.6% for CCAD, 82.6% for AERD, and 56.1% for CRSwNP NoS. Asthma incidence was found to be 17.1%

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for CCAD, 19% for AFRS, 30.8% for CRSwNP Nos, and 100% for AERD. Of a small group of patients with both central compartment polyps and CRSwNP, 84.6% had AR and 30.8% had asthma, falling between the incidence for CCAD and CRSwNP NoS. It would be expected that the CCAD patients would be allergic in 100% of cases. The AR rate of less than 100% can be explained by the concept of local allergy. In a recent study of 11 patients with CCAD, all tested positive for allergy using skin-prick testing, serum testing, and local allergy testing of the central compartment mucosa. Interestingly, there was specific immunoglobulin E (IgE) found in the central compartment that was not found on the other forms of testing. (DelGaudio et al., unpublished data). In a study of patients with AERD, DelGaudio et al.<sup>10</sup> found that 90% of patients had clinical AR, and 82% had central compartment involvement. We also found that as the number of sinus surgeries increased, the incidence of septal involvement increased. All 11 patients who had undergone previous middle turbinate resection had septal involvement with polyps. This likely reflects the protective antigen filtering process of the

middle turbinate. AERD patients should have aggressive allergy management and adequate surgery to clear the central compartment, such as a Draf 3.

CCAD is a nasal inflammatory process that results from inhalant allergy. It provides a definitive link between allergy and CRSwNP. The presence of central compartment changes are also found in AFRS (middle turbinate polypoid degeneration) and AERD, both CRSwNP subtypes with a high incidence of inhalant allergy. It is unclear why certain patients with AR develop CCAD. It is known that patients with isolated CCAD do well with conservative surgical management of the involved areas, with lower incidence of polyp recurrence and revision surgery than other CRSwNP subtypes (DelGaudio et al., unpublished data). Recognition of contribution of allergy to certain CRSwNP subtypes is critical for appropriate management of all contributing factors to the inflammatory condition.

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