

Allergen-specific sublingual immunotherapy in the treatment of migraines: a prospective study

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Abstract. – Background: Inflammation is a cardinal feature of migraines. A number of observations point to the possibility that an allergic component of a type I (IgE-mediated) nature may be involved in at least some migraineurs. Not only are migraines frequent among patients with allergic rhinitis but quite frequently the same medical approaches are beneficial in both diseases: anti-inflammatories, adrenergic tone modifiers, immune suppressants. The effect that immunotherapy for allergic rhinitis has upon migraines is studied.

Methods: Patients were recruited who suffered from typical migraines but were not treated with regular migraine controllers (beta blockers, antiepileptics, tricyclics, etc.). They underwent allergen-specific, sublingual immunotherapy with physician-formulated, individually-prepared airborne allergen extracts. Response to treatment was assessed with serum C-reactive protein level changes and symptom scores. Serum C-reactive protein (CRP), an acute phase reactant, was chosen as a marker because its usefulness has already been assessed in interictal migraine activity.

Results: Interictal serum CRP levels decline was observed in the course of sublingual immunotherapy. Concurrent improvement in symptom scores for both rhinitis and migraines was also observed.

Conclusions: In patients with allergic rhinitis, migraine development and course may have a significant allergic component. Assessment of migraineurs for the possibility of co-existing allergic rhinitis is justified. Treatment of allergic rhinitis by immune response modifiers, such as immunotherapy, may have a place in the management of migraines for these patients.

Key Words:

Migraine, Immunotherapy, Allergy, Serum C-reactive protein.

Introduction

Migraines are a frequent complaint of allergic patients. At least some types of migraines are postulated to overlap with the atopic spectrum of diseases¹. Neurogenic inflammation and impaired vaso-active lability, two cardinal features of migraines, are also important components of the allergic inflammation. A shared pathogenesis has been proposed, according to which immune competent and/or immune-responsive cells are believed to mediate the precipitation of migraine symptoms¹. That anti-inflammatory or immunomodulating drugs remain the mainstay treatment for migraines is consistent with this hypothesis². Furthermore, a causative association of food allergy with migraines has already been demonstrated³.

Mast cell, the leading effector cell of IgE-mediated allergic inflammation, has been hypothesized to trigger further pro-inflammatory responses in the brain by means of production of cytokines, but other effector cells are also believed to be operational. Among the many cytokines produced by the mast cell, interleukin 6 (IL-6) has been proposed as an operative factor in migrainous attacks¹. Literature supports such a role for IL-6, as this cytokine, in addition to its pro-inflammatory action, can also mobilize hypothalamic-pituitary-adrenal responses typical of stress^{4,5}. Interestingly, IL-6 also exerts a strong anti-inflammatory action in at least three distinct and independent ways: by terminating the mutual upregulatory inflammatory cascade of IL-1 and TNF; by inhibiting the synthesis of IL-1 and TNF; and by stimulating synthesis of IL-1 receptor antagonist (IL-1ra)⁶. Thus, presently, increased IL-6 activity is equally likely to eventually prove a secondary response to

inflammation as well as its instigator. Either way, upregulated IL-6 production appears to be associated with profound, constitutional changes in the cytokine profile of migraine sufferers and may be involved in the pathogenesis of migraines as much as in the precipitation of their exacerbations. Baseline production of IL-6, that is IL-6 produced constitutively between migrainous attacks, can be monitored: IL-6 is the one most important inducer of hepatocyte synthesis of acute phase proteins⁶. Thus, increased production of C-reactive protein (CRP) reflects upregulated IL-6 synthesis. This event, as mentioned above, may be the cause of either promotion or regulation of ongoing inflammation, but, in the absence of other stressors, such as infection, autoimmunity, neoplasia, or metabolic stress, elevated CRP in patients with migraines clearly indicates activation of immune competent cells, macrophages and mast cells being the most prominent among them.

C-reactive protein has been established as a marker of inflammation in cardiovascular disease and obstructive sleep apnea⁷⁻¹¹. In patients with obstructive sleep apnea, CRP has been shown to parallel both elevations of IL-6 before treatment and decreases of IL-6 upon successful treatment with nasal continuous positive airway pressure¹¹. Serum CRP is an established marker of migraine activity and has been evaluated as a possible predictor of vascular accidents. C-reactive protein has been found elevated in patients with migraines in two retrospective studies totaling 110 patients^{12,13}. Correlation, however, of serum CRP changes with active treatment of migraines has not been attempted so far. In this study, CRP is assessed in patients with typical migraines and allergic rhinitis. C-reactive protein levels are followed for 10-12 months after initiation of sublingual immunotherapy in the absence of any other active intervention to control the recurrence of migraines. Clinical response is assessed by two measures of improvement: symptom scores for migraines and symptom scores for allergic rhinitis.

Patients and Methods

Subjects with typical migraine headaches were recruited from among patients of the Allergy Associates of La Crosse. Subjects were recruited based on history and standard diagnostic

criteria for migraines^{14,15}. Inclusion criteria were: age 15-59 years; history of at least one episode of incapacitating headache within the previous month; diagnosis of allergic rhinitis by history and skin testing. Subjects with active infections, autoimmune diseases, immune deficiencies and neoplasia were excluded. Subjects with headaches secondary to metabolic diseases, trauma, space occupying lesions or hypertension were also excluded. Subjects with a diagnosis of or symptoms suggestive of cluster headaches or tension headaches were excluded. Patients with atopic disease other than allergic rhinitis were excluded: patients with asthma, nasal polyposis, atopic dermatitis, food allergy, hives, nonsteroidal anti-inflammatory (aspirin) sensitivity. Allergic rhinitis was treated with immunotherapy, regular nasal steroids and only anti-histamines with proven inability to cross the blood-brain barrier. Use of decongestants, mast cell stabilizers, anticholinergics, leukotriene modifiers and anti-histamines crossing the blood-brain barrier (including cetirizine), beta agonists and beta blockers were withheld for the course of the study. Subjects who suffered acute sinus or other infections, had to be treated with antibiotics or systemic steroids, or suffered any major stress, including major emotional challenges, during the course of the study were subsequently excluded.

The diagnosis of migraines was documented by response to a Headaches Questionnaire developed by the Authors which was administered at the time of enrollment to the study. The Headaches Questionnaire was specifically developed to only select patients with typical migraines: unilateral, pulsating, lasting from 4 to 72 hours, preceded by visual or olfactory aura, associated with nausea, responding to decreased sensory input, and successfully treated in the past with triptans and anti-inflammatories. Enrollment to the study was at the subject's first visit to the Clinic and patients already being treated with immunotherapy were not enrolled. Subjects on current treatment with long-term migraine controllers, such as tricyclic antidepressants, anti-epileptics, selective serotonin or serotonin/norepinephrine reuptake inhibitors etc., were also excluded.

C-reactive protein levels were measured upon enrollment to the study, and at two follow-up visits at four and again at ten-twelve months after initiation of sublingual immunotherapy. Serum CRP levels were determined by sandwich ELISA

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utilizing streptavidin conjugated to horseradish peroxidase by a kit developed by the R&D Systems, Inc, Minneapolis, MN, USA. With this method a standard curve of optical density versus concentration is obtained which remains linear to 1000 pg/mL.

The clinical course of allergic rhinitis was assessed by the Mini Rhino-Conjunctivitis Quality of Life Questionnaire" (MiniRQLQ), a self-administered instrument assessing symptoms and functional impairment in the seven day period preceding administration of the questionnaire. The MiniRQLQ parameters are organized in four groups: nasal symptoms (five questions), eye symptoms (three questions), constitutional symptoms (three questions), and effects of rhinoconjunctivitis on work/recreation/sleep (three questions)¹⁶. The potential MiniRQLQ score range is from 0 to 84 (answers to fourteen questions graded from 0 to 6). The clinical course of migraines was assessed by the "Migraine Disability Assessment Score" (MIDAS), a validated instrument endorsed by the American Headache Society, which assesses migraine severity by evaluating days of impaired function (missed days or days of decreased productivity/function) at work/school, household, and family/social/leisure activities over the preceding three month period¹⁷. The potential range of MIDAS scores is from 0 to 450 (five questions that can be graded 0-90). Both questionnaires, MIDAS and MiniRQLQ were administered upon enrollment to the study and at the first and second follow-up visits after initiation of immunotherapy.

Sublingual immunotherapy was employed as per protocol¹⁸. Indications for immunotherapy, initiation dosing and further dose escalations were all determined by a physician following skin testing. Formulation of extract mixtures were under physician supervision.

Results

Twenty patients fulfilled the study criteria and were recruited in the period July-November 2009. The recruitment period was deliberately chosen so that all subjects would have the benefit of a uniform immunotherapy effect from four-eight months of immunotherapy before the onset of spring in April 2010. Seven subjects were followed in two successive follow up sessions through November 2010 and it is their findings that are reported here. Data are not reported for thirteen subjects: six dropped out or failed to timely keep their appointments; three were removed from the study either at the four month or the tenth-twelfth month visit because of acute inflammatory events within one week prior to their visit (two with sinus infections, one bronchitis); one was removed because of a severe migraines attack preceding her visit; and, three patients were removed because, in the interim, migraines-controlling treatment had been introduced, such as beta blockers, tricyclics and serotonin reuptake inhibitors.

Diagnosed allergies included dust mites, weeds, tree pollen, grass, various molds and animal dander. Sublingual immunotherapy was used per protocol. C-reactive protein levels, as expected, since all subjects were free of inflammation at the times of assessment, were below levels typically established as associated with acute inflammation, that is, below 1 mg/dL. C-reactive protein values in this study are expressed in mg/L.

At the time of recruitment the CRP value range in patients with migraines and allergic rhinitis was wider than controls' and CRP values were higher than controls' (Table I). This finding is consistent with previously published studies of serum CRP in patients with migraines^{12,13}.

Table I. CRP in migraines and rhinitis.

	Subjects with migraines & allergic rhinitis	Controls
Number of subjects	7	9
Age range (mean)	15-59 (42) years	16-55 (41) years
C-RP range at recruitment time	0.44-5.71 mg/L	0.43-1.39 mg/L
C-RP mean	2.08 mg/L	0.79 mg/L
C-RP standard deviation	0.97 mg/L	0.31 mg/L

p: 0.009.

Reduction in interictal serum CRP over a period of 10-12 months was clearly noted for four out of seven subjects. Reduction of serum CRP for all seven subjects yielded a p value of 0.013. (Figure 1). MiniRQLQ scores upon enrollment ranged from 13 to 67 (mean = 33.2) and invariably improved for all seven subjects over the study period, their range changing to 5-42 (mean = 18.5) (Figure 2). MIDAS scores which originally varied from 8 to 41 (mean = 21.1) also improved for all seven subjects and their range fell to 0-37 (mean = 9.5). For six subjects the MIDAS range declined to 0-9 (Figure 3).

Discussion

Patients' expectations upon enrollment into an immunotherapy program can cause a significant bias affecting the outcome of symptom scores, especially in small studies. Assessment of an independent marker change, such as serum CRP, is therefore necessary to evaluate response to treatment. It is noted that the serum CRP levels recorded are technically within what commercial laboratories would report as "normal range". This finding is consistent with previously published observations⁷⁻¹¹. Elevated baseline CRP, within what is accepted as "normal" for the purpose of ruling out acute infection, is still considered a satisfactory predictor of ongoing inflammation in coronary artery disease and obstructive sleep apnea⁷⁻¹⁰. The value of such variations of constitutionally-produced serum CRP (as opposed to acute phase production) may

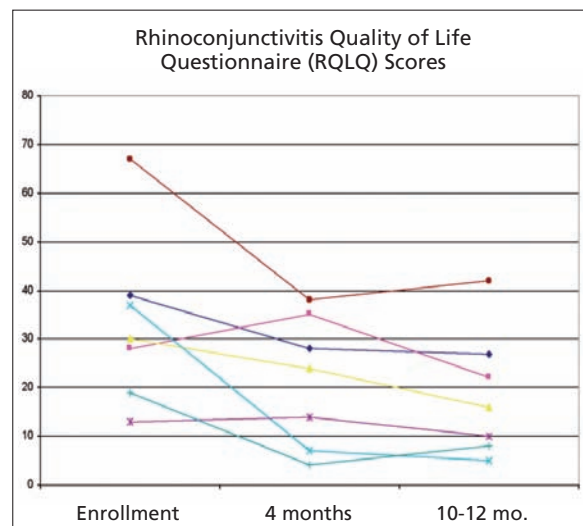


Figure 2. Rhinoconjunctivitis Quality of Life Questionnaire Scores changes at 4 and at 10-12 months of treatment for allergic rhinitis.

rest with its Gaussian type distribution as a continuous trait and it is possible that baseline CRP in subjects with underlying inflammatory conditions, such as migraines and atopy, may lie in the higher end of the normal distribution curve of constitutional CRP production. This hypothesis would confirm previous data supporting the use of serum CRP in identifying high risk patients for a number of conditions with an inflammatory background⁷⁻¹¹. For practical purposes, use of low range reference values (below 1 mg/dL) may be necessary if constitutional secretion of CRP is to be assessed as an independent factor of inflammation in migraines.

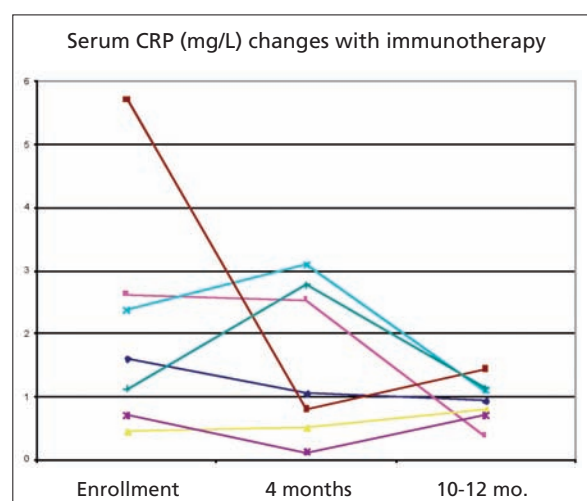


Figure 1. Reduction of interictal serum CRP in patients with migraines and allergic rhinitis treated with immunotherapy, at 4 and at 10-12 months of treatment.

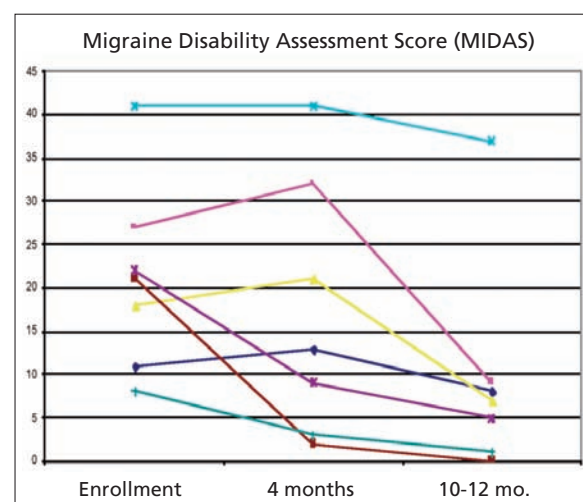


Figure 3. MIDAS score change at 4 and at 10-12 months of treatment for allergic rhinitis.

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The association of chronic sinusitis and/or sinus headaches with migraines is a well established fact. It appears, however, that even in the absence of sinus inflammation migraines can be triggered by events in the upper airway. Our data support a functional association of migraines with allergic inflammation in the select subgroup of patients with migraines with allergic rhinitis. Symptom scores declined together for both conditions and serum CRP paralleled these changes. That sublingual immunotherapy directly caused these changes can be safely argued as, except for immunotherapy, no other therapeutic long term (controlling) intervention was initiated for management of migraines in the course of the study. More importantly, the response of migraines to the treatment of allergy indicates an allergic component to the mechanism of migraines. Obviously the studied group is small and limited by its peculiar characteristics. Thus, response to immunotherapy may provide an insight to the operating mechanisms of inflammation in migraines. To extend the value of these observations to all migraineurs is beyond the scope of this study which mostly raises two issues. The first is the clinical relevance of allergy to migraines and the need to question for and possibly diagnose allergic disease as an association to migraines. A continuum of pathophysiology may eventually become necessary in order to understand and manage migraines in allergic patients. The second, and more important issue, is the evidence of a chronically dysregulated immune response as evidenced by the finding of elevated serum CRP during migraines-free intervals. The response of interictal serum CRP to immunotherapy and other therapeutic immune manipulation, such as environmental changes to control exposure to allergens, nasal steroids, and anti-histamines, indicates that migraines and allergic inflammation may share a significant part of their pathophysiologies. Long term immunomodulation to control inflammation in migraines is supported by the present study.

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