

## Serotonin in Allergic Rhinitis: a Possible Role for Behavioural Symptoms

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### ABSTRACT

Allergic rhinitis (AR) is a very frequent disease which is not only characterized by nasal symptoms, but also with behavioural changes. This study evaluated the serum serotonin levels in patients with pollen-induced AR during and outside the pollen season.

One-hundred-two (56 females, 46 males, median age: 28.7 years) were included in this study: 56 with seasonal AR (SAR) evaluated outside the pollen season and so without allergic inflammation and symptoms, and 46 with SAR evaluated during the pollen season with symptoms. Blood specimens were collected to assess serum concentrations of serotonin and to compare results to scores of a Quality of Life (QoL) questionnaire which was performed in all subjects.

Serotonin serum concentrations were higher in AR patients out of pollen season than in ( $p < 0.01$ ). There was a very strong direct relationship between QoL and serotonin concentrations.

This preliminary study demonstrates that SAR influences serotonin concentrations and that serum serotonin could serve as a biomarker in AR patients with behavioural symptoms.

**Key words:** Allergic Rhinitis; Behavioral Symptoms; Pollen Allergen Exposure; Serum; Serotonin

### INTRODUCTION

Allergic rhinitis (AR) is the most frequent immune-mediated disease. Its prevalence is high in the general population, reaching up to 40 % in some countries, and

is still progressively increasing.<sup>1</sup> Allergen exposure activates mast cells with consequent release of preformed mediators, mainly histamine and leukotrienes, and cytokines capable of inducing the recruitment and activation of inflammatory cells, including eosinophils, neutrophils, and Th2-type lymphocytes.<sup>2</sup> These inflammatory events lead to the onset of typical nasal symptoms, including itching, sneezing, rhinorrhea and obstruction.<sup>3</sup> Moreover, many AR patients complain also about other non-nasal

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behavioral symptoms, including tiredness, somnolence, depression, apathy, impaired attention, all of them may reduce the school and/or work performance and overall impair the Quality of Life (QoL). In fact, it is well known that AR patients have a markedly impaired QoL.<sup>4</sup>

However; the exact pathogenic mechanisms of these non-nasal behavioral symptoms are still obscure. In addition, antihistamines are prescribed as first-line AR treatment: they may induce psychomotor and cognitive side effects.<sup>3</sup>

Very recently, it has been reported that AR patients evaluated during the pollen season, with active AR and so with symptoms, had lower serum tryptophan levels than AR patients evaluated outside the pollen season without symptoms and nasal inflammation.<sup>5</sup> The rationale of this study was that tryptophan catabolism-dependent mechanisms exert relevant immune-regulatory activities.<sup>6</sup>

Tryptophan is an essential amino acid which is metabolized through two different biosynthetic pathways: the generation of the neurotransmitter 5-hydroxy-tryptamine (5HT, serotonin) and the formation of kynurenine derivatives.<sup>7</sup> Serotonin is formed by tryptophan<sup>5</sup> hydroxylase following decarboxylation. Serotonin is a bioamine that functions as a neurotransmitter, tissue mediator and vasoactive agent which can either apparently up regulate or down regulate a given biological response.<sup>8,9</sup> It has been reported that human mast cells may synthesize and release serotonin.<sup>10</sup> In this regard, serum serotonin levels were related with clinical neurological and gastrointestinal complaints in patients with mastocytosis.<sup>11</sup> In addition, Shariati et al demonstrated that treatments with Olanzapine may effect serotonin receptor gene expression in schizophrenic patients.<sup>12</sup>

Moreover, it has been demonstrated that serotonin is an important modulator of maladaptive behaviors, and low levels of serotonin together with low cholesterol levels may cause aggressive behavior.<sup>13</sup>

On the other hand, the role of serotonin in AR was investigated several years ago. The same group of researchers conducted a series of studies exploring the effect of serotonin on nasal function.<sup>14-18</sup>

However, no study evaluated a possible role of serotonin in the occurrence of non-nasal behavioral symptoms. This preliminary study was performed to measure serum serotonin levels in seasonal AR (SAR) patients during or outside the pollen exposure.

## MATERIALS AND METHODS

One-hundred-two patients (56 females, 46 males, median age: 28.7 years) were included in this study: 56 with SAR evaluated outside the pollen season and so without allergic inflammation and symptoms, and 46 with SAR evaluated during the pollen season with symptoms.

AR diagnosis was made according to the Allergic Rhinitis and its Impact on Asthma (ARIA) document.<sup>6</sup> All allergic patients had been sensitized to pollens alone and suffered from moderate to severe persistent allergic rhinitis for at least 4 years.

The Ethical Committee approved the study and an informed consent was obtained from each of the subjects.

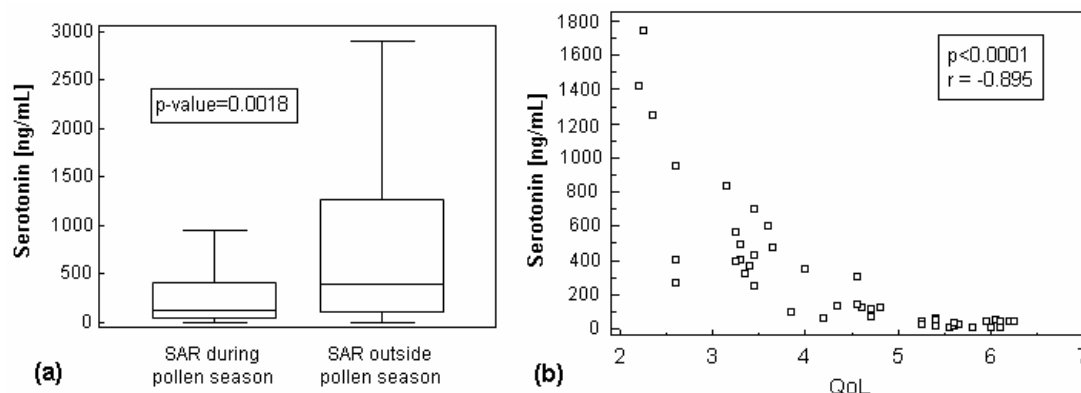
### Quality of Life

Health-Related Quality of Life (HRQL) assessment included the above mentioned Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ), it consists of items distributed in relevant dimensions: sleep problems (3 items), non-hay fever symptoms such as general problems (7 items), practical problems (3 items), activities (3 items), and emotions (4 items). Responses to the items were scored on a 7-point Likert scale, while dimensions and overall scores were scored on a 0-6 scale, the lower the score; the better the HRQL.<sup>4</sup> HRQL was performed in SAR patients exposed to pollen allergen.

### Serotonin Assay

Serotonin concentrations were measured by a commercial available competitive ELISA (Serotonin Fast Track, DIAsource, Immunoassays S.A., Nivelles, Belgium) after serotonin was quantitatively acylated.

Statistical analysis was performed using the statistical software package Medcalc 9 (Frank Schoonjans, BE). Descriptive statistics were first performed, and quantitative parameters were reported as the means (M) with interquartile ranges (IQR). Comparison of the serotonin levels in the two groups of patients was performed by the non-parametric Mann-Whitney test. Correlation between quantitative variables was evaluated by means of the Spearman's correlation coefficient (r). All tests were two sided and a *p*-value less than 0.05 was considered statistically significant.



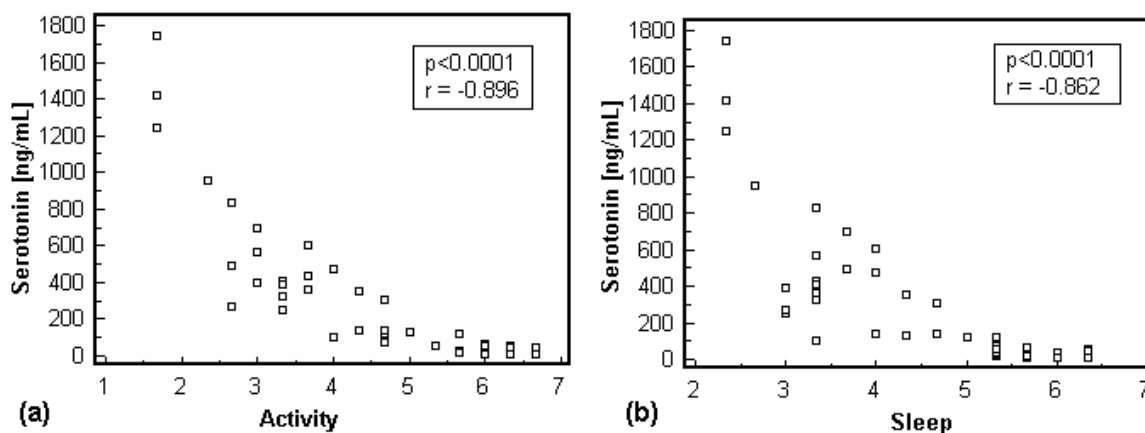
**Figure 1a.** (a) Serum concentration of serotonin (ng/mL) in patients with seasonal allergic rhinitis evaluated during and outside pollen season. Data are represented as medians (horizontal lines), interquartile ranges (boxes), ranges (vertical lines, excluding outliers) and  $p$ -value between the groups. (b) Correlation between serum concentration of serotonin ( $\mu$ M) and QoL in patients with seasonal allergic rhinitis evaluated during the pollen season; Spearman's correlation coefficient ( $r$ ) and  $p$ -value are given.

## RESULTS

Serum serotonin concentrations significantly differed between SAR patients evaluated outside pollen season, they were higher outside pollen season (M: 770.44 ng/mL, IQR: 111.45-1273.35 ng/mL) as compared with concentrations measured during pollen season (M: 305 ng/mL, IQR: 42.3-408 ng/mL;  $U = -3.11$ ,  $p < 0.01$ , Figure 1a).

There was a significant correlation between serum serotonin levels and QoL (M: 4.41, IQR: 3.35-5.6) in SAR patients evaluated during the pollen season ( $r_s = -0.895$ ,  $p < 0.0001$ ; Figure 1b).

Table 1 shows the mean values with IQR of QoL, distributed for each item of relevant dimensions. In the table there are  $p$ -values and  $r_s$  coefficients of correlations between serotonin levels (ng/mL) and each item. Moreover, there were significant correlations between serum serotonin levels and Activity QoL (M: 4.6, IQR: 3.3-6;  $r_s = -0.896$ ), Sleep QoL (M: 4.55, IQR: 3.33-5.67;  $r_s = -0.862$ ), as shown in figure 2, and General problems QoL (M: 4.39, IQR: 3.43-5.57;  $r_s = -0.887$ ), Practical problems QoL (M: 4.3, IQR: 3.3-5.3;  $r_s = -0.865$ ) and Emotional aspects QoL (M: 4.28, IQR: 3.25-5.5;  $r_s = -0.853$ ), as shown in figure 3.



**Figure 2.** Correlation between serum concentration of serotonin (ng/mL) and QoL in patients with seasonal allergic rhinitis evaluated during the pollen season, evaluated separately for Activity (a) and Sleep (b); Spearman's correlation coefficient ( $r$ ) and  $p$ -value are given.

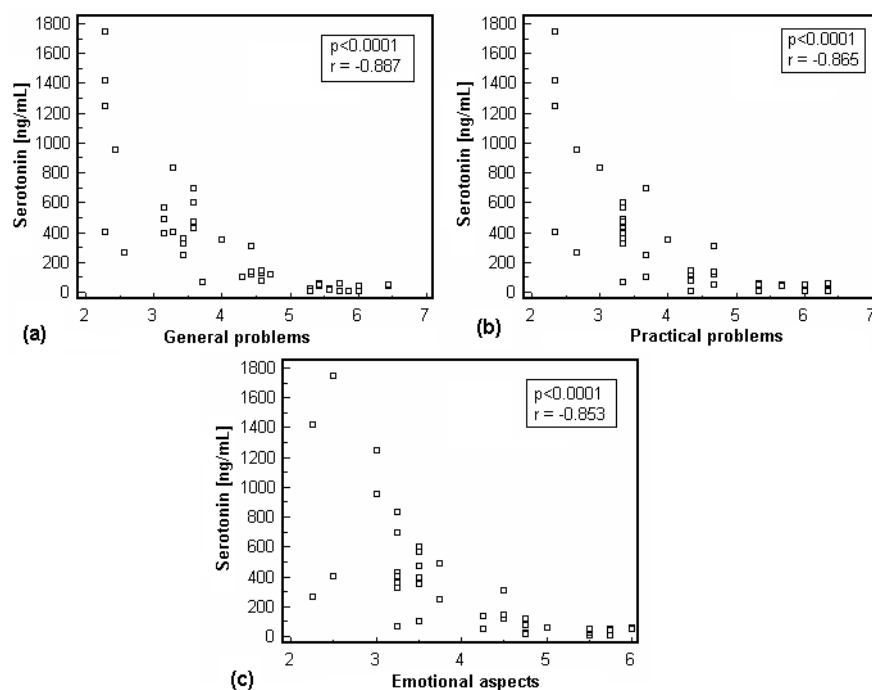


Figure 3. Correlation between serum concentration of serotonin (ng/mL) and QoL in patients with seasonal allergic rhinitis evaluated during the pollen season, evaluated separately for General Problems (a), Practical Problems (b) and Emotional Aspects (c); Spearman's correlation coefficient (r) and p-value are given.

Table 1. Mean value and IQR of QoL, distributed for items of relevant dimensions; Spearman rank correlation coefficient (rs) and p-values of correlations between serotonin levels (ng/mL) are given for each item

		Mean value	IQR	rs	p-value
Activity	1	4.63	4-6	-0.912	<0.0001
	2	4.61	3-6	-0.825	<0.0001
	3	4.57	3-6	-0.832	<0.0001
Sleep	1	4.57	3-6	-0.832	<0.0001
	2	4.44	3-6	-0.858	<0.0001
	3	4.65	3-6	-0.829	<0.0001
General problems	1	4.52	3-6	-0.849	<0.0001
	2	4.26	4-6	-0.863	<0.0001
	3	4.44	3-5	-0.862	<0.0001
	4	4.24	3-5	-0.826	<0.0001
	5	4.37	3-5	-0.809	<0.0001
	6	4.48	3-5	-0.831	<0.0001
	7	4.44	3-6	-0.872	<0.0001
Practical problems	1	4.28	3-5	-0.805	<0.0001
	2	4.17	3-5	-0.846	<0.0001
	3	4.44	4-6	-0.823	<0.0001
Emotional aspects	1	4.24	3-5	-0.801	<0.0001
	2	4.15	3-5	-0.795	<0.0001
	3	4.44	4-5	-0.825	<0.0001
	4	4.28	3-5	-0.822	<0.0001

## DISCUSSION

AR is characterized by an inflammatory reaction. Various populations of effector and regulatory T cells have been shown to play a crucial role in allergic inflammation, mainly Th2-type cells.<sup>19</sup> Th2-derived cytokines, such as IL-4 and IL-13, are the primary pathogenic factors in inducing, maintaining, and amplifying inflammatory allergic inflammation. Mast cells are considered the primary effector cell able to start the nasal allergic inflammation after allergen exposure. The pathogenetic model of pollen allergy is particularly useful as allows to evaluate patients with inflammation and symptoms during the pollen season as well as patients without any symptom and inflammatory event outside the pollen season. Mast cell activation determines the release of several relevant mediators, mainly histamine, able of inducing symptom occurring. However, several non nasal behavioural symptoms may annoy AR patients, but the real pathogenetic background still remains obscure.

Tryptophan and its metabolites may be influenced during activation of the immune system.<sup>20</sup> However, few studies investigated the role of tryptophan

metabolism in allergic disorders.<sup>21,22</sup> Very recently, it has been reported that pollen allergen exposure is associated with low tryptophan levels.<sup>5</sup> In fact, this preliminary study demonstrated that serum tryptophan metabolism could serve as a biomarker in allergic patients as depends on allergen exposure, such as on inflammatory phenomena. In this regard, serotonin, 5HT, is a tryptophan metabolite and its role has been related to behavioural disorders and is a relevant neurotransmitter.<sup>23</sup> A role of serotonin in AR was investigated several years ago, but only concerning the nasal function.<sup>14-18</sup> On the other hand, QoL evaluation represents an important step in the study of AR concerning both clinical and therapeutical trials. A recent study provided the evidence that QoL in AR is strictly associated with allergic inflammation and behavioural symptoms significantly contribute to impair QoL.<sup>24</sup>

This study explored a possible role of serotonin in AR patients by evaluating both in and out the pollen season. The first finding is interesting as it shows that pollen allergen exposure is associated with lower serum serotonin levels than outside the pollen season. This outcome confirms previous report that demonstrated lower tryptophan and its metabolite kynurenine during the pollen season. The increased tryptophan concentrations in AR patients outside pollen season are considered to be due to diminished activity of tryptophan-degrading enzyme indoleamine 2,3-dioxygenase (IDO).<sup>21,22</sup> Also the increase of serotonin might relate to this, because different from tryptophan 2,3-dioxygenase, IDO is less specific for tryptophan and also cleaves other indoleamines like serotonin. Because IDO is inducible preferentially by Th1-type cytokine interferon- $\gamma$ ,<sup>20</sup> the coincident increase of serotonin and tryptophan might relate to an imbalance of Th1- and Th2-type immunity.

Secondly, the serum serotonin concentrations are very strongly related with impaired behavioural items of QoL. This fact underlines the possible pathogenic role in non nasal symptom occurrence in AR patients. A link between QoL and serotonin availability is well documented for chronic inflammatory conditions,<sup>25</sup> but to the best of our knowledge, this is the first evidence about this issue in AR patients. Moreover, it should be noted that antihistamines are broadly prescribed in AR: their use may induce relevant side effects. In addition, some of them may have anti-serotonin effects.

The correlations between serotonin concentrations and QoL scores turned out to be very close. This was true although only serum but not cerebrospinal fluid measurements were available. From the data it is unclear whether brain serotonin concentrations are influenced in the same direction or remain unaffected. It appears that at least some of the associations between QoL items and serum serotonin concentrations reflect an influence of the vasoactive compound serotonin on the precipitation of specific symptoms of rhinoconjunctivitis which then affect QoL. We also observed that serotonin correlated inversely albeit rather weakly with tryptophan levels, measured in another study,<sup>5</sup> which may argue against a role of subnormal IDO activity in the increase of tryptophan. Rather high activity of tryptophan 5-hydroxylase could underlie this observation when tryptophan declines because of an accelerated biosynthesis of serotonin. In addition, a close link between allergic rhinitis, mood disorders, exacerbation of depression, and suicidal behaviour has been underlined by a recent study.<sup>26</sup> It is well known that some mediators of inflammation may modulate sleep, such as Th1-dependent cytokines (depressed during allergic reaction) promote NREM sleep and increase sleepiness, whereas Th2-associated cytokines (increased during allergic inflammation) impairing sleep. Moreover, sleep impairment is a rapidly modifiable suicide risk factor strongly associated with mood disorders. In this regard, there is growing interest about the hypothesis that allergic rhinitis leads to mood and anxiety disorders and an increased risk of suicide via sleep impairment. Specifically, allergic rhinitis can impair sleep through mechanical (obstructive) and molecular (cytokine production) processes. The high prevalence of mood and anxiety disorders and allergy might explain this pathophysiological link.

On the other hand, a relevant limitation of this study is the lack of direct measurement of serum serotonin in the same patients in and out the pollen season, thus there is the need for further studies that should be conducted to assess this mediator both during and outside the pollen exposure in a larger cohort of patients.

In conclusion, this preliminary study demonstrates that serum serotonin could serve as a biomarker in AR patients with behavioural symptoms. However, further studies should be performed to confirm these findings.

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