Allergic rhinitis and School Performance

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Abstract

Allergic rhinitis is presently the most common chronic disorder in the pediatric population. It can affect sleep at night and cause daytime sleepiness, with school absenteeism, "presenteeism" or inattention, mood disturbances and psychosocial problems. All this in turn can contribute to reduce school performance. The correct treatment of allergic rhinitis can improve school performance, though the first generation antihistamines have unacceptable central and anticholinergic effects that can actually worsen the situation. The second generation antihistamines constitute the drug treatment of choice for allergic rhinitis in children. Vasoconstrictors should not be used in pediatric patients, due to their unpredictable pharmacokinetics and very narrow therapeutic margin. Intranasal corticoids could improve school performance in some patients, by reducing nose block or congestion, the nocturnal sleep disturbances, and daytime sleepiness. Concrete studies of the impact of chromones, anticholinergic agents, antileukotrienes and immunotherapy upon school performance are lacking.

Key words: Allergy. Pediatric allergy. Learning. Quality of life. School performance. Psychomotor performance. Allergic rhinitis. Allergic rhinoconjunctivitis.

Resumen

En la actualidad, la rinitis alérgica es la enfermedad crónica más común en la población pediátrica. Puede afectar el sueño nocturno y provocar somnolencia diurna, y produce absentismo escolar, "presentismo" o inatención, alteraciones del humor y problemas psicosociales, todo lo cual puede contribuir a un rendimiento escolar disminuido. El tratamiento correcto de la rinitis alérgica puede mejorar los resultados escolares; si bien los antihistamínicos de 1ª generación producen efectos centrales y anticolinérgicos inaceptables y pueden empeorar la situación. Los antihistamínicos de 2ª generación constituyen el tratamiento farmacológico de elección de la rinitis alérgica pediátrica. Los vasoconstrictores no deben emplearse en edades pediátricas, debido a una farmacocinética impredecible y un margen terapéutico muy estrecho. Los corticoides intranasales podrían mejorar el rendimiento escolar en algunos pacientes, a través de una reducción de la obstrucción/congestión nasal, las alteraciones del sueño nocturno y la somnolencia diurna. Las cromonas, los anticolinérgicos, los antileucotrienos o la inmunoterapia carecen de estudios concretos sobre su impacto en el rendimiento escolar.

Palabras clave: Alergia. Alergia pediátrica. Aprendizaje. Calidad de vida. Rendimiento escolar. Rendimiento psicomotor. Rinitis alérgica. Rinoconjuntivitis alérgica.

Introduction

Allergic rhinitis is a worldwide health problem that generates an important healthcare burden in terms of outpatient visits by adults, children and adolescents. According to the recent *Alergológica* 2005 study, conducted by 300 allergologists in a total of 4500 new patients, rhinitis or rhinoconjunctivitis represents the main cause of consultation among 55.5% of all patients seen in Spanish allergology clinics [1]. In turn, the International Study of Asthma and Allergies in Childhood

(ISAAC) reports that the prevalence of allergic rhinitis in children and adolescents shows great variability throughout the world, but that the disease may affect up to 15% of all children in the 6-7 years age range, and up to one-third of the population in the 13-14 years age interval [2].

It is an established fact that allergic rhinitis and the adverse effects of its treatment significantly alter patient social life [3] and occupational productivity [4]. A study published in 1998 demonstrated an association between daytime sleepiness and nasal congestion in a group of patients with allergic rhinitis, in which nasal corticoid therapy reduced congestion and improved sleep [5]. Since then, several studies have attempted to determine whether allergic rhinitis intrinsically exerts a negative effect upon patient cognitive function and quality of life, independently of the negative side effects of treatment.

In an attempt to clarify this aspect, a number of comparative trials have been conducted in treated and untreated patients, based on the use of cognitive test batteries [6], visual analog scales, and evoked potentials [7,8]. More specifically, the effects upon school performance have been evaluated based on questionnaires adapted to young subjects [9,10], or using experimental computer-based tests in school settings [11].

The results of these studies have not been unanimous: some suggest that there is no association between untreated allergic rhinitis and cognitive function [6], while others consider that the disorder exerts a limited effect upon concentration and attention [12]. However, other studies indicate that allergic rhinitis intrinsically impairs activities such as visual coordination, retention capacity or short term memory, reaction time, psychomotor speed, vigilance and attention [13,14] – this logically resulting in professional and school activity problems. Nevertheless, it has not been possible to confirm that allergic rhinitis intrinsically impairs ultimate learning capacity among children and adolescents.

Allergic rhinitis as a cause of learning problems

The main causes of learning difficulty and school failure [15] are summarized in Table 1, with particular mention of those chronic disorders characterized by hearing or visual deficiencies, and which affect the central nervous system. Considering that it is the most common chronic illness in childhood, untreated allergic rhinitis could affect learning in children and adolescents through different routes (Table 2), as detailed below.

Chronic nasal blockade and nasal failure

Nasal blockade or congestion is intrinsically able to alter sleep at night, as a result of microawakenings and daytime sleepiness [16], and the excessive production of IFN-γ, TNF-α, IL-1b, IL-4 and IL-10 can contribute to sleep disturbance in patients with allergic rhinitis [17]. A secondary effect of all this is school absenteeism, "presenteeism" (inattention, distraction, lack of concentration), irritability and restlessness, mood disturbances, and even social and family problems.

The symptoms of allergic rhinitis predominate in two key seasons of the school year: spring and autumn. In fact, allergic diseases are among the most common causes of school absenteeism in the United States, where an estimated two million teaching days are lost as a result of such disorders

Table 1. Causes of learning difficulties and school failure

- Psychosocial problems:
  - Psychiatric diseases
  - Drug and substance abuse
  - Family problems
  - Poor sociocultural environment
  - Low socioeconomic level
  - Other psychosocial stress factors
- Neurobehavioral problems:
  - Mental retardation
  - Autism
  - Specific disability (dyslexia, dysgraphia, dyscalculia)
  - Attention deficit/hyperactivity disorder (ADHD)
  - De la Tourette syndrome
- Medical problems, including:
  - Vision and/or hearing defects
  - Chronic diseases
  - Drugs affecting the central nervous system

Table 2. Untreated allergic rhinitis and school perfomance problems

- Associated to rhinitis itself/nasal insufficiency
  - Sleep disturbances and daytime sleepiness
    - secondary to nasal blockade and nocturnal microawakenings
    - due to allergic inflammation
  - Absenteeism
  - "Presenteeism" (inattention, distraction, lack of concentration)
  - Irritability, restlessness
  - Mood disorders (anxiety, depression)
  - Secondary social/family deadjustments
- Associated to nocturnal hypopnea and snoring
  - Without intermittent hypoxemia: low performance in mathematics, sciences
  - With intermittent hypoxemia: low performance in mathematics, sciences, and reading and writing
- Associated to secondary eustachian tube inflammation:
  - Hearing defects
  - Low performance in mathematics and reading and writing in early childhood (under 4 years of age)

[18]. Due to the resulting irritability, tiredness, inattention, lack of concentration, sleep disturbances and daytime sleepiness, untreated allergic rhinitis could reduce short term memory in children, compared with non-allergic children [12].

Attempts have even been made to correlate pediatric allergic rhinitis to attention deficit/hyperactivity disorder (ADHD), based on the fact that most children with ADHD are atopic and suffer rhinitic symptoms, including sleep disturbances, which in some cases could explain cognitive patterns seen in ADHD, such as daytime fatigue, inattention, irritability and impulsiveness [19].

The impact of allergic rhinitis in children and adolescents can extend beyond the school setting to affect quality of life in all its aspects, as in any other age group [20]. According to a recent consensus review, it is accepted that allergic rhinitis in children, and its complications, can lead to emotional disorders (shame, loss of self-esteem), family problems (parent anxiety, overprotection, hostility), and even to an increased risk of depressive disorders. All this logically may increase the likeliness of school failure [21].

Associated diseases or complications

A number of concomitant processes or complications can contribute to worsened school performance in children with allergic rhinitis, such as asthma, rhinosinusitis, pharyngitis, eustachian tube inflammation with or without hypoacusia, adenoid (tonsil) hypertrophy with or without sleep apnea, or the so-called "long face syndrome" or facial hypoplasia with ogival palate and dental malpositioning.

Hypoacusia associated to otitis media in the first four years of life can be a cause of diminished performance in mathematics and in reading and writing – though posteriorly the performance of these children is seen to be similar to that of children who have never experienced otitis media [22].

According to a recent epidemiological study involving parent questionnaires and direct home monitoring, habitual snoring is very frequent in pre-school children (up to 35% of all those under 6 years of age), and can be associated to apneic patterns in 18% of cases, and to episodic hypoxemia in up to 13% [23]. Nocturnal hypopnea with snoring is commonly associated with lessened school performance in mathematics, sciences and reading and writing activities [24], particularly in the concomitant presence of intermittent nocturnal hypoxia, but also intrinsically and in the absence of desaturations [25].

Antiallergic drug treatments and school performance

The recently analyzed ARIA (Allergic Rhinitis and its Impact on Asthma) consensus document [26] recommends a stepwise therapeutic approach to allergic rhinitis, in an attempt to control the symptoms and prevent complications without altering normal patient functional capacity. It is considered

Table 3. Antiallergic medications and School performance

Medication	Crosses BBB	Affects performance	Mechanism
Classical antihistamines	Yes	Yes	Sedation due to H_1 receptor interaction in CNS (saturation up to 80% central H_1 receptors)
2nd Generation antihistamines	Variable	Variable	Sedation due to H_1 receptor interaction in CNS (saturation up to 20% central H_1 receptors)
Chromones	No	No	
Ipratropium bromide	No	No	
Topical vasoconstrictors	Yes	Yes	Drug induced or rebound rhinitis Stimulation of CNS Cardiovascular effects
Systemic vasoconstrictors	Yes	Yes	Stimulation of CNS Unpredictable pharmacokinetics in children
Antileukotrienes	No	Improbable	Behavioral alterations?
Intranasal corticoids	Yes	Probable	Improved nocturnal sleep and daytime sleepiness
Systemic corticoids	Yes	Yes	Reversible alteration of short term memory Mood changes (anxiety/depression) Behavioral effects ("steroid psychosis")
Immunotherapy	No	No	

Table 4. Most commonly used drugs in pediatric allergic rhinitis and recommendation levels according to the ARIA consensus document [26]

Medication	Seasonal AR	Perennial AR	Persistent AR	Minimum age
Classical antihistamines	A	A	No data	6 months
2nd Generation antihistamines	A	A	A	
Ketotifen, Cetirizine,				6 months
Levocetirizine, Loratadine, Desloratadine, Ebastine,				2 years
Fexofenadine, Mequitazine, Mizolastine, Rupatadine,				12 years
Azelastine, Levocabastine				4 years
Chromones	A	B	No data	6 years
Ipratropium bromide	No data	A	No data	12 years
Topical vasoconstrictors	C	C	No data	6 years
Systemic vasoconstrictors	B (+ anti-H_1)	B (+ anti-H_1)	No data	6 years
Antileukotrienes (Montelukast)	A (>6 años)	No data	No data	2 years
Intranasal corticoids	A	A	No data	
Fluticasone,				4 years
Budesonide, Beclomethasone, Triamcinolone, Mometasone				6 years
Immunotherapy (SC or SL)	A	A	No data	2 years

that the correct management of allergic rhinitis can reduce the impact of the disease upon the future health of children and adolescents, avoid complications, and improve quality of life and school performance. However, suboptimal treatment of allergic rhinitis is common in schoolchildren, due to less effective self-management than in adults, or to unacceptable side effects of the medication, which can worsen school performance even further.

Table 3 shows the different drugs approved for the treatment of pediatric allergic rhinitis (in addition to the antihistamines), and their possible effects upon school performance.

Chromones

Since neither disodium cromoglycate nor sodium nedocromil cross the blood-brain barrier, they are not believed to affect learning [27]. The ARIA consensus document establishes level A recommendation for intranasal chromones in children, in application to both seasonal and perennial allergic rhinitis (Table 4). These drugs can be used in children aged 6 years old and above.

Anticholinergic agents

Although atropine exerts dose-dependent effects upon the central nervous system, its quaternary salt ipratropium bromide administered via the nasal inhalatory route does not cross the blood-brain barrier, and is therefore likewise not believed to affect learning. The ARIA consensus document establishes level A recommendation for ipratropium bromide in perennial rhinitis in adults. However, its use is not authorized or recommended in children under 12 years of age [28].

Nasal decongestants (vasoconstrictors)

Imidazolic or α2-adrenergic (such as oxymetazoline or naphazoline) vasoconstrictors are effective in application to nasal congestion when administered topically, though they can induce sympathomimetic-type systemic effects and a characteristic local rebound effect that constitutes the basis of drug induced rhinitis. In children under one year of age, where the therapeutic and toxic margins are very narrow [29], imidazolic vasoconstrictors have been correlated to cardiovascular effects and central nervous system depression [30].

Systemic decongestants derived from ß-phenylethylamine (such as ephedrine, pseudoephedrine or phenylpropanolamine) have been used on an empirical basis in many over-the-counter anticatarrhal formulations [28]. The joint use of antihistamines with modified-release pseudoephedrine has demonstrated greater effects upon the symptoms of rhinitis (including congestion) than antihistamines alone – though at the expense of increased adverse effects: these substances are rapidly absorbed within the gastrointestinal tract, and reach high concentrations in the central nervous system. Intoxication due to systemic decongestants may produce irritability, anxiety, diaphoresis, hypertension, seizure episodes, psychotic states and hallucinations [28]. The pharmacokinetics of vasoconstrictors in children are independent of the dose and are less predictable than in adults [31]. However, there are no concrete studies in relation to school performance for any topical or systemic decongestant medication.

The ARIA consensus document establishes level C recommendation for topical vasoconstrictors in application to seasonal and perennial rhinitis in both children and adults. Oral decongestants alone receive level A recommendation only in adult seasonal rhinitis. When combined with antihistamines, these drugs receive level B recommendation in schoolchildren for both seasonal and perennial rhinitis [26].

Antileukotrienes

The cysteinyl-leukotriene inhibitors (less effective than antihistamines or intranasal steroids in application to allergic rhinitis) are considered to be safe and well tolerated. In pediatric patients (2-14 years of age), the most common side effects of montelukast are headache and upper airway infections [32]. Montelukast does not cross the blood-brain barrier, and in principle has not been associated with alterations in psychomotor performance. However, the United States Food and Drug Administration (FDA) very recently has alerted to the possibility of an association between cysteinyl-leukotriene inhibitors and behavioral and mood disorders, including suicide tendency [33]. The ARIA consensus document establishes level A recommendation only for seasonal rhinitis, and in children over 6 years of age.

Intranasal steroids

Although considered to be practically equivalent in terms of efficacy, the different nasal steroids differ in terms of their pharmacology and dosing characteristics. In children, fluticasone has been approved in patients >4 years of age, while mometasone, beclomethasone, budesonide and triamcinolone have been approved for children >6 years of age [28]. All these substances can produce local adverse effects such as mucosal dryness and nosebleed.

The topical nasal steroids exert their antiinflammatory effect upon the mucosa, and are effective against all the symptoms of rhinitis. The ARIA consensus document therefore establishes level A recommendation in children for both seasonal and perennial allergic rhinitis. However, a recent Cochrane review has detected weak and scantly convincing evidence of the efficacy of topical nasal corticoids in application to pediatric allergic rhinitis. This has been attributed to methodological deficiencies in the few trials amenable to inclusion in a metaanalysis [34].

Nevertheless, randomized clinical trials with budesonide, flunisolide and fluticasone have demonstrated a reduction in sleep problems and daytime sleepiness among the treated patients, as well as a direct correlation between the improvement of nasal congestion and sleep disturbances (P<0.01)[5,35]. These findings would be in favor of the idea that intranasal steroids not only do not impair school performance but may actually improve such performance in certain patients.

Systemic steroids

The risk/benefit ratio of the oral corticoids limits their use to short periods of time for severe cases of allergic rhinitis and nasosinusal polyposis. Systemic steroids can produce different psychological side effects in children and adolescents, ranging from mild behavioral alterations, mild symptoms of anxiety/depression or cognitive effects, to more notorious behavioral reactions (insomnia, irritability, aggressivity, crying tendencies) sometimes referred to as "corticoid psychosis" [36]. The cognitive effect most often reported in adults and children is reversibly altered short term memory or retention capacity. As a result, it is very likely that systemic corticoids may, at least transiently, exert adverse effects upon school performance [36].

Immunotherapy

There are no concrete studies in relation to school performance in the case of specific allergen-based immunotherapy, though the experience gained suggests that such therapy does not affect school performance beyond the need to administer the treatment periodically in a medical center. Moreover, this need can be reduced or obviated by using rapid regimens or sublingual immunotherapy. The ARIA consensus document establishes level A recommendation for subcutaneous and sublingual immunotherapy in application to seasonal and perennial rhinitis with or without asthma, in both adults and children [26].

Role of antihistamines in learning problems

Histamine is an important neurotransmitter in maintenance of the waking state. Drowsiness induced by antihistamines is a result of their interaction with the H_1 receptors located at hypothalamic level, which account for 40% of the total H_1 receptors of the human body. The capacity of a given antihistamine to cross the blood-brain barrier depends on factors such as its molecular size, binding to serum proteins, volume of distribution, affinity for glycoprotein P expressed by the cerebrovascular endothelium [37], and the existence of an adequate degree of lipophilia [38]. The first generation antihistamines are small lipophilic molecules that occupy 75% of the H_1 receptors in the brain, while the second generation antihistamines occupy only up to 20% of these same central receptors [39].

As a result, sedation and drowsiness are seen in up to 55% of all patients administered antihistamines at therapeutic doses [40], along with anticholinergic effects that are known to affect school performance [41]. These effects are much more common with the first generation antihistamines, but are not limited to these drugs.

Methods for estimating antihistamine effects upon school performance

Antihistamine induced sedation and its possible consequences for school performance have been evaluated in children using a range of methods (Table 5):

- Cognitive tests, which explore different higher cortical functions and motor, coordination and sensory capacities [38].
- Visual analog scales (VAS). These pose a problem in that they are subjective, and drowsiness itself may affect self-scoring, particularly in children [21].

Table 5. Methods for evaluating sedation induced by antihistamines, and their possible impact upon school performance

1. Objective psychometric tests – Sensory-motor coordination tests: Critical tracking test, reaction time – Evaluation of cortical functions: Processing (mental calculation), integration (critical flicker fusion), memory (digit span), learning (list of words), etc. – Evaluation of sensory functions and alertness: Vision and hearing acuity, spatial perception, color tests, digit symbol substitution, etc.
2. Visual analog scales
3. Specific quality of life questionnaires – Rhinitis Quality of Life Questionnaire (RQLQ) – Allergy Specific-Work Productivity and Activity Impairment Questionnaire (WPAI-AS)
4. Experimental school environments Classes and lectures on specific subjects for allergic children, with test-type examinations and other computed tests with and without medication
5. Neurophysiological tests – Multiple Sleep Latency Test – Auditory evoked potentials (P-300)

– Specific questionnaires adapted to young subjects, with questions relating to lack of sleep, school absenteeism and concentration difficulties in class [9,10].
– Experimental computer-based tests in the school setting [11].
– Neurophysiological studies, such as the Multiple Sleep Latency Test (measuring the time needed to induce EEG stage 1 sleep after repeated daytime sleep opportunities under standardized conditions) [42], or auditory evoked potential studies (e.g., P-300), which reflect the speed of active cognitive information processing and the way in which it is influenced by drugs [7,8].

Based on such studies, manifest differences have been demonstrated between the first and second generation antihistamines. However, although the psychomotor performance studies suggest certain differences between them, no comparative studies have been made of the different second generation antihistamines in the concrete area of school learning.

First generation antihistamines

The most classical antihistamines such as triprolidine, diphenhydramine, chlorpheniramine or hydroxyzine have been available without a prescription for many years – a situation that to some degree has favored their indiscriminate use in children. These drugs exert anticholinergic and sedative effects upon the central nervous system that are often difficult to distinguish from the signs and symptoms of the disease itself. As a result, not all authors agree that the first generation antihistamines affect school performance.

A study of 63 allergic children (8-10 years of age) in an experimental school setting, with classes imparted on weekends after medication with diphenhydramine, loratadine or placebo, revealed no differences in the results of computed reaction time tests, examinations or drowsiness analog scales [11]. However, another study involving a computer-based didactic program in a real school setting demonstrated significant differences between diphenhydramine and loratadine in the evaluation of learning [41] – this agreeing better with the studies based on cognitive tests [43,44]. Likewise, the use of visual analog scales and neurophysiological tests has detected increased subjective sedation and greater P-300 alteration in children treated with diphenhydramine or hydroxyzine [7], and chlorpheniramine or cetirizine [8], versus the placebo group ($P<0.05$) – though without significant differences between the active treatment groups.

In any case, due both to their sedative and anticholinergic effects and to their possible paradoxical actions upon the central nervous system (such as restlessness, irritability and insomnia) [28], the classical antihistamines interfere with daytime activities even when administered the night before [45]. They therefore should not be considered in children and adolescents.

Second generation antihistamines

At present, the second generation (or non-sedating) antihistamines constitute the drug treatment of choice for allergic rhinitis. Due to their greater molecular weight and lesser lipophilia compared with the first generation antihistamines, these drugs are less inclined to cross the blood-brain barrier. Although none of them is considered to be free of sedating actions, there are documented differences in their effects upon psychomotor performance. At therapeutic doses, greater sedating action is attributed to cetirizine than to loratadine or fexofenadine [46], and in schoolchildren a study of chlorpheniramine versus cetirizine revealed no differences

in subjective sedation or P-300 alteration between the two active drug groups [8].

However, this alteration of psychomotor performance is not seen with the enantiomer levocetirizine, at therapeutic doses [43,44].

Desloratadine also has been shown not to affect cognitive function in pollinic rhinitis triggered in an exposure chamber [47].

The ARIA consensus document establishes level A recommendation for second generation antihistamines in relation to both oral and intranasal formulations, in seasonal as well as perennial rhinitis, and in both children and adults. Ketotifen and cetirizine have been approved for use in children over 6 months of age; levocetirizine, loratadine, desloratadine and ebastine can be used from two years of age onwards; fexofenadine, mequitazine, mizolastine and rupatadine are only approved after 12 years of age; and the topical antihistamines azelastine and levocabastine can be administered to children over four years of age [28].

In addition to specific quality of life questionnaires such as the Rhinitis Quality of Life Questionnaire (RQLQ) developed by Juniper [48], some studies involving second generation antihistamines have employed other specific questionnaires adapted to young subjects, with questions on lack of sleep, school absenteeism and concentration difficulties in class, such as the Allergy Specific-Work Productivity and Activity Impairment Questionnaire (WPAI-AS) [9]. In a joint analysis of two multicenter trials and in a subgroup of 556 schoolchildren, these tools were able to show improvement from the first week of treatment in those patients administered fexofenadine 60 mg/12 hours versus placebo not only in all the domains of the RQLQ (except sleep) ($P<0.05$), but also specifically in terms of school absenteeism and general performance in class ($P<0.05$) [10].

Conclusion

Allergic rhinitis is presently the most common chronic disorder in the pediatric population, and can affect learning as a consequence of the frequent sleep disturbances and resulting daytime sleepiness. A secondary effect of all this is school absenteeism, "presenteeism" (inattention, distraction, lack of concentration), irritability and restlessness, mood disturbances, and even social and family problems that can further contribute to worsen school performance.

The correct management of allergic rhinitis can reduce the impact of the disease upon the future health of children and adolescents, avoid complications, and improve quality of life and school performance – though certain drugs, particularly the classical antihistamines, can produce unacceptable central and anticholinergic side effects that may further worsen school performance.

The treatment of choice for pediatric allergic rhinitis therefore should include second generation antihistamines, though none of them are considered to be fully free of sedating action. Combinations with pseudoephedrine should not be used in pediatric patients, due to their central effects and more unpredictable pharmacokinetics than in adults. Intranasal corticoids could improve school performance in some patients, by reducing nasal congestion, nocturnal sleep disturbances, and daytime sleepiness. Other therapies (chromones, anticholinergic agents, antileukotrienes, immunotherapy) have not been studied in this sense, though extrapolation of their results in relation to general cognitive functions suggest that they do not significantly affect school performance.

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