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1 **Emergence of pollen food allergy syndrome in asthmatic children in Paris**

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29 **ABSTRACT**

30 **Background:** Over the last few decades, the level of pollen from birch and homologous trees
31 has increased in parts of Europe. Sensitization to birch pollen allergens (principally Bet v 1)
32 has been associated with food cross-reactivity called pollen-food-allergy syndrome (PFAS).

33 **Objective:** To evaluate changes in allergic diseases due to IgE sensitization over 25 years in
34 asthmatic children.

35 **Methods:** This was a cross-sectional retrospective study conducted in Paris. We analyzed two
36 cohorts of asthmatic children with similar characteristics explored between 1993-1999 (old
37 cohort=OC) and 2012-2018 (recent cohort = RC).

38 **Results:** 121 children were in the OC and 120 in the RC. An increase in sensitization to tree
39 pollens was found especially for birch pollen which was 11.6% in the OC and 31% in the RC
40 ($p=0.0002$). Allergic rhinitis prevalence was significantly higher in the RC than in the OC
41 (96% vs 52%, respectively, $p<0.0001$). IgE-mediated food allergy increased from 6% to 16%
42 in the OC and RC, respectively, ($p = 0.01$) mainly due to PFAS. In the RC, a higher mean Bet
43 v 1-specific IgE level was observed in children with PFAS compared to children without
44 ($105.7 \text{ KU/L} \pm 17.8$ and $48.9 \text{ kU/L} \pm 15.7$, respectively, $p<0.05$).

45 **Conclusion:** Allergic rhinitis and food allergy with tree-pollen sensitization has increased in
46 Paris over 25 years mainly due to PFAS. Environmental factors could be responsible for these
47 modifications as described in literature.

48 228 words

49 **Key Words**

50 Allergic rhinitis, Pollen-food-allergy syndrome, Asthma, Betv1 specific IgE

51

52

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54 INTRODUCTION

55 With the rapid increase in the prevalence of allergic diseases over the last century, the World
56 Health Organization (WHO) ranks allergy as the 4th chronic disease in the world after cancer,
57 cardiovascular pathologies and AIDS (1). It is estimated that half of the world's population
58 will be allergic by 2050.

59 Allergic asthma is the most common asthma phenotype in children (2). The percentage of
60 patients in whom asthma is attributed to atopy varies from 35 to 50% depending on the study
61 (3). Nevertheless, allergic rhinitis, atopic dermatitis and food allergy are strong risk factors for
62 asthma inception and severity both in children and adults (2,4).

63 Moreover, pollens, and mainly birch pollen, are responsible for seasonal asthma attacks (5).

64 In northern and central Europe, birch and other trees of the Betulaceae and Fagaceae families
65 are the most dominant tree pollens and represent the most potent elicitors of allergy in early
66 spring. Over the last few decades, the level of birch pollen and pollens from trees of the same
67 group has increased in some parts of Europe (6).

68 Birch pollen allergens induce IgE cross-reactivity, predominantly observed in relation to Bet
69 v 1, including food cross-reactivity which is called pollen-food-allergy syndrome (PFAS).

70 PFAS typically consists of an immediate mild local reaction (oral food syndrome) including
71 itching, tingling and angioedema of the lips, tongue, and throat. It rarely causes systemic
72 reactions such as anaphylaxis. In the north of Europe, the principal PFAS mechanism results
73 in cross-reactivity toward molecular components of tree pollens and food allergens mainly
74 due to the presence of PR-10 proteins. Recent studies suggest that PFAS might be more
75 frequent in childhood than previously recognized (7).

76 The aim of our study was to evaluate changes in allergic diseases, and specially PFAS, over
77 25 years in children with asthma.

78

79 **METHODS**

80 **Study design and population**

81 This was a cross-sectional retrospective study conducted in the Department of allergology in a
82 French pediatric hospital (Trousseau Hospital, Paris).

83 The study population consisted of two random cohorts of children aged 7-15 years and
84 admitted to the department for a follow-up assessment of their asthma between 1993-1999
85 (old cohort = OC) or 2012-2018 (recent cohort = RC). The inclusion criteria were: (1)
86 sensitization to at least one aeroallergen; (2) living in Paris or neighbouring suburbs
87 (departments 92, 93 and 94). The study data were extracted from medical information
88 gathered during the hospital stay and entered in a computerized database.

89 **Study data**

90 The following data were recorded and compared between the two cohorts:

- 91 1. Demographic characteristics: age, sex, geographic distribution (Paris or its suburbs)
92 and whether the child was overweight (including obesity) defined by a Body Mass
93 Index ($BMI = \text{weight} / \text{height}^2$) $>IOTF-25$ (International Obesity Task Force)
94 threshold.
- 95 2. Personal and family atopic diseases: allergic rhinitis and active atopic dermatitis
96 (defined by a flare-up within the previous year) mostly assessed by questions from the
97 International Study of Asthma and Allergies in Childhood (8).
- 98 3. Asthma characteristics:
 - 99 a. Proximal limitation of expiratory airflow was defined by a forced expiratory
100 volume 1 second/forced volume vital capacity ratio (FEV_1/FVC) <0.9 and/or
101 prebronchodilator $FEV_1 < 80\%$
 - 102 b. Long-term treatment prescribed on discharge especially inhaled corticosteroids
103 (ICS) and Long-Acting-Beta2-Agonists (LABA). ICS doses were classified

104 according to the Global Initiative for Asthma (9): low (200-500 µg
105 beclometasone), medium (500-1000 µg beclometasone) or high dose (>1000
106 µg beclometasone).

107 4. Biological inflammatory atopic markers were measured in peripheral blood through:
108 blood eosinophilia (cell counting by automated Sysmex, France), total
109 immunoglobulins E (IgE) and specific IgE measured by ImmunoCAP™ (Phadia,
110 Uppsala, Sweden). Bet v 1 specific IgE levels were available in children in the RC if
111 they tested positive to birch-pollen specific IgE.

112 5. Allergenic sensitization was defined as a positive skin prick test (wheal allergen ≥3
113 mm in the absence of a positive reaction to the negative control), and confirmed by
114 positive specific IgE ≥0.35 kU/L (ImmunoCAP®; Phadia, Uppsala, Sweden) (10).

115 The battery of allergens explored included the common allergens (house dust mites
116 (HDM), cat and dog dander, grass and birch pollen, *alternaria alternata*, cow's milk
117 proteins, egg, and peanut) and allergens detected as being responsible for symptoms
118 and/or present in the environment.

119 6. IgE-mediated food allergy was defined by relevant symptoms of food allergy
120 occurring within 6 hours following consumption of the food allergen associated with
121 an allergic sensitization to the same allergen (11).

122 **Ethics**

123 The study was declared to the French “Commission Nationale d’Informatique et Libertés”
124 under the reference number MR-5714060420 and a letter of information was sent to the
125 patients’ family. Informed consent was not required because of the retrospective nature of the
126 analysis.

127 **Statistical analysis**

128 Analysis was performed per patient. Quantitative variables are reported as mean ± SD

129 and compared by unpaired t-test. If the sample was small equality of variances was tested
130 with Fisher's test and the Welch t-test was used if variances differed. Categorical variables
131 are reported as count and proportions. Statistical significance was considered at the $p < 0.05$
132 level. Statistical analysis was performed using Graphpad Prism version 7.0 (GraphPad
133 Software, San Diego, CA, USA).

134

135 **RESULTS**

136 **Characteristics of the two cohorts**

137 One hundred twenty-one children were included in the OC and 120 in the RC.

138 *Demographic characteristics* (Table I): There was no significant difference regarding age, sex
139 ratio, number of overweight children. The geographical distribution was homogenous
140 between Paris and the suburbs.

141 *Asthma characteristics* (Table II): There was no significant difference in proximal limitation
142 of expiratory airflow which was present in nearly 30% of the population in the two cohorts.
143 The most commonly prescribed long-term discharge treatment mainly corresponded to step 3
144 and 4 of the GINA guidelines for the majority of the children in both cohorts.

145 *Atopic inflammatory biomarkers* (Table II): Blood eosinophilia and serum total IgE were at
146 similarly high levels in both cohorts.

147 **Changes in sensitization to inhaled allergens (Table III)**

148 The three most frequent allergens were HDM, animal dander and grass pollen, in a similar
149 proportion for the two cohorts. Children in the RC were three-times more likely to have a tree
150 pollen sensitization ($p = 0.0002$) and especially for birch (9.9% in the OC vs 29% in the RC, p
151 $= 0.0001$) and oak (5% in the OC vs 16% in the RC, $p = 0.005$). There was a slight decrease
152 in sensitization to perennial allergens in the RC compared to the OC: HDM ($p = 0.0001$) and
153 *alternaria alternata* ($p = 0.04$).

154 **Changes in atopic diseases except food allergy (Table IV)**

155 Children in the RC were twice more likely to have allergic rhinitis compared to those in the
156 OC ($p < 0.0001$) and a family history of asthma ($p = 0.005$). There was no difference in the
157 percentage of children with a personal history of atopic dermatitis or with active atopic
158 dermatitis between the two cohorts.

159 **Changes in Pollen-Food-Allergy Syndrome**

160 A significant increase in IgE-mediated food allergy was observed in the two cohorts: 6% in
161 the OC versus 16% in the RC ($p = 0.01$). The difference was mainly due to PFAS related to
162 tree pollens sensitization. In the OC, only one of the seven children with IgE-mediated food
163 allergy had PFAS (due to cross reactivity between oak pollen and apple, kiwi, peach,
164 hazelnut). In the RC, ten children with IgE-mediated food allergy had PFAS: four with
165 isolated PFAS and six with PFAS associated with another IgE-mediated food allergy. More
166 precisely, in the RC: one child had a PFAS due to a cross reactivity between isolated oak
167 pollens and soybean; four children due to a cross reactivity between birch and oak pollens and
168 hazelnut, peanut, carrot, kiwi; one child due to a cross reactivity between birch and plane tree
169 pollens and hazelnut, kiwi and banana; and four children due to a cross reactivity between
170 isolated birch pollen and apple, celery, peanut, hazelnut.

171 In the RC, in children with tree pollens sensitization a higher mean Bet v 1 IgE level was
172 observed in children with PFAS compared to children without ($105.7 \text{ KU/L} \pm 17.8$ and 48.9
173 $\text{ kU/L} \pm 15.7$, respectively, $p < 0.05$), as well as a tendency for elevated mean oak IgE levels in
174 children with PFAS versus those without ($22.5 \text{ kU/L} \pm 4.6$ ($n = 5$) and $16.2 \text{ kU/L} \pm 4.7$ ($n =$
175 15), respectively, $p = 0.4$).

176

177 **DISCUSSION**

178 This study of two cohorts of asthmatic children showed a huge increase in allergic rhinitis
179 since the year 2000 due to sensitization to tree pollens associated with an increase in the
180 number of cases of PFAS.

181 **Changes in allergic sensitization to inhaled allergens observed in the two cohorts**

182 Several studies, mostly conducted in adults, have shown a similar increase in tree pollens
183 sensitization. A study of adult asthmatic patients performed in Belgium (12) found rates
184 similar to ours with an increase in sensitization to birch pollen from 13% (1975-1979) to 34%
185 (1992-1995) with no increase in sensitization to grass or artemisia pollen. Similarly, a study
186 conducted in northern Sweden in the general population also found an increase in
187 sensitization to birch pollen albeit lower than that found in ours: 13% in 1994 to 18% in 2009
188 (13). In the same manner, a Danish study reported an increase in birch pollen sensitization in
189 the general population from 12.1% to 13.7% between 1990 and 1998 (14).

190 Several other studies have explored changes in allergic sensitization with different
191 conclusions. Rönmark's study (15), conducted in northern Sweden between 1996 and 2006 in
192 7–8-year-old children, showed that the prevalence of positive skin prick tests increased from
193 21% in 1996 to 30% in 2006. The allergens tested were birch, timothy, mugwort, dog, cat,
194 horse, HDM, cladosporium and *alternaria alternata*. Despite an increase in the prevalence of
195 allergic sensitization of all allergens tested, no increase in the prevalence of symptoms of
196 asthma, rhinitis or eczema was found.

197 A study conducted in Denmark by Thomsen SF et al. (16) evaluated atopic sensitization by
198 skin prick test reactivity from 1986 and 2001 in two random population samples of children
199 aged between 7-17 years. There was a non-statistically significant decline in the prevalence of
200 sensitization to most allergens (birch, horse, dog, cat, HDM) with a statistically significant
201 decrease in mugwort and *alternaria alternata* sensitizations. In the same study, the prevalence
202 of sensitization to grass pollens remained stable.

203 Changes in atopic diseases observed in the two cohorts

204 We found a statistically higher prevalence of allergic rhinitis and family atopy in the RC
205 compared to OC as reported by other authors. Conversely, the prevalence of atopic dermatitis
206 remained unchanged contrary to other findings in the literature (17). This is probably because
207 we only noted atopic dermatitis that was active during the study period and because atopic
208 dermatitis is often in remission at 7 years which was the minimum age for inclusion in our
209 study (18).

210 Changes in Pollen-Food-Allergy Syndrome observed in the two cohorts

211 Our study showed a 3-fold increase in PFAS in the RC compared to the OC.

212 The first description of PFAS dates back as far as 1942 (19) (20). In 1995, the term PFAS was
213 used to better characterize the pathogenesis (21) and relationship principally to the PR-10
214 family.

215 In our study, children sensitized to tree pollens with PFAS had higher Bet v1 IgE levels
216 compared to patients without ($p < 0.05$). This result is in accordance with the study by Asero
217 R. et al. (22) who showed that birch pollen allergic patients with PFAS were more likely to
218 have asthma and higher specific IgE levels to birch pollen than patients without. In the same
219 manner, the Italian study by Ciprandi et al. (23) conducted in 245 adults sensitized to Bet v 1
220 with allergic rhinitis, showed that patients with PFAS had higher Bet v 1 levels and more
221 severe symptoms of allergic rhinitis than patients without. Our results are also in agreement
222 with the Swedish birth cohort study by Westman et al. (24) who found that the risk of later
223 onset or persistence of symptoms of allergic rhinitis to birch pollen increased with increasing
224 levels of Bet v 1 specific IgE.

225 Although less described in literature, oak pollen allergy can also cause food allergy toward
226 the PR-10 proteins. However, oak pollen is close to birch pollen: birch pollen allergy

227 immunotherapy can be effective for other tree pollens especially alder, hazel and oak, a group
228 of trees that we call the “birch homologous group” (25).

229 **Environmental factors to explain the changes in allergen sensitization**

230 The plane tree is by far the most planted tree in Paris currently, mainly as an alignment tree,
231 against 4 330 oak trees and 2 413 birch trees. The plane tree is an aerobiological polluter
232 which can also be a provider of food allergies (26). While the high allergenic potential of the
233 birch is well known by urban planning departments, that of oak and plane trees, although
234 lower, is less so as is their role in food allergies. It is important that urban developers as well
235 as the general public are made aware of their allergenic risk and consequently restrict the
236 planting of such trees through diversification. Introducing diversity in landscaping is a simple
237 way of reducing the concentration of pollen of the same species in the air (27).

238 Climate change, with the marked increase in the earth’s temperature observed over the last 50
239 years, has had an impact on birch pollen for several decades now (28) (29). The rates of
240 change in annual pollen cycles have been shown to be associated with the rates of change in
241 the annual cycles of several meteorological parameters with overall warmer temperatures
242 (29). In Beck’s study in Munich, pollen from birch exposed to higher ozone levels induced
243 larger wheals and flares in skin prick tests compared to lower ozone-exposed pollen
244 suggesting an allergenicity increasing effect of ozone (30).

245 The decrease in perennial allergen sensitization found in our study could be explained by the
246 improvement of the indoor environment and recent measures taken against HDM and molds
247 (15).

248 **Strengths and limits of the study**

249 The main limits of our study lie in the fact that it is retrospective and that all the patients were
250 recruited from one center albeit a tertiary care center for allergic diseases. However, atopic
251 disease was assessed by standardized questionnaires in both cohorts to minimize the risk of

252 misinterpretation, and allergic sensitization was measured by validated parameters – skin
253 prick tests and specific IgE levels – in the same way. Furthermore, the two cohorts in our
254 study were homogenous phenotypes: a predominance of boys, a high rate of overweight
255 patients and atopic comorbidities, and the same severity of asthma. Finally, the homogeneous
256 geographic distribution of our population in Paris and suburbs makes it possible to compare
257 allergen sensitization within a similar environment, in particular with tree plantations which
258 can affect the development of allergies.

259 **Conclusion**

260 Allergic rhinitis, sensitization to trees and PFAS has increased in Paris and the surrounding
261 suburbs over 25 years as shown in our two cohorts of asthmatic children of the same severity.
262 Environmental factors could be responsible for these modifications as mentioned in literature.

263

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Table I: Demographic characteristics

	Old Cohort	Recent Cohort	p value*
Number of patients	121	120	-
Age, (years)	10.6 ± 0.2	10.2 ± 0.2	0.1
Male, nb. (%)	78 (64)	84 (70)	0.4
Overweight †, nb. (%)	21 (19) n=110	22 (18) n = 118	0.9
Geographical distribution, nb. (%)	n = 121	n = 120	
Living in Paris (75)	60 (50)	51 (43)	0.3
Living in suburbs	61 (50)	69 (57)	0.3
-All inhabitants of 92 / 92 close to Paris (<5km)	10 (8) / 9 (7)	3 (2.5) / 3 (2.5)	-
-All inhabitants of 93 / 93 close to Paris (<5 km)	26 (21) / 17 (14)	34 (28) / 21 (18)	-
-All inhabitants of 94 / 94 close to Paris (<5 km)	25 (21) / 24 (17)	32 (26.5) / 27 (23)	-

Abbreviations: Admitted to the department for a follow-up assessment of their asthma between 1993-1999 (Old Cohort) or 2012-2018 (Recent Cohort).

Definitions: * Statistical significance was considered at the p <0.05 level; † Overweight (included obesity): Body Mass Index > IOTF-25 (International Obesity Task Force) threshold

Table II: Asthma characteristics

	Old Cohort	Recent Cohort	P value*
Number of patients	121	120	-
Early onset of asthma†, nb. (%)	64 (54)	80 (67)	0.07
Proximal limitation of expiratory airflow ‡: nb. (%)	30 (31) n= 97	34 (30) n= 114	0.9
Prebronchodilator FEV1 < 80 % (%)	29 (30) n= 97	23 (22) n= 106	0.2
Uncontrolled asthma § (%)	82 (70) n= 116	77 (64) n= 120	0.3
Discharge treatment, nb. (%) :			
No ICS	15 (13) n = 118	14 (12) n= 118	0.8
ICS only, low doses (200-500 µg beclometasone)	29 (26) n = 112	28 (24) n = 118	0.7
ICS low or medium doses + LABA / ICS only medium doses (500-1000 µg beclometasone)	56 (50) n = 111	63 (53) n = 118	0.7
ICS high doses (>1000 µg beclometasone)	11 (10) n = 111	10 (8) n = 118	0.7
Blood eosinophilia count ¶ (cells/mm ³) mean ± SD	624 ± 35	605 ± 38	0.7
Total IgE count (kUI/L) mean ± SD	638 ± 67	755 ± 85	0.3

Abbreviations: Admitted to the department for a follow-up assessment of their asthma between 1993-1999 (Old Cohort) or 2012-2018 (Recent Cohort).

Definitions: ICS, inhaled corticosteroid; LABA, Long-Acting-Beta2-Agonist; Total-IgE, total immunoglobulin E *Statistical significance was considered at the p <0.05 level † asthma onset before 3 years of age ‡defined by FEV₁/FVC < 0.9 in children § uncontrolled asthma as defined as GINA guidelines ¶ cell counting by automated Sysmex®, France || measured by ImmunoCAP™ (Phadia, Uppsala, Sweden)

Table III: Changes in allergic sensitization to inhaled allergens

	Old cohort	Recent cohort	p value*
Number of patients	121	120	-
Sensitization to inhaled allergens †			
House dust mites, nb. (%)	113 (93)	91 (76)	0.0001
Dermatophagoides pteronyssinus	113 (93)	91 (76)	0.0001
Dermatophagoides farinae	6 (5)	17 (14)	0.02
Animal dander, nb. (%)	53 (44)	58 (48)	0.5
Cat	41 (34)	48 (40)	0.3
Dog	20 (16)	28 (23)	0.2
Horse	7 (5.7)	4 (3.3)	0.4
Rabbit	2 (1.6)	0	0.2
Hamster	3 (2.5)	2 (1.6)	0.7
<i>Alternaria alternata</i>, nb. (%)	38 (31)	24 (20)	0.04
Aspergillus, nb. (%)	5 (4.1)	3 (2.5)	0.5
Grass pollen, nb. (%)	50 (41)	45 (37.5)	0.5
Artemisia pollen, nb. (%)	2 (1.6)	3 (2.5)	0.6
Trees, nb. (%)	14 (11.6)	37 (31)	0.0002
Birch	12 (9.9)	35 (29)	0.0001
Oak	6 (5)	19 (16)	0.005
Plane tree	1 (0.8)	1 (0.8)	0.6
Cypress	0	1 (0.8)	0.3
Ash	0	1 (0.8)	0.3

Abbreviations: Admitted to the department for a follow-up assessment of their asthma between 1993-1999 (Old Cohort) or 2012-2018 (Recent Cohort).

Definitions: IgE, immunoglobulin E * Bold characters means p-value reaching statistical significance ($p < 0.05$); † Sensitization to inhalant allergen was defined as a specific IgE level ≥ 0.35 kU/L, measured by ImmunoCAP™ (Phadia, Uppsala, Sweden).

Table IV: Personal and family history of atopic diseases

	Old Cohort	Recent Cohort	p value*
Number of patients	121	120	-
History of atopic dermatitis † nb. (%)	54 (45)	53 (44)	0.9
Active atopic dermatitis† ‡, nb. (%)	14 (11)	17 (14)	0.6
Allergic rhinitis, nb. † (%)	63 (52)	111 (96)	<0.0001
Family history of atopy §, nb. (%)	45 (37)	84 (70)	<0.0001
Family history of asthma, nb. (%)	39 (32)	60 (50)	0.005

Abbreviations: Admitted to the department for a follow-up assessment of their asthma between 1993-1999 (Old Cohort) or 2012-2018 (Recent Cohort).

*Definitions:** Bold characters means p-value reaching statistical significance ($p < 0.05$); † Assessment by the questions from the International Study of Asthma and Allergies in Childhood (ISAAC); ‡ defined by flare-up in the last year; § defined as food allergy, eczema or allergic rhinitis