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Nine-Year Follow-Up of Children with Atopic Dermatitis by General Practitioners

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Key Words
Follow-up · Children · Atopic dermatitis · General practitioners

Abstract
The frequency of associated comorbidity and the cost of treatments in patients with atopic dermatitis (AD) followed up in primary care settings are poorly known. We carried out a retrospective cohort study on a longitudinal electronic medical records database of patients consulting a panel of general practitioners in France. All subjects with AD diagnosed during the first year of life were selected and matched with infants without the disease according to sex (1,163 vs. 1,163). Subjects were followed up for 9 years. Associated diseases, drug consumptions and available medical costs were detailed. Comparisons between subjects and controls were carried out. Subjects with AD had more comorbidities than others, especially in respiratory and ophthalmic system organs. The number of prescribed treatments in the field of skin diseases as well as overall medical costs (general practitioner consultations and prescribed drugs) were higher among atopic subjects, but differences were attenuated with age.

Introduction

Atopic dermatitis (AD) is an inflammatory disease characterized by pruritic skin lesions, immune deregulation, disrupted epidermal barrier function and frequent IgE-mediated hypersensitivity to food and environmental allergens [1, 2]. The prevalence of AD seems to have reached a plateau of around 20% in countries with the highest prevalence, suggesting that AD may not be on a continuous rise but that a finite number of individuals may be susceptible to the condition [3]. The disease is heavy for patients and their caregivers [4, 5]. The difficulties of treatment and the phobia toward topical steroids jeopardize patient care [6]. Research for new treatments is necessary [7]. The economic cost of disease management is high [8].

The study of the natural history of AD may allow the identification of factors influencing its prognosis. A major cohort study evaluated the natural history of patients with AD over a long period of time [9]. However, this study, conducted from 1958 to 1998 in the United Kingdom, focused on the British population and was restricted to the prevalence of AD. The relationship between asthma or allergic rhinitis and prior or current AD is clearly

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demonstrated through other studies [10, 11], which showed that there are other manifestations of atopy, a collection of common inflammatory disorders characterized by a Th2-polarised cytokine profile and type 1 antigen hypersensitivity.

Despite high levels of comorbidity, relatively low levels of genomic coincidence have been observed between atopic triad disorders. Conversely, current mapping data reveal a striking co-localization pattern between AD loci and those mapped using other chronic dermatological diseases such as psoriasis [10]. Polymorphisms or mutations of filaggrin [12, 13] or beta-adrenergic receptor [14] genes suggest association of AD with ichthyosis [12, 13, 15] or stress-aggravated inflammatory skin diseases [14]. These data suggest that people with a history of AD could suffer from other skin diseases, especially inflammatory dermatoses.

In a previous study, we did not find any relationship between AD and psoriasis, and showed that people with a history of AD were less affected by acne or rosacea [16]. In this new study, we used a database to perform a 9-year follow-up of patients suffering from AD to evaluate the frequency of associated diseases and the cost of treatments.

Patients and Methods

We carried out a retrospective cohort study using IMS Lifelink EMR Disease Analyzer (from the private institute IMS Health, Paris La Défense, France), a longitudinal electronic medical records database of patients consulting a panel of around 1,200 general practitioners.

Two cohorts of subjects with and without AD are formed: (1) AD subjects were infants diagnosed with AD (ICD 10 codes: L200, L208, L209 and L309) before the age of 1 year between January 2000 and December 2003. The date of the registration of the diagnosis in the database was considered as the date of the diagnosis, the beginning of the disease and the start of the follow-up period for each subject. Patients with less than 1 year of follow-up history were not selected. (2) Non-AD subjects (controls) were infants without any diagnosis of AD and at least a 1-year follow-up history in the database. They were matched to AD patients according to sex.

Statistical analysis was performed using the SAS system software version 9.1 (SAS Institute Inc., Cary, N.C., USA). Qualitative data were described using counts and percentages and quantitative data were described using means and standard deviations. For the analysis of differences, χ^2 test was used for proportions and Student's t test or Fischer's exact test for means. Comparisons were conducted using 95% confidence interval and 5% alpha-1 error.

The follow-up period was divided in years. Associated diseases of the first year were described; drug consumption and medical costs were detailed for each year, and comparisons between subjects and controls were carried out. Drugs were coded and classified according to the classification of the European Pharmaceutical Marketing Research Association (EphMRA).

Table 1. Number of patients according to the number of years of follow-up

Follow-up	Number of patients	Sex ratio, m/f
Year 1	1,163	1.3
Year 2	766	1.3
Year 3	534	1.2
Year 4	403	1.2
Year 5	327	1.5
Year 6	283	1.4
Year 7	228	1.3
Year 8	198	1.3
Year 9	147	1.2
Year 10	81	1.5
Year 11	38	0.8

An economic analysis was performed with direct medical costs available in Disease Analyzer (consultations with general practitioners and registered prescriptions). The cost of consultations was estimated at EUR 23, which is the official rate in 2012. The reimbursement rate was 70%. The cost of drugs was calculated including taxes.

Results

Overall, 1,723 individuals had a diagnosis of AD during the first year of life. Among them, 1,163 had a follow-up of 1 year or more in the database and were included as AD subjects. Of these, 56% were boys (n = 651) and 46% girls (n = 512). As the number of patients with more than 9 years of follow-up was low (table 1), the observation period was cut off to 9 years.

In the course of their first year of life, infants with AD had significantly ($p < 0.05$) more comorbidity than those without AD (table 2). Especially, they had more respiratory diseases (85 vs. 76%), ophthalmic diseases (47 vs. 28%) and other skin diseases (27 vs. 10%). More specifically on respiratory diseases, 9% of infants with AD suffered from asthma (vs. 5% in others, $p < 0.05$).

Prescribed treatments from general practitioners in the field of respiratory and skin diseases were compared. Patients with a history of AD were more likely to receive dermatological treatments during the follow-up period. During the first year, these were 9 of 10 subjects (emollients: 1 of 2, topical steroids: 1 of 2, antiseptics: 1 of 4). Infants with AD were significantly more likely to have prescriptions of topical steroids than others in the 6 first years of follow-up (fig. 1). Among the former, the prescription of emollients decreased dramatically over the

Table 2. Associated diseases in the first year of follow-up (diagnoses under 1% are not shown)

Associated diseases in the first year of follow-up	AD subjects		Non-AD subjects	
	patients	%	patients	%
J – Diseases of the respiratory system	988	85.0	881	76.0
J00 – Acute nasopharyngitis	705	60.6	618	53.1
J40 – Bronchitis, not specified as acute or chronic	315	27.1	231	19.9
J31 – Chronic rhinitis, nasopharyngitis and pharyngitis	247	21.2	78	6.7
J02 – Acute pharyngitis	236	20.3	161	13.8
J21 – Acute bronchiolitis	114	9.8	106	9.1
J04 – Acute laryngitis and tracheitis	111	9.5	80	6.9
J45 – Asthma	104	8.9	53	4.6
J06 – Acute upper respiratory infections of multiple and unspecified sites	86	7.4	66	5.7
J20 – Acute bronchitis	85	7.3	61	5.2
J30 – Vasomotor and allergic rhinitis	30	2.6	21	1.8
J98 – Other respiratory disorders	27	2.3	13	1.1
J11 – Influenza, virus not identified	23	2.0	25	2.1
J34 – Other disorders of nose and nasal sinuses	17	1.5	5	0.4
R – Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified	664	57.1	380	32.7
H – Diseases of the eye and adnexa	545	46.9	328	28.2
A – Certain infectious and parasitic diseases	362	31.1	256	22.0
L – Diseases of the skin and subcutaneous tissue (excluding L200, L208, L209 and L309)	319	27.4	116	10.0
L22 – Diaper (napkin) dermatitis	141	12.1	51	4.4
L74 – Eccrine sweat disorders	45	3.9	8	0.7
L08 – Other local infections of skin and subcutaneous tissue	35	3.0	9	0.8
L21 – Seborrheic dermatitis	28	2.4	5	0.4
L01 – Impetigo	18	1.5	10	0.9
L23 – Allergic contact dermatitis	18	1.5	3	0.3
L50 – Urticaria	14	1.2	6	0.5
L70 – Acne	14	1.2	2	0.2
B – Certain infectious and parasitic diseases	306	26.3	161	13.8
K – Diseases of the digestive system	304	26.1	153	13.2
T – Injury, poisoning and certain other consequences of external causes	142	12.2	39	3.4
E – Endocrine, nutritional and metabolic diseases	99	8.5	40	3.4
G – Diseases of the nervous system	84	7.2	21	1.8
N – Diseases of the genitourinary system	47	4.0	14	1.2
D – Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	26	2.2	2	0.2
M – Diseases of the musculoskeletal system and connective tissue	19	1.6	7	0.6
Q – Congenital malformations, deformations and chromosomal abnormalities	13	1.1	–	–

follow-up period, from 50% in the first year to 16% in the second year, falling to 4–8% between the third and ninth year. The prescription of treatments for respiratory diseases was very high in children (9 of 10 patients in the first 4 years), then decreased to 8 of 10. In the case of an initial diagnosis of AD, 75% of children had medicine for cough during the first 4 years whereas the figure was 70% in non-AD patients ($p < 0.05$). This difference disappeared later. Subjects with AD were twice more likely to have the EphMRA drug class R02 'throat preparations' (7–8 vs. 3–4% in others; $p < 0.05$). The consumption of antihistamines was different only after the sixth year. Significant differences were also observed for bronchodilators and anti-asthmatics (R03).

The annual average cost was calculated on the basis of consultations with general practitioners and registered prescriptions. As the number of patients decreased over time, a new draw was performed to select controls for each year. The annual average cost was higher in patients with a diagnosis of AD (fig. 2), especially in the first year (+73%). The difference especially was due to consultations, dermatological drugs and other drugs. After 6 years, differences were attenuated but still present (+21% in the ninth year).

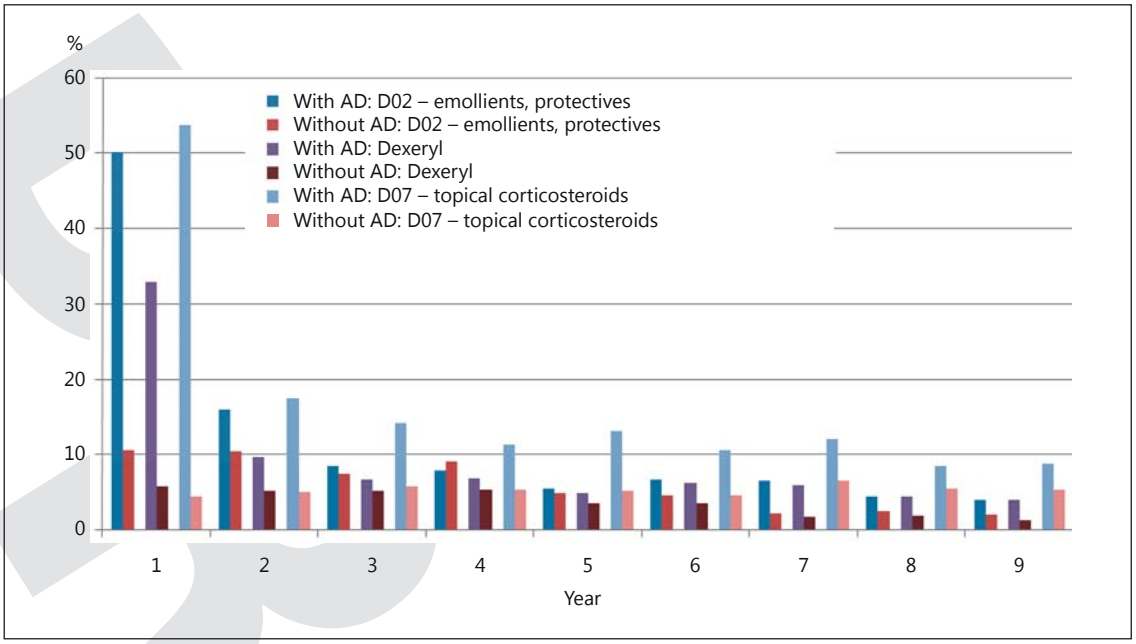

Fig. 1. Prescription of topical steroids in patients with or without initial AD.

In order to select children who were regularly managed by a general practitioner, a subgroup was formed with patients who had an initial diagnosis of AD, a follow-up of 7 years or more and at least one consultation every year. There were 147 patients, 86 boys and 61 girls, in this subgroup. This subgroup was compared to a control subgroup of matched non-AD subjects. The analyses confirmed previous observations. In these patients, the average cost of drug consumption during the first year of follow-up was EUR 140 vs. EUR 94 in controls ($p < 0.05$). The differences ($p < 0.05$) were not only due to dermatological drugs (+ EUR 10), but also to drugs for the digestive and metabolic system (class A: + EUR 13) and systemic anti-infectious drugs (class J: ++ EUR 18). The most prominent differences were seen on vitamins (EUR 10.7 vs. EUR 3.2), systemic antibiotics (EUR 21.7 vs. EUR 12.5) and vaccines (EUR 36.7 vs. EUR 27.9). The average costs of drug consumption decreased over the years to become very close in the seventh year.

Discussion

One of the main interests of this study is the use of a large cohort of patients with AD before the age of 1 year and its comparison for 9 years with subjects without AD. Since the prospective cohort of Williams and Strachan [9], few cohorts of patients with AD have been reported in the literature [17]. A recent report showed that eczema in infancy and childhood usually remits, but in adolescence more often persists into adulthood, and confirmed the value of following up a birth cohort through to early adulthood in revealing long-term associations with eczema [18].

Our study confirms the known natural history of atopy and the concurrence of asthma or allergic rhinitis [2, 9]. We found that the 'atopic march' [19], from AD to these diseases, began early. The study brings new arguments about the association of AD and respiratory infections, which is more debated [20]. Indeed, infants with AD more frequently suffered from these infections than non-AD infants. Although keratoconjunctivitis is known to occur in the atopic context [21], the high number of patients with eye disease among atopic patients may suggest an association with other eye diseases.

The medical cost of patients with AD was found to be higher than that of controls in our study. This difference is not only due to the dermatological disease, but also to associated diseases such as infections, asthma, rhinitis, eye diseases, etc. Interestingly, it was also due to medical prescriptions with limited interest (vitamins) or even with negative effect on AD (antiseptics), although this lat-

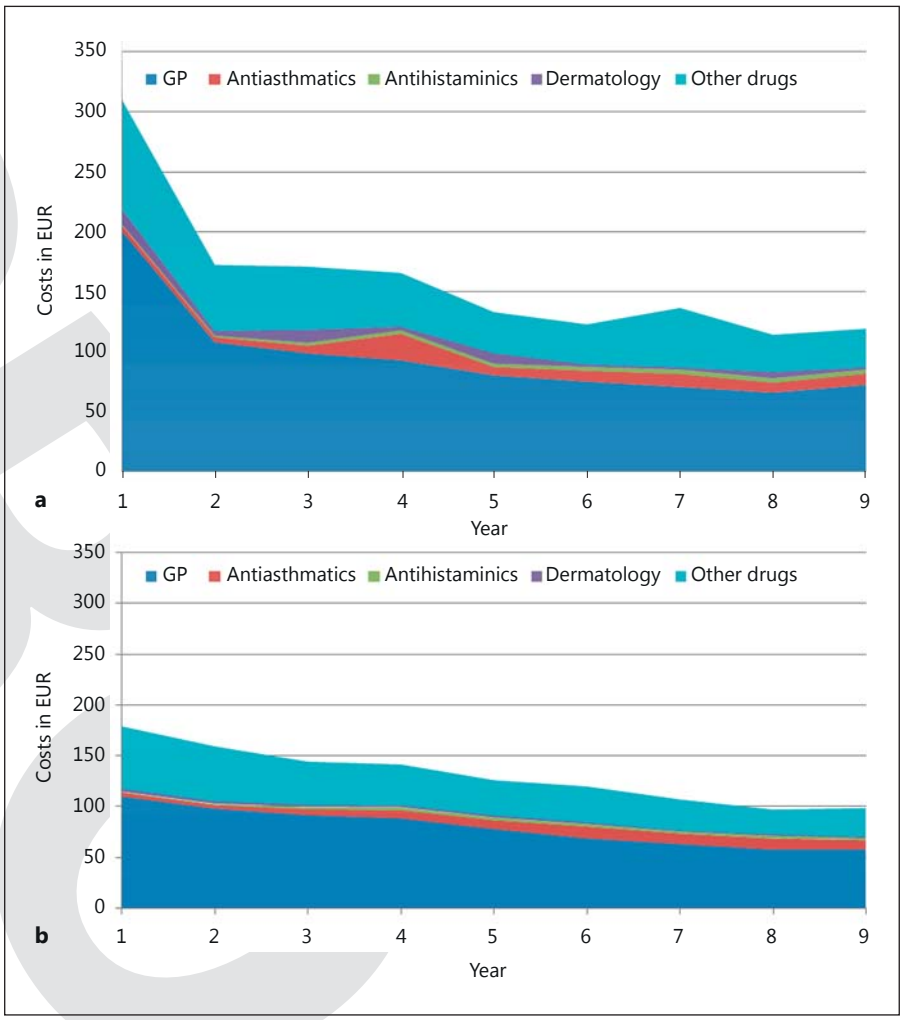

Fig. 2. Annual average cost (societal perspective) of patients with an initial diagnosis of AD (**a**) and controls (**b**). GP = General practitioner.

ter assumption is debated [22]. The cost decreased over time, in line with the fact that AD usually heals after the age of 2 years [2].

Only a few studies exist on the medical cost of AD. Schuttelaar et al. [23] in 2011 studied the cost-effectiveness of the substitution of dermatologists by nurse practitioners. Four other studies are addressed by Mancini et al. [8] in their systematic review. They concluded that few studies estimated the socioeconomic burden of AD comprehensively and measured both direct and indirect costs. They also noted that the high costs of AD were unlikely to diminish in the future, especially in light of the increasing prevalence of the disease, and that the burden on the health care system merits further exploration. Potential actions to address these costs include earlier recognition, appropriate training of primary care physicians in the diagnosis and management of dermatological diseases, especially AD, and increased funding assignment for subspecialist training (i.e., pediatric dermatologists and pediatric allergists) to meet the needs of patients and referring physicians [8]. In addition, they declared that cost-effectiveness studies of disease prevention measures were needed. Such evaluations may increase our understanding of the burden of AD to individuals and society, and support the need for more specific disease prevention and intervention studies. An earlier detection of AD by patients [24] or health care workers [25] and of its severity could be helpful. Prolongation of flare-free time and reduction in severity are not only desirable for the patients, but also of economic interest [26].

Finally, to our knowledge this is the only study to have evaluated the cost of disease in children with AD in a primary care setting. In France, children with AD are more frequently treated by pediatricians or dermatologists than

general practitioners. This may suggest that these young patients who were included in our study probably suffered from less severe disease than those who are treated by specialists, although our data do not allow to exclude an occasional interference with dermatologists or pediatricians. Nonetheless, they had many associated diseases, directly related to the atopy or not, which suggests that AD is not such a mild disease.

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Disclosure Statement

Laurent Misery has been a consultant, speaker or investigator for Pierre Fabre Group, Bailleul-Biorga, Bioderma, Galderma, GSK, Jonzac, Maruho, MSD, Roche-Posay and Sinclair. Xavier Ansolabehere and Nathalie Grandfils are employees of IMS Health. Victor Georgescu and Charles Taieb are employees of Pierre Fabre Group.

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