Type 1 diabetes mellitus and asthma: A follow-up study

To the Editor,

Type 1 diabetes mellitus (T1DM), obesity, and allergic disorders, including asthma, are common chronic diseases with clinical onset in childhood and represent continuously growing health issues.[1] The relationship between these diseases and their influence on lung function is complex. T1DM autonomic neuropathy could decrease pulmonary reactivity, and poor metabolic control impairs lung function, measured by some parameters, including FVC, MMEF, and PEF.[2] BMI is related to decreased respiratory volumes and fluxes.[3] Sensitisation to indoor inhalant allergens is an important risk factor for asthma.[4] Allergic rhinitis (AR) is the biggest risk factor for asthma onset.[5] T1DM and allergy share common pathogenic mechanisms: such as a functional defect of T regulatory cells.[6] Recently, a study compared the bronchodilator response in two well-differentiated groups of children: one including children with AR and T1DM, and the other consisted of children with AR without diabetes.[7] An intragroup analysis demonstrated a statistically significant difference in the pre- and post-bronchodilator FEF_{25-75} change: +7% in children with both disorders and +15.94% in children with rhinitis alone. This study suggested that the reduced response to bronchodilator in children with AR and diabetes might reflect some kind of protective effect against a possible development of asthma. An Editorial commented this study, underlying some significant flaws, such as the small sample of patients as well as the lack of an appropriate follow-up.[8] Moreover, there are conflicting data reported in literature.[9]

For these reasons, a follow-up study was performed to longitudinally investigate the possible asthma onset, also considering AR incidence, sensitisation number, and metabolism, including glycaemic control and BMI.

Forty-three T1DM patients (25 males, median age visit 18.4 years, 1st–3rd q: 16.7–20.8), belonging to the group of 67 patients previously studied,[10] were re-evaluated after six years. HbA1c, insulin requirement, and BMI were measured in all patients at baseline and after six years. In addition, 27 AR patients (17 males, median age visit X years, 1st–3rd q: 16.7–20.8), belonging to the group of 59 AR patients previously studied,[10] were re-evaluated together. Skin prick test and lung function were performed as previously described.[10]

AR was diagnosed by the demonstration of a cause/effect relationship between exposure to the sensitising allergen and the occurrence of nasal symptoms. Asthma diagnosis was based on typical symptoms and confirmed by bronchial obstruction reversibility.

Descriptive statistics were performed; qualitative data were reported as frequencies and percentages; means or medians and first-third quartiles (1st–3rd q) were reported in the case of quantitative variables. BMI values were standardised according to age and gender by the LMS method. Comparisons of qualitative data between the first and last visit were made by the McNemar test. Quantitative measures' comparison between the two groups was made by the Mann–Whitney *U* test and between the first and last visit (paired data) by the Wilcoxon test. Correlations between quantitative variables were evaluated by the Spearman's correlation coefficient (r_s). All tests were two-sided; a *p*-value <0.05 was considered statistically significant. The Statistica package release 9 (StatSoft Corp., USA) was used for the analyses.

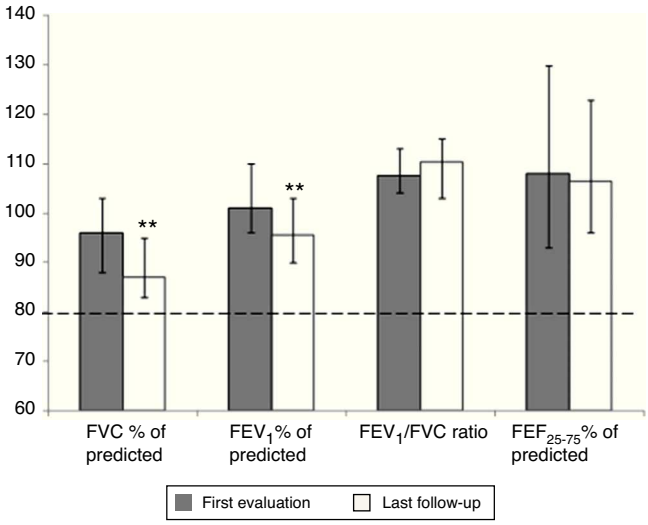

Figure 1 Median values of respiratory parameters at first and last follow-up visit. Bars indicate first and third quartile. $^{**}P < 0.01$.

The local Ethical Committee approved the protocol. Signed informed patients' consent and parental consent (if patient was <18 years old) were obtained.

Diabetic patients – No diabetic patient developed asthma during follow-up. At follow-up, a slight but not clinically relevant worsening in FVC (median value: from 96 to 87, $P = 0.003$) and FEV_1 (median value: from 101 to 95.5, $P = 0.001$) was observed (Fig. 1); however, none of the patients showed bronchial reversibility at bronchodilation test (defined as $\Delta\%$ $FEV_1 > 12\%$ or $\Delta\%$ $FEF_{25-75\%} > 40\%$). $FEF_{25-75\%}$ values remained stable from the first to the last follow-up visit (median: from 108 to 106.5; $P = 0.56$), as well as FEV_1/FVC ratio values (from 107.5 to 110.5; $P = 0.87$). At first evaluation, 29 patients (67.4%) were sensitised, and remained substantially unchanged at follow-up (28 patients, 65.1%); on the contrary, mean number of sensitisations per patient increased from 1.6 to 2 ($P = 0.04$). Sensitisation to dog increased from 0/43 to 8/43, ($P = 0.013$); all these eight patients were sensitised to other allergens at first evaluation. The number of patients with AR increased from 13 at first visit to 20 at follow-up ($P = 0.096$). At follow-up median insulin dose was 0.87 U/Kg/die (1st–3rd q: 0.8–1), and median BMI-SDS was 0.33 (1st q–3rd q: −0.36; +0.87), both substantially unchanged with respect to baseline. Obesity was present in three of 43 patients at the first visit (7%); none of the 43 patients was obese and only two were overweight at the last follow-up. Median HbA1c level was 8% (64 mmol/mol) (1st–3rd q: 7.5–8.4%) (1st–3rd q: 58–68 mmol/mol); with a significant decrease with respect to the first evaluation (8.2%; 1st–3rd q: 7.7–9.1; $P = 0.038$) (median: 66 mmol/mol; 1st–3rd q: 61–76 mmol/mol), demonstrating improved metabolic control. No correlation was found among BMI-SDS, insulin

requirement, HbA1c levels, number of sensitisations, and lung function.

AR patients – Three patients developed asthma during follow-up. At follow-up, a significant decrease of FEV_1 (median value: from 111 to 103, $P < 0.001$), FEV_1/FVC (value: from 112 to 103, $P = <0.01$), and $FEF_{25-75\%}$ (median value: from 118 to 98, $P = 0.001$) was observed (although without clinical relevance), whereas FVC values remained substantially unchanged (median value: from 99 to 97, $P =$ n.s.). Two patients were obese and six were overweight at follow-up.

The present follow-up study demonstrated that T1DM patients followed for six years did not develop asthma, although a slight worsening, but not clinically relevant, in FVC and FEV_1 at follow-up was observed. In any case median levels of all lung function indexes remained persistently above normal values. In particular, FEF_{25-75}, an early marker of bronchial impairment in allergic rhinitis,[5] remained unchanged over the time. A significant increase in the number of patients sensitised to dog or cat and in the mean number of sensitisations per patient was observed. An increment in the frequency of AR was found but without reaching statistical significance. However, these last findings did not promote a possible asthma development. No relationship was found between the degree of metabolic control and auxological parameters and number of sensitisations, lung function parameters or presence of AR. Moreover, median BMI-SDS was in the range of normality and almost all patients had a satisfactory control of diabetes.

On the contrary, three AR patients developed asthma and lung function significantly changed during the follow-up. In addition, BMI-SDS was higher in AR patients than that in diabetic patients.

Some factors might explain why T1DM patients might be protected from asthma development.[11] Firstly, an autonomic nervous system dysfunction reduces sensory neuropeptide release in the airways related to an increased inhibitory neuronal M2 muscarinic receptors function.[12,13] On the contrary, animal diabetes models evidenced that insulin treatment was able to: (a) normalise M2 receptor function (and therefore the vagal-mediated hyper-reactivity);[14,15] (b) reverse the down-regulation of eosinophil accumulation in the airways following allergen challenge;[14] (c) re-establish the bronchial contraction associated with mast cell degranulation and histamine release.[15] However, a more convincing explanation of the possible ''protective'' role exerted by T1DM on asthma occurrence may be the result of the clinically correct management of these patients, followed by well-trained personnel with counselling programmes and educational courses, which included constant controls on compliance and adherence to treatment, on metabolic balance, while physical activity programmes and in general adequate life-style were closely addressed. These issues translate into weight control. In this regard, it has been recently pointed out that overweight/obese AR patients had more altered functional and inflammatory parameters than normal weight ones.[16] In particular, BMI > 25 was a risk factor for: (i) early bronchial airflow limitation (OR 3.81), (ii) high FeNO values (OR 1.96), and BHR (OR 3.29). Therefore, adiposity is a relevant risk factor for asthma development in AR patients. In fact, our diabetic patients had lower BMI values than AR patients.

The main limitation of the present study is the very limited number of patients visited at follow-up, mainly concerning the AR group (it occurred as many of them were followed by adult medical centres and some of them were treated with allergen-immunotherapy: an exclusion criterion).

In conclusion, despite increased allergic rhinitis prevalence, number of sensitisations, and slight lung function deterioration, no subject developed asthma. Good metabolic control as far as weight control could be relevant for this outcome. Therefore, the present study confirms the preliminary findings.

Ethical disclosures

Protection of human subjects and animals in research. The authors declare that the procedures followed were in accordance with the regulations of the responsible Clinical Research Ethics Committee and in accordance with those of the World Medical Association and the Helsinki Declaration.

Confidentiality of data. The authors declare that they have followed the protocols of their work centre on the publication of patient data and that all the patients included in the study have received sufficient information and have given their informed consent in writing to participate in that study.

Right to privacy and informed consent. The authors have obtained the informed consent of the patients and/or subjects mentioned in the article. The author for correspondence is in possession of this document.

Conflict of interest

All authors declare that have no conflict of interest concerning the present study.

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http://dx.doi.org/10.1016/j.aller.2014.01.005

Use of intravenous immunoglobulin for Stevens–Johnson syndrome and toxic epidermal necrolysis in children: Report of two cases secondary to anticonvulsants

To the Editor,

Stevens–Johnson syndrome (SJS) and Lyell's syndrome or toxic epidermal necrolysis (TEN) is the most serious and potentially fatal mucocutaneous reactions in paediatric patients. Both diseases are currently considered hypersensitivity variants of the same disease. The condition is referred to as SJS in patients with typical skin lesions covering less than 10% of the body surface, whereas the cutaneous detachment of more than 30% of the body surface leads to TEN. The intermediate percentages (between 10 and 30%) are defined as an SJS-TEN overlap.[1]

The incidence of SJS and TEN is low and is estimated to be between 1.5 and 2.0 cases per million people per year in the general population. Although these reactions are infrequent, they can cause grave sequelae and even lead to death.[1]

Various aetiological factors have been implicated as precipitating the hypersensitivity reactions that occur mainly in SJS and TEN, particularly infectious agents, systemic diseases, neoplasms, radiation therapy, vaccines, and multiple drugs, identifying these agents as causative in 65% of cases. More than 200 drugs have been included as possible causes in the development of these diseases. The most common of these drugs are anticonvulsants, antibiotics (such as sulphonamides and penicillins), allopurinol, and non-steroidal anti-inflammatory drugs (NSAIDs).[1,2]

Although the pathogenesis of both entities (SJS-TEN) is not yet fully understood, it is recognised that the final mechanism is the apoptosis of keratinocytes. This phenomenon is due to the Fas/FasL interaction, cytotoxic T cells, TNF-alpha, and nitric oxide synthase.[2]

There is no specific treatment for SJS and TEN. The first step is to suspend the use of the drug suspected to be the cause. Concurrently, supportive care should be administered, and any complications should be treated. The state of hydration and nourishment of the patient is essential for the disease management.[1,2] Considering the immunological basis of SJS and TEN, the use of intravenous immunoglobulin (IVIG) as a treatment in paediatric patients has been proposed, with certain studies reporting successful results.[2] In this work, two SJS-TEN patients, in whom IVIG was successfully used, are presented, and the existing literature is reviewed.

The first case was a four-year-old male patient diagnosed with Doose syndrome, who was prescribed Lamotrigine (Lamictal) for generalised atonic and tonic myoclonic seizures that were difficult to stabilise. Three weeks later, he was admitted, suffering from eight days of disease development characterised by fever up to 40 °C, headache, asthenia, adynamia, and pruritus, as well as the onset (on the 5th day) of a generalised dermal eruption on the face, with progression to the trunk, limbs, and genitals. On admission, the patient presented with widespread dermatosis manifested by papuloerythematous injuries and blisters that were mainly on the face, neck, trunk, limbs, and genitals;