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Near-fatal asthma phenotype in the ENFUMOSA Cohort

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Summary

Background Near-fatal asthma (NFA) is characterized by severe asthma attacks usually requiring intensive care unit admission. This phenotype of asthma has been studied mainly in acute conditions.

Methods The aim of our study was to compare the clinical, functional and inflammatory characteristics of NFA patients with mild to severe asthmatics in stable conditions. We recruited 155 asthmatic patients from five centres of the European Network for Understanding Mechanisms of Severe Asthma: 67 patients with mild-to-moderate asthma controlled by low/medium doses of inhaled corticosteroids; 64 with severe asthma that, despite treatment with high doses of inhaled corticosteroids, long-acting β_2 -agonists and for 1/3 also with regular oral corticosteroids, had at least one asthma exacerbation in the previous year; 24 with an NFA episode in the previous 5 years in the absence of inclusion criteria for the previous groups. All the patients were examined in stable conditions.

Results NFA patients were taking less corticosteroids and were less compliant to prescribed asthma medications than the other two groups of patients. Lung function, blood gases, atopic status, sputum and blood inflammatory cell count of NFA patients were similar to mild-to-moderate, but not severe, asthmatic patients.

Conclusions In stable conditions patients with an NFA attack in the previous 5 years cannot be distinguished from patients with mild-to-moderate asthma, while they are different from severe asthmatics both in terms of lung function and of airway inflammation. The risk factor that characterizes this group of patients is reduced usage of prophylactic corticosteroids.

Keywords inflammation, near-fatal asthma, severe asthma, sputum

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Introduction

Near-fatal asthma (NFA) represents the most severe clinical phenotype of asthma, outside of fatal asthma [1–3]. There are no universally agreed diagnostic criteria for NFA [1]. NFA is usually defined by the appearance of various events such as cardiorespiratory arrest, hypercapnia, acidemia, the need for orotracheal intubation and mechanical ventilation, or admission to an intensive care unit [4, 5]. However, an episode of hypercapnia occurs 10–20 times more frequently than the need for orotracheal intubation and mechanical ventilation and does not necessarily imply a poor prognosis [3]. Similar to fatal

asthma, most of these patients have slow-onset NFA and, on average, no more than one-third of the patients has rapid onset NFA [4, 5].

There have been no large-scale prospective multi-centre studies in unselected clinical populations to define the incidence of NFA and its relationship to severe persistent asthma and fatal asthma [1]. The long-term prognosis after an NFA episode depends in part on how such event is defined, but appears to be poor [3].

Several retrospective, mainly case-control, studies have identified multiple risk factors for NFA [2, 6–15], but these patients have never been fully characterized when in stable condition.

A report from the European Network for Understanding Mechanisms of Severe Asthma (ENFUMOSA) indicates

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that patients with severe persistent asthma, characterized by at least one asthma exacerbation in the last year despite treatment with high dose inhaled corticosteroid associated with long-acting β_2 -agonists or theophylline and/or oral corticosteroids, have chronic irreversible air-flow limitation, neutrophilic inflammation and low prevalence of atopy when compared with patients with well-controlled mild-to-moderate asthma [16].

During the ENFUMOSA study, severe asthmatic patients that experienced one NFA episode within the preceding 5 years were also included among severe asthmatics, even when they did not fulfil the criteria of severity previously indicated.

These subjects were then not included in the first report of the ENFUMOSA cohort [16] and were analysed separately. Here we report the clinical, functional and inflammatory characteristics of these patients and compare with mild-to-moderate and severe persistent asthma.

Materials and methods

Study design and subjects

The study population was selected in parallel with the asthmatic patients enrolled in the ENFUMOSA study [16].

From 1998 to 2000 the ENFUMOSA study group recruited across Europe patients with severe and mild-to-moderate asthma. The study was performed in 12 centres belonging to nine European countries [16].

Patients were divided in three groups:

- (1) *NFA*: history of at least one respiratory arrest and/or $\text{PaCO}_2 \geq 50$ mmHg within the 5 years before study entry, in the absence of inclusion criteria for severe and control groups.
- (2) *Severe asthma*: at least one asthma exacerbation in the last year, despite treatment for at least a year with ≥ 1200 $\mu\text{g/day}$ beclomethasone or equivalent, long-acting β -agonists or theophylline, with or without oral corticosteroids (≥ 5 mg/day prednisone or equivalent for at least 3 months before the start of the study).
- (3) *Control group*: well controlled mild-to-moderate persistent asthma: absence of exacerbations in the last year, treatment with low to medium dose of inhaled corticosteroids (< 1200 $\mu\text{g/day}$ beclomethasone or equivalent).

Smokers with a smoking history of ≥ 5 pack/years were excluded from the study.

At enrolment, in addition to complete physical examination, each subject was asked to complete a clinical questionnaire adapted from the expert system for asthma severity developed in Montpellier [17]. This standardized the collection of data on the presence and the severity of

the asthma symptoms, the medical history and on the compliance to prescribed asthma medications. The local Ethics Committees of all Centres approved the study.

Pulmonary function

Pulmonary function tests were performed according to published guidelines and were expressed as percent predicted values [16, 18]. To obtain the carbon monoxide diffusion constant (K_{CO}), carbon monoxide transfer factor (DL_{CO}) was measured using the single-breath method and the result divided by the alveolar volume ($DL_{\text{CO}}/V_A = K_{\text{CO}}$).

Peripheral blood measures

Venous blood was taken using ethylenediamine tetraacetic acid filled vials for measurement of the total and differential white blood cell count using a standard Coulter counting. An arterial puncture was performed, when the patient, at rest, was breathing room air for measurement of arterial blood gases, accordingly to standard clinical methods.

Atopic status

All patients underwent epicutaneous skin-prick testing to common aeroallergens, including common local aeroallergens chosen according to the prevalence of allergens in each country, as previously described [16]. The maximum weal diameter and its perpendicular diameter were measured at peak response 15-min post-skin puncture. A positive (histamine) and a negative (diluent) control were applied on the same forearm. A positive response was taken as > 3 mm larger than the negative control.

A venous blood sample was taken for total serum IgE measurement by fluoroimmunoassay [16].

Sputum collection and analysis

Sputum was induced using a standardized protocol in which hypertonic followed by hypertonic saline (3%, 4% and 5%) was administered after the inhalation of 200 μg of salbutamol. After each 5-min inhalation, spirometric tests were performed, and subjects were then asked to rinse their mouths and throats and to expectorate sputum into a Petri dish. The more viscid portions were selected for sputum cell count as previously described [16].

Data analysis

Statistical analysis of normally distributed data are reported as mean $\pm$ standard error and skewed data by median [interquartile range (IQR)]. Comparisons of continuous variables between subgroups were made using the parametric ANOVA followed, if significant, by between-

groups tests with Student *t*-test, and the non-parametric Kruskal–Wallis followed, if significant, by Mann–Whitney U-tests when appropriated. Bonferroni's correction was applied when appropriated. Categorical binary variables were compared using the χ^2 test. A probability value of <0.05 was considered statistically significant.

Results

Clinical characteristics

Only five of the 12 centres participating the ENFUMOSA study had patients recruited in the NFA group. These five centres were all located in the South Europe region: Barcelona, Spain (six NFA, eight severe, 15 control); Crete, Greece (six NFA, 11 severe, 22 control); Ferrara, Italy (five NFA, 14 severe, four control); Montpellier, France (six NFA, 15 severe, 13 control); Palermo, Italy (one NFA, 16 severe, 13 control).

Therefore, the population recruited in these five centres during the ENFUMOSA study was considered for statistical analyses and comparisons.

A total of 155 patients were recruited, of which 64 had severe persistent asthma, 67 had mild-to-moderate persistent asthma and 24 had a history of an NFA episode within 5 years before study entry, in the absence of inclusion criteria for severe and control groups. Groups were comparable in terms of age, but not of gender, since as previously reported, females dominated the severe persistent asthma group [16] (Table 1).

According to the inclusion criteria, none of the mild-to-moderate asthmatics were treated with high-dose inhaled corticosteroids and long-acting β -agonists. Less than half of NFA patients were taking inhaled corticosteroids (Table 1). In the NFA group the majority (58.8%) of patients treated with long acting inhaled β_2 agonists (LABA) were not receiving ICS.

Compared to severe and mild-to-moderate asthmatics, NFA patients admitted significantly more frequently to forgetting taking their asthma medications as assessed by a specific item in the medical history section of the clinical questionnaire (15/24, 18/64 and 23/67 admitted to forgetting taking asthma medications in NFA, severe and mild-to-moderate asthma groups, respectively, $P < 0.01$ NFA vs. severe asthma and $P < 0.05$ NFA vs. mild-to-moderate asthma).

In the month preceding recruitment, a significantly higher proportion of NFA patients (18/24) and of severe asthmatics (54/64) reported asthma symptoms (wheezing and/or dyspnoea; any intensity) as compared with mild-to-moderate asthma (30/67), as assessed by a specific item in the medical history section of the clinical questionnaire ($P < 0.05$ mild-to-moderate asthma vs. NFA and vs. severe asthma).

Atopy status

Patients with severe persistent asthma showed lower prevalence of positive skin prick tests, and this difference was significant in the comparison to mild-to-moderate asthma (Table 1). Severe asthmatics had lower levels of total IgE as compared with both NFA and mild-to-moderate asthmatics (Table 1).

Lung function and blood gas characteristics

No difference was found between patients with NFA and those with mild-to-moderate asthma (Table 2). Forced expiratory volume in 1 s (FEV₁), FEV₁/forced vital capacity (FVC) ratio and K_{CO} were lower and residual volume higher in patients with severe asthma as compared with the other two groups. FVC was significantly decreased in severe vs. mild-to-moderate asthmatics (Table 2). Patients with NFA showed PaO₂ values similar to mild-to-moderate asthmatics and significantly higher compared with severe asthma (Table 2).

Sputum and blood inflammatory total and differential cell count

Patients with severe asthma had higher total sputum cell counts when compared with NFA and mild-to-moderate asthmatics (Table 3). Sputum neutrophil percentage was significantly elevated in severe as compared with mild-to-moderate asthma (Table 3).

Similarly, total and differential cell counts in peripheral blood showed increased total white blood cells and percent neutrophils in severe as compared with NFA and mild-to-moderate asthma (Table 3).

Discussion

In this study we found that patients with a history of NFA episodes in the previous 5 years have clinical, functional and inflammatory characteristics of mild-to-moderate asthmatics and that they are different from severe asthmatics. As compared with both severe and mild-to-moderate asthmatics, NFA patients had lower adherence to anti-asthma treatment.

In accordance with the ENFUMOSA study [16], patients with severe asthma had more compromised lung function. Our data showing that NFA patients have lung function and blood gas data comparable to mild-to-moderate asthmatics confirm and extend previous reports (mostly limited to FEV₁ in NFA [7, 8, 12]).

For the first time we report sputum and peripheral blood inflammatory total and differential cell count in NFA when in a stable condition. To our surprise we did not find any significant difference between NFA and mild-to-moderate persistent asthma in the sputum and peripheral

Table 1. Patient clinical characteristics

	NFA	Severe	Mild to moderate
No. of patients	24	64	67
Age	43.2 (5.6)	45.4 (7.4)	43.9 (8.6)
Male/female	8/16	15/49	30/37 [†]
<i>Treatment</i>			
Oral corticosteroids	4.1% [†]	29.7%	0 ^{††}
Inhaled corticosteroids	37.5 % ^{**††}	100%	100
Mean dose (µg beclomethasone equivalents)	682 (153)	1790 (615)	715 (226)
Short-acting inhaled β ₂ -agonists	85.7%	95.3%	94%
Long-acting inhaled β ₂ -agonists	70.8% ^{**}	100% ^{**}	0
Short-acting anticholinergics	12.5%	14%	5.9%
Theophylline	8.3%	23.4%	0 [†]
Others	12.5%	7.8%	4.5%
<i>Atopy</i>			
Positive skin prick test [§]	62.5%	42.1%	67.1% ^{††}
Serum IgE (kU/L)	141.8 [61.6–283.2] [†]	89.9 [43.8–158.2]	168.2 [87.5–294.9] ^{††}

Data are expressed as number or percentage of cases or mean (SD) or median [95% CI].

^{**} $P < 0.01$ vs. mild-to-moderate group.

[†] $P < 0.05$ vs. severe group.

^{††} $P < 0.01$ vs. severe group.

[§]To at least one tested allergen.

NFA, near-fatal asthma.

blood cell counts. Conversely, in accordance to the general findings of the ENFUMOSA [16], severe persistent asthma was associated with increased neutrophils both in sputum and in peripheral blood.

Notably, although receiving less inhaled glucocorticoids NFA patients did not display a higher sputum eosinophil count than mild-to-moderate group. This would suggest that their inflammatory background in

the airways is relatively mild when analysed in stable condition. It obviously does not exclude a burst of inflammation at exacerbations, particularly when severe. Interestingly, despite very high dose of inhaled glucocorticoids the patients with severe asthma still have markedly raised sputum eosinophilia (around 5% in this study and more of 10% in the previous ENFUMOSA report [16] as compared with values found in healthy subjects

Table 2. Lung function and blood gases

	NFA	Severe	Mild to moderate
<i>Lung function</i>			
FEV ₁ % predicted	83.1 (19.2)*	73.5 (17.6)	88.2 (17.2)**
FEV ₁ post-bronchodilator (%) predicted	89.3 (15.8)*	80.1 (15.2)	95.3 (18.0)*
FEV ₁ /FVC post-bronchodilator (%) predicted	88.3 (9.8)*	81.2 (12.5)	91.2 (10.6)**
FVC% predicted	101.2 (14.9)	94.4 (16.6)	101 (15.9)*
RV% predicted	118.7 (15.2)*	130.1 (15.8)	116.4 (13.5)**
TLC% predicted	105.4 ± 3.2	106.9 ± 1.9	104 ± 1.7
K _{CO} % predicted	89.7 (15.1) [§]	82.8 (14.4)	95 (13.1)*
<i>Blood gases</i>			
Pa,O ₂ (kPa)	12.10 (1.47)*	11.30 (1.42)	12.43 (1.21)**
Pa,CO ₂ (kPa)	5.15 (0.6)	5.17 (0.6)	5.21 (0.5)
PH	7.40 (0.04)	7.42 (0.02)	7.41 (0.03)

Data are expressed as mean (SD).

* $P < 0.05$ vs. severe group.

** $P < 0.01$ vs. severe group.

[§] $P = 0.076$ vs. severe group.

NFA, near-fatal asthma; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; TLC, total lung capacity; RV, residual volume; K_{CO}, carbon monoxide diffusion constant; Pa,O₂, arterial oxygen tension; Pa,CO₂, arterial carbon dioxide tension.

Table 3. Inflammatory cells

	NFA	Severe	Mild to moderate
<i>Sputum cell counts</i>			
Total sputum cells $\times 10^6/\text{mL}$	1.8 [1.1–3.3]*	4.66 [1.65–8.5]	2.96 [1.34–5.02]*
Neutrophils (%)	30.3 [11.1–43]	41 [13.5–59.5]	26 [9.8–40.4]*
Eosinophils (%)	4.2 [0.72–11.6]	5.85 [0.95–10.85]	4 [1.15–8.52]
Macrophages (%)	49.9 [21.5–72]	45.5 [19.2–67.6]	50.5 [26.2–73.4]
Lymphocytes (%)	1.3 [0–5]	1.8 [0.3–3]	1.2 [0–3.4]
<i>Peripheral blood</i>			
Total WBC ($\times 10^3/\text{mL}$)	6.68 (1.7)*	8.48 (1.2)	6.53 (0.7)**
Neutrophils (%)	56.8 (4.3)**	62.4 (5.5)	57.0 (6.5)**
Monocytes (%)	7.4 (2.5)	6.7 (1.8)	7.2 (1.6)
Lymphocytes (%)	30.9 (3.7)	26.5 (5.6)	31.1 (5.1)
Eosinophils (%)	4.2 (2.0)	3.5 (2.4)	3.9 (2.2)
Basophils (%)	0.7 (0.7)	0.6 (0.7)	0.7 (0.8)

Data are median [95% CI] or mean (SD).

* $P < 0.05$ vs. severe asthma.

** $P < 0.01$ vs. severe asthma.

NFA, near-fatal asthma; WBC, white blood cells.

(<0.5%). Therefore sputum eosinophilia in severe asthma can be regarded as resistant to inhaled glucocorticoids.

Another novel finding of this report leads to the same concept, i.e. the similar prevalence of atopy between the NFA and mild-to-moderate persistent asthma. At variance, in accordance with the ENFUMOSA study [16] we found that a low prevalence of atopy is a characteristic profile of the severe phenotype of asthma, suggesting that mechanisms different from atopy might be more relevant to the pathogenesis of severe asthma. The differences observed in this study in terms of airway/systemic inflammation when severe asthma was compared with less severe forms of the disease are in line with this interpretation. Thus, NFA cannot be simply considered as a subgroup of severe asthma, but it represents a different disease entity that cannot be distinguished for mild asthma when in stable conditions.

NFA patients were less treated than the other groups: less than half of NFA patients were taking inhaled corticosteroids. According to our inclusion criteria only patients with a history of at least one NFA episode in the previous 5 years, in the absence of inclusion criteria for severe and control groups, were included in the NFA group. Intriguingly, out of the 131 patients here considered outside the NFA group, only one (belonging to the severe group) reported an NFA episode in the previous 5 years. This suggests that when asthma, including severe asthma, is properly treated, the risk for near fatal episodes is reduced, in agreement with previous studies indicating that therapy with bronchodilators alone may lead to loss of asthma control, including severe asthma exacerbations and hospitalizations [19]. Noteworthy, despite 75% of NFA patients had asthma symptoms in the preceding month, the vast majority of this group of patients admitted to forgetting their asthma medications as assessed

by a specific item of the clinical questionnaire, indicating that a lower adherence to treatment, which might be associated with cultural/social/regional differences, could be an issue for loss of disease control, and for severe-up to near fatal exacerbations following the exposure to trigger factors. Indeed, a previous study documented that poor compliance to therapy is a characteristic feature of patients hospitalized with severe asthma, including NFA [7]. A recent systematic meta-analysis of risk factors associated with NFA did not demonstrate that exposure (dose independent) to inhaled corticosteroids has a clear protective effect against NFA [9]. However, when exposure was measured using a dose-dependent formula there was an overall protective effect of inhaled corticosteroids, as previously indicated in the study of Suissa et al. [20].

Interestingly, we observed that the majority of NFA patients treated with LABA were not receiving inhaled glucocorticoids, which is in line with the concerns recently raised on the use of LABA without inhaled glucocorticoids [21].

An unexpected finding of our study is represented by the fact that patients with NFA were found and enrolled only in countries of the South Europe area. Possible explanations might be related to the exposure to different allergens in the different geographical areas of Europe and to the above-mentioned regional cultural/educational differences particularly in relation to anti-inflammatory regular treatment compliance. We recognize that because of the size of our group the spectrum of NFA might only partly be represented in this study.

In conclusion, this study has highlighted that, when in stable condition, patients with a previous history of NFA episodes, at variance with severe asthmatics, have clinical functional and inflammatory characteristics similar to patients with mild-to-moderate asthma. Reduced

compliance towards the regular treatment with inhaled glucocorticoids is an attitude that characterizes NFA patients. Further studies are required to explore the mechanisms by which a patient with apparently mild-to-moderate asthma develop a near-fatal asthmatic exacerbation.

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