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Nasal polyposis, bronchial asthma and analgesic intolerance

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SUMMARY

A retrospective case-control study was conducted in 1042 arbitrarily selected bronchial asthma patients (197 patients with AIA and 845 controls with normal analgesic tolerance). Two thirds of all AIA patients reported one or more diseases in the region of the upper airways. Quite different from the control group, highly significant coincidence of AIA with nasal polyposis (42.6%), paranasal sinus diseases (39%), and chronic rhinitis (42,1%) was recorded in the AIA patients. AIA was characterized by stronger inclination to recurrence of nasal polyps and more frequent negative impact of polypectomy upon the course of asthma. The classical triad of "intrinsic asthma – nasal polyps – analgesic intolerance" was established in 39% of the AIA patients. The pathogenetic factors causing the association of asthma with polyps and the even more strongly association of AIA with polyps are still unknown. The presumed pathogenetic relationship between chronic hyperplastic alterations in the upper airways and the phenomenon of AIA might be caused by disorders in phospholid metabolism (liberation of arachidonic acid, lipoxygenase products, radical mechanisms).

INTRODUCTION

Fits of bronchial asthma following intake of an analgesic were reported as early as the beginning of this century. The characteristic pattern of this syndrome, which primarily included chronic hyperplastic alterations of the upper airways and alcohol intolerance has often been defined under the term of "aspirin-induced asthma". However, to all intents and purposes, acetylsalicylic acid is not the only syndrome-triggering substance. All other non-steroidal antiphlogistics with prostaglandin-synthesis-inhibiting action, mainly pyrazolone derivatives, must be taken into due consideration as well (Slapke et al., 1983). Hence, the syndrome can be more thoroughly characterised by the term of "analgesic-induced asthma" (AIA). AIA is quite often not identified and is then a severe danger to the patient afflicted. Minimal analgesic doses are often sufficient to cause severe, even life-threatening asthma fits. The typical phenomena of this non-allergic form of asthma, resembling immediate allergic Type I reaction according to Coombs and Gell, have been described in many publications (Chafee et al., 1974; Farr et al.,

1978; Samter et al., 1968). The AIA incidence data recorded from random sampling of bronchial asthma patients were found to differ widely. This difference was caused by the usage of different diagnostic methods and ranged from 2.3 to 44% (Bruce-Pearson, 1963; Weber et al., 1979).

Knowledge regarding epidemiological correlations and pathogenetic mechanisms has not been safely established yet. The comparability of epidemiological results is a bit doubtful in view of the wide variety of methods used by different authors. Still, with regard to pathogenesis, there seems to be a wide-ranging agreement as to the effect that AIA is probably not based on immunological mechanisms (Schlumberger, 1982; Slapke et al., 1982). Certain aspects relating to regulation of the metabolism of arachidonic acid are obviously of crucial importance to the pathogenesis (Chand et al., 1981; Ito et al., 1981; Slapke et al., 1982, 1983). AIA is relatively often preceded or, characteristically, accompanied by rhinitis, sinusitis, and nasal polyposis (Holopainen et al., 1979; Moloney et al., 1980). The triad "nasal polyposis - intrinsic asthma - aspirin intolerance" had been actually described in detail by Widal et al., as early as 1922. However, other authors (Speer et al., 1981; Weber et al., 1979) have expressed some doubt about the existence of a specific association of AIA with changes in the upper airways. Just as controversial findings have been reported on the inclination of recurrence of nasal polyposis (Chafee et al., 1974; Grzelewski-Rzymowska et al., 1981; Schlumberger, 1982) and on the relevance of polypectomy to the course of AIA (Brown et al., 1979; Schenk, 1974). The authors have tried to verify the existence of relationships between chronic hyperplastic alterations in the upper airways and AIA. Their study also included an epidemiological survey.

MATERIAL AND METHODS

This study was based on the modified experimental arrangement of a case-control (retrospective) study. Most of the subjects were out-patients whose bronchial asthma had been diagnosed as their primary ailment. From these patients 1042 subjects were selected by random sampling. Data were compiled by means of a computer-assisted documentation of case histories (questionnaire). One coherent reply model was attached to all questions. All data were recorded and compiled under the supervision of the physician in charge of the treatment. The interviewers received special training to ensure methodically and uniform questioning. A total of 1440 parameters was explored. Some of these 1440 parameters were logically interconnected by means of a computer programme to come out at a total of 100 parameters. Included in the latter were data on family case histories, course of asthma, severity of the disease, disease of the upper airways, polypectomy, therapeutic medication, causative analgesics as well as intolerance reactions to foodstuffs, foodstuff additives (preservative agents and colouring matter), and alcoholic drinks.

Statistical analysis was carried out using basic methods for case-control studies. We compared the relative incidence of the parameters tested in the group AIA subjects with that in the group of subjects with "non-analgesic asthma". We applied the formula by Ascombe (1956) to estimate the parameter Ω("relative risk rate") in order to be able to describe the ratio of relative incidences. The zero hypothesis, $Ho: \Omega = 1$ (no difference between the two groups regarding occurrence of a given parameter) was checked by a common Chi-square test, to which a correction was added to ensure continuity. The approximate 95% confidence interval, as in Cornfield (1956), was additionally calculated by iteration for parameter Ω. For this parameter an initial value was estimated as described by Miettinen (1976). An account of these methods has been given by Fleiss (1979). In this paper the results are presented which were obtained from studies of the selected parameters which were considered relevant to the problem.

RESULTS

Unambiguous information as to the presence of AIA was recorded by 197 of the 1042 subjects (≙ 18.9%). The sex ratio was highly significant: women accounted for 71% of the AIA patients and for 58% in the control group of bronchial asthma patients with normal analgesic tolerance (Table 1).

Table 1. Percentual sex ratio of analgesic-induced ashtma (AIA) to asthma without analgesic intolerance ($\overline{AIA}$)

	male	female
AIA (n = 197)	29	71
$\overline{AIA}$ (n = 845)	42	58

In contrast with the data described by Santiago et al. (1976) as well as with the authors' own observations in the past, no evidence could be produced to the effect that intrinsic asthma was a clearly typical "primary disease" of AIA, except for those AIA patients with concomitant nasal polyps (see details below). The authors recorded a frequent occurrence of AIA together with nasal polyposis. It must also be expected that AIA patients are more liable than others to recurrence of nasal polyposis. The effect that surgical removal of nasal polyps had on the course of asthma, was more often negative than the effect it had on patients with normal analgesic tolerance. The outcome of the study of the parameter "paranasal sinus diseases" suggested a close correlation with AIA too. A more differentiated examination of additional characteristics revealed a pronounced liability by AIA patients to recurrence of paranasal sinus disease: occurrence of maxillary sinus and ethmoidal surgery was reported by 23.4% of all AIA patients interviewed. They differed with high significance from the control group (7.6%). Chronic rhinitis frequently accompanied AIA (Table 2). This phenomenon was striking.

Table 2. Relative incidence and relative risk, Ω, of various anamnestic and clinical parameters.
Ωu, Ωo: Cornfield's 95-per-cent approximate confidence interval
Ω* : p 0.05 for Ho : Ω = 1
AIA : analgesic-induced asthma
$\overline{AIA}$: asthma without analgesic intolerance

parameter	AIA (%) n = 197	$\overline{AIA}$ (%) n = 845	Ω	Ωu	Ωo
nasal polyposis	42.63	25.74	2.89*	2.052	4.062
paranasal sinus diseases	39.08	22.36	2.23*	1.582	3.135
chronic rhinitis	42.13	25.33	2.15*	1.535	3.002
coincidence in time	21.59	6.80	3.86*	2.367	6.266
one removal of nasal polyps	19.29	12.31	1.71*	1,108	2.612
repeated removal of nasal polyps	19.8	5.68	4.10*	2.535	6.622
asthma after polypectomy	7.11	2.84	2.65*	1.258	5.393
repeated fits a day	16.24	12.54	1.36	0.859	2.120
permanent corticosteroid medication	42.13	28.28	1.85*	1.324	2.574

When coupling several parameters the incidence of a typical "analgesic-asthma triad" among AIA patients was estimated to be 39% (n = 77). In other words, the triad of "intrinsic asthma - nasal polyposis - analgesic intolerance" was present in about 90% of those AIA patients who had concomitant nasal polyposis (n = 84). A three-dimensional statistical approach (contingency tables) was additionally used to find out if correlations could be statistically secured between AIA, chronic hyperplastic alterations in the upper airways, and severe course of asthma (with severity being defined by the criteria of "several fits on one and the same day" and/or "permanent peroral application of corticosteroids"). Chronic hyperplastic changes in the upper airways were seen in about 64% of the AIA patients (n = 126), whose ailments were rhinitis and/or sinusitis and/or polyposis. Almost 50% of these patients were additionally afflicted with severe bronchial asthma. In the control group, on the other hand, signs of chronic hyperplastic changes were seen only in 39.6% of the patients (n = 232 out of n = 845), and severe cases of asthma were found in only 37.8%.

DISCUSSION

One or several of the diseases located in the upper airways (rhinitis, sinusitis, polyposis) were affirmatively reported by almost two thirds of the AIA patients. A differentiated definition of "chronic hyperplastic changes" leads to an observation that AIA frequently occurs nasal polyposis (42.6%), paranasal sinus diseases (39%), and chronic rhinitis (42.1%). This finding is fully congruent with what had been reported by other authors (Chafee et al., 1974; Grzelewska-Rzymowska et al., 1981; Holopainen et al., 1979; Moloney et al., 1980), except for some authors (Speer et al., 1983; Weber et al., 1979). Our own results have suggested AIA to be

quite often associated with severe asthma, even more so when it is accompanied by polyposis. Contra-dictory views have been expressed in the literature on the liability of AIA patients to recurrent polyposis, the effects of polypectomy on the course of asthma, and the incidence of the "analgesic-asthma triad" (Chafee et al., 1974; Grzelewska-Rzymowska et al., 1981; Schenk, 1974). Results obtained so far appear to support the view of higher liability of such patients to recurrence of nasal polyps and paranasal sinus diseases. Another characteristic of AIA is that polypectomy more frequently has a negative impact on the course of asthma. Taking the present knowledge into consideration no new facts can be added to the first description of the "triad" by Widal et al., (1922). Findings which indicate the presence of the classical triad "intrinsic asthma - polyposis - analgesic intolerance" were recorded by the authors of this study in 39% of their AIA patients. Because of methodical reasons it was not possible to draw accurate conclusions from the retrospective study as to "typical courses" of AIA in certain phases as recorded from individual patients (rhinitis - sinusitis - polyposis - asthma). Although 90% of AIA patients with concomitant polyposis do show a classical triad and, consequently, suffer from infectious asthma, as has been found in studies so far conducted, this does not mean that atopic diseases are rare in AIA patients (Delaney, 1973). Our own findings are likely to suggest that AIA patients with nasal polyposis are also characterised by extremely high "sensitivity to analgesics". This implies an extremely low threshold dose beyond which asthma can be triggered (unpublished results). It is, therefore, important to see that the upper airways are also involved, in one third of all acute "analgetic-asthma reactions". Quite obviously this is an indicator to the existence of a link between AIA and chronic hyperplastic alterations in the upper airways.

We have reported elsewhere (Slapke et al., 1982, 1983) that the causes of AIA should be ascribed to changes in the release and conversion of arachidonic acid from membrane phospholipids. However, the pathogenetic background behind the association of asthma with polyps have so far remained fully obscure and so has the even more strongly pronounced association of AIA with polyposis remained obscure. Moloney et al. (1980) presumed an involvement of the HLA system, though his presumption was merely based on observations with three patients. Yurchak et al., (1970) discussed the primary polyposis-causing role of the analgesic. Since changes in phospholipid metabolism seem to be of crucial importance to the pathogenesis of AIA (Chand et al., 1981; Ito et al., 1981; Slapke et al., 1982, 1983; Szczeklik et al., 1977), the assumption seems to be somewhat justified that the development of chronic hyperplastic changes was also linked to that process. Thus, the following explanation might be found for the accompanying phenomenon of "chronic hyperplastic alterations in the region of the upper airways": the majority of AIA patients with nasal polyposis suffers from intrinsic asthma. Induction of myeloperoxidase in neutrophils with polymorphous nuclei,

resulting from recurrent infections (Clark et al., 1981) leads to the formation of "free radicals" (Kitagawa et al., 1980). The extreme concentrations of hydroperoxides of arachidonic acid in AIA patients are potent radical formers. Taking this into consideration, the radical mechanisms might well offer an explanation for alterations in connective tissue (Bradley et al., 1980) with a growing hyperplastic component in them.
These are theoretical considerations which call for experimental verification.
The conclusion may be drawn that a statistically secured correlation does exist between AIA and polyposis and that knowledge about this correlation should be relevant to medical practice. Further studies will have to be conducted for the purpose of finding out, if the pathogenetic relationship between these two phenomena is based on disorders in phospholipid metabolism (liberation of arachidonic acid, lipoxygenase products, radical mechanisms).

ZUSAMMENFASSUNG
In einer retrospektiven Fall-Kontroll-Studie an 1042 nicht-ausgewählten Asthma-bronchiale-Patienten (197 Patienten mit AIA und 845 Patienten mit normaler Analgetikatoleranz /Kontrolle/) gaben etwa 2/3 alle AIA-Patienten eine oder mehrere Erkrankungen im Bereich der oberen Luftwege an. Im einzelnen bestand im Vergleich zur Kontrollgruppe eine hochsignifikante Koinzidenz des AIA mit Polyposis nasi (42,6%), Nasennebenhöhlenerkrankungen (39%) sowie chronischer Rhinitis (42,1%). Charakteristisch für das AIA ist die höhere Rezidivneigung von Nasenpolypen sowie der haufiger negative Einfluß der Polypektomie auf den Asthmaverlauf. Die klassische Trias "intrinsic asthma - Nasenpolypen - Analgetika-Intoleranz" wurde bei 39% der AIA-Patienten ermittelt. Die pathogenetischen Grundlagen der Assoziation von Asthma und Polypen und der noch stärker ausgeprägten Assoziation von AIA und Polypen sind noch unklar. Der vermutete pathogenetische Zusammenhang zwischen chronisch-hyperplastischen Veränderungen der oberen Luftwege und dem Phänomen des AIA könnte auf Störungen im Phospholipidmetabolismus (Arachidonsäureliberation, Lipoxygenaseprodukte, Radikalmechanismen) beruhen.

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