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CASE REPORT

Familial spontaneous pneumothorax

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Familial spontaneous pneumothorax. P. Lenler-Petersen, N. Grunnet, T.W. Jespersen, P. Jaeger.
ABSTRACT: In a three generation family with 27 members we examined a relationship could be found between spontaneous pneumothorax and HLA-haplotypes, alpha$_1$-antitrypsin phenotypes or concentration or lung volumes and ventilatory capacity. Eight individuals in the family suffered from spontaneous pneumothorax. No relationship with the investigated markers could be found in this informative family. All patients showed normal lung volumes and ventilatory capacity after recovery.
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Familial occurrence of spontaneous pneumothorax is seldom reported in the literature [1]. Attempts to reveal aetiological factors have not so far been successful, probably because the number of cases in the families have been too few [2]. We present a family of 27 persons of whom 8 suffered from spontaneous pneumothorax (fig. 1).

We studied a possible relationship between HLA-antigens, alpha$_1$-antitrypsin, lung volumes, ventilatory capacity and spontaneous pneumothorax.

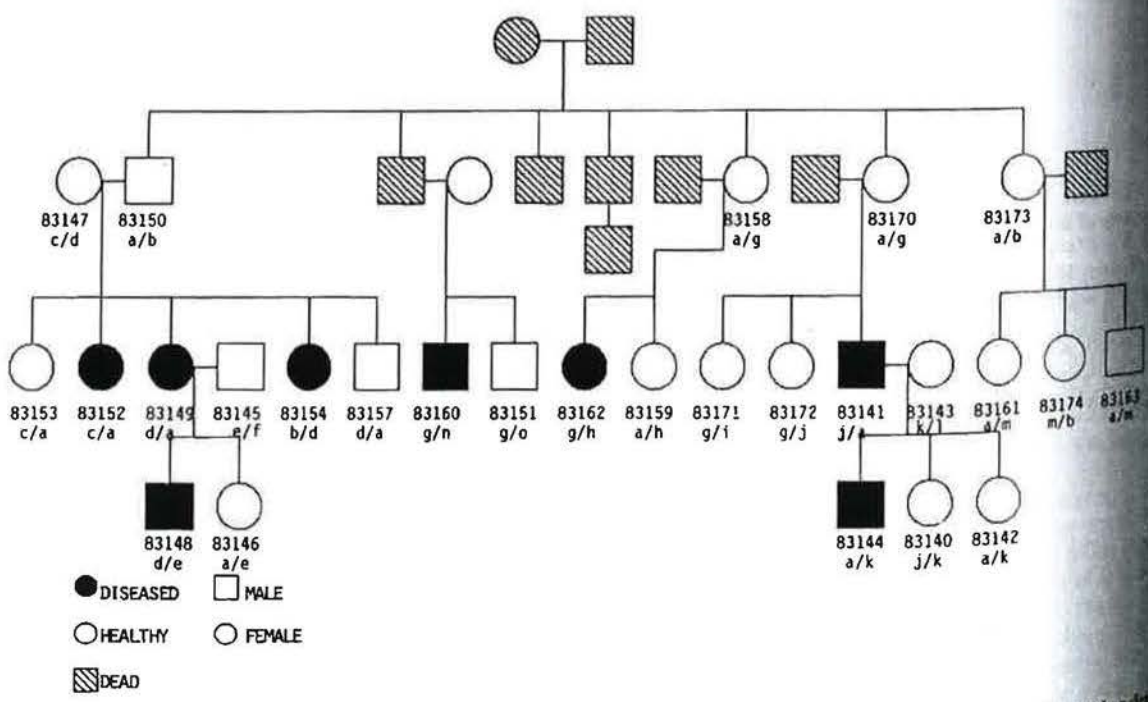

Fig. 1. – Pedigree of family with 8 cases of spontaneous pneumothorax. The letters a–o refer to HLA-haplotypes, see table 2 for further details, *e.g.* haplotype a=HLA-A9(24); B7. The number refers to identification of the individual.

Case report

The proband

A 26 yr old woman (83154) was admitted to hospital with an X-ray verified pneumothorax. She was an otherwise healthy nonsmoker, without known trauma. She was treated with pleural drainage for 7 days and discharged. Two weeks later, in the out-patient clinic, the right-sided pneumothorax had reformed and persisted during the next 2.5 months. She was admitted to hospital, drained for a further 7 days and discharged with a fully expanded lung. During hospitalization, she reported that two sisters, two cousins and two of their sons had suffered from spontaneous pneumothorax. The reported family members had all suffered from X-ray verified pneumothorax.

Methods

The whole family, three generations with 27 individuals, went through a careful interview about pulmonary symptoms, cardiac symptoms and working history. Static lung volumes and dynamic ventilatory capacity test were performed by a trained nurse using a Vicatest V.G. 2000 S (Mijnhardt, Bunnik, Holland).

Total lung capacity (TLC), residual volume (RV), functional residual capacity (FRC), forced vital capacity (FVC) and forced expiratory volume in the first second (FEV_1) were recorded. FRC determinations were calculated using the Helium dilution technique.

X-rays of the thorax were performed as posterior-anterior as well as lateral projections and described in a blind manner by the radiologist associated with the department of pulmonary diseases. X-rays were evaluated for characteristics of emphysema [3]. Due to pregnancy, 83153 was excluded from X-ray.

Serum concentrations of $alpha_1$-antitrypsin were measured by rocket immunoelectrophoresis [4]. The Pi-phenotypes of $alpha_1$-antitrypsin were determined by isoelectric focusing [5] using LKB® 2177 Multiphor with LKB® 1804-111 polyacrylamide gels (pH 4.0–5.0) (LKB, Broma, Sweden).

All persons were HLA-ABC typed. The HLA typing was performed with the NIH lymphocytotoxity micro method using 150 highly selective typing sera.

Table 1. – Results of lung volumes and ventilatory capacity in percentage of predicted value, X-ray, concentration and phenotype of $alpha_1$-antitrypsin

Individual No.	Sex	Lung parameters				Smoker	Thorax	$Alpha_1$-antitrypsin	
		TLC %	FRC %	RV %	FEV_1 %		X-ray	Concn. $\mu mol \cdot l^{-1}$	Phenotype
83154*	F	95	79	73	89	-	Normal	51	MM
83153	F	79	63	78	85	-	Pregnant	104	MM
83152*	F	88	106	101	81	+	Bullae/Hi/Pl ch	69	MM
83149*	F	83	81	76	105	-	Normal	52	MM
83145	M	112	128	113	109	+	Normal	55	MM
83157	M	93	90	128	81	-	Normal	44	MM
83160*	M	98	85	93	101	+	Normal	54	MS
83151	M	94	107	78	113	+	Incr vessels	73	MM
83162*	F	106	118	126	103	-	Pneumothorax	47	MM
83159	F	105	103	75	117	+	Normal	56	MM
83171	F	111	101	91	127	+	Normal	52	MS
83172	F	93	106	94	103	+	Bullae/Pl effusion	46	MS
83141*	M	93	86	99	94	-	Pl ch	68	MM
83143	F	101	65	88	95	-	Normal	46	MM
83161	F	104	117	116	90	-	Bullae/Incr vessels	52	MM
83174	F	87	101	108	79	+	Normal	55	MM
83163	M	81	64	65	96	-	Normal	36	MS
83148*	M	104	113	93	110	+	Incr vessels	62	MM
83146	F	84	84	76	101	-	Bullae	56	MM
83144*	M	89	75	66	101	-	Bullae/Incr vessels/Pl ch	52	MM
83140	F	101	103	84	117	-	Normal	56	MM
83142	F	99	89	75	104	-	Normal	53	MM
83147	F	106	94	84	115	-	Hi	61	MM
83150	M	80	87	97	65	+	Bullae/Incr vessels	56	MM
83158	F	103	80	101	91	-	Normal	58	MM
83170	F	80	85	85	83	-	Pl ch	62	MS
83173	F	82	64	69	114	-	Normal	59	MS

*: Spontaneous pneumothorax; Hi (hyperinflation): flattening of the diaphragmatic domes; Bullae: thin walled cystic spaces within the lung ≥1 cm; Pl ch (pleural changes): pleural thickening; Incr vessels (increased vessels): redistribution of blood flow to the apical part of the lung. [3]; M: male; F: female; TLC: total lung capacity; FRC: functional residual capacity; RV: residual volume; FEV_1: forced expiratory volume in one second.

The Mann-Whitney non-parametric test for independent data was used to compare the results of alpha$_1$-antitrypsin, TLC, FRC, RV and FEV$_1$ in persons with spontaneous pneumothorax to the results of the group of persons without spontaneous pneumothorax. Rank sums were calculated and non-parametric 95% confidence limits for the rank sums were found. A $p<0.05$ value was considered significant (two-tailed). The mean of the alpha$_1$-antitrypsin results from all the persons examined was compared to population mean by a two-tailed Z-test (significance $p<0.05$).

All persons took part in the study after giving informed consent. The study was approved by the Regional Ethical Committee.

Results

The mean age of the family members was 40 yrs (SD ±17 yrs; range 11–75 yrs), mean height was 168 cm (SD ±10 cm; range 141–190 cm), and mean weight was 71 kg (SD ±13 kg; range 39–91 kg). Mean age at first pneumothorax was 28 yrs (SD ±9 yrs; range 17–43 yrs). Five of the eight subjects had recurrence of pneumothorax. 83162 presented an asymptomatic spontaneous pneumothorax at examination. Ten were smokers, three of whom had pneumothorax. None of the family members had hyperextendible bone joints or other clinical characteristics of connective tissue disorders. None of the women had lung symptoms that could be related to menstrual cycles. X-rays presented 11 subjects with either flattening of the diaphragmatic domes (hyperinflation), thin-walled cystic spaces within the lung ≥1 cm (bullae), pleural thickening (pleural change) or redistribution of blood flow to the apical part of the lung (increased vessels). In the group with spontaneous pneumothorax 2 had bullae, 1 hyperinflation and 3 pleural thickening. In the group without pneumothorax 4 had bullae, 1 hyperinflation, 3 increased vessels, 1 pleural thickening and 1 a small pleural effusion (table 1).

Static lung volumes were essentially normal. TLC measured for 83153 may be explained by pregnancy. FEV$_1$ was normal in all except 83174, who had 79% of predicted value and 83150, who had 65% of predicted value. Only 83150 had a history of bronchitis. There were no significant changes in TLC, RV or FEV$_1$ in persons with spontaneous pneumothorax compared to persons without (Mann-Whitney non-parametric test for independent data).

Alpha$_1$-antitrypsin determinations were essentially within normal limits (22–56 $\mu mol \cdot l^{-1}$) without low values (table 1). For 83153, values were increased because of pregnancy. Concentrations of alpha$_1$-antitrypsin in persons with spontaneous pneumothorax were not significantly different from persons without spontaneous pneumothorax (Mann-Whitney non-parametric test for independent data) or from the reference population (Z-test; $p=0.15$). Alpha$_1$-antitrypsin phenotypes were 21 MM and 6 MS. Seven affected persons had MM phenotypes, one had MS.

HLA-ABC phenotypings are presented as HLA-haplotypes in table 2 being used in the family pedigree presented in figure 1.

Table 2. – A list of HLA-ABC haplotypes identified in the family presented in figure 1

HLA haplotype	HLA-ABC antigens in the haplotype
a:	A9(24); B7
b:	Aw19(32); B13; Cw6
c:	A9(24); B40; Cw2
d:	A9(24); B35; Cw4
e:	Aw19(32); B7; Cw7
f:	A2; B8
g:	A1; B8
h:	A11; B16(39)
i:	A1; B14; Cw8
j:	A2; B40; Cw3
k:	A3; B7
l:	A2; B5
m:	A9(23); B44
n:	A28; B18
o:	A2; B27; Cw1

Discussion

Spontaneous pneumothorax is most often seen in tall young men [2, 6, 7]. The frequency amongst men aged 20–29 yrs is 1:3000, and in the general population it is 1:11,500 [8], with a sex ratio (male/female) of 5:1 [9]. In our study the sex ratio appeared to be (male/female) 4:4. This ratio is slightly different from that of WILSON and AYLSWORTH [10], who found male to female cases to be 1:8 when reviewing reports of familial spontaneous pneumothorax.

Spontaneous pneumothorax appears to result from rupture of subpleural, thin-walled blisters varying from blebs of a few mm to genuine cysts [2, 6, 11–14]. Emphysema, either general or localized, is known to cause blebs or cysts. In 1965, emphysema was shown to be associated with alpha$_1$-antitrypsin deficiency in 1965 by ERIKSSON [15]. An association between alpha$_1$-antitrypsin deficiency and spontaneous pneumothorax has not been found [7]. This was confirmed by this study since the concentrations of alpha$_1$-antitrypsin in subjects with spontaneous pneumothorax were not significantly different from persons without or from the reference population as found by others [1, 16].

Alpha$_1$-antitrypsin is one of the acute phase reactant proteins. Concentrations of alpha$_1$-antitrypsin in persons with deficiency may therefore increase to normal levels in case of infection, oestrogenic medication, pregnancy or cancer [17].

Phenotyping of alpha$_1$-antitrypsin by isoelectric focusing reveals variants of which Z, S, P, Null and Mduarte are known to be associated with antitrypsin deficiency. The Z variant is the most common cause of antitrypsin deficiency. M is the normal variant [17]. We found seven affected persons with the phenotype MM and one with MS. The results do not imply any relationship between alpha$_1$-antitrypsin phenotype and spontaneous pneumothorax.

None of the affected women indicated signs of catamenial pneumothorax, a special form of pneumothorax related to menstruation. The pathogenesis of this condition is not clear, but intrathoracic endometriosis is a possibility [18].

PAWLOWICZ and DROSZCZ [7] revealed definite evidence of emphysema in only 7% of 65 persons examined one year after they suffered idiopathic spontaneous pneumothorax. In our study, the pulmonary tests showed signs of relative hyperinflation in 3 subjects, of whom only one had spontaneous pneumothorax. TLC, however, were normal, even though 2 had bullae recognized by X-ray. None of these subjects had any changes in the dynamic pulmonary function tests, and all were without symptoms. All bullae found by X-ray were small and thin-walled. The helium dilution technique is potentially inaccurate when seeking emphysema. Whole body plethysmography would have been more accurate, especially accompanied by diffusion capacity measurements. We did not have the opportunity to use a body plethysmograph in this study, but we would not expect large differences of measurements in this group of otherwise pulmonary healthy subjects. Our results confirm that patients essentially have normal pulmonary function after idiopathic spontaneous pneumothorax.

SHARPE *et al.* [1] suggested a possible linkage of the HLA-A2;B40 haplotype to familial spontaneous pneumothorax. In our study, HLA-ABC typing did not reveal any relationship between familial spontaneous pneumothorax and a certain HLA haplotype, since of three pairs of siblings, HLA-haplotype identical, only one showed spontaneous pneumothorax in each pair. If HLA is related to spontaneous pneumothorax one would expect these pairs to be either healthy or sick according to their HLA-identity judged by haplotypes. None of the subjects with spontaneous pneumothorax had the same HLA-A or B antigens.

Our results do not imply any relationship between HLA-ABC tissue type and familial spontaneous pneumothorax. We did not find any relationship between alpha$_1$-antitrypsin concentration, phenotype and spontaneous pneumothorax.

We found that patients who had fully recovered from idiopathic spontaneous pneumothorax had normal lung volumes and ventilatory capacity.

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RÉSUMÉ: Nous avons examiné, dans une famille comportant trois générations et 27 membres, si l'on pouvait trouver une relation entre le pneumothorax spontané, les haplotypes-HLA, les phénotypes, la concentration d'alpha$_1$-antitrypsine, ou la fonction pulmonaire. Chez huit individus de la famille, on a relevé des pneumothorax spontanés. Dans cette famille type, l'on n'a pas trouvé de relation de ce pneumothorax avec les marqueurs investigués. Tous les patients avaient une fonction pulmonaire normale après guérison.

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