



Physical and social impact of alpha 1-antitrypsin deficiency: results of a survey

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- **BACKGROUND** Emphysema associated with alpha 1-antitrypsin deficiency can impose serious impairment.
- **OBJECTIVE** To gather information about the impact of severe alpha 1-antitrypsin deficiency.
- **METHODS** Mail survey, descriptive statistics.
- **RESULTS** We sent a survey to 1730 subscribers to a national newsletter, 850 of whom had previously stated they had alpha 1-antitrypsin deficiency. A total of 414 questionnaires were returned; 398 respondents said they had alpha 1-antitrypsin deficiency, and 300 said they had the PiZZ phenotype. Sixty-six respondents who said they had the disease did not know their phenotype. Among the 304 respondents with severe deficiency, the mean age at the time symptoms first appeared was 35.0 years, but the mean age when the disease was diagnosed was 41.3 years. Overall, 75.3% of respondents with severe deficiency reported at least one adverse effect: 44.4% retired early, and 19.1% changed to a physically easier job. The duration of diagnostic delay correlated with the degree of adverse psychosocial effects.
- **CONCLUSIONS** Alpha 1-antitrypsin deficiency frequently escapes diagnosis despite many medical encounters. Affected individuals are often unaware of basic details of their disease. Many patients report adverse psychosocial effects. Delay in diagnosing this disease is associated with adverse psychosocial effects.

■ **INDEX TERMS:** ALPHA 1-ANTITRYPSIN; QUALITY OF LIFE; QUESTIONNAIRES; SELF-HELP GROUPS ■ CLEVE CLIN J MED 1994; 61:461-467

LIKE many diseases that afflict young and middle-aged adults, emphysema associated with alpha 1-antitrypsin deficiency can impose serious physiologic and functional impairment on people who are in life's prime. Despite estimates that up to 100 000 Americans have severe alpha 1-antitrypsin deficiency, the difficulty of studying a large patient group and the paucity of available series have precluded fully assessing the human impact of this disease.

We present here the results of a mail survey of the readers of the *Alpha-1 News*, the official publication of the Alpha-1 National Association (the newly formed national association of patients with alpha 1-antitrypsin deficiency). In addition to clarifying the demographic characteristics of the readers, the questionnaire was designed to elicit impressions about the social, financial, and psychologic impact of severe alpha 1-antitrypsin deficiency on affected patients.

METHODS

In December 1991, we included the study questionnaire (*Figure*) with the mailing of the *Alpha-1 News* (the official quarterly newsletter of the Alpha-1 National Asso-

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1. Code: No XXXX 2. Birthdate:
Month _____ Day _____ Year _____
3. Sex (circle one): M F
4. Race (circle one): Caucasian Black Hispanic
Other (specify) _____
5. Marital Status (circle one): M D S Widowed
6. Do you have alpha 1-antitrypsin deficiency? (circle one)
Yes Tested and no Never tested but possible
Never tested but doubt it
- 6a. If you do have alpha 1-antitrypsin deficiency, specify type (circle one):
ZZ SZ MZ Unknown Other (specify) _____
7. At what age was your alpha 1-antitrypsin deficiency diagnosed? _____
8. Do you have any lung-related symptoms? (circle one) Y N
9. Do you have liver disease that is said to be due to alpha 1-antitrypsin deficiency?
(circle one) Y N Unknown whether I have liver disease
(circle one) Y N I have liver disease but do not know the cause
10. Do you have a skin disease called panniculitis? (circle one)
Y N Do not know
11. Circle any lung symptoms that you have:
A. Shortness of breath
B. Wheezing at all times
C. Wheezing with colds
D. Cough with phlegm production at all times
E. Other (please specify): _____
12. At what age did your lung symptoms begin? _____
13. Do any family members of yours have alpha 1-antitrypsin deficiency? Yes No
- 13a. If yes, specify person and type of deficiency (if known):
Example: Father: Type MZ
Father: Type _____ Type not known
Mother: Type _____ Type not known
Brother 1: Type _____ Type not known
Brother 2: Type _____ Type not known
Brother 3: Type _____ Type not known
Sister 1: Type _____ Type not known
Sister 2: Type _____ Type not known
Sister 3: Type _____ Type not known
Child 1: Type _____ Type not known
Child 2: Type _____ Type not known
Child 3: Type _____ Type not known
Child 4: Type _____ Type not known
Others (specify) _____
14. Do you smoke cigarettes now? Yes No
15. Have you ever smoked cigarettes (more than 2 packs of cigarettes in lifetime)? Yes No
16. Do you smoke cigars now? Yes No
17. Have you ever smoked cigars (more than 20 cigars total in your life)? Yes No
18. Are you the main breadwinner of your household?
Yes No
- 18a. If not, who is? Specify _____
19. What is your combined family yearly income range:
\$ 0 — \$ 5,000 _____
\$ 5,001 — \$ 10,000 _____
\$ 10,001 — \$ 20,000 _____
\$ 20,001 — \$ 30,000 _____
\$ 30,001 — \$ 40,000 _____
\$ 40,001 — \$ 50,000 _____
\$ 50,001 — \$ 100,000 _____
\$ 150,001 — _____
20. What is the impact of alpha 1-antitrypsin deficiency on your life? (circle all that apply)
Having alpha 1-antitrypsin deficiency has caused me to:
A. Retire early (age at retirement: _____)
B. Lose my job (I am now unemployed)
C. Change my health insurance carrier
E. Lose my health insurance
F. Lose one or more friends
G. Make one or more new friends
H. Have a worse marriage
I. Have a better marriage
J. Other (specify) _____
21. How many doctors did you see for symptoms before alpha 1-antitrypsin was diagnosed? (circle one)
A. First doctor I saw made the diagnosis
B. Second doctor
C. Third doctor
D. Fourth doctor
E. Fifth doctor
F. Sixth to tenth doctor
G. More than ten
22. Have you considered transplants as an option? (circle all that apply)
A. Have had a liver transplant _____ months ago
B. Am on a waiting list for a liver transplant for _____ months
C. Have had a lung (single, double, heart/lung) transplant _____ months ago
D. Am on a waiting list for a lung transplant for _____ months
E. I was turned down for a lung transplant
F. I was turned down for a liver transplant
G. Transplants were never considered an option
H. My insurance coverage prevents me from looking into transplants

FIGURE. Questionnaire used in the study.

ciation, sent to 1730 subscribers). One of us (P.S.) had previously conducted a telephone poll in which 850 of the subscribers reported having some form of alpha 1-antitrypsin deficiency. This group of 850 self-reported individuals was the target group for this survey. We received 414 questionnaires in return, representing an overall response rate of 48.7%. Of the respondents, 325 specified having a type of alpha 1-antitrypsin deficiency, for a response rate of 38.2% among the 850 subscribers who previously said they have the disease.

The questionnaire asked whether the respondent had the deficiency, and if so, what phenotype. It also elicited demographic information; the medical and smoking history (including the respondent's age when symptoms began and the age when the disease was diagnosed); socioeconomic information (employment status, income, insurance status); and the perceived effect of alpha 1-antitrypsin deficiency on the respondent's life (ie, adverse effects on employment, relationships, and insurance status).

Data were analyzed using SAS software (Cary, NC). Correlations were analyzed using the Spearman rho statistic for ordinal variables. Because only nine respondents reported having the PiSZ phenotype and only 12 reported having the PiMZ phenotype, we did not perform any statistical comparisons between them and respondents with the PiZZ phenotype.

TABLE 1
DEMOGRAPHIC FEATURES OF PEOPLE
WITH ALPHA 1-ANTITRYPSIN DEFICIENCY

Feature	Type of alpha 1-antitrypsin deficiency		
	Severe (n = 304)*	PiSZ (n = 9)	PiMZ (n = 12)
Mean age, years (range)	48.8 (2-79)	53.0 (3-69)	50.2 (31-70)
Male, %	50	33	83
Caucasian, %	100	100	100
Marital status, %			
Married	74.7	66.7	100
Divorced	15.8	11.1	—
Widowed	2.3	11.1	—
Single	7.2	11.1	—
Smoking status, %			
Current cigarette smoker	1.3	0	0
Ever smoked cigarettes	81.2	77.8	75.0
Currently smoke cigars	0	0	0
Ever smoked cigars	12.9	0	25
Main breadwinner, %	48.0	33	50

*Comprising PiZZ (n = 300), Pi null (n = 2), PiZ null (n = 1), and PiZMheerlen (n = 1)

TABLE 2
DELAY IN DIAGNOSING ALPHA 1-ANTITRYPSIN DEFICIENCY

Feature	Type of alpha 1-antitrypsin deficiency		
	Severe (n = 304)*	PiSZ (n = 9)	PiMZ (n = 12)
Mean age at onset of lung symptoms, years (range)	35.0 (21-70)	45.6 (39-53)	36.9 (12-45)
Mean age at initial diagnosis, years (range)	41.3 (1-76)	48.1 (1-60)	44.6 (20-65)
Number of doctors seen before alpha 1-antitrypsin deficiency diagnosed, %			
First doctor made diagnosis	25.1	11.1	40
Second doctor	31.2	22.2	40
Third doctor	17.6	44.4	10
Fourth doctor	9.5	—	—
Fifth doctor	4.1	22.2	10
Sixth to tenth doctor	12.5	—	—
Required three or more doctors, %	43.7	66.7	20
Interval between first lung symptom and diagnosis of alpha 1-antitrypsin deficiency, years (mean \pm SD) ^{†‡}	7.2 \pm 8.3	7.6 \pm 3.0	10.1 \pm 12.4

*Comprising PiZZ (n = 300), Pi null (n = 2), PiZ null (n = 1), and PiZMheerlen (n = 1)

[†]Mean intervals vary from difference between mean age at diagnosis and mean age at onset of lung symptoms because data are missing in some

[‡]ANOVA F value 0.53; did not achieve significance for any difference between three groups

RESULTS

Of the 414 respondents, 398 said they had alpha 1-antitrypsin deficiency; and 325 were able to indicate a specific phenotype (Table 1).

Three hundred four respondents had severe deficiency, ie, they had the PiZZ (n=300), Pi null (n=2), PiZ null (n=1), or PiZMheerlen (n=1) phenotypes. Their mean age was 48.8 years. Smoking was common: 247 (81.2%) of respondents with severe defi-

TABLE 3
SYMPTOMS AND SELF-REPORTED IMPACT OF DISEASE
AMONG ALPHA 1-ANTITRYPSIN DEFICIENT PATIENTS

Feature	Type of alpha 1-antitrypsin deficiency, %		
	Severe deficiency (n = 304) [*]	PiSZ (n = 9)	PiMZ (n = 12)
Any lung symptom present	92.9	81.9	72.7
Shortness of breath	90.5	88.9	66.7
Wheezing all the time	26.1	22.2	25.0
Wheezing with colds	60.7	44.4	33.3
Frequent cough with phlegm	36.3	33.3	50.0
Liver disease due to alpha 1-antitrypsin deficiency?			
Yes	9.5	0	0
No	74.6	87.5	81.8
Unknown	15.9	12.5	18.2
Panniculitis present	0.3	0	0
Impact of alpha 1-antitrypsin deficiency on respondents' lives			
Retired early	44.4	88.9	33.3
Lost job	15.8	11.1	8.3
Changed to a physically easier job	19.1	0	0
Changed insurance	11.8	11.1	8.3
Lost health insurance	10.5	11.1	16.7
Lost a friend	39.3	0	8.3
Have a worse marriage	20.4	11.1	16.7
Made a friend	46.4	33.3	33.3
Have a better marriage	22.0	0	8.3
Transplantation status			
Had a liver transplantation	1.1	0	0
On waiting list for liver	0	0	11.1
Had a lung transplantation	14.4	0	0
On waiting list for lung	15.5	0	11.1
Turned down for lung transplant	3.7	25.0	22.2
Turned down for liver transplant	1.1	0	0
Transplantation never considered	49.2	25.0	44.4
Insurance precludes transplantation	10.2	50.0	11.1
Pretransplantation evaluation underway	4.8	0	0

^{*}Comprising PiZZ (n = 300), Pi null (n = 2), PiZ null (n = 1), and PiZMheerlen (n = 1)

ciency had ever smoked and four (1.3%) were current smokers. The preponderance of Caucasians reflects the rarity of the PiZZ and less common deficient phenotypes in non-Caucasian groups.

Among respondents with severe deficiency, the mean age at onset of lung symptoms was 35.0 years (range 21 to 70 years), and the mean age at initial diagnosis was 41.3 years (Table 2). A mean of 7.2 ± 8.3 (SD) years elapsed between the first appearance of lung symptoms and the diagnosis in these respondents, which differs slightly from the difference between their ages at initial lung symptoms and initial diagnosis because some respondents did not answer both questions. The duration between first diagnosis and first symptom ranged from -13 to 43 years, indicating that some patients were diagnosed before symptom onset, and others experienced long delays in diagnosis.

Notably, in only 25.1% of respondents with severe

deficiency did the first doctor seen make the diagnosis. In fact, 12.5% saw at least six doctors before the diagnosis was made, and 43.7% saw at least three doctors.

Table 3 lists the symptoms reported by respondents with alpha 1-antitrypsin deficiency and the effect the disease has on their lives. As in earlier studies (Table 4),¹⁻⁵ the most prevalent symptom in respondents with severe deficiency was dyspnea (90.5%); wheezing continuously or with colds was reported by 26.1% and 60.7%, respectively. Liver disease due to alpha 1-antitrypsin deficiency was reported by 9.5% of respondents with severe deficiency, but was not reported in patients with PiSZ or PiMZ phenotypes. Panniculitis was reported by a single PiZZ individual (0.3%).

Many respondents with severe deficiency reported adverse effects on their em-

ployment status, relationships (friendships, marriage), and insurance status. Overall, 75.3% of respondents with severe deficiency reported at least one adverse effect. The most common adverse socioeconomic effect was early retirement (reported by 44.4%), followed by changing to a physically easier job (19.1%). Given that the mean age of respondents with severe deficiency was 35, the frequency of early retirement suggests these people had substantial impairment or considerable difficulties with insurance.

On the other hand, some respondents with severe deficiency also reported that their marriage improved (22%) and that they made new friends (46.4%) as a result of having alpha 1-antitrypsin deficiency.

Transplantation was never considered in 49.2% of respondents with severe deficiency, but 14.4% had received a lung transplant, 1.1% had received a

TABLE 4
CLINICAL FEATURES OF PATIENTS WITH SEVERE DEFICIENCY OF ALPHA 1-ANTITRYPSIN IN AVAILABLE SERIES

Author	No. of PiZ individuals	% male	Mean age at onset of symptoms, years	% frequency of reported dyspnea	Interval between first symptom and initial diagnosis, years
Larsson, 1978 ¹	246	57	40*	95 [†]	—
Janus et al, 1985 ²	84	48	32 ± 2	—	—
Brantly et al, 1988 ³	120	67	35–40	98	—
Evald et al, 1988 ⁴	65	54	—	—	—
Holden et al, 1991 ⁵	27	—	—	—	12 ± 14 [‡]
Current series	300	50	35	90.5	7.2 ± 8.3

*Median age among smokers

[†]Among patients with emphysema

[‡]In PiZ patients presenting with asthmatic features

liver transplant, and 4.8% were undergoing pre-transplantation evaluation. As another example of the financial strain imposed by severe alpha 1-antitrypsin deficiency, 10.2% of respondents with severe deficiency reported that their insurance coverage "prevented looking into transplants."

Table 5 presents a correlation matrix among the number of adverse psychosocial effects (questions 20a–f, 20h), the number of doctors seen before the diagnosis was made (question 21), and the interval between the first lung symptom and the diagnosis (age in question 7 – age in question 12).

For respondents with severe deficiency, the mean number of adverse psychosocial effects correlated weakly but significantly with the number of doctors seen before diagnosis (Spearman rho = .20, $P = .0005$), but not with the interval between the first lung symptom and the diagnosis (Spearman rho = .05, $P = .43$). Not surprisingly, the number of doctors seen before the diagnosis was made correlated significantly with the interval between the first lung symptom and the diagnosis (Spearman rho = .37, $P = .0001$).

DISCUSSION

The major findings from this mail survey of the readers of a national newsletter from the Alpha 1-National Association are as follows: (1) alpha 1-antitrypsin deficiency frequently escapes diagnosis despite many medical encounters; (2) despite knowing they are deficient in alpha 1-antitrypsin, affected individuals are often unaware of basic details of their disease (as suggested by the inability of 16.6% of respondents to specify their phenotype); (3) many patients with alpha 1-antitrypsin deficiency report

adverse psychosocial effects of this disease; and (4) delay in diagnosing alpha 1-antitrypsin deficiency is associated with adverse psychosocial effects, which are common among patients with severe deficiency.

Except for forthcoming reports from the Registry for Patients with Severe Deficiency of Alpha 1-Antitrypsin,⁶ the current report assembles the largest available single-study cohort of patients with severe deficiency. Also, the current study examines patient features that have not been studied to date (eg, the psychosocial impact of alpha 1-antitrypsin deficiency).

Our conclusion that alpha 1-antitrypsin deficiency is misunderstood by both physicians and patients is not surprising, for several reasons. First, the disease was discovered relatively recently, in 1963⁷; thus, older physicians may not be familiar with it. Second, two features of severe alpha 1-antitrypsin deficiency conspire against easy recognition by clinicians: the relative infrequency of the PiZZ phenotype (fewer than 1 in 1600 Caucasians, and even fewer in non-Caucasian groups)^{8–10} and the possibility that patients with severe deficiency may not have symptoms.^{9,10}

Our finding that affected individuals may poorly understand the disease may reflect inadequate teaching by health care providers. However, this finding also highlights an opportunity to enhance recognition of the disease, because informed patients can encourage their first-degree relatives to be tested and can be effective patient educators themselves. Indeed, the newsletter with which this questionnaire was distributed and the association it represents reflect the success of patients' efforts to disseminate information and to "demystify" this disease and its diagnosis.

TABLE 5
CORRELATION MATRIX FOR FINDINGS AMONG PATIENTS
WITH SEVERE DEFICIENCY OF ALPHA 1-ANTITRYPSIN

Feature	Feature	N	Correlation (Spearman rho)	P value
Number of adverse psychosocial effects	Interval between first lung symptom and initial diagnosis	272	.05	.43
Number of adverse psychosocial effects	Number of doctors seen before initial diagnosis	295	.20	.0005
Number of doctors seen before initial diagnosis	Interval between first lung symptom and initial diagnosis	266	.37	.0001

The long mean delay between first lung symptoms and diagnosis of alpha 1-antitrypsin deficiency in this study (7.2 ± 8.3 years) is consistent with previous findings. For example, Holden et al⁵ examined 11 patients with alpha 1-antitrypsin deficiency presenting with asthmatic features and reported a 12-year interval between the onset of asthmatic symptoms and the diagnosis of alpha 1-antitrypsin deficiency. Though available studies do not support a role for routine testing of asthmatic patients for alpha 1-antitrypsin deficiency,^{11,12} this observed delay suggests that the availability of an alternate diagnosis (eg, asthma, smoking-related emphysema) may truncate evaluation of chronic lung symptoms before the diagnosis of alpha 1-antitrypsin deficiency is pursued. Thus, in addition to clinicians' general unfamiliarity with alpha 1-antitrypsin deficiency, the availability of an alternate pulmonary diagnosis may contribute to a delay in diagnosing alpha 1-antitrypsin deficiency.

Our finding that this disease is associated with adverse psychosocial effects is also not surprising, though previous psychosocial studies have been confined to examining the effects of severe alpha 1-antitrypsin deficiency in screened newborn infants¹³ or on parents' well-being and interactions with their screened children.^{14,15} In our study, the significant correlation between the duration of diagnostic delay and the degree of adverse psychosocial effects suggests that failure to diagnose the disease in symptomatic individuals may be harmful, just as harm may result from labeling asymptomatic screened children.¹⁴ Adults with pulmonary symptoms often feel relief when an underlying disorder such as alpha 1-antitrypsin deficiency is identified. Similarly, minimizing diagnostic uncertainty mitigates anxiety

among patients at risk. For example, in a recent study, people at risk for Huntington's disease welcomed diagnostic testing, even when the results indicated increased likelihood of carrying the gene for the disease.¹⁶

There are no previous studies with which to compare our findings regarding the psychosocial impact of severe alpha 1-antitrypsin deficiency.

Furthermore, because our study was not a population-based survey, the validity and generalizability of our conclusions require assurance that several sources of bias are not present. These biases may be articulated by the following two questions.

Is the self-reported information from this survey reliable?

It was not possible to validate responses by blood testing or patient interviews in this anonymous survey. Nonetheless, the close agreement between the characteristics of our study cohort and other cohorts of patients with alpha 1-antitrypsin deficiency described previously (Table 4) strengthens the credibility of our findings. For example, the equal gender distribution among patients with severe deficiency and the lack of non-Caucasian groups among respondents with severe deficiency are expected. The onset of lung symptoms in the fourth and fifth decades of life and the identification of dyspnea as the most common symptom resemble findings in other cohorts of patients with severe deficiency. Finally, the mean 7.2-year interval between the onset of symptoms and diagnosis of severe deficiency of alpha 1-antitrypsin agrees with the long delay (mean 12 years) reported previously in 11 patients who were not part of the current study cohort.⁵ Overall, the strong agreement between self-reported features of this study group and observed traits of previously reported cohorts buttresses the accuracy of these self-reported data.

Are the respondents' answers representative?

The 48.7% overall response rate in this survey and the 38.2% response rate among people who specified their alpha 1-antitrypsin deficiency pheno-

type raises concern that respondents reflect a biased subset of patients. Because no information is available on nonrespondents in this anonymous survey, we cannot compare respondents with nonrespondents, and concern about sampling bias cannot be discounted. On the other hand, the aforementioned similarity of our responding group to other previously described cohorts of patients with severe deficiency of alpha 1-antitrypsin makes sampling bias in this study less likely. Because none of the available reports describes demographic and clinical features of a truly population-based cohort of patients with severe deficiency of alpha 1-antitrypsin, the generalizability of these findings to all patients cannot be assured. Furthermore, several features of our cohort suggest that respondents are severely affected by alpha 1-antitrypsin deficiency. First, more respondents were smokers (> 80%) than we would expect. Also, the 14.4% prevalence of lung transplantation indicates severe physiologic impairment. Thus, caution must be exercised in applying our findings to alpha 1-antitrypsin-deficient patients who have never smoked or who have less physiologic impairment. Nonetheless, we believe that our

results accurately portray features of patients with severe deficiency who subscribe to a national newsletter. The high prevalence of symptoms in this group (Table 3) is expected because symptomatic patients are more likely to be clinically recognized^{9,10} and because this survey was directed at those members of the Alpha-1 National Association who reported having severe deficiency.

In summary, this study presents clinical features of people with severe alpha 1-antitrypsin deficiency who responded to a questionnaire distributed through a national newsletter, the *Alpha 1-News*. Our findings emphasize the need for enhanced awareness of alpha 1-antitrypsin by both clinicians and affected individuals, so that accurate diagnosis can be made more frequently and promptly and so that affected individuals and their caregivers can become better informed. Though the benefits of more prompt diagnosis in affected individuals remain unproven and require careful cost-benefit analysis, the suggestion that diagnostic delay incurs psychosocial harm to patients with severe deficiency should encourage prompt diagnosis in patients who have symptoms.

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