Differences Between ZZ and SZ patients on the AlphaNet Program

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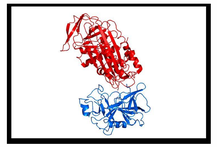
INTRODUCTION

Alpa-1 Antitrypsin deficiency (AATD):

- autosomal co-dominant disorder
- results from mutations of the SERPINA1 gene
- typically associated with the increased risk of early onset pulmonary emphysema in adult population, liver disease in children as well as adults and, more rarely, panniculitis-inflammation of the subcutis.
- the most common mutations associated with AATD are PiZ and PiS mutations

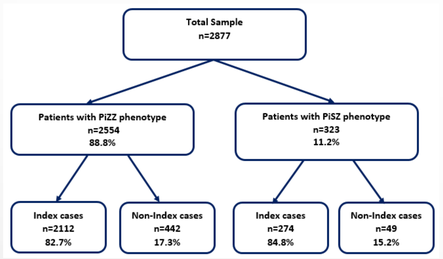


SERPINA1 gene

AATD was first discovered in 1963 by Laurell and Eriksson. It is considered a common genetic disorder, however it is still often underdiagnosed

MATERIALS AND METHODS

Our study population consisted of members of AlphaNet - a not-for-profit health management company that coordinates management and treatment of Alpha-1 antitrypsin deficient patients.



Flow chart of study participants

Study inclusion criteria :

- members of AlphaNet
- carry either ZZ, ZNull (analyzed in combination with ZZ) or SZ phenotype of AATD

Index cases:

- defined by the symptoms (lung and/or liver) that prompted the diagnosis of AATD

Non-index cases:

- diagnosed by family screening of known AATD patients

Primary analysis:

- compared AATD patients with the ZZ genotype to those with the SZ genotype by the main baseline characteristics

Secondary analysis:

- explored the differences between index and non-index cases within each variant group

Six sections of the baseline questionnaire administered by AlphaNet:

1. Demographic information and specified genotype and ascertainment status (index vs. non- index).
2. Work and productivity (employment, disability and productivity scale).
3. Pulmonary symptoms, current treatment, exacerbation frequency and "other therapies" such as oxygen use.
4. Details of augmentation therapy and lung and/or liver transplant data (if any). Complete data on augmentation therapy was not available for this study.
5. Self-perceived fitness and health and smoking and drinking habits.
6. Shortness of breath and its causes, and compliance with AlphaNet's Disease management program (ADMAPP) and Big Fat Reference Guide (BFRG).

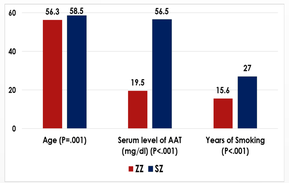
STATISTICAL ANALYSES

Descriptive statistics:

- for the overall sample
- stratified by variant (ZZ vs. SZ)
- sub-stratified by index status (index vs. non-index status)

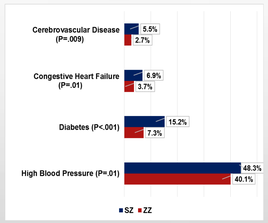
The results for categorical variables were reported by frequencies and proportions, and for continuous variables as mean + SD (min, max).
Values between the groups were compared using t-test and ANOVA, and Chi-squared test respectively.
SAS software (SAS 9.4 for Windows) was used for the statistical analysis. The significance level was set at 0.05.

RESULTS



- ZZs were slightly younger than their SZ counterparts.
- As anticipated, serum levels of Alpha-1 Antitrypsin in SZs were higher
- SZs report heavier and longer history of smoking compared to PiZZs

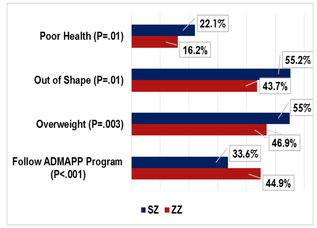
Our study found significant differences in comorbidities between the two genotypes with greater proportion of patients with SZ phenotype in our cohort were diagnosed with high blood pressure, diabetes, congestive heart failure and cerebrovascular disease compared to the patients with ZZ phenotype



Significantly higher proportion of patients with ZZ phenotype (27.5%), compared to 15.6% of patients with SZ phenotype, report being diagnosed with AATD due to an early onset of lung disease (before age 53) (p<0.001).

Self-perceived health and fitness. Adherence to ADMAPP program

- greater proportion of patients with PiSZ compared to PiZZs view themselves being overweight and out of shape
- more patients with PiSZs consider themselves being in "poor health" compared to PiZZs
- greater proportion of the patients with PiZZ compared to PiSZ) report following ADMAPP program



Summary of sample baseline characteristics according to genotype.

Variable	Total (n=2877) (%)	ZZ (n=2554) (%)	SZ (n=323) (%)	*p*
Age	56.5 ± 11.4	56.3 ± 11.3	58.5 ± 12.3	0.001*
Male	1476 (51.7)	1301 (51.3)	175 (55.0)	0.2
Race				<0.001*
Black	12 (<1.0)	10 (<1.0)	2 (<1.0)	
Hispanic	19 (<1.0)	13(<1.0)	6 (1.9)	
White	2800 (98.3)	2495 (98.6)	305 (95.6)	
Other	19 (<1.0)	13 (<1.0)	6 (1.88)	
Serum level of AAT (mg/dl)	25.4 ± 24.5	19.5 ± 15.2	56.5 ± 37.2	<0.001*
Reason for diagnosis				
Lung disease (early onset)	747 (26.2)	697 (27.5)	50 (15.6)	<0.001*
COPD	611 (21.4)	501 (19. 8)	110 (34.3)	<0.001*
Medical Conditions				
High Blood Pressure	971 (41.6)	831 (40.1)	140 (48.3)	0.01*
Diabetes	193 (8.3)	149 (7.3)	44 (15.2)	<0.001*
Congestive Heart Failure	96 (4.1)	76 (3.7)	20 (6.9)	0.01*
Cerebrovascular Disease	71 (3.0)	55 (2.7)	16 (5.5)	0.009*
Do you exercise				
No	686 (25.7)	586 (24.7)	100 (34.4)	<0.001*
Irregularly	882 (33.1)	794 (33.5)	88 (30.2)	0.27
Regularly at Home	652 (24.5)	595 (25.1)	57 (19.6)	0.04*
Regularly at Gym	213 (8.0)	185 (7.8)	28 (9.6)	0.28
Regularly at Medical Center	183 (6.9)	168 (7.1)	15 (5.2)	0.22
Perception of Weight				0.003*
Overweight	1248 (47.8)	1093 (46.9)	155 (55.0)	
Underweight	296 (11.3)	258 (11.1)	38 (13.5)	
About Right	1068 (40.9)	979 (42.0)	89 (31.6)	
Perception of Fitness				0.01*
Very Fit	85 (3.3)	79 (3.4)	6 (2.1)	
Pretty Fit	827 (31.8)	764 (32.9)	63 (22.4)	
Getting Fit	521 (20.0)	464 (20.0)	57 (20.3)	
Out of Shape	1169 (44.9)	1014 (43.7)	155 (55.2)	
Perception of Health				0.01*
Excellent	116 (4.4)	110 (4.7)	6 (2.1)	
Good	979 (37.5)	869 (37.3)	110 (38.6)	
Fair	1078 (41.3)	972 (41.8)	106 (37.2)	
Poor	440 (16.8)	377 (16.2)	63 (22.1)	
Ever smoked	1925 (73.6)	1696 (72.7)	229 (80.6)	0.004*
Number of Packs/Day	1.2 ± 0.9	1.2 ± 0.9	1.6 ± 1.0	<0.001*
Years of Smoking	16.9 ± 11.6	15.6 ± 10.8	27.0 ± 13.3	<0.001*
Still Smoking	89 (4.6)	58 (3.4)	31 (13.6)	<0.001*
Consume Alcohol	1183 (45.9)	1073 (46.7)	110 (39.6)	0.02*
Follow ADMAPP Program	1134 (43.7)	1040 (44.9)	94 (33.6)	<0.001*
Compliant with % of ADMAPP	39.6 ± 42.1	38.2 ± 42.1	58.0 ± 37.0	<0.001*

In the second step of our analysis we explored the characteristics of index and non-index cases among both genotypes. Analysis of the basic demographic characteristics did not reveal any statistically significant differences in either genotypes. Index and non-index cases did not appear to differ in number of reported comorbidities in either genotype groups.

Index ZZs were more frequently unable to work due to their medical condition and reported to miss greater number of days from work due to illness. Higher proportion of index ZZ cases received disability benefits (60.2% vs. 50.8%, p=0.007).

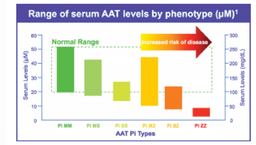
Higher number of index PiZZ patients reported ever smoked compared to non-index cases (74.1% vs. 66.3%; p=0.001), with greater number of years smoked.

	PiZZ			PiSZ		
Variable	**ZZ index**	**ZZ non-index**	***p***	**SZ index**	**SZ non-index**	***p***
Any Lung Disease	1894 (97.0)	382 (93.9)	0.002*	230 (96.2)	38 (86.4)	0.01*
Perception of Weight			0.03*			0.02*
Overweight	888 (45.9)	205 (51.8)		123 (51.5)	32 (74.4)	
Underweight	227 (11.7)	31 (7.8)		34 (14.2)	4 (9.3)	
About Right	819 (42.4)	160 (40.4)		82 (34.3)	7 (16.3)	

DISCUSSION

- The present research is one of a few studies in North America that focuses on looking into the differences and similarities not only between genotypes but also between index and non-index cases.
- Our study detected differences in disease progression and quality of life measures between patients with ZZ and SZ genotypes.
- Augmentation therapy with human serum derived α-1-antitrypsin still remains the only specific treatment option for patients with AATD aiming at the prevention of pulmonary disease progression and increasing survival.

Genotype/Pi-type & AAT Deficiency:



Modified from D. Walkrop

- Our study demonstrated that patients with ZZ and SZ genotypes significantly differ in their perception of health and fitness as well as their health behaviors
- Compared to ZZs, SZ patients present with significantly higher prevalence of cardiovascular comorbidities, including hypertension, cerebrovascular disease, as well as congestive heart failure, diabetes, arrhythmia. This association with SZ phenotype is not well understood, nor sufficiently investigated previously.
- Greater proportion of SZs (compared to ZZs) view themselves as "overweight", "out of shape" and "in poor health", however they exercise less and report heavier and longer history of smoking compared to ZZs.
- Significantly lower proportion of SZ patients compared to ZZs report following the guidelines of ADMAPP -a vital part of AlphaNet's commitment aimed to improve patients' health outcomes.. This lower adherence to the program may be due to the concept of the low self-perceived seriousness of their condition compared to the more severe ZZ mutation.

CONCLUSION

- In summary, the main take away message of this study was that ZZ and SZ patients differ not only in serum levels of their Alpha-1 antitrypsin, but also in their self- perception of quality of life as well as their health behaviors, adherence to management program and other characteristics.
- Despite the availability of the ADMAPP program and other resources directed on improvement of the quality of life of the patients with AATD, it appears that more severely affected ZZ individuals adhere to ADMAPP recommendation and maintain healthier lifestyle that are known to improve the overall quality of life of the patients with this disorder.