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Pulmonary Function in Children and Young Adults With Ataxia Telangiectasia

Sharon A. McGrath-Morrow, MD¹, Howard M. Lederman, MD PhD², Angela D. Aherrera, BA¹, Maureen A. Lefton-Greif, PhD¹, Thomas O. Crawford, MD³, Timothy Ryan¹, Jennifer Wright, RN^{1,2}, and Joseph M. Collaco, MD¹

¹Eudowood Division of Pediatric Respiratory Sciences, Johns Hopkins University School of Medicine, Baltimore, Maryland. ²Division of Allergy and Immunology, Department of Pediatrics, The Johns Hopkins University School of Medicine, Baltimore, Maryland. ³Department of Neurology and Adjunct in Department of Pediatrics, The Johns Hopkins Medical Institutions, Baltimore, Maryland.

Summary

Background—Pulmonary disease contributes to significant morbidity and mortality in people with ataxia telangiectasia (A-T). To determine the association between age and lung function in children and young adults with A-T and to identify factors associated with decreased lung function, pulmonary function tests were performed in 100 consecutive people with A-T.

Methods—Children and adults ranging from 6 to 29 years of age and with the diagnosis of A-T were recruited, and underwent pulmonary function tests.

Results—The mean forced vital capacity % predicted (FVC %) in the population was 56.6 ± 20.0 . Males and females between 6 and 10 years of age had similar pulmonary function. Older females were found to have significantly lower FVCs % than both older males ($P < 0.02$) and younger females ($P < 0.001$). The use of supplemental gamma globulin was associated with significantly lower FVC %. A modest correlation was found between higher radiation-induced chromosomal breakage and lower FVC % in males. No significant change in FVC % was found in a subset of subjects ($n = 25$) who underwent pulmonary function testing on two or more occasions over an average of 2 years.

Conclusion—In children and young adults with A-T, older females and people who required supplemental gamma globulin had significantly lower lung function by cross-sectional analysis. Stable lung function is possible over a 2-year period. Recognition of groups who are at higher risk for lower pulmonary function may help direct care and improve clinical outcomes in people with A-T.

Keywords

pulmonary function; ataxia telangiectasia; lung

INTRODUCTION

Lung disease is a significant cause of morbidity and mortality in people with ataxia telangiectasia (A-T). Individuals with A-T are at higher risk for developing interstitial lung disease (ILD), recurrent lung infections and bronchiectasis, in part due to their immune dysregulation.¹⁻⁴ Furthermore, it has been suggested that dysfunctional swallow, impaired mucociliary clearance, and dyscoordination of cough may increase the risk of pneumonia with feeds and viral infections.⁵ Unfortunately, variation in lung disease phenotype and disease progression can make it difficult to predict the natural course of lung decline in people with A-T and recognize who may be at increased risk for developing lung disease.

Up to now most studies examining lung disease and pulmonary function in the A-T population have been relatively small, retrospective and have primarily reported on people with respiratory complications.⁶⁻⁹ Recently, Vilozi and coworkers^{3,10} reported on spirometry data from people with A-T and found that spirometry was reproducible, obstructive disease was common, and hyper-reactive airway disease was associated with a greater decline in lung function per year in their population. Others, however, have reported that spirometry data and lung function in A-T was more consistent with a restrictive pattern due in part to underlying neuromuscular abnormalities and ILD.^{8,11}

Although it is well known that sinopulmonary disease is a hallmark of A-T, no large or longitudinal studies have been done to study the natural history of lung decline in A-T.¹² The primary objective of our study was to determine if an association between age and lung function in children and young adults with A-T exists and to identify factors associated with decreased lung function. In our study we performed cross-sectional analysis on 100 consecutive people with A-T who underwent pulmonary function tests (PFTs) in the out-patient setting. We also analyzed a subgroup of stable individuals with A-T who underwent PFTs on more than one occasion over an average of two years to assess the rate of decline in lung function over time.

In this study, we also hypothesized that radiation-induced chromosomal breakage was associated with lower lung function in people with A-T. Mutations in the disease-causing *ATM* gene have been shown to be associated with increased chromosomal breakage, cell senescence, inflammation, and impaired double-stranded DNA repair.^{13,14} As a secondary objective we therefore sought to determine if a correlation existed between increased chromosomal breakage and lower lung function in individuals with A-T.

METHODS

Study Population

All subjects met the diagnosis of A-T based on clinical symptoms and laboratory findings of either elevated alpha-fetoprotein, diminished ATM protein and/or increased chromosomal

breakage after in vitro exposure to x-rays as previously established.¹⁵ Subjects presented to our tertiary care center for evaluation as part of the Natural History A-T Study funded by the A-T Children's Project. All children and adults over 6 years of age were invited to participate in the study and all agreed to participate. The institutional review board of the Johns Hopkins Medical Institutions approved the study and written informed consent was obtained from every participant or his/her guardian. Studies were undertaken from 2005 to 2012. This study also includes pulmonary function test results from 15 subjects from a previous study.¹⁶

Spirometry

Similar to what is routinely used to assess lung function in people with neuromuscular disease,¹⁷ we chose to use FVC % predicted as a marker for lung function to determine if age, gender, need for supplemental gamma globulin replacement, BMI% or gastric tube placement correlated with FVC % predicted. Subjects underwent standard spirometry according to recommendations by the American Thoracic Society.¹⁸ During each visit a minimum of 3 flow-volume curves were attempted per person (MedGraphics). The best flow volume loop per visit was selected for further evaluation. Wang predicted values were used for children up to 16 years of age,¹⁹ and NHANES III predicted values were used for adolescents over age 16 years.²⁰

Chromosomal Breakage

Radiation-induced breakage was analyzed in the Kennedy-Krieger Institute Genetics Laboratory, Baltimore, MD. From peripheral blood samples, chromatid abnormalities per cell were measured based on the examination of 50 cells. In this laboratory, known A-T specimens had a range of chromatid abnormalities/cell between 1.40 and 4.00 compared to controls that had a range of chromatid abnormalities/cell between 0.06 and 0.32.

The average number of chromatid abnormalities was compared to an identically treated control sample to calculate fold change. This fold change was determined by dividing average number of chromatid abnormalities by the control.

Maximal Inspiratory Pressure (MIP) and Maximal Expiratory Pressure (MEP)

MIP and MEP measurements were performed at least two times per individual during each session. MIP was obtained by having the subject expire to residual volume (RV) and then inspire maximally. MEP was obtained by having the subject inspire to total lung capacity (TLC) and then expire maximally. Testing was done according to the American Thoracic Society recommendations.²¹ MIP and MEP measurements 60 cm H₂O, respectively, were considered within the lower limits of normal.²²

Body Mass Index Percentile (BMI %)

BMI % was calculated from CDC sex-specific norms for ages 2–20 years. Subjects over the age of 20 years were assigned the BMI % based on norms for 20-year olds for their height and weight at the time of pulmonary function testing. Growth failure was defined as 10th percentile of BMI.

Other Clinical Data

All other data used in this study were obtained through chart review; data were not available for four subjects on gastrostomy tube or supplemental gamma globulin status. Longitudinal clinical data were not available to determine the indications for initiating supplemental gamma globulin therapy or to follow the recurrence of infections. Of the 14 subjects who received gastrostomy tubes, all 14 had nutritional failure and 4 of them also had documented dysphagia.

Statistical Methods

Associations between demographic and clinical factors were assessed using *t*-tests. The relationship between cross-sectional measures and age was assessed using linear regression. For individuals with more than one pulmonary function test, a longitudinal comparison of FVC % predicted over time was conducted by comparing FVC % predicted via paired *t*-tests between their first and last visit, provided the visits occurred at least 6 months apart. STATA IC 11 (StataCorp LP, College Station, TX) was used for all statistical analyses. *P*-values <0.05 were considered statistically significant.

RESULTS

Demographics

The mean age of the 100 children and young adults in this study was 14.5 ± 5.9 years with an approximately even sex distribution (52% males; 48% females). The mean BMI % was $25.3 \pm 29.9\%$. Gastrostomy tubes were present in 14.6% of people in the study with 18.8% of people receiving supplemental gamma globulin at the time of pulmonary function testing (Table 1).

Factors Influencing Pulmonary Function Tests

The mean FVC % predicted for the entire population was 56.6 ± 20.0 . No differences in FVC % predicted, FEV1% predicted, MIPs or MEPs were found between females and males (Table 2). When we plotted FVC % predicted by age, we noted a subgroup of patients (>25 years of age) that had FVC % predicted values at the mean or higher (Fig. 1).

The need for supplemental gamma globulin at the time of pulmonary function testing was associated with lower FVC % predicted compared to those who did not (47.6 ± 17.8 vs. 59.3 ± 30 , $P < 0.025$; Table 3). In contrast, we did not find an association between FVC % predicted and BMI % or gastric tube placement for nutritional supplementation.

Influence of Gender and Age on Pulmonary Function Tests

We further examined correlations between gender, age, and lung function in our A-T population. We found that females between 6 and 10 years of age had higher mean FVC % predicted than males of the same age ($P < 0.035$). Older males (> 11 years of age) with A-T had similar mean FVC % predicted, compared to younger males ($P < 0.63$). However, older females (> 11 years of age), had significantly lower mean FVC % predicted compared to younger females ($P < 0.001$) and older males ($P < 0.023$; Fig. 2). This finding suggested that females may be disadvantaged with increasing age with respect to pulmonary function. To

determine if lower FVC % predicted in the older females was associated with growth failure, we compared BMI % to FVC % predicted. Significance with linear regression was noted in this group ($P < 0.030$; Fig. 3A) indicating that a correlation between growth failure and lower FVC % predicted may exist in the older females. However, no association between BMI % and FVC % predicted was found in the older males (Fig. 3B).

We also studied 25 subjects who underwent pulmonary function testing on more than one occasion over an average of 2 years. In this group we found no significant decline in lung function over a mean 2-year period (Table 4).

Chromosomal Breakage and FVC % Predicted

In people who had chromosomal breakage analysis performed on peripheral white blood cells, we examined whether an association existed between FVC % predicted and radiation-induced (RI) chromosomal breakage (RI chromosomal breakage/control). Of the 66 subjects who had RI chromosomal breakage studies done, we found no correlation between RI fold changes and FVC % predicted. However, when we examined differences by gender, males demonstrated a positive correlation between lower FVC% predicted and higher RI chromosomal breakage ($P < 0.035$; Fig. 4).

DISCUSSION

In a large cross-sectional descriptive study of individuals with A-T, we found several potential factors associated with lower lung function. Females who were 11 years of age and older had lower FVC % predicted compared to males and younger females with A-T. Furthermore, the use of supplemental gamma globulin was significantly associated with lower FVC % predicted. We also found a modest correlation between higher chromosomal breakage and lower FVC % predicted in males with A-T. Interestingly, in a subset of 25 people who underwent pulmonary function testing on more than one occasion over an average of 2 years, we found no significant decline. This is the first study to identify potential factors associated with lower lung function in A-T and it is the largest cross-sectional study of lung function in people with A-T.

In this study we found that older females with A-T may be disadvantaged with regard to lung function. This has been seen in other chronic lung diseases. In chronic obstructive lung disease (COPD), females have been shown to be at increased risk for more rapid decline in lung function. Indeed it was recently shown that females in the COPD gene study were significantly more likely to develop severe early onset COPD than males.²³ Also, it has been shown that females are more likely to carry the diagnosis of asthma after puberty compared to males.²⁴ In our study, we observed that older females with A-T had lower lung function as measured by FVC % predicted compared to younger females and older males suggesting that older females with A-T may be at increased risk for lung decline compared to males. The cause of this is unknown however there was a trend towards growth failure (<10% BMI %) correlating with lower FVC% predicted in the older females. This was not seen in the older males. Longitudinal studies are needed to validate these cross-sectional findings and to determine if they are generalizable to other A-T populations. In addition, further studies to identify factors that can influence lung function in older females such as puberty, growth

failure, neurological decline, and the cumulative effect of respiratory infections should be pursued.

We also found that supplemental gamma globulin administration in individuals with A-T was associated with lower FVC % predicted. This association may be due to a greater frequency of sinopulmonary infections in those individuals with more severe immunodeficiency, thus accounting for their lower pulmonary function.²⁵ If so, then earlier recognition of significant immunodeficiency and earlier supplementation of gamma globulin may help attenuate decline in lung function in people with A-T. We also examined whether an association existed between people with gastric tube placement and lung function. Although there was a trend towards lower FVC % predicted in people with gastric tubes it did not reach significance. This trend towards lower lung function in people with gastric tubes may again suggest a relationship between growth failure and respiratory pathology, however determining causality would require a longitudinal study.

An increase in chromosomal breakage with exposure to ionizing radiation (IR) is a hallmark of A-T.²⁶ We found a modest correlation between an increase in chromosomal breakage with IR and lower FVC % predicted in males with A-T. This could indicate that individuals at risk for greater chromosomal damage may have slower or less complete recovery following respiratory insults. We did not however find this correlation in females with A-T. Other cellular factors may account for the lung decline in A-T. For instance, an increase in cell senescence and inflammation in the lungs of people with A-T could contribute to a more rapid decline in lung function but study of these factors was beyond the scope of this study.

Interestingly, we found no significant decline in pulmonary function in a subgroup of individuals with A-T followed longitudinally over an average of 2 years, suggesting that a rapid decline in lung function is not necessarily inevitable in A-T. Alternatively, our results could be due to the small number of subjects studied or that the subjects studied represented a subgroup of healthier individuals. Nevertheless, larger longitudinal studies are needed to identify additional factors apart from age and gender that may influence pulmonary function decline in individuals with A-T.

People with A-T often have a restrictive pattern on spirometry, reflected as a decreased FVC % predicted and a high FEV1/FVC ratio. Our study as did others, found a moderate restrictive pattern by spirometry.¹⁰ This could be due to an inability to completely expire to residual volume, as found in people with neuromuscular disease. Alternatively it may represent fixed restrictive lung disease due to ILD or chronic lung injury.^{1,8} Nevertheless, most people with A-T are able to perform PFTs in a reproducible manner (references ² and ¹⁶) and trends can be followed over time for decline in lung function.

Our study had several limitations. First we compared pulmonary function results in our A-T population, with normal predicted values from a healthy reference population. This was done since normative PFT values are not available for the A-T population. The establishment of normative PFT values for the A-T population may allow for better tracking of lung decline in this population. We also did not measure lung diffusion capacity or routinely perform lung volume testing to confirm restrictive lung disease in the 100 people

studied. In a previous study however, we found that 12 of 15 stable individuals with A-T had near normal TLC but increased residual volume values; suggesting that most had a decreased ability to expire to residual volume, due to neuromuscular dysfunction rather than ILD.¹⁶ The population that we studied may also be subject to selection biases as it may represent a healthier population or a population with greater motivation and/or financial means to travel to our tertiary care center. Lastly, the cross-sectional nature of our data collection does not allow us to confirm any causal relationships.

In conclusion, we found that older females with A-T had lower lung function compared to older males and younger females and that people requiring supplemental gamma globulin had lower lung function than those who did not. Interestingly, we also found stable lung function in a subgroup of individuals with A-T who were followed longitudinally over a period of several years. These findings suggest that recognition of groups who may be higher risk for lower pulmonary function may help direct care and improve clinical outcomes in people with A-T.

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Fig. 1.
FVC% predicted versus age. Line represents a linear regression for the entire population.

Fig. 2.

Significantly lower forced vital capacity % predicted in females 11 years and greater compared males 11 years of age and greater and to females 10 years of age and less [†]*T*-test $P < 0.001$ between females 6–10 years of age and females 11 years of age and *T*-test $P < 0.023$ between females 11 years of age and males 11 years of age. [‡]*T*-test $P < 0.001$ between females 6–10 years of age and males 6–10 years of age. Females 6–10 years of age ($n = 21$), females 11 years of age ($n = 27$), males 6–10 years of age ($n = 15$), and males 11 years of age ($n = 37$). Horizontal bar in each group represents mean FVC% predicted for each group.

Fig. 3.

Lower FVC% predicted correlating with lower BMI% in older females with A-T (A), $P < 0.030$. No correlation between FVC% predicted and BMI% in older males (B), $P < 0.26$. Lines represent linear regressions.

Fig. 4. Higher radiation-induced breakage fold change/control associated with lower FVC % predicted in males with A-T (A), $P < 0.035$, but not in females (B), $P < 0.89$. Lines represent linear regressions.

TABLE 1

Study Population Demographics *

	Mean $\pm$ SD [range] (n = 100)
Sex (% male)	52.0
Age (years)	14.5 $\pm$ 5.9 [5.9, 29.2]
BMI percentile	25.4 $\pm$ 29.9 [0.1, 99.4]
Gastrostomy tube (% yes)	14.6 (n = 96)
Supplemental gamma globulin therapy (% yes)	18.8 (n = 96)

*
At the time of recruitment.

TABLE 2

Spirometry and Maximal Inspiratory/Expiratory Pressures for Entire Population

	Entire study pop.	Males	Females	<i>T</i> -test <i>P</i> value
n	100	52	48	—
Age (years)	14.5 ± 5.9	15.4 ± 6.0	13.5 ± 5.7	0.13
FVC (% predicted)	56.6 ± 20.0	56.8 ± 17.4	56.3 ± 22.7	0.91
FEV ₁ (% predicted)	59.1 ± 20.3 (n = 99)	60.4 ± 17.6	57.7 ± 23.1 (n = 47)	0.51
FEV ₁ /FVC ratio	94.0 ± 8.1 (n = 99)	93.7 ± 7.9	94.4 ± 8.3 (n = 47)	0.68
MIP	45.8 ± 24.5 (n = 79)	48.4 ± 25.6 (n = 44)	42.7 ± 23.0 (n=35)	0.31
MEP	49.2 ± 23.8 (n = 79)	53.2 ± 26.2 (n = 45)	44.0 ± 19.3 (n=34)	0.09

TABLE 3

Spirometry and Maximal Inspiratory/Expiratory Pressures

	BMI: 0–10th %tile	BMI: >10th %tile	T-test P value	G-tube present	G-tube absent	T-test P value	Supp. gamma globulin	No supp. gamma globulin	T-test P value
n	46	54		14	82	—	18	78	—
Age (years)	14.7 ± 6.2	14.3 ± 5.7	0.76	14.3 ± 4.2	14.4 ± 6.2	0.96	12.7 ± 5.4	14.8 ± 6.1	0.19
FVC (% predicted)	52.9 ± 20.2	59.7 ± 19.4	0.09	49.1 ± 19.1	58.5 ± 20.1	0.11	47.6 ± 17.8	59.3 ± 20.1	0.025
FEV ₁ (% predicted)	55.2 ± 20.4	62.5 ± 19.8 (n = 53)	0.07	53.1 ± 20.1	61.0 ± 20.3 (n = 81)	0.18	49.0 ± 19.2 (n = 17)	62.2 ± 20.0	0.014
FEV ₁ /FVC Ratio	94.1 ± 7.6	94.0 ± 8.5 (n = 53)	0.99	96.3 ± 5.1	93.9 ± 8.4 (n = 81)	0.31	95.5 ± 5.8 (n = 17)	93.9 ± 8.5	0.46
MIP	40.5 ± 22.6 (n = 37)	50.5 ± 25.3 (n = 42)	0.07	37.6 ± 20.0 (n = 12)	47.0 ± 25.2 (n = 63)	0.23	36.7 ± 22.2 (n = 15)	47.7 ± 24.8 (n = 60)	0.12
MEP	47.6 ± 22.5 (n = 37)	50.6 ± 25.1 (n = 42)	0.58	40.4 ± 14.7 (n = 12)	49.7 ± 24.7 (n = 63)	0.21	42.5 ± 22.2 (n = 15)	49.6 ± 23.9 (n = 60)	0.30

Bolding represents values that are significant.

TABLE 4

Longitudinal Spirometry (n = 25)*

	First test	Last test	Paired <i>T</i> -test <i>P</i> value	Annual rate of change
Age (years)	14.9 ± 4.5	18.0 ± 4.7	<0.001	—
FVC (% predicted)	55.3 ± 19.8	53.0 ± 18.1	0.33	−0.5%/year
FEV ₁ (% predicted)	58.2 ± 20.6	57.4 ± 19.3	0.75	−0.1%/year
FEV ₁ /FVC ratio	94.1 ± 7.7	94.0 ± 7.7	0.93	0.0/year

* Although 29 subjects had 2 or more spirometry tests available, we arbitrarily used only the 25 subjects with spirometry measurements at least 6 months apart.