

# Reversible Airway Obstruction in Children With Ataxia Telangiectasia

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**Summary.** Introduction: Lung disease is a significant cause of the short life span of ataxia telangiectasia (A-T) patients. Objective lung function measurements are difficult to achieve in A-T. Aim: To assess lung function by spirometry in relation to the clinical characteristics of A-T patients followed up at the Israeli Ataxia Telangiectasia National Clinic. Patients and Methods: Medical and spirometry data were collected from 27 A-T patients during 2004–2007. Laboratory, nutritional condition, mode of treatment, pulmonary status, and malignancies were assessed. The spirometry values FVC, FEV<sub>1</sub>, FEV<sub>0.5</sub>, FEF<sub>25–75</sub>, PEF and time rise to peak flow were analyzed individually and values were compared to those of healthy age-matched children. Results: Eleven patients (40.7%) were found to suffer from asthma according to clinical symptoms and response to bronchodilators. We found significant reduction in FEV<sub>1</sub> and FEV<sub>0.5</sub> (z-scores:  $-0.84 \pm 0.7$  SD,  $-0.7 \pm 0.6$  SD;  $P=0.0014$  and  $P=0.003$ , respectively), in relation to healthy predicted values. FEF<sub>25–75</sub> was significantly lower than that in healthy children in 5 of 11 asthmatic patients. All 27 patients showed higher than healthy FEV<sub>1</sub>/FVC and FEV<sub>0.5</sub>/FVC ratios (z-scores  $0.68 \pm 0.99$  SD,  $P < 0.0015$ , and  $2.12 \pm 1.50$  SD,  $P < 0.0015$ , respectively). The rise time to peak flow was three-fold longer than that of healthy children. Conclusion: Obstructive lung disease is common among A-T patients. Maximal peak flow reduction and prolonged rise time to peak flow may be the first signs of pulmonary involvement in these patients. Early treatment with anti-asthma therapy, bronchodilators, and steroids, may prevent further pulmonary deterioration and improve the prognosis of A-T patients. **Pediatr Pulmonol.** © 2010 Wiley-Liss, Inc.

**Key words:** airway obstruction; children; ataxia telangiectasia; children.

## INTRODUCTION

Ataxia telangiectasia (A-T) is a rare autosomal recessive multisystem disorder characterized by oculocutaneous telangiectasia, immunodeficiency, and progressive neurodegeneration and cerebellar ataxia, which lead to severe neuromotor dysfunction.<sup>1–3</sup> The prognosis for A-T patients is poor, and median survival is only 25 years. The leading causes of death in A-T patients are cancer and pulmonary disease.<sup>4</sup> Lung disease develops in more than 70% of A-T patients,<sup>5</sup> due to recurrent infections,<sup>6</sup> ineffective cough and abnormal airway secretion clearance, oropharyngeal dysphagia, and recurrent aspiration.<sup>7</sup> Interstitial lung disease is found in a significant number of A-T patients even in the absence of immune deficiency.<sup>8</sup> In addition, the patients are wheelchair-bound at an early age and their neurological disease may contribute to further respiratory deterioration.<sup>7</sup>

Pulmonary function tests (PFT) may provide important information about lung disease progression and the treatment effect in A-T patients. Forced flow volume curves measured by spirometry is the most common method of assessing pulmonary function, but attempts to measure spirometry in A-T patients are scarce.

McGrath-Morrow et al.<sup>9</sup> have recently reported results of forced expiratory maneuvers in a group of ten adolescent A-T patients. Reproducibility of the spirometry and decreased ability to expire to residual volume (RV)

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without restrictive defect were observed, and therefore analysis was performed on FVC and FEV<sub>1</sub> values only. In children with A-T, reliable spirometry measurements are problematic due to the difficulty in performing forced inhalation to total lung capacity and forced exhalation to RV, which can cause erroneous results. The question of whether simple spirometry can be an objective measure used as a valuable clinical tool to assess the A-T children's lung condition is yet to be explored.

The aim of this study was to evaluate spirometry indices in relation to the clinical characteristics of A-T patients followed up at the Israeli Ataxia Telangiectasia National Clinic.

## PATIENTS AND METHODS

A total of 44 patients followed at the Ataxia Telangiectasia National Clinic at the Safra Children's Hospital, Sheba Medical Center, Tel Hashomer, Israel, met the diagnostic criteria for A-T.<sup>10</sup> The study cohort (n = 27) of A-T patients underwent PFT during 2005–2007. Their medical records were analyzed. The study was approved by the Ethics Committee of Sheba Medical Center.

Twenty-three (85.2%) patients were homozygous for the mutations in the ATM gene. For the remaining participants, the diagnosis was confirmed by chromosomal breakage or Western blot analysis of ATM.

## LABORATORY AND MEDICAL DATA

Nutritional status was assessed by body mass index (BMI). History of lung involvement was assessed by the existence of asthma, recurrent pulmonary infection or bronchitis, and by the number of hospitalizations due to lung disease. Immunologic status was evaluated by recording the patients' immunoglobulin levels, lymphocyte count, and history of IVIG treatment.

## PULMONARY FUNCTION TESTS—SPIROMETRY

Each patient performed spirometry tests at least once during the study. Spirometry was measured with the ZAN100 spirometer (n-Spire Health, Inc., Longmont, CO). The measurement was performed according to ATS/ERS standardization in the sitting position with a nose clip,<sup>11</sup> with a nurse standing behind the patient and assisting in maintaining the head in a natural position during the examination. Special attention was given to avoiding a leak around the mouthpiece. Height was measured by arm-span.

## Inspection of Measurements

The flow volume curves were first inspected for technical abnormalities (cough, glottis closing, lack of cooperation, or abrupt cessation of expiration). The curve

with the highest FVC + FEV<sub>1</sub> (or FVC + FEV<sub>0.5</sub>) was chosen for analysis. Spirometry values were compared to healthy, age-matched predicted values for height and presented as percent of predicted values<sup>12,13</sup> and as the number of standard deviations from the norm (z-score).

## Statistics

The difference between the patients' spirometry indices and healthy values (calculated for height) were tested by Student's unpaired *t*-tests. Spirometry indices included FVC, FEV<sub>0.5</sub>, FEV<sub>1</sub>, PEF, FEF<sub>25–75</sub>, and time rise to peak flow. Airway obstruction severity was defined according to GINA guidelines<sup>14</sup> in relation to healthy. *P* < 0.05 was considered to be statistically significant.

## RESULTS

Twenty-seven of the 44 patients (18 male, 66.7%) with a median age of 8.8 years (range 3.7–19.3 years) performed spirometry. The mean (±SD) age at diagnosis was 3.9 ± 2.6 years. The presenting symptom in 26 (96.3%) of the patients was ataxia, appearing at the age of 1.4 ± 0.6 years. Sixteen (59.3%) of the patients had a family history of A-T, with 10 being in a first-degree relative. Consanguineous marriages were seen in 20 (74.1%) patients, 9 of them first degree. The cohort consisted of 12 patients of Arab descent (of whom 7 were Bedouin), 11 Jewish patients (7 of North African origin, 3 from Yemen, and 1 Ashkenazi), and 4 Druze patients. Fifteen (55.6%) patients were wheelchair-bound at the time of the study, with time in a wheel chair being 2.0–12.3 years. Alpha-fetoprotein was high in all of our patients with a median level of 239 ± 101 kU/L (range 75–418 kU/L). Severe failure to thrive was observed in 13 of the 27 patients (48%), with a mean BMI of 15.9 ± 3.2.

## Respiratory Illnesses

During the study period, 22 (81.5%) children were hospitalized at least once, 12 of them due to respiratory disease. Eleven (40.7%) patients suffered from asthma diagnosed by clinical symptoms and clinical response to bronchodilators. In 5 patients with asthma we observed an improvement of FEV<sub>0.5</sub> or FEV<sub>1</sub> ranging from 12% to 35% after bronchodilators.

Nineteen (70%) patients had a history of at least one episode of pneumonia. Three patients with recurrent respiratory infections developed clubbing. Thirteen (48%) patients received replacement intravenous immune globulin therapy during the study period.

Two patients underwent polysomnography testing, exhibiting pathological results with an apnea and hypopnea index of 10–55 (normal 1–3) and de-saturations below 90% during 20–26% percent of sleep time.

**TABLE 1—Baseline Spirometry in Young Children (n = 27)**

Index	% Predicted <sup>12,13</sup>	Z-score	P-value from healthy
FVC	48 ± 14	-1.02 ± 0.67	<i>P</i> < 0.0001
FEV <sub>0.5</sub>	64 ± 20	-0.70 ± 0.67	<i>P</i> < 0.005
FEV <sub>0.5</sub> /FVC	131 ± 23	2.33 ± 1.58	<i>P</i> < 0.0001
FEV <sub>1</sub>	44 ± 7	-1.17 ± 0.59	<i>P</i> < 0.0001
FEV <sub>1</sub> /FVC	109 ± 12	0.95 ± 1.41	<i>P</i> < 0.005
PEF	67 ± 20	-0.68 ± 0.62	<i>P</i> < 0.005
FEF <sub>25-75</sub>	97 ± 28	-0.04 ± 0.91	NS
Time rise to PEF (msec)	220 ± 145		
Expiratory time (sec)	1.2 ± 0.5		

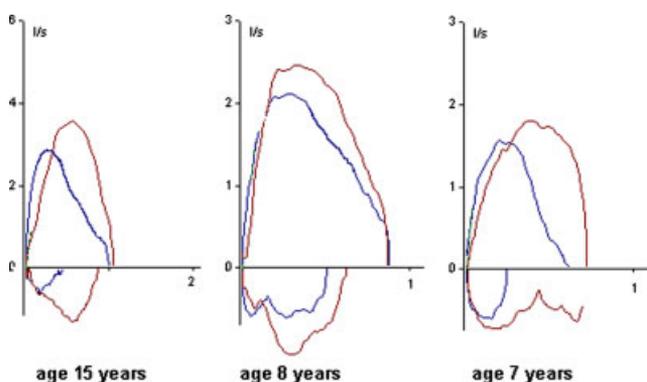
All values are presented as % predicted.

### Pulmonary Function Tests

All twenty-seven patients performed technically accurate spirometry maneuvers. In eight patients expiration time was shorter than 1 sec regardless of age. In these cases we used forced expiratory flow in half a second (FEV<sub>0.5</sub>) measure. All spirometry indices values are presented in relation to the predicted values in Table 1. Inter-subject reproducibility for each parameter was as follows: FVC = 4.3 ± 2.6%; FEV<sub>1</sub> = 4.3 ± 2.7%; FEV<sub>0.5</sub> = 5.3 ± 2.6%; PEF = 2.7 ± 3.0%, and FEF<sub>25-75</sub> = 5.3 ± 5.1%. We found that FVC values were moderately to severely reduced (z-score of -1.01 ± 0.06 SD; *P* = 0.0001). FVC, FEV<sub>1</sub> and FEV<sub>0.5</sub> deteriorated significantly with age.

The examples of authentic scan of three “flow volume curves” before and after bronchodilators are presented in Figure 1. The percent change in the different spirometry indices in response to bronchodilators are shown in five patients with good response ((+) = 10% change) in Table 2.

Obstructive airways were found by the reduction in FEV<sub>1</sub> (z-score -0.84 ± 0.7 SD, *P* = 0.0014) and FEV<sub>0.5</sub> (z-score -0.7 ± 0.6 SD, *P* = 0.003), in relation to healthy predicted values. FEV<sub>1</sub>/FVC values were higher than



**Fig. 1.** Example of three typical flow volume curves before and after bronchodilator. Smallest curve = baseline; large curve = after bronchodilator.

expected (110.9 ± 13.6% of predicted, z-score 0.68 ± 0.99 SD, *P* < 0.0015) as were FEV<sub>0.5</sub>/FVC values (124.8 ± 29.5 and z-score of 2.12 ± 1.50 SD, *P* < 0.0015). Obstructive airway abnormalities as presented by FEF<sub>25-75</sub> were found in five of the eleven children designated as asthmatic. Bronchodilators produced a marked improvement of over 12% in FEV<sub>1</sub> or, FEV<sub>0.5</sub>; in PEF, and/or over 20% in FEF<sub>25-75</sub>.

A prolonged rise time to peak expiratory flow was found in 20 (74%) of the children, unrelated to age (normal 60–100 msec).<sup>12,15</sup> A strong positive correlation was found between the increment of FEV<sub>0.5</sub>/FVC and prolonged rise time to peak flow, far above the normal range. Correlations are presented in Figure 2.

### DISCUSSION

The present study shows that children with A-T have the ability to perform spirometry. Despite the technical obstacles, such as the need to seal the mouthpiece and hold the head in place during testing, and ensuring inhalation to TLC and/or expiration to RV, values were reproducible. The study demonstrates that regular lung function testing may aid clinical respiratory assessment in patients of all ages with A-T.

Results demonstrated decreased vital capacity and decreased respiratory flows in all subjects. A prolonged rise time to peak flow, along with an FEV<sub>0.5</sub>/FVC elevation, was shown. Clinically, 40% of the patients

**TABLE 2—Percent Change in the Different Spirometry Indices in Response to Bronchodilators Shown in Five Patients With Good Response**

Patient	FVC	FEV <sub>1</sub>	FEV <sub>0.5</sub>	PEF	FEF <sub>25-75</sub>	Response
1	-2.2	-3.7	7.4	16.0	20.4	++
2	5.8	0.0	15.9	38.6	27.3	+++
4	6.1	0.0	11.7	31.9	40.3	+++
12	2.2	1.1	16.4	6.9	28.3	++
23	6.5	1.7	24.5	15.9	36.1	+++

+ = 10% change.

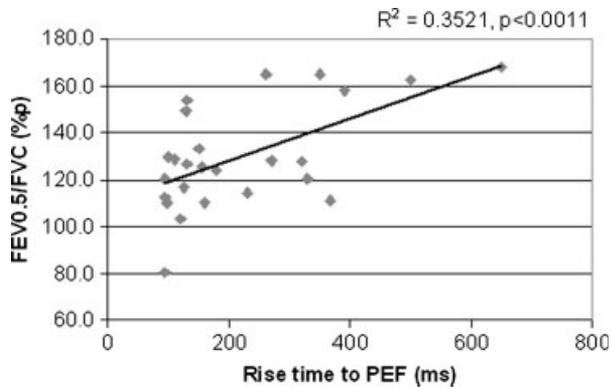


Fig. 2. Correlation between the increment of  $FEV_{0.5}/FVC$  and prolonged rise time to peak flow.

reported symptoms of asthma and improved with bronchodilator therapy. However, obstructive ventilatory abnormalities with bronchial dilator effect were found by spirometry in 45% of the asthmatic patients only. Improvements were pronounced by the increase in peak flow and  $FEV_{0.5}$ . These observations, to our knowledge, have not been previously reported in the literature.

The baseline spirometry findings in this investigation are similar to those presented recently by McGrath-Morrow et al.,<sup>9</sup> illustrating a high degree of reproducibility in performing PFT in A-T patients. FVC values in their study were low compared to normal and were accompanied by high RVs. One could claim that the use of spirometry can be problematic in A-T due to problems expiring to RV and short expiratory time. Both may result in pronounced decreased FVCs and  $FEV_{1s}$  that may not truly represent restrictive disease. However, this knowledge should not contraindicate observation of obstructive disorders, as was evident by clinical and spirometric response to bronchodilators. We did not measure the RV in our patients; however, patients'  $FEV_1$  (Table 1) and  $FEV_{0.5}$  were moderately impaired, together with the clinical symptoms and challenge test (cough and good response to bronchodilators), suggesting that many of our A-T patients suffer from reversible airway obstruction. Pronounced improvements in both  $FEF_{25-75}$  values (in 45% of the asthmatic patients) and in peak expiratory flow in response to bronchodilators, supports the reversible airways obstruction revealed in our patients (Fig. 1).

Several factors may contribute to the abnormal obstruction pattern in these patients. Lefton-Greif et al.<sup>7</sup> found that oropharyngeal dysphagia and aspiration are very common in A-T patients. They also demonstrated that silent aspiration had occurred in 71% of their A-T patients, by performing video fluoroscopy swallow studies. In addition, gastro-esophageal reflux disease may lead to hyper-reactive airway disease and thus contribute to the obstructive findings of our population.<sup>15</sup>

McGrath-Morrow et al.<sup>16</sup> did not demonstrate a tendency for obstructive sleep apnea syndrome or night-time hypoxemia in A-T patients in their recent work. However, some of their patients showed mild hypoventilation with increased end-tidal  $CO_2$ . In our study, only two patients underwent polysomnography testing, which revealed moderately obstructive sleep apnea (OSAS) (13–15 RDI) and hypoxemia  $<90\%$  during 22–25% of the night. The trend of OSAS could also contribute to the high prevalence of wheezing and asthma symptoms in A-T patients.<sup>17,18</sup> All of these factors, taken together with the spirometry data presented, may explain the clinical asthma-like symptoms and good response to bronchodilators of our patients. This once again gives support to the finding that A-T patients may suffer from a reversible airway obstruction.<sup>18</sup>

Recurrent respiratory infection and the involvement of lung parenchymal abnormality is always part of the natural history of AT patients,<sup>6</sup> and 50% die as a result of bronchopulmonary involvement.<sup>5</sup> Moreover, many of the patients suffer from a cellular and humoral immune deficiency.<sup>2,4,6</sup> Seventy-eight percent of our patients demonstrated some degree of immune deficiency, the most frequent of which were lymphopenia and IgA deficiency, in accordance with other studies.<sup>6,19</sup>

The varied immunologic problems, combined with impaired muscle coordination, in particular of the upper airways, and the generalized muscle weakness may worsen the lung disease.<sup>7</sup> In corroboration, our results show three abnormalities in the spirometry indices: a significant reduction of PEF ( $P < 0.005$ ) combined with a reduction in expiratory time with age and a very long rise time to PEF compared with healthy expected findings.<sup>20,21</sup>

The rise time to peak flow was three to four times longer than that of healthy values in the major part of our patients (250–350 msec vs. 70–80 msec in the healthy population; Table 2). In healthy subjects time rise to peak flow is wide and larger PEFs are strongly associated with a shorter rise time.<sup>19</sup> However, in patients with airflow limitation the opposite was found: short rise time is associated with a small PEF due to air-trapping and small inspiratory capacity. In A-T patients the force-velocity relationship of the respiratory muscles with airflow limitation may be very different from that of normal patients due to progressive muscle weakness from the underlying disease and chest wall deformation in relation to a long period of time wheelchair-bound. Fifteen of the 27 patients tested were wheelchair-bound between 3 and 8 years. The connection between development of scoliosis and time bound to a wheelchair has been established in various muscle diseases.<sup>22</sup> One should keep in mind that the delay in initiation of the breath may not be due to obstructive lung disease per se, but in part secondary to neurological dysfunction and delayed processing before initiating the

expiratory breath. We propose that this finding is an important clinical observation that should be explored in the future.

We found a higher than predicted flow to volume (FEV<sub>1</sub>/FVC) ratio (Table 1), which could be due to poor technique. Since we were very strict on proper performance, we suggest that the expiratory muscle weakness and lack of coordination of AT patients may explain the enormous fall in FVC observed, greater than the previously established FEV<sub>1</sub> reduction,<sup>9</sup> thus bringing about a higher than predicted FEV<sub>1</sub>/FVC ratio (Table 1).

We found no change post-bronchodilator in the FEV<sub>1</sub> values compared with baseline. FEV<sub>1</sub> is the gold standard for assessing positive response to bronchodilators in an obstructive phenotype. A-T patients often do not exhale for more than 1 sec; therefore, FEV<sub>1</sub> may not be an accurate parameter for describing bronchial obstruction in this particular group. It is therefore suggested that FEV<sub>0.5</sub> (forced expiratory volume in half a second) may be a better index for describing changes in lung function than FEV<sub>1</sub> in AT patients.

We found that FEV<sub>0.5</sub>/FVC was higher than predicted. In practice, one would expect a lower than predicted FEV<sub>1</sub>/FVC or FEV<sub>0.5</sub>/FVC in obstructive lung diseases. It is interesting to note, however, that FEV<sub>0.5</sub>/FVC found in non-asthmatic patients was  $2.3 \pm 1.6$  SD above normal, while in the asthmatic patients this value was only  $-0.4 \pm 0.9$  SD from normal ( $P < 0.0001$ ).

It may be that in order to describe airway obstruction in A-T more than a single parameter will be needed even though none of the conventional parameters showed significant strength over the others. It could be best to combine changes of FEV<sub>1</sub>, FEV<sub>0.5</sub>, PEF, and FEF<sub>25-75</sub>.

Respiratory and bulbar muscle weakness, as well as the retention and increase of secretions, in particular during viral infections, may lead to atelectasis, airway obstruction, and the reduced pulmonary compliance seen in A-T patients.<sup>9,23-26</sup> Gozal has shown that the fall in peak cough flow is related to a reduction in spirometry values, in particular FVC and/or FEV<sub>1</sub>, in Duchenne Muscular Dystrophy patients.<sup>23</sup> Peak-cough flow is an important parameter for long-term follow-up in children with muscle weakness and is related to FVC and FEV<sub>1</sub> reduction. Although peak cough flow was not validated in our A-T patients, the reduced lung function in these patients could be the first sign of the expected reduction in peak-cough flow. Therefore, techniques to assist mucociliary clearance, physiotherapy, steroid treatment, inhalation, prophylactic antibiotics, and prevention therapy for asthma exacerbation should be promptly considered in these patients.<sup>8,9</sup>

We acknowledge the importance and additional information we could have gained by measuring lung volumes. It was recently found that A-T adolescents have normal functional residual capacity, near normal total lung

capacity, but high RV values.<sup>9</sup> High RV values may be due to short expiration but it could also be due to trapped air in the presence of airway obstruction. Future exploration of the relation between reversed high RV and response to bronchodilators may have strengthened our suggestion of reversible airways obstruction in A-T patients.

We conclude that obstructive lung disease may be common among A-T patients. Forced expiratory maneuvers may provide important information about lung disease progression in A-T, despite the skewed pattern of the curves. A reduction in maximal peak flow, FVC, FEV<sub>1</sub>, or FEV<sub>0.5</sub>, and mid-expiratory flows, as well as the positive response to bronchodilators, may be the first signs of pulmonary obstruction in these patients. Early treatment and with anti-asthma therapy, bronchodilators, and steroids, may prevent further pulmonary deterioration.

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