

Clinical and Immunologic Outcome of 42 Individuals with Trimellitic Anhydride-Induced Immunologic Lung Disease after Transfer to Low Exposure

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ABSTRACT

The purpose of this study is to determine the clinical and immunologic status of trimellitic anhydride (TMA)-exposed employees who have had immunologic lung disease and who have been moved to lower-exposure jobs. In a case series design, 42 consecutive employees with TMA-induced immunologic lung disease were studied after they had been moved to low-exposure jobs for more than 1 year. Pulmonary symptoms were obtained by physician-administered questionnaire. Immunologic studies were performed using ELISA techniques. Spirometry and chest films were obtained annually. Employees with late asthma ($n = 4$), late respiratory systemic syndrome (LRSS) ($n = 13$), or both LRSS and asthma ($n = 4$) had improved symptoms, improved pulmonary functions, and lower IgE against TM-HSA. Fourteen of 21 employees with asthma had improved symptoms, improved pulmo-

nary functions, and lower IgE against TM-HSA. The 7 who did not improve with transfer to low-exposure jobs did improve with transfer to jobs with no TMA exposure. There were no chest film findings in any group that were definitely related to TMA. Most individuals who develop TMA hypersensitivity syndromes improve with transfer to low-exposure jobs, but occasionally, individuals require transfer to a no-exposure job. (Allergy and Asthma Proc 21:355–359, 2000)

Trimellitic anhydride (TMA) is a reactive, low-molecular-weight acid anhydride that has been used for more than six decades as a curing agent for epoxy resins. The most important adverse health effect of TMA is immunologic sensitization, causing respiratory diseases such as asthma and rhinitis (A/R), late asthma (LA), and late respiratory systemic syndrome (LRSS).¹ A variety of other acid anhydrides have been reported to cause similar immunologic syndromes.²

There are relatively few studies of prognosis and natural history of occupational immunologic lung disease after removal from exposure; the most-studied disease is occupational asthma.³ Some of the earliest investigations reported that more than half of individuals had persistence of asthma symptoms after termination of exposure.⁴ Continuation of exposure once clinical symptoms occur is believed to be an important determinant of whether permanent asthma develops.⁵ Following cessation of exposure, maximal improvement in spirometry generally occurs within 12 months.⁶

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Supported by The Ernest S. Bazley Grant to Northwestern Memorial Hospital and Northwestern University Medical School, and Amoco Corporation

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More recent investigations of prognosis of occupational asthma have reported more optimistic outcomes, provided that affected individuals are diagnosed and removed early in their disease. In a longitudinal study of lung function in 280 men with western red cedar asthma, it was reported that those who continued exposure had a more rapid decline in FEV1 than controls. The authors concluded that early diagnosis and removal were important in the prevention of further deterioration of lung function and respiratory symptoms.⁷ A similar conclusion was reached by Douglas and co-workers in their investigation of occupational asthma in salmon processing plant employees.⁸ In a study of 15 individuals with occupational asthma due to high- and low-molecular-weight agents by Lemiere and her colleagues, they observed that nine removed individuals (60%) had a decrease in both specific and nonspecific bronchial reactivity.⁹

Relative to acid anhydride-induced occupational asthma, Baur and co-investigators have reported that approximately half of affected individuals normalized their pulmonary functions when removed.¹⁰ Our experience with participants in annual surveillance programs with two different groups of workers exposed to two different acid anhydrides is that relatively few individuals with anhydride asthma have asthma symptoms or permanently abnormal pulmonary functions.^{11,12} Because of the annual nature of the surveillance programs and because there are onsite medical personnel familiar with anhydride-induced respiratory disease at each site, the great majority of individuals are diagnosed and removed after having symptoms for a relatively short period of time.

The purpose of the current study was to extend our previous observations of 29 individuals with TMA-induced immunologic lung disease who were transferred to low-exposure jobs. We now have data on 42 individuals, longer follow-up, and seven individuals who were removed from any TMA exposure because of recurrent symptoms with low-level exposure.

METHODS

Study Population

The study population was composed of 42 individuals employed at a TMA manufacturing plant. Each of the individuals had been diagnosed as having an immunologic lung disease due to TMA:A/R, LA, LRSS, or both A/R and LRSS. Criteria for these diagnoses have been previously published.¹ Each employee had been transferred to low-exposure duties for at least one year. Seven individuals continued to have moderate or severe symptoms and were therefore transferred to another facility in which there was no TMA. All transferred subjects had positive signs, symptoms, and serology. Each subject gave written, informed consent, and the study was approved by the IRB at Northwestern University.

Exposure Classification

Exposure classifications were assigned by an industrial hygienist based on data obtained from personal monitoring of some employees, air sampling data, and knowledge of each job description. The reaction vessels in which TMA is produced require heat, but that is not the area where employees are working with TMA. Most of the employees in category 1 either ran the bagging machine or transported the finished bags with a forklift. Rarely, the bagging machine would malfunction or the forklift driver would puncture the bags, resulting in higher exposures to TMA. Respiratory protection is routinely provided. The exposure categories ranged from 1 to 5, with 5 being the lowest exposure and 1 being the highest. Exposure range and mean are shown in Table I. The exposures are time-weighted averages (TWA) of specific acid anhydride.

Clinical Evaluation

A questionnaire modified from that developed by the National Institute for Occupational Safety and Health (NIOSH) and the University of Cincinnati was administered to each employee by a physician.¹³ The questionnaire was formulated to elicit type, timing, and severity of symptoms. Demographic data were also obtained. Physical examination was conducted after the questionnaire was completed. Chest film and spirometry were also performed.

Immunologic Studies

Blood was drawn annually from each employee to evaluate IgE and IgG antibodies against TM-HSA in serum. TM-HSA was prepared and characterized as previously described. The immunologic assays were performed using an enzyme-linked immunosorbent assay, as reported previously.¹⁴ Positive and negative control sera are used to standardize the assay. The titer is the lowest dilution of serum that is greater than twice the optical density of the mean of the control sera. The serum dilutions used for IgG are 1:10, 1:100, and 1:1000, while the serum dilutions for IgE are 1:5, 1:10, and 1:50. If the optical density were less than twice the control sera at 1:10 for IgG or 1:5 for IgE, then the results would be expressed as <1:10 or <1:5, respectively.

TABLE I

Personal Monitoring Data

Exposure Class	Range (mg/m ³)	Mean (mg/m ³)
1	0.0029–1.7	0.13
2	0.023–1.9	0.036
3	0.0001–0.12	0.002
4	0.00023–0.0024	0.00051
5	<0.00045–<0.00060	<0.00053

Statistics

The Wilcoxon rank sum test was used to compare antibody titers pre- and post-removal from exposure. Gender, smoking, race, and severity of symptoms at diagnosis were compared by Fisher's Exact or Chi square. Symptoms for asthma severity were cough, dyspnea, wheeze, and chest tightness, whereas symptoms for LRSS were cough, dyspnea, fever, and myalgias. Statistics were performed using Sigma Stat. (SPSS, Chicago, IL)

RESULTS

Study Population

Demographic data on the 42 individuals in this study are listed in Table II. Four individuals had LA, 21 had A/R, 13 had LRSS, and 4 had both LRSS and A/R. Age, gender, and race were similar among the groups. The individuals were in one of the three categories with the highest exposure at the time of diagnosis. The duration of exposure prior to the onset of symptoms varied widely from as short as 2 months to as long as 21 years.

Clinical Evaluation

The clinical data at most recent follow-up are listed in Table III. Chest films were all normal or non-contributory. All individuals had been transferred to lower exposure jobs for at least one year; the median time at low exposure was 5 years.

All individuals had moderate to severe symptoms at the time of diagnosis. None of the four individuals with LA reported symptoms after transfer to a low exposure job; one

had mildly restricted lung function and another had mildly obstructed lung function.

Three of 21 individuals with A/R had occasional mild symptoms when the wind would blow from the TMA unit to the unit at which they worked; those 3 individuals had normal spirometry. Seven of the 21 individuals had been completely removed from exposure because they had moderate to severe symptoms despite being transferred to low-exposure jobs; two of those individuals had mildly obstructed pulmonary function. One of those two individuals was on inhaled β agonists and inhaled corticosteroids.

None of the 11 employees with LRSS had symptoms after transfer to low-exposure jobs. Two of those had mildly obstructed pulmonary function.

Of the four individuals with both LRSS and A/R, one had mild asthma symptoms with wind shifts from the TMA unit. All four had normal spirometry. We compared symptomatic and asymptomatic individuals with histories of TMA asthma (Table IV). Gender, race, and cigarette smoking were not significantly different. Symptomatic individuals were more likely to have severe symptoms at time of diagnosis, but this did not reach statistical significance ($p = 0.11$). Duration of exposure before onset of symptoms and length of following were similar.

Immunologic Studies

As is shown in Table III, the median antibody titer declined or remained constant when the employees were transferred to low-exposure jobs. While the changes were not statistically significant, 4 of 11 employees with LRSS had declines in IgE and IgG against TM-HSA. In

TABLE II
Demographic Data on Employees with TMA Lung Disease

	Late Asthma (n = 4)	Immediate Asthma (n = 21)	LRSS (n = 13)	Both (n = 4)
Age				
Median	34	38	39	31
Range	23-46	22-58	26-58	25-42
Gender F/M	0/4	2/19	0/13	1/3
Race B/W	0/4	3/18	1/12	1/3
Cigarette smoking N/E/C*	4/0/0	7/3/11	2/0/10	1/1/2
Exposure Category				
1	3	11	2	3
2	1	3	6	1
3	0	7	5	0
4	0	0	0	0
5	0	0	0	0
Exposure Duration				
Median	2 yr	1 yr	3 yr	6 mo
Range	1-3 yr	2 mo-21 yr	2 mo-20 yr	30 mo-5 yr

*N = never; E = ex; C = current.

TABLE III

Clinical and Laboratory Data on Follow-Up of Employees with TMA-Induced Lung Disease

		Late Asthma (n = 4)	Immediate Asthma (n = 21)	LRSS (n = 13)	Both (n = 4)
Time Since Moving to Lower TMA Exposure					
Median		3½ yrs	5 yrs	5 yrs	10 yrs
Range		19 mo–8 yrs	13 mo–20 yrs	1 yr–15 yrs	2–18 yrs
Respiratory Symptoms with TMA Exposure	None	4	18*	13	3
	Mild	0	3	0	1
	Mod	0	0	0	0
	Severe	0	0	0	0
Spirometry					
Normal		2	19	11	4
Mild Obstruction		1	2	2	0
Mild Restriction		1	0	0	0
Median Specific IgE Antibody Titer					
Before Removal		1:10	≥1:50	≥:50	≥1:50
After Removal		1:5	1:10	1:10	1:10
Median Specific IgG Antibody Titer					
Before Removal		≥1:1000	≥1:1000	≥1:1000	≥1:000
After Removal		≥1:1000	1:100	≥1:1000	1:100

*Seven had no TMA exposure.

TABLE IV

Comparison of Characteristics of Symptomatic and Asymptomatic TMA Asthmatics after Exposure Reduction

	Symptomatic	Asymptomatic
Gender (F/M)	0/4	2/19
Race (B/W)	0/4	4/17
Cigarette smoking (N/E/C)*	1/1/2	7/1/12
Duration of TMA Exposure Before Symptom Onset		
Median	6 months	2 years
Range	2 months–20 years	1 month–10 years
Severity of Symptoms at Diagnosis	Mild Mod Severe	Mild Mod Severe
	0 0 4	6 6 9
Time at Lower Exposure		
Median	12 years	3 years
Range	5–20 years	1½–18 years

*N = never; E = ex; C = current.

those 21 with A/R, 11 had a decline in IgG and 14 had a decline in IgE. Those declines were statistically significant by Wilcoxon's sign rank test ($p < 0.05$). Two of four with LA had reduction in titer of both antibodies. In those with both LRSS and A/R, one had a reduction in IgG while two had reduction in IgE. No employee had a rise in titer for either antibody.

DISCUSSION

Long-term follow-up studies of individuals with occupational immunologic lung disease are important in order to assess the full impact of these diseases. Occupational asthma due to several different agents has been stud-

ied with somewhat variable results, which are probably explained by the variability in length of time to diagnosis and removal from exposure.¹⁵ In addition to studying a TMA-exposed population we also perform annual surveillance studies for a population exposed to hexahydrophthalic anhydride (HHPA). We have reported optimistic outcomes in that population as well.¹⁶ Immunologic respiratory disease due to HHPA was diagnosed in 28 employees, each of whom had been removed from exposure for at least one year. Only one individual still had mild asthma.¹⁶

We have previously reported 29 individuals with occupational immunologic lung disease induced by TMA who had been moved to jobs with low exposure (categories 4 and

5).¹¹ We found that most of them were asymptomatic, with normal spirometry and chest films. However, approximately half of those with immediate-type asthma had intermittent moderate to severe symptoms. In this study we also found that a significant majority of the 42 individuals studied were asymptomatic, with normal spirometry. In addition, we noted that the seven individuals with moderate to severe symptoms became asymptomatic when removed from any exposure; two had mildly obstructed pulmonary functions, one of whom was on regular inhaled medication for asthma.

When we compared those 3 asthmatics who were still symptomatic with the 21 who weren't, the only factor that was somewhat associated with continued symptoms was the severity of symptoms at diagnosis. This was only a trend and did not reach statistical significance.

In a study of pyromellitic dianhydride (PMDA)-exposed employees, it was reported that abnormal lung function parameters normalized in only about half of the subjects.¹⁰ Why their outcome was not as favorable as ours is not clear. Perhaps it is because they studied the individuals after only 10 months of avoidance, while our study subjects had been in lower-exposure jobs for a longer period of time. Another possibility is that our study subjects were in a surveillance program and could go to onsite medical personnel at any time to be evaluated for anhydride-induced respiratory disease; therefore, the time to diagnosis might have been shorter.

In summary, in this population of 42 individuals with TMA-induced lung disease who had been transferred to low or no exposure for at least one year, 36 were asymptomatic, with normal spirometry. Only mild intermittent symptoms or mild abnormalities on spirometry were present in the other six individuals. Approximately half of the individuals had a decline in antibody titer.

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14th Year of Publication

AMERICAN JOURNAL OF RHINOLOGY

Official journal of the American Rhinologic Society

ISSN 1050-6586

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