Case Report

Alpha$_1$-Antitrypsin Replacement Therapy Controls Fibromyalgia Symptoms in 2 Patients with PI ZZ Alpha$_1$-Antitrypsin Deficiency

IGNACIO BLANCO, HORTENSIA CANTO, FREDERICK JOSEPH de SERRES, ENRIQUE FERNANDEZ-BUSTILLO, and MARIA CARMEN RODRÍGUEZ

ABSTRACT. Two Spanish sisters with α_1-antitrypsin (AAT) deficiency and fibromyalgia (FM) started AAT replacement therapy with commercial α_1-antitrypsin infusions in 1992. They both experienced a rapid, progressive, and constant control of their FM symptoms during the next 6 years (1992-98). However, in 1998, treatment of both patients was affected by the worldwide commercial shortage of AAT replacement therapy; replacement therapy infusions were halted for about 4–6 consecutive months every year for 5 years. As a result, we observed a striking recurrence of FM symptoms. Equally striking was the total disappearance of these symptoms when AAT replacement therapy infusions were resumed. (J Rheumatol 2004;31:2082–5)

Key Indexing Terms:
ALPHA$_1$-ANTITRYPSIN FIBROMYALGIA

Alpha$_1$-antitrypsin (AAT) deficiency is a heritable autosomal recessive metabolic disease that results in the synthesis and secretion of defective α_1-antitrypsin. This genetic disorder is related to a high risk for development of liver disease in children, adolescents, and adults, and pulmonary emphysema in adults. Moreover, AAT deficiency predisposes subjects to a variety of other diseases such as bronchiectasis, relapsing panniculitis, and systemic vasculitis[1]. About 100 genetic variants of AAT deficiency are recognizable. The alphabetic designation of these variants is based upon their electrophoretic mobility. PI M (medium mobility) is the normal allele, and the 2 most frequent deficient alleles are PI S and PI Z. PI ZZ phenotype results in very low serum concentration of AAT (10–15%). PI SS, PI MS, PI MZ, and PI SZ phenotypes result in intermediate serum AAT concentrations (35–70%). In clinical practice, most (95%) AAT deficiency-related diseases are linked with the PI ZZ phenotype. Calculated values of PI ZZ prevalence are as follows: 1:1000 to 1:4500 in Western and Northern Europe, 1:4500 to 1:10,000 in Central Europe, and 1:10,000 to 1:90,000 in Eastern Europe. In the Caucasian populations of the USA, Canada, Australia, and New Zealand, PI ZZ prevalence ranges from 1:2000 to 1:7000[2-5].

A current approach to specific therapy (not fully proven yet) of severe AAT deficiency involves weekly infusion with purified AAT (Prolastin®) derived from pooled human serum.

Human AAT is a glycoprotein secreted by hepatocytes, which is normally present in high concentrations in serum and most body tissues, where it acts as a serine-protease inhibitor whose principal substrate is neutrophil elastase. AAT also inhibits protease 3, cathepsin G, plasminogen activator, and lymphocyte granzymes. As well, AAT blocks neutrophil defensins, modulates cytokine production by fibroblasts, and upregulates the epithelial cell production of interleukin 8. Moreover, AAT may also act as an antioxidant, and this antioxidant activity may be an important biological function separate from its role as an antiprotease[6].

CASE REPORTS

In a family study performed 20 years ago, 2 Spanish sisters, 51 and 56 years old, were identified as PI ZZ non-index cases when their brother was diagnosed with pulmonary emphysema related to his PI ZZ phenotype. He was a heavy smoker and died at age 44 years severely handicapped by respiratory insufficiency that required oxygen therapy for several years. Their father had died at age 54 years due to hepatic failure secondary to advanced hepatic cirrhosis related to his PI ZZ phenotype (Figure 1).

The 2 sisters were diagnosed with fibromyalgia syndrome (FM) at ages 27 and 41 (Figure 2). Both complained of diffuse pain in all the 4 quadrants of the body, fatigue after minimal exertion, nonrestorative sleep, anxiety,

From the Department of Internal Medicine, Respiratory Diseases Branch, Hospital Valle del Nalón, Asturias, Spain; the Environmental Toxicology Program, Laboratory of Molecular Toxicology, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina, USA; the Biostatistics Unit, Hospital Universitario Central de Asturias; and the Biochemistry Laboratory, Instituto Nacional de Silicosis, Hospital Universitario Central de Asturias, Asturias, Spain.

I. Blanco, MD; H. Canto, MD, Respiratory Diseases Branch, Hospital Valle del Nalón; F.J. de Serres, PhD, National Institute of Environmental Health Sciences; E. Fernandez-Bustillo, PhD, Biostatistics Unit; M.C. Rodríguez, MD, Instituto Nacional de Silicosis, Hospital Universitario Central de Asturias.

Address reprint requests to Dr. I. Blanco, Department of Internal Medicine, Respiratory Diseases Branch, Hospital Valle del Nalón, 33920 Langreo, Asturias, Spain. E-mail: ignacio.blanco@sespa.princast.es

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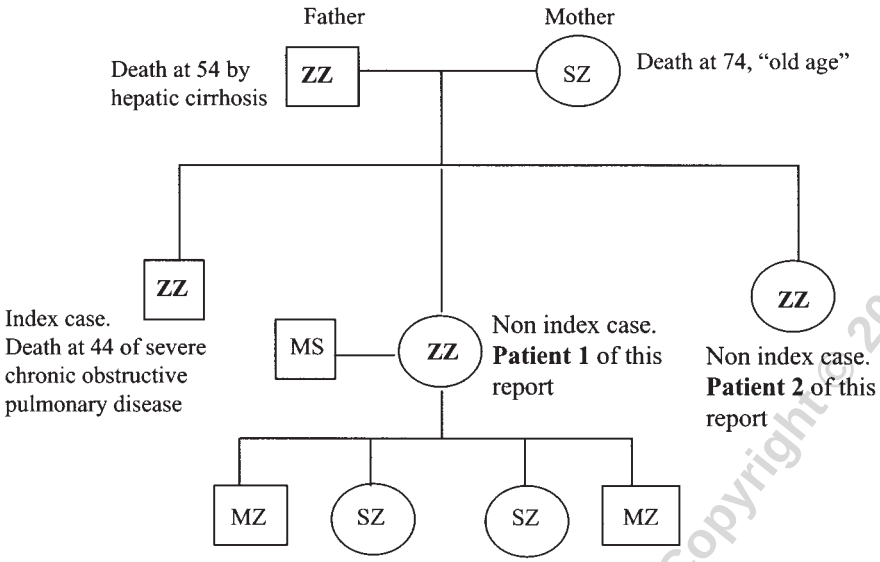

Figure 1. The pedigree of the family.

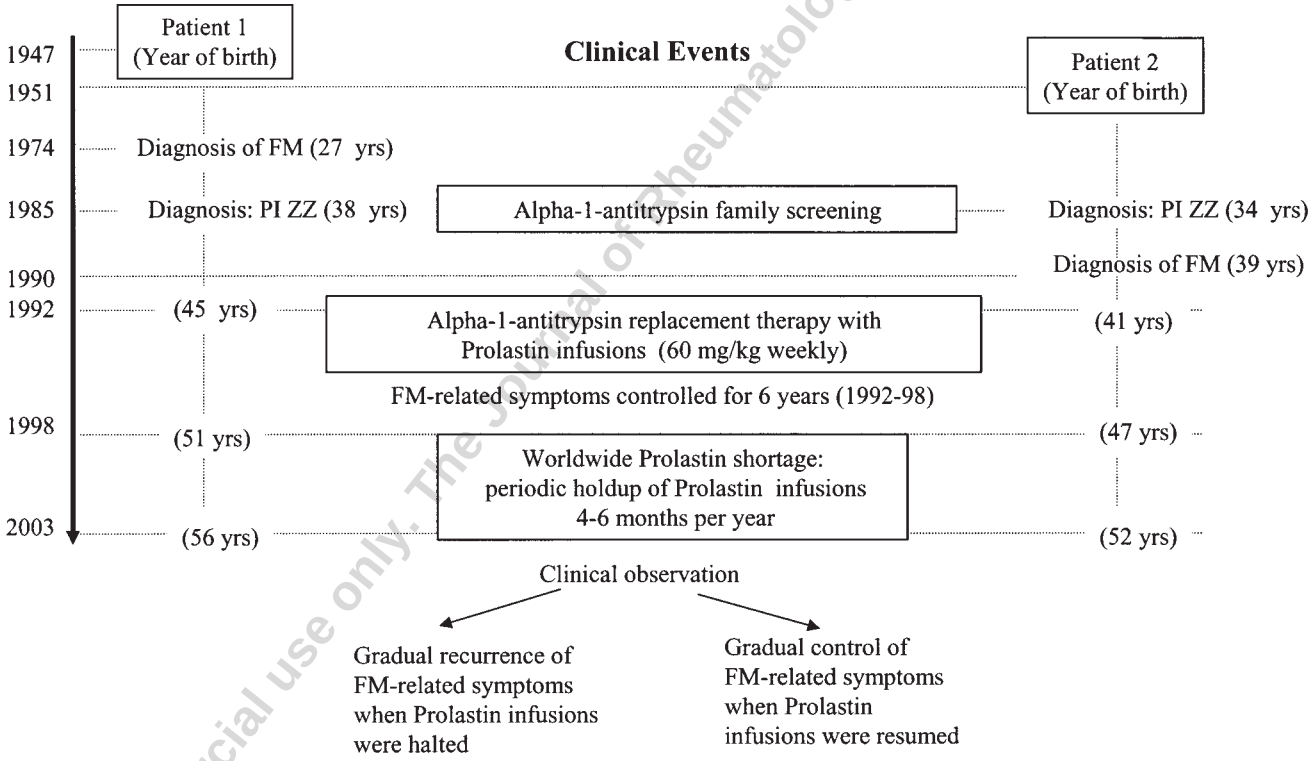

Figure 2. Chronology of clinical events. Numbers in brackets indicate the age of each patient.

and urinary frequency. All these chronic symptoms resulted in considerable disability and handicap that made it difficult for them to perform ordinary household activities. Tests for hepatitis C, syphilis, and acquired immune deficiency syndrome were negative. Other conditions that may present with widespread pain, weakness, or fatigue, such as hypothyroidism, polymyalgia rheumatica, hyperparathyroidism, hyperprolactinemia, multiple sclerosis, systemic autoimmune disorders (systemic lupus erythematosus, rheumatoid arthritis, ankylosing spondylitis), major psychiatric disorders, neuropathy, metabolic and inflammatory myopathy, etc., were excluded by appropriate investigation. They showed multiple FM-specific tender sites (Patient 1: 18 out of 18, and Patient 2: 13 out of 18). Both had negative control nontender sites (such as forehead, distal forearm, and lateral fibular head), and according to all these data, it was considered that both patients clearly fulfilled the 1990 American College of Rheumatology criteria for FM[7]. Diagnosis of FM was corroborated by several internal medicine specialists, neurologists, and rheumatologists.

In spite of these major physical problems, each woman had only slight pulmonary functional impairment (Table 1). Considering the premature deaths of their father and brother, both requested taking part in a therapeutic protocol with AAT replacement therapy. They were vaccinated against hepatitis B, and after giving informed consent, both were enlisted in the Spanish AAT Deficiency Registry, and later in the Alpha$_1$ International Registry, where their PI*Z genotype was corroborated at the molecular level. Both sisters started Prolastin® infusions in 1992. Surprisingly, after 2–3 doses of Prolastin®, they both experienced a progressive, absolute, and constant control of their FM symptoms during the next 6 years (1992-98). However, in 1998, treatment of both patients was affected by the worldwide commercial shortage of Prolastin®. As a result, Prolastin® infusions were halted for about 4–6 consecutive months every year for 5 years (1998-2003). According to the policy of the Spanish AAT Registry, Prolastin® infusions were stopped during the spring and summer months, to be resumed again in autumn and winter of every year, in consideration that colder months might imply a higher risk of suffering respiratory infections. As a result, their physicians were able to verify a striking recurrence of FM-related physical symptoms. Equally striking was the total disappearance of these physical symptoms when Prolastin® infusions were periodically resumed. These observations were verified about 5 times during the last 5 years. We referred both patients again to a neurologist, a psychologist, and another rheumatologist, who corroborated their initial diagnosis of FM. In addition, serial measurements were carried out of serum AAT levels (determined by radial immunodiffusion) in basal conditions, after 24 hours of Prolastin® infusion, and just before the next weekly Prolastin® infusion (Table 1).

DISCUSSION

The prevalence of FM in North America and Europe is about 2–4%[8-10]. Most patients are women (80–90%) from about age 30 to 50 years, and although familial occurrence has been observed, data on the genetic role in this condition are limited. The pathogenesis of FM is unclear, and there is no effective treatment for this condition.

Recently, altered inflammatory cytokine profiles and products closely related to oxidative stress in FM sera, skin, and muscle tissues, as compared to healthy controls, have been described[11-15], but there appear to be no studies on AAT and FM in the literature.

Since AAT should be conceptualized as a molecule with broad antiinflammatory properties, our clinical observations suggest that normal AAT may play an important role controlling a possible inflammatory component in the muscle/skeletal connective tissue responsible for the induction of pain and physical impairment in these 2 patients with FM and PI ZZ. If this effect is more general in patients with FM, infusions with Prolastin® could be a therapeutic option for treatment of FM related symptoms. Although replacement therapy might have benefitted these 2 patients for psychological reasons and fluctuations in FM symptoms might be seasonally rather than causally related to infusions, our observations may suggest new options for therapy. Further studies focusing on these observations should be encouraged.

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Table 1. Pulmonary studies in the described cases. Data are mean ± standard deviation.

	Lung Function						Arterial Blood Gasometry	AAT Serum Concentration, mg/dl*		
	FVC, % Pred	FEV$_1$, % Pred	FEV$_1$, % FVC	TLC, % Pred	RV, % Pred	DLCO, % Pred	PaO_2, $PaCO_2$ (mm Hg)	Basal	24 h After Prolastin	7 Days After Prolastin†
Patient 1	95	88	99	96	104	72	70, 38	43.8 ± 7.4	356.3 ± 39.9	71.0 ± 17.0
Patient 2	138	110	84	119	93	73	75, 37	40.3 ± 6.9	364.3 ± 13.7	103.8 ± 15.6

Pred: predicted; FVC: forced vital capacity; FEV$_1$: forced expiratory volume in 1 second; TLC: total lung capacity; RV: residual volume. * Quantitative values of AAT determined by radial immunodiffusion (normal values in our laboratory: 150–350 mg/dl). † 7 days after the last Prolastin infusion, and just before the next Prolastin infusion.

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