Cystic Fibrosis Diagnosis After Age 40 on the Rise

BY TIMOTHY F. KIRN
Sacramento Bureau

In his adult cystic fibrosis clinic in Denver, Dr. Jerry A. Nick has patients who were not diagnosed until they were 40 years of age or older.

These patients represent the tip of an iceberg of unrecognized patients, and clinicians need to be on the lookout for these individuals, Dr. Nick suggests.

His patients reflect the fact that the clinical presentation of cystic fibrosis can vary along a spectrum of severity. This has become clearer as more and more specific genetic mutations causing cystic fibrosis have been identified.

With that awareness, patients who were once just considered a curious aberration are now recognized as representing something significant, said Dr. Nick, director of the Adult Cystic Fibrosis Clinic of the National Jewish Medical and Research Center.

"These cases have shown up sporadically for years," he said in an interview.

Dr. Nick recently published a paper on 27 of his late-diagnosis patients (Am. J. Respir. Crit. Care Med. 2005;171:621-6), comparing them with 28 patients diagnosed early who have survived into their 40s. He has also published a review article on long-term survival with cystic fibrosis (Curr. Opin. Pulm. Med. 2005;11:513-8).

Dr. Nick's patients are some of the oldest cystic fibrosis patients yet reported. The median age of his late-diagnosis patients is at present more than 52 years.

They may not be an exclusive group for long, however. Adult diagnosis is already becoming more common, Dr. Nick noted in his article. In 1982, only 3% of patients enrolled in the Cystic Fibrosis Foundation patient registry had been diagnosed after the age of 18 years. By 2002, 10% of the new patients added to the registry that year were diagnosed during adulthood.

By 2002, 10% of the new patients added to the Cystic Fibrosis Foundation registry that year were diagnosed during adulthood.

Many of the late-diagnosis patients that Dr. Nick described in his article had been seeing physicians for years for recurrent and chronic lung infections, or similar symptoms. They were thought to have asthma, or chronic obstructive pulmonary disease, or something else.

But there is no question about their cystic fibrosis diagnosis, Dr. Nick said. The patients all meet Cystic Fibrosis Foundation diagnostic criteria, and they have had genetic analysis, sweat chloride testing, and/or nasal potential difference testing.

European centers also have begun to take note of late-diagnosis patients, but most of the European patients have been diagnosed in their 20s and 30s.

The importance of Dr. Nick's older patients is that they may help to identify factors associated with long-term survival. The median survival of cystic fibrosis patients is still only 35 years of age, despite improvements in cystic fibrosis treatment.

Dr. Nick has not uncovered any notable clues yet. But there are intriguing, observed differences between the early-diagnosed and late-diagnosed patients. The late-diagnosed patients were less likely to have pancreatic insufficiency, so they tended to have better lung function and nutritional status. They were also less likely to have cystic fibrosis–related diabetes.

One unexpected difference was that 74% of the late-diagnosis patients were women. In the early-diagnosis group, most older patients were male (64%), which is consistent with data in cystic fibrosis patient registries in general, Dr. Nick said. Males also tend to have a longer median survival, by 3-5 years on average.

In addition, a large proportion of the late-diagnosis patients carried nontuberculous mycobacteria. These findings may be the most interesting, Dr. Nick said, as they may indicate something about the airway environment that could be a clue to the patients' long-term survival.

SARA BRAYSHAW, MSN

These patients represent the tip of an iceberg, and clinicians need to be on the lookout for these individuals, Dr. Jerry A. Nick says.

That is also the sole finding so far that might be helpful in identifying the patients who go without a diagnosis for so long. Physicians who see a patient with a nontuberculous mycobacteria infection should have a strong suspicion of cystic fibrosis, he said.

The comparison study found that only 4 of the 27 early-diagnosis patients had at least one positive culture for nontuberculous mycobacteria, whereas 14 of the 28 late-diagnosis patients did. None of the early-diagnosis patients met criteria for an infection, while six of the late-diagnosis patients did.

In contrast, *Pseudomonas aeruginosa* was found less frequently in cultures from the late-diagnosis patients, although mucoid and nonmucoid strains were still found in more than 50% of cultures.

In general, the late-diagnosis patients had less severe manifestations, but not all of them had mild disease, Dr. Nick noted in the interview. Four of the patients have died. Two required lung transplant. Some had the same genotypes as early-diagnosis patients. ■

Hypertonic Saline Inhalation Helps Manage CF Symptoms

BY MARY ANN MOON
Contributing Writer

Hypertonic saline inhalation using a nebulizer reduced pulmonary exacerbations in patients with cystic fibrosis and decreased their absenteeism from school, work, and their usual activities, researchers found in two separate randomized clinical trials.

The trials provided the first evidence of the long-term efficacy of this safe and relatively inexpensive treatment. The therapy appears to work by restoring the volume of liquid on the airway surfaces, which is depleted because of excessive absorption of salt from the airway lumen. This rehydration seems to produce a sustained acceleration of mucus clearance, both groups of investigators theorized.

In the first study, 164 adults and children with stable cystic fibrosis (CF) were randomly assigned to inhale 4 mL of either hypertonic (7%) saline plus a taste-masking agent or a control solution (isotonic saline) plus a taste-masking agent via nebulizer twice a day for 48 weeks. A bronchodilator was administered before each treatment to prevent or minimize narrowing of CF patients' hyperresponsive airways during nebulizer therapy, reported Dr. Mark R. Elkins, of Royal Prince Alfred Hospital, Sydney, Australia, and the University of Sydney, and his associates.

The treatment had only a moderate effect on lung function as measured by forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV_1), and no apparent effect on the typical decline in lung function over the course of the year-long study. However, it had "dramatic" effects on several clinical factors, they noted (N. Engl. J. Med. 2006;354:229-40).

The mean number of symptom exacerbations was 1.32 per person in the treatment group, compared with 2.74 per control subject. The mean duration of exacerbations was 22 days in the treatment group, compared with 69 days in the control group. And the length of time spent free of exacerbations, expressed as "48-week exacerbation-free survival rate," was 41% in the treatment group, compared with 16% in the controls. All of these differences were highly statistically significant. Similarly, antibiotic use during exacerbations was much lower for the active treatment group.

Patients in the active treatment group reported a mean of 7 days (range, 0-21) when they could not participate in school, work, or usual activities, compared with a mean of 24 days (range, 12-48) for the controls. The treatment group also scored significantly higher on quality of life measures.

The treatment did not alter the levels of *Pseudomonas aeruginosa* or *Staphylococcus aureus* in the sputum, nor did it affect the rate of acquisition of these organisms, *Burkholderia cepacia*, *Stenotrophomonas maltophilia*, *Candida albicans*, aspergillus species, or *Hemophilus influenzae*.

In the other clinical trial, investigators reasoned that slowing the absorption of nebulized hypertonic saline by premedicating CF patients with amiloride, a sodium channel blocker, would enhance patient response by extending the duration of airway rehydration.Twenty-four CF patients aged 14 years and older were randomized to pretreatment with either amiloride or a taste-masked placebo, followed by hypertonic saline via nebulizer four times daily for 14 days. All the subjects received a bronchodilator via inhaler 30-60 minutes before the nebulizer treatment.

The study confirmed that hypertonic saline improved CF symptoms, lung function, and quality of life, reported Dr. Scott H. Donaldson and Dr. William D. Bennett of the University of North Carolina at Chapel Hill Cystic Fibrosis Research and Treatment Center and their associates. Perhaps as important, the treatment hastened the rate of mucus clearance from the lungs and "produced a larger and more sustained increase in the volume of airway surface liquid" in CF patients than in healthy controls (N. Engl. J. Med. 2006; 354:241-50).

The findings suggest inhaled hypertonic saline may be an option for CF patients, Dr. Felix Ratjen of the University of Toronto said in an editorial comment accompanying the publication of both reports.

It was previously shown that hypertonic saline inhalation increased mucociliary transport in CF patients—but the effect was presumed to be short-lived because sodium deposited on epithelial surfaces would be taken up rapidly. The new research shows that the treatment "not only had a prolonged effect on the amount of airway surface liquid in epithelial cells . . . but also resulted in a sustained improvement of mucociliary transport," Dr. Ratjen said (N. Engl. J. Med. 2006;354:291-3).

Dr. Ratjen noted that the treatment has an unpleasant taste, induces coughing, and would add at least 30 minutes to patients' daily treatment schedules. ■