Early Mortality and Cardiorespiratory Failure in Patients with Fibrodysplasia Ossificans Progressiva

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Background: Fibrodysplasia ossificans progressiva, a rare genetic disorder of progressive extraskeletal ossification, is the most disabling form of heterotopic ossification in humans. However, little is known about the lifespan or causes of mortality in these patients. We undertook this study to determine the lifespan and causes of mortality in individuals who had fibrodysplasia ossificans progressiva.

Methods: We reviewed comprehensive mortality reports from two large registries of patients with fibrodysplasia ossificans progressiva. Together, these registries comprise >90% of all known patients with this condition in the world. We noted the sex, dates of birth and death, and the cause of death for each individual. We verified the cause of death with extensive medical records, when available. We also collected date of birth, current age, and sex information for each living patient member of the International Fibrodysplasia Ossificans Progressiva Association.

Results: Sixty deaths (thirty male and thirty female patients) were reported in the fibrodysplasia ossificans progressiva community during a thirty-three-year-period. For all sixty patients, the median age at the time of death was forty years (range, three to seventy-seven years). Data were sufficient to establish the cause of death in forty-eight (80%) of the sixty individuals. The median age at the time of death for the forty-eight patients (twenty-four male and twenty-four female patients) with an established cause of death was also forty years. The median lifespan estimated from the 371 individuals in the international fibrodysplasia ossificans progressiva community who were alive and the sixty who had died was fifty-six years (95% confidence interval, fifty-one to sixty years). The most common causes of death in patients with fibrodysplasia ossificans progressiva were cardiorespiratory failure from thoracic insufficiency syndrome (54%; median age, forty-two years) and pneumonia (15%; median age, forty years).

Conclusions: Fibrodysplasia ossificans progressiva is not only an extremely disabling disease but also a condition of considerably shortened lifespan. The most common cause of death in patients with fibrodysplasia ossificans progressiva is cardiorespiratory failure from thoracic insufficiency syndrome.

Fibrodysplasia ossificans progressiva (Mendelian Inheritance in Man [MIM] #135100) is a rare, disabling genetic disorder of progressive heterotopic ossification caused by a heterozygous activating mutation of the gene encoding activin receptor A type I/activin-like kinase 2 (ACVR1/ALK2), a bone morphogenetic protein (BMP) type-I receptor, in all classically affected individuals worldwide[1-4]. There is no racial, ethnic, sex, or geographic predilection[5].

While disease flare-ups in fibrodysplasia ossificans progressiva are episodic, disability is cumulative[3,6]. Most patients are confined to a wheelchair by the third decade of life[6,7]. Clinical management is symptomatic, and there is no effective treatment[3,8]. While much is known about the disabling complications of this disease, documentation of lifespan and causes of death in these patients have not been examined. We undertook a comprehensive study to determine the lifespan and cause of death in individuals with fibrodysplasia ossificans progressiva.

Materials and Methods

Mortality Records

We reviewed the comprehensive mortality records from the International Fibrodysplasia Ossificans Progressiva

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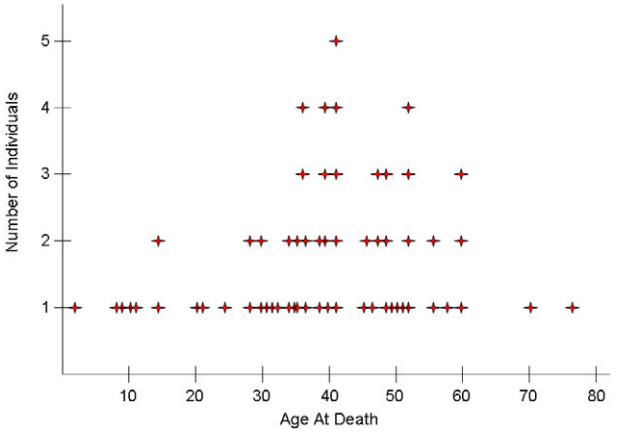

Fig. 1

Age distribution (in years) at the time of death for sixty patients with fibrodysplasia ossificans progressiva (1973 to 2006).

Association from its inception in 1988 through 2006, and from the International Fibrodysplasia Ossificans Progressiva Clinic at the University of Pennsylvania from its inception in 1973 through 2006. These two patient registries comprise >90% of the known patients with fibrodysplasia ossificans progressiva in the world. All patients were well known to at least one of the investigators and had a confirmed history of fibrodysplasia ossificans progressiva based on the presence of the two classic clinical criteria: congenital malformations of the great toes and progressive heterotopic ossification in characteristic anatomic patterns. Medical records were reviewed to establish the dates of birth and death and the cause of death for each individual. The study was granted an exemption by the institutional review board of the University of Pennsylvania.

Living Individuals

The membership records of the International Fibrodysplasia Ossificans Progressiva Association were reviewed for 2006, in order to provide a concurrent cross-sectional profile of living patients with the condition. The birth year and sex were noted for each individual with fibrodysplasia ossificans progressiva who was living in January 2006.

Statistical Analysis

Kaplan-Meier survival curves were constructed for the merged population of living and deceased individuals with fibrodysplasia ossificans progressiva with use of the R survival package[9,10]. The survfit function was used to construct the curve and delineate 95% confidence intervals[9,10]. A comparison survival curve was calculated from mortality data from the U.S. Census (1980) contained in the survexp.us[10]. The 1980 U.S. Census was prospectively chosen on the basis of two criteria: the need for: (1) a large well-documented control population within the study period, and (2) a multiethnic control population that best represented the geographic, ethnic, and racial diversity of the study population. Significant differences were analyzed by the log-rank test or by analysis of variance.

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Results

There were sixty reported deaths (thirty male and thirty female patients) in the fibrodysplasia ossificans progressiva study population during the thirty-three-year period (1973 to 2006). Data were sufficient to establish an unequivocal cause of death in forty-eight (80%) of sixty individuals (see Appendix). The median age at the time of death for these forty-eight patients (twenty-four male and twenty-four female patients) was forty years (range, three to sixty years), the same median age (forty years; range, three to seventy-seven years) at the time of death for all sixty patients (Fig. 1).

The Kaplan-Meier survival curve estimate from the combined data set of 371 living and sixty deceased individuals with fibrodysplasia ossificans progressiva revealed an estimated median life expectation of fifty-six years (95% confidence interval, fifty-one to sixty years) (Fig. 2). Substantial excess mortality in patients with fibrodysplasia ossificans progressiva began at about the age of thirty years, with only an estimated 30% of the patients with fibrodysplasia ossificans progressiva surviving to the age of sixty years. In contrast, approximately

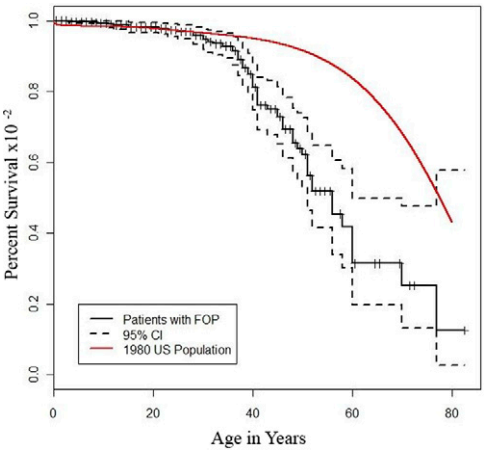

Fig. 2

Kaplan-Meier survival curves for patients with fibrodysplasia ossificans progressiva (FOP) and for the 1980 U.S. population. The dotted lines are 95% confidence limits. The solid red line represents the actual survival data (average of male and female) for the U.S. population from the U.S. Census Bureau (1980). The Y axis is the percent survival $\times 10^{-2}$, and the X axis is the age in years.

TABLE I Causes of Mortality in Patients with Fibrodysplasia Ossificans Progressiva

Cause	No.	Percentage	M	F	Age Range *(yr)*	Median Lifespan *(yr)*
Cardiorespiratory failure	26	54	12	14	8-58	42
Pneumonia	7	15	3	4	28-60	40
Falls	5	11	2	3	32-46	41
Sepsis	3	6	3	0	46-56	52
Complications of general anesthesia	2	4	0	2	12-15	14
Intestinal obstruction	1	2	1	0	28	28
Starvation	1	2	1	0	15	15
Drowning	1	2	0	1	3	3
Accident	1	2	1	0	25	25
Suicide	1	2	1	0	30	30
Total	48	100	24	24	3-60	40

84% of the population of the United States in 1980 survived to the age of sixty years. The median survival for the 1980 U.S. population is estimated to be seventy-eight years, some twenty-two years greater than the estimate for the cohort of patients with fibrodysplasia ossificans progressiva.

The most common causes of death in patients with fibrodysplasia ossificans progressiva were cardiorespiratory failure from thoracic insufficiency syndrome (54%; twenty-six [twelve male and fourteen female] individuals, with a median age of forty-two years; range, eight to fifty-eight years), pneumonia (15%; seven [three male and four female] individuals, with a median age of forty years; range, twenty-eight to sixty years), and complications of falls (11%; five [two male and three female] individuals with a median age of forty-one years; range, thirty-two to forty-six years) (Table I). All deaths from falls were ascribed to complications of head injuries, a well-known morbidity factor in patients with fibrodysplasia ossificans progressiva[3]. Surprisingly, there were no reports of complete autopsies in any patient.

The median age at the time of death was thirty-nine years for those with no clearly established cause of death, forty-two years for those who had cardiorespiratory failure from thoracic insufficiency syndrome, forty years for those who had pneumonia, and forty-one years for those who died from a fall. Deaths from cardiorespiratory failure and pneumonia occurred within a fifty-year range and a thirty-two-year range, respectively, while deaths from falls occurred in a narrower fourteen-year age range (between thirty-two and forty-six years; $p = 0.008$) (Table I), most likely reflecting an age range in which some patients were still able to walk or able to transfer with assistance but were at greatest risk of falls from progressive instability.

Discussion

There are two major findings of our study: (1) fibrodysplasia ossificans progressiva is not only an extremely disabling disease but also a condition of considerably shortened lifespan, and (2) the most common cause of death in patients with fibrodysplasia ossificans progressiva is cardiorespiratory failure from thoracic insufficiency syndrome. Numerous factors contribute to the development of thoracic insufficiency syndrome in patients with fibrodysplasia ossificans progressiva, including costovertebral malformations with early orthotopic ankylosis of the costovertebral joints; fusion of ribs; ossification of intercostal muscles, paravertebral muscles, and aponeuroses; and progressive spinal deformity including kyphoscoliosis or thoracic lordosis (Fig. 3)[11]. Scoliosis surgery is contraindicated in most patients as operative intervention exacerbates the disease process[12].

Thoracic insufficiency syndrome and severe restrictive lung disease occur in all individuals with fibrodysplasia ossificans progressiva[11]. In a large prospective study of young, active patients with fibrodysplasia ossificans progressiva, echocardiograms were still normal, but 40% of the patients had electrocardiographic evidence of right ventricular dysfunction, including right ventricular hypertrophy, P pul monale, incomplete right bundle branch block, and right ventricular strain pattern[13]. These changes are indicative of cor pulmonale.

In our study, individuals who died of cardiorespiratory failure had a terminal course that was similar to patients with severe pulmonary hypertension. These patients typically present with progressive dyspnea, edema, elevated jugular venous pressure with marked V waves, right ventricular heave, hypoxemia, and electrocardiographic evidence of right ventricular dysfunction[14]. Pulmonary hypertension, cor pulmonale, and cardiorespiratory failure are all terminal features of prolonged alveolar hypoventilation due to the severe thoracic insufficiency syndrome[14]. In one postmortem report, gross right ventricular hypertrophy was confirmed in a patient who died of respiratory failure after presenting with all of the classic signs and symptoms of severe pulmonary hypertension and electrocardiographic evidence of right ventricular dysfunction[15]. These studies indicate that periodic electrocardiographic evaluations of individuals with fibrodysplasia ossificans progressiva are useful to monitor the development of right ventricular dysfunction[16,17]. The patients with electrocardiographic evidence of right ventricular dys-

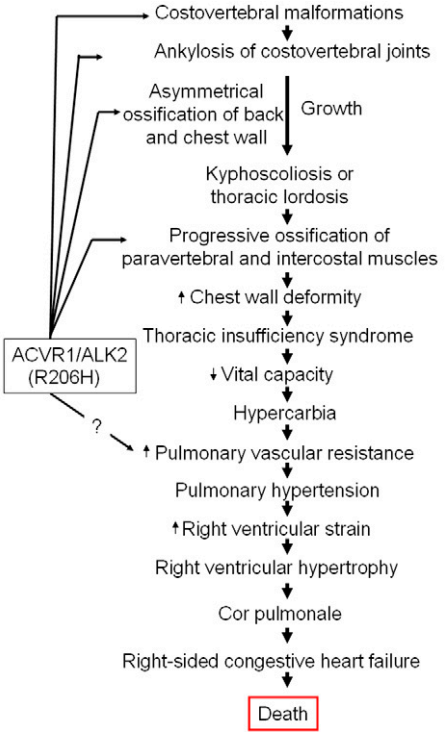

Fig. 3

Working model of the pathophysiology of thoracic insufficiency syndrome and cardiorespiratory failure in patients with fibrodysplasia ossificans progressiva.

function require additional care to guard against catastrophic hemodynamic collapse that can occur in the setting of severe pulmonary hypertension.

Nearly all individuals who died of cardiorespiratory failure from thoracic insufficiency syndrome had used supplemental oxygen at home in the week prior to their death despite warnings to the contrary. In several individuals who were hospitalized prior to their death, carbon dioxide levels were elevated in the arterial blood. Patients with end-stage thoracic insufficiency syndrome are chronically hypercarbic and have lost an important component of respiratory drive associated with acute hypercarbia[11,18]. In such a setting, the therapeutic use of supplemental oxygen can lead to the further loss of respiratory drive and a subsequent rapid demise[11]. Thus, patients with fibrodysplasia ossificans progressiva should not use unmonitored oxygen therapy, especially during sleep. However, individuals who have thoracic insufficiency may benefit from noninvasive mechanical methods to increase oxygen saturation and relieve chronic hypercarbia[11].

While pulmonary hypertension in patients with fibrodysplasia ossificans progressiva has been largely attributed to chronic hypoventilation from thoracic insufficiency, there is an intriguing possibility that the dysregulation of the BMP pathway that causes fibrodysplasia ossificans progressiva[19-23] may play a direct role in the pathogenesis of pulmonary hypertension. While the mutation in ACVR1/ALK2 in patients with fibrodysplasia ossificans progressiva leads to activation of BMP signaling[4,20,24], the BMPR2 mutations in primary pulmonary hypertension are generally thought to lead to down-regulation of BMP signaling[25-34]. However, given the functional redundancy among BMP type-II receptors, it is increasingly recognized that loss of BMPR2 may not necessarily lead to loss of Smad signaling[35,36]. In fact, evidence suggests that overactive BMP signaling, as in fibrodysplasia ossificans progressiva, may play a central role in the development of hypoxia-induced pulmonary hypertension[37]. In addition, recent studies have shown that activating mutations of ACVR1, similar to those seen in patients with fibrodysplasia ossificans progressiva, lead to paradoxical changes in the expression of BMP type-II receptors and in downstream BMP signaling in affected cells[38]. Thus, whether cardiorespiratory mortality in patients with fibrodysplasia ossificans progressiva is due to restrictive chest-wall disease alone or has a pulmonary vascular component resulting directly from aberrant ACVR1/ALK2 signaling is an intriguing area worthy of further investigation. Genetic knock-in animal models of fibrodysplasia ossificans progressiva are presently under development and may help to clarify this important question. Noninvasive echocardiographic studies late in the course of the disease coupled with thorough histopathologic evaluation of the myocardium and lung parenchyma following death in patients with fibrodysplasia ossificans progressiva may also help to resolve this critical issue.

Despite the decreased median lifespan of these patients, there is wide variation in lifespan, even among individuals with the identical ACVR1/ALK2 receptor mutation. This observation suggests that other genes in the BMP signaling pathway or other pathways might modify the enhanced signaling output of the mutant receptor and be responsible in part for lifespan variation. Additionally, environmental factors also play an important role in the postnatal phenotype of fibrodysplasia ossificans progressiva. In a recent study of three pairs of monozygotic twins with fibrodysplasia ossificans progressiva, each pair of twins had identical congenital toe malformations[39]. However, postnatal heterotopic ossification and chest wall deformity varied greatly between the twins in each pair, depending on life history and environmental exposure. Thus, the classic fibrodysplasia ossificans progressiva mutation strongly influences the phenotype of the condition during prenatal development, while environmental factors strongly influence postnatal progression of the disease[39].

In a recent study, we observed genotype-phenotype correlations between some exceedingly rare ACVR1/ALK2 mutations and the age of onset of heterotopic ossification or in embryonic patterns of skeletal development[40]. However, <2% of individuals with fibrodysplasia ossificans progressiva have phenotypic and genotypic variants[40]. Importantly, all of the individuals in our study had classic fibrodysplasia ossificans progressiva. In those for whom banked DNA was available for testing, the R206H mutation in ACVR1/ALK2 was confirmed. Thus, phenotype-genotype correlations were not possible.

Greater awareness of fibrodysplasia ossificans progressiva among clinicians, earlier diagnosis of the condition, and educational programs to avoid iatrogenic harm strongly suggest that mortality data should be stable, and perhaps even improving[3,41-43]. Importantly, the recent discovery of the fibrodysplasia ossificans progressiva gene has provided critical insight into the development of medications that have the potential to alter the natural history of this disorder[38,44,45].

In summary, there are two major findings of our study: (1) fibrodysplasia ossificans progressiva is not only an extremely disabling disease but also a condition of considerably shortened lifespan, and (2) the most common cause of death in patients with fibrodysplasia ossificans progressiva is cardiorespiratory failure from thoracic insufficiency syndrome. This study has important implications for understanding the natural history of the disease, for establishing baseline mortality profiles for life-care planning, and for designing studies to better understand the complex pathophysiology of cardiorespiratory failure in fibrodysplasia ossificans progressiva.

Appendix

eA A table listing all patients and their cause of death is available with the electronic version of this article on our web site at jbjs.org (go to the article citation and click on "Supporting Data"). ■

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