

## Influenza-like Viral Illnesses and Flare-ups of Fibrodysplasia Ossificans Progressiva

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Flare-ups of fibrodysplasia ossificans progressiva are most commonly triggered by soft tissue trauma. After observing severe flare-ups of fibrodysplasia ossificans progressiva in two half-sisters with culture-confirmed influenza B infections, we hypothesized that influenza-like viral illnesses also can trigger fibrodysplasia ossificans progressiva flare-ups. To address this hypothesis, we designed a questionnaire to assess whether patients with fibrodysplasia ossificans progressiva experienced influenza symptoms during the 2000 to 2001 influenza season, and whether these symptoms were correlated with flare-ups of the condition. The questionnaire was sent to patients with fibrodysplasia ossificans progressiva worldwide. Of the 264 patients surveyed, 123 (47%) responded. The survey revealed that the risk of a disease flare-up of fibrodysplasia ossificans progressiva during an influenza-like viral illness was increased at least threefold and possibly much more. The survey data strongly supported the hypothesis that influenza-like viral illnesses are associated with disease flare-ups in patients who have fibrodysplasia ossificans progressiva. Influenza-like viral illnesses may be a source of previously unrecognized muscle injury leading to heterotopic ossification and permanent loss of mobility in these patients. These findings have important implications for understanding and preventing environmental triggers of

disease activity in this population of patients genetically susceptible to progressive heterotopic ossification.

Fibrodysplasia ossificans progressiva (FOP) is an extremely rare and disabling genetic disease characterized by progressive postnatal ossification of soft connective tissue and congenital malformation of the great toes.<sup>5,14</sup> Autosomal dominant inheritance has been shown. However, the most cases arise from spontaneous mutations in an as yet unidentified gene.<sup>7,8,13</sup>

The first postnatal manifestations of FOP begin in childhood.<sup>4,14</sup> Classically, disease flare-ups begin as warm, painful, fibrous masses (lesions) in skeletal muscle.<sup>4,5,14,15</sup> In the early stages of lesional development, there is an intense perivascular lymphocytic infiltration into seemingly normal skeletal muscle followed by death of skeletal muscle and fibrovascular tissue proliferation.<sup>10,14</sup> Fibrodysplasia ossificans progressiva lesions mature through an endochondral process and form permanent foci of heterotopic bone that bridge and immobilize adjacent joints, rendering movement impossible.<sup>14,15</sup> Currently, there is no effective treatment or prevention.<sup>14</sup>

Disease flare-ups may be stimulated by soft tissue trauma, intramuscular injection, dental therapy, or may occur in the absence of an identified tissue-damaging event.<sup>4,5,14</sup> Anecdotal reports to the authors from patients, families, and referring physicians have suggested a temporal relationship between viral respiratory illnesses and flare-ups of FOP. The association of Epstein-Barr virus infections with FOP flare-ups, and the dysregulation of the bone morphogenetic protein (BMP) pathway in Epstein-Barr virus-infected FOP cells provide a background for cautionary surveillance of other viral triggers in patients with FOP.<sup>14,22</sup> Recently, we observed severe flare-ups of FOP leading to mobility restriction in two half-sisters with FOP within 12 hours of the onset of symptoms of culture-confirmed influenza B infection.<sup>14</sup>

Received: February 3, 2003

Revised: June 27, 2003

Accepted: July 3, 2003

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This work was supported in part by grants from the International FOP Association, the Center for Research in FOP and Related Disorders, The Fellowship Program In Academic Medicine for Minority Medical Students, The Betty Laue FOP Resource Center, and The Isaac and Rose Nassau Professorship of Molecular Orthopaedic Medicine.

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DOI: 10.1097/01.blo.0000129557.38803.26



**Fig 1.** A lateral radiograph was obtained of the cervical spine of a 5-year-old child, 6 months after a flare-up of FOP involving the neck that was coincident with culture-confirmed influenza B infection. The child had full ROM of the neck before the influenza-induced flare-up. However, as a result of the heterotopic ossification (arrow) from the occiput to the spinous process of C7, the neck became ankylosed.

The influenza viruses (subtypes A and B) infect millions of people worldwide annually.<sup>21</sup> The classic symptoms of influenza infection are fever, nonproductive cough, nasal congestion, myalgias, sore throat, headache, and malaise lasting between 1 and 2 weeks.<sup>21</sup> The generalized myalgias associated with influenza and other acute viral illnesses usually are mild and self-limiting. However, more severe muscle syndromes, ranging from myositis to rhabdomyolysis have been reported in patients with influenza infections.<sup>19</sup> Myositis and rhabdomyolysis most commonly are seen in children infected with influenza A or B.<sup>19</sup> The cause of muscle injury in influenza infections is unclear. Several possible mechanisms have been hypothesized, including direct invasion of muscle tissue by the virus,<sup>9</sup> activation of proinflammatory transcription factors,<sup>2</sup> and autoimmune processes.<sup>3</sup>

We hypothesized that influenza-like viral illnesses can trigger FOP flare-ups. To test this hypothesis a questionnaire was designed to assess whether patients with FOP experienced influenza-like viral symptoms during the 2000 to 2001 influenza season, and whether influenza-like viral symptoms were associated with flare-ups of FOP.

## MATERIALS AND METHODS

A detailed questionnaire was posted on the International Fibrodysplasia Ossificans Progressiva Association (IFOPA) website ([www.ifopa.org](http://www.ifopa.org)). The IFOPA includes 264 self-enrolled patient-members (115 males, 149 females) from 26 countries and five continents. Fibrodysplasia ossificans progressiva was verified in all patients either through previous examination by one of the authors (FSK) or through previous surveys and review of relevant photographs and radiographs. The study and questionnaire were approved by the institutional review board (IRB) of one of our institutions. Patient confidentiality was guaranteed in public reporting of all results in accordance with standards set by the IRB. Informed consent was obtained from all participants. As required by the IRB, patients were asked to sign a consent form in which they were informed that the “the data from this questionnaire will enable us to better examine the relationship (if any) between influenza and FOP.”

Members with e-mail addresses were contacted directly and requested to complete the electronic questionnaire. Questionnaires were sent by mail to members of the IFOPA who did not complete the electronic version within 4 weeks of its initial posting. Parents of affected children and caretakers of extremely disabled adults were requested to complete the questionnaires. The electronic version of the survey was posted on the IFOPA web site until the conclusion of the study. The survey was designed to ascertain each patient’s age, history of influenza vaccination, history of influenza-like viral symptoms (muscle aches, fever, chills, cough, nasal congestion, sore throat, enlarged lymph nodes, and fatigue), other symptoms (nausea, vomiting, and diarrhea), duration of symptoms, occurrence of similar symptoms in household members, and change in the status of FOP during the survey period (lesion formation, regression, changes in shape, size, and location of existing lesions, and the temporal association of influenza-like viral illnesses with flare-ups of FOP).

Patient histories were used to determine influenza-like viral illnesses and temporal relationship to changes in FOP. The survey investigated only the most recent influenza season (October 2000 through April 2001) because patient recall would be more reliable.<sup>18</sup> Although the seasonal prevalence of influenza is reversed in the two hemispheres of Earth, we did not exclude surveys from patients from the southern hemisphere as all non-seasonal influenza-like illnesses were accounted for by the questionnaire.

The two patients with FOP who prompted the initiation of this study had viral cultures that confirmed influenza B infections.<sup>14</sup> Although viral cultures are the most sensitive method of confirming influenza infection, such cultures were impossible to collect for this retrospective study. To avoid presumptions, we

refer to all persons having symptoms consistent with influenza as having an influenza-like viral illness.<sup>20</sup>

To be classified as having an influenza-like viral illness, patients had to report having fever or chills, cough, and nasal congestion, simultaneously for 7 to 14 days. Monto et al reported a positive predictive value of 81% for having laboratory-confirmed influenza when fever, cough, and nasal congestion were present within the first 48 hours of the onset of an influenza-like viral illness.<sup>20</sup>

Odds-ratio and relative risk confidence intervals and Fisher's exact test were used to calculate the statistical significance of the association between flare-ups of FOP and influenza-like viral illnesses.<sup>1</sup>

## RESULTS

A questionnaire to evaluate influenza-like symptoms in patients with FOP had 123 respondents (53 males, 70 females), representing 47% of the 264 patient-members of the IFOPA. Ninety of the 156 members (58%) with e-mail addresses completed the electronic questionnaire. Thirty-three of the 108 (31%) questionnaires sent by mail were completed. There were no duplicate responses. The age of the respondents ranged from 3 to 72 years (mean age, 27 years).

Of the 123 respondents, 10 (8%) met the criteria of having an influenza-like viral illness during the study period. All 10 respondents described having the three requisite signs (fever, cough, nasal congestion) and sore throat, enlarged lymph nodes, and severe fatigue. Nine of the 10 patients described having generalized myalgias. Eight of the 10 patients reported that other household members simultaneously experienced similar symptoms.

Of the 10 patients who were characterized as having had an influenza-like viral illness, six (one male, five females; mean age, 29 years) reported experiencing a dramatic decline in their FOP status as a result of the viral illness (Table 1). All six patients described symptoms consistent with a flare-up of FOP (pain, severe soft tissue swelling, and warmth) within 24 to 72 hours of the onset

of influenza-like viral symptoms. The neck was the most commonly affected site, with all six patients describing neck involvement. Other affected sites included the back, trunk, groin, and legs. One patient reported regression of her FOP lesions within 3 weeks of recovering from the infection. However, the five other patients described lesions that persisted for longer than 3 months and resulted in permanent loss of mobility. Four patients (one male, three females; mean age, 29 years) who met the criteria for having an influenza-like viral illness did not experience a flare-up of FOP (Table 1). Three patients in this group reported household members having similar flu-like symptoms.

Of the 113 patients (51 males, 62 females; mean age, 27 years) who did not meet the criteria for having an influenza-like viral illness, 12 (11%) described flare-ups during the influenza season (Table 1). All 12 patients (seven males, five females; mean age, 22 years) described some influenza-like symptoms (most commonly fever) but either lacked the two other mandatory symptoms (cough and nasal congestion), or did not experience the symptoms for the requisite 7 to 14 days. Commonly, patients having a flare-up of FOP report having fevers during periods of induration, which mistakenly can suggest an infectious process or tumor.<sup>14</sup> Four patients in this group reported that other household members experienced similar influenza-like symptoms. Only one of this group of 12 patients described a flare-up involving the neck whereas five of the six patients with flare-ups and influenza-like viral illnesses experienced a flare-up in the neck. Other affected sites for disease flare-ups in the patients who did not experience influenza-like viral illnesses included the legs, arms, abdomen, and submandibular region.

When compared with the incidence of flare-ups of FOP in the group without influenza-like symptoms (11%; 12/113), it was evident that individuals experiencing influenza-like viral illnesses were at a substantially greater risk (60%; 6/10) of having flare-ups of FOP ( $p = 0.0006$  by Fisher's exact test). The observed odds ratio was 12.62

**TABLE 1. Clinical Survey Data of Influenza-like Viral Illnesses and Disease Flare-ups in Patients With FOP**

FOP Status	Influenza-like Illness	No Influenza-like Illness	Total
Flare-up	6 (1 male, 5 females) (mean age, 28 years)	12 (7 males, 5 females) (mean age, 22 years)	18 (8 males, 10 females) (mean age, 24 years)
No flare-up	4 (1 male, 3 females) (mean age, 29 years)	101 (44 males, 57 females) (mean age, 28 years)	105 (45 males, 60 females) (mean age, 28 years)
Total	10 (2 males, 8 females) (mean age, 29 years)	113 (51 males, 62 females) (mean age, 27 years)	123 (53 males, 70 females) (mean age, 27 years)

with a 95% confidence interval of (3.11, 51.18). The relative risk was 5.65 with a 95% confidence interval of (2.70, 11.80). Therefore, it appears that the risk of an FOP flare-up is elevated during an influenza-like illness by at least a factor of 3 and possibly much more.

Twenty-eight (23%) of the study respondents reported receiving an influenza vaccination (which usually is administered intramuscularly) for the 2000 to 2001 influenza season. Of the 28 patients who received the influenza vaccine (mean age, 35 years), only one experienced symptoms that met our criteria for an influenza-like infection. Two patients reported having the influenza vaccination administered subcutaneously. None of the 28 patients who received the vaccination during the study period reported an adverse reaction.

## DISCUSSION

After observing severe flare-ups of FOP in two half-sisters with culture confirmed influenza B infections, we hypothesized that influenza-like viral illnesses can trigger FOP flare-ups. To test this hypothesis, we designed a questionnaire to assess whether patients with FOP experienced influenza-like viral symptoms during the 2000 to 2001 influenza season, and whether influenza-like viral symptoms were associated with flare-ups of FOP. Although this study was not designed to establish cause and effect by Koch's postulates, it determined a plausible relationship between influenza-like viral illnesses and flare-ups of FOP.

The design of this study may have introduced several methodologic biases. First, the consent form may have inadvertently biased recall and responses as the hypothesis was known to the study participants. Nevertheless, the patients were told that there may be no relationship between influenza-like illnesses and FOP. Second, the study relied on the memories of patients and their families to determine influenza-like viral illnesses and flare-ups of FOP. To minimize recall bias, the study was limited to the most recent (2000–2001) influenza season before commencement of data collection.<sup>18</sup> Although there is greater uncertainty from patient histories than from clinician-generated medical records, patients with FOP are reliable judges of disease flare-ups.<sup>4,18</sup> Third, although there was a large response to the survey, more than 1/2 of the targeted patients did not complete the survey. We were unable to obtain useful information with respect to influenza-like viral illnesses and flare-ups in these patients. Fourth, the survey criteria used to determine influenza infection are not as sensitive as viral cultures, the gold standard for confirming influenza infection. The 81% positive predictive value that Monto et al<sup>20</sup> described for culture-confirmed influenza infection in patients experiencing fe-

ver, cough, and nasal congestion examined only the first 48 hours of influenza-like symptoms.<sup>20</sup> To date, no published study has examined the most sensitive symptoms for establishing influenza infection for the duration of influenza-like viral illnesses. Despite these limitations, the data strongly suggest that influenza-like viral illnesses are associated with disease flare-ups in patients who have FOP.

The mechanism by which influenza-like viral illnesses may elicit flare-ups of FOP is not clear; however, several theories have been considered. Considering the sensitivity of FOP to trauma, it is reasonable to suggest that a flare-up might result from microtrauma caused by virus infecting muscle fibers,<sup>9</sup> or that the influenza virus might elicit an autoimmune response in skeletal muscle.<sup>3</sup> Additionally, many viral illnesses activate proinflammatory transcription factors *in vivo*, which may incite flare-ups of FOP.<sup>2</sup> Finally, influenza virus might affect the expression of BMPs or their antagonists in lymphocytes or muscle tissue of susceptible individuals.<sup>12,14,22</sup> Additional investigation is needed to establish the specific mechanisms by which influenza-like viruses induce flare-ups of FOP.

Patients who have FOP have severe restrictive disease of the chest wall at an early age and have a high risk throughout life for having life-threatening complications of respiratory infections.<sup>14,16</sup> The results of this study suggest that patients with FOP may have an additional substantial risk of having temporally-associated disease flare-ups from influenza-like viral illnesses. Such flare-ups affecting the chest wall would additionally imperil the already precarious respiratory status in a patient with FOP. Patients with FOP should promptly seek medical attention of influenza-like syndromes.

Although prospective studies are necessary to determine the exact identity, scope, and magnitude of influenza-like viral illnesses that trigger fibrodysplasia ossificans progressiva flare-ups, it is tempting to suggest that patients with FOP consider receiving influenza immunizations annually.<sup>6</sup> Additionally, unaffected household members of patients with FOP might consider annual immunizations. Prophylaxis with approved orally-inhaled antiviral medications after household contact may prevent clinical illness in unvaccinated individuals.<sup>6</sup>

It is recommended that patients who have FOP avoid intramuscular immunizations.<sup>17</sup> Influenza immunizations can be administered subcutaneously in patients with FOP to avoid the possibility of having heterotopic ossification develop at the inoculation site.<sup>11</sup> Other subcutaneous vaccinations (measles-mumps-rubella) have not been reported to elicit flare-ups in patients who have FOP.<sup>17</sup> An intranasal influenza vaccine now is available and is approved for administration, where not otherwise contraindicated, in individuals from 5 to 49 years of age.<sup>6</sup> This would circum-

vent the need for either an intramuscular or subcutaneous injection, and might be an attractive option in this patient population. Future studies also might be designed to determine if the intranasal influenza vaccine and approved treatments such as oseltamivir or zanamivir which are proven to be effective in reducing the severity and duration of influenza symptoms also might be effective in preventing flare-ups.<sup>6</sup>

Our study suggests that influenza-like viral illnesses are associated with disease flare-ups leading to mobility restriction in patients who have FOP. These findings have important implications for understanding and preventing environmental triggers of disease activity in this population of patients who are genetically susceptible to progressive and disabling heterotopic ossification.

### Acknowledgments

We thank Jeannie Peeper, founder and president of the IFOPA, for valuable support of this study and Constance Green for diligent observations and help in initiating this work.

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