Acute and Chronic Symptoms of Mononucleosis

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Background. The clinical symptoms and durations of illness of patients with infectious mononucleosis (IM) are variable and are poorly documented in the scientific literature.

Methods. Patients who presented for care at the Student Health Service of a Canadian university between September 1985 and May 1988 and had been diagnosed as having IM were surveyed. Health experience during the acute and convalescent phases of IM was compared with that of a group of patients matched for age, sex, date of diagnosis, and year of study, who had suffered acute upper respiratory tract infections (URI), other than Epstein-Barr virus (EBV)-induced, during the same period.

Results. Students were sicker for longer after IM than after non-EBV-induced URI. During the acute phase of illness, the symptoms of fatigue ($P = $ <.000001), night sweats ($P = .000001$), and painful neck swelling ($P = .00003$) were seen significantly more often in the IM group. The severity and duration of these symptoms were also significantly worse in IM patients. Getting tired easily ($P = .002$), diurnal somnolence ($P = .002$), and depression ($P = .002$) were significantly more common postacute symptoms. Eleven percent of IM patients reported persistence of symptoms longer than 100 days, and in 6% of patients the symptoms had persisted after 1 year. Convalescent cases showed a trend toward reduced alcohol intake and, perhaps, reduced alcohol tolerance.

Conclusions. IM involves excessive morbidity in a student community compared with URI that was other than EBV-induced, during both the acute and the postacute phases of infection.

Key words: Infectious mononucleosis; respiratory tract infections; chronic disease; comparative study.
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Infectious mononucleosis (IM), an acute lymphoproliferative disorder, is a clinical expression of infection by the Epstein-Barr virus (EBV). A member of the herpes group,[1] EBV has been isolated from the oropharynx of more than 80% of IM patients,[2] thus incriminating saliva as the main route of transmission of the infection ("kissing disease"). The most common victims are young college-aged individuals in whom the rate of EBV infection, clinical and subclinical, has been found to be as high as 12% per year.[2] Distinct acute and postacute phases of IM have been described in the literature.[3]

Clinical manifestations are variable. Many patients are asymptomatic, others develop mild respiratory infection symptoms, and a few patients develop the typical clinical, hematological, and serological features of IM.[4] The symptoms of initial infection usually resolve within a matter of weeks. The illness follows one of three courses: the patient recovers completely, the patient recovers but suffers a relapse,[5–8] or the patient suffers from persistent illness.[9] Published literature has been dominated by a considerable disparity with regard to the morbidity associated with IM. It has been variously reported that 75% of IM patients experience morbidity persisting for periods ranging from 8 to 39 months,[9] that 53 of 206 patients experienced continued illness after acute IM[10] with symptoms persisting for more than 1 year in 25 patients; and that prolonged illness occurred in only one of the 1000 patients with IM seen over a 20-year period.[11]

To test the hypothesis, based on clinical experience, that morbidity during and after IM occurs with a frequency different from previous estimates, we designed a survey to analyze the health experiences of university students who had suffered from IM. The survey instrument was designed to measure the frequency and severity of symptoms and the degree of reduced vitality during and after an acute episode of IM by comparing the health experience of these students with a matched sample of students who had upper respiratory tract infection (URI) cases diagnosed at approximately the same time.

Methods

The IM group was composed of 178 students at Queen's University who had been diagnosed at the student health service as having IM between September 1985 and May 1988, identified from a computer list generated by the student health service. Hoagland's criteria (clinical illness compatible with IM, demonstration of relative and absolute lymphocytosis, more than 20% atypical lymphocytes, and positive serology for heterophil antibody) were accepted for establishing the diagnosis.[12] Since 5% to 10% of patients with IM test negative for heterophil antibodies,[1] students who had met the clinical and hematological criteria and who had demonstrated a fourfold rise in titer of EBV capsid antigen antibodies were also included in the IM group. From this group students who had evidence of underlying or former chronic diseases (such as malignancy, chronic lung and heart diseases, diabetes mellitus, immunodeficiency, iron deficiency anemia, autoimmunity, and depression) or who had received previous immunosuppressive therapy were excluded. The URI group included students diagnosed as having pharyngitis, laryngitis, tonsillitis, otitis media, sinusitis, and bronchitis at the student health service during the same period. It was confirmed from the case records that these students had tested negative for Hoagland's hematologic and serologic criteria. Blood work was advised on these students in view of the severity of the episodes of URI and to rule out the possibility of EBV infection. These URI cases were identified from the medical records of all URI cases diagnosed during the same period. Exclusion criteria similar to those used for the IM group were applied to the URI group. Students of the IM and URI groups were matched for age (± 18 months), sex, date of diagnosis (± 30 days), and year of study. A list of 178 pairs of matched students of the IM and URI groups was generated. The addresses of students were obtained from a university publication, and those who had already left the university were tracked through the alumni office.

A questionnaire was sent to the individuals in the IM and URI groups. The questionnaire was mailed in a package containing a consent form, a stamped return envelope, and a cover letter that explained the study to the participants. Follow-up of nonresponders was done by telephone 4 weeks after the mailing of the questionnaire package. Seventeen second sets of questionnaire packages were mailed to those who either had not received the previous package or had misplaced it.

The questionnaire consisted of three parts. Part A requested personal information including personal habits and past medical history. Part B had questions on the acute index episodes of IM or URI, seeking information on the severity and duration of symptoms as well as on the impact of the ailments on school and work activities. Part C asked about the student's health experience since recovery from the acute ailment. Recovery was defined as resumption of day-to-day activities, and the postacute phase was defined as the period after complete recovery was reached. The Statistical Analysis System computer program was used to analyze the health experience of these matched pairs on a number of variables. The McNemar exact test and the Wilcoxon signed-ranks test were performed to analyze the data.

Results

Of 178 students in each group, 134 (75.28%) in the IM group and 105 (58.98%) in the URI group responded. The demographics of nonrespondents were similar in the IM and URI groups. The most frequent characteristic of nonresponders was that they were no longer students at Queen's University (77.2% of IM nonrespondents and 75.3% of URI nonrespondents). The proportion of women among the nonrespondents was slightly lower in the IM group (47.7%) than in the URI group (49.1%). The proportion of IM group nonrespondents who actually refused to participate in the study when contacted by telephone during the follow-up was 22.7%, compared with 24.6% of URI nonrespondents.

The initial responders in both groups included 82 matched pairs. A rematching was performed to the extent possible on the same variables for responders without a matching responder, and finally 105 matched pairs were included in the statistical analysis. The 29 additional IM responders who did not have matched cases of URI were excluded from the main analysis because it was thought that matched-pair analysis was a more controlled and more powerful method.[13] These cases were summarized separately, however, to ensure that their elimination did not affect the result.

There were 53 female pairs and 52 male pairs included in the analysis. The mean age of the students at the time of diagnosis of ailments was 20.19 years and at the time of filling in the questionnaire was 22.15 years. The health experiences of these matched pairs were compared for both the acute phase of the infections and the subsequent phase.

Acute Phase

Subjects in the IM and URI groups were asked if they had any of eight symptoms (fever, sore throat, bodyache, painful neck swelling, difficulty in swallowing, fatigue, night sweats, or jaundice) during the acute episodes.

Table 1. Symptoms That Occurred More Frequently in Patients with Infectious Mononucleosis Than in Patients with Respiratory Infection During the Acute Phases of the Diseases

| Symptoms | Untied Pairs | | P Values* |
	IM–Yes URI–No	IM–No URI–Yes	
Painful neck swelling	39	10	.00003
Fatigue	53	4	<.000001
Night sweats	61	1	<.000001

*Based on the McNemar exact test on untied-paired values in 105 pairs.
NOTE: Level of significance by Bonferroni method = .006.
IM denotes infectious mononucleosis; URI, upper respiratory tract infection.

Table 2. Symptoms That Occurred More Frequently in Patients with Infectious Mononucleosis Than in Patients with Respiratory Infection During the Postacute Phases of the Diseases

| Symptoms | Untied Pairs | | P Values* |
	IM–Yes URI–No	IM–No URI–Yes	
Tired easily	23	6	.002
Daytime sleepiness	23	6	.002
Depression	18	2	.002

*Based on the McNemar exact test on untied-paired values in 105 pairs.
NOTE: Level of significance by Bonferroni method = .003.
IM denotes infectious mononucleosis; URI, upper respiratory tract infection.

Individual symptoms were compared in the pairs separately, and the Bonferroni method[14] was used to eliminate the chance of error due to multiple comparisons. Eight tests were conducted on symptoms during the acute phase of the ailments; therefore the new significance level used was .006 (.05/8). Out of these eight symptoms, the incidences of painful neck swelling, fatigue, and night sweats were discovered to be significantly greater in the IM group (Table 1). The P values were computed by performing the McNemar exact test on yes–no and no–yes (untied) pairs.

The median duration of symptoms during the acute phase in the IM group was 3 to 4 weeks as opposed to 1 to 2 weeks in the URI group, the difference being statistically significant (P = .0001). Eleven percent of students who were diagnosed as having acute IM had symptoms for more than 100 days (Figure 1). It was estimated that 6% of the students who had IM had persistent symptoms at 1 year. The URI group had a more complete recovery (mean was 4.60 on a scale of 0 to 5 where 0 = no recovery and 5 = complete recovery) than the IM group (mean was 4.38), but the difference
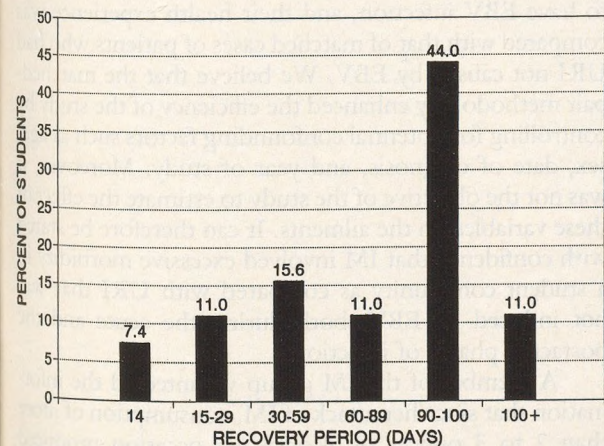

Figure 1. Graph illustrates the variations in the recovery period of students from symptoms of acute mononucleosis.

was not statistically significant (P = .01). The mean duration of the illness in the IM group, from the onset of the symptoms until recovery from the acute phase, was 62.5 days; in the URI group, it was 24.6 days. The difference was statistically significant (P = .0001).

Postacute phase

A comparison of 14 symptoms (tired easily, weakness, recurrent headache, fever, sore throat, night sweats, low energy, enlarged glands, recurrent bodyache, inability to concentrate, daytime sleepiness, depression, poor memory, and sleep disturbances) during the postacute phase was made between the matched pairs in the IM and URI groups by means of check-box items. The level of significance, .003 (.05/14), was determined using the Bonferroni method.[14]

Of these symptoms, the incidence of becoming tired easily, daytime sleepiness, and depression was significantly greater in the IM group. The incidence of these symptoms and their computed P values have been shown in Table 2. The remainder of the symptoms, except fever, were more frequent in the IM group, but the differences were not statistically significant. The McNemar exact test was performed on the untied pairs.

When these symptoms during the postacute phase were compared among the matched pairs for the frequency of occurrence (number of episodes per person in those who experienced the symptom) after recovery from the acute phases of IM and URI, it was observed that five of the symptoms recurred significantly more frequently in the IM group. Getting tired easily was the symptom most frequently recurring during the postacute phase in the IM group, and the difference was statistically significant (P = .0002). These symptoms and their mean number of episodes in the IM and URI group along with the P values are displayed in Table 3. The P values have been computed by using the Wilcoxon signed-ranks test comparing the matched pairs.

Significant differences were noted with respect to

Table 3. Number of Episodes of Symptom Occurrence
During the Postacute Phase in IM and URI Groups

Symptoms	Average No. of Episodes		P Values*
	IM	URI	
Tired easily	9.8	5.8	.0002
Low energy	7.7	3.8	.002
Enlarged glands	5.8	2.4	.002
Inability to concentrate	7.5	3.3	.002
Daytime sleepiness	7.6	5.1	.0005

*Based on the Wilcoxon signed-ranks test on paired values in all 105 pairs.
NOTE: Level of significance by Bonferroni method = .003.
IM denotes infectious mononucleosis; URI, upper respiratory tract infection.

the average duration of four symptoms per episode in the postacute phase when the matched pairs were compared in the IM and URI groups. The average duration of the student's inability to concentrate was longest (mean = 9.1 days) in the IM group among all these symptoms. These symptoms, their average duration in the IM and URI groups, and their P values have been indicated in Table 4. On the severity scale (0 to 5), there was no statistically significant difference found at the .003 level.

The median amount of time missed from job and school during the postacute phase in the IM group because of medical reasons was 3 to 4 weeks; in the URI group, it was under 1 week. The difference was statistically significant ($P = .0001$).

No difference between the groups was noted in the duration of exercise activities before acute illness episodes, but a statistically significant difference emerged post-illness ($P = .0001$). The average IM patient exercised for 2.8 hours per week and the average URI patient exercised for 4.6 hours per week after their acute illnesses.

The groups were fairly similar in the way in which their illnesses affected their drinking habits. Approximately 91.4% of the students in the IM group consumed alcohol before the acute episode, compared with 90.4% after the acute episode. In the URI group, 92.3% consumed alcohol before their illness, and 90.4% after the acute episode. An interesting finding with regard to

Table 4. Average Duration of Symptoms in Postacute Phase in IM and URI Groups

Symptoms	Average Duration (days)		P Values*
	IM	URI	
Low energy	7.7	4.2	.001
Enlarged glands	5.5	1.8	.003
Inability to concentrate	9.1	3.5	.002
Daytime sleepiness	7.5	2.2	.0002

*Based on the Wilcoxon signed-ranks test on paired values in all 105 pairs.
NOTE: Level of significance by Bonferroni method = .003.
IM denotes infectious mononucleosis; URI, upper respiratory tract infection.

alcohol intake was that the median quantity of alcohol consumed was reduced from 10 to 19 drinks per month to 1 to 9 drinks per month in students who suffered an acute episode of IM. The median quantity of alcohol consumed (10 to 19 drinks per month) remained the same, however, among students who suffered from an acute URI.

The 29 students with IM that were eliminated from the matched-pair analysis were similar to the rest of the sample with respect to their demographic characteristics. Their overall morbidity, during both the acute and postacute phase of IM, with regard to the frequency, duration, and severity of symptoms was also similar to the remaining 105 students in the IM group. To ensure that the exclusion of these 29 students did not affect the results, all 134 responders in the IM group were compared with the 105 responders in the URI group as unpaired groups. Chi-square tests were performed on these groups for various symptoms experienced during the acute and the postacute phases of the ailments. Except for the incidence of sleep disturbances in the postacute phase, in which the difference between the two unpaired groups was not statistically significant, the other results agreed with the matched-pair analysis.

Discussion

This study differs from most other studies on infectious mononucleosis in that it evaluated the health problems during both the acute phase of an EBV infection and the postacute phase. Unlike most other studies, it did not attempt to correlate persisting symptoms after an acute episode of IM with immunological abnormalities, which was not the objective of the study. Strict selection criteria[15] were applied before the students were included in the study, however; students were unequivocally proven to have EBV infection, and their health experience was compared with that of matched cases of patients who had URI not caused by EBV. We believe that the matched-pair methodology enhanced the efficiency of the study by controlling for potential confounding factors such as age, sex, date of diagnosis, and year of study. Moreover, it was not the objective of the study to estimate the effect of these variables on the ailments. It can therefore be stated with confidence that IM involved excessive morbidity in a student community as compared with URI that was not induced by EBV, both during the acute and the postacute phases of infection.

A member of the IM group volunteered the information that since her attack of IM, consumption of more than 2 to 3 ounces of alcohol per occasion produced unpleasant symptoms reminiscent of her IM infection. This study has indicated that the alcohol consumption of

students who had an acute episode of IM decreased from 10 to 19 drinks per month to 1 to 9 drinks per month. The questionnaire did not ask the students for a reason for the reduced alcohol intake. The reduction in alcohol consumption in students who had suffered from acute IM could be due either to the exacerbation of the symptoms after alcohol intake or to diminished social activities because of persistent illness. It was not the practice of the physicians at the student health service to advise against alcohol intake after IM.

It is less likely that the study instrument introduced bias into the study since the cover letter enclosed in the questionnaire package explained only the methodology of the study to the participants and requested their cooperation. We realize, however, that certain other methodologic limitations were inherent in the study. Although it would have strengthened our study, it was not feasible to screen the study participants extensively (chest radiography, sedimentation rate, studies of thyroid stimulating hormones, etc) before the study began for any underlying occult diseases.

Subjects were asked to recall aspects of an illness that occurred, on average, 2 years earlier, and the accuracy of such information may be questionable. If the two groups had actually had comparable experiences with their respective illnesses, however, it seems unlikely that errors in recall would consistently introduce one-sided differences in the reported information, such as are found in this study. It seems much more likely that consistent differences in the reported information between the two groups reflected a true difference in actual experience.

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