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Infectious Mononucleosis–Like Syndromes in Febrile Travelers Returning From the Tropics

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Background. Infectious mononucleosis (IM), resulting from Epstein–Barr virus (EBV) infection, and IM-like syndromes, mainly due to cytomegalovirus (CMV), *Toxoplasma gondii*, or human immunodeficiency virus (HIV), have been occasionally reported in travelers returning from the tropics. Our objective was to investigate the prevalence, outcome, and diagnostic predictors of these syndromes in febrile travelers.

Methods. Between April 2000 and March 2005, all febrile travelers and migrants presenting at our referral centers within 12 months after a tropical stay were prospectively included. We identified all patients serologically diagnosed with IM or IM-like syndrome and compared them with the rest of the cohort.

Results. During the 5-year period, 72/1,842 patients (4%) were diagnosed with an IM-like syndrome, including 36 CMV, 16 *T gondii*, 15 EBV, and 5 HIV primary infections. All patients were western travelers or expatriates. Mean delay before consultation was 2 weeks. Most patients had consulted other practitioners and/or received presumptive treatment. A minority of patients presented with IM clinical features. Lymphocytosis ≥40% of the white blood cells (WBC) and reactive/atypical lymphocyte morphology were observed in 60 and 30% of the patients. The four diseases were indistinguishable. Protracted fever and asthenia were common but complications rarely occurred. IM-like syndromes were independently associated with fever >7 days, lymphadenopathy, elevated liver enzymes, and lymphocytosis ≥40% of WBC. Diagnostic probability increased to >20% if at least three of these predictors were present.

Conclusions. Diagnosis of IM and IM-like syndrome is not uncommon in febrile travelers, with a higher proportion of primary CMV, *T gondii*, and HIV infections than in nonimported series. Consequently, classic IM clinical and laboratory features are often lacking. All four pathogens should be systematically considered because early diagnosis should avoid unnecessary investigations and treatment and allow early intervention in case of primary HIV infection.

Infectious mononucleosis (IM)-like syndromes are defined by analogy to the clinical and biological features of classic IM, resulting from Epstein–Barr virus (EBV) infection. The hallmarks of IM are fever, pharyngitis, lymphadenopathy, and a mononuclear cells count (lymphomonocytosis) ≥50% of the white blood cells (WBC) with atypical or reactive morphology of the lymphocytes in the peripheral blood.[1,2] Additional features include splenomegaly or exanthema and may contribute to the clinical diagnosis. The infectious agents most commonly causing IM-like syndromes are

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cytomegalovirus (CMV), *Toxoplasma gondii*, and human immunodeficiency virus (HIV).[2–7] Other conditions may also occasionally mimic classic EBV-induced IM, such as viral hepatitis, leptospirosis, brucellosis, secondary syphilis, cat-scratch disease, rubella, collagen vascular diseases, hematological disorders, and drug reactions.

In industrialized countries, infections with the leading pathogens causing IM-like syndrome have decreased in the past decades, except for HIV, and affect increasingly older adults.[1,3,8,9] In contrast, they remain highly endemic in developing countries and occur early in lifetime. Among young adults of most tropical countries, seroprevalence of EBV and CMV infection reaches 90%, while it is sometimes up to 30% for HIV infection and ranges from 30% to 90% for toxoplasmosis according to dietary habits.[1,3,6,9] In addition, transmission is mainly due to intimate contact for EBV and CMV (salivary shedding especially in children), sexual promiscuity for HIV and CMV (sexual shedding), and oral ingestion for *T gondii* (oocysts-contaminated food or water or tissue cyst-containing undercooked or raw meat). Therefore, western travelers to tropical areas may be susceptible to these diseases. We sought to describe the prevalence, etiology, and outcome of IM and IM-like syndromes in returning febrile travelers and to identify diagnostic predictors for these conditions.

Methods

Setting and Subjects

From April 2000 to March 2005, we included prospectively all travelers or migrants attended at the Institute of Tropical Medicine, Antwerp (ITMA) and the University Hospital of Antwerp (UHA) with ongoing fever within 12 months after a stay in the tropics. The ITMA is the national reference center for tropical diseases in Belgium, and the UHA is a tertiary care referral hospital. For this study, we recruited all patients diagnosed with a primary EBV, CMV, *T gondii*, or HIV infection. Clinical and laboratory findings were recorded at initial contact. All patients were followed for at least 3 months or referred to the HIV/acquired immunodeficiency syndrome clinic in case of HIV infection.

Case Definitions

For EBV, CMV, or *T gondii* infections, diagnosis was confirmed in case of documented seroconversion [appearance and/or increase of specific immunoglobulin (Ig)M and/or IgG antibody titer in paired blood sera] or was highly probable if a single positive IgM titer was found against one of these pathogens together with clinical and biological features suggestive of IM-like syndrome. This was defined by the presence of any of the signs pharyngitis, lymphadenopathy, splenomegaly, or exanthema and any of the laboratory abnormalities relative increase of mononuclear cells ≥50% of the WBC or presence of reactive or atypical lymphocytes. Serological tests used were enzyme-linked fluorescent assay (VIDAS, BioMérieux, Lyon, France) for CMV IgM and IgG as well as for *T gondii* IgM and IgG and enzyme-linked immunosorbent assay (ELISA) (Enzygnost Anti-EBV/IgG and Anti-EBV/IgM, Dade Behring, Harburg, Germany) for EBV IgM and IgG.

Diagnosis of primary HIV infection relied on detection of HIV P24 antigenemia (Innotest HIV Antigen mAb, Innogenetics) with negative antibody detection by ELISA (Enzygnost Anti-HIV 1/2 Plus, Dade Behring) at initial contact, and subsequent confirmed seroconversion (INNO-LIA HIVI-II Score, Innogenetics, Gent, Belgium). Patients diagnosed with a concomitant infection considered to be clinically predominant (like malaria) were not included in this study. All IM-like syndromes with fever onset occurring within the maximum incubation period (8 wk) after return were considered as travel-related.

Diagnostic Predictors of IM-Like Syndrome

Only confirmed patients were compared with the rest of the febrile cohort because the definition of probable patients included some diagnostic predictors we sought to investigate. Sensitivity and specificity of clinical and laboratory features were obtained by data processing. For those found with a sensitivity >30%, respective likelihood ratios (LR) were calculated by the standard formulas for binary outcomes. We then used the Spiegelhalter-Knill-Jones weighing system to obtain the adjusted LR of each single or combined independent predictor of IM-like syndrome.[10] The procedure involved calculating the natural logarithm of their respective positive and negative LR (crude weights) and multiplying them by the logistic coefficients (adjusted weights). A total weight could then be obtained for each combination of predictors (by addition if present and subtraction if absent), allowing calculation of respective adjusted LR.

Statistical Analysis

Analysis was performed using the SPSS program version 12.0 (SPSS Inc., Chicago, IL, USA). Pearson's chi-square test, *t*-test, and one-way analysis of variance were used for comparison between groups as appropriate.

Results

During the 5-year study period, 72 were diagnosed with IM-like syndromes (46 confirmed and 26 probable), corresponding to 4% of all included febrile episodes (n = 1,842). They were due to 36 CMV, 16 *T gondii*, 15 EBV, and 5 HIV primary infections. In 14 patients, a nonpredominant coinfection was also found, including protozoan/bacterial enteritis (n = 6), genitourinary infection (n = 4), and respiratory tract infection (n = 4). Seroconversion against CMV was also documented in four additional patients who were excluded from analysis because of concomitant infection with *Plasmodium falciparum* (n = 3) or HIV (n = 1). Prevalence of chronic HIV infection was 3% in our cohort of febrile travelers.

Table 1 shows the main epidemiological and follow-up data. Most patients were male. Mean age was 38 years (range 1.5–76 yr). Infection was considered as travel-related in nearly 90% of the patients. An IM-like syndrome was diagnosed in 2.5%, 7%, and 5% of febrile travelers returning, respectively, from Africa, Asia, or America. No migrant was found with an IM-like syndrome although they represented 12% of the febrile cohort.

Mean delay before consulting our centers was 2 weeks (range: 1–8.5 wk). Most patients had previously consulted another physician, and nearly half had already taken presumptive antibiotics (n = 22, 31%), antimalarials (n = 3, 4%), or both (n = 7, 10%).

The hospitalization rate was 25%. Two patients with acute toxoplasmosis required intensive care (one with severe polymyositis and another with subsequent deep venous thrombosis and lung embolism). Empiric antibiotic treatment was often initiated at the first consultation, mostly because of suspected enteric fever. Complications were observed in four patients with acute toxoplasmosis (polymyositis in two, lung embolism in one, and abortion in one), in two patients with acute HIV infection (mild encephalitis in one, severe and protracted enteritis in one), in one patient with acute EBV infection (pancreatitis), and in one with acute CMV infection (symptomatic hepatitis). All patients (except those with HIV infection) recovered completely, often after a protracted course. Fever lasted 3 weeks on average (range 0.5–10 wk). Most patients complained of invalidating fatigue lasting >3 months.

Sensitivity of clinical and laboratory findings is summarized per disease in Table 2. There was no difference between confirmed (n = 46) and highly

Table 1 Epidemiology, evolution, and outcome of patients with IM-like syndromes (n = 72)

	All IM-like syndromes (n = 72)	Primary CMV infections (n = 36)	Primary *Toxoplasma gondii* infections (n = 16)	Primary EBV infections (n = 15)	Primary HIV infections (n = 5)
Mean age ± SD (years)	38 ± 14.5	38 ± 14.5	44 ± 15	32.5 ± 13.5	33 ± 8
Males (%)	65	67	56	67	80
Short-term travelers (%)	78	78	75	73	100
Travel-related (%)	86	83	88	94	80
Continent of exposure (%)					
Africa	52	48	50	60	50
Asia	32	34	29	33	25
America	10	14	7	7	0
>1 continent	6	3	14	0	25
Mean delay from fever onset to consultation ± SD (days)	14.5 ± 11.5	15 ± 10.5	14 ± 11.5	16.5 ± 15	7 ± 3.5
Previous contact with another practitioner (%)	58	67	44	53	60
Previous antimalarial and/or antibiotic treatment (%)	45	42	44	53	40
Empiric antibiotic treatment at first contact (%)	26	26	12.5	31	60
Hospitalization rate (%)	25	29	25	12.5	40
Complication rate (%)	8	3	25	17	40
Mean duration of fever ± SD (days)	21.5 ± 14	21.5 ± 12	22 ± 13	24.5 ± 20	9 ± 1
Protracted asthenia >3 months (%)	60	57	75	44	80

CMV = cytomegalovirus; EBV = Epstein–Barr virus; HIV = human immunodeficiency virus; IM = infectious mononucleosis.

Table 2 Sensitivity of clinical and laboratory findings in all IM-like syndromes (n = 72) and per disease*

	All IM-like syndromes (n = 72)	Primary CMV infections (n = 36)	Primary *Toxoplasma gondii* infections (n = 16)	Primary EBV infections (n = 15)	Primary HIV infections (n = 5)
Symptoms and signs					
Fever >7 days	72	74	69	80	60
Headache	61	64	56	67	40
Myalgia	53	56	56	53	20
Temperature ≥39°C	50	53	50	40	60
Lymphadenopathy	33	31	38	40	20
Skin rash	19	11	25	20	60
Splenomegaly	15	11	19	27	0
Pharyngitis	12	9	0	25	40
Laboratory findings					
Elevated LDH ≥650 IU/L (66 tested)	65	72	62.5	60	40
Lymphomonocytosis ≥50% of WBC	64	81	29	79	0
Elevated ALT ≥70 IU/L	46	53	31.5	53	20
Lymphocytosis ≥40% of WBC	57	77	25	63	0
Reactive/atypical lymphocytes	31	29	19	56	0
WBC count ≥10,000/mL	24	25	19	33	0
Platelet count <150,000/mL	11	11	0	13	40
Mean lymphocytosis ± SD (% of total WBC)	43.7 ± 16.1	48.9 ± 14.3	33.3 ± 16.9	47.2 ± 14	29.5 ± 7.3
Mean lymphomonocytosis ± SD (% of total WBC)	55.5 ± 15	59.9 ± 13.9	46.5 ± 15	58.7 ± 13.7	42 ± 6.1

ALT = alanine aminotransferase; CMV = cytomegalovirus; EBV = Epstein–Barr virus; HIV = human immunodeficiency virus; IM = infectious mononucleosis; LDH = lactate dehydrogenase; WBC = white blood cell. None of these data were significantly different between diseases except mean lymphocytosis and lymphomonocytosis, respectively (p = 0.001 and p = 0.006, by analysis of variance).
*All results are expressed in percent unless otherwise mentioned.

probable patients (n = 26). Only a minority of patients had suggestive IM clinical features. Uncommon symptoms (cough, diarrhea) were also present, but in most patients, it related to concomitant infections. Lymphomonocytosis ≥50% of the WBC was the only IM laboratory feature frequently observed. Receiving operating characteristic curves of lymphomonocytosis and lymphocytosis had similar performances for the diagnosis of IM-like syndrome (area under the curve of 83 and 81%, respectively). Lymphomonocytosis ≥50% and lymphocytosis ≥40% of WBC were found with rather similar sensitivity (around 60%) and specificity (around 85%). Elevated alanine aminotransferase (ALT) ≥70 IU/L and elevated lactate dehydrogenase (LDH) ≥650 IU/L were other frequent abnormalities.

There were no significant differences between the four causative pathogens in terms of visited continent, type of travel, delay before consulting, referral pattern, clinical characteristics, and short-term morbidity. Laboratory findings were also similar between the four groups of patients, except that mean lymphomonocytosis and lymphocytosis were lower in patients with acute toxoplasmosis (p = 0.006 and p = 0.001, respectively). The small number of HIV primary infection did not allow robust comparisons.

In univariate analysis, confirmed IM-like syndromes (n = 46) were significantly associated with duration of fever >7 days before consultation, lymphadenopathy, fever ≥39°C, elevated ALT, elevated LDH, and lymphocytosis (chosen cutoff ≥40% of WBC). Multivariate analysis identified four independent diagnostic predictors: fever duration >7 days, lymphadenopathy, elevated ALT, and lymphocytosis ≥40% of WBC (Table 3). Assuming a prevalence of 4% in our setting, posttest probabilities were obtained for each possible combination of predictors (Table 4). It reached 60% if all four parameters were present, ranged between 20 and 40% if three of them were observed but dropped to 1% if all four were absent. When taking observed final diagnosis as reference, the true-positive rate of IM-like syndrome was 87% in patients presenting with all four predictors (7/8) and 47% if three of them were present (23/59). In the remaining patients presenting with three or four predictors but not found with IM-like

Table 3 Sensitivity, specificity, adjusted LR, and OR of the independent predictors of confirmed IM-like syndromes (n = 46) compared with all other febrile diseases (n = 1,770)

	Sensitivity	Specificity	LR+	LR–	OR (95% CI)	p Value
Fever >7 days	0.78	0.72	2.27	0.39	6.31 (3.03–13.16)	<0.001
Lymphocytosis ≥40% of WBC	0.52	0.88	3.23	0.62	5.49 (2.89–10.41)	<0.001
Lymphadenopathy	0.33	0.88	2.49	0.78	3.30 (1.67–6.70)	0.001
Elevated ALT ≥70 IU/L	0.46	0.84	2.09	0.73	2.66 (1.32–5.35)	0.006

ALT = alanine aminotransferase; CI = confidence interval; IM = infectious mononucleosis; LR = likelihood ratios; OR = odds ratio; WBC = white blood cell.

syndrome (n = 37), the following diagnoses were made: rickettsial infections (n = 9), malaria (n = 5), dengue (n = 5), and hepatitis A (n = 2). Six of the 16 remaining patients with another diagnosis had an underlying HIV infection.

Discussion

Fever after a stay in the tropics may be due to a wide variety of cosmopolitan infections, and most of them are more prevalent in developing countries, putting international travelers at risk of acquiring such diseases.[11,12] During a 5-year prospective study on imported fevers at our institutions, we observed that a substantial number of patients presented with features of IM, and were diagnosed with acute toxoplasmosis, or acute EBV, CMV, or HIV infection. As our definitions were strict, we are rather confident that only true-positive patients have been identified. The four diseases caused together 4% of all imported fevers, ranking third among cosmopolitan etiologies after bacterial enteritis and respiratory tract infections, and being as frequent as common tropical diseases like dengue or rickettsial infections. Moreover, prevalence reported here is underestimated because patients with nonspecific features and a single serologic test may have been falsely considered as negative. In addition, mononucleosis syndromes present sometimes also without fever (study entry criterion) although this feature is predominant in symptomatic patients.[13–15] Finally, most acute infections are subclinical, but this aspect is not relevant here.[1,3,6,15]

Information about the incubation period of these diseases remains somewhat speculative, especially for CMV infection and toxoplasmosis. By analogy with EBV infection, we considered a maximum incubation period of 8 weeks for all IM-like syndromes and assumed that all patients becoming symptomatic during this post-travel period had been infected during their stay abroad, although some of them might have contracted their infection after return. As such, nearly 90% of the patients

Table 4 Calculated posttest probabilities and observed rates of IM-like syndromes per combination of predictors

Duration of fever (before consultation), days	Lymphadenopathy	Lymphocytosis (% of WBC)	ALT (IU/L)	Calculated posttest probabilities (%)	Observed rates of IM-like syndrome % (n+/n present)
>7	Yes	≥40	≥70	61	87 (7/8)
>7	Yes	≥40	<70	36	22 (4/18)
>7	No	≥40	≥70	33	53 (16/30)
>7	Yes	<40	≥70	23	27 (3/11)
≤7	Yes	≥40	≥70	21	—
>7	No	≥40	<70	15	16 (8/50)
>7	Yes	<40	<70	10	6 (3/54)
≤7	Yes	≥40	<70	9	23 (3/13)
>7	No	<40	≥70	9	5 (4/77)
≤7	No	≥40	≥70	8	7 (2/28)
≤7	Yes	<40	≥70	5	0 (0/9)
≤7	No	≥40	<70	3	1 (1/103)
>7	No	<40	<70	3	3 (10/298)
≤7	Yes	<40	<70	2	3 (4/117)
≤7	No	<40	≥70	2	0.6 (1 /160)
≤7	No	<40	<70	1	0.7 (6/866)

ALT = alanine aminotransferase; IM = infectious mononucleosis; WBC = white blood cell.

became symptomatic during travel or within 2 months on return, suggesting that IM-like syndromes may be often acquired during a tropical stay.

In historical studies conducted in western countries, IM-like syndromes were mainly due to EBV infection and only 10% to 20% of them were due to CMV and *T gondii* infections.[2,5] Our observation suggests that the hierarchy of these diseases is profoundly altered when related to travel: CMV infection is predominant, and toxoplasmosis at least as frequent as classic EBV-induced IM. Although the importance of acute CMV disease after a stay in developing countries has been observed before,[16,17] the relatively high prevalence of acute toxoplasmosis in travelers has never been that obvious to date. Finally, primary HIV infection is also a crucial diagnosis to consider in febrile travelers.[18] Early diagnosis of acute HIV infection would allow fast interventions aimed at improving its long-term prognosis and at reducing its secondary spreading. This finding underscores the importance of assessing sexual behavior during travel, particularly in returning patients presenting with mononucleosis symptoms.[19–21]

There are various factors to explain such a prevalence of IM-like syndromes in travelers. First, an increasing number of western adults are susceptible to these diseases still occurring very early in the tropics. Second, these infections tend to be more symptomatic at a higher age. Finally, travels frequently offer the opportunity for close contacts with the local population and to carry the risk of hazardous alimentation and even sexual promiscuity.

Clinical features were similar to those reported in the literature, but classic IM symptoms were less prevalent than in historical series.[2,22] Enlarged lymph nodes were not frequently observed. Even laboratory hallmarks of IM were often absent. This could be explained by the relatively low prevalence of EBV as a cause of travel-related mononucleosis syndromes. Therefore, these conditions may be underdiagnosed and erroneously treated as we have observed in many second-line consultations.

As any single IM feature lacks sensitivity, combinations of various parameters might help predict diagnosis of IM-like syndrome more accurately. However, they may not have the same predictive weight and may not be independent from each other. Therefore, we used the Spiegelhalter's procedure that confers a logarithmic weight to each predictor and corrects it by logistic regression. In contrast to the classic logistic regression, this method allows adjusted addition or subtraction of each predictor and even neutralization of missing values that fits better into clinician's mind frame. We limited our investigation to the confirmed patients to get strong data. The four identified features (lymphocytosis ≥40% of WBC, fever >7 days, lymphadenopathy, and elevated ALT) have already been universally accepted as diagnostic predictors of IM-like syndrome. However, this study has tried for the first time to weigh each argument in combination with the others. Probability increased substantially if at least three predictors were present (from 4% to >20%). A first validation with the observed patients in our database showed a good correlation with these predictions but was limited by the small subsets of patients for some combinations of parameters. In addition, as the identified predictors are also observed in frequent imported illnesses like malaria, dengue, or rickettsial infections, these diseases should first be ruled out by specific investigations. Even if some conclusions may not be generalized to nonreferral centers, we think that our observations can help travel physicians confronted with the wide differential diagnosis of imported fever to early identification of an IM-like syndrome. However, as there is no feature fully discriminative for a specific pathogen, all four causative agents should be systematically looked for simultaneously.

It can be reasonably speculated that an early diagnosis of an IM-like syndrome would bring considerable benefits for both patients and physicians. This is obvious for HIV infection, but the burden of the other diseases should not be underestimated. Most patients consulted late, sometimes after extensive investigations, and often after administration of inadequate treatment. Although uncommon, complications like myositis, encephalitis, or hepatitis did occur.[23,24] Protracted fever and asthenia may provoke considerable anxiety if diagnosis is not rapidly established.[15,25,26] Finally, besides their substantial acute morbidity, long-term consequences of CMV and *T gondii* infections should not be neglected not only in travelers with a rather high prevalence of underlying HIV infection but also in an aging western population increasingly confronted with immunosuppressive conditions.

Conclusion

Primary EBV, CMV, *T gondii*, and HIV infections should be systematically considered in febrile travelers returning from the tropics after frequent tropical infections have been ruled out. Prevalence of EBV infection is lower than in nonimported series and consequently disease presentation is often less typical. Therefore, combination of classic predictors is necessary to increase substantially the post-test probability of a first-line workup. Precise

etiologic diagnosis requires serological testing against all four commonly associated pathogens. Early diagnosis would be evidently beneficial in case of primary HIV infection and would avoid unnecessary investigations and treatment for the other three pathogens.

Declaration of Interests

The authors state that they have no conflicts of interest.

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