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REVIEW

Delayed HIV testing in internal medicine clinics – a missed opportunity

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ABSTRACT

As HIV infection may be non-symptomatic for many years, many HIV-infected individuals are not aware of their infection. At a certain point in time non-specific symptoms may occur for which patients are likely be referred to internal medicine outpatient clinics. In the absence of systematic screening for HIV and in particular in patients who do not have classical risk factors for HIV, the diagnosis of HIV infection may easily be overlooked. In this manuscript it is illustrated that this diagnostic and therapeutic delay can lead to increased morbidity and mortality. Moreover, undiagnosed individuals are on average more likely to transmit HIV than diagnosed individuals. It is important for public health to identify people harbouring HIV infection, as this is expected to reduce the number of new infections. HIV infection should be considered a possible cause of unexplained symptoms in an early stage of the diagnostic process, in particular in patients with symptoms such as unexplained fever, lymphadenopathy or weight loss or in the presence of conditions suggestive of possible immune deficiency, regardless of the absence of risk factors.

KEYWORDS

HIV, late diagnosis, screening, opt-out, internal medicine, AIDS

INTRODUCTION

Human immunodeficiency virus (HIV) infection causes progressive destruction of the host immune system. Early diagnosis and initiation of antiretroviral treatment dramatically improves the prognosis of patients. As HIV infection can present with a broad variety of non-specific symptoms, a certain degree of awareness is necessary. However, in some cases clinicians disregard the possibility of HIV infection in patients who display symptoms which could be related to the disease, but who are not known to have any HIV-associated risk factors.[1] As a consequence, a broad array invasive investigations may precede serological testing for HIV.

In this article we present three patients with symptoms known to be associated with HIV infection, which remained undiagnosed or unexplained for a considerable time. None of them had apparent risk factors for an infection with HIV. All patients underwent multiple diagnostic and therapeutic interventions before an HIV test was performed. In the review section, we discuss factors that might contribute to diagnostic delay in HIV infections. In the Netherlands, as well as in many other industrialised countries, opt-in testing policies may feed general reluctance towards HIV testing and thus contribute to the high incidence of late HIV diagnosis.

Patient A, a 45-year-old female, was admitted to the department of internal medicine of a regional hospital on several occasions over a two-year period for analysis of fever and macrocytic anaemia which persisted despite vitamin B12 substitution. She also complained of fatigue which had been present since an episode of thoracic herpes zoster. The patient had a medical history of premature coronary artery disease with an episode of an acute coronary syndrome, hypertension and non-specific colitis. Laboratory investigation performed on her last admission showed anaemia (haemoglobin 4.1 mmol/l), atypical lymphocytosis, high erythrocyte sedimentation rate (ESR) and polyclonal hypergammaglobulinaemia. Temporal arteritis was suspected and a biopsy of the

temporal artery was performed, showing no abnormalities. Extensive evaluation with CT and PET scans showed a generalised lymphadenopathy. To exclude a lymphoproliferative disorder, an excision biopsy of a cervical lymphatic node was taken showing a reactive dysplasia. As a sampling error was suspected, a bronchoscopic biopsy of a mediastinal lymphatic node was performed, which confirmed the findings of the first biopsy. As an infectious cause seemed likely, treating physicians conducted serological screening aimed at several possible infectious causes. An HIV test was positive and the patient was referred to our centre. The CD4 cell count was 236/mm^3 upon referral. Shortly after transfer *Candida* oesophagitis was diagnosed and successfully treated with fluconazole. The patient received highly active antiretroviral therapy (HAART), consisting of tenofovir, emtricitabine and atazanavir boosted with ritonavir. The haemoglobin concentration normalised within a few months. The HIV RNA viral load became undetectable (<50 copies/ml) and the CD4 cell count increased to 450/mm^3 after six months of treatment.

Patient B, a 40-year-old heterosexual male, with a medical history of chronic hepatitis B was referred to an ophthalmologist because of pain and redness of his left eye, with decreased visual acuity. Toxoplasmic uveitis was diagnosed and treated with pyrimethamine and azithromycin with folic acid suppletion. The patient had a medical history of chronic hepatitis B, diagnosed five years earlier, and had been treated with entecavir for 18 months. In the previous year, the patient had experienced an episode of thoracic herpes zoster and pneumonia with prolonged recovery, and also reported weight loss of 10 kg. Because screening for HIV had never been performed, the ophthalmologist requested serological testing, and test results returned positive. A CD4 cell count of 53/mm^3 indicated advanced infection. An MRI of the brain showed a lesion in the right occipital lobe which could be a result of cerebral toxoplasmosis. Antitoxoplasmic treatment was adjusted (azithromycin was substituted by sulphadiazine). Antiretroviral treatment with tenofovir, emtricitabine and atazanavir boosted with ritonavir was prescribed. Entecavir was discontinued as tenofovir and emtricitabine, which also have an anti-HBV efficacy, were initiated. Use of entecavir as monotherapy in HIV/HBV-co-infected patients has been associated with the development HIV drug resistance compromising antiretroviral treatment options.[2] Fortunately, no resistance-related HIV mutations were detected in this case.

Patient C was a 64-year-old Dutch female who had been suffering from various unexplained symptoms for 12 years. Initially, she developed fatigue and myalgia, accompanied by a high ESR and thrombocytopenia. Her treating physicians suspected Sjögren's disease and idiopathic thrombocytopenic purpura. Treatment with prednisone was started but did not relieve her symptoms. During the following years, the patient experienced peripheral facial palsy, pneumonia, sensory polyneuropathy, mild cognitive impairment, deep venous thrombosis, septic shock of unknown origin, *Candida* oesophagitis and recurrent episodes of diarrhoea. In 2010, she was referred to our hospital for a second opinion due to dysarthria, dysphagia, apathy and sensory loss in both legs, rendering her unable to walk. HIV testing was performed and the results were positive. The CD4 cell count was 141 cells/mm^3. An MRI scan of the brain showed extensive leukoencephalopathy. Examination of the cerebrospinal fluid did not point to an opportunistic infection. Antiretroviral treatment was prescribed (tenofovir, emtricitabine, atazanavir boosted with ritonavir). During the following months, the patient was readmitted twice, first due to complicated urinary tract infection, and later due to bloody diarrhoea with stool samples positive for *Clostridium difficile* toxin. Her neurological condition remained unchanged after initiation of HAART. During the third readmission, three months after the HIV diagnosis, the patient suffered from pseudomembranous colitis with severe metabolic dysregulation due to dehydration, renal insufficiency and respiratory insufficiency, and died despite intensive treatment.

DISCUSSION AND REVIEW OF THE LITERATURE

Consequences of late diagnosis

The case histories presented above concern patients with symptoms that remained unexplained or undiagnosed for a considerable period of time, and ultimately appeared to result from infection with HIV. Although all patients had symptoms suggestive of cellular immune deficiency, HIV testing was not performed until considerable delay had occurred. Ensuingly, complications occurred that might have been avoided or possibly more adequately treated if HIV testing and treatment had been initiated in an earlier stage.

Late recognition of HIV infection has a number of important consequences regarding prognosis, transmission of infection and healthcare costs. It has been shown that testing positive in a late phase of the HIV infection, when a severe immunodeficiency is present, worsens the prognosis compared with early diagnosis.[3-5] Patients who started HAART in an advanced stage of the infection, prior to the development of AIDS, were shown to have a significantly greater risk of progression to AIDS and a higher mortality rate. [6] It is well known that if advanced immune deficiency is present, the risk of acquiring

an opportunistic infection or a malignancy is greatly increased. Moreover, antiretroviral treatment started in the setting of a profoundly impaired immune system often results in a slow and incomplete immunological recovery. From a public health perspective, early diagnosis is also beneficial as untreated patients with uncontrolled viral replication are more likely to transmit the virus to their sexual partners.[7] High morbidity in patients presenting late results in higher treatment costs.[8,9] Early diagnosis of HIV infection enables screening for other infections more frequently present in HIV patients, such as hepatitis C, which also has a better prognosis if treated early.[10]

European data indicate that in 33% of cases, the diagnosis of HIV infection is made in a late stage of the disease, at CD4 cell counts ≤350 cells/mm^3 or after the occurrence of an AIDS-defining event.[11] Until now, the presence of one of several well-known risk factors for HIV infection has been the main argument to perform an HIV test in Dutch clinical practice.[12] This could explain the large proportion of Dutch patients presenting late. According to the Dutch Athena cohort more than 50% of the heterosexual men and women and 40% of men who have sex with men (MSM) are late presenters.[13] Recent studies show that risk factors appear to be more often absent in patients who are diagnosed in a late stage of the infection. These patients have more frequently acquired HIV through heterosexual contact and belong to the older age groups.[14-18] These patient characteristics correspond with the case histories described above, in which the mean age was 47 years (range 40-64 years) and where heterosexual contact was the presumed transmission route.

An important cause of late diagnosis is patient delay. However, as the presented cases have shown, doctor's delay, due to postponing or not considering testing for HIV, also contributes to late testing. This has been recognised in other reports as well.[1,19-21] Several factors can be responsible for this delay. First, the diagnosis is often regarded as uncommon and as such is overlooked in the differential diagnosis of unexplained symptoms. Symptoms tend to be unspecific; complaints of weight loss, night sweats and fatigue are often present in advanced infection. If unexplained, such general symptoms as well as signs of immune deficiency should prompt HIV testing. Second, many physicians only expect the disease to affect patients involved in risk behaviour, such as male homosexual contact or intravenous drug use, and overlook cases of HIV infection when obvious risk factors are absent.[1,19] Last, doctors may fear that suggesting HIV testing could give the patient the impression of being suspected of risk behaviour, thus compromising the doctor-patient relationship.

HIV testing in the Netherlands

In the Netherlands, an opt-in testing policy for HIV infection is maintained in most clinical settings, requiring physicians to ask for patient consent for HIV testing. HIV infection is the only infectious disease to which this policy applies. This practice, combined with the tendency to only test patients if risk factors are clearly present, fuels the reluctance of doctors to perform an HIV test when risk factors are not apparent or when symptoms are ambiguous.

The reluctant attitude towards HIV testing in the Netherlands has its roots in the earlier days of the HIV epidemic.[22] Poor prognosis in the absence of effective treatment and social stigma associated with HIV infection implicated possible negative social consequences. The general feeling was that diagnosing the disease in an early stage only meant doing additional harm rather than being of benefit to the patient. This consideration led to repeated advice by the Dutch Health Council not to use the HIV test as a screening tool.[12] The introduction of HAART in the mid 1990s dramatically improved the prognosis of HIV-infected patients, prompting the Dutch Health Council to advise a more active HIV-testing policy in some situations. Still, in 2007 the percentage of Dutch people who had undergone HIV testing at least once in their life was lower than in other industrialised countries. Up to that year, only 70 to 80% of MSM in Amsterdam had undergone HIV testing at least once in their life, compared with 95% in Sydney and San Francisco.[23] Currently, all pregnant women are screened for HIV infection in an opt-out fashion and outpatient STD clinics have initiated opt-out screening for HIV infection in all patients.[24]

In 2005, the total number of HIV-infected individuals living in the Netherlands was estimated to be about 18,500, of which only two thirds were diagnosed. The remaining third, approximately 6000 individuals, were unaware of their seropositive status.[24] In 2010 the total number of HIV-infected individuals was expected to have risen to 21,500, and the number of unidentified cases to 8600.[25] In order to be able to identify at least some individuals who are unaware of their infection, it has been proposed to implement an opt-out policy towards HIV testing in the Netherlands regarding screening for HIV infection in pregnant women.[26] American research, published in 2005, has granted plausibility to the assumption that screening of all patients presenting in healthcare settings will be comparable in cost-effectiveness with common public health initiatives such as screening of blood transfusion products and vaccination, even if the nationwide prevalence of HIV-infected individuals is only 0.1%.[27] In line with this,

in 2006 the American Centre for Disease Control and Prevention (CDC) recommended nationwide screening for HIV infection in all patients between the ages of 13 and 64 presenting to all healthcare settings.[28] In the United Kingdom, a new policy calling for a low clinical threshold towards testing for HIV infection has been in use since 2008.[29] A pilot study performed in 2009 at the accident and emergency units of two London hospitals, in which all patients between 16 and 65 years of age were offered an HIV test, showed that routine HIV testing is accepted by most patients.[30]

In spite of this, in the majority of European countries, as well as in Australia and Canada, opt-in policies towards HIV testing have remained largely unchanged.

CONCLUSION

In industrialised countries, approximately one-third of HIV-infected individuals are unaware of their HIV status. As HIV infection often presents with non-specific symptoms, many undiagnosed individuals will likely be referred to internal medicine outpatient clinics. In European internal medicine practice, screening for HIV infection is uncommon, and the decision to test in patients with atypical symptoms is primarily prompted by the presence of risk factors for this infection. This policy causes HIV infection to be overlooked as a possible cause of unexplained symptoms in individuals without risk factors. The presented cases and literature illustrate that this diagnostic and therapeutic delay can lead to increased morbidity and mortality. Moreover, undiagnosed individuals are on average more likely to transmit HIV than diagnosed individuals. It is imperative to public health to identify people harbouring HIV infection, as this is expected to reduce the number of new infections. As the absence of risk factors is not sufficient to rule out the diagnosis, HIV infection should be considered as a possible cause of unexplained symptoms in an early stage of the diagnostic process. Furthermore, all conditions suggestive of possible immune deficiency, community acquired pneumonia, tuberculosis, viral hepatitis and symptoms such as unexplained fever, lymphadenopathy or weight loss should warrant an early HIV test, regardless of the absence of risk factors.

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