Lesson of the week

Acute meningoencephalitis and meningitis due to primary HIV infection

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Meningoencephalitis and meningitis can be associated with primary HIV infection

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A wide differential diagnosis exists for meningoencephalitis and meningitis: causes include tuberculosis and infections caused by viruses such as enteroviruses, human herpesviruses (types 1-4, 5 (cytomegalovirus), and 6), paramyxovirus (mumps), measles virus, and adenoviruses. In one cohort, viral genomes were detected in consecutive samples of cerebrospinal fluid from 5% of patients (22 of 410); enteroviruses and human herpesviruses types 1-5 accounted for over 95% of cases.[1] HIV infection was not detected. It is often overlooked as a potential cause of meningoencephalitis and meningitis.

The clinical manifestations of primary HIV infection are well characterised and include fever, lethargy, flu-like illness, headache, pharyngitis, generalised rash, lymphadenopathy, and gastrointestinal disturbances.[2] Neurological features, including aseptic meningitis, meningoencephalitis, and encephalitis, occur in up to 17% of patients and may be associated with more rapid progression of HIV related disease.[3–11] Neurological symptoms may occur or develop up to 3 months after the onset of symptoms of primary HIV infection, when the other symptoms have resolved. We discuss one patient with meningoencephalitis and two patients with meningitis associated with primary HIV infection. In each patient the underlying diagnosis of primary HIV infection was not suspected initially resulting in a delay to diagnosis.

Case reports

Over a 16 month period three men with viral symptoms had presented to their general practitioner (n=2) and local emergency department. One patient required immediate admission and the others were subsequently admitted through the emergency department and local genitourinary clinic. The patients failed to disclose any risk factor for acquiring HIV infection and none had clinical stigmata of immunosuppression. The table summarises the clinical details of these patients. Here we report on case 1.

A 34 year old man presented with a one week history of fever, nausea, and confusion. The previous month he had had a brief febrile illness associated with a non-specific rash on his limbs and a mild intermittent headache that persisted until presentation. He was previously fit and well and had returned, one month earlier, from a two week visit to the Caribbean. He was in a stable heterosexual relationship with his partner of over five years and denied being an injecting drug user.

His temperature and blood pressure were normal. Respiratory, cardiovascular, and abdominal examination was also normal. His mini-mental state examination score was 1 out of 10, indicating severe confusion. He was drowsy, had no meningism, and could move all four limbs. No focal neurological signs were evident.

Haematological and biochemical investigations were normal apart from a peripheral blood neutrophilia (11.7×10^9/l; reference range 3-10 $\times 10^9$/l). A septic screen including culture of urine and blood was negative and a chest *x* ray film was normal. Viral encephalitis was provisionally diagnosed and intravenous aciclovir started. A lumbar puncture, performed after a computed tomogram of the brain was shown to be normal, showed lymphocytic cerebrospinal fluid (33 lymphocytes).

The next day the patient became more obtunded, and empirical antituberculosis therapy with adjuvant glucocorticoids was started. Electroencephalography showed diffuse symmetrical slow wave activity consistent with a diffuse cerebral abnormality. A HIV antibody test was positive and a CD4 T lymphocyte count was 204×10^6/l (reference range 270-1350 $\times 10^6$/l). Serology showed no recent mycoplasma, legionella, or rickettsial infection, and a serum cryptococcal latex agglutination test was negative. Viral encephalitis secondary to cytomegalovirus or HIV infection was provisionally diagnosed. Foscarnet and ganciclovir were given empirically.

Seven days after admission he had several grand mal seizures. Another lumbar puncture showed monocytic cerebrospinal fluid (18 monocytes) and electroencephalography showed resolution of the diffuse slow wave changes, with no epileptiform activity. Over the next week the seizures reduced in frequency and the confusion resolved. Ganciclovir therapy was continued

Clinical details of patients with primary HIV infection

	Case 1	Case 2	Case 3
Clinical features:			
At presentation	Fever, headaches, confusion, rash (limbs), nausea	Flu-like illness, headache, sore throat	Flu-like illness, sore throat, nausea, diarrhoea
Subsequent	Obtunded, grand mal seizures	Headaches, meningism, maculopapular rash, nausea, lymphadenopathy, oral ulcers	Headache, meningism, generalised rash, lymphadenopathy
Time delay for diagnosis of infection*	3 days	8 days	9 days
Neurological diagnosis	Meningoencephalitis	Meningitis	Meningitis

Patients had primary HIV infection with presence of anti-HIV immunoglobulin M antibodies (n=1) or evolving HIV specific antibody profile (n=2). All described febrile illness preceding onset of headaches. Three had had a rash (two had received antibiotics) and two had had upper respiratory tract symptoms.
*Calculated from day of initial presentation to day that first positive HIV test result was confirmed.

until day 17, when cerebrospinal fluid was negative for human herpesviruses (types 1-5) and enteroviruses. Antituberculosis therapy was stopped 5 days later.

The CD4 T lymphocyte count 21 days after admission was 650×10^6/l (45%), and the HIV viral load was 5800 copies/ml. The initial serum sample was positive for anti-HIV immunoglobulin G, A, and M, and negative for p24 antigen, indicating recent acute HIV infection. Antiretroviral therapy was not started after confirmation of the diagnosis as the patient had improved, the CD4 T lymphocyte count had returned to normal, and the HIV viral load was low.

The patient recovered and had no further seizures. One year later the CD4 T lymphocyte count was 350×10^6/l (20% of total lymphocytes in blood; reference range 25-64%) and the HIV viral load was 68 000 copies/ml. Further history taking revealed that he had occasional homosexual relationships.

Discussion

It is important to consider a wide differential diagnosis in patients presenting acutely unwell with meningoencephalitis. Although tuberculosis and viral infections account for most of these cases other causes such as primary HIV infection should not be forgotten.

It is difficult to identify patients with primary HIV infection when they fail to disclose risk factors for acquiring the virus and there are no clinical stigmata of immunosuppression. The neurological manifestations of infection may occur several weeks after the resolution of other symptoms related to the infection, necessitating the need for thorough history taking. A recent negative HIV antibody test result does not exclude primary HIV infection. A diagnosis usually relies on serial HIV antibody tests in parallel with assays for detecting the virus, such as those for detecting p24 antigen, HIV proviral deoxyribonucleic acid, or plasma HIV ribonucleic acid. HIV p24 antigenaemia, as in case 1, may be present only during the first few weeks of primary HIV infection, therefore the test should be performed promptly.[12] Case 1 was not able to give informed consent to tests at the time of presentation.

Failure to identify primary HIV infection denies patients the opportunity of receiving potent antiretroviral therapy at the time of HIV seroconversion. Early therapy may result in a more rapid resolution of symptoms and a reduced chance of developing opportunistic infections. It may also reduce the risk of symptoms related to HIV infection or acquired immunodeficiency syndrome developing in the short term.[13] Early treatment has been associated with improvements in CD4 T lymphocyte cell counts, decreased immune activation, and preservation of HIV-1 specific T helper cell responses.[14 15]

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Commentary: Is testing for HIV without consent justifiable?

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Ethical guidance insists that people should normally be tested for HIV only with valid consent because although it is potentially beneficial medically, the social and psychological implications can be serious. This emphasis on voluntariness of testing remains strong even as the success of antiretroviral treatment increasingly highlights the benefits of early diagnosis. For most people those benefits are an overriding consideration. It can be argued, therefore, that most patients who know themselves to be at risk would be likely to accept HIV testing to ensure that they obtain optimal treatment. Nevertheless, there may be some patients for whom uncertainty about their status is preferable. If, when able to make a choice, they elect to avoid testing and take the risks associated with not knowing, that decision must be respected. They cannot normally be tested without their agreement. A third category of people lack information about risk factors and warning signs. Since it probably does not occur to them to ask for a test or to talk to doctors about their

private activities, they are dependent on health professionals to pick up potential symptoms. That is why Newton et al's article is so important for raising medical awareness but, by implication, it also raises questions about second guessing patients' views.

Problems arise when patients are mentally ill, unconscious, or otherwise so incapacitated that they cannot consent or refuse. Doctors are legally and ethically obliged to act in such patients' "best interests," which include, but are not restricted to, their clinical interests. Assessing best interests involves forming a view about a patient's likely preferences: a virtually impossible thing to do if there is no clue about whether they positively opposed testing or simply had never considered it. It is a harm to impose an intervention that patients have positively rejected but a benefit to provide one that they would want if they had knowledge of it. In other contexts, families can indicate what the patient wanted, but raising the spectre of HIV with partners or relatives is obviously problematic when nothing in the patient's record indicates that this is an appropriate question.

In the absence of evidence to the contrary, logic dictates that most people would want interventions that could save them. The General Medical Council acknowledges that unconscious patients can be tested where that would be in their immediate clinical interests for the purpose of making a diagnosis.[1] In urgent cases, therefore, where knowledge of the patient's HIV status would seriously affect treatment, it can be permissible to test without consent. If, however, appropriate prophylactic treatment could usefully be provided without obtaining a definitive diagnosis or if treatment options would be much the same regardless of HIV status, testing without consent is less likely to be justified. This is because legal and ethical guidance stresses the importance of taking the least invasive effective option when treating people with impaired capacity. If the incapacity is temporary, doctors are expected to wait for the patient to revive before making any life changing decisions or going beyond what is immediately essential. Obviously this raises questions about how to define "essential" and its limits.

The authors draw attention to the importance of considering HIV infection as a potential cause of neurological conditions. Failure to test for primary HIV infection might result in crucial delays in antiretroviral therapy or leave patients open to infection when immunosuppressed. But in case 1, testing when the patient was presumably too ill to consent seems to have had no impact on his actual treatment. He was given antivirals as a precaution but had improved by the time the diagnosis was known and so antiretroviral therapy was unnecessary. Although the action taken was reasonable, with hindsight it can be seen that treatment was not contingent upon a definite diagnosis and testing might have waited. In other—and perhaps most—cases, testing promptly without consent could save lives. Thus, as well as the important clinical message, the paper highlights the complex dilemmas that doctors increasingly face. Despite the generally positive approach among health professionals to early HIV testing, there still needs to be much more public awareness of it as an option so that patients who could benefit from prompt testing seek it and those who genuinely object can take steps to make those views known.

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A "good" fatwa

The word "fatwa" has come to have a rather sinister meaning in many Western countries. This misconception has arisen, in large part, as a result of one author and his work and the publicity given to a resulting fatwa. A fatwa is simply a legal opinion in Islam given by a mufti or other religious leader on a specific issue, and this account describes one with which I was involved.

In 1990 I was appointed chairman of surgery at a large hospital in Riyadh, Saudi Arabia. Most of the surgical patients had cancer, and many major and often futile resections were performed in patients who were really in need of good palliative care—there was no non-surgical alternative available at the time. The hospital's chief executive officer was made aware of the problem and asked me to explore the possibility of inviting an authority in palliative care to visit Riyadh to give advice. Dr Derek Doyle from St Columba's Hospice agreed to visit, and, as a result of his report, a palliative care service was established in the hospital in 1992.

In 1999 the European School of Oncology sponsored a symposium at the hospital. During the symposium a workshop was organised to address the problem of the availability and the distribution of narcotics to patients with advanced symptomatic cancer.[1] Many country-wide problems were identified. The goal of allowing patients with advanced cancer to die in dignity and without pain was identified as a worthy one, and one that would be appreciated by patients, their relatives, carers, and religious leaders. One of the obstacles to attaining this goal, however, related to the religious beliefs of patients and family members, which made the introduction of the "analgesic ladder" unacceptable to them. It was suggested that the religious acceptability of the appropriate use of pain relieving drugs in patients dying of cancer should be established through the Committee of the Leading Ulam'a (council of religious scholars).

One of my patients was a senior and respected imam and a member of the committee. We discussed the workshop and its findings, and he agreed to support a letter to the committee explaining the need to give parenteral opiates on a regular basis to patients with advanced cancer. He further agreed to invite the committee to issue a fatwa approving the use of parenteral opiates in patients with advanced cancer. About a year after the letter was sent, I received a fatwa from the Mufti General and President of the Committee of Leading Ulam'a. It stated that "there is no objection against using these analgesics [opium and other analgesics] in advanced cancer patients, because this is a necessity."

This fatwa will surely benefit many patients both within Saudi Arabia and in other parts of the Muslim world and is perhaps my most important contribution, surprisingly non-surgical, to patient care. I may be the first non-Muslim Westerner to have gained such a fatwa. It was certainly not a negative fatwa.

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