NEUROLOGICAL DISORDERS IN AIDS: A STUDY OF 18 CASES

Pages with reference to book, From 312 To 316

Aziz B. Sonawalla (Present Address: Faculty of Medicine, The Aga Khan University Hospital, Karachi.)
James W Lance, Andrew Lloyd (Departments of Medicine and Neurology, The Prince Henry Hospital and The Prince of Wales Hospital, Sydney, Australia.)

Abstract

Neurological disorders were studied in 18 patients diagnosed to have AIDS and their findings are analysed. Amongst the problems seen were toxoplasmosis (9), crgptococcal meningitis (5), tuberculous meningitis (1), AIDS dementia complex (3), peripheral neuropathy (2), vertebrobasilar stroke, and a possible AIDS myelopathy in one case each. Their findings are discussed, and literature on the neurological disorders in AIDS reviewed (JPMA 39, 312, 1989).

INTRODUCTION

Neurological disorders are a frequent cause of morbidity and mortality in patients afflicted with the Acquired Immune Deficiency Syndrome (AIDS), which is caused by the Human Immunodeficiency Virus (HIV). The incidence of neurological manifestationsvaries between 30% to 40% in adults[1,2]. Autopsy based surveys, however, reveal neuropathological changes to occur in 70% to 80% cases[3]. In certain cases, neurological dysfunction is the predominant clinical manifestation of AIDS4. Besides, 10% of all AIDS patients first present with symptoms of neurological illness. We report below our experience on the clinical patterns and management of these problems.

PATIENTS AND METHODS

Between October 1984 and December 1986, a total of 82 patients seen at this hospital were AIDS antibody positive. Of these, 16 were clinically asymptomatic, 14 had features of the AIDS lymphadenopathy syndrome, 5 had features of the AIDS Related Complex (ARC), and 47 satisfied the Centre for Disease Control (CDC) criteria for full blown AIDS[6]. All these patients were followed up regularly, and closely monitored. Of the 47 patients withAlDS, 18 had neurological disorders. Thefollowingis an analysis of the manifestations in these 18 patients.

RESULTS

Neurological Disorders:

Neurological disorders seen in these patients are listed in Table 1.

TABLE 1. Neurological Manifestations.

Type of Disease	No. of cases
Toxoplasmosis	9
Cryptococcal Meningitis	5
TB Meningitis	1
AIDS Dementia Complex	3
Peripheral Neuropathy	2
CVA	1
Myelopathy	1

Fourteen patients had a single neurological problem, 4 patients bad 2 neurological problems during the course of their illness.

Risk Factors:

Fifteen of these were homosexuals, 1 bisexual, and 2 developed AIDS after blood transfusion, 2 of the homosexuals were also drug addicts.

Toxoplasmosis:

Toxoplasmosis was diagnosed in 9 cases.

TABLE II. Toxoplasmosis.

Clinical Features	No. of Cases
Headaches, focal fits, right sided weakness, dysphasia	2
Headaches, focal fits, visual disturbances	2
Headaches, dysphasia	2
Dysphasia	1
Meningoencephalitic syndrome	1
Choreiform movements	1
Total	9

Table II shows the salient features in these cases. Focal fits, focal weakness, speech defects, visual

disturbances and headaches were the main fmdings. One patient developed choreiform movements of the left arm, along with cottonwool exudates in the fundus. Only one patient had a non-focal presentation in the form of meningoencephalitis. CT scans were done in 7 of 9 cases, 6 of these were abnormal and mainly showed focal hypodense areas which enhanced on contrast infusion. In addition, ring enhancement was seen in 3. In the 1 patient whose CT scan was normal, MRI showed a focal lesion. Radiological findings are shown in Table III.

TABLE III. Toxoplasmosis CT Scan Features.

Hypodense areas	– enhancement on contrast ± ring enhancement.
Site of Lesions	No. of Cases
Basal Ganglia	2
Thalamus	1
Parieto-Temporal Lobe	1
Temporal lobe	1
Frontal Lobe	1
Normal CT (Abnormal MRI)	1
Total	7

The diagnosis of toxoplasmosis was made on the basis of clinical suspicion, the radiological findings and serologic tests - the Sabin Feldman dye test (titres 1: 1000) and the ELISA test (titres > 6). Brain biopsies were attempted in the3 cases where the lesion was superficial, but was positive in only one. All patients were treated with a combination of sulfadiazine (approximately 100 mg/kg/day) and pyrimethamine (25-50 mg/kg/day) for the first 10 days, with a maintenance dose at one-fourth to half this amount for at least 6 weeks following resolution of all symptoms. Seven patients responded fully to treatment. Response to treatmentwas difficult to assess in2 cases inviewof multiple other problems present other than toxoplasmosis. One of the patients had basal-cell carcinoma and pneumocystis carinii pneumonia, while the other had persistent diarrhoea due to cryptosporidium infection, and pulmonary tuberculosis. Both these patients diedwithin2months of detection of toxoplasmosis.

Cryptococcal meningitis:

Cryptococcal meningitis was seen inS cases. The diagnosis was made with the help of CSF findings showing low sugar, lymphocytes, and a positive India Ink study. In addition, all patients had a positive cryptococcal antigen test, as well as positive serum latex agglutination test for cryptococci. The initial clinical picture in these cases resembled that of chronic bacterial meningitis. The subsequent course was protracted and difficult to treat. Four of these S patients eventually developed features of chronic basal meningitis, with varying combinations of multiple cranial nerve palsies, papilloedema, and long tract signs during their protracted course of treatment. Amphotericin B remained the primary drug of choice. Omaya Reservoirs were inserted in the 4 cases of chronic meningitis, for drug administration. One of these patients also needed an epidural catheter. Response to treatment was generally unsatisfactory. Only one patient was free of symptoms and had normal CSF findings at the end of 3 months. One patient improved initially, but relapsed 7 month later. Renal and bonemarrow complications devólopedin3 cases, resulting in adjustments in the dose of Amphotericin B. Flucytosine was added in

the therapeutic regimen in one case, and miconazôle in another, but with poor results. Of the4 patientswho didnot improve, 2 succumbed to the disease and to the systemic complications of therapy within 4 months of the diagnosis of cryptococcal meningitis. The remaining 2 patients including the patients with relapse - were in a poor state of health at the end of this study period.

Thberculous meningitis:

One patient developed TB meningitis, demonstratedbythepresence of tubercle bacillion CSF smear, and positive culture. Left sided hemiplegia developed during the course of illness, but he responded well to anti-kochs treatment. CT scan showed infarcts in the right frontal lobe, as well as in the right basal ganglia. He was left with a mild residual left sided deficit.

AIDS Dementia Complex (ADC):

Three patients showed evidence of a gradually progressive impairment of memory, behavioural disturbances and impaired mental task performance, without any evidence of opportunistic infection, tumor vascular or other lesions. The clinical features of these patients are listed in Table IV.

TABLE IV. AIDS Dementia Complex (ADC).

Clinical Features	Total No. of Cases-3
Impairment of Memory	3
Behavioural Disturbances	3
Impaired Mental Task Performance	3
Weakness and Pyramidal Signs in all 4 limbs, LL UL	3
Incontinence	3
Gen Convulsions	2
Myoclonic Jerks	1
Headaches	1

Besides higher function disturbances, the other important clinical features were gait apraxia, weakness, brisk reflexes, extensor plantar responses, and urinary incontinence. Two patients developed generalized seizures, one amongst them also bad myoclonic jerks. None of the patients had any evidence to suggest raised intracranial pressure. One patient, however, had persistent dull bifrontal headaches. CT scan showed evidence of generalized cortical atrophy in all 3 cases, EEG showed evidence to suggest a diffuse encephalopathic process in all three, and CSF findings were again non-specific, showing between 3 to 10 lymphocytes, without any other changes. All these patients showed a progressive downward trend in their neurological status. One of the patients died as a result of complicating intercurrent infections. The other 2 continued to show a progressive downward trend.

Peripheral Neuropathy

Involvement of the peripheral nerves was seen in 2 patients. One had distal symmetrical sensorimotor lesion both clinically as well as on nerve conduction studies. The other patient had features of mononeuritis multiple; with involvement of the right axillary nerve and the left lateral popliteal nerve. To the extent possible, other factors that could have caused peripheral neuropathy were ruled out.

Other Manifestations:
One patient - who was being treated for Kaposi's sarcoma and cryptosporidial gastrointestinal infection - developed features of right sided vertebrobasilar stroke. The clinical features cleared within the next 3 weeks. CT scan was normal; MRI scan showed evidence of right sided thalamic infarct. He was not a known hypertensive. Angiographic studies were not done. One of the patients - who was under treatment for eryptococcal meningitis with an Omaya reservoir, and later through an epidural catheter - developed an acute onset of paraplegia with a spinal level at T10 on the right side, and T12 on the left. Treatment with the above modalities was going on for quite a while before the onset of the above acute illness. Further work up was not done as he had a progressive downhill course due to multiple problems, and died of acute renal failure and generalized septicaemia.

DISCUSSION

AIDS related neurological disorders can involve the central nervous system[5] as well as the peripheral nervous system[7]. The main categories of central nervous system disorders are those due to opportunistic viral or non-viral infections, neoplasms — mainly lymphomas and metastatic Kaposi's sarcoma cerebrovascular disorders, and disorders due to primary invasion of the virus into the CNS cells. Amongs the recognised peripheral nervous system complications are different types of peripheral neuropathies, polymyositis and other myopathies of unclear etiology. Some of the main recognised disorders are enlisted in tables V and VI.

TABLE V. AIDS-related Central Nervous System Diseases.

I. Opportunistic Infections
   1. Viral infections
      - Cytomegalovirus
      - Herpes simplex virus, types I & II
      - Herpes varicella zoster virus
      - Papovirus (progressive multifocal leucoencephalopathy)
   2. Non-viral infections
      - Toxoplasma gondii
      - Cryptococcus neoformans
      - Candida albicans
      - Aspergillus fumigatus
      - Mycobacterium tuberculosis
      - Mycobacterium avium intracellularis
      - Nocardia asteroides
      - Cryptosporidiosis

II Neoplasms
   - Primary central nervous system lymphoma
   - Metastatic systemic lymphoma
   - Metastatic kaposis sarcoma

III Cerebrovascular Disorders
   - Infarction
   - Haemorrhage
   - Vasculitis

IV Primary Viral (Human Immunodeficiency Virus) Syndromes
   - AIDS Dementia Complex (ADC)
   - Atypical aseptic meningitis
   - Vacuolar myelopathy

TABLE VI. AIDS and Peripheral Nervous System Diseases.

Peripheral neuropathies
– Guillian Barre Syndrome
– Chronic progressive inflammatory demyelinating polyneuropathy (CIDP)
– Mononeuritis multiplex
– Distal symmetrical polyneuropathy
Muscle Involvement
– Polymyositis
– Proximal myopathy with type II muscle fibre atrophy
– Rods (nemaline) myopathy
– Subclinical neuromuscular involvement

Infectious diseases accounted for the largest number of cases in our series, with 15 out of 18 cases affected, 9 of these 15 bad toxoplasmosis, which, until the AIDS problem, was a relatively rare disorder in adults, occurring principally in the setting of organ transplantation, lymphoretieular malignancies and other disorders of impaired cell mediated immunity[8]. The incidence of toxoplasmosis in AIDS is between 2 to 13%[5]. Whereas, in the immunocompetent individual, lymphadenopathy is the most commonly recognised clinical manifestation of acute acquired toxoplasmosis[9], focal central nervous system manifestations are most common in AIDS[8], which was also the feature in 8 out of our 9 patients. The favourable response to treatment with sulfadiazine and pyrimathamine in this series is also the experience of others[2]. The poor response in cases was most probably due to other associated problems. Unlike in toxoplasmosis, the response to treatment in cases with cryptococcal meningitis was poor, with only one improvement. This is also the experience of Kovacs et al[10], who reported improvement in 5 out of 24 cases. Levy et al[2] however report a good response with Amphotericin B and fluocytosine, although no figures are mentioned. The single case with tuberculous meningitis and bemiplegia secondary to mycobac terium tuberculosis fared well on a 4 drug antituberculous regimen. This would be in contrast to mycobacterium avium CNS infections in AIDS, which, though uncommon, are usually fatal[2]. Three patients who presented with gradually progressive dementia without any other apparent - cause, satisfied the salient features of AIDS encephalojathy, or AIDS dementia complex (ADC) [1,11] although we did not obtain histopathological proof. ADC has emerged as a major clinical problem in AIDS patients[3]. The presence of HIV in these cases has been documented by viral isolation. Immunocytochemical and in situ hybridization studies have found HIV antigens and nucleic acids in neural tissues[11]. Besides ADC, the other conditions that result from direct invasion of the virus into the central nervous system are vacuolar myelopathy and aseptic meningitis[5]. Our patient with Cryptococcal meningitis, who was on treatment with Amphotericin B with an Omaya reservoir, and later byepidural catheter, couldwell have had vacuolar myelopathy in view of the acute onset, although drug toxicity and other related problems could not be ruled out. Vacuolar myelopathy may not be infrequent, and Petito et al[12] demonstrated vacuolar myelopathyin 20 out of 89 consecutive

autopsies on AIDS patients. Peripheral neuropatbies — as seen in 2 of our patients — and muscle involvement in AIDS, is also presumed to be due to direct viral invasion[13], although immune dysregulation could be the cause in the majority[14]. The use of immunosuppressants, is controversial, since it may facilitate spread of opportunistic infections[15]. Some of the neuropathies, especially the inflammatory demyelinatingpolyneuropathies, have been shown to respond to plasmapheresis[15]. The incidence of cerebrovascular manifestations in AIDS is relatively low[1-3] and our patient with stroke and right thalamic lesion on MRI could have had AIDS related cerebrovascular complication, since he was relatively young and did not have hypertension or any other overt risk factor for cerebrovascular disease. Amongst the complications described are cerebral infarction, intracerebral haemorrhage, herpes zoster arteritis[2], embolus from non-bacterial thrombotic endocarditis1 and vasculitis[3]. The last few years have seen the emergence of 3' — Azido —2', 3' — dideoxythymidine (AZT) as a useful toolin the control of AIDS infection. AZT is a thymidine analog that has been shown to be a potent inhibitor of HIV infection in vitro[4]. Preliminary studies have shown that AZT improves the immunological and clinical status of these patients[4,14,17]. Besides the treatment of AIDS in general, AZT has been shown to be also directly useful in those neurological conditions that are caused by direct viral invasion such as "ADO' and peripheral neuropathies[16,18]. Although most data is still small, and AZT is not without side effects, some more powerful and potentially less toxic agents could well hold hope for the future[19]. AIDS has come a long way since the Centre of Disease Control (CDC) reported the first cases in 1981[3]. Neurological problems, which are an important cause of morbidity and mortality, still need a lot of unravelling, we need more information about the natural history of involvement of the central as well as peripheral nervous system, its pathophysiology; need non-invasive diagnostic methods and more effective therapeutic strategies[20]. In conclusion, the fact remains that never in recent history had so much been understood in so short a time about so lethal a disease. Yet, as is apparent, much remains to be done. Among other things, countries in which AIDS is still unknown or sporadic need greater vigilance and preventive efforts, in addition to a timely study of this disease.

REFERENCES

1. Snider, W.D., Simpson, D.M., Nielsen, S., Gold, J.W., Metroks, C.E. and Posner, J.B. Neurological complications of acquired immune deficiency syndrome; analysis of 50 patients. Ann. Neurol., 1983; 14 :403.
2. Levy, R.M., Bredesen, D.E. and Rosenblum, M.L. Neurological manifestations of the acquired immunodeficiency syndrome (AIDS); experience at UCSF and review of the literature. 3. Neurosurg., 1985; 62:475.
3. Elder, G.A. and Sever, J.L. AIDS and neurological disorders; an overview. Ann. Neurol., 1988; 23 (Suppl): S4.
4. Yarchoan, R.,Thomas, LV., Grafman,J. etal. Longterm administration of 3' - azido . 2', 3'-dideoxythymidine to patients with AIDS-related neurological disease. Ann. Neurol., 1988; 23 (Suppl) : 582.
5. Levy, ItM., Bredesen, D.E. and Rosenblum, M.L. opportunistic central nervous system pathology in patients with AIDS. Ann. Neurol., 1988; 23 (Suppl) : 57.
6. Fanci, A.S., Masur, H., Gelmann, E.P., Markham, P.D., Han, B.H. and Lane, H.C. The acquired immune deficiencysyndrome; an update. Ann. Intern. Med., 1985; 316:102:800.
7. Dalakas, M.C. and Pezeshkpour, G.H. Neuromuscular diseases associated with human immunodeficiency virus infection. Ann. Neurol., 1988; 23 (Suppl): S38.

8. Navia, BA., Petito, C.K., Gold, J.W.M. et al. Cerebral toxoplasmosis complicating the acquired immune deficiency syndrome: clinical and neurological findings in 27 patients. Ann. Neurol., 1986; 19: 224.
9. Mcleod, R., Remington, iS. Toxoplasmosis, in Harrison's principles of internal medicine. 11th ed. Mc Craw-Hill, 1987.
10. Kovacs, i. A., Kovacs, A. A., Polis, M., et al. Cryptococcosis in the acquired immunodeficiency syndrome. Ann. Intern. Med., 1985; 103:533.
11. Price, LW., Sidtis, J. and Rosenblum, M. The AIDS dementia complex; some current questions. Ann. Neurol., 1988; 23 (Suppl): S27.
12. Petito, C., Navia, B.A., Cho, ES., Jordan, B.D., George, D.C. and Price, LW. Vacuolar myelopathy pathologically resembling subacute combined degeneration in patients with the acquired immunodeficiency syndrome. N. EngI. J. Med., 1985; 312: 874.
13. de la Monte, S.M., Gabuzda, D.H., Ho, D.D., Brown, ItH. Jr., Hadley-whyte, E.T., Schooley, P.. T., Hirsch, M.S., and Bhan, A. K. Peripheral neuropathy in the acquired immunedeficiency syndrome. Ann. Neurol., 1988; 23: 485.
14. Parry, GJ. Peripheral neuropathies associated with human immunodeficiency virus infection. Ann. Neurol., 1988 :23 (Suppl) :549.
15. Cornblath, D.R. Treatment of the neuromuscular complications of human immunodeficiency virus infection. Ann. Neurol., 1988; 23 (Suppl): 588.
16. Yarchoan, P.., K.lecker, LW., Weinhold, K. J., et al. Administration of AZT, an inhibitor of HTLV-III/LAV replication, to patients with AIDS or AIDS related complex. Lancet, 1986; 1 : 575.
17. Yarchoan, R., Berg, 0., Prouwers, P., Fischi, M.A., Spitzer, A.R., Wichman, A., Grafman, 3. et al. Response of human immunôdeficiency virus-associated neurological disease to 3' - azido - 3' - deoxythymidine. Lancet, 1987; 1: 132.
18. Dalakas, M.C., Yarchoan, P.., Spetzer, It, Elder, G. and Sever, J.L. Treatment of human immunodeficicncyvirus related polyneuropathy with 3' - azido -2' 3' -dideoxythymidine. Ann. Neurol., 1988; 23 (Suppl); S92.
19. Brady, R.O. and O'Neill, K. Therapy for neurological involvement in AIDS. Ann. Neurol., 1988; 23 (Suppl): S211.
20. McKhann, G.M. Research relative to AIDS. Ann. Neurol., 1988; 23 (Suppl) : S208.