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Presentation and course of AIDS Dementia Complex: ten years of follow-up in Amsterdam, The Netherlands

2

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Abstract

Objective: *To assess the clinical presentation and course of the AIDS dementia complex (ADC).*

Design: *Retrospective study of a consecutive series of symptomatic HIV-1 infected patients (Centers for Disease Control (CDC) groups IVA, B, C, and D) evaluated for neurological symptoms between 1982 and 1992.*

Setting: *An academic referral center for AIDS.*

Patients: *536 symptomatic HIV-1 infected patients examined for neurological symptoms from 1982 to 1992.*

Interventions: *Zidovudine treatment, which was introduced to The Netherlands on 1 May 1987 for patients with severe symptoms of HIV infection (CDC groups IVA, B, C, and D).*

Main outcome measures: *Diagnosis of ADC and CD4 cell count, clinical features, neuropsychological abnormalities, computerized tomography and magnetic resonance imaging abnormalities, cerebrospinal fluid findings and course in patients with the ADC.*

Results: *The ADC was diagnosed in 40 of 536 (7.5%) symptomatic HIV-1 infected patients. In 6 of them ADC was the AIDS-defining illness. The mean CD4 cell count in 40 patients with ADC was 109.10^6/l. Neuropsychological abnormalities, in 15 of 17 patients tested, were in accordance with a subcortical dementia. On CT-scan of the brain 70% showed none or only mild cortical atrophy. For detecting white matter abnormalities MRI of the brain was more sensitive than CT-scan: abnormalities in 73% versus 35% (p=0.02). Cerebrospinal fluid examination showed mononuclear pleocytosis in 25%, protein level increase in 55%, and HIV-1 p24 core protein in 38% (13/34).*

The mean survival in 40 patients was 6.7 months. However, in 20 patients who never used zidovudine the mean survival was 4 months, compared to 14.8 months in 10 patients who started on zidovudine after they were classified as having ADC (p<0.001). In those 10 patients 3 improved remarkably after starting with zidovudine and 2 slightly. In 9 patients ADC developed after discontinuation of zidovudine. Only one patient developed ADC while on 600 mg zidovudine.

Conclusions: *ADC developed in 40 of 536 (7.5%) neurologically symptomatic HIV-infected individuals in CDC group IV. All patients with ADC were immunosuppressed. MRI is more sensitive than CT in detecting white matter abnormalities. To date there is no specific and no sensitive CSF-marker for ADC. Zidovudine may improve symptoms and may prolong survival in patients with ADC. In our experience ADC rarely developed (n=1) in patients who continue to use zidovudine.*

INTRODUCTION

One of the most important neurological syndromes in patients with AIDS is the AIDS dementia complex (ADC)[1] or HIV-1-associated cognitive/motor complex, as it has been designated recently.[2]

This dementia is characterized by disturbances in cognition, motor performance and behavior, and usually becomes clinically overt in the advanced stages of HIV-1 infection.[1,3] The clinical and neuropsychological abnormalities in ADC are compatible with socalled 'subcortical dementia'.[4] The diagnosis of ADC is one of exclusion.[5] Cerebrospinal fluid (CSF) and neuroimaging procedures are mandatory to rule out other conditions that could explain the clinical findings. There is still uncertainty about the prevalence of ADC. In some retrospective series prevalences of 16-21% have been reported.[6-8] Furthermore the epidemiology of ADC has been influenced by the introduction and widespread use of zidovudine. Recent prevalence studies, however, suggest that a third of patients with AIDS still eventually develop a mild or severe form of ADC.[9]

Computerized tomography (CT) and magnetic resonance imaging (MRI) scanning of the brain in ADC often reveal widened cortical sulci and enlarged ventricles.[1] MRI scan may show patchy or diffuse increased signal intensity on T2-weighted images in the white matter of the hemispheres.[10,11] Examination of the CSF in ADC may reveal aspecific abnormalities like a mononuclear pleocytosis and increased protein level. More specifically detection of HIV-1 p24 antigen, the presence of which is independent of HIV-1 p24 antigen in the serum, is correlated with ADC in adults and progressive encephalopathy in children with AIDS.[12] Nonspecific CSF-markers of immune activation, β-2-microglobulin, neopterin and quinolinic acid correlate with both the severity of the ADC and its response to antiretroviral therapy.[13-15]

The principal histopathological abnormalities in ADC are most prominent in the subcortical structures.[16] Two patterns of abnormalities are distinguished: 1) HIV encephalitis, with multiple disseminated foci of multinucleated giant cells and other inflammatory cells and 2) HIV leukoencephalopathy, with diffuse white matter damage, but little or no inflammatory infiltrates.[17] These two patterns may overlap and transition between them may occur. The multinucleated giant cells are now considered to be essential for the diagnosis of HIV-1 infection of the central nervous system (CNS).[18] Although patients with more severe clinical manifestations tend to have more severe neuropathology, clinico-pathological correlation may be poor in about one third of patients.[19]

Substantial evidence supports a direct causal role for HIV-1 in the pathogenesis of ADC.[20-24] In this pathogenetic process the production and release of cell-coded toxins, particularly cytokines and/or viruscoded neurotoxins (e.g. viral proteins like gp120) may contribute to CNS dysfunction.[15,25,26]

It has been demonstrated that ADC may improve after treatment with zidovudine.[27] Besides this therapeutic efficacy, there is an important prophylactic efficacy of zidovudine use. The incidence of ADC has declined strikingly after the introduction of zidovudine.[28]

The purpose of this study was to review our experience with the ADC in order

to further define the clinical characteristics of ADC, to determine the usefulness of diagnostic procedures and to assess any influence of zidovudine treatment. Therefore we reviewed the medical records of all neurologically symptomatic HIV-1 infected individuals of the past ten years and analyzed in detail the patients with ADC.

METHODS

The medical records of all 536 symptomatic HIV-infected patients (CDC group IV) with neurological symptoms seen in the outpatient clinic and in consultation of the Academic Medical Center in Amsterdam, an academic AIDS referral center, between August 1982 and January 1992, were reviewed. This review of 536 records revealed 40 patients who met the CDC criteria for AIDS dementia complex.[5] These criteria include: a) disabling cognitive and/or motor dysfunction, progressing over weeks to months, (disabling is defined as: interfering with occupation or activities of daily living) b) the absence of a concurrent illness or condition other than HIV-infection that could explain the cognitive and/or motor dysfunction, and c) the absence of an opportunistic infection or tumor of the CNS complicating HIV-1 infection , as ruled out by neuro-imaging studies and CSF-analysis. The 40 patients who met these criteria were included in this study.

In these patients the following data were reviewed: age, sex, risk factor for HIV-infection, CDC-classification at presentation and CD4 cell count. CD4 cell numbers in peripheral blood were determined by flow cytofluorometry as previously described.[29] A CD4 cell count > 500.10^6/l was considered normal.

CT scans of the brain were reviewed by two of us (PP, RHE). Cortical atrophy, ventricular enlargement and diffuse white matter hypodensity were scored as: none, mild, moderate and severe. MRI scans of the brain were performed in 15 patients. MRI scan was not easily available until 1986. MRI scans were reviewed by two of us (PRA, PP). Cortical atrophy, ventricular enlargement and white matter hyperintensity on T2-weighted images were scored as: none, mild, moderate, severe.

Routine analysis of the CSF (cells, protein, cultures) was performed. The CSF was tested for HIV-1 p24 antigen by a solid phase, sandwich type enzyme immunoassay (Abbott Laboratories, North Chicago, United States) as previously described.[30] The cut off value indicating a positive result varied from 30 to 50 pg/ml among assays. Neuropsychological assessment was performed by one of us (MMAD). Neuropsychological testing was not part of the work-up right from the start of the epidemic and some end-stage patients were unable to perform the tests, we have test results for only 17 patients. The neuropsychological test battery, which is described elsewhere[31,32], included the Mini Mental State Examination (MMSE) and the Groninger Intelligence Test (GIT), except for one patient for whom the WAIS-R was used. In addition tests for assessment of perceptual-motor speed and concentration, attention and memory, word fluency, and a screening test for the presence of aphasia, anomia, apraxia, alexia, agraphia and agnosia were included. The results of each of these tests were dichotomized to obtain a binary score of 'normal' and 'abnormal'.[31,32]

Zidovudine was introduced in The Netherlands in May 1987. All patients diagnosed with ADC afterwards have been treated with zidovudine for variable periods of time and with variable dosages (400-1200 mg) in the course of their HIV-infection. All 40 records were reviewed for zidovudine-use, course and survival. Survival was defined as the interval between the date of diagnosis, arbitrarily defined as the day when ancillary investigation had excluded other diagnoses, and death.

RESULTS

I. Base-line characteristics of patients with ADC

Of the 536 symptomatic HIV-1 infected patients, examined by a neurologist between August 1982 and January 1992, 40 (7.5 %) were diagnosed as having ADC. Of the 40 patients with ADC 39 were homo/bisexual men and one patient was a female intravenous drug user. The mean age was 39.5 years (range: 23-62 years). At the time of diagnosis six of the 40 patients (15 %) were classified in CDC-group IV-A; in these patients ADC was the AIDS-defining illness. The other 34 patients were, at the time of diagnosis, already classified as having AIDS (31 patients CDC-group IV-C1, 3 patients CDC-group IV-D).

The mean CD4 cell count at the time of diagnosis in 40 patients was $109.10^6/l$ (range:8-420). The six patients who presented with ADC had a mean CD4 cell count of $165.10^6/l$ (range: 50-400). The 34 patients not presenting with ADC had a mean CD4 cell count of $100.10^6/l$ (range:8-420) (Mann-Whitney U test: p=0.19).

In these base-line characteristics no significant differences were found between patients who presented with ADC and patients who did not (data not shown).

Table 1
Neurological diagnoses and mean CD4+ cell counts in 536 symptomatic HIV-infected patients evaluated between 1982-1992

diagnosis	no (%)	mean CD4 cell count (x10⁶/l)
AIDS dementia complex	40 (7,5)	109
cerebral toxoplasmosis	64 (12)	65
cryptococcal meningitis	32 (6)	100
PML	15 (3)	200
CMV-polyradiculitis	7 (1)	10
primary CNS lymphoma	13 (2)	50
leptomeningeal metastasis	8 (1)	150
vacuolar myelopathy	12 (2)	210
peripheral neuropathy	124 (23)	165
miscellaneous	221 (41)	-

PML= progressive multifocal leukoencephalopathy
CMV= cytomegalovirus
CNS= central nervous system
Miscellaneous included: headache e.c.i., febris e.c.i., seizures, aseptic meningitis, neurolues, tuberculous meningitis, psychosis, myopathy, listeria meningitis, cerebrovascular complications, and undefined intracranial mass lesions.

The principal neurological diagnoses (with mean CD4 cell counts) in the other patients are shown in Table 1.

II. Clinical Features, neuro-imaging studies, CSF-analysis

Clinical features

In all patients the triad of cognitive, motor, and behavioral dysfunctions, as described in the original paper on ADC[1], was present. In six patients (15%) the dementia was accompanied by a severe myelopathy.

Neuropsychological assessment was performed in 17 patients (mean age 37.7; mean school education 12.9 years). The cognitive profile in 15 patients was in accordance with a diagnosis of subcortical dementia. In addition to intellectual deterioration, their main cognitive deficits consisted of slowed down psychomotor speed and impaired concentration, defective attention and memory deficits, and in a subgroup of ten patients reduced word-fluency. One patient performed below cut-off scores on some of the tests measuring memory and psychomotor speed, but otherwise scored within normal limits, and one patient was severely impaired and performed poorly on all tests. In those patients, the most severely impaired individuals, who perform poorly on most if not all tests, it is not possible to make the differentiation cortical versus subcortical pattern based on neuropsychological assessment. A summary of the testresults of the various tests is given in Table 2.

Neuro-imaging

CT-scans of the brain, performed in 40 patients with ADC, showed no cortical atrophy in 12 patients (30%), mild atrophy in 16 (40%), moderate atrophy in 6 (15%), and severe atrophy in 6 (15%). The ventricles were normal in 13 patients (33%), mildly enlarged in 13 (33%), moderately enlarged in 7 (18%) and severely enlarged in 7 (18%). The white matter was normal in 26 patients (65%), mildly hypodense in 10 (25%), moderately hypodense in 3 and severely hypodense in 1. (Table 3)

MRI scans of the brain were performed in 15 patients. In 4 patients there was no cortical atrophy, in 7 mild, in 2 moderate and in 2 severe peripheral atrophy. In 6 patients the ventricular size was within normal limits, in 5 there was mild ventricular enlargement, in 2 moderate and in 2 severe ventricular enlargement. Diffuse white matter abnormalities on T2-weighted images were present in 11 patients (mild: 3, moderate: 5 and severe: 3). (Table 3)

Cerebrospinal fluid

CSF examination was performed in 40 patients with ADC. The CSF showed mononuclear pleocytosis in 10 patients (25%) (range 6-50 cells/mm^3) and increased protein level in 22 (55%) (range 0.53 - 1.71 g/l). CSF was assayed for HIV-1 p24 antigen in 34 patients. None of them used zidovudine at the time of lumbar puncture. Antigen was detectable in 13 patients (38%).

III. Zidovudine-use, course and survival

Twenty of the 40 patients did never use zidovudine during the course of their disease. In 10 patients zidovudine was started after the diagnosis ADC was made.

Table 2
Neuropsychological test results in 17 patients with ADC

	abnormal test results
Mental state	
– MMSE raw score	mean score 21 (range: 8-28)
Intelligence	
– Groninger Intelligence Test	16/17
Attention	
– Digit Span WAIS– R	8/17
Memory	
– 15 Word– test immediate recall	15/16
– 15 Word– test delayed recall	15/16
– WMS Visual Memory (immediate recall)	11/15
Language	
– Category bound word fluency	10/17
Psychomotor speed	
– Trailmaking A	17/17
– Digit Symbol WAIS– R	13/17
– Stroop Colour Word I	13/15
– Stroop Colour Word II	13/15
Executive control functioning	
– Trailmaking B	15/17
– Stroop Colour Word III	14/16
Cortical functions	
– communicative ability	3/17
– naming	2/17
– reading	2/17
– writing	1/17
– arithmetic	1/17
– visual gnosis	1/17
– praxis	1/17
– perseverative behavior	6/17

For criteria and test references see references 31 and 32

Table 3
Neuro-imaging findings in 40 patients with ADC

	CT-scan in 40 patients (MRI in 15 patients)			
	none CT (MRI)	mild CT (MRI)	moderate CT (MRI)	severe CT (MRI)
cortical atrophy	30% (27%)	40% (47%)	15% (13%)	15% (13%)
ventricle enlargement	33% (40%)	33% (33%)	18% (13%)	18% (13%)
white matter abnormalities	65% (27%)	25% (20%)	8% (33%)	3% (20%)

white matter abnormalities: hypodense white matter on CT and white matter hyperintensity on MRI

Six of them started with 1200 mg per day (which later had to be changed to 500/600 mg in 3 patients), and 4 patients were treated with 400-600 mg per day (duration of treatment: 1-32 months) (Table 4). In 9 other patients ADC devel-

Table 4
Patients with ADC treated with zidovudine

patient	zidovudine dose (duration)	survival	CSF Ag	CT	MRI	clinical improvement
1	500-1200 (32)	32	–	0	0	+
2	500-600 (24)	24	–	+	nd	+
3	500 (16)	16	+	+	nd	+
4	600-1200 (10)	22	–	+++	nd	±
5	500 (14)	14	+	++	nd	±
6	1200 (1)	2	–	+	nd	–
7	400-500 (7)	7	+	+++	+++	–
8	600-1200 (14)	16	+	+++	+	–
9	600-1200 (8)	9	–	0	0	–
10	1000-1200 (6)	6	+	+	+++	–

zidovudine dose in mg/day; duration: duration of treatment in months; survival in months; CSF Ag: HIV–1 p24 antigen in cerebrospinal fluid; CT: ventricular enlargement on CT–scan of the brain; MRI: white matter hyperintensity on MRI scan of the brain; 0 = none, + = mild, ++ = moderate, +++ = severe; improvement: + = remarkably, ± = slightly, – = no improvement
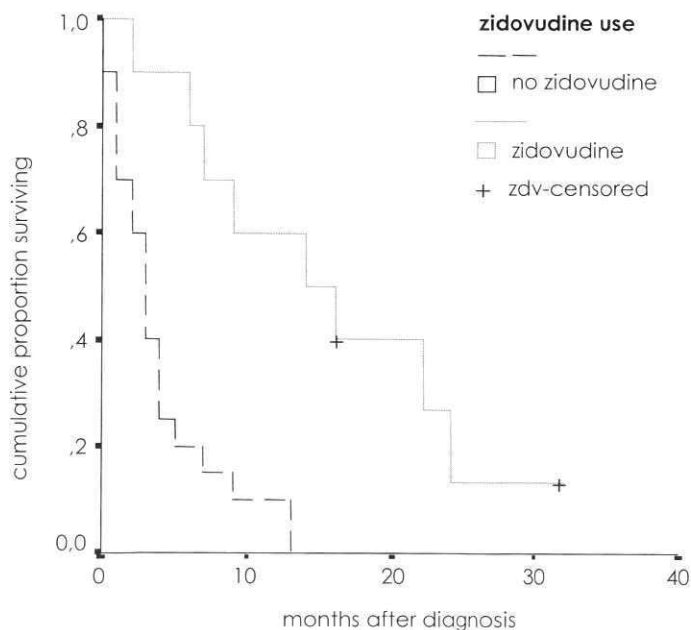
Figure 1
Kaplan-Meier curves comparing 20 patients with AIDS dementia complex (ADC) who never received zido-vudine (— —) with 10 patients who started zidovudine after the diagnosis (————).

oped after zidovudine (in 8/9: 500 mg per day) was discontinued (one improved after a rechallenge with 500 mg), which means that 39 of the 40 patients with ADC did not use zidovudine at the time of diagnosis. Only one patient developed ADC while on 600 mg of zidovudine treatment.

In the group of ten patients who started with zidovudine after the diagnosis was made, three improved remarkably (at least 1 stage according to the staging scheme for ADC[33]; stage 3 to 2 or stage 2 to 1; 2 high-dose zidovudine, 1 low-dose zidovudine), 2 slightly (less than 1 stage; 1 high-dose zidovudine, 1 low-dose

zidovudine) and 5 patients did not improve. In those who improved remarkably improvement lasted for 16, 24 and 32 months respectively; two of them are still alive.

The mean survival in the group of 40 patients was 6.7 months (median: 4 months; range: 0-32 months). In 20 patients who never used zidovudine the mean survival was 4 months (median: 3 months; range 0-13 months). In 10 patients who started with zidovudine after they were classified as having ADC the mean survival was 14.8 months (median:14 months; range 2-32 months) (Table 4). The difference in mean survival between these two groups was significant (Mann-Whitney test: p<0.001). Differences in survival between these two groups were also calculated according to the product-limit method of Kaplan-Meier, and are shown in Figure 1. The mean survival in the patients who developed ADC after zidovudine was discontinued, was 2.8 months (median: 3 months; range 0-5 months).

DISCUSSION

ADC occurred in 40 of 536 symptomatic HIV-infected individuals evaluated for neurological problems between 1982 and 1992 in an academic referral center for AIDS in Amsterdam. All ADC-patients were immunosuppressed at the time of diagnosis, with a mean CD4 cell count of 109.10^6/l. Although ADC usually appears after the development of the major opportunistic infections or neoplasms that define systemic AIDS, it may occur before major systemic complications.[34] This is supported by our data; in six patients (15 %) ADC was the AIDS-defining illness. No significant differences in base-line characteristics were found between these six patients and the 34 patients who were already diagnosed with AIDS.

The ADC-incidence of 7.5% found in this study is lower than incidences reported in other retrospective studies, in which 16-21 % of untreated patients in the late stages of HIV infection (CDC group IV) evaluated for neurologic complaints, were diagnosed with ADC.[6-8] The introduction of zidovudine has probably contributed to this difference; the overall study-period included one period before introduction of zidovudine and one thereafter (with a lower incidence). A CDC-analysis over the period 1987-1991 revealed an incidence of 7.3%. However this represented an underestimate of the actual incidence, because in these patients ADC was the AIDS-defining illness. Patients developing ADC later in their course are often not reported to the CDC.[35] A recent Italian study reported an incidence of 5.5% (15/271) for ADC as AIDS-defining illness.[36]

The results of this study emphasize that CSF- and CT/MRI-abnormalities correlate poorly with the clinical syndrome. Widened cortical sulci and enlarged ventricles are well-established CT/MRI-scan features of ADC.[1] However, 70% of the patients in the present study showed none or only mild cortical atrophy on CT-scan and 33% had a normal ventricle size. In 4 patients (27%) there were no white-matter abnormalities on MRI-scan. For detecting white matter abnormalities in ADC MRI is more sensitive than CT (74% versus 28%; Fisher's exact test p=0.02) (Table 3). Severe neurodiagnostic abnormalities did not correlate

with a poor prognosis. Survival in patients with severe white matter abnormalities on MRI was not significantly shorter than survival in patients with none or mild abnormalities (5.25 versus 10.66 months, p=0.40). And survival in patients with severely enlarged ventricles on CT-scan was not significantly shorter than survival in patients with normal or mildly enlarged ventricles (5.8 versus 6.8 months, p=0.72). In our series CSF-examination offered little help in supporting an ADC diagnosis. An aspecific mononuclear pleocytosis was found in 25%, and protein level increase in 55%. HIV-1 p24 core protein in the CSF was detectable in 38% of patients examined.

With the introduction of zidovudine the prevalence of ADC has changed. Our observations on a declining incidence of ADC after the introduction of zidovudine, have been confirmed by others[37] and neuropathological data indicate that zidovudine reduces the incidence of HIV infection of the brain.[38,39] The results of the present study suggest that in symptomatic HIV-1 infected individuals, ADC rarely develops during zidovudine treatment. A recent zidovudine study, comparing early versus late treatment in symptomatic patients, supported this finding.[40] In this study ADC was the AIDS-defining illness (and clinical end point) in 0 of 170 patients in the early treatment arm, compared to 6 of 168 patients in the late treatment arm (starting with zidovudine when CD4 cell counts fell below $200.10^6/l$ or when AIDS developed) (Fisher's exact test, p=0.03).

The only patient in our series who did develop ADC while on zidovudine treatment used 600 mg per day, which may not be sufficient in preventing ADC. A recently published double-blind dose-response study of zidovudine in AIDS and advanced HIV infection showed a trend towards fewer ADC-cases with the higher doses, with 13 of 160 patients (8%) in the 400 mg group, 10 of 158 (6%) in the 800 mg group and 5 of 156 (3%) in the 1200 mg group who developed ADC.[41]

Furthermore, our study suggests that zidovudine may prolong survival in patients with ADC who start with the drug after a diagnosis of ADC is made. However, one could argue that survival may have been seemingly prolonged because of earlier recognition of the syndrome without real gain in survival, or that survival in patients with AIDS has been prolonged anyway by improved prophylactic and therapeutic options in the past few years. Nevertheless we believe that zidovudine has definitely contributed to prolonged survival in patients with AIDS (with and without ADC), which for example has been shown in the Italian study already mentioned (22.1 months versus 10.6 months; n=271).[36]

As long as we have no definitive test for ADC, we will have to accept the clinical syndrome as the gold standard. ADC is a diagnosis of exclusion, although white matter abnormalities on MRI, HIV-1 p24 antigen detection in the CSF and a 'subcortical' profile on neuropsychological test may support the clinical diagnosis. Zidovudine treatment is warranted in all cases of ADC in order to alleviate symptoms and prolong survival. Most importantly however, the results of our study suggest that ADC rarely develops in patients who continue to use zidovudine. In our opinion, the decision whether an HIV-infected patient is zidovudine-intolerant should be made cautiously.

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