

New-onset delusions and hallucinations in patients infected with HIV

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Objective: To assess the relationship between HIV-associated psychotic symptoms (i.e., delusions, hallucinations) and demographic, psychopathological and medical variables by comparing patients with and without cerebral opportunistic infections or metabolic encephalopathy. **Design:** Cross-sectional study. **Patients:** 26 patients admitted to hospital with HIV and new-onset psychotic symptoms, defined according to DSM-III-R criteria. **Outcome measures:** A semistructured psychiatric interview using the Psychopathology Assessment Scale (AMDP-4) of the Association for Methodology and Documentation in Psychiatry system. Comprehensive medical assessments, including laboratory tests and computed tomographic scans, were also performed. **Results:** Patients with cerebral opportunistic infections or metabolic encephalopathy (i.e., "secondary" psychosis, $n = 13$) were more likely to show disorders of consciousness, disorders of orientation and disturbances of attention and memory than those with no evidence of HIV-related cerebral disease (i.e., "primary" psychosis, $n = 13$); 10 patients (77%) with cerebral opportunistic infections or metabolic encephalopathy and only 1 (8%) patient without ($p < 0.001$) were diagnosed with delirium. These associations were stronger for the "secondary" patients with no focal brain lesions than for those with lesions. **Conclusions:** These findings suggest that "organic" symptoms of psychosis in those infected with HIV are related to the systemic and cerebral complications of HIV infection rather than to the psychotic process itself.

Objectif : Évaluer les liens entre les symptômes psychotiques associés au VIH (c.-à-d. délire, hallucinations) et des variables démographiques, psychopathologiques et médicales en comparant des patients atteints d'infections opportunistes cérébrales ou une encéphalopathie métabolique à d'autres qui n'en avaient pas. **Conception :** Étude transversale. **Patients :** Vingt-six patients hospitalisés infectés par le VIH et présentant des symptômes psychotiques d'apparition récente, définis selon les critères DSM-III-R. **Mesures de résultats :** Entrevue psychiatrique semi-structurée réalisée à l'aide de l'échelle d'évaluation de la psychopathologie (AMDP-4) du système de l'Association de méthodologie et de documentation en psychiatrie. On a aussi procédé à des examens médicaux complets comportant des analyses de laboratoire et des tomographies. **Résultats :** Les patients atteints d'infections opportunistes cérébrales ou d'encéphalopathie métabolique (c.-à-d. psychose «secondaire», $n = 13$) étaient plus susceptibles d'avoir des troubles de la conscience, de l'orientation, de l'attention et de la mémoire que ceux qui ne montraient aucun signe de

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cérébropathie reliée au VIH (c.-à-d. psychose «primitive», $n = 13$). On a diagnostiqué un délire chez dix patients (77 %) atteints d'infections opportunistes cérébrales ou d'encéphalopathie métabolique et chez un (8 %) patient seulement qui n'était pas atteint ($p < 0,001$). Ces corrélations étaient plus solides dans le cas des patients «secondaires» qui n'avaient aucune lésion cérébrale focalisée que chez ceux qui avaient des lésions. **Conclusions** : Ces résultats indiquent que les symptômes «organiques» de psychose chez les patients infectés par le VIH sont reliés aux complications systémiques et cérébrales de l'infection par le VIH plutôt qu'au processus psychotique même.

Introduction

Among patients infected with HIV, most psychiatric disturbances, such as adjustment disorders or symptoms of anxiety and depression, arise from the distress associated with being diagnosed with the infection and from the implications of the diagnosis. In a minority of patients who present with major mood disorders and psychotic syndromes, the association with HIV infection is more complex and still poorly understood. Severe psychotic symptoms contribute to the difficulties of medical care and require immediate management. However, despite the seriousness of the problem, psychoses in patients with HIV have received little attention; the available data are mainly limited to case reports.

Sewell and colleagues¹ compared 20 men infected with HIV who had noniatrogenic new-onset psychosis without delirium and current substance abuse with 20 men with HIV who were psychosis free. Those diagnosed with psychosis had significantly higher rates of past stimulant and sedative-hypnotic abuse or dependence and a significantly higher mortality rate at follow-up than the controls with HIV.

In this study, we compared the psychopathological, medical and demographic data of 2 groups of patients who presented with HIV-related psychosis: those with "primary psychosis" (i.e., no HIV-related neurological disease or acute metabolic dysfunction) and those with "secondary psychosis" (i.e., with opportunistic cerebral infection or metabolic encephalopathy related to pulmonary, hepatic and renal failure).

Method

Subjects

Patients who presented to either of 2 departments of infectious diseases with delusions, prominent hallucinations or both, as defined in *Diagnostic and Statistical Manual of Mental Disorders*, 3rd revised edition (DSM-III-R),² between 1993 and 1995 were recruited for the

study. Inclusion criteria were as follows: age between 18 and 50 years, HIV infection documented by enzyme-linked immunosorbent assay (ELISA) and confirmed by Western blot and knowledge of HIV status at least 6 months before the onset of psychotic symptoms. Patients were excluded from the study if they had a history of psychosis before the diagnosis of HIV infection, used illicit drugs within 3 months of the onset of psychotic symptoms, were diagnosed with HIV-dementia on the basis of cognitive, behavioural or motor decline (documented by neurological or neuropsychological examination and consistent with the diagnostic criteria of the American Academy of Neurology AIDS Task Force³) or if psychotic episodes were associated with substantial mood symptoms.

Medical and psychiatric assessment

HIV-related diseases were diagnosed according to the Centers for Disease Control (CDC) classification system for HIV infection.⁴

Psychiatric evaluations were based on all available data, including a chart review of presenting signs and symptoms, psychiatric history, medical history, daily progress notes and a semistructured psychiatric interview. Informed written consent was obtained from each patient or from a relative (for patients who were delirious) after the procedure and aims of the study were explained.

All patients were assessed using the Psychopathology Assessment Scale (PAS; AMDP-4) of the Association for Methodology and Documentation in Psychiatry system.⁵ The PAS items explore the following 13 areas of psychopathology, following a systematic traditional approach to the evaluation of mental status: disorders of consciousness, disorders of orientation, disturbances of attention and memory, formal disorders of thought, phobias and compulsions, delusions, disorders of perception, disorders of ego, disturbances of affect, disorders of drive and motility, circadian disturbances, other disturbances and other symptoms. Each of these broad categories consists of a

number of descriptive items rated on a 5-point intensity scale (absent, mild, moderate, severe and extremely severe). All ratings were made independently by 2 board-certified psychiatrists (A.A. and A.F.). Inter-rater reliability was high, with good intraclass correlation (ICC = 0.95).

The patients underwent a complete medical assessment including a physical examination and laboratory tests. All of the patients underwent a computed tomographic (CT) scan of the brain within 15 days of their psychiatric interview; 7 patients also underwent lumbar puncture and 3 had magnetic resonance imaging for reasons unrelated to this research. Patients with no HIV-related neurological disease or acute metabolic dysfunction were categorized as having "primary psychosis" and those with opportunistic cerebral infection or metabolic encephalopathy related to pulmonary, hepatic and renal failure were diagnosed with "secondary psychosis."

Statistical analyses

Student's *t*-tests were used to compare normally distributed data, Mann-Whitney *U* tests to compare non-normally distributed data and χ^2 analyses to compare categorical variables (2-tailed *p* values).

Results

Of the 35 patients presenting with new-onset psychotic

symptoms, 9 were excluded from the study — 5 because of a previous psychotic episode, 2 for substantial mood symptoms, 1 for recent use of illicit drugs and 1 because of a diagnosis of HIV dementia. Of the remaining 26 patients, 20 were men; age ranged from 25 to 46 years (mean 34.9, standard deviation [SD] 6.3 years), and the mean CD4+ cell count was $59 \times 10^6/L$ (range 2–424 $\times 10^6/L$, SD $84 \times 10^6/L$). Seventeen patients had a history of injection drug use, 6 of heterosexual risk behaviours and 2 of homosexual intercourse; 1 patient was not aware of risk factors for HIV infection. All of the patients had known their serological status for some months (mean 61, SD 36, range 6–116 mo). Twenty-one patients were in CDC stage C3, 1 in stage B3, 2 in stage B2, and 2 were in stage A2 (Table 1). The 22 patients (84.6%) with a diagnosis of AIDS represented 2.1% of all AIDS cases ($n = 1050$) observed during the study period. Protease inhibitors were not available when patients were recruited for the study.

Psychiatric diagnoses, according to the DSM-III-R criteria, included delirium ($n = 11$), organic hallucinosis ($n = 5$), organic delusional syndrome and organic hallucinosis ($n = 9$), organic delusional syndrome ($n = 1$); 14 (53.9%) of the 26 patients had delusions and 3 had more than 1 type of delusion (persecutory, $n = 11$; of reference, $n = 2$; somatic, $n = 2$; religious, $n = 2$; grandiose, $n = 1$). As well, 23 (88.5%) reported hallucinations; 15 (65.2%) patients reported auditory experiences (10 auditory only and 5 with a secondary visual component), 4 experi-

Table 1: Demographic and clinical characteristics of patients diagnosed with HIV and primary or secondary psychosis

Characteristic	Patients with primary psychosis <i>n</i> = 13	Patients with secondary psychosis <i>n</i> = 13	Results of statistical comparisons*
Mean age (and SD), yr	34.8 (6.6)	35 (6.2)	$t = -0.06$, $df = 23$, $p = 0.94$
Mean education (and SD), grade	9.5 (2.7)	8.0 (0)	$t = 1.23$, $df = 11$, $p = 0.24$
Mean CD4+ count (and SD), $\times 10^6/L$	45.8 (39)	72 (113)	$t = -0.78$, $df = 24$, $p = 0.43$
No. of men : no. of women	9:4	11:2	$p = 0.4$, Fisher's exact test
Risk factors, no. of patients			$\chi^2 = 0.68$, $df = 2$, $p = 0.70$
Intravenous drug user	8	9	
Heterosexual activity	4	2	
Homosexual activity	1	1	
HIV stage			$\chi^2 = 1.05$, $df = 3$, $p = 1.0$
A2	1	1	
B2	1	1	
B3	1	0	
C3	10	11	
AIDS diagnosis, no. of patients	11	11	$p = 1$, Fisher's exact test

Note: SD = standard deviation.

* Student's *t*-test for continuous variables and χ^2 analysis for categorical data.

enced pure visual hallucinations, 2 pure tactile and 2 reported visual and somatic hallucinations.

Neuroimaging data derived from CT scans, were evaluated by a neuroradiologist. Various types of brain atrophy were found in 11 (42.3%) of 26 patients. Cortical atrophy accompanied by ventricular dilatation was the most common diagnosis ($n = 5$), followed by periventricular atrophy ($n = 4$) and cortical atrophy alone ($n = 2$). Six (23.1%) patients showed a space-occupying lesion without atrophy, and the CT scans of 9 (34.6%) patients showed no neurological abnormalities.

Among the 26 patients, 13 with opportunistic cerebral infection or metabolic encephalopathy related to pulmonary, hepatic or renal failure were defined as having "secondary psychosis" and 13 were diagnosed with "primary psychosis" because they had no HIV-related cerebral disease or acute metabolic dysfunction. Of the 13 patients with "primary psychosis," 8 (61.5%) showed brain atrophy; ventricular enlargement was found in 4 patients, cortical atrophy and ventricular dilatation in 3 and cortical atrophy only in 1 patient. The secondary psychosis group was subdivided on the basis of whether the patient had a focal brain lesion, defined as a space-occupying lesion revealed by CT. Six patients had a focal brain lesion, diagnosed as cerebral toxoplasmosis, and were classified as "lesional secondary"; the remaining 7 had no space-occupying lesion (including 3 patients with uremic encephalopathy, 2 with hepatic encephalopathy, 1 with hypoxia in *Pneumocystis carinii* pneumonia and 1 with cryptococcal meningitis) and were classified as having "non-lesional secondary psychosis."

There were no significant differences between the

primary and secondary psychosis groups on variables of sex, age, education level, CD4+ absolute cells counts, number of risk factors for HIV infection, CDC stage or the number of patients diagnosed with AIDS (Table 1).

The secondary psychosis patients scored significantly worse on AMDP-4 disorders of consciousness, ($p = 0.01$), disorders of orientation ($p < 0.001$) and disturbances of attention and memory ($p = 0.004$) (Table 2), but the 2 groups were similar with regard to the presence of formal disorders of thought ($p = 0.83$), delusions ($p = 0.23$) and disorders of perception ($p = 0.61$). Delirium, diagnosed according to DSM-III-R criteria (Table 3), was identified in 10 (76.9%) secondary patients and in only 1 (7.7%) primary patient ($p < 0.001$).

When the "lesional" and "non-lesional" secondary patients were considered separately and compared with the primary group, only the scores on disturbances of consciousness, orientation and attention and memory for the non-lesional patients were significantly higher than those for the primary patients ($p = 0.01$, $p = 0.001$ and $p = 0.003$, respectively). The association between delirium and secondary psychosis was also largely due to the non-lesional subgroup ($p < 0.001$ v. 0.07 for lesional patients, Fisher's exact test).

From the beginning of the study (January 1993) to the time of this analysis (October 1999) all but 1 of the 26 patients had died. All of the patients with non-lesional secondary psychosis died within a short time (mean 31 days). All of the patients with focal brain lesions (i.e., lesional secondary) recovered from their psychosis with neuroleptic drug treatment but died several months later (mean survival time 158 days)

Table 2: Psychopathological test results of patients with HIV and primary or secondary psychosis

Psychopathology	Patients with primary psychosis	Patients with secondary psychosis	Results of statistical comparisons *
Disorders of consciousness, mean AMDP-4 score	0	0.36	$U = 39, z = -2.3, p = 0.01$
Disorders of orientation, mean AMDP-4 score	0.13	1.23	$U = 20, z = -3.30, p < 0.001$
Disturbances of attention and memory, mean AMDP-4 score	0.16	0.98	$U = 29.5, z = -2.8, p = 0.004$
Formal disorders of thought, mean AMDP-4 score	0.21	0.26	$U = 80.5, z = -0.2, p = 0.83$
Delusions, no. of patients	9	5	$p = 0.23$, Fisher's exact test
Disorders of perception, no. of patients	12	11	$p = 0.61$, Fisher's exact test
Delirium, no. of patients	1	10	$p < 0.001$, Fisher's exact test

* Mann-Whitney U test for ordinal measures and χ^2 analysis for categorical variables.

from opportunistic infections. The patients with primary psychosis also recovered with neuroleptic treatment, although 3 developed AIDS dementia within a year of the onset of psychotic symptoms. The mean survival time for this group was 160 days.

Discussion

The patients we assessed are similar to those described in the Harris et al⁶ review of case reports and in Sewell et al.¹ Our patients were comparable in age (mean 35 v. 34 years of age in the literature) and the proportion of patients with hallucinations (88% v. 75%) to the patients described in both studies. However, the percentage of patients with delusions was lower in our sample than in the 2 published studies (54% v. 93%). This may be related to our patient selection criteria; we included "secondary" patients but excluded subjects with mood symptoms. A higher proportion of our "pure" primary psychosis patients (i.e., more similar to the patients included in previous studies) were delusional (69%).

The prevalence of new-onset psychosis among the patients with AIDS seen during this study was 2.1%. Although there are few studies with which to compare our findings, Halstead et al⁷ described the cases of 5 men with HIV and "functional" psychosis with no evidence of organic components and commented that the

5 cases were all they were able to find in their health district, in which over 2200 patients had presented with HIV infection. This suggests the prevalence of new-onset "functional" psychosis in HIV-seropositive patients in their sample was 0.2%. In our study, if we consider only the patients with AIDS with "primary" psychosis (i.e., similar to the functional psychosis of Halstead et al), the prevalence falls to 1.05%.

High scores on disorders of consciousness, orientation and attention and memory distinguished patients with secondary from those with primary psychosis. Many of these patients with secondary psychosis were also diagnosed with delirium. The organic symptoms (i.e., disorientation, impaired consciousness and memory) were most likely to be represented in patients with non-lesional secondary psychosis and were least frequent in those with primary psychosis. When psychotic symptoms occurred with organic symptoms, they were generally related to a global central nervous system impairment associated with a metabolic encephalopathy. Thus, the organic symptoms are more likely to be related to the presence of HIV-related cerebral complications than to the psychotic process itself. This is consistent with reports of "functional" psychosis in the absence of organic signs.^{7,8}

The pathogenesis of "pure" primary psychosis among HIV-positive patients remains unclear. Psychotic symptoms could be considered a psychological

Table 3: DSM III-R diagnostic criteria for delirium

- A. Reduced ability to maintain attention to external stimuli (e.g., question must be repeated because attention wanders) and to appropriately shift attention to new external stimuli (e.g., perseverate on answer to a previous question)
- B. Disorganized thinking, as indicated by rambling, irrelevant or incoherent speech
- C. At least 2 of the following:
 - reduced level of consciousness (e.g., difficulty staying awake during examination)
 - perceptual disturbances: misinterpretations, illusions or hallucinations
 - disturbances of sleep-wake cycle, with insomnia or daytime sleepiness
 - increased or decreased psychomotor activity
 - disorientation to time, place or person
 - memory impairment (e.g., inability to learn new material, such as the names of several unrelated objects after 5 minutes, or to remember past events, such as history of current episode of illness)
- D. Clinical features develop over a short period of time (usually hours to days) and tend to fluctuate over the course of a day
- E. Either 1 or 2
 1. Evidence from the history, physical examination or laboratory tests of a specific organic factor (or factors) judged to be etiologically related to the disturbance
 2. In the absence of such evidence, an etiologic organic factor can be presumed if the disturbance cannot be accounted for by any nonorganic mental disorder (e.g., manic episode accounting for agitation and sleep disturbance)

reaction to the diagnosis of HIV, but the patients in this study had known about their HIV status for at least 6 months before the onset of psychotic symptoms.

A link between antiretroviral medication and psychotic symptoms has been hypothesized, but there was no temporal relation between a change in antiretroviral therapy and the course of psychotic symptoms in any of our patients. Moreover, zidovudine has been linked to cases of mania and depression but not to psychosis.⁹

The design of our study excludes the hypothesis that psychosis might be induced by drug abuse because none of our patients had used illicit drugs within the 3 months before the onset of psychotic symptoms. However, from our data, we cannot discount the theory that at least some of the psychotic episodes of our patients may have been related to new-onset schizophrenia.

The suggestion that the psychosis may relate to neurotropic activity of the HIV infection and may be a direct result of brain infection seems plausible on the basis of our data. We found that the association between secondary psychosis and disorders of consciousness, orientation and memory was largely due to the non-lesional patients, as was the prevalence of patients with delirium.

The lesional secondary and primary patients not only shared similar outcomes, but also a similar clinical profile. All of our patients with brain lesions were affected by cerebral toxoplasmosis, which was located in the left temporo-parietal lobes in 2 cases, the left front-parietal lobes in 2 cases and the left basal ganglia in 2 cases. We hypothesize that left-sided temporal-limbic and subcortical toxoplasmosis may be etiologically significant in producing psychotic symptoms. In their extensive review of the literature on psychosis associated with organic disorders of the central nervous system, Davidson and Bagley¹⁰ concluded that schizophrenia-like psychoses were more common among patients with temporal-limbic or diencephalic dysfunction. Moreover, data support the tendency of left-sided lesions to produce schizophrenia-like syndromes more often than right-sided injuries. In addition, modern imaging techniques (i.e., CT, magnetic resonance imaging) have shown volumetric deviations of left temporal lobe anatomy in schizophrenic patients.¹¹

There were no significant differences in the most important clinical findings in our admittedly small samples of "lesional secondary" and "primary" patients; this might reflect a common pathogenetic process — mediated by toxoplasma in lesional secondary patients and by the HIV in primary patients — that involves

cerebral areas that are critical for the development of psychotic symptoms, such as the left temporal-limbic and diencephalic regions. This finding may give further support to the hypothesis of the direct involvement of HIV in new-onset psychosis.

Three of the 13 patients with primary psychosis developed AIDS dementia complex within a year of the onset of psychotic symptoms. Thus, HIV itself can cause "primary psychosis" or produce an organic brain syndrome presenting with psychotic disorders. From a pathogenic view, it is possible that psychotic symptoms may derive from a coincidental occurrence of schizophrenia or from an HIV-related organic mental syndrome.

Finally, this study might be helpful in orienting the clinical approach to new-onset psychosis in HIV-positive patients. Furthermore, given the differences between our groups in mean survival time, the distinction between "lesional secondary," "non-lesional secondary" and "primary" psychosis could have important prognostic value. Further studies involving more patients are necessary to confirm this.

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