Incidence, Clinical Presentation and Outcome of Cerebral Toxoplasmosis in HIV-infected patients during the Highly Active Antiretroviral Therapy Era: A Nationwide Cohort Study

Raquel Martin-Iguacel1, Magnus Glindvad Ahlström2, Madeleine Toume1, Frederik Neess Engsig3, Nina Breinholt Stærke1, Mette Stærkind4, Niels Obel5, Line D. Rasmussen1

1 Department of Infectious Diseases, Odense University Hospital, Odense, Denmark,
2 Department of Infectious Diseases, Rigshospitalet, Copenhagen, Denmark,
3 Department of Infectious Diseases, Copenhagen University Hospital, Hvidovre, Denmark,
4 Department of Infectious Diseases, Aarhus University Hospital, Aarhus, Denmark,
5 Department of Infectious Diseases, Aalborg University Hospital, Aalborg, Denmark

Introduction
Cerebral toxoplasmosis (CTX) is the most common of the opportunistic infections (OI) in the central nervous system (CNS) of HIV-infected patients. Since the introduction of cART, the overall IR of OI and the post-OI mortality rate (MR) have declined dramatically (1-4). Still, incidence and mortality of CTX vary considerably between studies probably due to differences in sociodemographic characteristics, access to care and percentage of late presentation of HIV-infection of the different study populations. As CTX still remains an important cause of morbidity and mortality in HIV-infected patients (1,5,6), it is important to further investigate the incidence, presenting symptoms, risk factors and prognosis of HIV-associated CTX as of today.

Objectives
We conducted a cohort study to assess the risk of CTX and associated mortality in HIV-infected patients during the pre-cART (1995-1996) and cART-era (1997-2014), and assessed the associated predictive and prognostic factors. We further described the presenting characteristics and the clinical course of patients with CTX.

Materials & Methods
From the Danish HIV Cohort Study (DHCS), we identified 6,325 Danish HIV-infected individuals aged ≥21 years (study period: 1995–2014). Data on CTX were obtained through medical files review. We assessed incidence rate (IR), mortality rate (MR), predictive factors, clinical presentation and prognosis of CTX during the pre-combination antiretroviral therapy (pre-cART: 1995-1996) and cART-era (1997-2014). We used Poisson regression analysis to assess adjusted incidence rate ratios (aIRR), mortality rate ratios (aMRR) and 95% confidence intervals (CI).

Results
72 patients were diagnosed with CTX (IR: 1.17; 95% CI 0.93-1.47), of whom the majority (56.9%) were diagnosed with HIV before 1995. All CTX patients had advanced HIV-disease (table 1).

Table 1. Demographics and HIV-related characteristics of the study patients and the patients who developed cerebral toxoplasmosis (CTX) diagnosed during the study period

Incidence and predictive factors associated with CTX: From the pre-cART to the cART-era we observed an unchanged risk of CTX during the first year after study inclusion (i.e. HIV diagnosis) (aIRR: 0.81; 95%CI: 0.42-1.56). In contrast, a substantial reduction in risk of CTX was observed in the subsequent years during the cART-era (aIRR: 0.00; 0.03-0.11). Higher risk of CTX was significantly associated with a low CD4+ cell count (< 200 cells/μL) and high VL (VL ≥ 100,000 c/mL) (table 2).

Table 2. Predictive factors for cerebral toxoplasmosis in HIV-infected individuals

Mortality: Forty-two patients (58.3%) diagnosed with CTX died during the study period of whom thirty (71%) died within the first year and nine (25%) within 30 days after the CTX diagnosis (data not shown).

We observed a substantial reduction in post CTX mortality with later calendar periods (1995-1996 vs. 1997-2014) during the first and second years (aMRR: 0.13; 0.06-0.30) and subsequent years (aMRR: 0.02; 0.01-0.04). And, during 1997-2014, no statistically significant difference in risk was observed between patients who had survived the first year after CTX diagnosis and in whom CTX was diagnosed before and after year 1996 (aMRR: 0.36; 0.08-1.74).

When evaluating prognostic factors, age at CTX diagnosis, injection drug use, and no exposure to cART before CTX diagnosis were associated with a statistically significant higher risk of mortality in univariate models (table 3).

Table 3. Prognostic factors for death in HIV-infected individuals diagnosed with cerebral toxoplasmosis.

Conclusions
In conclusion, CT still remains an important cause of morbidity and mortality among HIV-infected patients with advanced immunosuppression. However, the incidence of CT and post CT mortality has declined substantially during the cART-era, especially when surviv- ing the first year of HIV-infection and CT, respective- ly. As a result, individuals diagnosed with HIV or CT during the pre-cART-era can be assured a low risk of CT or post CT mortality when compliant to cART. Hence, early diagnosis of HIV and cART initiation remains paramount.

References