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CNS infections in 2014: guns, germs, and will

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Important advances in neurological infections during 2014 spanned antimicrobial treatments (guns), pathogenesis and detection of germs, including viruses and prions, and the will to develop and implement prevention programmes in resource-limited settings.

One study addressed the complex issue of appropriate timing of initiation of combined antiretroviral therapy (CART) in patients with AIDS-associated opportunistic infections. Clinical decision making must weigh the potential risk of delaying treatment in patients with profound immunosuppression against the risks associated with co-administration of treatments for opportunistic infections with CART, including potential drug interactions and risk of immune reconstitution syndrome. Although previous studies have shown a potential benefit of early initiation of antiretroviral drugs in patients with non-CNS opportunistic infections, available data suggests that there might be separate considerations for individuals with CNS opportunistic infections. In the COAT trial, done in Uganda and South Africa, David Boulware and colleagues¹ provide evidence that helps to clarify when to start CART in patients with cryptococcal meningitis. After 7–11 days of antifungal treatment, 177 CART-naïve individuals were randomly assigned to receive early (started 48 h after randomisation) or deferred (started 4 weeks after randomisation) CART. Mortality at 26 weeks (the primary study endpoint) was significantly higher in the early-CART group than in the deferred-CART group, although secondary endpoints (including survival at 46 weeks, cryptococcal meningitis relapse, and virological suppression at 26 weeks) did not differ. Surprisingly, the number of identified cases of immune reconstitution syndrome did not significantly differ between the two groups. These findings suggest that the appropriate timing of CART in patients with HIV who have CNS opportunistic infections might differ from those with non-CNS opportunistic infections.

Why is natalizumab, a monoclonal antibody against α 4-integrin that is used in the treatment of multiple sclerosis, associated with a much higher incidence of progressive multifocal leukoencephalopathy (PML) than other immune suppressive or modulatory drugs? One hypothesis is that the development of PML might be linked to the well recognised ability of natalizumab to promote mobilisation of some mononuclear cell populations from the bone marrow into the periphery. To address this question, Elliot Frohman and colleagues² looked for JC virus, the causative agent of PML, within subsets of circulating mononuclear cells. The investigators used a highly sensitive PCR assay for the JC virus genome on serially

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sampled peripheral blood cells from patients with multiple sclerosis undergoing natalizumab therapy over 24 months.² Notably, 31% of patients had JC virus DNA in CD34-positive cells at different times, and 24% had JC virus DNA in CD19-positive cells. JC virus copy numbers were low overall but tended to rise with duration of treatment, and were higher in CD34-positive than in CD19-positive cells. Importantly, 61% of JC virus seronegative individuals had cell-associated JC virus at some point during the study. Taken together, these findings suggest that bone-marrow-derived CD34-positive cells might be latently infected with JC virus and mobilise to the periphery during natalizumab treatment, thus providing a mechanism for viral entry into the CNS and subsequent development of PML.

Although possible or probable Creutzfeldt-Jakob disease (CJD) can be diagnosed with a combination of clinical and paraclinical findings, definitive diagnosis depends on the acquisition of brain tissue for neuropathological or immunohistochemical confirmation of prion protein. Thus, there is a need for non-invasive, prion-specific diagnostic tests to permit the definitive diagnosis of CJD antemortem. The findings of two studies show important advances in this realm. Both studies used tests that rely on the ability of the abnormally folded prion protein (PrP^{Sc}) to induce conformational changes in normal prion protein (PrP^C), thus resulting in amplification of the misfolded protein. Building on evidence that PrP^{Sc} is widespread in peripheral tissues in variant CJD, with more restricted expression in sporadic and genetic forms, Fabio Moda and colleagues³ used a protein misfolding cyclic amplification (PMCA) assay to detect PrP^{Sc} from urine in patients with variant CJD. They noted small amounts of PrP^{Sc} in the urine after extensive amplification in 13 (93%) of 14 patients with variant CJD, with no evidence of the protein in more than 70 patients with sporadic or genetic CJD, or 150 patients with neurological diseases other than CJD and healthy controls. The second study focused on the diagnosis of sporadic CJD. Since PrP^{Sc} has been found in olfactory epithelial tissue, Christina Orrú and colleagues⁴ investigated whether real-time quaking-induced conversion (RT-QuIC; a technique currently being applied in a few centres to CSF) can detect PrP^{Sc} from nasal brushings. 30 (97%) of 31 patients with sporadic CJD tested positive, whereas all 43 controls tested negative. Importantly, the sensitivity was higher for nasal brushings than it was for CSF, and the test seemed to do at least as well as traditional CSF 14-3-3 and tau assays for diagnosis of sporadic CJD. Although larger studies are needed to fully assess these approaches, they hold great promise for the specific and sensitive diagnosis of variant and sporadic forms of CJD.

The meningitis belt of Saharan and sub-Saharan Africa continues to be ravaged by epidemic *Neisseria meningitidis* despite the virtual disappearance of this bacterium in developed countries. In 2010, a *N meningitidis* serogroup A polysaccharide–tetanus toxoid conjugate vaccine (PsA-TT) developed by the Meningitis Vaccine Project (MVP) was deployed in Burkina Faso and largely reduced the carrier rate and incidence of meningitis. Although these results were encouraging, some researchers have argued that the reduction might have been due to the falling incidence of serogroup A disease before the introduction of the vaccine. Now, Doumagoum Daugla and colleagues⁵ have provided persuasive evidence for the effectiveness of PsA-TT, assessed during an ongoing epidemic in Chad. Approximately 1.8 million individuals aged 1–29 years received one dose of PsA-TT during a vaccination campaign in three regions of Chad in 2011. The incidence and carrier rates of meningitis

during the 2012 meningitis season in these regions were markedly reduced when compared with unvaccinated regions, with a 94% difference in crude incidence. This study provides compelling evidence for the effectiveness of PsA-TT and shows the importance, will, and resolve of organisations such as MPV to address major global health concerns.

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