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CNS Infections 1

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CNS Infections 1
Clinical profile and outcome in AIDS related progressive multifocal leukoencephalopathy — A large cohort from India

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Background: Progressive multifocal leukoencephalopathy (PML) is an opportunistic infection by JC virus seen in immunodeficient individuals, especially those with AIDS. Poor outcome despite highly active antiretroviral therapy is a cause of concern.
Objective: This study was undertaken to assess the clinical profile and survival in patients with PML.
Patients and methods: Data of AIDS patients with laboratory confirmed PML (JC virus positive) and possible PML (clinicoradiological) from 2004 were studied. Demographic profile, clinical assessment, laboratory parameters and outcome were analyzed.
Results: Study group included 33 patients (25 men; 8 women) with age ranging from 26 to 67 years (39.48 ± 9.11). Symptom duration was 47.15 ± 55.63 days. Presenting symptoms were limb weakness (18), cognition and behavioral changes (13), aphasia/dysarthria (12), gait ataxia (7), seizures (6), impaired vision (5), impaired consciousness (5), sensory disturbance (3), involuntary movement (2) and Gerstmann syndrome (1). PML was the presenting manifestation of immunodeficiency in 7 patients. 18 patients were on HAART. Radiological lesions were present in supratentorial white matter in 29 patients (bilateral 21, unilateral 8). Six had brainstem lesions and 5 had cerebellar involvement. Five patients had lesions in supra and infratentorial compartment. CSF was acellular in 15 while 14 had elevated protein. Laboratory confirmation of JC virus was available in 4 patients. Fourteen patients were lost for follow-up and 15 (6 women; 9 men) succumbed. Follow-up on surviving 4 patients who remained neurologically static on HAART was 12 to 96 months (median 43).
Conclusion: This is a descriptive study of large cohort of PML patients from a single center. 21% of the patients had PML as the presenting manifestation of AIDS.

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Assessment of neurocognitive disorders in patients with HIV infection

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Introduction: Neurocognitive disorders associated with HIV infection (NDAH) are relatively common manifestations that may affect the everyday functionality and patient adherence to treatment. Currently we have no validated screening tools for early detection of these disorders that can be made in the routine visit. Montreal Cognitive Assessment (MoCA) test is a multidimensional tool, rapid deployment that has already been validated in Alzheimer's disease and allows the evaluation of several domains.
Objective: To determine the usefulness of MoCA as a quick, sensitive and specific tool for the detection of NDAH, compared to a comprehensive cognitive evaluation and MiniMental Test (MMSE).
Materials and methods: Patients over 18 years old with HIV infection were included in a prospective study. MoCA test, Beck Depression Scale and a comprehensive neurocognitive battery were performed. Sex, age, education, length of infection by the HIV virus, CD4 and viral load at the time of evaluation were analyzed.
Results: we evaluated 21 patients, 19 male; mean age 46.9 years, education 14 years, time of infection by HIV 60 months and median CD4 563 cells/ml. 13/21 had undetectable viral load. MoCA presented 66.67% S (IC34.95–89.87%), E 88.89% (CI 51.7498.16%). VPP 88.89% (CI 51–98%) and VPN 66.67 (CI 35–90%). MMSE results were analyzed, showing 9.9% S (IC1, 5–41%) E 100% (CI 69–100%) VPP100% (CI 16–100%) and NPV 50% (IC27–73%).
Conclusions: MoCA is a good screening test for NDAH, higher than MMSE. The continuation of this cohort will help to determine the usefulness of this tool in clinical practice.

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Neurological manifestations in dengue seropositive patients

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Objective: To study the incidence and spectrum of neurological manifestations in dengue seropositive patients.
Background: Dengue is an infectious disease caused by a flavivirus. It is an acute febrile illness causing considerable morbidity and mortality. The neurological complications in dengue have been hypothesized to occur through three different pathogenic mechanisms: (1) direct

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neurotropic effects leading to encephalitis, meningitis, myelitis and myositis (2) indirect effects due to metabolic complications resulting in encephalopathy and cerebrovascular complications due to thrombocytopenia and platelet dysfunction and (3) postinfectious immune-mediated acute disseminated encephalomyelitis, Guillain Barré syndrome and optic neuritis.
Material and methods: This was a descriptive cross sectional study including seropositive patients diagnosed with Dengue fever (DF), Dengue with warning signs and Severe Dengue with neurological manifestations presenting to Medicine Department of LLR Hospital, Kanpur.
Results: 10 (2.6%) patients had neurological manifestations out of 383 seropositive patients. Out of ten, nine patients were male and only one patient was female. Among them 10% patients come under category of classical dengue fever, 10% patients suffered from dengue with warning signs and 80% with severe dengue .4 patients had encephalopathy,3 other patients had encephalitis, 2 patients presented with single episode of symptomatic generalized seizure and 1 patient presented as having an intra cranial hemorrhage.
Conclusions: Neurological manifestations of dengue are manifold and it is necessary to consider dengue as a cause for the above neurological presentations in endemic zones of the disease.

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Safflower yellow inhibits the inflammatory response and regulates microglial polarization in LPS-stimulated bv2 cells

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Background: Safflor Yellow (SY), the main active constituent of the traditional Chinese medicine Safflower, is known as a neuroprotective agent that indirectly attenuates neuroinflammation. Macrophage/microglia have different phenotypic and functional states, M1 is associated with inflammatory responses, while M2 results in anti-inflammatory effects.
Objective: The purpose of this study is to discover the effect of SY on anti-inflammation and polarization of microglia stimulated with LPS as well as related molecular mechanism.
Material and methods: BV-2 microglial cell line was treated with LPS and/or SY. Molecular biological technique, flow cytometry, and immunohistochemistry were adopted.
Results: LPS-stimulated BV2 cells upregulated the expression of TLR4 ($p < 0.01$), Myd88 ($p < 0.01$), p-NF-κB ($p < 0.05$), p-P38 ($p < 0.01$) and p-JNK ($p < 0.001$), and the expression of inflammatory cytokines IL-1β ($p < 0.05$),IL-6 ($p < 0.05$),TNF-a ($p < 0.05$),NO ($p < 0.01$) and COX-2 ($p < 0.05$), but didn't influence the expression of p-ERK ($p > 0.05$). After SY stimulation, the expression of TLR4, Myd88, p-NF-κB and p-P38, and inflammatory cytokines declined ($p < 0.05$). Simultaneously, M1 markers iNOS ($p < 0.05$), CD16/32 ($p < 0.05$), IL-12 ($p < 0.05$) and M2 markers CD206 ($p < 0.05$), IL-10 ($p < 0.05$) were elevated after LPS stimulation, but M1 markers significantly declined after SY intervention ($p < 0.05$), while M2 marker CD206 ($p < 0.05$) and IL-10 ($p < 0.05$) were significantly elevated ($p < 0.001$). SY had no influence on M2 marker Arg-1, but the ratio of iNOS/Arg-1 declined compared with LPS-stimulated group ($p < 0.05$), indicating SY converted inflammatory M1 BV2 cells toward anti-inflammatory M2 microglia.
Conclusion: SY exhibited anti-inflammatory effect on BV2 microglia possibly through TLR-4/NF-κB/MAPK signaling pathways and the conversion of M1 to M2 microglia. (Grant: The 2011 Cultivation Project of Shanxi University of Traditional Chinese Medicine, 2011PY-1).

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Rabies virus phosphoprotein induces mitochondrial dysfunction, oxidative stress, and neuronal process degeneration: Implications for future therapy of human rabies

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Background: Our previous studies in a mouse model of experimental rabies showed neuronal process (dendrites and axons) degeneration in association with severe clinical disease. Cultured adult rodent (mouse and rat) dorsal root ganglion neurons infected with the challenge virus standard-11 (CVS) strain of rabies virus (RABV) showed axonal swellings and reduced axonal growth with evidence of oxidative stress. We have shown that CVS infection alters a variety of mitochondrial parameters and increases mitochondrial Complex I activity and reactive oxygen species (ROS) production.
Objective: To understand basic mechanisms important in rabies pathogenesis.
Materials and methods: We have studied interactions of the RABV and Complex I using immunoblotting, immunoprecipitation, and immunofluorescence. We have expressed rabies virus proteins in cells after transfection of plasmids, including alanine mutagenesis of the RABV phosphoprotein (P), and evaluated Complex I activity and ROS generation.
Results: RABV P was detected by immunoblotting in RABV-infected purified mitochondrial extracts and in Complex I immunoprecipitates from the extracts. A plasmid expressing P in cells increased Complex I activity and increased ROS generation, whereas expression of other RABV proteins did not. Expression of a peptide from amino acid 139–172 of the P increased Complex I activity and ROS generation similar to expression of the entire P protein. Mutational analysis suggests particular importance of the 157 to 169 region of P.
Conclusion: Rabies virus infection is a mitochondrial disorder initiated by interaction of the RABV P and Complex I. This information will be important for the future development of novel therapies for rabies.

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