[3] Cairns B, List T, Michelotti A, Ohrbach R, Svensson P. JOR-CORE recommendations on rehabilitation of temporomandibular disorders. Journal of Oral Rehabilitation 2010;37:481–9.

http://dx.doi.org/10.1016/j.sjpain.2012.05.012

HIV-associated painful polyneuropathy

Andrew S.C. Rice

Pain Research, Department of Surgery and Cancer, Imperial College, London, United Kingdom

According to WHO/UNAIDS data, there are approximately 33 million people in the world who are currently living with HIV, with the major burden of disease affecting low/middle resource communities in sub-Saharan Africa, Asia and South America. In the Scandinavian/Nordic countries, where there are effective infection prevention programmes and essentially full antiretroviral (ARV) drug access, there are ~24,000 people living with HIV (prevalence ~0.1–0.4%). A success story has been the advent of combined ARV therapy, which is now available to essentially all patients in wealthy countries and an increasing number of people in low and middle resource regions. This advance is converting HIV infection from a largely fatal disease (via the manifestations of AIDS), into a controlled chronic illness where people live relatively normal lives, and perhaps even normal life expectancies (although it is too early to tell), as a result of undetectable viral loads and lack of suppression of CD4 cell function. Therefore, a major issue in the management of people living with HIV is now the control of quality of life-limiting symptoms resulting from the manifestations of HIV infection which are either not suppressed by ARV therapy or occur as a result of the adverse effects of ARV drugs. Thus, although new infection rates may be decreasing, the increasing number of HIV positive people surviving by accessing effective ARV therapy implies an increasing healthcare burden.

Data from both high and poor resource settings indicates that HIV-associated peripheral sensory polyneuropathy (HIV-SN), usually accompanied by neuropathic pain, afflicts ~40% HIV positive people whose infection is otherwise well suppressed by ARV drugs. This makes HIV-SN one of the most prevalent manifestations of HIV infection in the ARV era and thus it will assume increasing healthcare importance as global access to ARVs continues to improve. Although, particularly in the context of AIDS, many, often exotic, mono- and poly-peripheral neuropathies have been described as being associated with HIV infection, HIV-SN is now by far the most prevalent. The broad banner of HIV-SN covers two aetiologically distinct, but clinically indistinguishable entities, originally called AIDS-Associated Sensory Neuropathy and ARV Toxic Neuropathy. However, since there are now clear data from a number of regions demonstrating that the incidence of HIV-SN has not decreased as less neurotoxic ARV drugs have been introduced, perhaps the importance of ARV Toxic Neuropathy in contributing to the clinical picture of HIV-SN may have been overestimated. The usual clinical presentation of HIV-SN is of a painful distal symmetrical sensory polyneuropathy characterised by a "die back" pattern of axonal degeneration, mainly of small fibres.

The lecture will commence with a brief summary of what is known about the prevalence of, risk factors for and clinical presentation of HIV-SN. This will be followed by a meta-analysis of analgesic clinical trials for HIV-SN, revealing an area of therapeutic need. Drugs that are effective for other forms of peripheral neuropathic pain, such as amitriptyline, gabapentin and pregabalin are not effective for pain relief in HIV-SN, although pregabalin does have efficacy for a subset of patients characterised by a pin prick hyperalgesia sensory profile. Cannabis is efficacious, although the barriers to this approach, particularly that of long term psychosis risk and legality preclude this as a routine therapy. Although the initial clinical trial of topical 8% capsaicin for HIV-SN indicated efficacy, this is now counterbalanced by a more recent study in which efficacy was not demonstrated. Surprisingly, despite their widespread use and guidelines promoting their use, opioids have not been adequately assessed for analgesic therapy in HIV-SN. The discussion will then move to what we have learned about the pathophysiology of HIV-SN from animal models. In particular, the role of the HIV glycoprotein GP120 will be discussed: although it was originally hypothesised that this was due to a direct interaction between GP120 and sensory neurones involving CCR5 and/or CxCR4 chemokine receptors, it is now apparent that an indirect GP120 driven processes via macrophages, Schwann cells and/or other non-neuronal intermediary cells predominates. The release of neurotoxic cytokines, such as TNF-α, appears to be a key intermediary step in GP120-induced axonal degeneration. Finally, identification of novel analgesic targets using gene microarrays of dorsal root ganglia harvested from animal models of HIV-SN will be briefly described.

Funding: Wellcome Trust (London Pain Consortium), Innovative Medicines Initiative – EUROPAIN (European Commission and selected EFPIA members) and Derek Butler Trust.

Recommended reading

[1] Wallace VCJ, et al. Characterisation of rodent models of HIV-gp120 and antiretroviral associated neuropathic pain. Brain 2007;130:2688–702.
[2] Wallace VCJ, et al. Pharmacological, behavioural and mechanistic analysis of HIV-1 gp120 induced painful neuropathy. Pain 2007;133:47–63.
[3] Maratou K, et al. Comparison of dorsal root ganglion gene expression in rat models of traumatic and HIV-associated neuropathic pain. European Journal of Pain 2009;13:398.
[4] Phillips TJC, et al. Painful HIV-associated sensory neuropathy. Pain: Clinical Updates 2010;XVIII:1–8.
[5] Phillips TJC, et al. Pharmacological treatment of painful HIV-associated sensory neuropathy: a systematic review and meta-analysis of randomised controlled trials. PLoS ONE 2010;5:e14433.

http://dx.doi.org/10.1016/j.sjpain.2012.05.013

Keynote: Neuronal and glial signalling in pain neuroplasticity

M.W. Salter

Neurosciences & Mental Health Program, Hospital for Sick Children, University of Toronto Centre for the Study of Pain, Toronto, Canada

A body of evidence has emerged indicating that pain behaviours resulting from injury to peripheral nerves are critically dependent upon interactions between neurons and glia in the dorsal horn of the spinal cord. Microglia have been found to play a causal role in neuropathic pain behaviours resulting from peripheral nerve injury, and specific neuron–microglia–neuron signalling pathways have been elucidated. Within the dorsal horn, microglia suppress neuronal inhibition by a sequence of steps involving activation of microglial P2X4 receptors causing the release of BDNF. BDNF acts on trkB receptors, which leads to a rise in intracellular chloride concentration in dorsal horn nociceptive output neurons, transforming the response properties of these neurons.

In addition to suppressed inhibition, evidence indicates that following nerve injury there is activity-dependent facilitation at dorsal horn glutamatergic synapses which enhances nociceptive transmission. This enhancement is mediated by intracellular signalling networks involving serine/threonine and tyrosine kinases within nociceptive transmission neurons. Key for this enhancement is facilitation of NMDA receptor function by the non-receptor tyrosine kinase Src. Src is anchored within the NMDA receptor complex by the protein ND2. Disrupting the ND2-Src interaction in vivo