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Central Post-stroke Pain and Pharmacological Treatment: Work in Progress

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Editorial

The International Association for the Study of Pain (IASP) defines central pain as "pain initiated or caused by a primary lesion or dysfunction of the central nervous system (CNS)" [1], at levels of spinal cord, brainstem or cerebral hemispheres. Central pain is less common in stroke than in other neurological diseases [2-4]. Central pain following stroke is a neuropathic chronic pain syndrome due to a post-stroke damage of CNS, resulting in anatomical, neurochemical, toxic, and inflammatory changes, causing an increase in neuronal excitability. Its frequency vary widely (8%–55%), reflecting small sample sizes, heterogeneous populations as well as differences in both study design, and chronic pain definition [3,5,6]. Central post-stroke pain can develops after both haemorrhagic and ischemic lesions occurring at any level of somato-sensory pathway of the brain, including medulla, thalamus, and cerebral cortex. Data from several studies indicate that the prevalence of central post-stroke pain is dependent on the location of the lesion, and occurrence is particularly high after lateral medullary infarction (or Wallenberg's syndrome) or lesions in the ventroposterior thalamus [5]. Many of these patients will fulfil the diagnostic criteria for neuropathic pain, despite the pain being of nociceptive origin. In these cases, might be difficult to identify a central neuropathic element to the hemiplegic shoulder pain, spasticity, or other musculoskeletal pain and, in some cases, several pain types might be present in the same area of the body. The clinical manifestations of central post-stroke pain resemble those of other central and peripheral neuropathic pain syndromes [3,5]. There are no pathognomonic features or uniform signs with regard to onset, presentation, and intensity [5], and the characteristics and descriptions of central post-stroke pain vary substantially between patients. The presence of allodynia, hyperalgesia, or dysesthesia in response to the sensory examination is a predictor of central post-stroke pain [7]. The pathophysiology of central post-stroke pain is not well understood even if lack of central inhibition, imbalance of stimuli and central sensitization has been suggested. Moreover, a decrease of GABAergic inhibition has been observed at cortical, thalamic and spinal levels. Incomplete understanding of mechanisms underlying central post-stroke pain makes the development of targeted treatment demanding [3,5]. Moreover, the lack of published data from large and/or well-designed clinical trials involving patients with central post-stroke pain has created a situation where treatment guidelines are based upon "uncontrolled studies, clinical experience and expert opinion" [3].

Usually, drugs used to treat central post-stroke pain are membrane stabilizers, aminergic agents, glutamate antagonists, GABA agonists, and N-type calcium channel blockers [5] suggesting that central post-stroke pain has a complex pathophysiology with neuro-pharmacological changes in different brain areas. In clinical practice, the treatment of patients with central post-stroke pain is often based on trial and error until pain relief is found, and the result is usually a combination of several drugs. There are only few randomised controlled studies on central post-stroke pain treatment [3,5], and there are no published trials on polytherapy for central post-stroke pain. Since short-term treatment is possible, the chronic treatment is very difficult. The drugs used in the management of post-stroke pain are antidepressants (tricyclic antidepressants, selective serotonin–norepinephrine-reuptake inhibitors) antiepileptic drugs (carbamazepine, lamotrigine, gabapentin,), opioids, with low benefit, lidocaine and propofol [3,5]. In a recent systematic review we summarised the results related to the use of antiepileptic drugs in central post-stroke pain reporting that the effectiveness of these drugs is still inadequate and conclusive evidences have not been published [3]. In contrast, tricyclic anti depressants and gabapentin or pregabalin could represent the first-choice, while selective serotonin–norepinephrine-reuptake inhibitors, lamotrigine, opioids, and drug combinations could be use when the first-line treatment fails. At present, there are no evidences for recommendations of preventive treatment [5].

Despite central post-stroke pain is a common, but underestimated, consequence of stroke, there are not clear diagnostic criteria that allow a differentiation of neuropathic pain from other types of pain in these patients. More carefully study designs addressing "when and how" to treat are needed. When clinicians prescribe drugs for central post-stroke pain, they

should consider the presence of polytherapy and comorbidity (e.g. physiologic changes and cognitive impairment). In elderly patients both pharmacokinetic and pharmacodynamic age-related changes were observed [3,8]. In fact, gastric secretion, blood volume, blood flow, and gastrointestinal motility are lower in elderly patients [3]. Cytochrome P450 enzyme complex, one of the main pathways for drug metabolism, loses about 10% of its functional capacity every 10 years from age 40 onward. However, there are no clinical parameters able to evaluate liver's ability to metabolize medications [3]. Likewise, kidney becomes smaller and its functional capacity is reduced as patients get older, so drug excretion is reduced [3]. Also the neuropsychological performance may worsen during a pharamacological treatment [3]. The lack of significant conclusive evidence lead to the necessity of prospective clinical trials to confirm the effectiveness of drugs in the central post-stroke pain and to better estimate the proportion of responders in larger groups of patients. In the future, a better understanding of the effects of above indicated drugs in the treatment of central post-stroke pain might be provided through an increased knowledge of the physiopathology of central post-stroke pain.

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