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LEADING ARTICLE

Perispinal Etanercept for Post-Stroke Neurological and Cognitive Dysfunction: Scientific Rationale and Current Evidence

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Abstract There is increasing recognition of the involvement of the immune signaling molecule, tumor necrosis factor (TNF), in the pathophysiology of stroke and chronic brain dysfunction. TNF plays an important role both in modulating synaptic function and in the pathogenesis of neuropathic pain. Etanercept is a recombinant therapeutic that neutralizes pathologic levels of TNF. Brain imaging has demonstrated chronic intracerebral microglial activation and neuroinflammation following stroke and other forms of acute brain injury. Activated microglia release TNF, which mediates neurotoxicity in the stroke penumbra. Recent observational studies have reported rapid and sustained improvement in chronic post-stroke neurological and cognitive dysfunction following perispinal administration of etanercept. The biological plausibility of these results is supported by independent evidence demonstrating reduction in cognitive dysfunction, neuropathic pain, and microglial activation following the use of etanercept, as well as multiple studies reporting improvement in stroke outcome and cognitive impairment following therapeutic strategies designed to inhibit TNF. The causal association between etanercept treatment and reduction in post-stroke disability satisfy all of the Bradford Hill Criteria: strength of the association; consistency; specificity; temporality; biological gradient; biological plausibility; coherence; experimental evidence; and analogy. Recognition that chronic microglial activation and pathologic TNF concentration are targets that may be therapeutically addressed for years following stroke and other forms of acute brain injury provides an exciting new direction for research and treatment.

Key Points

Accumulating evidence suggests that chronic post-stroke intracerebral microglial activation and neuroinflammation mediated by pathologic levels of tumor necrosis factor constitute new therapeutic targets that may persist for years after stroke.

Perispinal etanercept for chronic post-stroke neurological and cognitive dysfunction is an emerging treatment modality that may lead to rapid and sustained clinical improvement in this patient population.

1 Introduction

Post-stroke disability represents a major public health problem throughout the world [1, 2]. Current drug

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