



## Neurogenically Originated Inflammatory Response Syndrome: Role in the Neurocritical Patient

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The systemic inflammatory response syndrome (SIRS) consists of an inflammatory phenomenon as a response of the immune system against infections, as well as non-infectious injuries, which includes manifestations that affect multiple organs, among which hyperthermia or hypothermia, leukopenia or leukocytosis, tachycardia, and tachypnea. SIRS accompanies different acute brain and spinal cord injuries, including subarachnoid hemorrhage, intracerebral hemorrhage, spinal cord trauma, traumatic brain injury, and status epilepticus. We suggest a new term for this condition neurogenically originated systemic inflammatory response syndrome (NoSIRS). NIRS can be considered a new syndrome associated with pathological neurological conditions. However, more research is needed to figure out the true severity of this clinical picture and also figure out the best way to treat this condition.

**Keywords:** Systemic inflammatory response syndrome; Inflammation; Intracerebral hemorrhage; Head trauma; Spinal cord injuries; Epileptic status

### INTRODUCTION

Traditionally, the inflammatory response syndrome has been used as a concept to describe a generalized pathophysiological response to the entire body against a stimulus or injury such as infection, trauma, burns, and pancreatitis, among others. According to the consensus of the American College of Physicians Chest and the American Society for Critical Medicine published in 1992, the existence of two out of four criteria defines the process: temperature ( $36^{\circ}\text{C}$  or  $> 38^{\circ}\text{C}$ ), the white blood cell count ( $4000/\text{mm}^3$  or  $> 12,000/\text{mm}^3$ ), heart rate ( $> 90$  beats/minute) and respiratory

rate ( $> 20$  breaths/minute)<sup>1</sup>. This constellation of clinical manifestations reflects a systemic process associated with endothelial activation and dysfunction, which in turn alters tissue perfusion<sup>2</sup>. The overreaction causes tissue damage, organ dysfunction, and even organ failure, which makes the prognosis worse for patients<sup>1,3</sup>.

The systemic inflammatory response syndrome (SIRS) accompanies various forms of brain injury and acute spinal cord injury, including subarachnoid hemorrhage, ischemic cerebrovascular accident, intracerebral hemorrhage, brain trauma, and spinal cord injury. In the following review, the overview about the concept of

neurogenically originated systemic inflammatory response syndrome (NoSIRS) and the relationship between some forms of acute injury and the development of SIRS will be explained.

## THE CONCEPT OF NEUROGENICALLY ORIGINATED SIRS

As described above, SIRS is a syndrome characterized by symptomatic indications. If a patient has SIRS, the body's inflammatory response is stimulated. The effects of the responses quickly spread to the other organs. Typically, bloodstream chemicals, such as cytokines or hormones are constituting the delivery key<sup>3</sup>. However, the Brain is less impacted by SIRS due to its blood brain barrier system, which has a tight connection between the arterial lumen and brain parenchyma<sup>4</sup>. Therefore, the key molecules cannot cause brain inflammation. However, when the brain is harmed, an inflammatory response might be initiated. In cases of brain damage, the blood brain barrier is generally compromised. The systemic responses might be stimulated by central cytokines and white blood cells (microglia)<sup>3-5</sup>. Various subtypes of brain disease can be involved such as examples mentioned below. They sometimes make systematic inflammations, and this is called NoSIRS.

## SUBARACHNOID HEMORRHAGE

Subarachnoid hemorrhage (SAH) produces acute brain injury, secondary to both cerebral and systemic processes<sup>4</sup>. This phenomenon gives rise not only to a local inflammatory response propagated by blood degradation but also to a state of systemic inflammation as a result of the action of released cytokines or the release of high amounts of catecholamines into the circulation that promote activation of the immunological process<sup>5</sup>. Clinically identified SIRS occurs in the acute phase after SAH as the manifestation of the systemic inflammatory process, with non-infectious inflammation manifesting mainly with hyperthermia and leukocytosis. The presentation of SIRS is related to mortality and morbidity rates in patients with SAH. Having SIRS criteria increases the risk of intracranial and systemic problems, such as vasospasm and hydrocephalus, as well as other health problems<sup>6</sup>.

Patients with SAH will develop SIRS in more than half of the cases, with prevalences of 29% to 89% of patients<sup>6-8</sup>, without relationship to the method chosen for the treatment of the aneurysm<sup>7,8</sup>. The intimate connection between the brain and the heart through vessels and nerves means that once brain damage occurs after SAH, sympathetic dysfunction can contribute to cardiac arrhythmias, generating the release of cytokines that enter the circulation<sup>8</sup>, which, by interacting with the modified vascular markers

released after the rupture of the aneurysm, perpetuate brain inflammation<sup>9</sup>. Similarly, activated neutrophils in the peripheral circulation can damage microvessels in the brain<sup>10</sup>. Leukocyte diapedesis can happen through damaged microvessels after an injury, allowing immune cells from the outside to move into the cerebrospinal fluid and brain<sup>11</sup>.

Patients with SAH exhibit greater serum tiers of interleukin-6 (IL-6) and C-reactive protein, with larger peaks related to late cerebral ischemia<sup>12</sup>. Similarly, it has been found that SIRS not only promotes extracerebral organ dysfunction, exacerbating late cerebral ischemia, thus contributing to a worse prognosis, but also acute lung injury<sup>8,13</sup>. The rising level of acute-phase proteins, like C-reactive protein, is related to active vasospasm. This is also true if there is a diversion device in place to keep an eye on the output of cerebrospinal fluid. Contraction band necrosis, one of the hallmarks of neurogenic cardiac dysfunction, is seen due to marked catecholamines surge with high-grade SAH. One of the presentations of high-grade SAH can be sudden cardiac arrest, resistant to resuscitative measures, and significantly poor prognosis<sup>2</sup>.

## INTRACEREBRAL HEMORRHAGE

Intracerebral hemorrhage (ICH) represents the main cause of mortality and morbidity in patients with stroke, with a poor prognosis. However, it is important to know that this will depend on factors such as the severity of the bleeding observed clinically and radiologically, the age of the patient, the previous use of anticoagulants, and superimposed infections, as well as the neuroinflammatory processes that are triggered in this type of affection. In the same way, strokes can cause initial inflammation, which can lead to future problems caused by reperfusion<sup>14,15</sup>. These problems can also have an impact on both morbidity and mortality.

Patients with early ICH produce cytokine activation as a protective mechanism that results in a systemic inflammatory response that is characterized by the absence of infection and the presence of two or more of the following: hypothermia or hyperthermia; leukocytosis; or leukopenia; tachycardia; or tachypnea; which are associated with worsening of the patient's prognosis. Boehme et al. established the association between SIRS and intracranial hemorrhage in patient prognosis, finding that 20% of their population developed SIRS, with a worse prognosis<sup>16</sup>.

High levels of C-reactive protein correlate with inflammatory responses to a traumatic event or infection. Increased levels have been linked to a poorer prognosis and an increased risk of mortality in patients with brain injury. When Lopponen et al. looked at people who had intracranial trauma, they found that people who had high levels of C-reactive protein when they first got hurt were

more likely to have a bad outcome. They also said that this high level wasn't linked to other diseases or infections<sup>15</sup>.

## STATUS EPILEPTICUS

Status epilepticus (SE) is a life-threatening neurological emergency that requires early anticonvulsant treatment as well as determination of the causative etiology. There is evidence, mainly in animal models, that the noninfectious inflammation that occurs may be a consequence of the prolonged seizure, and the exacerbated inflammation could be the cause of it<sup>17</sup>. Other studies based on procalcitonin and albumin levels have shown an association with SE morbidity<sup>18</sup>. It has been found that about half of the people who have SE have SIRS, and this is a risk factor for drug resistance and death<sup>19</sup>.

## SPINAL CORD INJURY

In any spinal cord injury (SCI), considerable damage is generated that is represented by physical disabilities, which are established by spinal cord compression, decreased local blood flow, or intraspinal hemorrhage. Any of these phenomena generate mechanisms of neurodegeneration, gliosis, and inflammation, favoring the establishment of an inflammatory environment with the collection of degenerating neurons and activated glial cells, which, at the same time, favors the activation of different pro-inflammatory mediators with the possibility of triggering SIRS<sup>20</sup>. SIRS may cause pneumonia, deep vein thrombosis, urinary tract infections, emboli, and sepsis in these individuals. Kesani et al. demonstrated that patients with severe SCI who present with criteria for SIRS have more complications, longer hospital stays, and worse prognosis<sup>21</sup>.

## TRAUMATIC BRAIN INJURY

Traumatic Brain Injury (TBI) is an intracranial injury as a result of an external force against the head that exceeds the protective mechanisms of the brain and the cranial vault<sup>22</sup>. It might be acute or chronic, local or widespread, mild, moderate, or severe<sup>22,23</sup>. The severity can be judged with the Glasgow Coma Scale, which plays a fundamental role due to its ease of use and reproducibility in clinical practice<sup>24</sup>. Neurological trauma is a serious health problem throughout the world, and it is a complex process that involves a wide spectrum of symptoms and long-term consequences, including disabilities<sup>25</sup>. It has recently been found that neuroinflammatory processes play a role in the pathophysiology of trauma in the central nervous system<sup>26</sup>.

Once the brain receives a mechanical insult, a series of short-

term and long-term processes begin to affect the central nervous system (CNS)<sup>25</sup>. The initial contusion produces damage by shearing, tearing, and/or stretching of neurons, their axons, glia, and blood vessels (forming hematomas)<sup>22,25</sup>. This is known as a primary lesion, and it can be focal, diffuse, or a combination of both. In most cases, any type of primary injury induced by trauma leads to neuronal loss<sup>22</sup>. The primary injury triggers a second wave of biochemical mediators that produce cellular and metabolic changes. This may happen seconds or minutes after trauma and persist for days, months, or years. This secondary injury is mainly located at the site of the trauma and the surrounding tissue<sup>23</sup>. This mechanism causes excitotoxicity, oxidative stress, mitochondrial dysfunction, blood-brain barrier disruption, and neuroinflammation<sup>22,25,27</sup>.

Neuroinflammation plays a fundamental role in the damage produced after neurological trauma. This concept refers to any inflammatory process located in the central nervous system and includes the activation of immune cells (particularly glia) and non-immune cells, as well as the release of inflammatory mediators such as cytokines<sup>26</sup>. After the insult, there is a massive release of excitatory neurotransmitters, mainly glutamate, which interacts with neurons and astrocytes, causing an increase in the flow of  $\text{Na}^+$ ,  $\text{Ca}^{2+}$ , and  $\text{K}^{+}$  ions (excitotoxicity)<sup>22,25</sup>. A catabolic reaction occurs, and the blood-brain barrier is altered. An injured blood-brain barrier allows the passage of pro-inflammatory molecules into and out of the CNS. The release of mediators into the circulation can manifest clinically as SIRS with possible involvement of other organs<sup>28</sup>. The complex nature of both acute and chronic inflammatory reactions could aggravate the pathological outcome or promote the repair process. On the other hand, multiorgan damage in some polytraumatized patients could be increased by mediators in the circulation and this could also contribute to neurological pathology<sup>25</sup>.

## ACUTE PULMONARY INJURY

The pathophysiology of acute pulmonary injury (API) in the setting of acute brain insult is complex. Studies demonstrated that API was prevalent in individuals with elevated intracranial pressure in contrast to cerebral perfusion pressure after brain insult<sup>29,30</sup>. The crucial landmark of these studies is that API developed on top of normal apparent lungs on a chest x-ray at admission, explaining that brain insult was the contributing factor. Capillary pressures rise in the lung bed, endothelial deterioration occurs, and capillary leakage into the alveoli and pulmonary interstitial occurs in response to adrenergic surge<sup>31</sup>. Also, inflammatory mediators like IL-6 may contribute to API development<sup>32,33</sup>. To this aim, an “adrenergic surge” and systemic generation of inflammatory mediators have been proposed as a “double hit” paradigm<sup>34</sup>.

The function of mechanical ventilation in API is well-known. Hyperventilation for permissive hypocapnia may cause substantial lung harm<sup>35</sup>. With tidal volumes larger than 6–8 ml/kg, modest permissive hypocapnia (30–35 mmHg) may be achieved without risking ventilator-induced lung damage<sup>36</sup>.

Thus, pulmonary injury with a capillary leak, high pressures on the ventilator, pneumonia, and neurogenic pulmonary edema are part of this systemic process<sup>37</sup>. The pulmonary relationship with acute brain injury is better explained by improvement in pulmonary mechanics with improvement in acute brain injury<sup>38</sup>.

## CONCLUSION

The various neurological pathologies can be a potential source of proinflammatory biochemical mediators, which, when released into the systemic circulation, can constitute SIRS. NoSIRS can therefore be considered a new syndrome associated with pathological neurological conditions. However, future research is required to study the true severity of this clinical picture and also establish the ideal management for this disease.

## NOTES

### CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

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