

## Hyper acute reversible encephalopathy related to cytokine storm following influenza vaccine

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**Background:** As the worldwide mass vaccination is fully operational, the reports of accidentally related or causally linked neurological complications are also arising. It is essential, as we await solid epidemiological evidence, to pay meticulous attention to neurologic disorders timely related to vaccines. Cytokine storm-associated encephalopathy (CySE) has been described as a distinct clinical condition whose biological underpinnings have not been wholly unveiled.

**Case report:** A 59-year-old previously healthy male presented to the ED for confusion and single episode of epilepsy. A week earlier, he received influenza vaccine. At admission, he was extremely agitated, needing intravenous sedation, and he presented fever (T = 39.0°C) without meningeal irritation or neurological focal signs. Diagnostic tests including brain contrast-enhanced CT scan, MRI, nasopharyngeal SARS-CoV-2 swabs and lumbar puncture resulted unremarkable except for slightly increased CRP and increase of CSF and serum IL-6. On the 3<sup>rd</sup> day, after hydration, steroids and empirical antibiotic therapy, the patient presented a complete recovery with normal mental status, though amnesic for the previous 72 hours. An EEG on the 5<sup>th</sup> day and serum levels of IL-6 on the 8<sup>th</sup> day was normal. The patient was discharged at 10<sup>th</sup> day in good clinical conditions.

**Discussion:** The acute onset after vaccination in absence of other documented etiologies, the overproduction of intrathecal

Neuroinflammatory mediators, the downward trend of cytokines and the prompt recovery after corticosteroid therapy, seem the typical picture of a brain dysfunction associated to cytokine storm. Recently, a unifying definition of cytokine storm-associated encephalopathy (CySE) was proposed. The cytokine storm umbrella encompasses several disorders at the intersection of Hematology, oncology, rheumatology and virology, but it has not described a relationship with influenza vaccination. This phenomenon is characterized by a dysregulated immune response to various triggers and is defined by elevated circulating cytokine levels, acute systemic inflammatory symptoms, and secondary organ dysfunction, including the brain. Activated macrophages and monocytes appear to be responsible for the pathological hyper inflammation, regardless of the triggers. Peripheral inflammation may lead to endothelial activation and blood-brain barrier (BBB) disruption, resulting in microglia and astrocyte activation. This induces a Neuroinflammatory process that promotes CNS cytokine production, oxidative stress, and immune-cell trafficking, further contributing to BBB disruption, resulting in a vicious circle.

**Conclusion:** We documented the first hyper acute reversible encephalopathy following influenza vaccination, suggesting cytokine storm as its causative mechanism, and highlighting the need to deepen our knowledge on this immune-mediated phenomenon.