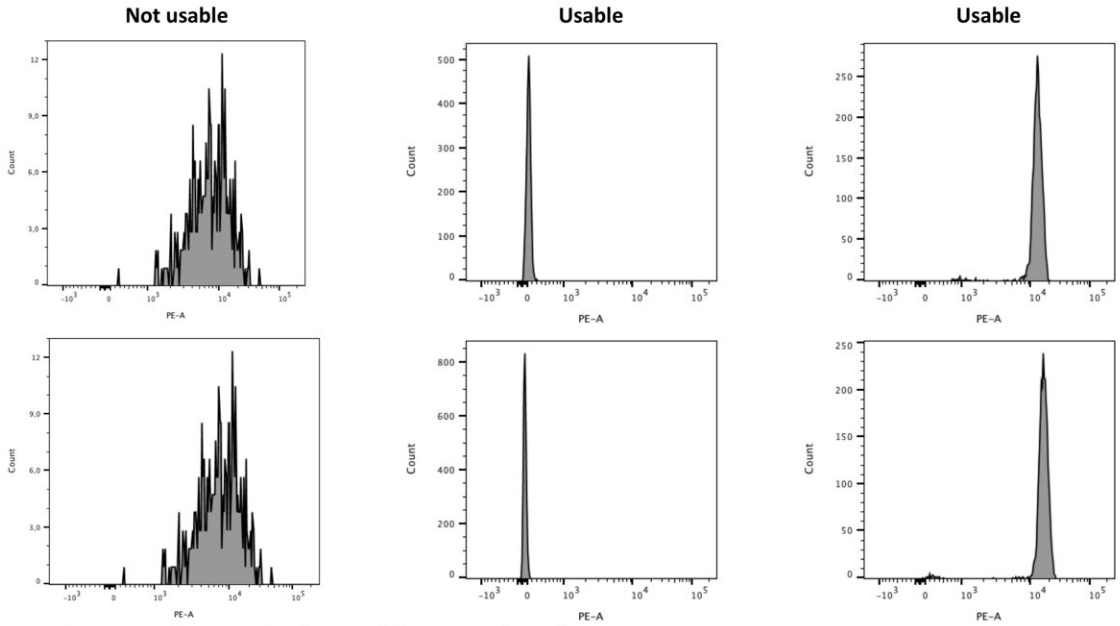
Status epilepticus: New inflammatory markers to improve patient care

March 31 2023



Supplementary Figure 1: Visual control about sample quality
PE fluorescent signal obtained with the multiplexed fluorescent bead-based immunoassay detection

Visual control about sample quality. Credit: *Annals of Neurology* (2023). DOI: 10.1002/ana.26627

A rare and nevertheless formidable event in the landscape of epilepsies, new-onset refractory status epilepticus (NORSE) is a form of prolonged seizure in which the neurons of the epileptic focus endure a continuous discharge of neurotransmitters.

It is a medical emergency requiring intensive care management. Indeed, it can cause significant long-term neurological sequelae and is associated with an average mortality rate of 12% in children and 16 to 27% in adults. NORSE can occur in response to an infection or tumor development. However, its origin remains unknown in half of the affected patients despite extensive clinical and biological examinations.

"Currently, there is no consensus on the best therapeutic options for patient care," explains Vincent Navarro, head of the Cellular Excitability and Neuronal Network Dynamics team at Paris Brain Institute. "Understanding the pathophysiological mechanisms in NORSE is crucial to intervene early with the most appropriate treatment, hoping to prevent neuronal damage related to status epilepticus. At the moment, patients are empirically treated with immunotherapies to reduce inflammation. But this recommendation is not based on solid scientific evidence."

The first-ever large-scale study on NORSE

Identifying prognostic markers for the disease proved difficult because NORSE is rare and highly heterogeneous. To overcome this lack of data, Aurélie Hanin, a postdoctoral fellow, together with Vincent Navarro's team at the Brain Institute and Lawrence Hirsch's team at Yale University, recruited a cohort of 61 NORSE patients hospitalized in the United States, Canada, and La Pitié-Salpêtrière Hospital (AP-HP). Among them, 51 had cryptogenic NORSE, in which the cause of status epilepticus was not found.

The researchers assessed the patient's clinical status right after they had been discharged from ICU, then after 12 months, and looked for inflammatory markers in the blood and cerebrospinal fluid. The same data was collected on a cohort of 37 patients with status epilepticus of known cause and 52 control patients.

"Our results show that the concentration of several cytokines—small proteins that attract inflammation cells—was higher in patients with status epilepticus than controls, Aurélie Hanin explains. Moreover, in subjects with an unknown cause of NORSE, the increase in cytokines related to innate immunity—CXCL-8/IL-8, CCL2, and MIP-1α—was correlated with poor short-term and long-term prognosis."

Perspectives for patient care

These results suggest that an innate immunity disturbance is involved in the onset of NORSE and its long-term consequences. They also confirm the interest in anti-inflammatory therapeutic strategies targeting one or more cytokines in these patients.

"In the long run, quantifying and analyzing cytokines upon arrival in the ICU could give us a better understanding of the inflammatory state of NORSE patients and provide essential information support for the choice of specific immunomodulatory treatments, Aurélie Hanin says. One of this study's major challenges was determining whether the increase in cytokines resulted from prolonged epileptic seizures or was directly related to a specific immune abnormality in NORSE. Now, we know that the latter hypothesis is more likely."

Further research will confirm that cytokines are promising biomarkers for NORSE—both for establishing the diagnosis, monitoring the patient's condition, and estimating neurological recovery capabilities after intensive care.

The paper is published in the journal *Annals of Neurology*.

More information: Aurélie Hanin et al, Cytokines in New-Onset Refractory Status Epilepticus Predict Outcomes, *Annals of Neurology* (2023). DOI: 10.1002/ana.26627

Provided by Institut du Cerveau (Paris Brain Institute)