Reply to the article entitled “International consensus recommendations for management of new onset refractory status epilepticus (NORSE) including febrile infection-related epilepsy syndrome (FIRES): Summary and clinical tools”. Doi: 10.1111/epi.17391

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Dear Editor, NORSE/FIRES cases are a riddle for epileptologist. In fact, since the first description in 2005 where the acronym was created, many case reports and literature revision have been made in order to identify clear etio-pathological triggers and to hypothesize newer more effective and specific therapy but the relative rarity of these cases makes difficult the construction of prospective large studies.

We recently read with much interest the “International consensus recommendations for management of New Onset Refractory Status Epilepticus (NORSE) including Febrile Infection-Related Epilepsy Syndrome (FIRES): Summary and Clinical Tools” published on the number 63 of Epilepsia in August 2022 [1]. Although we really appreciated the concept of “saving time and brain” contained in the recommendation of a quick introduction of immunomodulant therapy, we would like to bring out some issues about the immunological ladder actually suggested by the literature in order to open a scientific discussion.

In particular we take advantage by the revision of a recent treated case, a 19 years old man affected by FIRES, transferred from a peripheral hospital to our institute on the 5th day of status epilepticus. The onset of seizures occurred on Thursday (D1), preceded by fever in the previous 2 days. On Friday (D2) CSF was done with evidence of slight lymphocytic pleocytosis. Negative viral PCR was known only 3 days later (D5). The patient was sent to our hospital, which a referral center for treatment of refractory status epilepticus (with availability of a neurocritical unit with 24 hours continuous EEG recording). The same day (D5) blood and CSF tests were repeated in order to search for antibodies against onconeural or neuronal cell-surface proteins, to exclude haematological diseases and mitochondrial pathologies and to measure interleukin 6 and 8. We also started corticosteroids at high dose, unfortunately without any results. We subsequently tried a triplet of apheresis and finally IVIg and on the 21st day from the onset of status we administered cyclophosphamide, waiting for local agency approval of tocilizumab therapy. Ten days after leukopenia reached its nadir seizures disappeared allowing the gradual elimination of anesthetic drugs. The patient recovered completely in following weeks.

As shown by this case, we followed the recommendation to begin a first line immunological therapy as soon as possible, without having any results. Unfortunately, the ineffectiveness of these immunological therapy is extremely widespread in literature. We wonder whether it makes sense to begin with a first line immunological treatment, in particular with corticosteroids when current literature is devoid from evidence to support it.

Corticosteroids at high dosage are well known to potentially induce severe side effects, especially in mechanically ventilated patients and their use need to be confined to real and ascertained indications.

As correctly argued by the Authors, NORSE/FIRES diagnosis is actually often founded on exclusion criteria more than in the demonstration of an etiology and the medical tests suggested in the paper require more than a week to get a response, even in a third line care center. The risk is to “specifically/generically” treat the very different NORSE/FIRES entities in order to spare time without thinking about iatrogenic complications, when instead a better delineation of the immunological picture of the patient would avoid useless therapy and point out a more specific immunological treatment (i.e., Rituximab in case of NMDA-NORSE). In particular, if specific tests turned out to...
be negative, confirming the diagnosis of cryptogenic FIRES/NORSE, the old-fashioned option of cyclophosphamide might be an eligible suggestion. Beyond being a low cost, easily procurable and well-known therapy, it has been demonstrated significantly useful at least in cryptogenic NORSE if used before 21 days since the status epilepticus onset [2].

Furthermore, despite a known slight risk of acquired sterility for doses suggested, it offer also the possibility to measure the time of the response which is superimposable to the time of achievement of blood leukopenia.

In conclusion we would like to suggest a possible role of a direct “second” line treatment as “first” option in NORSE/FIRES cases, in order to spare time in a rare disease burdened by high rate of mortality.

Conflict of Interest: None

References