■ Clinical commentary

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Epileptic Disorders

Super-refractory status epilepticus in autoimmune encephalitis treated with interleukin-1 receptor antagonist, anakinra

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ABSTRACT – Autoimmune encephalitis is increasingly recognised as a major cause of new-onset refractory status epilepticus. Early immunotherapy with agents such as methylprednisolone is recommended. Anakinra is an interleukin-1 receptor antagonist used for various inflammatory disorders. It has been used successfully in the treatment of febrile infection-related epilepsy syndrome in children and in one adult case. In this case report, we describe a case of super-refractory status epilepticus in a 38-year-old female due to autoimmune encephalitis who was treated successfully with anakinra after 16 weeks of therapeutic coma and failing multiple immunotherapies. Despite a prolonged period of therapeutic coma, this patient made a reasonable recovery with effective communication and ability to walk with assistance upon discharge. We propose that the successful treatment with anakinra in our case could be due to elevated inflammatory cytokines in the pathogenesis of autoimmune encephalitis, although we acknowledge that interleukin levels were unfortunately not available. We conclude that anakinra can be a valuable alternative option in patients with autoimmune encephalitis refractory to conventional immunotherapies.

Key words: super-refractory status epilepticus; autoimmune encephalitis; temporal mesial; anakinra

Limbic encephalitis was first described in 1960, characterised by a constellation of subacute onset of episodic memory loss, change in mental state and frequent seizures, with a predominant lesion in the medial temporal lobe and hippocampus [1]. Even though autoimmune encephalitis is not as rare as stipulated in the past, clinical experience is still limited and treatment is often challenging. Methylprednisolone, intravenous immunoglobulin and plasma exchange are considered first-line immunotherapy, while rituximab and cyclophosphamide are considered second-line [2]. Alternative agents such as tocilizumab, low-dose interleukin-2 therapy and bortezomib have been reported for the treatment of autoimmune encephalitis [2].

In patients with new-onset refractory status epilepticus (NORSE), autoimmune and paraneoplastic encephalitis are the most commonly identified causes [3]. Early immunotherapy is recommended as delayed treatment may contribute to worse outcome [4]. Besides rituximab and cyclophosphamide, anakinra, cannabidiol and the ketogenic diet are also suggested as second-line immunotherapy (expert opinions) in cases of cryptogenic NORSE [4].

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Anakinra is a recombinant interleukin-1 receptor antagonist (IL-1Ra) used for the treatment of various disorders, ranging from common diseases such as gouty arthritis to rare genetic disorders such as familial Mediterranean fever and cyropyrin-associated periodic syndrome [5]. In the past few years, anakinra has been used successfully for the treatment of febrile infection-related epilepsy syndrome (FIRES) in children as well as a 21-year-old female diagnosed with FIRES, published in 2019 [6-10]. We hereby present a case of super-refractory status epilepticus (SRSE) due to limbic encephalitis resistant to multiple immunotherapeutic agents, who was successfully treated with anakinra after 16 weeks of therapeutic coma. To the best of our knowledge, this is the second reported adult case with SRSE treated successfully with anakinra (the first being the aforementioned 21-year-old female with FIRES in whom the authors considered FIRES as the primary diagnosis rather than autoimmune encephalitis), and the first reported case of autoimmune limbic encephalitis with SRSE.

Case study

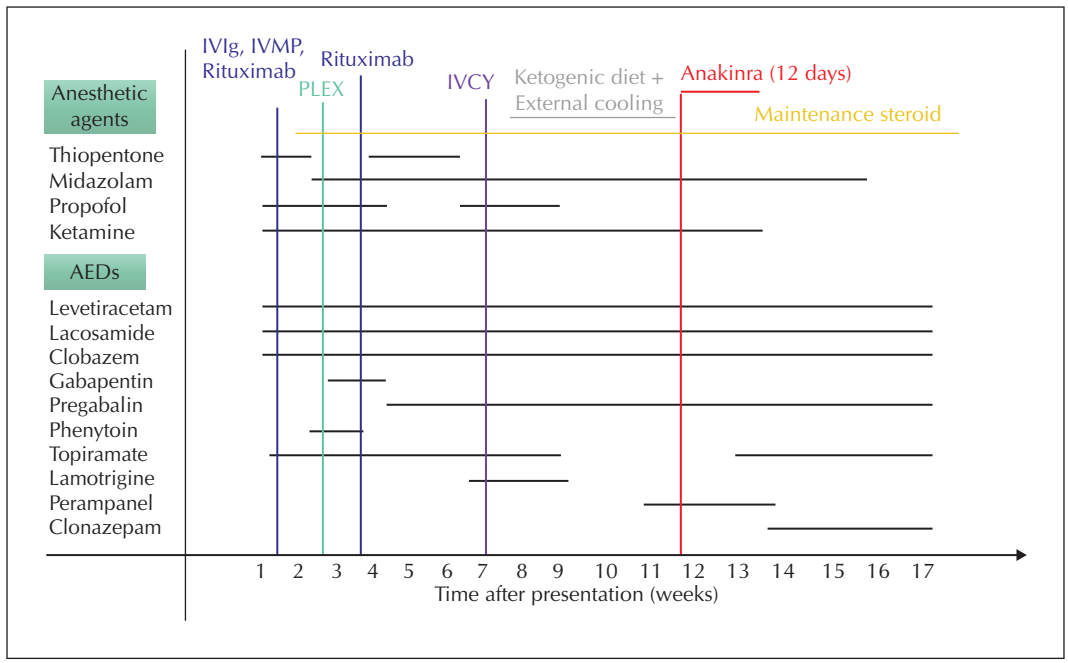
This patient was admitted to our hospital with new-onset refractory status epilepticus. The patient was a 38-year-old female with two children, with unremarkable past medical history and negative family history for neurological conditions. She presented with subacute onset of confusion and repeated generalized tonic-clonic seizures following one week of upper respiratory tract symptoms. General examination did not reveal focal neurological signs except for fever upon presentation. Status epilepticus was diagnosed when her seizure failed to be aborted by intravenous lorazepam and phenytoin. Tracheal intubation was performed for airway protection and she was directly transferred to the intensive care unit.

Shortly after admission, the patient required multiple general anaesthetic agents including thiopentone, propofol and ketamine for seizure control, inducing burst suppression on EEG monitoring. Empirical rocephin and acyclovir were started for possible central nervous system infection. Multiple antiepileptic drugs (AEDs) were also started. An overview of the treatment timeline is illustrated in *figure 1*.

Initial investigations

Routine laboratory blood tests were remarkable only for mildly elevated alanine transaminase (ALT). Infectious workup was also unremarkable.

Lumbar puncture was performed for CSF analysis which showed a white cell count of 3 10^6/L, a mildly elevated total protein level 0.95 g/L and normal



■ **Figure 1.** Treatment timeline up to discharge from the intensive care unit.
IVIg: intravenous immunoglobulin; IVMP: intravenous methylprednisolone; PLEX: plasma exchange.

glucose level. Bacterial culture, acid fast bacilli culture, and virology were all unremarkable. Urine toxicology screening revealed no possible culprit.
Non-contrast-enhanced brain CT and initial contrast-enhanced brain MRI performed on Day 2 of admission were unremarkable.

Management progress

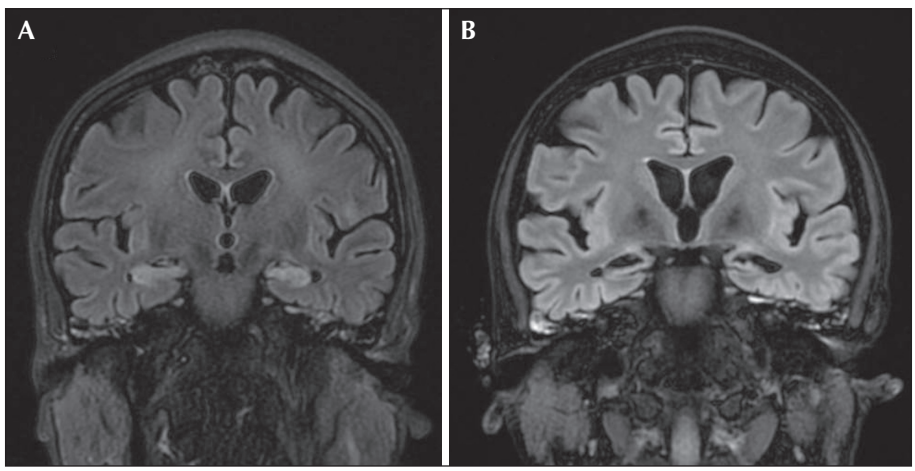
SRSE was diagnosed when seizures recurred upon an attempt to wean off anaesthetic agents at 24 hours after initiation. Early immunotherapy was initiated with intravenous immunoglobulins (1 g/kg over five days) on Day 1 of admission for presumed autoimmune encephalitis. Intravenous methylprednisolone (1 g daily for five days) was subsequently started on Day 3 of admission, followed by rituximab on Day 4 given the over-whelming course of disease.
The choice of AEDs was limited by recurrent abnormal liver function tests (ALT in the range of 150-200 IU/L; 3-4-fold higher than the upper normal limit) which was deemed to be most likely drug related after extensive investigations and assessment by the hepatologist.
While waiting for a second dose of rituximab, another attempt to wean off the anaesthetic agent was unsuccessful with recurrence of clinical and electrographic seizures. Five sessions of plasma exchange were thus performed.

Further investigations

A second round of contrast-enhanced brain MRI on Day 38 (*figure 2A*) showed increased T2/FLAIR signal intensity over bilateral mesial temporal regions, substantiating the presumed diagnosis of autoimmune limbic encephalitis.
Contrast-enhanced whole-body CT was negative for occult tumour (as PET/CT was not available in our centre), as were tumour markers. Autoimmune markers were only positive for anti-nuclear antibody and anti-Ro antibody. Complement levels were normal. No other auto-antibodies were detected and there were no clinical or laboratory findings suggestive of an underlying rheumatological disease.
Anti-neuronal antibody detection was unrevealing, including negative anti-NMDA-R antibody in both serum and CSF, negative anti-AQP4 antibody in serum, and negative antibody panels (provided by Mayo Clinic Laboratories and by another local institute) in serum (*table 1*), performed after two days of IVIg.

Management progress

Repeated attempts of weaning off anaesthetic agents were unsuccessful. EEGs recorded upon one attempt are shown in *figure 3A-E*, demonstrating evolution of 3-3.5-Hz spikes from a burst suppression background. Further treatments with cyclophosphamide, the ketogenic diet and external cooling were of limited success. The patient was tracheostomised for prolonged intubation. A third round of brain MRI demonstrated reduced T2/FLAIR signal intensity and development of bilateral mesial temporal atrophy (*figure 2B*).
The patient's clinical course was complicated by recurrent episodes of septicaemia, a large infected sacral sore requiring repeat debridement, pneumonia requiring a ventilator, right iliac vein thrombosis treated with anti-coagulation, and lamotrgine-related skin eruption.



■ **Figure 2.** (A) Coronal FLAIR MRI on Day 38 of presentation demonstrating increased T2/FLAIR signal intensity over bilateral mesial temporal regions. (B) Coronal FLAIR MRI on Day 80 of presentation demonstrating resolution of the increased T2/FLAIR signal intensity and development of bilateral mesial temporal sclerosis/atrophy.

▼ **Table 1.** Anti-neuronal antibody panels.

1. Anti-neuronal antibody panel by the Mayo Clinic Laboratories
- AChR ganglionic neuronal Ab, AMPA-RAb , Amphiphysin Ab, AGNA-1, ANNA-1, ANNA-2, ANNA-3, CASPR2-lgG, CRMP-5 lgG, DPPXAb, GABA-B-RAb , GAD65 Ab, GFAP, LGl1-lgG, mGluR1 Ab, NMDA-RAb, N-Type calcium channel Ab, P/Q type calcium channel, PCA-1, PCA-2 and PCA-Tr
2. Anti-neuronal antibody panel by another local institute
- CASPR2 LGl1 AMPAR 1/2 DPPX GABAR B1/B2

Treatment with anakinra and successful weaning off anaesthetic agents

Four weeks after the first dose of cyclophophamide, treatment options including a second cycle of cyclophophamide, tocilizumab and anakinra were discussed with the patient's family members. Taking into account the profile of side effects, infection risks and costs, anakinra was chosen as the next step. A two-week course of anakinra (100 mg daily) was administered subcuntaneously at the 12th week of admission when the patient was still sedated with ketamine and midazolam infusion. The last two doses of anakinra were suspended due to recurrent fever.

■ **Figure 3.** (A-E) EEGs upon an attempt to wean the patient off general anaesthetic agents, demonstrating evolution of 3-3.5-Hz spikes from a burst suppression background. (F) EEG after completion of anakinra, demonstrating a more organised background without interictal discharges.

We managed to wean the patient off ketamine infusion, approaching the end of the course of anakinra. Two weeks afterwards, midazolam infusion was also slowly weaned off successfully without recurrence of status epilepticus. A subsequent EEG demonstrated a more organised background without interictal discharges (*figure 3F*).

The patient was subsequently discharged from the intensive care unit to the neurology unit after 16 weeks of therapeutic coma. She underwent further sacral wound care, medication titration and intensive rehablitation. She was weaned off trachostomy and the feeding tube. There was no recurrence of SE although she developed refractory epilepsy. She was discharged from hospital six months later with maintenance prednisolone at 7.5 mg daily and multiple AEDs (including pregabalin at 225 mg twice a day, topiramate at 50 mg twice a day, clobazam at 20 mg twice a day, lacosamide at 100 mg twice a day, and levetiracetam at 1,500 mg twice a day). After a prolonged course of rehabilitation, she managed to walk with assistance upon discharge and had effective communication, albeit with cognitive impairment.

Upon follow-up in the clinic, one month post discharge, the patient had improved mobility with continual out-patient rehabilitation.

Discussion

We describe a previously healthy 38-year-old female who developed SRSE due to autoimmune encephalitis. In hindsight, her disease course fulfilled the diagnostic criteria for definite autoimmune limbic encephalitis with new-onset refractory seizures, T2/FLAIR abnormalities restricted to bilateral temporal lobes and epileptiform discharges involving temporal regions, although no auto-antibody was identified despite two separate antibody panels [11]. We acknowledge the fact that the nosology of this case report may also fall under the clinical presentation of FIRES, but this does not contradict the prevailing diagnosis of autoimmune encephalitis [12]. After multiple treatment failures, the patient responded to anakinra with successful weaning off all anaesthetic agents within two weeks after completion of anakinra. Although it is arguable that her improvement could have been due to the delayed effect of prior immunotherapies, treatment response to anakinra was more compelling given the temporal relationship from initiation of anakinra to termination of SRSE. Measurements of inflammatory cytokines in serum and CSF might have been of value if these had been available.

The role of inflammatory cytokines, particularly IL-1β, and the innate immune system in the pathogenesis of central nervous system autoimmunity has been increasingly recognised [13, 14]. We propose that the therapeutic response in our case was due to elevation of pro-inflammatory cytokines, particularly IL-1β, in the pathogenesis of autoimmune encephalitis which is targeted specifically by anakinra and less so by the other preceding immunomodulatory therapies. The successful treatment of autoimmune encephalitis with SRSE by anakinra in this patient suggests that anakinra could be a valuable alternative treatment option in adult cases of autoimmune encephalitis with or without SRSE.

Conclusion

We herein present this adult case of NORSE due to autoimmune encephalitis whose seizures failed to respond to all conventional immunotherapies, but were successfully treated with a 12-day course of anakinra. She managed to walk with assistance and have effective communication after a very long duration of therapeutic coma. Given its well-established safety profile [5], anakinra may be considered for patients with autoimmune encephalitis refractory to conventional immunotherapies. ■

Supplementary material.
Summary slides accompanying the manuscript are available at www.epilepticdisorders.com.

Disclosures.
None of the authors have any conflicts of interest to declare.

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TEST YOURSELF

(1) What is the diagnostic criterion for super-refractory status epilepticus?

(2) What are the diagnostic criteria for possible autoimmune encephalitis?

(3) What are the first-line treatments for autoimmune encephalitis?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".