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Frontal Intermittent Rhythmic Delta Activity Is a Useful Diagnostic Tool of Neurotoxicity After CAR T-Cell Infusion

Sophie Huby, MD, Philippe Gelisse, MD, Jean-Jacques Tudesq, MD, Pierre Labauge, MD, PhD, Claire Duflos, MD, Guillaume Cartron, MD, PHD, Marc-Antoine Gallerand, MD, Laura Platon, MD, Stephanie Badiou, MD, Sylvain Lamure, MD, Nicolas Menjot de Champfleu, MD, PHD, Xavier Ayrygnac, MD, PHD,* and Guillaume Taieb, MD*

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Abstract

Background and Objectives

Chimeric antigen receptor (CAR) T-cell therapies have dramatically improved the prognosis of patients with relapsed or refractory hematologic malignancies; however, cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome (ICANS) occur in ~100 and 50% of patients, respectively. This study aimed to determine whether EEG patterns may be considered as diagnostic tools for ICANS.

Methods

Patients who received CAR T-cell therapy at Montpellier University Hospital between September 2020 and July 2021 were prospectively enrolled. Neurologic signs/symptoms and laboratory parameters were monitored daily for 14 days after CAR T-cell infusion. EEG and brain MRI were performed between day 6 and 8 after CAR T-cell infusion. EEG was performed again on the day of ICANS occurrence, if outside this time window. All collected data were compared between patients with and without ICANS.

Results

Thirty-eight consecutive patients were enrolled (14 women; median age: 65 years, interquartile range: [55–74]). ICANS was observed in 17 of 38 patients (44%) after a median time of 6 days after CAR T-cell infusion (4–8). The median ICANS grade was 2 (1–3). Higher C-reactive protein peak (146 mg/L [86–256], $p = 0.004$) at day 4 (3–6), lower natremia (131 mmol/L [129–132], $p = 0.005$) at day 5 (3–6), and frontal intermittent rhythmic delta activity (FIRDA, $p < 0.001$) on EEG between days 6 and 8 after infusion were correlated with ICANS occurrence. FIRDA was only observed in patients with ICANS ($N = 15/17$, sensitivity of 88%) and disappeared after ICANS resolution, usually after steroid therapy. Except for hyponatremia, no other toxic/metabolic marker was associated with FIRDA ($p = 0.002$). The plasma concentration of copeptin, a surrogate marker of antidiuretic hormone secretion, assessed at day 7 after infusion, was significantly higher in patients with ($N = 8$) than without ($N = 6$) ICANS ($p = 0.043$).

Discussion

FIRDA is a reliable diagnostic tool for ICANS, with a sensitivity of 88% and a negative predictive value of 100%. Moreover, as this EEG pattern disappeared concomitantly with ICANS resolution, FIRDA could be used to monitor neurotoxicity. Finally, our study suggests a pathogenic pathway that starts with increased C-reactive protein, followed by hyponatremia and eventually ICANS and FIRDA. More studies are required to confirm our results.

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 **Class of Evidence**
Criteria for rating therapeutic and diagnostic studies
[NPub.org/coe](https://www.npub.org/coe)

Glossary

ADC = apparent diffusion coefficient; **CAR** = chimeric antigen receptor; **CRP** = C-reactive protein; **CRS** = cytokine release syndrome; **DWI** = diffusion weighted imaging; **FIRDA** = frontal intermittent rhythmic delta activity; **FLAIR** = fluid-attenuated inversion recovery; **ICANS** = immune effector cell-associated neurotoxicity syndrome; **SIADH** = syndrome of inappropriate antidiuretic hormone secretion.

Classification of Evidence

This study provides Class III evidence that FIRDA on spot EEG accurately distinguishes patients with ICANS compared with those without after CAR T-cell therapy for hematologic malignancy.

Chimeric antigen receptor (CAR) T-cell therapies targeting CD19 are an effective treatment for relapsed and refractory B-cell lymphoma and acute leukemia.¹⁻³ Adverse events related to CAR T-cell therapies include cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) are observed in ~100% and 50% of patients, respectively.⁴⁻⁷ CRS usually occurs in the first week and ICANS early in the second week after CAR T-cell infusion. CRS symptoms are well characterized and include fever, hypotension, and hypoxia, leading to end-organ damage. CRS management is based on the administration of interleukin-6 inhibitors, sometimes associated with corticosteroids. ICANS clinical presentation is more variable, ranging from mild and reversible encephalopathy to fatal cerebral edema in rare cases. In addition, miscellaneous neurologic manifestations have been described, including headache, tremor, seizure, dysgraphia, aphasia, apraxia, and focal weakness. ICANS is usually responsive to steroids but may be worsened by interleukin-6 inhibitors, unlike CRS. Therefore, a simple and reliable diagnostic tool to support ICANS diagnosis is needed for the early detection of patients at risk of developing high-grade ICANS.

In patients with ICANS, brain MRI remains typically normal. Conversely, pathologic EEG findings are commonly observed in 78%–100% of patients.⁸⁻¹⁰ EEG is an accurate tool for the detection of encephalopathy. However, the exact prevalence of pathologic EEG findings in patients with ICANS is unknown because (1) EEG is mainly performed in patients with severe ICANS, especially in the presence of signs or symptoms suggestive of seizures, and (2) EEG is not systematically performed in all patients receiving CAR T-cell therapies, regardless of ICANS occurrence or not.

In this study, we assessed the sensitivity of EEG to distinguish patients with ICANS compared with those without after CAR T-cell therapy for hematologic malignancy.

Methods

Patients and Study Design

This prospective study included patients who received CAR T-cell therapy in the Montpellier University Hospital between

September 2020 and July 2021. The inclusion criteria were ≥18 years of age and histologic confirmation of relapse/refractory hematologic malignancy (i.e., diffuse large B-cell lymphoma, follicular lymphoma, or mantle cell lymphoma and B-cell acute lymphoblastic leukemia) for that CAR T cells were indicated according to French Agency authorization. Before CAR T-cell infusion, each patient had a whole-body 18F-fluorodeoxyglucose PET/CT and a brain MRI.

Standard Protocol Approvals, Registrations, and Patient Consents

In the present study, routine healthcare data were assessed. All data were anonymously collected with the patient's agreement in accordance with the general regulations on data protection applicable in France, which is available in eAppendix 1, links.lww.com/NXI/A824. Ethics approval was obtained from the Institutional Review Board of Montpellier University (approval number: IRB-MTP_2021_06_202100806 is available in eAppendix 2, links.lww.com/NXI/A825). Our manuscript is in accordance with guidelines of STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) that is available in eAppendix 3, links.lww.com/NXI/A826.

Data Collection

Clinical Assessment

The following patient characteristics were prospectively collected: sex, age, personal neurologic history, and hematologic malignancy characteristics (age at onset, Ann Arbor staging, and central or peripheral nervous system involvement). Each patient was evaluated following the American Society for Blood and Marrow Transplantation consensus definition and grading system for CRS that include the presence of fever ($\geq 38^\circ\text{C}$), hypotension (requiring or not vasopressors), and hypoxia (requiring or not the use of oxygen delivered with a low-flow, ≤ 6 L/min, nasal cannula or a blow-by method).¹¹

Neurologic signs/symptoms of ICANS were monitored and scored using the Chimeric Antigen Receptor Toxicity-10 questionnaire¹¹ (the list is available in eAppendix 4, links.lww.com/NXI/A827) twice per day for 14 days after CAR T-cell infusion. The clinical evaluation included (1) mental status:

awareness level and immune effector cell encephalopathy score¹¹ (which is available in eAppendix 4, links.lww.com/NXI/A827), (2) speech and language (fluency, comprehension, writing, naming, and verbal fluency), (3) motor and sensory systems, (4) tremor and ataxia, (5) oculomotricity, (6) praxis, and (7) hallucinations. All neurologic signs and symptoms were recorded. Neurotoxicity was evaluated with the American Society for Transplantation and Cellular Therapy ICANS Consensus Grading for Adults.¹¹ Patients were seen again at month 1 after infusion to record any new neurologic event. All drugs administered during hospitalization were recorded, especially tocilizumab, dexamethasone, antibiotics, antiepileptics, and sedative drugs.

EEG

As neurotoxicity symptoms usually reach their peak at day 7 after CAR T-cell infusion, EEG was performed between day 6 and day 8 after infusion and on the day of ICANS occurrence, if outside this time window. A new EEG was performed in patients with neurologic worsening and then every 2 days until neurologic normalization. EEG electrodes were placed according to the 10–20 international system using 21 electrodes and a 240 Hz sampling rate. EEG recording lasted up to 30 minutes. Signals were obtained using the Micromed Brain quick amplifier and Micromed Brainspy software (Micromed, Italy). A notch filter (60 Hz) and bandpass filter (0.5–70 Hz) were applied. The EEG background was graded according to the Synek scale from 0 (i.e., normal) to 5 (i.e., severe amplitude suppression).¹² Besides the predominant posterior rhythm, focal slowing and paroxysmal activities were assessed (i.e., rhythmic delta activity, periodic discharges, spikes, and sharp waves). Their prevalence, duration, and localization (i.e., generalized, lateralized, or focal) were specified. According to their cortical distribution, intermittent rhythmic delta activities (i.e., slow waves with a frequency of 1.0–4.0 Hz lasting up to 2 seconds) are classified as frontal intermittent rhythmic delta activity (FIRDA), temporal intermittent rhythmic delta activity, or occipital intermittent rhythmic delta activity. All EEG recordings were reviewed by 2 expert neurologists (G.T. and P.G.) who were aware that patients received CAR T-cell therapy but were blinded to their CRS/ICANS severity. The correlation between ICANS severity or focal neurologic deficit and EEG findings (i.e., Synek scale, focal slowing, and paroxysmal activities) was assessed.

Blood Tests

Blood samples were collected each day for 14 days after CAR T-cell infusion to assess C-reactive protein (CRP), blood electrolytes, complete blood count, lactate dehydrogenase, ferritin, prothrombin time, urea and creatinine, aspartate and alanine transaminases, gamma-glutamyl transferase, and alkaline phosphatase. The plasma concentration of copeptin (a surrogate marker of antidiuretic hormone secretion) was retrospectively assessed in 14 of the 38 included patients (8 patients with ICANS and 6 patients without ICANS) on day 7 after infusion.¹³ In the other 24 patients, plasma samples were not available in our biobank to perform this analysis.

CSF Analysis

CSF samples were collected in patients with signs and symptoms suggestive of encephalitis for cytologic, biochemical, bacteriologic, virologic (including PCR detection of herpes viruses 6, 1, and 2 and varicella-zoster virus, Epstein-Barr virus, and cytomegalovirus), and hematologic analyses.

Brain MRI

MRI was performed with a 1.5T or a 3T scanner between day 6 and day 8 after CAR T-cell infusion (33/38 patients). Standard pre- and post-gadolinium T1w, T2w, fluid-attenuated inversion recovery (FLAIR), diffusion weighted imaging (DWI), and susceptibility-weighted images were available. All neuroimaging data were reviewed by an expert neurologist (X.A.). A control MRI was systematically performed in patients with neurologic worsening.

Statistical Analysis

Associations between categorical variables were evaluated using the χ^2 test or the Fisher exact test when the χ^2 test conditions of application were not met. Differences in continuous variables between patients with and without ICANS were assessed with the Wilcoxon-Mann-Whitney test. All covariates of interest with a *p* value of <0.2 in the logistic univariate analysis were kept, and a stepwise selection using the Akaike information criterion was performed for the final logistic multivariate model. Correlation coefficients were estimated using the Pearson product-moment correlation coefficient. The Youden index calculated from a receiver-operator characteristic analysis was used to determine the optimal cutoff value for biological parameters associated with ICANS.

Data Availability

The anonymized data supporting the findings of our study are available from the authors (S.H., X.A., and G.T.) on request.

Results

Patients' Baseline Characteristics

Among the 39 patients enrolled in the study, one was excluded because he developed posterior reversible encephalopathy syndrome related to the chemotherapy performed before the CAR T-cell infusion (Table 1). Among the remaining 38 patients (N = 14 women), the median age was 65 years (interquartile range: 55–74); 26 had diffuse large B-cell lymphoma or primary mediastinal B-cell lymphoma, 7 had follicular lymphoma, 3 mantle cell lymphoma, and 2 B-cell acute lymphoblastic leukemia. Extranodal involvements were detected in the CNS (N = 4 patients) and peripheral nervous system (N = 2) by brain MRI and whole-body 18F-fluorodeoxyglucose PET/CT, respectively. One patient had both central and peripheral nervous system involvement. No patients had a previous history of neurologic diseases. The median number of previous lines of chemotherapy was 2 (2–3). The CAR T-cell therapies are listed in eTable 1, links.lww.com/NXI/A830. No patient received oral preventive antiepileptic drugs. ICANS was observed in 17 of 38 (44.7%) patients, ranging from grade 1 (N =

Table 1 Patients' Baseline Characteristics in the Whole Population (N = 38)

Comparison of baseline characteristics and biological, EEG, and radiologic findings between patients with and without ICANS after CAR T-cell therapy				
	Total (N = 38)	Patients without ICANS (N = 21)	Patients with ICANS (N = 17)	p Value
Age, median (range), y	65 (55–74)	60 (52–66)	73 (60–77)	0.066
Women, n (%)	14 (37%)	6 (29%)	8 (47%)	0.2
Median Ann Arbor stage ^a	IV (III–IV)	IV (III–IV)	IV (III–IV)	0.8
Blood malignancy				
Diffuse large B-cell lymphoma	26 (68.4%)	12 (57%)	14 (82%)	0.3
Follicular lymphoma	7 (18.4%)	6 (29%)	1 (5.9%)	
Mantle cell lymphoma	3 (7.9%)	2 (9.5%)	1 (5.9%)	
B-cell acute lymphoblastic leukemia	2 (5.3%)	1 (4.8%)	1 (5.9%)	
CD19-CAR constructs				0.1
Coreceptor CD28	26 (68%)	12 (57%)	14 (82%)	
Coreceptor 4-1BB	12 (32%)	9 (43%)	3 (18%)	
CRS	36 (95%)	19 (90%)	17 (100%)	0.5
Peak C-reactive protein (d)	4.5 (3–6)	5 (4–6)	4 (3.6)	0.4
Peak C-reactive protein (value, mg/L)	87 (62–148)	68 (57–87)	146 (86–256)	0.004
Sodium nadir (d)	5 (3–7)	4 (3–7)	5 (3–6)	0.8
Sodium nadir (value, mmol/L)	130 (132–134)	134 (133–134)	131 (129–132)	0.005
Natremia (value, mmol/L) on the day of EEG	136 (133–138)	137 (134–138)	133 (131–137)	0.035
EEG abnormalities				
FIRDA	15 (39%)	0 (0%)	15 (88%)	<0.001
Moderate slowing (theta)	9 (24%)	0 (0%)	9 (53%)	<0.001
Focal slowing	1 (2–5%)	0 (0%)	1 (6%)	0.3
Median EEG frequency (Hz)	8 (8–9)	9 (8–9)	8 (7–8)	<0.001
Pathologic MRI	2 (5%)	0 (0%)	2 (12%)	0.2

Abbreviations: CAR = chimeric antigen receptor; CRS = cytokine release syndrome; FIRDA = frontal intermittent rhythmic delta activity; ICANS = immune effector cell-associated neurotoxicity syndrome.

^a For lymphoma.

6; 35.3%) to grade 2 (N = 5; 29.4%) and grade 3 (N = 6; 35.3%) with a median neurotoxicity grade of 2 (1–3). The median ICANS onset time was day 6 after infusion (4–8), and the median duration of symptoms was 4 days (2–8).

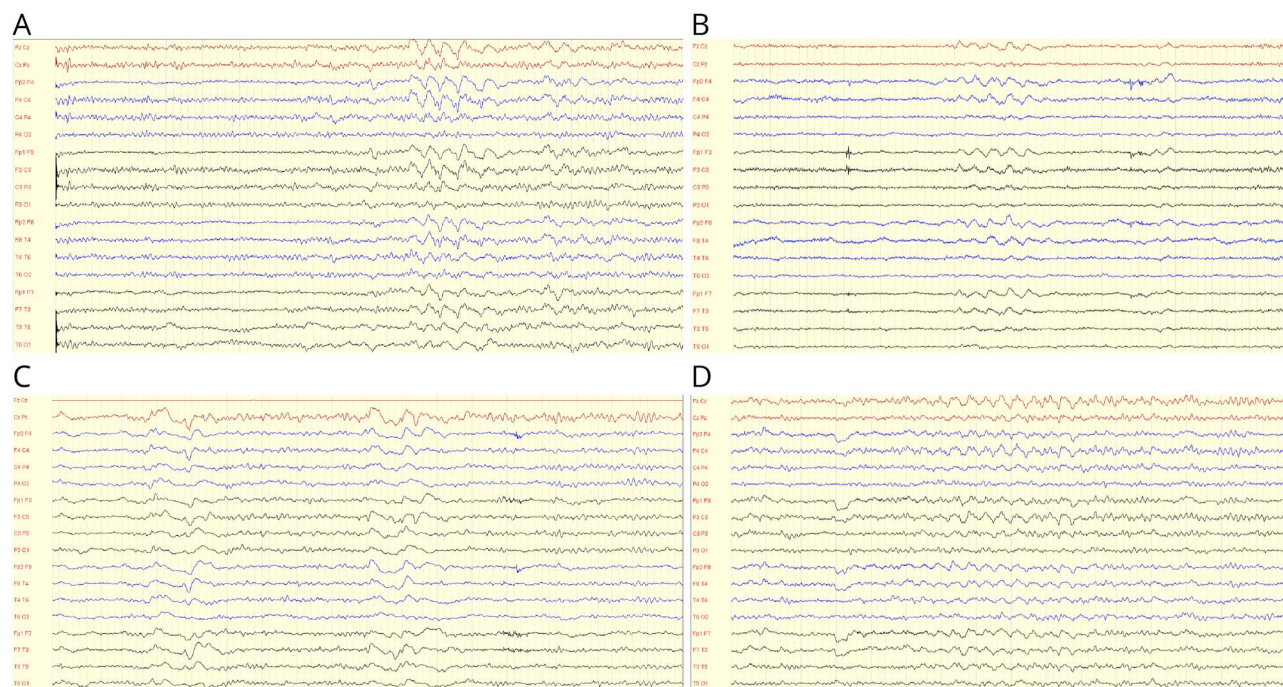
Characteristics of Patients With ICANS

The most common neurologic sign was verbal fluency impairment (i.e., expressive aphasia, N = 13; 76%), followed by kinetic and/or postural tremor with writing disorder (N = 8; 47%). Ten patients showed confusion (59%), and 5 patients (29%) had complex visual hallucinations or illusions. One (6%) patient experienced a generalized tonic-clonic seizure.

Pathologic EEG findings were observed in 15 of 17 patients with ICANS (sensitivity of 88%). FIRDA was present in all

EEG recordings with pathologic findings (15/15, 100%) and preceded ICANS onset in 3 patients (18%) (Figure 1). This EEG pattern was always bilateral, synchronous, and symmetric. The median maximum discharge duration in FIRDA was 3 seconds (range: 2–5). Generalized, lateralized, or focal (except the frontal region) rhythmic delta activity was not recorded. EEG recording analysis also revealed moderate background slowing (theta rhythm, grade 2 of the Synek scale) in 9 patients (56%) and left temporal focal slowing in 1 patient (6%). This patient also had T2-weighted fluid-attenuated inversion recovery (T2/FLAIR) hyperintensity in the left hippocampus with a high signal on both DWI at b1000 and apparent diffusion coefficient (ADC) images (i.e., T2 shine through, eFigure 1, [links.lww.com/NXI/A829](https://www.lww.com/NXI/A829)). Among patients with visual hallucinations or illusions, EEG showed

Figure 1 EEG Recordings With FIRDA in Patients With ICANS (Different Severity)



(A) EEG with longitudinal bipolar montage (midline, right, left, right, and left) showing FIRDA in an asymptomatic patient (day 6) who developed grade 2 ICANS at day 9. (B–D) FIRDA in 3 patients with grade 1 (B), grade 2 (C), and grade 3 ICANS (D). FIRDA = frontal intermittent rhythmic delta activity; ICANS = immune effector cell-associated neurotoxicity syndrome.

FIRDA in all ($n = 5$) without further abnormalities, including in occipital areas. The EEG background was not reactive in 2 patients (12%), and the anteroposterior gradient was not preserved in 7 patients (41%). Electroclinical or subclinical seizures, interictal discharges (i.e., spikes and sharp waves), generalized or focal/lateralized periodic discharges, and triphasic waves were not recorded, including in the patient with generalized tonic-clonic seizure. EEG findings (i.e., Synek scale grade and FIRDA presence) were not correlated with ICANS severity and neurologic signs or symptoms (data are available in eTable 2, links.lww.com/NXI/A831). However, FIRDA was observed in all patients with expressive aphasia ($N = 13/13$). Abnormal EEG findings (e.g., FIRDA) and ICANS disappeared concomitantly after steroid therapy ($N = 13, 87\%$) or spontaneously ($N = 2, 13\%$).

MRI was normal in 15 of 17 patients with ICANS. The 2 patients with abnormal MRI findings (FLAIR hyperintensities in the left hippocampal body in one and in the periventricular white matter around the right occipital horn in the other) had ICANS grade 3. These MRI lesions matched with the DWI and ADC map hyperintensities, suggestive of vasogenic edema (eFigure 1, links.lww.com/NXI/A829).

Lumbar puncture was performed in 10 patients with ICANS, confusion, and fever. No sample showed signs of infection or cancer cell invasion (CSF characteristics are described in eAppendix 5, links.lww.com/NXI/A828).

Comparison Between Patients With and Without ICANS

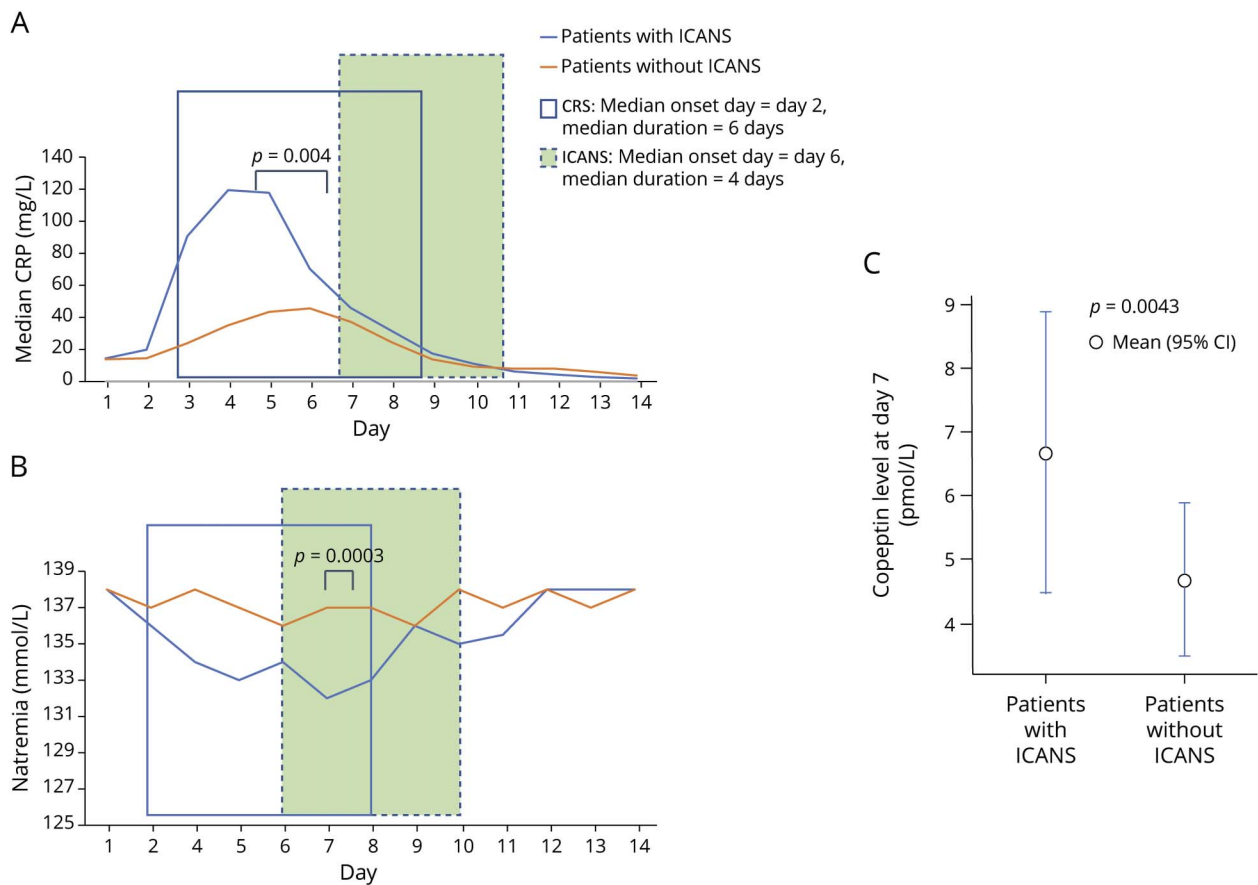
The baseline characteristics were not different between patients with ($N = 17$) and without ICANS ($N = 21$) (Table 1). Notably, the risk of ICANS was not higher in patients with peripheral nervous system and/or CNS involvement compared with the others. CRS occurred in all patients with ICANS and in 19 of 21 patients without ICANS. CRS characteristics and incidence were not significantly different between groups (data are available in eTable 3, links.lww.com/NXI/A832).

Parameters significantly correlated with neurotoxicity were divided into 2 groups according to their occurrence (before and during ICANS).

Parameters Correlated With Neurotoxicity Before ICANS Onset

The median CRP peak was significantly higher in patients with than without ICANS (146 mg/L [86–256] vs 68 mg/L [55–87], $p = 0.004$) and was reached at day 4 [3–6] after CAR T-cell infusion (Figure 2A). The median sodium nadir (131 mmol/L [129–132] vs 134 mmol/L [133–134], $p = 0.005$) and median natremia on the EEG day (133 mmol/L [131–137] vs 137 mmol/L [134–138], $p = 0.035$) were significantly lower in patients with ICANS (Figure 2B, Table 1). The median sodium nadir was reached on day 5 (3–6) after infusion. All patients were euvoletic (urea/creatinine ratio level ≤ 100), including those with hyponatremia ($n = 18$).

Figure 2 Parameters Correlated With Neurotoxicity



(A) C-reactive protein level (mg/L) monitoring in patients with (N = 17) and without ICANS (N = 21) in the 14 days after CAR T-cell infusion. (B) Monitoring of natremia (mmol/L) in patients with (N = 17) and without ICANS (N = 21) in the 14 days after CAR T-cell infusion. (C) Plasma concentration of copeptin (pmol/L) at day 7 after infusion in patients with (N = 8) and without ICANS (N = 6). FIRDA = frontal intermittent rhythmic delta activity; ICANS = immune effector cell-associated neurotoxicity syndrome.

Copeptin levels assessed on day 7 in 8 patients with ICANS and 6 patients without ICANS were significantly higher in patients with ICANS ($p = 0.043$) (Figure 2C). The cutoff value for CRP to differentiate patients with ICANS from those without ICANS was 84.1 mg/L (maximal Youden index = 0.49). This value had a sensitivity of 82%, a specificity of 67%, a positive predictive value of 67%, and a negative predictive value of 82%. Concerning natremia, the cutoff value was 132 mmol/L (maximal Youden index = 0.58), with a sensitivity of 82%, a specificity of 76%, a positive predictive value of 74%, and a negative predictive value of 84%. Among the 13 patients with CRP >84.1 mg/L and natremia \leq 132 mmol/L, 11 had ICANS, and among the 12 patients with CRP \leq 84.1 mg/L and natremia >132 mmol/L, 11 had no ICANS. Diagnostic performance of natremia and CRP in patients with ICANS is described in eTable 4, links.lww.com/NXI/A833.

Parameters Correlated With Neurotoxicity Occurring During ICANS

Between day 6 and day 8 after CAR T-cell infusion, 15 of 17 patients with ICANS had FIRDA (88%), whereas EEG was normal in all patients without ICANS ($p < 0.001$). FIRDA

preceded ICANS in only 3 patients (18%). FIRDA disappeared after steroid therapy (N = 13, 87%) or spontaneously (N = 2, 13%), when patients no longer had signs of neurotoxicity. Abnormal MRI findings (N = 2 patients with ICANS) were not associated with neurotoxicity ($p = 0.2$).

Patients with FIRDA (N = 15, all had ICANS) had higher CRP levels ($p = 0.02$) and lower sodium levels ($p = 0.003$). Univariate regression analysis confirmed these results. Data are available in eTable 5 and eTable 6, links.lww.com/NXI/A834 and links.lww.com/NXI/A835.

Classification of Evidence

This study provides Class III evidence that FIRDA on spot EEG accurately distinguishes patients with ICANS compared with those without after CAR T-cell therapy for hematologic malignancy.

Discussion

In this prospective study, EEG recordings were analyzed in 38 consecutive patients after CAR T-cell infusion, regardless of

the presence/absence of neurotoxicity. In previous studies, EEG recordings were performed only in patients with ICANS, and their diagnostic value could not be determined.^{8-10,14-17} Our results indicate that FIRDA could be considered a reliable marker of ICANS, with a sensitivity of 88% and a negative predictive value of 100%. Previous studies showed more frequent background slowing in patients with ICANS compared with our samples (78%–100% vs 56%) and less frequent diffuse rhythmic delta activities (i.e., 5%–55% of FIRDA/generalized rhythmic delta activity).^{8-10,14} In addition, these studies found a correlation between background slowing and neurotoxicity severity. These discrepancies may be explained by the low median neurotoxicity grade in our patients (i.e., no patient with grade 4 ICANS). Indeed, the most prevalent manifestation in our patients was expressive aphasia and not coma. Of interest, all patients with aphasia had FIRDA, and brain MRI was normal in all but 2. A recent study described 18 patients with aphasia after CAR T-cell infusion in whom generalized EEG abnormalities were detected, including generalized rhythmic delta activity as the most frequent pattern.¹⁶ Brain MRI was considered abnormal and related to ICANS in only one patient. Altogether, these results underscore that frontal or generalized intermittent rhythmic delta activity may be a surrogate marker of mild neurotoxicity, especially in patients with expressive aphasia.

The thalamocortical network, including the anterior cingulate cortex, plays an important role in FIRDA appearance.¹⁸ FIRDA may be caused by all conditions, structural or not (e.g., metabolic encephalopathy and intracranial hypertension), that affect these structures. Of interest, the verbal fluency task selectively activates prefrontal cortex regions, including the anterior cingulate cortex.¹⁹ Therefore, both FIRDA and expressive aphasia may result from a dysfunction of the same cerebral regions. As brain MRI is usually normal in patients with ICANS, a functional rather than a structural underlying mechanism is strongly suspected. Proinflammatory cytokines or direct T-cell-mediated effects could alter this thalamocortical network, leading to FIRDA.

As our results demonstrated a significant correlation between FIRDA and hyponatremia, we could hypothesize that hyponatremia may be implicated in FIRDA appearance. Indeed, metabolic disorders (e.g., electrolyte imbalance) are the main etiology of FIRDA in the absence of structural brain lesions.²⁰

Furthermore, our findings reveal a sequence of events that start with increased CRP, followed by hyponatremia and, eventually, ICANS accompanied by FIRDA. CRP is a well-known predictive parameter of neurotoxicity, and our study shows a correlation between hyponatremia and ICANS.^{7,21} Moreover, the increased copeptin levels suggest that hyponatremia might be related to a syndrome of inappropriate antidiuretic hormone secretion (SIADH).¹³ Interleukin 6, the main inflammatory cytokine in CRS, may

explain these results. This cytokine promotes CRP synthesis in the liver and the secretion of antidiuretic hormone.²² Therefore, hyponatremia may play a role in ICANS pathophysiology, as evidenced by FIRDA. More studies are needed to determine whether hyponatremia is implicated in ICANS/FIRDA occurrence, or whether it is an incidental parameter related to CRS. This is an important question because drugs to prevent antidiuretic hormone synthesis are available and could be used instead of immunosuppressive therapies that can impair CAR T-cell therapy efficacy.

Besides showing that EEG is useful for the diagnosis of neurotoxicity, the design of our study allowed us to evaluate whether EEG recordings can be used to monitor ICANS. Indeed, EEG recordings were performed every 2 days in patients with ICANS until neurologic normalization. Our results showed that FIRDA disappeared concomitantly with the neurotoxicity symptom resolution, especially after steroid therapy. This entanglement between FIRDA and ICANS suggests that FIRDA could be used not only as a diagnostic tool but also to monitor neurotoxicity.

A major limitation of this study is the small sample size that decreased its statistical power. Our study showed EEG high sensitivity for ICANS diagnosis but did not find any association between EEG patterns and ICANS severity. In addition, as pre-ICANS EEG recordings were performed in only 4 patients, its predictive value for neurotoxicity occurrence could not be determined. More prospective studies on EEG prediction performance are required. Finally, although peak values of hyponatremia and CRP arose earlier than ICANS, we did not achieve to determine a reliable cutoff value that could efficiently predict the development of neurotoxicity (i.e., maximal Youden index was close to 0.5). At best, patients with low natremia and high CRP seemed to have a high risk for ICANS, whereas patients with natremia close to normal value and low CRP seemed to have a low risk for ICANS. Further studies with larger sample sizes are needed to assess this issue.

In conclusion, FIRDA seems to be a reliable tool for ICANS diagnosis and monitoring. Moreover, our study identified a correlation between hyponatremia related to SIADH and both ICANS and FIRDA. However, more studies are needed to determine whether hyponatremia is involved in ICANS/FIRDA development or is an incidental finding.

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Disclosure

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Appendix Authors

Name	Location	Contribution
Sophie Huby, MD	Department of Neurology, CHU Montpellier, University of Montpellier, Montpellier, France	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; and analysis or interpretation of data
Philippe Gelisse, MD	Department of Neurology, CHU Montpellier, University of Montpellier, Montpellier, France	Analysis or interpretation of data
Jean-Jacques Tudesq, MD	Department of Hematology, CHU Montpellier, University of Montpellier, France	Major role in the acquisition of data
Pierre Labauge, MD, PhD	Department of Neurology, CHU Montpellier, University of Montpellier, Montpellier, France	Analysis or interpretation of data
Claire Duflos, MD	Clinical Research and Epidemiology Unit, CHU Montpellier, University of Montpellier, France	Analysis or interpretation of data
Guillaume Cartron, MD, PhD	Department of Hematology, CHU Montpellier, University of Montpellier, France	Analysis or interpretation of data
Marc-Antoine Gallerand, MD	Department of Neurology, CHU Montpellier, University of Montpellier, Montpellier, France	Analysis or interpretation of data
Laura Platon, MD	Department of Intensive Care, CHU Montpellier, University of Montpellier, France	Analysis or interpretation of data
Stephanie Badiou, MD	Department of Biochemistry and Hormonology, CHU Montpellier, University of Montpellier, France	Major role in the acquisition of data
Sylvain Lamure, MD	Department of Hematology, CHU Montpellier, University of Montpellier, France	Major role in the acquisition of data
Nicolas Menjot de Champfleury, MD, PhD	Department of Neuroradiology, CHU Montpellier, University of Montpellier, France	Study concept or design
Xavier Ayrignac, MD, PhD	Department of Neurology, CHU Montpellier, University of Montpellier, Montpellier, France; University of Montpellier, INSERM (INM), Department of Neurology, Montpellier University Hospital, France	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; and analysis or interpretation of data

Appendix (continued)

Name	Location	Contribution
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