# Relapsing, steroid-refractory ICANS after CAR T-cell therapy: diagnostic work-up and response to delayed repeated intrathecal chemotherapy

Chimeric antigen receptor T-cell (CAR T) therapy has significantly improved survival rates in patients with refractory hematologic malignancies, and its indications have expanded considerably over the past decade. Despite these remarkable advances, cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) remain potentially life-threatening complications. These toxicities can occur in isolation or concurrently and encompass a wide spectrum of clinical manifestations.[1-3]

Current standard treatment for ICANS consists of high-dose corticosteroids,[2] although prolonged exposure is associated with inferior progression-free survival (PFS) in CAR-T-treated diffuse large B-cell lymphoma (DLBCL) patients.[4] Additionally, severe ICANS increases the risk of infection, posing a significant clinical challenge, as high-dose corticosteroids may further raise susceptibility to life-threatening infections such as pulmonary aspergillosis.[5] Moreover, there is still no standard-of-care for steroid-refractory ICANS.

We present a case of a 54-year-old male treated with CAR T-cell therapy who suffered relapsing, high-grade ICANS and uniquely achieved near-complete neurological recovery following two late administrations of intrathecal (IT) chemotherapy, 45 days post-CAR-T infusion. This study respects the ethical rules and regulations in force in the Netherlands.

The patient was diagnosed with stage IV DLBCL involving bone, spleen, lymph nodes, and adrenal glands. Following six cycles of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) chemotherapy, PET-CT scan demonstrated chemo-refractory disease, indicating CAR T-cell therapy as second-line treatment. Given the high tumor burden, the patient was considered high-risk for both CRS and ICANS.

After leukapheresis, bridging therapy consisted of radiotherapy (4 x 5 Gy) to the adrenal glands because of progressive back pain. However, a subsequent $18^{F}$-Fluorodeoxyglucose (FDG)-PET scan showed marked progression outside the radiation field. A day-to-day case description is given in Table 1 and an overview of the timeline of the patients' disease trajectory and treatment is available in Figure 1.

Several significant measures were taken following CAR T-cell infusion. On day 5, the patient concomitantly suffered a worsening ICANS (to grade 2) and a grade 3 CRS which required ICU admission. He was treated with corticosteroids for ICANS and tocilizumab (600 mg) to treat the CRS. On day 19, the patient developed acute respiratory deterioration. At this time, there was significant diagnostic uncertainty as to whether this deterioration reflected occult CRS, pulmonary infection or neurotoxicity-related respiratory compromise. In this acute setting, tocilizumab was again administered to address potential occult CRS. Both on day 19 and day 41, a full work-up with ancillary testing, including brain magnetic resonance imaging (MRI), electroencephalography (EEG), and cerebrospinal fluid (CSF) analysis was carried out to exclude other possible causes of neurological decline. The day 41 MRI demonstrated pronounced barrier dysfunction with extensive leptomeningeal enhancement (Figure 2A and B). The differential diagnosis included leptomeningeal lymphoma and infection. However, CSF testing showed low leukocyte counts, negative microbiological studies, and no detectable $CD19^{+}$ B cells or clonal B-cell population (Table 1), while systemic disease evaluation supported treatment response. Collectively, these findings supported prolonged high-grade ICANS rather than central nervous system (CNS) lymphoma.

High-dose corticosteroids and anakinra were administered as ICANS treatment throughout the patient's disease course and although transient improvement was observed, steroid-refractory neurological decline developed (Table 1). After this, the patient was treated with IT chemotherapy on days 45 and 47 after CAR-T infusion.

After these IT administrations, clinical improvement was observed (Table 1). Brain MRI performed on day 81 showed a marked reduction in leptomeningeal enhancement (Figure 2C and D). Despite ongoing neurological recovery, the patient developed multiple nosocomial infections and an $18^{F}$-FDG-PET performed on day 84 post-CAR-T showed progressive lymphoma. The patient died on day 88 after CAR T-cell infusion due to respiratory failure resulting from combined infectious and oncologic causes.

The exact pathophysiology for ICANS is still not completely understood. Current hypotheses suggest that systemic inflammation after CAR T-cell therapy leads to endothelial cell activation and disruption of the blood-brain barrier, resulting in cytokine and immune cell infiltration into the CNS and, subsequently, neuroinflammation. In severe cases, this can progress to cerebral edema.[3]

Immune effector cell-associated neurotoxicity syndrome typically occurs within one week after CAR T-cell infusion, with a median onset of approximately five days, but onset

**Table 1.** Day-by-day case description.

| Day | Symptoms | Diagnostics | Treatment |
|---|---|---|---|
| -10 to -6 | Pre-CAR-T. No neurological symptoms | CSF: CC <7x10$^6$. TP 0.37 g/L. FCM: no B lymphocytes, 7% T-cells CD4/CD8 ratio of 0.10. Blood: CRP 176.2 mg/L, ferritin 4,046 ug/L | Lymphodepletion: CTX + fludarabine<br>DEX (40 mg) |
| 0 | Day of CAR T-cell infusion | ICE score: 10. Blood: CRP 263.3 mg/L, ferritin 7,933 ug/L | Axi-cel. prophylactic DEX (10 mg) |
| 1-2 | Fever (38.4-38.7°C) (grade 1 CRS) | ICE score: 10. Blood: CRP 201.9 mg/L, ferritin 9,329 ug/L | Prophylactic DEX (10 mg) |
| 3 | Dysgraphia (grade 1 ICANS) | ICE score: 9. Blood: CRP 131.4 mg/L, ferritin 11,413 ug/L | DEX (10 mg) |
| 5 | Fever (38.6°C), $SpO_2$ 95%, BP (78/55 mmHg) (grade 3 CRS). Bradyphrenia, mild aphasia (grade 2 ICANS) | ICE score: 5. Blood: CRP 103.6 mg/L, ferritin 14,491 ug/L | ICU admission. Tocilizumab (600 mg)<br>DEX (10 mg 4 times daily) |
| 7 | Aphasia, bradyphrenia (grade 3 ICANS) | ICE score: 1. CSF: CC <7x10$^6$, TP 0.36 g/L, glc 5.6 mmol/L. Lactate 2.98 mmol/L. Culture CSF: no bacterial or fungal growth. CSF PCR: negative (CMV; EBV; HSV 1.2; L. *monocytogenes; N. meningitides; S. pneumoniae*; VZV). CT brain: no hemorrhage. Blood: CRP 57.3 mg/L | High-dose MPS (1,000 mg daily for three days) |
| 8 | Focal epileptic seizures (grade 3 ICANS) | ICE score 0-2. Blood: CRP 26.7 mg/L | Levetiracetam (500 mg twice daily) |
| 10 | No improvement despite MPS (grade 3 ICANS) | - | Anakinra SC (100 mg daily). DEX (40 mg daily) |
| 12 | Partial improvement (grade 1 ICANS) | ICE score 8-9 | Anakinra SC discontinued. ICU discharge |
| 13 | Worsening bradyphrenia, ongoing aphasia | ICE score 7 | Anakinra SC (100 mg daily) restarted |
| 15-19 | Recurrent generalized seizures. Decreased consciousness. Respiratory insufficiency.<br>GCS: E3M1V1 - E4M5V1 | ICE score 0-1. EEG: no epileptic status. Brain MRI: mild cytotoxic edema around hippocampi, attributed to postictal changes. CSF: CC <7x10$^6$, TP 0.51 g/L, glc 5.6 mmol/L, lactate 3.1 mmol/L. 65.7% of T lymphocytes were CAR T-cells. CSF PCR negative. (*Enterovirus*; HSV 1,2; *Listeria monocytogenes*; *N. meningitides*; *Parechovirus*; *S. pneumoniae*; VZV) Bacterial culture CSF: no growth. Blood CRP 2.5 mg/L | Day 15: readmitted to ICU. Levetiracetam increased to 1,000 mg twice daily<br>Day 19: intubation. Tocilizumab 600 mg |
| 25-40 | Gradual increasing bradyphrenia, varying degree of drowsiness and aphasia. GCS E3-4M6V3-4 | Day 30: blood CRP 1.6 mg/L<br>Day 31: PET-CT: good PMR of malignant lymphoma. Adrenal localizations show residual necrotic/cystic lesions. Only few small foci with Deauville 4 | - |
| 41 | Sudden decrease in the level of consciousness. GCS E1M1V1.<br>Recurrent seizures (grade 4 ICANS) | Brain MRI: pronounced BBB disruption; persistent hippocampal swelling, extensive leptomeningeal enhancement. EEG: diffuse slow activity. CSF: CC <7x10$^6$. TP 0.62 g/L. Glc 5.3 mmol/L. No B lymphocytes. 6% NK lymphocytes, 31% T lymphocytes CD4/CD8 ratio of 1.96. CSF PCR: negative (CMV; *Cryptococci*; EBV; HSV 1,2; *JC polyomavirus*, *L. monocytogenes*; *N. meningitides*; S. *pneumoniae*; VZV). CSF culture: no bacterial, cryptococcal or fungal growth. Blood: CRP 2.3 mg/L, ferritin 4,143 ug/L | Levetiracetam increased to 1,250 mg twice daily<br>MPS (1,000 mg daily for three days) |
| 45 | Limited effect of MPS. GCS E1M3V1 | - | IT MTX (15 mg), Ara C (40 mg), HC (20 mg) |
| 47 | Slight improvement in GCS E3M4Vtube | CSF: CC <7x10$^6$. TP 0.69 g/L, glc 4.7 mmol/L. Lactate 2.41 mmol/L. 43.5% of T lymphocytes are CAR T-cells | IT MTX (15 mg), Ara C (40 mg), HC (20 mg) |
| 49-88 | GCS E4M6V tube. Adequate non-verbal responses. Short sentences after extubation | - | Day 74: discharged from ICU. Anakinra discontinued. DEX tapered from 10 mg/day |

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Ara C: cytarabine; axi-cel: axicabtagene ciloleucel; BBB: blood-brain barrier; BP: blood pressure; CAR-T: chimeric antigen receptor T-cell; CC: cell count; CTX; cyclophosphamide; CMV: cytomegalovirus; CRP: C reactive protein; CRS: cytokine release syndrome; CSF: cerebrospinal fluid; CT: computed tomography; DEX: dexamethasone; EBV: Epstein-Barr virus; EEG: electroencephalography; FCM: flow cytometry; GCS: Glasgow Coma Scale; Glc: glucose; HC: hydrocortisone; HSV: Herpes simplex virus; ICANS: immune effector cell-associated neurotoxicity syndrome; ICE: immune effector cell-associated encephalopathy; ICU: Intensive Care Unit; IT: intrathecal; MPS: methylprednisolone; MRI: magnetic resonance imaging; MTX: methotrexate; NK: natural killer cells; PCR: polymerase chain reaction; PET: positron emission tomography; PMR: partial metabolic response; SC: subcutaneous; $SpO_2$: peripheral oxygen saturation; TP: total protein; VZV: Varicella Zoster virus. CRS and ICANS grading according to the American Society for Transplantation and Cellular Therapy (ASTCT).[2]

up to three weeks after treatment has been described.[6,7] Early manifestations commonly include expressive aphasia, dysgraphia and altered mental status,[2] all of which were observed in our patient. ICANS most often follows a monophasic course and resolves within three weeks after CAR-T.[8] However, as in our case, symptoms may persist and can recur.

The immune effector cell-associated encephalopathy (ICE) score grades the severity of ICANS-related encephalopathy, while the overall grade is further influenced by the presence of additional neurological features such as seizures.[2] Guidelines recommend continuous neurological reassessment and adjusting treatment accordingly. More severe ICANS (> grade 2) may require diagnostics (e.g., brain MRI, CSF analysis, and EEG) to rule out other causes of neurological deterioration or to evaluate ICANS-associated abnormalities.[9]

Brain MRI abnormalities in ICANS are variable and may be absent even in severe cases; however, patterns including leptomeningeal enhancement and mesial temporal or hippocampal abnormalities have been reported and may reflect neuroinflammation and blood–brain barrier dysfunction.[1,3,6,8] CSF analysis, including flow cytometry and microbiological testing, can differentiate between alternative diagnoses (i.e., leptomeningeal lymphoma or infection) that fit with radiological findings or new neurological decline. EEG in ICANS commonly reveals diffuse slow activity, as observed in our patient, and may be used to detect seizure activity or to evaluate unexplained changes in consciousness.[1,3,6]

High-grade ICANS (≥ grade 3) occurs in 10% of CAR T-treated patients.[10] Risk factors for neurotoxicity include treatment with axicabtagene ciloleucel (axi-cel), high tumor burden, early and severe CRS, and pre-existing neurological disorders.[2,3,10] Our patient exhibited several of these risk factors.

Standard management consists of high-dose corticosteroids and supportive care,[1] yet there is still no standardized treatment for steroid-refractory ICANS. Tocilizumab, an IL-6 receptor antagonist, is effective for CRS but has limited efficacy in ICANS, possibly due to poor blood–brain barrier penetration.[1,3] Moreover, peripheral IL-6 receptor blockade may even worsen ICANS by increasing IL-6 levels in the CSF.[3] Guidelines thus recommend tocilizumab only in the presence of concomitant CRS, limiting its role in ICANS treatment.[10] Anakinra, an IL-1 receptor antagonist, shows promise in steroid-refractory cases. In a retrospective cohort study (N=40), high-dose anakinra was associated with faster neurological recovery without compromising CAR T-cell efficacy.[11] In our patient, improvement was initially observed following its introduction, although symptoms later recurred.

Intrathecal chemotherapy administered early after ICANS onset has shown encouraging results in case studies. This treatment is hypothesized to mitigate neurotoxicity through suppression of CNS inflammation and reduction of neurotoxicity-driving CAR T-cells in the CSF.[12] Two independent case reports described rapid improvement in patients with high-grade, steroid-refractory ICANS treated with IT hydrocortisone in combination with chemotherapeutic agents.[12,13] Furthermore, a 2024 case series reported 12 lymphoma patients who received IT chemotherapy (methotrexate, cytarabine, or both) a median of three days after ICANS onset. All patients had previously been treated with systemic corticosteroids, and neurotoxicity resolved in all but one case, with a median time to improvement of two days. Notably, only half of the patients had high-grade ICANS, similar to our patient. The patient who did not experience neurological recovery suffered grade 3 ICANS and was treated at the longest time point after symptom onset (23 days).[14] In contrast, our patient, who suffered high grade ICANS, showed marked improvement even 42 days after initial symptom onset.

Another case series described 7 patients who received IT hydrocortisone within five days of developing high-grade, steroid-refractory ICANS, 4 of whom also received IT chemotherapy.[15] Amongst those treated with IT chemotherapy, no patient received chemotherapeutic agents later than 15 days after ICANS onset. All 7 patients recovered, showing improvement to low-grade ICANS within a median of two days. In contrast, 8 patients who either did not receive IT therapy or were treated later after onset (i.e., with IT hydrocortisone day 24 after ICANS onset) had higher cumulative steroid exposure and significantly lower PFS. Among these, 4 patients with steroid-refractory ICANS had an estimated one-year PFS of 0%, and 2 of these experienced no resolution of neurotoxicity. This study suggests a clear benefit of early IT treatment in promoting neurological recovery and reducing systemic steroid exposure, potentially contributing to preserved CAR T-cell function.

Of note, all previous reports are retrospective in nature and limited by the heterogeneity of CAR T-cell indications, treatment modalities and concomitant systemic

treatment. The beneficial effect attributable solely to IT chemotherapy cannot be fully determined from these findings; however, the consistent temporal relationship between IT administration and clinical improvement across reports is compelling.

Importantly, previous studies have focused exclusively on early IT chemotherapy, typically initiated within a few days of ICANS onset. In contrast, our report provides the first evidence of clinical benefit even when administered as late as 42 days after initial symptoms. This finding directly extends the currently recognized therapeutic window for IT intervention and suggests that even in prolonged and refractory ICANS, intrathecal treatment may still meaningfully modulate CNS-driven neurotoxicity. In our experience, repeated dosing was well tolerated and IT chemotherapy effectively managed relapsing, steroid-refractory ICANS, leading to near-complete symptom resolution.

Intrathecal chemotherapy may induce meaningful neurological improvement in high-grade ICANS unresponsive to systemic therapy, even when administered weeks after CAR-T infusion. A second dose appeared to be safe and proved to be effective in relapsing ICANS, suggesting its

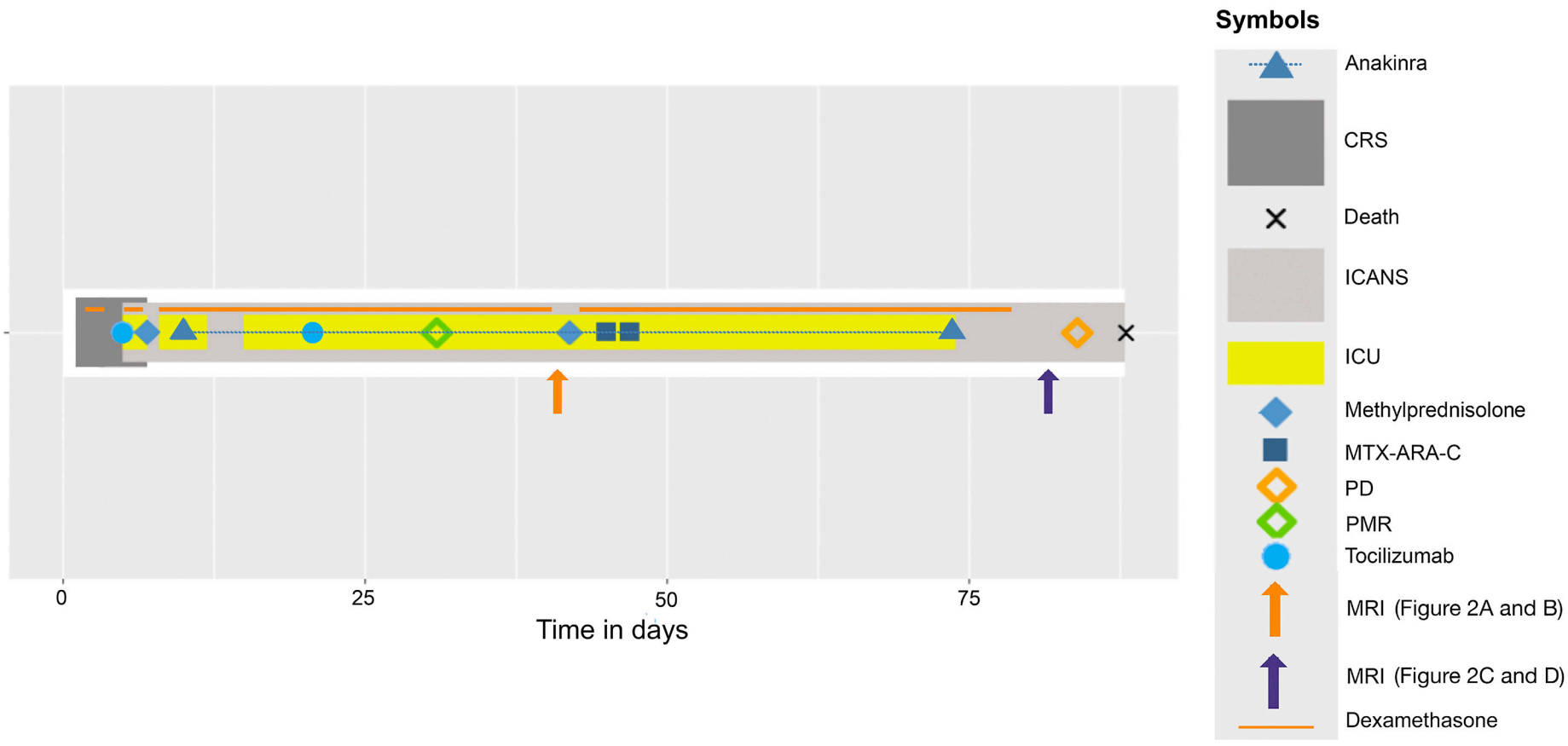


**Figure 1. Timeline of patients' disease trajectory and treatment for cytokine release syndrome / immune effector cell-associated neurotoxicity syndrome.** CRS: cytokine release syndrome; ICANS: immune effector cell-associated neurotoxicity syndrome; ICU: Intensive Care Unit; MTX-Ara-C: methotrexate and cytarabine (intrathecal); PD: progressive disease; PMR: partial metabolic response.

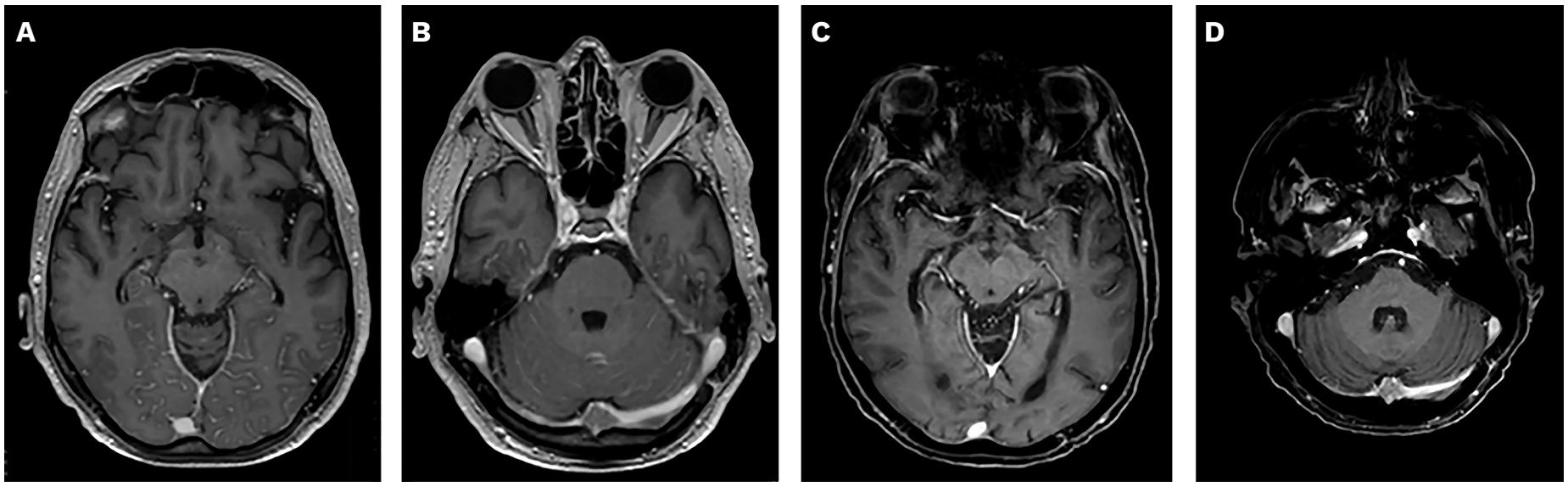


**Figure 2. Brain T1 magnetic resonance imaging with gadolinium.** (A and B) Axial T1 magnetic resonance imaging (MRI) with gadolinium day 41, leptomeningeal enhancement in the cerebellar and occipital cerebrospinal fluid. (C and D) Axial MRI T1 with gadolinium day 81, leptomeningeal enhancement resolved.

utility beyond acute presentations. This case highlights a broader therapeutic window for IT treatment than previously recognized and underscores the need for prospective studies to define its role in ICANS management.

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**Contributions**

RVN drafted the initial manuscript; JSPV and MVDM contributed to writing and editing the manuscript; VJG and TJAD revised the paper and approved the final version for publication.

**Data-sharing statement**

For data sharing and any further information, please contact r.m.van_nijendaal@lumc.nl

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