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Original Research

Characteristics of immune checkpoint inhibitor-induced encephalitis and comparison with HSV-1 and anti-LGI1 encephalitis: A retrospective multicentre cohort study

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Herpetic encephalitis

Abstract ***Aim:*** Immune checkpoint inhibitor-induced encephalitis (ICI-iE) is a rare but life-threatening toxicity of immune checkpoint inhibitor treatment. We aim to identify the characteristics of ICI-iE and describe factors that discriminate it from herpes simplex virus (HSV)-1 encephalitis and anti-leucine-rich glioma-inactivated 1 (anti-LGI1) encephalitis, as two alternative entities of encephalitis.
Methods: In this retrospective multicentre cohort study, we collected patients with ICI-iE reported to the Side Effect Registry Immuno-Oncology from January 2015 to September 2021 and compared their clinical features and outcome with 46 consecutive patients with HSV-1 or anti-LGI1 encephalitis who were treated at a German neurological referral centre.
Results: Thirty cases of ICI-iE, 25 cases of HSV-1 encephalitis and 21 cases of anti-LGI1 encephalitis were included. Clinical presentation of ICI-iE was highly variable and resembled that of HSV-1 encephalitis, while impairment of consciousness (66% vs. 5%, p = .007), confusion (83% vs. 43%; p = .02), disorientation (83% vs. 29%; p = .007) and aphasia (43% vs. 0%; p = .007) were more common in ICI-iE than in anti-LGI1 encephalitis. Antineuronal antibodies (17/18, 94%) and MRI (18/30, 60%) were mostly negative in ICI-iE, but cerebrospinal fluid (CSF) showed pleocytosis and/or elevated protein levels in almost all patients (28/29, 97%). Three patients (10%) died of ICI-iE. Early immunosuppressive treatment was associated with better outcome (r = 0.43).
Conclusions: ICI-iE is a heterogeneous entity without specific clinical features. CSF analysis has the highest diagnostic value, as it reveals inflammatory changes in most patients and enables the exclusion of infection. Early treatment of ICI-iE is essential to prevent sequelae and death.

1. Introduction

Immune checkpoint inhibitors (ICIs) have been a breakthrough in the treatment of many malignancies. However, owing to their powerful immune activation, 15–59% of patients develop severe (Common Terminology Criteria for Adverse Events, CTCAE, grade ≥3) autoimmune phenomena, referred to as immune-related adverse events (irAEs) [1–3]. Neurological irAEs (irAE-n) occur in 4–12% of patients [4] and can affect the central nervous system (CNS), the peripheral nervous system and the neuromuscular junction [5–9]. Besides myasthenic syndromes and myositis - which can be accompanied by fatal myocarditis [10] - ICI-induced encephalitis (ICI-iE) is a particularly severe irAE-n with a complex differential diagnosis and a mortality rate of 13–32% [11–14].

Until now, data on the clinical features and diagnostic criteria of ICI-iE have been limited [12–15]. Yet, defining the characteristics of ICI-iE is essential to differentiate it from other types of encephalitis or progressive tumour disease. For example, patients with advanced cancer are at risk of infectious encephalitides, such as herpes simplex virus (HSV)-1 encephalitis, which could worsen in the case of erroneous immunosuppressive treatment [16–19]. Moreover, recent studies have described limbic encephalitis as a common presentation of ICI-iE [14] and reported anti-leucine-rich glioma-inactivated 1 (anti-LGI1) antibodies in patients with ICI-iE [20]. Therefore, anti-LGI1 encephalitis – one of the most prevalent limbic encephalitis in the elderly – might share clinical features with ICI-iE but has different therapeutic and prognostic implications [21,22].

Here, we systematically investigated the characteristics and outcome of ICI-iE and compared these with cases of HSV-1 and anti-LGI1 encephalitis to enhance the awareness of ICI-iE and improve its diagnostic and therapeutic management.

2. Methodology

To identify patients with ICI-iE, we screened the Side Effect Registry Immuno-Oncology (SERIO), an international online registry coordinated from the Ludwig-Maximilian University Hospital in Munich in cooperation with the Paul-Ehrlich Institute. Additionally, cancer centres in Germany, the Netherlands, Japan, and Australia were queried for cases.

To diagnose ICI-iE, patients had to fulfil consensus criteria of *definite*, *probable* or *possible* ICI-iE, as described previously [23]. We only included cases of *possible ICI-iE* if symptoms improved with immunosuppressive treatment and disease course made differential diagnoses implausible. Clinical, laboratory and radiologic characteristics as well as outcome measures were assessed using standardised case report forms.

For patients with HSV-1 and anti-LGI1 encephalitis, we searched electronic medical records of a German neurological referral centre (Charité Universitätsmedizin Berlin) for the ICD-10 diagnoses B00.4 (herpetic encephalitis) and G.04.x (encephalitis, myelitis, and encephalomyelitis). HSV-1 encephalitis was diagnosed if signs of encephalitis were present, and HSV-1 desoxyribonucleic acid was detected in the cerebrospinal fluid (CSF) by polymerase chain reaction, or HSV-1-specific CSF/serum antibody ratio was elevated. Anti-LGI1 encephalitis was diagnosed according to criteria described previously [24].

We evaluated all consecutive patients presenting between January 2015 and September 2021. *LMJ* and *SK* verified the diagnosis of ICI-iE, HSV-1, and anti-LGI1 encephalitis; in cases of disagreement, *PH* was consulted until consensus was reached.

Group comparisons of categorical and continuous data were performed using Chi-squared or Fisher's exact test and the Kruskal–Wallis test, respectively. Correlation analysis was performed using the two-sided Spearman's correlation coefficient. An alpha level of ≤ 0.05 was defined as statistically significant. P-values were adjusted for multiple comparisons using the false discovery rate method [25]. Statistical analyses and illustrations were performed using Microsoft Excel (version 16.52), GraphPad Prism (version 7) and IBM SPSS Statistics (version 27.0).

The study was approved by the ethics commission in Erlangen (17_16_Bc; 2_20_B) and Munich (20–1122). For patients enrolled at the Charité Universitätsmedizin, Berlin §25 of the Berlin legislation for hospitals allows the use of routine care data for scientific purposes. For patients enrolled elsewhere, each cancer center had approval or exemption of the respective institutional review board.

3. Results

A total of 96 patients were screened for the study: Fifty reported cases of suspected ICI-iE (Supplemental Table 1 and 2), 25 cases of HSV-1 encephalitis and 21 cases of anti-LGI1 encephalitis. After application of consensus disease definition [23], we included 30 patients with ICI-iE. For patient's characteristics, see Table 1 and Supplemental Table 1.

3.1. Signs and symptoms

Most common features of ICI-iE were disorientation (25/30 [83%]), confusion (25/30 [83%]), memory deficits (17/25 [68%]) and impaired consciousness (19/29, [66%]; Fig. 1). Focal deficits included aphasia (13/30 [43%]), cerebellar dysfunction (e.g., vertigo, dysarthria, ataxia; 11/30 [37%]) and other signs such as tremor, myoclonus, hemiparesis and diplopia (9/30 [30%]). Meningoencephalitis without focal signs was observed in eight patients (27%). Interestingly, 11 of 27 patients for whom data were available

Table 1
Characteristics of patients with ICI-iE, HSV-1 encephalitis and anti-LGI1 encephalitis.

Variable	ICI-iE (n = 30)	HSV-1 (n = 25)	LGI1 (n = 21)
Female	13/30 (43)	14/25 (56)	9/21 (43)
Age at onset, y	66 (56–78)	67 (51–78)	68 (51–73)
Neoplasm			
Melanoma	17/30 (57)	0 (0)	0 (0)
Lung (NSCLC, SCLC)	4/30 (13)	0 (0)	0 (0)
Squamous cell carcinoma	2/30 (7)	0 (0)	0 (0)
Renal cell carcinoma	2/30 (7)	0 (0)	0 (0)
Other	5/30 (17),[a]	5/25 (20) [b]	0 (0)
Brain metastases	5/29 (17)	0 (0)	0 (0)
ICI therapy[c]			
PD-1	13/29 (45)		
PD-L1	3/29 (10)		
CTLA-4	3/29 (10)		
ICI combination	10/29 (35)		
Comorbidities			
Neurological/psychiatric comorbidity	5/30 (17)	10/25 (40)	3/21 (14)
Additional irAE	21/30 (70)		
MRI			
Signs of encephalitis	9/30 (30)	23/24 (96)	15/21 (71)
Signs of meningitis	4/30 (13)	6/24 (25)	0/21 (0)
Normal	18/30 (60)	1/24 (4)	6/21 (29)
EEG			
Epileptiform abnormal activity	2/17 (12)	5/15 (33)	2/18 (11)
Non-epileptiform abnormal activity	13/17 (77)	15/15 (100)	6/18 (33)
Normal	4/17 (24)	0/15 (0)	11/18 (61)
Antineuronal antibodies (serum or CSF)	1/18 (6)	1/11 (9)	21/21 (100)
Onset after first ICI administration, weeks (n = 29)	12 (4–21)		
No. of ICI cycles (n = 26)	2 (1–7)		
CTCAE grade of ICI-iE	3 (3-4)		
mRS at onset (n = 22/25/21)	3 (3-4)	3 (2-3)	3 (2-3)
ICU treatment	11/30 (37)	14/25 (56)	2/21 (10)
Treatment			
Corticosteroids	29/30 (97)	3/25 (12)	19/21 (91)
Plasma exchange/apheresis	5/29 (17)	0 (0)	11/21 (53)
IVIG	3/26 (12)	0 (0)	8/21 (38)
Rituximab	2/29 (7)	0 (0)	17/21 (81)
Other	1/29 (3)	24/25 (96)	0/21 (0)
Full recovery	13/30 (43)	5/25 (20)	5/20 (25)
Time from treatment to improvement of symptoms, days (n = 24/16/17)	14 (3–21)	18 (7–28)	56 (28–84)
Recovery with sequelae / ongoing symptoms	14/30 (47)	14 (56)	15/20 (75)
Lethal outcome	3/30 (10)	6 (24)	0/20 (0)
ICI rechallenge	6/29 (21)		
Follow-up, months (n = 29/25/20)	7 (3–30)	1 (0–2)	17 (7–29)

Values are median (interquartile range, IQR) or n (%). In cases of missing data, numbers of cases for ICI-iE, HSV-1 encephalitis and anti-LGI1 encephalitis, respectively, are given as a fraction or in brackets next to each item. CTCAE = Common Terminology Criteria for Adverse Events; CSF = cerebrospinal fluid; CTLA-4 = cytotoxic T-lymphocyte-associated protein 4; HSV-1 = herpes simplex virus 1 encephalitis; ICI = immune checkpoint inhibitor; ICU = intensive care unit; irAE = immune related adverse event; ICI-iE = ICI-induced encephalitis; IVIG = Intravenous immune globulin; LGI1 = anti-LGI1 encephalitis; mRS = Modified Rankin Scale; NSCLC = non-small cell lung cancer; PD-1 = programmed cell death protein 1; PD-L1 = programmed death-ligand 1; SCLC = small cell lung cancer; y = years.

[a] breast cancer, cholangiocarcinoma, endometrial cancer, hepatocellular carcinoma, Merkel cell carcinoma.

[b] breast cancer, glioblastoma, leukaemia, multiple myeloma, thyroid cancer.

[c] One patient was blinded for ICI-type (nivolumab ± ipilimumab).

(41%) developed mild hyponatremia (median, 131 mmol/l [IQR, 129–132]), which was linked to syndrome of inappropriate antidiuretic hormone secretion (SIADH) in two patients (18%). One of them had coexisting ICI-induced hypophysitis explaining the SIADH. In the other cases the cause of hyponatremia remained unknown.

Impaired consciousness, confusion, disorientation, and aphasia were more common in patients with ICI-iE compared to patients with anti-LGI1 encephalitis (19/29 [66%] vs. 1/21 [5%], p = .007; 25/30 [83%] vs. 9/21 [43%], p = .02; 25/30 [83%] vs. 6/21 [29%], p = .007; 13/30 [43%] vs. 0/21 [0%], p = .007, respectively; Fig. 1). While memory deficits – a characteristic of limbic encephalitis – were common in both groups (17/25 [68%] and 18/21 [86%] for ICI-iE and anti-LG1 encephalitis, respectively; p = .16), seizures occurred more frequently in patients with anti-LGI1 encephalitis (18/21 [86%] vs. 8/30 [27%], respectively; p = .007).

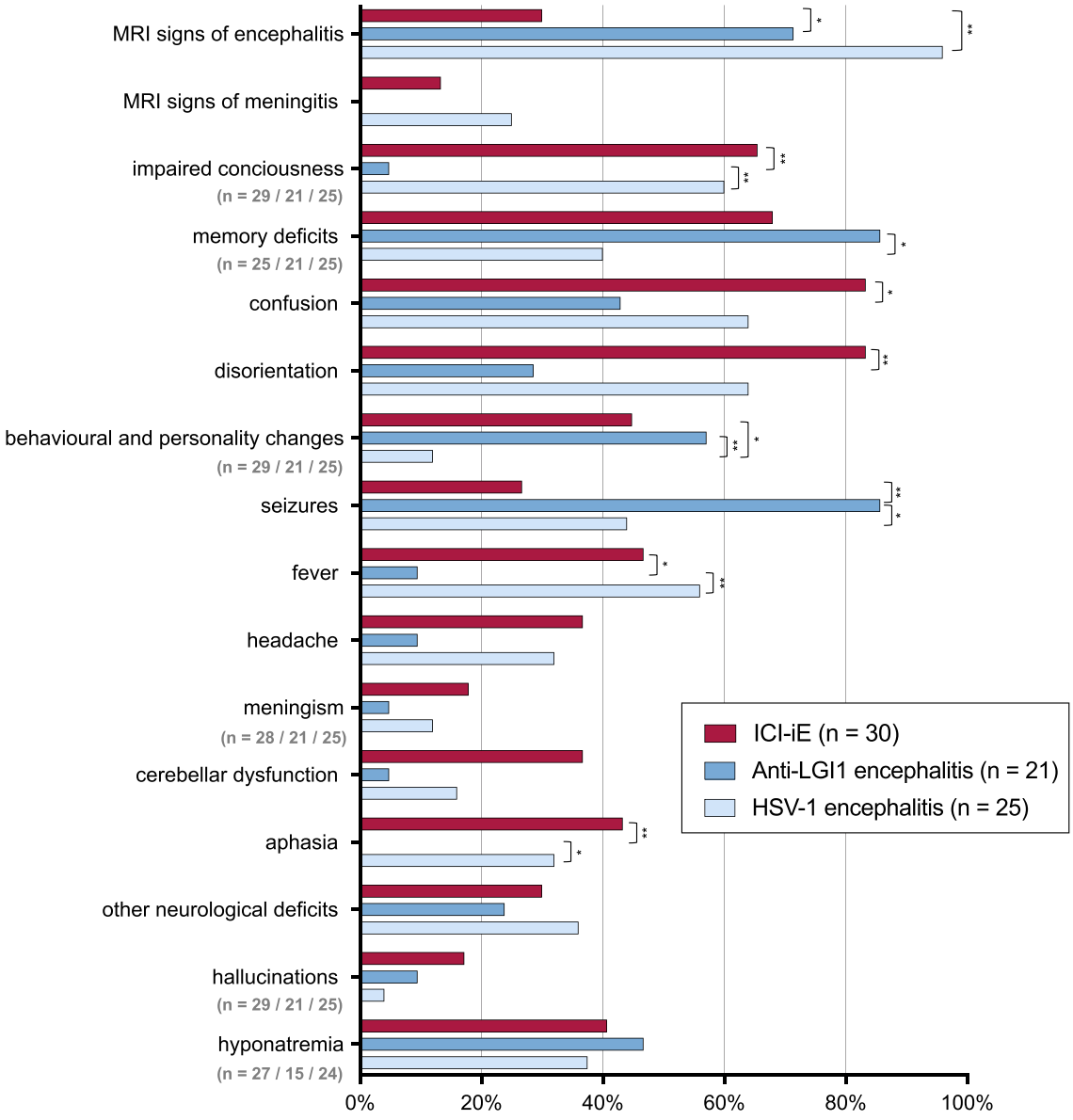

Fig. 1. **Comparison of clinical and diagnostic characteristics of patients with ICI-iE, HSV-1 encephalitis and anti-LGI1 encephalitis.** Bars depict frequencies. In cases of missing data, numbers of cases for ICI-iE, HSV-1 encephalitis and anti-LGI1 encephalitis, respectively, are given in brackets below each characteristic. Group comparisons were performed using the Chi-squared test or Fisher's exact test, if >20% of expected values were less than five. * = $p \leq 0.05$, ** = $p \leq 0.01$; anti-LGI1 = anti-leucine-rich glioma-inactivated; HSV-1 = herpes simplex virus 1, ICI-iE = immune checkpoint inhibitor-induced encephalitis.

In contrast, the clinical presentation of HSV-1 encephalitis highly resembled that of ICI-iE. Only behavioural and personality changes were more common in patients with ICI-iE than in those with HSV-1 encephalitis (11/23 [48%] vs. 3/25 [12%]; p = .03; Fig. 1).

3.2. MRI

Brain MRI was normal in 60% of ICI-iE cases (18/30; Table 1, Fig. 2B). If MRI lesions were present, they were often nonspecific and included focal contrast enhancement or T2 hyperintensities in the white matter, leptomeninges and ependyma (Supplemental Table 1). Typical lesions in the medial temporal lobes and meningeal involvement were described in only three (10%) and four (13%) patients with ICI-iE, respectively (Fig. 2A). In contrast, patients with HSV-1 and anti-LGI1 encephalitis presented typical MRI features of encephalitis more frequently (23/24 [96%] and 15/21 [71%] vs. 9/30 [30%], p = .007 and p = .02, respectively; Figs. 1, 2C and 2D).

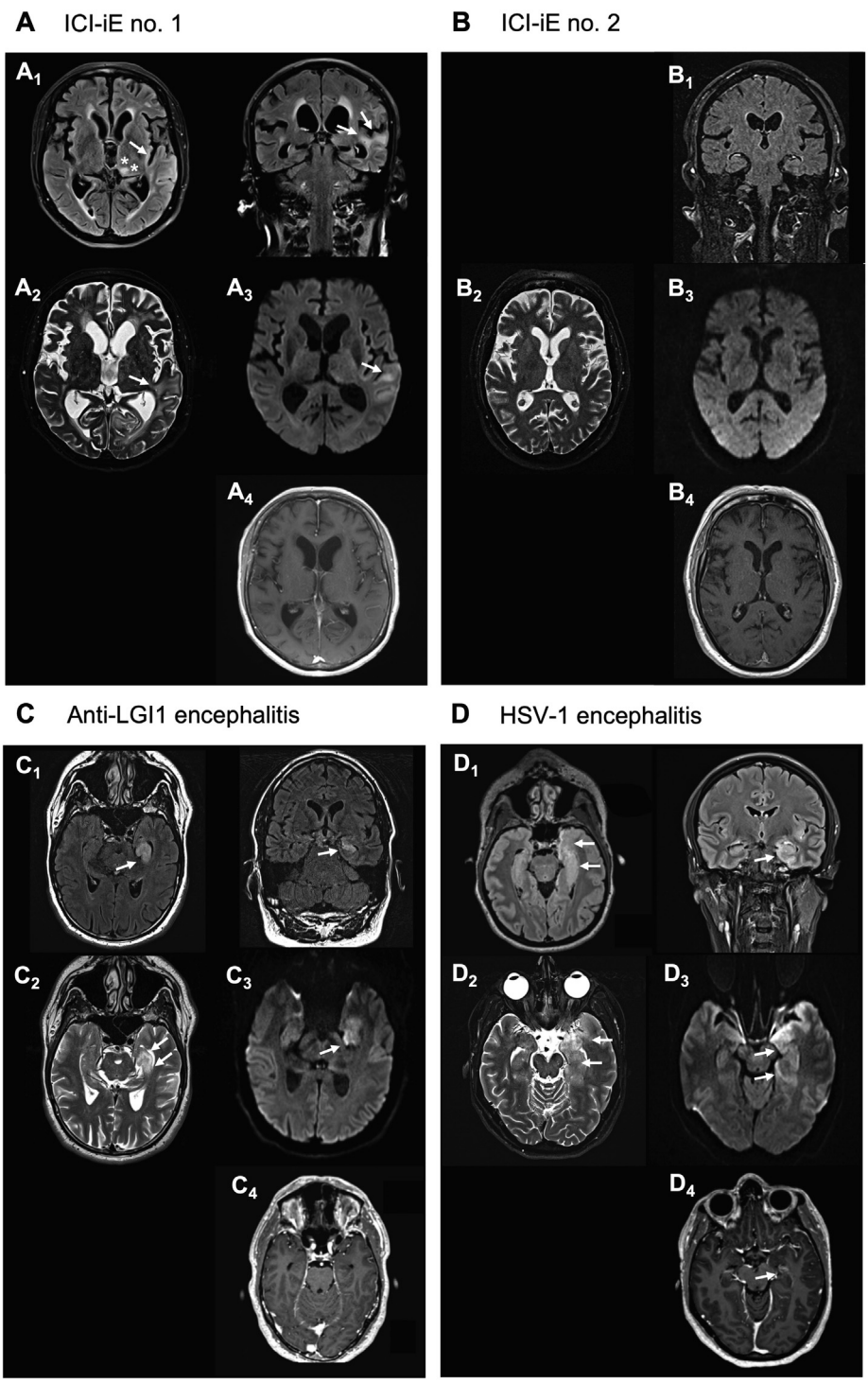

Fig. 2. **MRI in patients with immune checkpoint inhibitor-induced encephalitis (ICI-iE), anti-LGI1 encephalitis and HSV-1 encephalitis.** (A) ICI-iE no.1: Axial (left) and coronal (right) fluid-attenuated inversion recovery (FLAIR) images (A1) and axial T2-image (A2) show a hyperintense signal of the temporal lobe and insular cortex (arrows) and the left thalamus (stars) in a patient with ICI-iE. Diffusion-weighted imaging (DWI) shows discrete signal alterations indicative for vasogenic oedema (arrow, A3), while contrast-enhanced T1-image is normal (A4). (B) ICI-iE no. 2: Normal presentation of FLAIR- (B1), T2- (B2), DWI- (B3), and contrast-enhanced T1-images (B4) in a patient with ICI-iE. (C) Anti-LGI1 encephalitis: Characteristic hyperintense signal and oedema of the left hippocampus (arrows) in axial (left) and coronal (right) FLAIR image (C1) and T2-image (C2). T2-shine-through effect in DWI image (arrow, C3). Normal presentation of contrast-enhanced T1-image (C4). D) HSV-1 encephalitis: Distinct hyperintense signal and oedema of the left hippocampus (arrows) in axial (left) and coronal (right) FLAIR image (D1) and T2-image (D2). T2-shine-through effect in DWI image (arrows, D3). Contrast-enhanced T1-image with discrete leptomeningeal enhancement of left-temporal sulci (arrow, D4).

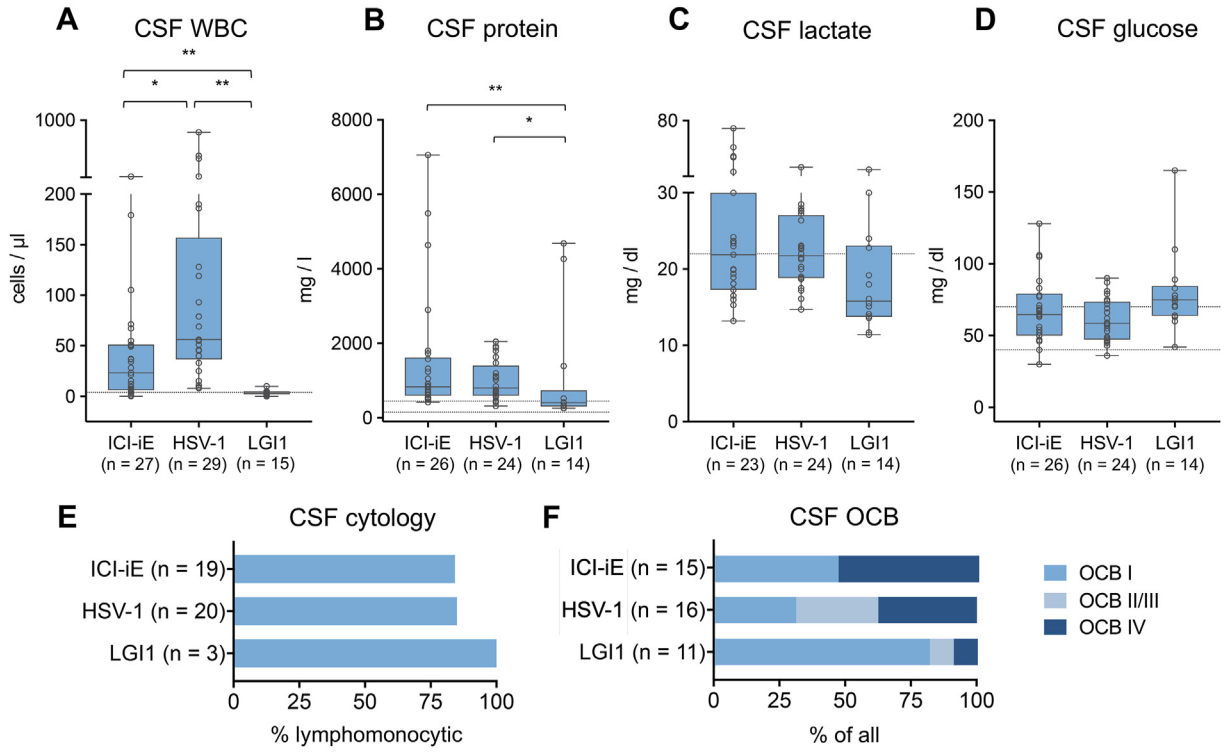

Fig. 3. **Comparison of CSF parameters in patients with ICI-iE, HSV-1 encephalitis and anti-LGI1 encephalitis.** Box plots depict median (horizontal bar), interquartile range (hinges) and minimum and maximum values (whiskers) (A–D). Bar graphs depict frequencies (E, F). Dotted lines depict normal ranges. Group comparisons were performed using the Kruskal–Wallis test. In patients with ICI-iE, CSF WBC (A) and CSF protein levels (B) were elevated compared to patients with anti-LGI1 encephalitis. Levels of CSF lactate (C) and CSF glucose (D) were comparable between all three groups. Patients with ICI-iE showed lymphomonocytic cytology (E), but no intrathecal synthesis of immunoglobulins (F). CSF = cerebrospinal fluid; HSV-1 = herpes simplex virus 1 encephalitis; ICI-iE = immune checkpoint inhibitor-induced encephalitis; LGI1 = anti-LGI1 encephalitis; OCB type I = no oligoclonal bands in CSF or serum; OCB type II/III = oligoclonal bands in CSF indicative for intrathecal synthesis of immunoglobulins; OCB type IV = identical oligoclonal bands in CSF and serum. WBC = white blood cell count; * = $p \leq 0.05$, ** = $p \leq 0.01$.

3.3. CSF

In 29 of 30 patients with ICI-iE (97%), CSF was analysed. Most patients with ICI-iE presented lymphomonocytic pleocytosis (23/29 [79%]; Fig. 3A and 3E) and elevated protein levels (24/26 [92%]; Fig. 3B). Only one patient (3%) showed normal CSF results. The median CSF white blood cell count was 23/µL (IQR, 7–51), which was higher than that in patients with anti-LGI1 encephalitis (median, 3/µL [IQR, 2–5]; p = .007) and lower than that in patients with HSV-1 encephalitis (median, 63/µL [IQR, 38–143]; p = .02; (Fig. 3A). Likewise, CSF protein levels (median, 835 mg/l [IQR, 613–1515]) were higher in ICI-iE compared to anti-LGI1 encephalitis (median, 409 mg/l [IQR, 318–418]; p = .01; Fig. 3B). Levels of CSF glucose and lactate were predominantly normal in all three groups (Fig. 3C and 3D). Intrathecal synthesis of immunoglobulins (type II or III oligoclonal bands) was not observed in any patient with ICI-iE, but in 5 of 16 (31%) and 1 of 11 (9%) patients with HSV-1 and anti-LGI1 encephalitis, respectively (Fig. 3F).

3.4. Antineuronal antibodies

In 11 of 18 patients who were tested for antineuronal antibodies (61%), serum and CSF were analysed for the following IgG antibodies: amphiphysin, Ma2/Ta, Ri, Yo, Hu, CRMP5, DNER, NMDA-R, GABA-b-R, AMPA-R1/2, mGluR5, glycin-R, dopamine-2-R, DPPX, LGI1, CASPR2, aquaporin-4, myelin and GAD65. In the remaining patients, antibody panels were not specified. Only in one patient (6%), antineuronal antibodies were reported. This female patient had positive serum anti-CASPR2 antibodies and clinical signs of limbic encephalitis but no involvement of the peripheral nervous system (e.g., neuromyotonia or dysautonomia).

3.5. Systemic inflammation

Most patients with ICI-iE presented discretely elevated CRP levels (median, 14 mg/dl [IQR, 2–36]), which were higher than those in patients anti-LGI1 encephalitis (0.7 mg/dl [IQR, 0.6–3.9]; p = .04; Fig. 4A). White blood cell count (median, 9/nl [IQR, 6–10]) and procalcitonin levels

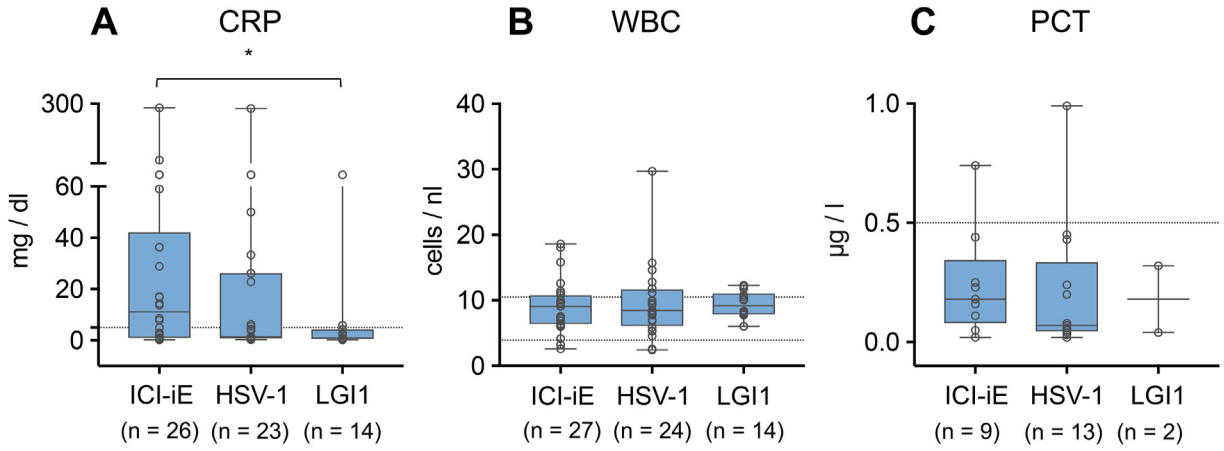

Fig. 4. **Peripheral blood inflammatory markers in patients with ICI-iE, HSV-1 encephalitis and anti-LGI1 encephalitis.** Box plots depict median (horizontal bar), interquartile range (hinges), and minimum and maximum values (whiskers). Dotted lines depict normal ranges. Group comparisons were performed using the Kruskal–Wallis test. Patients with ICI-iE showed higher CRP levels compared to patients with anti-LGI1 encephalitis (A). Median levels of WBC (B) and PCT (C) were normal in all three groups. CRP = c-reactive protein; HSV-1 = herpes simplex virus 1 encephalitis; ICI-iE = immune checkpoint inhibitor-induced encephalitis; LGI1 = anti-leucine-rich glioma-inactivated encephalitis; PCT = procalcitonin; WBC = white blood cell count; * = $p \leq 0.05$.

(median, 0.2 µg/l [IQR, 0.1–0.3]) were normal in patients with ICI-iE (Figure 4B and 4C). Importantly, 21 patients with ICI-iE (70%) had other irAEs at the time of ICI-iE diagnosis (Table 1 and Supplemental Table 1).

3.6. Treatment

The median time from onset of ICI-iE to immunosuppressive treatment was 8 days (IQR, 2–15). Twenty-nine patients with ICI-iE received corticosteroids (97%). Of these, 14 (48%) were treated with high-dose (1.000 mg daily for 3–5 days) intravenous steroids. Additional immunomodulatory therapies or treatment in an intensive care unit were required in 8 (27%) and 11 patients (37%), respectively (Table 1, Supplemental Table 1).

ICI treatment was terminated in all patients, but six (20%) were rechallenged during follow-up. Of these, none presented a flare of ICI-iE after ICI-reintroduction, but three showed an aggravation of other irAEs (namely myositis, myocarditis, and polyradiculitis).

3.7. Outcome

After a median follow-up of 7 months (IQR, 4–27), 24 patients with ICI-iE (80%) were alive. Tumor progression was observed in 5 of 27 patients for whom data were available (19%).

Three (10%), 6 (24%) and 0 (0%) patients died of ICI-iE, HSV-1 encephalitis and anti-LGI1 encephalitis, respectively. Full recovery of symptoms occurred in 13 patients with ICI-iE (43%), which was almost twice as high as in patients with HSV-1 and anti-LGI1 encephalitis (5/25 [20%] and 5/20 [25%]; p = .14 and p = .30, respectively; Table 1). In 14 patients with ICI-iE (47%), sequelae such as cognitive impairment or seizures remained.

Of note, seven patients with ICI-iE (23%) only fulfilled consensus criteria of *possible* ICI-iE [23] but were included as they responded to corticosteroids and the disease course made alternative diagnoses implausible. This might have artificially improved outcome measures in this subgroup. Indeed, no patient with *possible* ICI-iE died of encephalitis (Supplemental Table 1). However, the proportion of patients with full recovery was equal in patients with *possible* and patients with *definite* or *probable* ICI-iE (3/7 [43%] versus 10/23 [43%]).

Time from treatment initiation to improvement of symptoms was 14 (IQR, 3–21), 18 (IQR, 7–28) and 56 (IQR, 28–84) days for ICI-iE, HSV-1 encephalitis and anti-LGI1 encephalitis, respectively. Earlier immunosuppressive treatment correlated with better outcome in patients with ICI-iE (p = .02; Spearman coefficient, r = 0.43 for the outcome categories "full recovery," "recovery with sequelae or ongoing symptoms" and "death of ICI-iE", bootstrap 95% confidence intervals 0.10–0.67).

4. Discussion

In this retrospective analysis, characteristics and outcome of 30 patients with ICI-iE were analysed and compared with 46 patients with HSV-1 or anti-LGI1 encephalitis. Several key messages can be derived from this study. First, presentation and onset of ICI-iE are variable, but impairment of cortical functions (organised thinking, language, orientation, consciousness) is more prevalent compared to anti-LGI1 encephalitis and equally common compared to HSV-1 encephalitis. Second, MRI abnormalities and antineuronal antibodies are less frequent in ICI-iE than previously reported [13–15], while CSF shows signs of inflammation in 97% of patients. Third, ICI-iE requires intensive care unit

treatment in one third of cases and has a mortality rate of 10%, but early immunosuppressive treatment is associated with full recovery.

The clinical spectrum of ICI-iE ranged from diffuse meningoencephalitis to focal encephalitis with diverse neurological deficits. ICI-iE occurred in the context of both ICI monotherapy and combination therapy. Symptom onset varied between one and 59 weeks after initiation of ICI therapy. This heterogeneity of ICI-iE is in line with previous studies [13,14,26] and indicates that ICI-iE encompasses different phenotypes of CNS inflammation, potentially with distinct pathomechanisms [27].

Diagnosing ICI-iE is further complicated by the lack of characteristic MRI features. Consistent to previous data [14–17], MRI was normal in 60% of patients. In contrast, others reported normal MRI in only 36–44% of cases [13,14]. In a meta-analysis of 54 patients with ICI-iE, bitemporal hyperintensities were observed in 52% of cases [15]. However, the dataset was based on case reports focusing on ICI-induced limbic encephalitis, where bitemporal lesions are a characteristic feature. Our data suggest that extra-limbic or unclassifiable forms of ICI-iE – that present MRI abnormalities less frequently – have been underestimated in previous studies. We therefore hypothesise that brain imaging is essential primarily for the exclusion of differential diagnoses (e.g., metastases, leptomeningeal carcinomatosis).

Moreover, the diagnostic value of antibody testing is limited. In our cohort, only one patient was positive for serum anti-CASPR2 antibodies, which have been described in one other case of ICI-iE [28]. Previous data reported positive antineuronal antibodies in 37–58% of patients [12,14,15,20]. However, published data on antibodies are – similar to MRI data – based on literature reviews and case series, which are prone to reporting bias.

On the other hand, unknown antineuronal antibodies with novel reactivity patterns against myelin components [29] and unclassified neuronal structures [20] have been discovered for ICI-induced Guillain-Barré syndrome and ICI-iE, respectively. As antibody-positive forms of ICI-iE seem to be associated with inferior outcome compared to antibody-negative syndromes [13,15,30,31], patients with suspected ICI-iE should be evaluated for novel antibodies using brain tissue-based immunofluorescence assays.

Ten per cent of patients died of ICI-iE. Others reported even higher mortality rates at 13–32% [12–15,20]. To achieve recovery, early treatment initiation is essential. A recent study on ICI-induced myocarditis also highlights the benefit of early (<24 h after admission), high-dose (500–1.000 mg/d) corticosteroid treatment in improving outcome [32].

Therefore, all patients with cancer who received ICIs and present with neurological symptoms should be evaluated for ICI-iE rapidly, especially if they already developed other irAEs. In the emergency setting, we recommend immediate brain imaging (preferably MRI, otherwise contrast-enhanced computed tomography) to exclude brain metastases and stroke. CSF analysis is paramount to exclude CNS infection – including HSV-1 encephalitis – and to confirm brain inflammation.

We identified hyponatremia as a common feature of ICI-iE. To date, only one other case of ICI-iE-associated hyponatremia has been reported [15]. Albeit the mechanisms of hyponatremia in ICI-iE need further investigation, patients with suspected ICI-iE should be examined for SIADH and coexisting ICI-induced hypophysitis, as two alternative causes of hyponatremia [33–35]. Further, clinicians should search for additional irAEs, because 70% of patients with ICI-iE present multiple autoimmune phenomena and coexisting irAE can enhance diagnostic certainty [36].

If ICI-iE is suspected, ICIs ought to be interrupted. After exclusion of tumour progression, infection and metabolic disturbances, high-dose intravenous corticosteroids should be started immediately. In steroid-refractory cases additional immunomodulatory therapies can be necessary [37,38]. Most importantly, further diagnostic work-up (e.g., antineuronal antibodies, EEG) should not delay immunosuppressive treatment.

4.1. Strengths and limitations

To our knowledge, this study presents the largest primary dataset of patients diagnosed with ICI-iE to date. We are the first to show that rapid treatment of ICI-iE is associated with better outcome and to compare ICI-iE with other types of encephalitis. Because this is an international, multicenter study, representativeness of the data is ensured. However, certain limitations must be acknowledged. Because of the retrospective study design, the data might be affected by inaccurate assessment. Observed features might be confounded by the malignancy itself or comorbidities. And even though we used the most recent disease definition [23], diagnostic criteria might have led to the exclusion of atypical cases.

5. Conclusion

ICI-iE is a life-threatening toxicity of ICI treatment with a heterogenous clinical presentation and long-term sequelae in almost half of patients. Careful analysis of CSF is essential as it reveals CNS inflammation in most patients and enables rapid exclusion of infection to ensure early treatment and thereby better outcome. To further improve the safety of ICIs, future research is needed to answer open questions regarding risk factors, treatment strategies and ICI rechallenge in patients with ICI-iE.

Data availability statement

The datasets analysed during this study are available from the corresponding author upon request.

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Conflict of interest statement

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

LMJ, JMV, WB, PH, RM, AC, TH, FM, LR, PB, JAS, TE, MT, CH, LvB, THu, declare no conflicts of interest.

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GVL is consultant advisor for Agenus, Amgen, Array Biopharma, Boehringer Ingelheim, BMS, Evaxion, Hexal AG (Sandoz Company), Highlight Therapeutics S.L., Innovent Biologics USA, MSD, Novartis Pharma AG, OncoSec, PHMR Limited, Pierre Fabre Pharmaceuticals, Provectus, Qbiotics, Regeneron.

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List of abbreviations

AMPA-R1/2 α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor
Anti-LGI1 anti-leucine-rich glioma-inactivated
CASPR2 contactin associated protein 2
CRMP5 collapsin response mediator protein 5
CRP C-reactive protein
CSF cerebrospinal fluid
CTCAE Common Terminology Criteria for Adverse Events
CTLA-4 cytotoxic T-lymphocyte-associated protein 4
CNS central nervous system
DNER delta/notch-like epidermal growth factor-related receptor
Dopamin-2-R dopamine 2 receptor
DPPX dipeptidyl-peptidase-like protein-6
DWI diffusion weighted imaging
EEG electroencephalogram
FLAIR fluid-attenuated inversion recovery
GABA-b-R: gamma-aminobutyric acid B receptor
GAD65 glutamate decarboxylase 65
Glycin-R: glycin receptor
HSV-1 herpes simplex virus 1
ICI immune checkpoint inhibitor
ICI-iE immune checkpoint inhibitor-induced encephalitis
ICU intensive care unit
IgG immunoglobulin G
IQR interquartile range
irAE immune-related adverse events
i.v. intravenous
mGluR5 metabotropic glutamate receptor 5
MRI magnetic resonance imaging
mRS modified Rankin Scale
NMDA-R: N-methyl-D-aspartate receptor
OCB oligoclonal bands
PCT procalcitonin
PD-1 programmed cell death protein 1
PDL-1 programmed death-ligand 1
PNS peripheral nervous system
SERIO Side Effect Registry Immuno-Oncology
SIADH syndrome of inappropriate antidiuretic hormone secretion
WBC white blood cell count

Appendix A. Supplementary data

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