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ORIGINAL COMMUNICATION

Isolated seizures are a common early feature of paraneoplastic anti-$GABA_B$ receptor encephalitis

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Abstract

Objective To report the clinical features and long-term outcome of 22 newly diagnosed paraneoplastic patients with $GABA_B$ receptor antibodies ($GABA_B$R-Abs).

Methods Retrospective clinical study of CSF-confirmed cases of $GABA_B$R-Abs encephalitis.

Results We identified 22 patients (4 female) with $GABA_B$R-Abs, with a median age of 64 years (range 55–85). All were paraneoplastic: 20 small-cell lung cancer, one malignant thymoma, and one uncharacterized lung mass. The most frequent first symptom was the isolated recurrent seizures without cognitive inter-ictal impairment in 17 patients (77%). In the other, three presented the first behavioral disorders and two presented de novo status epilepticus (SE). After a median delay of 10 days (range 1–30), the recurrent seizures' phase was followed by an encephalitic phase characterized by confusion in 100% of cases and SE in 81% ($n=17$), with 53% ($n=9$) non-convulsive SE. Dysautonomic episodes were frequent (36%, $n=8$, bradycardia and central apnea) and killed three patients. CSF study was abnormal in 95% of the cases ($n=21$). At the encephalitic phase, MRI showed a temporal FLAIR hypersignal in 73% ($n=16$) of the cases. First-line immunotherapy was initiated after a median delay of 26 days (range 6–65) from disease onset, and a partial response was observed in 10 out of 20 patients (50%). There was no complete response. Two years after onset, a massive anterograde amnesia affected all still alive patients. Nine patients died from cancer progression (median survival: 1.2 years).

Conclusion Paraneoplastic $GABA_B$R-Abs encephalitis is characterized by a stereotype presentation with an epilepsy phase before an encephalitic phase with dysautonomia. The functional prognosis is poor.

Keywords Paraneoplatic neurological syndromes · Epilepsy · Status epilepticus · GABAB receptor autoantibodies · Small cell lung cancer

Introduction

Autoimmune encephalitis is a growing field of new neurological diseases associated with autoantibodies as biomarkers [1]. An increasing number of surface receptor and synaptic proteins have been identified as targets of these autoantibodies [2]. It is reported that specific neurological symptoms are associated with the type of autoantibody. For example, encephalitis with anti-NMDAR antibodies are characterized by the association of abnormal behavior, seizures, orofacial dyskinesia, and dysautonomia [3], and anti-LGI1 encephalitis is characterized by facio-brachial dystonic seizures [4, 5]. Autoimmune encephalitis associated with autoantibodies targeting the GABA-B receptor ($GABA_B$R-Abs) were first described in 2010 [6]. GABA-B receptor is a pre- and post-synaptic receptor involved in the glutamate regulation system [7]. The associated neurological symptoms were first described as limbic encephalitis with prominent seizures, often paraneoplastic with associated small-cell lung cancer (SCLC), and with poor prognosis [6, 8–13]. Non-limbic phenotypes were also described in some cases [8, 14–16]. A total of 83 cases have been described; however, the initial symptoms and long-term autonomy remain to be fully described. To address this, we provide herein a systematic description of clinical and paraclinical presentation, progression of symptoms over time, response

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to treatment, long-term cognitive, and functional outcome of 22 patients with paraneoplastic $GABA_BR$-Abs encephalitis.

Methods

Patients

This observational retrospective study is based on 22 patients diagnosed after the examination of CSF samples tested for autoimmune encephalitis at the French Paraneoplastic Neurological Syndrome Reference Center from January 2011 to March 2017. To be considered positive, CSF analysis had to fulfill the following criteria: CSF samples that produced an indicative pattern on rat brain hippocampus immunostaining and a positive cell-based assay (CBA) on HEK293 cells expressing $GABA_{B1a}$ and $GABA_{B2}$ receptors. End-point dilution of CSF and serum $GABA_BR$-Abs were calculated using CBA (Table 1); all the CSF samples had an anti- $GABA_bR$ titer > 1/100 and were negative for all other onconeural antibodies (Hu, Yo, Sox-1, CV2/CRMP5, Ri, amphiphysine, GAD, Ma2/Ma1, Tr/DNER, $AMPA_R$, and $NMDA_R$). Clinical information was obtained by the authors when they followed the patients or from telephone interviews, questionnaires filled out by the referring neurologists, and hospitalization reports obtained at the time of the biological diagnosis and during the follow-up. As we performed a retrospective study, cognition evaluation was not standardized, but all the patients had at least MMSE and frontal assessment battery and most of them a MOCA or a more extensive neuropsychological test (ADAS-Cog). None of the patients have been previously published. Sera and CSF samples are deposited, with signed informed consent, in the biobank "Neurobiotec" (Hospices Civils de Lyon, France, n° 0033–00046, AC-2013-1867, NFS96-900). The institutional review board of the Hospices Civils de Lyon approved this study.

Definition of clinical events

The first symptoms were those initially reported by the patients and/or their relatives (seizure and/or behavioral or affective disorders), or observed at the first medical assessment for very acute cases. The subsequent symptoms were those that arose after an interval of at least 24 h after the first symptom. They were categorized in subgroups: (1) isolated seizures, (2) status epilepticus (SE), (3) confusion, (4) behavioral disorders, (5) coma (Glasgow coma scale score < 8), and (6) dysautonomia. The interval between the first neurological symptoms and subsequent symptoms, between the first symptoms and the diagnosis of $GABA_BR$-Abs encephalitis, and that between the first symptoms and the first immunomodulatory and oncologic treatment were calculated. Neurological disability was assessed using the modified Rankin Scale (mRS) [17]. MRI and EEG results were classified according to referring neurologist conclusions. Complete response to immunotherapy was defined as full autonomy recovery at 3 months. In patients without full recovery, partial response was defined by end of the seizures, extubation, or cognitive/autonomy improvement according to referring neurologist within the 2 weeks following therapy. When response was followed by a new worsening within a month, the response was considered as transient.

Results

Patients

We identified 22 patients (4 female, see Table 1) with $GABA_B$-Abs, who had a median age of 64 years (range 55–85). All cases were paraneoplastic. Nearly all the patients ($n = 20$, 91%) had concomitant SCLC, one malignant Thymoma, and the last one an uncharacterized lung mass. The median interval from symptom onset to diagnosis was 27 days (range 9–63). Three patients (14%) had the previous autoimmune disease: myasthenia gravis, systemic lupus erythematosus, and idiopathic thrombocytopenic purpura. No seizure had been previously reported in any of the patients. All but one patient had the previous history of smoking, and one-third ($n = 8$, 36%) alcohol abuse. Careful systematic investigation of the course of the disease found that 17 patients (77%) had a similar stereotyped progression (Fig. 1) that included three different phases and which were classified as (i) isolated seizure phase, (ii) encephalitic phase, and (iii) recovery phase. In the other patients ($n = 5$, 23%), the seizure phase was lacking: at the initial presentation, these patients developed suddenly confusion and status epilepticus (two cases), or cognitive disturbances without seizures (three cases).

Isolated seizure phase

Seizures were the first symptom to occur in 77% of cases ($n = 17$). Seizures were focal ($n = 5$, 29%), focal secondarily generalized ($n = 4$, 24%) or generalized ($n = 8$, 47%). In case of focal seizures, the symptoms suggested a temporal medial starting point. No cognitive or affective inter-ictal impairment was observed and the neurological examination was normal between episodes of seizure in all the patients during this phase of the disease. The median duration of isolated seizures was 10 days (range 1–30). The interval between first and second seizure ranged from a few hours to 10 days. During this seizure phase, most of the patients ($n = 13/17$, 76%) had a first hospitalization but were discharged in regard to

Table 1 Clinical characteristics of all patients

Pt	Age/sex	Autoantibodies titers (< 1/100)	1. First symptom 2. Second symptom (days between)	Brain MRI; Hippocampus hypersignal	CSF	Immunotherapy (delay days)	Effect of immunotherapy	Associated cancer	Initial response to cancer treatment	Follow-up (months) Cognitive outcome
1	61/M	CSF: > 1/100 Serum; NA	1. PS 2. RNCSE (4 days)	Left	WC: 128/mm^3 Prot :0.49 g/L OCBs; Pos	Steroids then IVIg (43)	End of seizures	SCLC	No response	Cancer progression (9[a], cardiac arrest)
2	69/M	CSF: 1/10,240 Serum: 1/81,920	1. PS 2. RNCSE (15 days)	Bilateral	WC: 24/mm^3 Prot:0.58 g/L OCBs: NA	Steroids then IVIg (23)	No	SCLC	Partial response	Cancer progression (15[a], unknown) Severe diffuse cognitive impairment (mRS 4/institution)
3	55/F	CSF: 1/2560 Serum :1/20,480	2. Partial SE	None	WC: 4/mm^3 Prot:1.02 g/L OCBs: Pos	Steroids then IVIg (65)	End of seizures	SCLC	Not evaluated	Death (13[a], mesenteric ischaemia) Stabilization, partial seizures (mRS 3/home)
4	60/M	CSF: 1/320 Serum:1/5120	1. Partial SE 2. NCSE	Left	WC: 43/mm^3 Prot:0.79 g/L OCBs: NA Tau: 1109 ng/L Ptau181: 52 ng/L Aβ 1–42: 1194 ng/L 14–3–3: Equivocal	None first, then CP (93)	No	SCLC	Complete response	Remission (38) Anterograde amnesia, behavioral disorders (mRS 2/home)
5	75/M	CSF: > 1/100 Serum: NA	1. GS 2. confusion (3 days)	None	WC: ↗ Prot: ↗ OCBs ; NA	Steroids (19)	No	SCLC	Not evaliuated	Death from LE (1[a], respiratory arrest)
6	70/M	CSF: 1/640 Serum:1/40,960	1. GS 2. RNCSE (30 days)	Bilateral	WC: 2/mm^3 Prot: 0.30 g/L OCBs: NA	Steroids and IVIg (44)	No	SCLC	Complete response	Remission (51) Anterograde amnesia, depression (mRS 3/home)
7	61/M	CSF: 1/10,240 Serum:1/10,240	1. Anxiety, irritability 2. GSE (15 days)	Left	WC: 17/mm^3 Prot: 0.77 g/L OCBs: Pos	IVIG (39)	No	SCLC	Not evaluated	Cancer progression (12) MAA, disorientation, behavioral disorders (mRS 5/home)
8	70/M	CSF: > 1/100 Serum: NA	1. Perseverations, 2. GSE (60 days)	None	WC; 20/mm^3 Prot :0.30 g/L OCBs; Neg	None	NA	SCLC	Not evaluated	Death from LE (1[a], acute respiratory distress syndrome)

Table 1 (continued)

Pt	Age/sex	Autoantibodies titers (< 1/100)	1. First symptom 2. Second symptom (days between)	Brain MRI; Hippocampus hypersignal	CSF	Immunotherapy (delay days)	Effect of immunotherapy	Associated cancer	Initial response to cancer treatment	Follow-up (months) Cognitive outcome
9	66/M	CSF: 1/1280 Serum:1/20,480	1. PS 2. NCSE (1 days)	Left	WC; 0/mm^3 Prot :0.70 g/L OCBs; NA	Steroids and IVIg, then CP (24)	No	B2 (Thymome)	Complete response	Remission (30) Light anterograde amnesia (mRS 2/home)
10	85/M	CSF: > 1/100 Serum:1/2560	1. GS 2. GSE (15 days)	None	WC: 10/mm^3 Prot :0.52 g/L OCBs: NA	Steroids and IVIg, then CP (41)	No	SCLC	Not evaluated	Death (26 †, unknown) Anterograde amnesia (mRS 1/home)
11	65/M	CSF: 1/2560 Serum:1/5120	1. GS 2. RNCSE (15d)	None	WC: 12/mm^3 Prot :0.29 g/L OCBs: Pos Tau; 1274 ng/L Ptau181; 48 ng/L Aβ 1–42; 1481 ng/L 14-3-3: Pos	IVIG then CP (38)	End of coma	SCLC	Complete response	Cancer progression (43[a], cerebral metastatic relapse) MAA, disorientation, depression MMSE: 21/30 (mRS 3/home)
12	60/M	CSF: 1/40,960 Serum:1/81,920	1. Anxiety, Apathy Insomnia 2. Confusion (90 days)	Bilateral	WC; 90/mm^3 Prot; NA g/L OCBs: NA	Steroids and IVIg (6)	No	SCLC	Not evaluated	Death from LE (1†, acute respiratory distress syndrome)
13	76/F	CSF: 1/2560 Serum: NA	1. PS 2. PSE (5 days)	Right	WC: 15/mm^3 Prot :0.91 g/L OCBs: Pos	Steroids and IVIg (29)	Autonomy improvement	SCLC	Complete response	Cancer progression (8†, unknown)
14	61/M	CSF: 1/1280 Serum: NA	1. GS 2. Confusion (10 days)	Bilateral	WC: 1/mm^3 Prot:0.67 g/L OCBs: Neg Tau; 1120 ng/L Ptau181; 40 ng/L Aβ 1–42; 1006 ng/L 14-3-3: Neg	IVIG (13)	Autonomy improvement	SCLC	Complete response	Remission (24) Anterograde amnesia, depression, MMSE 24/30 (mRS 3/home)
15	62/M	CSF: 1/20,480 Serum:1/40,960	1. GS 2. GSE (3v)	Bilateral	WC: 44/mm^3 Prot:0.86 g/L OCBs; Pos	Steroids then IVIg (14)	No	SCLC	Partial response	Stability (12) MAA, behavioral disorders, seizures (mRS 3/institution)

Table 1 (continued)

Pt	Age/sex	Autoantibodies titers (< 1/100)	1. First symptom 2. Second symptom (days between)	Brain MRI; Hippocampus hypersignal	CSF	Immunotherapy (delay days)	Effect of immunotherapy	Associated cancer	Initial response to cancer treatment	Follow-up (months) Cognitive outcome
16	64/M	CSF: 1/5120 Serum:NA	1. GS 2. NCSE (12 days)	Right	WC; 30 /mm^3 Prot :NA g/L OCBs; NA	Steroids then IVIg then CP (19)	Extubation	SCLC	Partial response	Death (15[a], unknown) MAA, behavioral disorders, seizures (mRS 5/home)
17	62/M	CSF : > 1/100 Serum:NA	1. PS 2. Confusion (6 days)	None	WC; 23 /mm^3 Prot :0.44 g/L OCBs; Pos	IVIG (26)	End of seizures	SCLC	Complete response	Cancer progression (14) Light anterograde and retrograde amnesia (mRS 2/ home)
18	58/M	CSF: 1/640 Serum:1/10,240	1. PS 2. SE (13 days)	Left	WC; 8/mm^3 Prot; 0.46 g/L OCBs; Neg	Steroids then IVIg (36)	No	SCLC	No response	Cancer progression (25[a], unknown)
19	71/F	1/2560 Serum: NA	1. PS 2. RNCSE (9 days)	Bilateral	WC; NA Prot; NA OCBs; Pos	IVIg then Steroids (14)	No	Probable lung cancer	Not evaluated	Cancer progression (17[a], lung infection) MAA, bed-ridden (mRS 3/ home)
20	63/M	CSF: 1/320 Serum:1/5120	1. PS 2. RNCSE (4 days)	Bilateral	WC; 10/mm^3 Prot; O.81 g/L OCBs; NA	IVIg and steroids (16)	End of coma	SCLC	Not evaluated	Still hospitalized (3)
21	63/F	CSF: 1/5120 Serum: 1/20,480	1. GS 2. SE (3 days)	Bilateral	WC; 100/mm^3 Prot :0.40 g/L OCBs; NA	IVIg and steroids (32)	End of seizures	SCLC	Not evaluated	Still hospitalized (4)
22	72/M	CSF: 1/5120 Serum: 1/20,480	1. PS 2. Confusion (12 days)	Right	WC; 80 /mm^3 Prot :↗ OCBs :NA	IVIg (43)	No	SCLC	Not evaluated	Cancer treatment (2)

All the autoantibodies' titers were higher to 1/100 in the CSF, but further dilution was not always achievable and some sera were not available (NA)

CSF cerebro-spinal fluid, OCBs oligoclonal bands, *WC* white cells, *NA* not available, *PS* partial seizure, *GS* generalized seizures, *(P/G) SE* (Partial/Generalized) status epilepticus, *(R)NCSE* (Refractory) non-convulsive status epilepticus, *IVIg* intravenous immunoglobulin, *CP* cyclophosphamide, *SCLC* small-cell lung cancer, *LE* limbic encephalitis, *CT* chemotherapy, *mRS* modified ranking scale, *MAA* massive anterograde amnesia

[a]Death

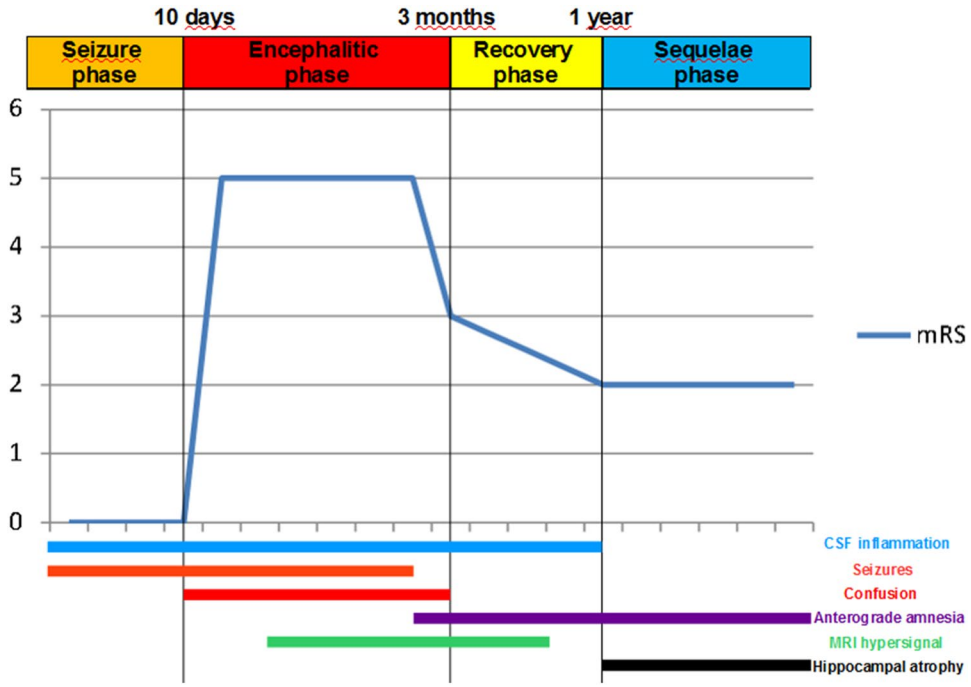

Fig. 1 Schematic view of disease course of GABABR-Abs encephalitis. This figure summarizes the clinical evolution of the patients with GABABR-Abs encephalitis during time in three different phases

their good inter-ictal general status and the absence of obvious cognitive impairment. No neuropsychological test was performed; for these patients, appearance of the encephalitic phase led to a second hospitalization. In ten patients, we had sufficient data to assess the dynamics of epilepsy progression: 7/10 patients had an increasing frequency of seizures, up to several times a day, and 3/10 patients had increasing severity of the seizures (from focal to generalized).

Encephalitic phase

All patients eventually presented with an encephalitic phase defined by the association of cognitive and behavioral disturbances with seizures. This phase started by confusion (100%) and focal or generalized SE ($n=17$, 81%); a third of them were refractory ($n=6$, 35%).. Non-convulsive SE was observed in nine of the patients (53%). Just over one-third of patients ($n=8$, 38%) developed dysautonomic episodes with central apnea and bradycardia that could be life threatening: one patient died from a respiratory arrest, another one suffered from a cardiac arrest and subsequently needed cardiac pacing. Transfer to ICU was frequent ($n=14$, 64%), due to status epilepticus ($n=9$, 64%), coma ($n=4$, 29%), or dysautonomia ($n=1$, 7%). Endotracheal intubation was necessary in 13 patients; the median duration was 12.5 days (range 2–54). Lung infection was frequently observed ($n=8$, 38%) and its association with bradypnea was lethal in two patients. Hospitalization in ICU seemed associated with a better survival ($n=13/13$, 100% in ICU, $n=6/9$, 67% in the conventional ward). At this stage, general status and superior functions were heavily altered with coma (59%), behavioral disorders, or agitation episodes (59%), sometimes alternating. Physical examination found unexplained fever ($n=3$, 14%), hemiparesis ($n=2$, 9%), or extrapyramidal symptoms ($n=1$, 5%). At the end of this acute period, the main feature was severe behavioral disorders ($n=13$, 59%) with agitation and confusion. The median interval between onset of the acute encephalitis and the end of the hospitalization was 79 days (range 18–106).

Recovery and sequelae phase (Table 1)

After the encephalitic phase, slowly progressive improvement occurred in all the surviving patients. Most were heavily handicapped at first: the median modified Rankin score (mRS) was 4 (range 2–5). The neurological symptoms were anterograde amnesia ($n=13$), temporal and spatial disorientation ($n=14$), and behavioral disorders ($n=9$). Detailed information was available in 13/14 patients alive at 12 months, and 6/7 still alive at 24 months. In 6 patients with sufficient follow-up to ascertain stabilization, median duration of the recovery phase was 10 months (range 8–22). Seizures were rarer at 12 months ($n=5$, 38%) and absent at 24 months. Anterograde amnesia remained a cardinal symptom and affected all patients. Neuropsychological testing usually showed pure severe amnestic dysfunction with mild dysexecutive troubles. Behavioral disorders decreased over time: from 100% (22/22), to 54% (7/13) at 12 months, and 17% (1/6) at 24 months. Depression affected two-thirds of the patients at 24 months. Autonomy improved: median mRS was 3 (range: 2–5) at 12 months and 2 (range 1–3) at 24 months. At 12 months, 83% ($n=10/12$) of the patients

had been discharged; none recovered pre-morbid cognitive status and occupation.

Paraclinical features

During seizure phase, brain MRI and most of inter-ictal EEG were normal ($n=5/5$,100% and $n=7/9$, 78% respectively). Only one EEG found a temporal focus of slow waves without seizures. CSF studies were rare during the seizure phase ($n=3/17$, 18%) but were all abnormal, including lymphocytic pleocytosis ($n=3$, range 10–184 cells/mm^3) and elevated CSF protein levels ($n=2$, 0.52 and 0.92 g/L). Oligoclonal bands were researched in 2/3 patients and were positive in both cases. All the patients had CSF and serum $GABA_B$ receptor antibodies. Anti-Hu and Sox-1 antibodies were respectively found in one and three patients, and we identified no other associated autoantibodies.

During the encephalitic phase, 77% ($n=17/22$) of brain MRI were abnormal and often showed medial temporal lobe hypersignal ($n=16$, 73%; bilateral in five cases), with in some cases weak temporal contrast enhancement ($n=4$, 18%). We also observed bilateral T2 hypersignal of the pallidum in one patient. Median delay to assess temporal hypersignal on MRI was 19 days (range 9–49) after first symptom. EEG showed more specific features with temporal lobe seizures ($n=7/17$, 41%) or slowing focus ($n=2/17$, 12%). Normal EEG was much rarer ($n=6/17$, 35%). Inflammatory CSF was almost constant ($n=20/21$, 95%) showing pleocytosis ($n=17/21$, 81%, median: 20.5 cells/mm^3, range 8–128), activated plasmocytes and oligoclonal bands ($n=8/11$, 73%). CSF neopterin was moderately elevated when dosed ($n=3$, range 7.1–7.4 nmol/L, $N<5$ nmol/L). In three patients, CSF biomarkers for Alzheimer's disease diagnosis were studied during encephalitic phase and provided the indirect evidence of neuronal lysis: strong increase of tau protein (1109, 1274 and 1120 ng/L, $N<350$ ng/L) with normal phospho-tau and Aβ1–42 levels (Table 1), 1/3 patients had positive p14-3-3 protein in CSF.

Patient management

Immunotherapy

Most of the patients ($n=20/22$; 91%) received a first line of immunotherapy (Fig. 2) included IVIg and steroids ($n=13$, 65%), IVIg only ($n=5$, 25%), IV steroids only ($n=1$, 5%), and IVIg, steroids, and plasma exchange ($n=1$, 5%). Median treatment delay after symptoms onset was 26 days (range

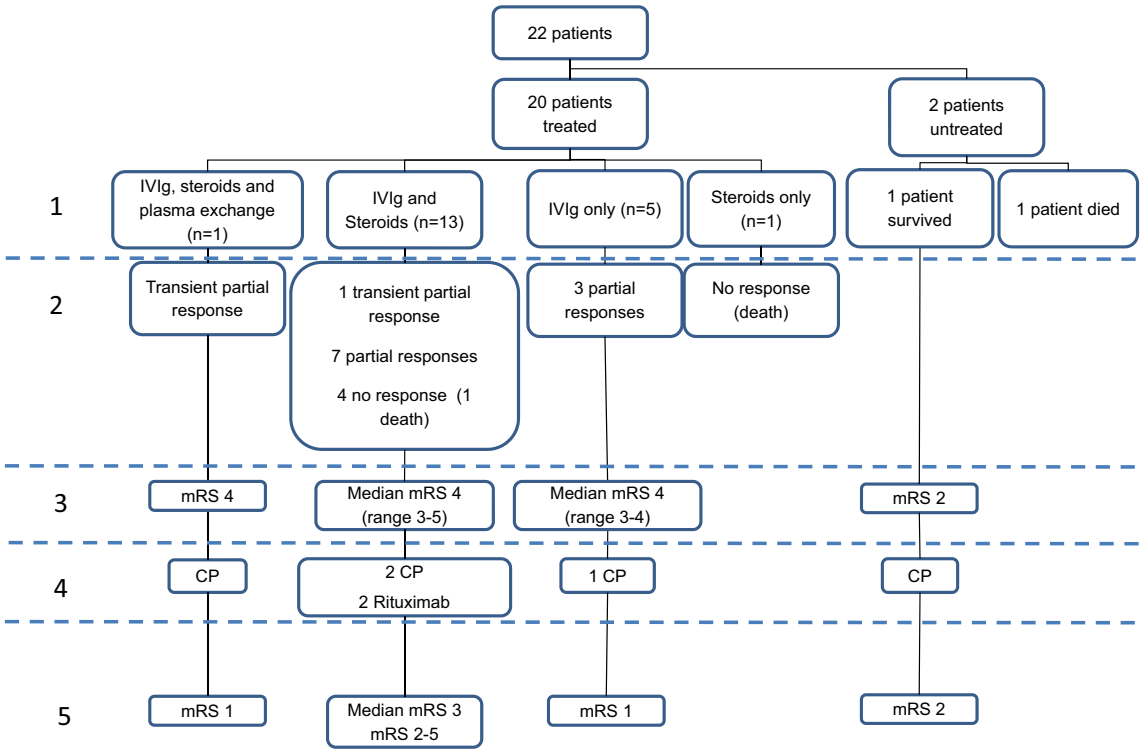

Fig. 2 Immunotherapy management. Flowchart summarizing the different immunological treatments as well as patient outcomes. *IVIg* Intravenous immunoglobulins, *mRS* modified Rankin Score, *CP* cyclophosphamide. 1—first line of immunotherapy; 2—initial response after the first line of immunotherapy; 3—Patients' mRS 3 months after first-line immunotherapy onset; 4—second line of immunotherapy; 5—final mRS of patients after stabilization

6–65). All these patients were treated after encephalitic phase onset within a median delay of 17 days (range 3–65). Two patients (9%) did not receive immunotherapy at the encephalitic phase. In two patients (9%), transient partial response was reported (cognitive improvement); in 9 other patients (41%), sustained partial response was obtained (end of seizures in four cases, conscience improvement in four cases, and cognitive improvement in one case). No complete response was observed. Ninety-five percent of those still alive ($n=18/19$) received maintenance treatment during the cognitive phase with IVIg (61%, $n=11$), cyclophosphamide (28%, $n=5$), or rituximab (11%, $n=2$).

Cancer

All 22 cases had a history of cancer; either SCLC ($n=20$, 91%), malignant thymoma, and patient 19 had a lung mass, without histology. The neurological syndrome preceded the cancer diagnosis in 95% of patients ($n=21$), within a median delay of 7 weeks (range 2–47). In one patient, the initial oncological evaluation (CT-scan and PET-scan) was negative and an SCLC was diagnosed at a disseminated stage 8 months after encephalitis onset. In one patient, the neurological syndrome began 18 weeks after cancer diagnosis, while she was considered in remission. One patient was cured from an SCLC without paraneoplastic syndrome 8 years before recurrence concomitant with the encephalitis onset. Only 14% of the SCLC ($n=3$) were disseminated at diagnosis. A syndrome of inappropriate anti-diuretic hormone secretion (SIADH) was observed in three patients (14%). Among the patients with SCLC, three died before oncological treatment; the 17 other patients were treated by chemotherapy (platinum salts and etoposide) after a median 10 weeks (range 4–48). Two patients were too recently treated to assess cancer response. Two patients (12.5%) died before response assessment, three patients (18.75%) showed no response, one patient (6.25%) had stabilization, and nine patients (56.25%) had a documented the initial tumor response. During the follow-up of these nine patients, four were in remission, three had secondary local relapse, and two had metastatic relapse.

Postmortem neuropathological findings (Fig. 2)

An autopsy was performed in patient 12 who died from respiratory distress during the encephalitic phase, despite treatment with IVIg and steroids. Gross examination did not reveal any macroscopic lesion. Microscopic analysis found inflammatory infiltrates and gliosis in both temporal lobes and especially in hippocampi. These inflammatory infiltrates were mainly composed of a mixed population of CD4 and CD8 positive T lymphocytes distributed in the parenchyma and around the vessels regardless of their size, associated with activated astrocytes and microglia (Fig. 3). In perivascular areas, T cells were associated with B-cell cuffs and macrophages. In the hippocampus, the pyramidal neurons of the cornu ammonis were dispersed and sometimes shrunken and necrotic (Fig. 3). Although these neuronal lesions might be secondary to hypoxia or seizures, cytotoxic T lymphocytes were observed in close contact with neurons and glial cells, suggesting a cell-mediated cytotoxicity. Other examined brain structures (frontal, parietal and occipital cortices, thalami, brainstem, cerebellum, and hemispheric white matter) were spared of neuron damage and inflammation.

Discussion

To the best of our knowledge, the present study is the first to highlight a pre-encephalitic phase of paraneoplastic $GABA_BR$-Abs encephalitis and provides further data on its early and late stages as well as its long-term functional and cognitive outcome. Due to the retrospective design, missing data can introduce a bias. However, a general picture of paraneoplastic $GABA_BR$-Abs encephalitis does emerge. The population is homogeneous compared to other series [6, 8–11] with a high titer of $GABA_BR$-Abs in all patients both in the serum and the CSF, an homogeneous clinical presentation, and the presence of a cancer in all patients. We did not find any patient under the age of 55 and all cases were paraneoplastic, usually associated with an SCLC, which is also the most frequently observed cancer elsewhere (89%) [6, 8–11]. The outcome of our series seems also poorer than in the others [6, 8–13, 16, 18]. In the literature, $GABA_BR$-Abs limbic encephalitis is not associated with cancer in about 40% of the cases ($n=38/94$) [6, 8–11] .The patients without associated cancer are younger with a lower level of $GABA_BR$-Abs, that are sometimes only present in the serum [10, 11]. Furthermore, non-paraneoplastic $GABA_BR$-Abs encephalitis seems to better respond to immunomodulatory treatment and have a better prognosis [6, 8–11]. The poor outcome of our patients is probably explained by the paraneoplastic origin of our patients. Interestingly, when occurring before the age of 45, $GABA_BR$-Abs encephalitis seems to be never associated with a cancer and $GABA_BR$-Abs are frequently observed only in the serum [6, 8–13, 16, 18]. As we screened first only CSF to identify the patients with $GABA_BR$-Abs encephalitis, it is, therefore, possible that our technique missed some patients and that the clinical pattern reported herein is more specific to paraneoplastic cases.

In our series, at the earliest stage of the disease, only a minority of patients presented with classical limbic encephalitis, as defined by the association of epilepsy and behavioral/cognitive disorders; most experienced a subacute seizure phase that could precede behavior disorders by up to 1 month. Interestingly, inter-ictal neurological

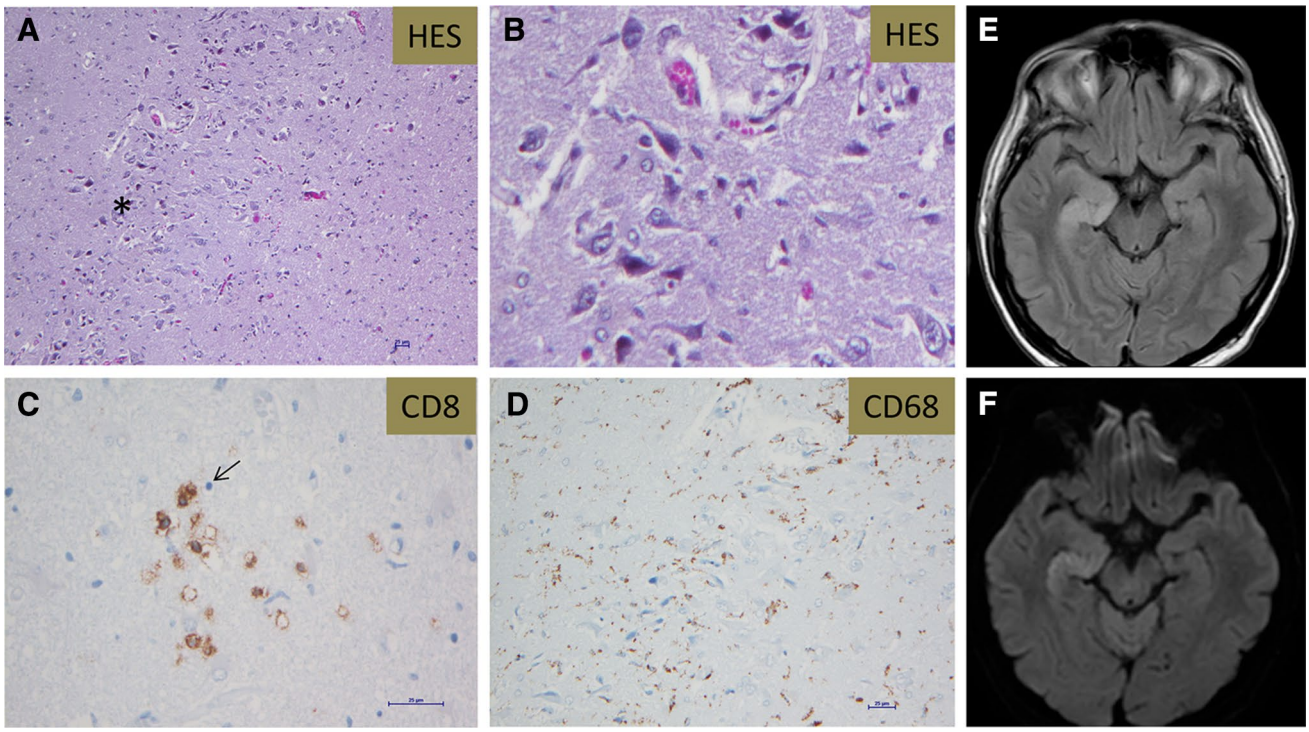

Fig. 3 Pathological microscopic findings of postmortem examination and Brain MRI (patient 12). **a, b** HES staining reveals altered hippocampal cornu Ammonis (CA, asterisk) with dispersed and acidophilic shrunken neurons (arrows) and gliosis; low (**a**) and high (**b**) magnification. **c** CD8 immunostaining revealing the abnormal presence of cytotoxic T lymphocytes in the hippocampus. CD8-positive cells are found in close contact with neurons (arrows). **d** CD68 immunostaining of the same area representative of the massive microglial activation found in the two temporal lobes; low (**c**) and high (**d**) magnification. **e** FLAIR sequences of the hippocampi during the encephalitic phase with high hypersignal on both temporal lobes. **f**: Diffusion sequences with right hippocampus hypersignal

examination and brain MRI were normal during this phase, while most EEG recordings had only non-specific features. Only three patients had lumbar puncture at this stage, but CSF analysis revealed inflammation in all of them, suggesting that CSF analysis could be the most reliable and sensitive exam to suggest autoimmune encephalitis at this phase. This phase seems responsible for a diagnosis delay.

The role of $GABA_BR$-Abs in the encephalitis symptoms is unclear. $GABA_BR$ are pre and post-synaptic G-protein-coupled receptors [19]. $GABA_{B1a}R$ are on axon terminals and mediate presynaptic inhibition of glutamate release; they are key agents of network oscillations by modulating NMDA receptor activation, limiting duration of high-activity states, firing frequency and thus preventing excessive neuronal synchronization, particularly in the hippocampus [20]. $GABA_{B1b}R$ are more frequently found in post-synaptic in dendritic sites and induce a slow inhibitory post-synaptic potential [7]. Disruption of $GABA_BR$ in mice [21, 22], especially $GABA_{B1a}$ [23, 24], and some genetic variants in human [25] are associated with temporal epilepsy. We can speculate that blockage by $GABA_BR$-Abs at the initial stage of the disease promotes synchronization of large groups of neurons and consequently seizures. $GABA_BR$-Abs could play a major role in the initial phase of the encephalitis.

The encephalitic phase was constant and followed seizure phase. Acute mortality was due to dysautonomia, suggesting that the initial management and monitoring of these patients in the ICU should be systematically proposed. We found that the number of abnormal brain MRI dramatically increased during this phase with bi-temporal FLAIR hypersignal and increased volume of hippocampi, suggesting an intense immune reaction in the temporal lobes. CSF increased total tau level and the autopsy findings provided evidence for a substantial neuronal death during this phase, likely to be due to T-cell-mediated neuron cytotoxicity rather than functional antibody-induced neuronal blockade.

A slow and partial improvement occurred during the weeks after the acute encephalitic phase that lasted about 8–11 months. Massive anterograde amnesia and disorientation remained key features of all patients, suggesting neuronal death limited to the hippocampus. $GABA_BR$ are also involved in mood regulation, anxiety [26] and sleep [24, 25], in learning and memory processes [19, 27]. $GABA_BR$ blockade by autoantibodies could explain in part these symptoms, but the lack of improvement of

anterograde amnesia under treatment could suggest neuronal death rather than functional impairment of synaptic transmission. One possible cause could be excito-toxicity due to extended SE, but the hypothesis of a T-cell-mediated cytotoxicity could also be considered; it is supported by the pathological observations herein and previously reported [8, 18], that found the presence of cytotoxic CD8 + T lymphocytes in close contact to damaged neurons, evoking direct immune neuron injury. These pathological findings are similar to those observed in encephalitis with intracellular targets [28–31]. We could speculate that encephalitis with intracellular targets is directly mediated by immune T cells, whereas in paraneoplastic $GABA_BR$-Abs encephalitis, functional blockade by autoantibodies could play a first role during the seizure phase, before neuronal death at the encephalitic phase.

The present study demonstrates that three different steps characterize paraneoplastic $GABA_BR$-Abs encephalitis. In a first step, patients develop recurrent seizures with normal inter-ictal examination that could correspond to a "glutamatergic storm" in a relationship to a possible direct role of anti-$GABA_BR$-Abs and a $GABA_BR$ blockage. In a second step, characterized by refractory SE and dysautonomia, the immune reaction could lead to neuronal damage limited to the temporal lobes, maybe, favored by hippocampal cellular immune infiltration of cytotoxic CD8 T cells. After this immune attack, the patients progressively improve, although severe memory deficit persisted in all the cases. Immunotherapy is probably too weak and proposed too late, after the onset of a substantial neuronal injury. Earlier diagnosis and treatment are probably necessary to improve the functional prognosis of paraneoplastic $GABA_BR$-Abs encephalitis.

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Compliance with ethical standards

Conflicts of interest All authors report no conflicts of interest. The principal author, Jerome Honnorat, takes full responsibility for the data, the analyses and interpretation, and the conduct of the research; He has full access to all of the data; and he has the right to publish any and all data separate and apart from any sponsor. It also exists in no financial or other relationships that might lead to a perceived conflict of interest.

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