Case Report

All’s well that ends well? Long-term course of a patient with anti-amphiphysin associated limbic encephalitis

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1. Introduction

Cognitive impairments, altered mental status, behavioral problems, and seizures are hallmarks in the diagnosis of patients with limbic encephalitis (LE), especially when autoantibody testing in serum and cerebrospinal fluid (CSF) and brain imaging findings are non-specific [1]. LE is a severe autoimmune disease of the brain, linked to inflammatory processes involving auto-antibodies against neuronal cell surface proteins, intracellular targets, or synaptic receptors [2,3]. Magnetic resonance imaging (MRI) studies initially describe unilateral or bilateral hyperintensities in and swelling of mesial temporal structures, indicative of inflammation, and ultimately in many cases, a volume and internal architecture loss, indicative of irreversible hippocampal damage [4]. Consequently, the associated cognitive and behavioral alterations can be chronic or dynamic and reversible or irreversible [5,6]. Together with other markers (i.e., MRI, auto-antibodies, seizure frequency), the extent of cognitive impairments and behavioral problems serve as important follow-up parameters for monitoring the course of the disease and the response to treatments, including pharmacotherapy with antiseizure medication and immunotherapy [3,7].

Amphiphysin is an intracellular antigen usually found in paraneoplastic neurological syndromes associated with breast or small cell lung cancer. LE and stiff-person syndrome are the most common clinical syndromes seen in patients with anti-amphiphysin antibodies [8,9]. We present a case of a patient diagnosed with anti-amphiphysin antibodies LE.

2. Case report

A previously healthy 25-year-old female student first experienced a series of three tonic-clonic seizures in November 2007 (Table 1). The initial clinical workup showed normal MRI cranial computed tomography (CT), and electroencephalography (EEG). Antiseizure medication (lamotrigine 200 mg, clobazam 10 mg) was initiated a few days later after another tonic-clonic seizure. She was admitted to the Department of Epileptology, University Hospital Bonn (UKB), Venusberg-Campus 1, D-53127 Bonn, Germany.

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## Table 1
Clinical Course of the Patient.

| Date      | Symptoms                                                                 | ASM (mg)          | Other treatment                                                                 | EEG                                      | MRI                        | Other                      |
|-----------|--------------------------------------------------------------------------|-------------------|--------------------------------------------------------------------------------|------------------------------------------|---------------------------|----------------------------|
| 11/17/2007| 3 GTCS                                                                   | TPM 50 mg         | Admission to specialized epilepsy clinic                                        | normal                                   | Normal CCT: normal        |                            |
| 11/25/2007| 1 GTCS                                                                   | LTG 25 mg, CLB 15 mg | Theta/Delta bi-temporal > R                                                     | SSW L temporal, no seizures             | Suspected lesion right insular |                            |
| 11/26/2007| Admission to specialized epilepsy clinic                                  | LTG 25 mg, CLB 10 mg | theta/Delta bi-temporal L>R                                                      | SSW L. temporal, no seizures            |                           |                            |
| 11/30/2007| Amnestic/dysexecutive syndrome, psychotic symptoms                        | LTG 50 mg, CLB 15 mg | > 200 ictal patterns                                                            | Mesial bi-temporal signal intensity change & increased volume le > ri |                           |                            |
| 12/07/2007| 2 GTCS                                                                   | LTG 25 mg, CLB 15 mg | slowing of background activity, Theta/Delta bi-temporal slowing                 |                                          |                           |                            |
| 12/11/2007| LTG 50 mg, CLB 15 mg, LEV 3000 mg, OXC 600 mg                            | LTG 50 mg, MPred 1g/5 days | Acyclovir 1.5g/ 2 days                                                         |                                        |                           |                            |
| 12/12/2007| Amnestic problems, mildly improved cognition                              | LTG 50 mg, IVIg 25mg/4 days |                                        | Theta/Delta bi-temporal slowing         | Mesial bi-temporal signal intensity change & increased volume le > ri | PET: bi-temporal hypermetabolismL>R no tumor |
| 01/2008   | Amnestic problems, mild orientation & attention problems, no seizures   | LTG 150 mg, LEV 4000 mg, OXC 1200 mg | Escitalopram 20 mg, LZP 1, MPre 1g/5 days                                      |                                        | Mesial bi-temporal volume lossL>R | PET: L temporal hypometabolism |
| 04/2008   | Minor mnemonic improvement, no seizures                                  | LTG 150 mg, LEV 4000 mg, OXC 600 mg | 5 x 1g/ 2 months escitalopram 20 mg MPre 1g/3 days – 3 x 1g monthly             |                                        | Onset of atrophy of mesial temporal lobeL>R |                            |
| 10/2008   | LTG 150 mg, LEV 4000 mg, OXC 600 mg                                      | LTG 150 mg, MPre 1g/3 days |                                        |                                        | Anti-amphiphysin positive |                            |
| 09/2009   | No seizures                                                              | LTG 150 mg, LEV 4000 mg |                                        |                                        | Anti-amphiphysin positive |                            |
| 05/2010   | No seizures, depressive symptoms                                        | LEV 4000 mg       |                                        |                                        | Anti-amphiphysin negative |                            |
| 09/2010   | 2–3 auras                                                                | LEV 2000 mg       |                                        |                                        | Anti-amphiphysin negative |                            |
| 01/2011   | No seizures                                                              | LEV 3500 mg       |                                        |                                        | Anti-amphiphysin negative |                            |
| Date   | Symptoms                              | ASM (mg)       | Other treatment | EEG                          | MRI                                      | Other                                      |
|--------|---------------------------------------|----------------|----------------|------------------------------|------------------------------------------|--------------------------------------------|
| 08/2011| High irritability, subjective cognitive impairment | LEV 3500 mg    | Escitalopram 10 mg | no EDs                       | Discrete le. temporal theta, no EDs      | le > r                                     |
| 02/2012|                                                      | LEV 3500 mg    | Escitalopram 20 mg |                             | Atrophy of mesial temporal lobe> R       |                                            |
| 05/2014| Drowsiness, subjective cognitive impairment     | LEV 3500 mg    | Escitalopram 10 mg |                             | Atrophy of mesial temporal lobe> R       |                                            |
| 08/2015| Drowsiness, subjective cognitive impairment     | LEV 3000 mg    | Escitalopram 10 mg |                             | Atrophy of mesial temporal lobe> R       |                                            |
| 08/2016|                                                      | LEV 3000 mg    | Escitalopram 15 mg |                             | Atrophy of mesial temporal lobe> R       |                                            |
| 12/2017|                                                      | LEV 3000 mg    | Escitalopram 15 mg |                             | Atrophy of mesial temporal lobe> R       |                                            |
| 06/2018|                                                      | LEV 2000 mg    | Escitalopram 15 mg |                             | Atrophy of mesial temporal lobe> R       |                                            |
| 11/2019| Panic attacks, depressive symptoms            | LEV 2000 mg    | Escitalopram 20 mg |                             | Atrophy of mesial temporal lobe> R       |                                            |
| 09/2020|                                                      | LEV 2000 mg    | Escitalopram 20 mg |                             | Atrophy of mesial temporal lobe> R       | Significant increase right amygdala volume |

ASM, anti-seizure medication; CCT, cranial computer tomography; CLB, clobazame; EEG, electro-encephalography; ED, epileptiform discharges; GTCS, generalized tonic-clonic seizures; IVlg, intravenous immunoglobulins; Le, left; LEV, levetiracetam; LZP, lorazepam; LTG, lamotrigine; MPred, intravenous methylprednisolone; MRI, magnetic resonance imaging; OXC, oxcarbazepine; PET, positron emission tomography; Ri, right; SSW, sharp slow waves; TPM, topiramate.
Hospital Bonn. At first, the patient was fully oriented and showed no psychiatric symptoms. The routine neuropsychological assessment [1] indicated a mild impairment of executive functions, including phonemic fluency, verbal working memory, and fine motor skills with average psychomotor speed and sustained attention. Visual memory was unimpaired, and episodic verbal memory performance was mildly impaired (Fig. 1). The profile indicated a mild left fronto-temporal dysfunction. No mood disturbances were reported. The EEG showed an alpha background with left temporal sharp-waves.

Three days later, the patient’s mental status rapidly changed into a delirious state with confusion, impaired awareness, psychotic symptoms, global anterograde, and retrograde amnesia. Psychomotor speed appeared severely reduced. Comprehension of instructions was partly impaired and allowed bedside testing on an elementary level [10]. Language difficulties (spontaneous language, naming, reception) were prominent. There were no signs of apraxia or ataxia. A fronto-temporal dysexecutive syndrome with a bitemporal global amnestic syndrome and a posterior affection in terms of mild aphasia was diagnosed. In the EEG, up to 250 ictal patterns per day were recorded, starting independently from the left and right temporal lobe (see Fig. 2). A subsequent MRI showed T2-weighted fluid-attenuated inversion recovery (FLAIR) hyperintense signals in the mesial temporal lobes with a focus on the left side (see Fig. 2). CSF indicated a moderate lymphocytic pleocytosis (21 cells per μl) and an intrathecal immunoglobulin G (IgG) synthesis. Since the initial testing for neuronal autoantibodies remained unremarkable, antibody-negative LE was suspected.

A corticosteroid-pulse therapy with methylprednisolone (mPRED) 1000 mg over five days was administered. Acyclovir 1500 mg was given for two days until herpes simplex encephalitis was excluded. Antiseizure medication was escalated to include lamotrigine, levetiracetam, oxcarbazepine, clonazepam, and lorazepam. Despite these efforts, serial seizures continued for another ten days (see Fig. 1). Impaired consciousness, psychotic symptoms, and the amnestic syndrome persisted. Attention and executive functions deteriorated and were severely impaired. Escitalopram was given as an antidepressant. An 18F-fluorodeoxyglucose brain positron emission tomography (FDG PET) demonstrated bilateral hypermetabolism of the mesial temporal structures, which would be compatible with LE (see Fig. 1). Whole-body PET/CT revealed no malignancies.

Accordingly, a further immunomodulatory approach was chosen, i.e., intravenous immunoglobulins (IVIg) were administered over four days. While the seizures and psychiatric symptoms began to cease, neuropsychological testing revealed only mild improvements in orientation, attention, and executive functions. Moreover, the retro- and anterograde amnesia persisted.

In January 2008, the patient claimed to be seizure-free. Notwithstanding that no seizures were detected during her inpatient video-EEG recording, epileptiform discharges in bilateral fronto-central regions were recorded. A subsequent MRI now indicated mild atrophy of the left hippocampus, indicative of developing hippocampal sclerosis (HS) or atrophy. A PET hypometabolism in the left temporal lobe with a mesial focus appeared in favor of this development. The patient continued to complain about problems with episodic memory and her spatial orientation.

Consequently, another inpatient corticosteroid pulse therapy was initiated over three days and continued intermittently over the following months (until September 2009) in an outpatient setting together with a combination of levetiracetam, oxcarbazepine, and escitalopram. During that time, neuropsychological follow-up in April 2008 indicated recovered attention and executive functions, but only mildly improved and continuing verbal learning and memory impairments. Visual memory performance remained moderately impaired and was less affected than verbal memory. The neuropsychological profile indicated visual memory deteriorated five months later (September 2008), marking the intra-individual low point, while verbal memory improved even further and was now normal.

In September 2009, the patient was re-evaluated during a routine clinical visit. Attention, executive functions, verbal and visual memory, and fine motor skills had fully recovered to baseline. Since disease onset, this was the first assessment no longer indicative of any severe cognitive dysfunction. EEG showed no epileptiform activity. The initially collected sera were analyzed once

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**Fig. 1.** Neuropsychological course of the patient following immunotherapy. The left y-axis refers to the cognitive performance which is presented in standard values. The below average range is highlighted in grey. The right y-axis refers to the Beck Depression Inventory (BDI) score. A score > 10 indicates a depressed mood. IVIg Intravenous immunoglobulins.
again, and now anti-amphiphysin antibodies were detected retro-
spectively. The diagnosis was changed to anti-amphiphysin associ-
ated LE.

In the light of continuous seizure freedom, a normal EEG, and
normal cognition, the immunotherapy was discontinued. Whole-
body PET/CT remained unremarkable.

Fig. 2. Imaging and electroencephalographic findings of the patient. The figure displays the long-term course of clinical features. MRI described as hyperintensity of the temporommesial structures at disease onset (inflammation) to a mild atrophy of the left hippocampus 1 year after treatment. PET abnormalities change from mesial temporal hypermetabolism at disease onset to mesial temporal hypometabolism 1 month after disease onset. At long-term follow-up swelling and hyperintensity of right amygdala. (1) Normal MRI after 4 tonic-clonic seizures, (2) 1 month after disease onset (global amnesia), (3) 2 months after disease onset (with continued severe amnesia), (4) 10 months after start of immunotherapy (no seizures, functional recovery), (5) 12 years after disease onset (with a swelling of the right amygdala) (6) PET (a) hypermetabolism (b) hypometabolism (7) left temporal seizure onset on scalp EEG (Dec 2007).
In 2010, the patient showed a worsened verbal memory performance, which was attributed to accentuated depressive symptoms. Two years later, in 2012, mood improved, and verbal memory impairments resolved. Analysis of serum revealed no more antiamphiphysin antibodies. The patient finally resumed her studies in 2010 and successfully graduated in 2012. She has been working as an employment agent ever since. In 2016, she continued to complain about daytime drowsiness, irritability, and difficulties in attention and memory. While the formal assessment indicated that the previously unimpaired visual memory performance had mildly deteriorated, all other neuropsychological parameters, including attention, executive functions, and verbal memory, were normal. Monotherapy with levetiracetam was continued.

In 2018, during an outpatient visit, EEG showed right temporal theta-slowing and sharp-waves. Even though the patient did not experience recurring seizures, she complained about headaches and was admitted to a clinic and polyclinic for neurology. She sought treatment for the persisting headaches, anxiety symptoms, high tension, and muscle cramps, classified as somatic symptom disorders, and treated with a short administration of benzodiazepines and a dose escalation of escitalopram. At the same time, she underwent another MRI with a stable finding.

A more recent MRI from 2020, which was conducted because of continuing headaches, confirmed previous findings of left HS. In addition, and this was new, the right amygdala appeared hyperin- tense and swollen (see Fig. 2), which could be compatible with recurring LE, now mainly affecting the right temporal lobe structures. Unfortunately, the patient was not referred for neuropsychological assessment.

3. Discussion

This case report describes a female patient with various neurological, neuropsychological, and psychiatric symptoms due to antiamphiphysin associated limbic encephalitis. Since disease onset, a tumor was never diagnosed, despite previous research pointing at a frequent co-occurrence of onconeuronal antibodies in patients with epilepsy [11]. The precipitating events consisted of four generalized tonic-clonic seizures, and a few days later, a nonconvulsive focal seizure series, psychotic symptoms, and global amnesia. While the dysexecutive symptoms remitted early on, the amnestic syndrome lasted up to three months. Following various immune-modulating therapies, seizure freedom was achieved promptly, while cognition and behavior improved gradually with complete remission of attention, executive functions, and verbal memory two years after disease onset. Persistent visual memory deficits with intermittent recoveries are common [12].

One explanation for the atypical memory profile could be the crowding hypothesis which describes sacrificing right hemisphere functions in favor of a relative sparing of left-hemispheric functions [12,13]. Another explanation might relate to the recurring right mesial temporal lobe inflammation, as indicated by an MRI in 2020. Together with the frontotemporal focal EEG slowing since 2018, accentuated anxiety and depressive symptoms, persisting subjective cognitive and sleep problems, we cannot fully exclude a clinical relapse at this point, even though the patient has reported no seizures. Even in so-called monophasic nonparaneoplastic anti-LGI-1 encephalitis, between 35% and 40% of patients relapsed [12,13]. Since visual memory is dependent on the functional and structural integrity of the right temporal lobe, the described impairment can indicate a disruption of these structures [14].

MRI and PET indicated a bilateral inflammatory process in the acute phase that ultimately resulted in left hippocampal atrophy. The development of HS following LE is consistent with previously reported cases [15,16]. Our case remarkably illustrates the severe cognitive impairment of the patient at disease onset and the excellent response to immunotherapy, as described in other case series [9].

Even though patients with autoantibodies against intracellular antigens are less responsive to treatment, early diagnosis, anti-seizure medication, and immunotherapy are fundamental prerequisites for profound clinical improvement [16,17]. This approach serves as a symptomatic treatment (seizure reduction) and a causal therapy (immunomodulation).

One limitation of our study lies in the repeated test administration involving both the same and alternate formats. Practice effects might mask a worsening of cognition or mistakenly indicate improvement. However, previous data have shown that practice effects are to be considered primarily in the early phase of frequent repetitive testing (first 3 months) [18]. Our test intervals ranged from days in the early phase to several months to years in the chronic phase, which make it unlikely that our results can be explained solely by practice effects. Furthermore, for the assessment of memory we used four alternate forms, which lead to significantly smaller practice effects [19]. For the assessment of attention and executive dysfunction we applied two parallel versions of a screening test in an alternating manner reducing the likelihood of practice effects. Thereby, lack of improvement or worsening of performance can be qualitatively considered as actual decline.

Overall, our patient remained seizure-free since 2008, suffered from mild neuropsychological sequelae following LE, and was able to return to her previous life. However, the cognitive and behavioral consequences of the resurgent inflammation of the right amygdala have not been re-evaluated. Thus it remains open whether all’s well that ends well.

4. Conclusion

Prompt diagnosis of anti-amphiphysin associated LE allows for the initiation of early immunotherapy, and led to a rapid cessation of seizures and a slow recovery of cognition in our patient. Long-term outcome appears favorable with moderate neuropsychiatric sequelae and mild residual cognitive impairments. Even though patients may respond to immunotherapy and achieve complete remission of recurrent seizures, our case highlights the need for long-term neurocognitive monitoring of clinical outcome parameters to identify an early relapse.

Declaration of interest

The authors declare no conflict of interest with regard to the current work.

J. Taube has nothing to disclose; Dr. Witt reports personal fees from Eisai, outside the submitted work; Dr. Baumgartner reports personal fees from Eisai and UCB, outside the submitted work; Prof. Dr. Helmstaedt reports personal fees from Precisis, Eisai, UCB, and GW, outside the submitted work.

Ethical statement

This work has been done in accordance with the WMA Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects as far as applicable.

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Appendix A. Supplementary data

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