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Case Report

Case Report: Autoimmune Encephalitis Associated with GABA-B Antibody Mimicking Cerebral Infarction

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Abstract

Autoimmune encephalitis associated with GABA-B antibodies varies in its clinical presentation. Without testing for anti-GABA-B antibodies in blood serum or cerebrospinal fluid, the disease is difficult to distinguish from some other conditions. Cerebral lesions are typically detected by magnetic resonance imaging (MRI) in the medial temporal lobe or hippocampus. We describe a patient with an autoimmune encephalitis caused by anti-GABA-B antibodies who presented with an initial focal epilepsy. The 65-year-old man reported memory loss, seizures, and altered consciousness prior to presentation to the emergency department (ED). The left arm showed reduced autonomous movement to painful stimuli, and MRI showed abnormal hyperintensities in the left frontal lobe on T2 and fluid-attenuated inversion recovery sequences, restricted diffusion, and decreased cerebral blood flow. Contrast-enhanced T1-weighted MRI showed gyral enhancement involving the cortex and subcortical white matter. Computed tomography angiography did not identify culprit blood vessels. Screening for autoimmune encephalitis-related serum antibodies revealed anti-GABA-B antibodies. A course of corticosteroids, intravenous immunoglobulin therapy and plasmapheresis didn't really improve the symptoms. In this particular case, the patient had no cancer. However, subsequent analysis and diagnosis raised the suspicion of a lung tumour. However, this could not be confirmed due to the patient's death. The early and specific diagnosis of autoimmune encephalitis in many neurological and psychiatric symptom complexes is now possible through the detection of autoantibodies against nerve or glial cells. This has fundamentally changed the approach to immunotherapeutic treatment of this group of diseases, as well as the understanding of the underlying pathophysiology and triggering factors. The still growing number of new autoantibodies requires a regular update on the state of antibody diagnostics, the frequency of associated tumours as well as the antibody-specific spectrum of clinical symptoms ranging from personality changes and cognitive disorders to epileptic seizures, movement disorders, vegetative and consciousness disorders.

***Keywords:** Autoimmune Encephalitis, GABA-B, GABA-B Receptor, Encephalitis, Antibodies, Diagnostic Criteria, MRI, CSF, Therapy, Outcome*

Introduction

GABA-B receptor encephalitis presents with a typical limbic encephalitis and frequent epileptic seizures in about half of the cases. (1) The origin of the antibodies is usually due to small cell bronchial carcinoma or neuroendocrine tumours. Accordingly, MRI shows unilateral or bilateral T2/FLAIR enhancement of the medial temporal lobe, sometimes with frontotemporal or hippocampal atrophy. (2)

The discovery of autoantibodies against neurons or glial cells as the cause of autoimmune encephalitis has led to a major change in the approach to neurological and psychiatric diseases in recent years.(3)

This has not only affected diagnostic and therapeutic algorithms, prognosis or tumour association, but has also led to new insights into the fundamental origins of brain diseases and, not least, has made it possible to treat a large number of patients whose symptoms were previously classified as dissociative, infection-associated, cryptogenic or "unclear"(4) (5).

Diagnosis has been greatly simplified, and sensitive antibody tests are now widely available, in parallel with increasing clinical knowledge. As a result, therapy can now be initiated much more rapidly in many patients, which, in addition to a sufficiently effective therapy, is considered to be an important factor in the long-term prognosis (6) (7). Treatment approaches now target different cells and receptors of the immune system, and the number of treatment options is constantly growing. Some antibodies are associated with very specific clinical syndromes, including epileptic seizures, disorders of consciousness, movement, cognitive, vegetative or psychotic disorders. As new autoantibodies continue to be discovered, their pathogenetic significance will be investigated in future studies and there is no end in sight to this development (8).

Case Presentation

The male patient aged 65 years presented to the emergency department with a left hemiparesis that started in the morning. There was no report of fever, headache or urinary incontinence, but his family reported that he had a history of hypertension, a diagnosis of diabetes and had been discharged from the stroke unit in 2014 after a right middle cerebral artery infarction.

On admission, the patients' vital signs were stable. He had bilateral equal pupil diameters, bright reflex sensitivity and symmetric nasolabial folds. Meningeal irritation and Babinski reflex were absent.

His medical history included a "twitch" on the left side of the body. The patient had a history of right brain ischaemia and was already receiving secondary prophylaxis with ASA and a statin. Subsequently, we saw a somnolent patient with left hemiparesis and left positive pyramidal tract signs. In the emergency department, a myoclonia of the left side of the body was observed. It was accompanied by impaired consciousness. Emergency CCT with angiography showed no infarct, haemorrhage or high-grade vascular stenosis. However, in comparison with the previous image, there was a questionable newly delineated hypodense parenchymal change in the right temporopolar and temporomesial areas and in the right cerebellar hemisphere. An older defect could not be visualised. The ECG showed a sinus rhythm. There were no acute conduction or repolarisation abnormalities. Midazolam and levetiracetam were given. We also started anticonvulsant therapy with levetiracetam 500mg two times a day.

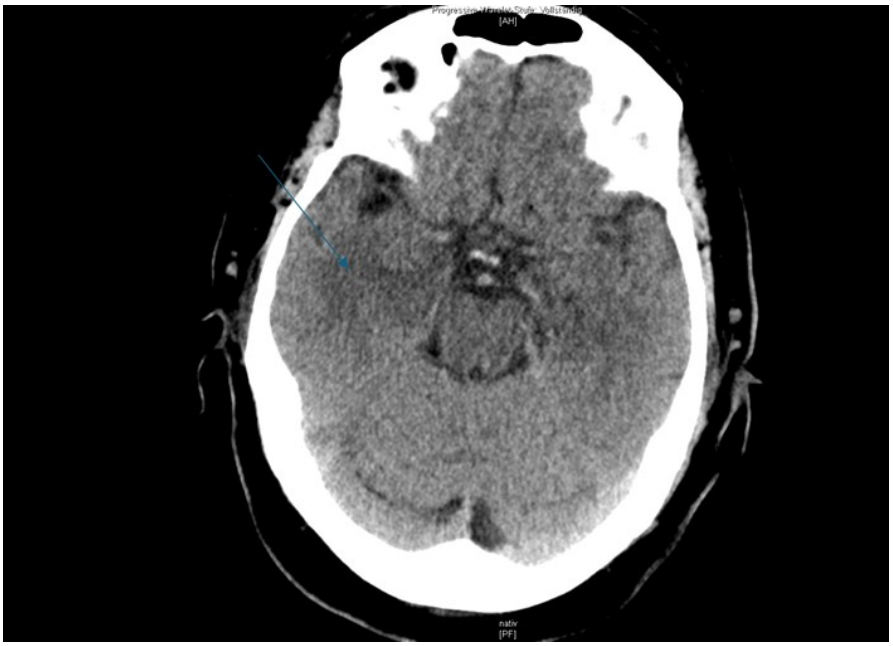

Figure 1. *CT Image newly delineated hypodense parenchymal changes right temporopolar and temporomesial.*

For further treatment and diagnosis, the patient was admitted to the stroke unit. There was a persistent disturbance of consciousness with a drop in oxygen saturation to 82% with 6 litres of oxygen. Arterial blood gas analysis showed inadequate oxygenation with increasing pCO2. This was consistent with CO2 anaesthesia. Differential diagnoses were considered. These included cerebral infarction, encephalitis, lactic acidosis, stroke-like episodes (MELAS) and cortical venous thrombosis.

There was evidence of infiltrates on the chest x-ray. On the assumption of aspiration pneumonia, we started antibiotic therapy with piperacillin/tazobactam.

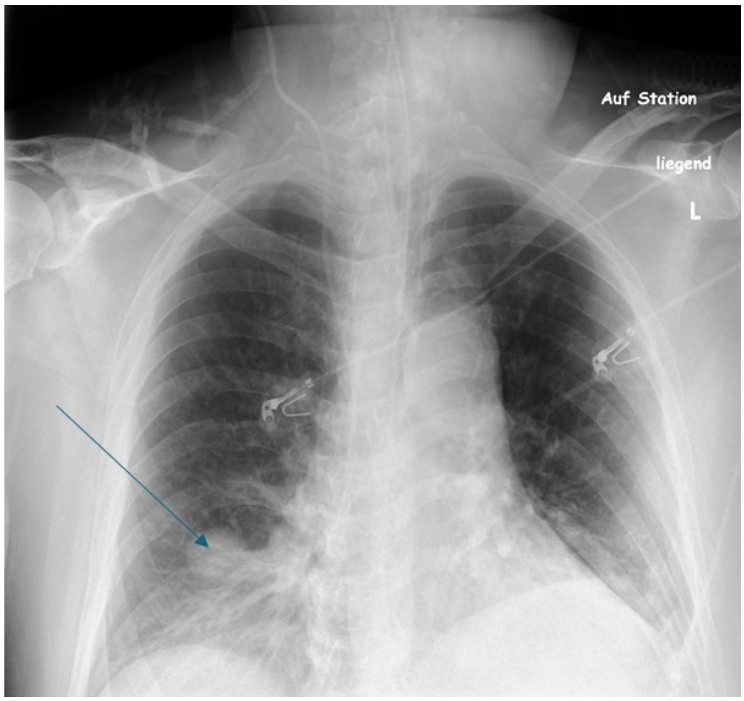

Figure 2. *Increasing right pleural effusion discharging cranially with additional decreased ventilation on the right infrahilar DD newly delineable pneumonic infiltrate.*

Arrow: In addition, there is a roundish decrease in transparency in projection to the right inferior field

The patient was admitted to the intensive care unit for treatment with non-invasive ventilation (NIV).

In the intensive care unit, the patient's symptoms worsened with a drop in GCS to 8, increasingly poor oxygen saturation and lack of protective reflexes, so we decided to intubate the patient.

An MRI of the head was performed but the initial diagnosis was uncertain. It was possible that he had herpes encephalitis. Acyclovir was started and dexamethasone was added as an autoimmune encephalitis remained in the differential diagnosis. A chest CT scan was performed in an attempt to exclude pulmonary embolism. Since CT angiography of the incised thoracic segments showed a mass lesion in the lung, the suspicion of autoimmune disease was particularly high.

Routine laboratory tests, including blood tests, were unremarkable except for elevated creatinine kinase (1592 U/L; normal range, <174 U/L) and leucocytosis (18.96/nll; normal range, 4.3-10.0/ml). The initial serological tests for infection, malignancy or autoimmunity were all normal.

Analysis of the cerebrospinal fluid showed 143 leukocytes, of which 83% were lymphocytes, 11% were segmental granulocytes and 3% were monocytes; no malignant lymphocytes were detected. There was no evidence of DNA from the herpes simplex virus, the Epstein-Barr virus or the human cytomegalovirus. The patient was also tested negative for HIV and Syphilis.

The immunological tests of the cerebrospinal fluid showed the presence of antibodies against GABA B. Antibodies against NMDA receptors, LGI1, AMPA receptors 1 and 2, or GABA A and CASPR2 receptors were not detected in the serum or in the cerebrospinal fluid. Based on the clinical manifestations, epidemiological features, laboratory results and MRI imaging changes, the patient was diagnosed with anti-GABA B antibody-associated autoimmune encephalitis.

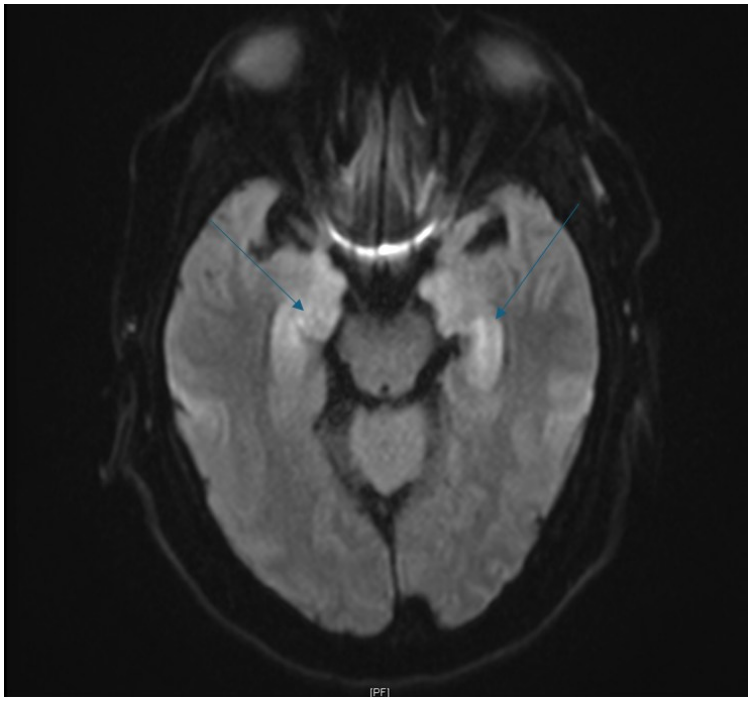

Figure 3. *Suspected autoimmune encephalitis with swelling of both hippocampal regions.*

The patient was treated with high doses of methylprednisolone for a total of 5 days (3 + 2 days). There was no sign of improvement. The initial refractory epilepsy was treated with levetiracetam, lacosamide and phenytoin. No status epilepticus was seen on subsequent EEGs. After high-dose corticosteroid therapy, the patient developed a hemodynamically relevant duodenal ulcer. It was treated with 2 clips and 2 erythrocyte transfusions.

A CT scan of the lungs was performed. It showed a suspected solid round focus in the left lung segment 10 and a mediastinal lymphadenopathy up to 1.8 cm in diameter.

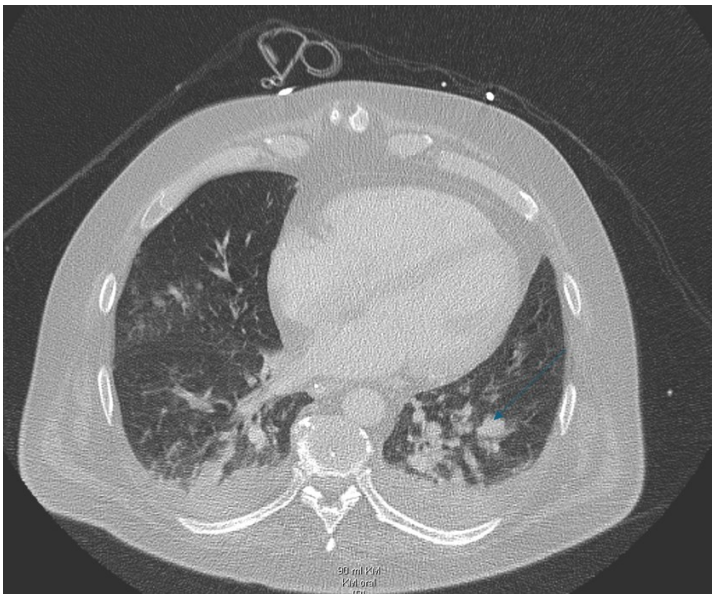

Figure 4. *Suspected solid round focus in the left lung.*

We decided to perform a tracheotomy in the second week of ICU admission, as the patient did not wake up or improve his level of consciousness.

As there was no improvement, a total of 7 plasmaphereses were performed between 12 May 2023 and 26 May 2023. In addition, the patient developed a diffuse coagulopathy with superficial necrosis on both lower arms. The patient developed multiple organ failure and was on continuous dialysis during the course of the disease. At the tumour conference, in view of all the findings and the current condition of the patient, a palliative concept was recommended, with no possibility of a causal therapy.

In view of the limited options for causal therapy and the progressive clinical deterioration, we initiated palliative therapy after lengthy discussions with the family. The patient died on 01/06/2023.

Conclusion

Autoantibodies against transmembrane receptors are present in the pre- and postsynaptic membranes of the entire central nervous system in particular in the hippocampus, thalamus and cerebellum. GABA-B receptors are heterotetramers. Each consists of two subunits, GABAB1 and GABAB2. They are associated with KCTD proteins (potassium channel tetramerisation domain-containing proteins). These proteins determine the kinetic and pharmacological properties of the receptors. The immunorelevant epitopes are mainly localised in the GABAB1 subunit of the receptor. (9)

Function - Pathophysiology

GABA-B receptors are metabotropic G protein-coupled receptors. Binding of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) to the GABAB1 subunit leads to activation of pre- and postsynaptic potassium channels, closure of calcium channels, and decreased transmitter release from the presynapse via a decrease in calcium concentration. The binding of specific antibodies inhibits the function of the receptor and autoimmune reactions lead to limbic encephalitis (seizures, confusion, memory deficits and others). Correspondingly, an increased risk of temporal lobe epilepsy has been observed. The possibility of a tumour-induced pathological immune response against GABAB receptors is supported by the frequent association of anti-GABAB receptor encephalitis with small cell lung cancer (SCLC) and its ability to express synaptic proteins. (10)

Clinical

An important feature of anti-GABA-B is the relatively rapid onset with prodromal symptoms including fever or unspecific respiratory symptoms (11).

The disease primarily affects the limbic system and typically manifests with epileptic seizures up to and including status epilepticus, behavioural abnormalities, and impaired memory (11) (12). There have also been few reports of initial presentation with cerebellar symptoms or opsoclonus (11). This is not surprising given the high density of GABA-B in the cerebellum (13). Furthermore, as GABA-Bs are widely distributed throughout the brain, systematic investigation will probably identify more "atypical" cases in the future (13).

Therapy and prognosis

In many patients, immunotherapy or antitumour therapy can help to improve or eliminate symptoms (14). In addition, there are allosteric agonists of the GABA-B2 subunit (15), which can block the antibody-blocked GABA-B1 subunit. These are a potential therapeutic option (15). In this case, in addition to immunotherapy, activation of the GABA-B2 subunit by an allosteric agonist could suppress the pathogenic effect of antibodies (16).

The neurological outcome of patients with and without a tumour does not differ much from each other, but the long-term prognosis is strongly dependent on the association with the tumour. Tumour recurrence or progression, and less frequently refractory status epilepticus (17) (18), are the most common causes of death.

Conflict of Interest

None declared.

References

1. [Lancaster E, Lai M, Peng X, et al. Antibodies to the GABA(B) receptor in limbic encephalitis with seizures: case series and characterisation of the antigen. Lancet Neurol. 2010;9:67–76. doi: 10.1016/S1474-4422(09)70324-2.].
2. [Heine J, Prüss H, Bartsch T, et al. Imaging of autoimmune encephalitis—relevance for clinical practice and hippocampal function. Neuroscience. 2015;309:68–83. doi: 10.1016/j.neuroscience.2015.05.037.].
3. Prüss H. Autoantibodies in neurological disease. Nat Rev Immunol. 2021 doi: 10.1038/s41577-021-00543-w
4. Dalmau J, Armangué T, Planagumà J, et al. An update on anti-NMDA receptor encephalitis for neurologists and psychiatrists: mechanisms and models. Lancet Neurol. 2019;18:1045–1057. doi: 10.1016/S1474-4422(19)30244-3.
5. [Dalmau J, Armangué T, Planagumà J, et al. An update on anti-NMDA receptor encephalitis for neurologists and psychiatrists: mechanisms and models. Lancet Neurol. 2019;18:1045–1057. doi: 10.1016/S1474-4422(19)30244-3.;
6. Graus F, Titulaer MJ, Balu R, et al. A clinical approach to diagnosis of autoimmune encephalitis. Lancet Neurol. 2016;15:391–404. doi: 10.1016/S1474-4422(15)00401-9.)
7. [Heine J, Kopp UA, Klag J, et al. Long-term cognitive outcome in anti-N-methyl-D-aspartate receptor encephalitis. Ann Neurol. 2021 doi: 10.1002/ana.26241.
8. Thompson J, Bi M, Murchison AG, et al. The importance of early immunotherapy in patients with faciobrachial dystonic seizures. Brain. 2018;141:348–356. doi: 10.1093/brain/awx323
9. Schwenk J, Metz M, Zolles G, Turecek R, Fritzius T, Bildl W, Tarusawa E, Kulik A, Unger A, Ivankova K, Seddik R, Tiao JY, Rajalu M, Trojanova J, Rohde V, Gassmann M, Schulte U, Fakler B, Bettler B. Native GABA(B) receptors are heteromultimers with a family of auxiliary subunits. Nature. 2010 May 13;465(7295):231-5. doi: 10.1038/nature08964. Epub 2010 Apr 18. PMID: 20400944.
10. Terunuma M. Diversity of structure and function of GABAB receptors: a complexity of GABAB-mediated signaling. Proc Jpn Acad Ser B Phys Biol Sci. 2018;94(10):390-411. doi: 10.2183/pjab.94.026. PMID: 30541966; PMCID: PMC6374141.
11. Lin J, Li C, Li A, Liu X, Wang R, Chen C, Zhou D, Hong Z. Encephalitis With Antibodies Against the GABAB Receptor: High Mortality and Risk Factors. Front Neurol. 2019 Sep 26;10:1030. doi: 10.3389/fneur.2019.01030. PMID: 31681135; PMCID: PMC6798040.
12. Nathalia Rossoni Ronchi, Guilherme Diogo Silva, Comparison of the clinical syndromes of anti-GABAa versus anti-GABAb associated autoimmune encephalitis: A systematic review, Journal of Neuroimmunology, Volume 363, 2022, 577804, ISSN 0165-5728, https://doi.org/10.1016/j.jneuroim.2021.577804. (https://www.sciencedirect.com/science/article/pii/S0165572821003313)
13. Höftberger R, Titulaer MJ, Sabater L, Dome B, Rózsás A, Hegedus B, Hoda MA, Laszlo V, Ankersmit HJ, Harms L, Boyero S, de Felipe A, Saiz A, Dalmau J, Graus F. Encephalitis and GABAB receptor antibodies: novel findings in a new case series of 20 patients. Neurology. 2013 Oct 22;81(17):1500-6. doi: 10.1212/WNL.0b013e3182a9585f. Epub 2013 Sep 25. PMID: 24068784; PMCID: PMC3888170.
14. Dalmau J, Geis C, Graus F. Autoantibodies to Synaptic Receptors and Neuronal Cell Surface Proteins in Autoimmune Diseases of the Central Nervous System. Physiol Rev. 2017 Apr;97(2):839-887. doi: 10.1152/physrev.00010.2016. PMID: 28298428; PMCID: PMC5539405.
15. Jiang X, Su L, Zhang Q, He C, Zhang Z, Yi P, Liu J. GABAB receptor complex as a potential target for tumor therapy. J Histochem Cytochem. 2012 Apr;60(4):269-79. doi: 10.1369/0022155412438105. Epub 2012 Jan 20. PMID: 22266766; PMCID: PMC3351242.
16. Binet V, Brajon C, Le Corre L, Acher F, Pin JP, Prézeau L. The heptahelical domain of GABA(B2) is activated directly by CGP7930, a positive allosteric modulator of the GABA(B) receptor. J Biol Chem. 2004 Jul 9;279(28):29085-91. doi: 10.1074/jbc.M400930200. Epub 2004 May 4. PMID: 15126507; PMCID: PMC2557059.
17. Wang, DR., Wu, XL. & Sun, YL. Therapeutic targets and biomarkers of tumor immunotherapy: response versus non-response. Sig Transduct Target Ther 7, 331 (2022). https://doi.org/10.1038/s41392-022-01136-2

18. Li Q, Zhang X, Zeng T, Yang B, Duan J, Tang Y. Clinical characteristics and prognosis of anti-GABABR encephalitis: A single-center experience. Medicine (Baltimore). 2023 Feb 17;102(7):e32956. doi: 10.1097/MD.0000000000032956. PMID: 36800611; PMCID: PMC9936044.

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