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LETTER TO THE EDITOR

# Efficacy of subcutaneous immunoglobulin therapy in a patient with autoimmune encephalitis: a case report

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Dear Editor,

Encephalitis is defined as inflammation of the brain parenchyma associated with neurological dysfunction [1]. Limbic encephalitis (LE) is characterized by rapid development of confusional episodes, memory deficits, mood changes, and epileptic seizures.

While paraneoplastic LE generally has a poor prognosis, autoimmune LE often responds well to immunotherapy [2]. In case series, but not controlled studies, patients with autoimmune encephalitis have been shown to benefit from first-line immunotherapies that include corticosteroids, intravenous immunoglobulins (IVIG) therapy, and plasma exchange, either alone or in combination [3].

In this paper, we report on the efficacy of 20%-concentrated subcutaneous immunoglobulin G (SCIG, Hizentra®, CSL Behring AG) in a patient with autoimmune encephalitis, treated initially and successfully with IVIG. To our knowledge, this is the first clinical case with SCIG showing a maintenance of the outcomes with IVIG. In December 2016, a 74-year-old male patient (70 kg) was admitted to our Neurology Department after access to the Emergency Department for left-sided hemiparesis. Family members reported a state of confusion lasting several days, as well as behavioral and sleep disorders, accidental falls and gastrointestinal disorders with fever a few months before. The patient's medical history included type 2 diabetes, ischemic heart disease, and arterial hypertension.

Routine hematochemical and instrumental tests (electroencephalography, EEG; brain computed tomography, CT; total body CT; electrocardiogram, ECG and echocardiogram; chest X-ray) were in the normal range except for the EEG, which showed generalized background slowing and epileptic discharges. Possible brain or other systems infections were excluded: the search for neurotropic viruses by lumbar puncture and infectious blood tests gave a negative result. Thus, a diagnosis of psycho-organic syndrome with a seizure crisis was made, and an antiepileptic therapy was prescribed (levetiracetam 500 mg, twice a day).

During hospitalization, the patient progressively worsened to a coma state. The patient's clinical features were analyzed again, and a diagnosis of autoimmune limbic encephalitis (ALE) was suspected. An appropriate strategy for immune modulation was initiated: intravenous (IV) methylprednisolone (1 g/day for 7 days) and followed by IV immunoglobulin (210 g administered in 7 days). The patient's state of consciousness slowly improved. At the discharge, the patient continued the antiepileptic therapy.

Within the next month, the patient was hospitalized again, first because of epileptic seizures and then because of a rapid deterioration of the state of consciousness with a grade I coma, inability to swallow, and respiratory disorders.

Epileptic seizures were poorly controlled; therefore, a new antiepileptic therapy was prescribed: phenobarbital (100 mg, 2 times/day intramuscularly) and valproate (400 mg, 3 times/day IV).

To confirm the diagnosis of encephalitis, a positron emission tomography with fluorodeoxyglucose ($^{18}$F-FDG PET) was performed, and a marked reduction of metabolic activity in the brain, especially in temporal areas, was found (Figs. 1 and 2). The analysis of cerebrospinal fluid (CSF) showed pleocytosis (7 polymorphonuclear cells per mm$^3$), increased L-lactate dehydrogenase (LDH) values (35 U/l), and hyperproteinorrhachia (83 mg/dl). The onconeural antibodies test was negative, so we excluded a paraneoplastic encephalitis.

In this phase, the cranial and peripheral nerves were also affected, with hyposthenia in the four limbs: the patient was tetraplegic with squint and facial paresis. Treatment with IV

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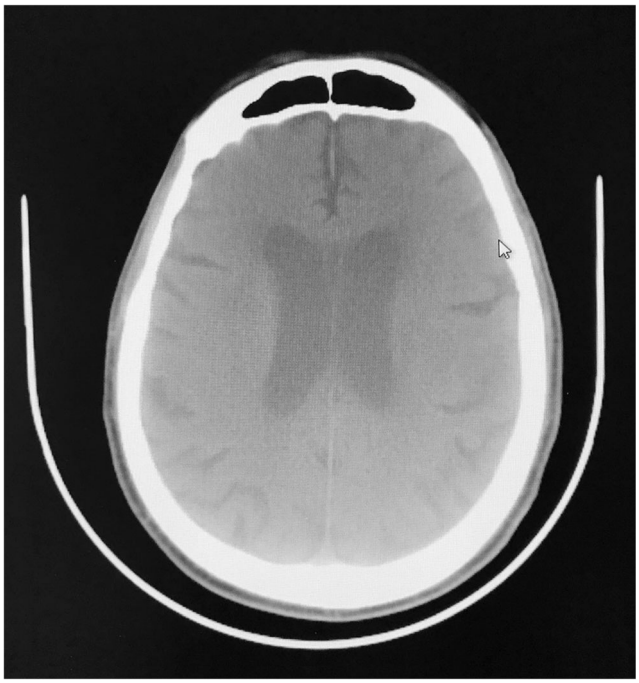

**Fig. 1** PET-TC FUSION imaging in the acute phase: temporal lobes signal abnormality

methylprednisolone (1 g/day for 7 days), IVIG (210 g administered in 7 days), and azathioprine (50 mg, 2 times/day) was prescribed.

At discharge, the patient's neuropsychiatric condition was severely compromised, with inability to walk, mental confusion, disorientation, language disorders, dysphagia, and apraxia. IVIG infusions (210 g administered in 7 days, every 4 weeks) continued through outpatient care. The patient began to improve, with sphincter control, improved swallowing and the ability to walk with some support.

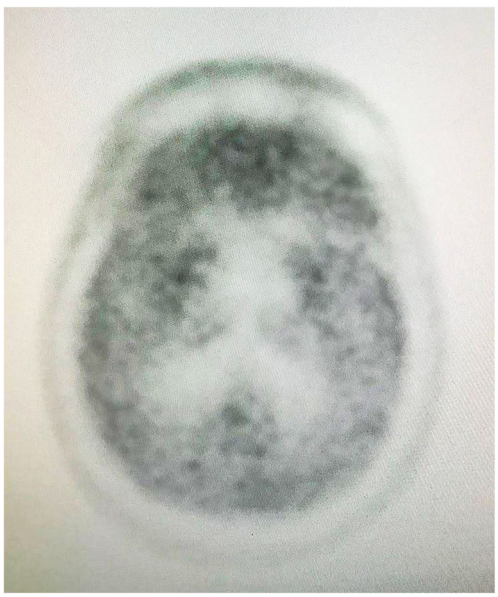

**Fig. 2** PET imaging at baseline

In May 2017, the patient's condition did not allow further venous access; therefore, the patient switched to therapy with SCIG 20% (200 g per month, administered in 5 days a week), with progressive and slow recovery of motor and cognitive functions. In the first month, the patient regained the use of his upper limbs, and in the second month, he recovered a fair degree of autonomy in walking and balance, and then his capacity for language improved.

The last PET carried out in April 2018 confirmed the positive clinical results observed in December 2017: the hypocaptation was reduced in the whole brain and the metabolism of the basal and cerebellum nuclei was normal (Fig. 3).

Overall, the patient was treated with IVIG from December 2016 to April 2017 and with SCIG from May 2017 to May 2018 (to date, treatment is still ongoing).

The Barthel Index for the functional assessment of activities of daily living was 22 points at baseline and 100 in January 2018.

The main clinical manifestations of limbic encephalitis for which we can hypothesize the involvement of the limbic system are non-specific and can call into question pathologies with different etiologies: neurological, infectious, psychiatric, degenerative, and oncological [4]. The diagnosis of LE is a challenge for neurologists, who must carefully consider the conditions that can mimic encephalitis [4]. Furthermore, these patients could be mistakenly diagnosed as suffering from rapidly evolving degenerative dementia and could be deprived of adequate immunological therapy.

Usually, the diagnosis is based on a combination of clinical, laboratory, neuroimaging, and electrophysiological findings: CSF examination, EEG, MRI, $^{18}$F-FDG PET, and neuronal antibodies in the serum and CSF [1].

Since antibody testing is not available in our hospital, we applied the diagnostic criteria for autoimmune limbic encephalitis proposed by Graus et al. [5], which are of considerable importance in our case because, underlining the difficulty for many centers of having antibody tests in a short time, the criteria allow the diagnosis of encephalitis with the support of conventional neurological evaluation and standard diagnostic tests.

In particular, in our case, the following findings made us hypothesize and subsequently confirm the diagnosis of ALE: a subacute onset of working memory deficits, seizures, and psychiatric symptoms; the presence of a mild infectious disease a few months earlier (gastrointestinal disorders); the detection of seven polymorphonuclear cells and hyperproteinorrhachia in the CSF; the $^{18}$F-FDG PET imaging (enhanced captation at the temporal lobe, bilaterally); and the EEG trace (slow and epileptiform abnormalities). We have excluded both cancer-related and infectious etiologies. CSF examination including oligoclonal bands was performed; no intrathecal immunoglobulin synthesis was found.

Due to high number of pathologies resulting in neurological impairment in elderly patients, too often these patients are

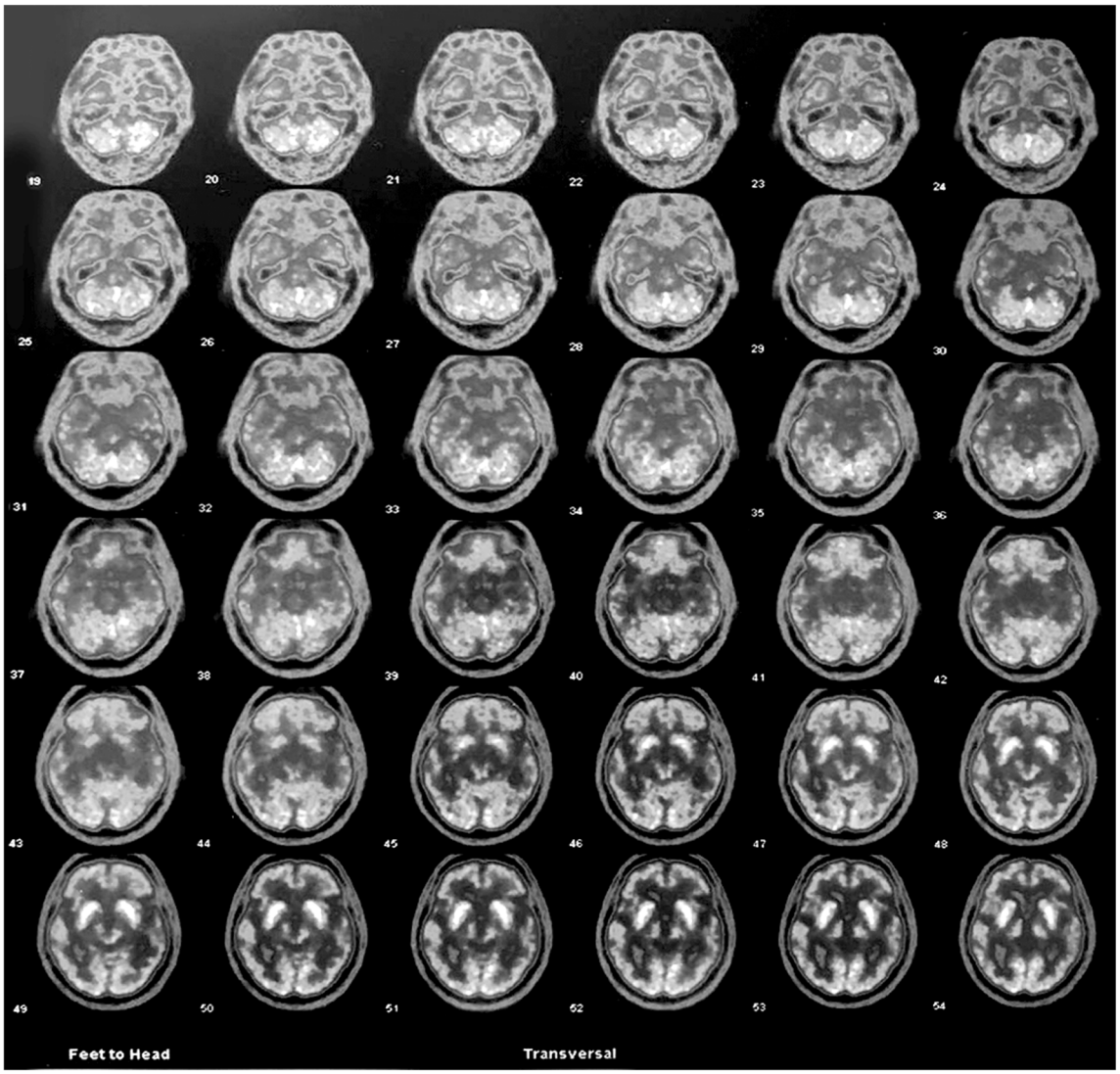


**Fig. 3** PET imaging in April 2018: signal normalization during remission

underdiagnosed. On the contrary, proper treatment may lead to significant improvements.

Response to first-line immunotherapies used in autoimmune encephalitis is typically monitored over several weeks, and if the response is suboptimal, second-line treatments are recommended, usually including cyclophosphamide or rituximab [1]. Immunotherapy is usually continued for a period of months and gradually tapered [3].

Our patient has responded well to IVIG therapy from the beginning, albeit with very slow improvements. Plasmapheresis has been ruled out due to insufficient cardiac output. When the patient's condition no longer allowed intravenous administration due to the impossibility of obtaining venous access, treatment with SCIG was initiated in order not to interrupt the therapy with immunoglobulins, which, up to that moment, had been conducted with good results. The patient has maintained the therapeutic response, with slow and constant improvement of cognitive and motor functions.

The subcutaneous, rather than intravenous, administration of immunoglobulins is increasingly used in clinical practice due to its effectiveness in primary immunodeficiency, good safety profile, and ease of self-administration. The current literature suggests that SCIG can be used also in patients with poor venous access and is probably less costly than IVIG [3].

The case presented here, even in its limited value, as a report on a single patient, confirmed the therapeutic efficacy of IVIG and suggested an equal or superior efficacy of SCIG in chronic therapy.

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## Compliance with ethical standards

**Informed consent** Informed consent was obtained from the patient described in this report.

**Conflict of interest** Author A has received financial support for attending symposia from AB Pharm, Ihms Health, Sanofi Genzyme, CSL Behring. Author B and author C declare that they have no conflict of interest.

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