metabolism and decreased responsiveness to opioid analgesic pathways. Pregabalin has an anti-seizure effect following from its binding to the alpha-2-delta binding site of voltage-gated calcium channels in the central nervous system, a receptor known to play a major role in pain sensitization processes. We suggest three possible mechanisms for the analgesic effect of pregabalin in senile depression. First, pregabalin might reduce depolarization-induced calcium influx at nerve terminals and then decrease the release of excitatory neurotransmitters, including glutamate, noradrenaline and substance P (Ben-Menachem, 2004). Second, decreased progressive desensitization of the μ-opioid receptor might occur after continuous administration of opioids (Bannister et al., 2011). Third, pregabalin might bind to the alpha-2-delta site of voltage-gated calcium, which is up-regulated during the hypersensitization process in senile pain (Gajraj, 2007).

Our case illustrates the benefit of augmentation with pregabalin for the treatment of refractory pain in an elderly depressed patient. However, the possible antiepileptic effect and interaction with the serotonergic system that causes mood change should be elucidated in future studies.

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Atypical N-methyl-D-aspartate receptor encephalitis and a hippocampal tumour

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To the Editor

Anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis is caused by a reversible decrease of synaptic N-methyl-D-aspartate receptor (NMDAR) through cross-linking and internalization by an immunoglobulin G (IgG) antibody (Dalmau et al., 2011). The disease can be autoimmune or paraneoplastic; it responds to immune therapy and removal of causative tumour. Early stages of NMDAR encephalitis are characterized by anxiety, insomnia, grandiose and paranoid delusions and mania, which are often misdiagnosed as schizophreniform psychosis (Dalmau et al., 2011). A presentation with isolated depression has been described in only one case (Kayser et al., 2013).

An 18-year-old Caucasian male, with no psychiatric or medical history, reported 3 months of depressive symptoms and brief mood-congruent derogatory auditory hallucinations, culminating in intentional overdoses. Preceding this was a relationship breakdown and difficulty completing university studies. He was admitted and commenced on mirtazapine 15 mg nocte. Physical and neurological examination was normal. Serum metabolic, inflammatory and tumour markers were normal. NMDAR-IgG was detected in serum. Cerebrospinal fluid (CSF) examination found a lymphocytic pleocytosis (white cell count [WCC]: 30×10^6/L); CSF NMDAR-IgG was initially negative, but positive on repeat sampling. Electroencephalogram showed diffuse encephalopathy without epileptiform activity. Magnetic resonance imaging (MRI) of the brain showed a non-enhancing right hippocampal mass, interpreted as a low-grade tumour. He received 5 days of intravenous immunoglobulin (IVIG) and rapidly improved, returning to premorbid mental state within 4 days.

He had two further deteriorations in mood within the next 8 weeks, each time responding rapidly to IVIG. After administration of Rituximab, both clinical and imaging parameters stayed unchanged over an 11-month follow-up.

We describe an NMDAR encephalitis case, characterized by isolated psychotic depression, highlighting the heterogeneity of early presentations of this illness. The presence of a right temporal lobe tumour is unusual and its relationship to the encephalitis is unclear. No histology is available, but tumours can express NMDAR and could provide a basis for sensitization (Dalmau et al., 2011). Also, focal disruption of the blood–brain barrier could facilitate an immune response to NMDAR. Reversible MRI abnormalities resembling glioma have been seen in a single case of seronegative autoimmune limbic encephalitis (Najjar et al., 2011), but in our case successful treatment did not alter MRI appearances. A direct effect of the tumour on brain parenchyma seems insufficient to explain the clinical presentation and rapid treatment response, as does the effect of anti-depressant therapy.

To our knowledge, this is the first case report of NMDAR encephalitis presenting with depression in context of a hippocampal lesion; it could provide additional insights into the underlying mechanisms and immunopathology of NMDAR encephalitis.

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Zotepine-associated vitamin B12 deficiency and pancytopenia

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To the Editor

Among antipsychotic drugs, only clozapine, olanzapine and quetiapine have been associated with pancytopenia. Here, we report the first case of zotepine-associated pancytopenia.

A 46-year-old Asian male with a history of schizophrenia presented because of an exacerbation of psychotic symptoms. He had no medical or family history of note. After treatment with 250 mg/day of zotepine, the patient's psychotic symptoms were improved, and he was transferred to our chronic ward. However, 16 months later, the complete blood count (CBC) revealed a white blood cell count of 2410 cells/mm^3; neutrophils/lymphocytes, 41%/52%; haemoglobin, 8.6 g/dL; mean corpuscular volume, 108.9 fL; and platelet count, 7.1×10^3/mm^3.

The patient was transferred to the haematology unit where laboratory examinations showed serum levels of vitamin B12, 165 pg/mL; folate, 1.5 ng/mL; ferritin, 173 ng/mL; and normal coagulation tests. All other haematological examinations were normal. The patient did not show any signs of malignancy, liver cirrhosis or virus infection. There were no changes in diet, body weight or use of psychotropic drugs. Zotepine was switched to risperidone, and cobalamin and folic acid were administered for 4 weeks. Surprisingly, while the CBC returned to normal limits, the psychotic symptoms became exacerbated. Switching from risperidone back to zotepine led to the recurrence of blood dyscrasia. Therefore, zotepine was continued, and folic acid and vitamin B complex were given, causing a return to normal CBC results.

The score on the Naranjo scale was 6, and the recurrence of pancytopenia on rechallenge supports zotepine as a probable causative factor (Liang et al., 2014). Preliminary evidence suggests that second-generation antipsychotics (SGAs) might decrease the serum levels of vitamin B12 (Misiak et al., 2014) because of the potential of SGAs to increase DNA methylation of several genes, particularly those involved in metabolic homeostasis. As vitamin B12 plays an important role in haematopoiesis, zotepine might decrease the levels of vitamin B12, which in turn contributes to pancytopenia.

Clozapine-associated neutropenia and agranulocytosis might be related to the formation of a nitrenium cation catalysed by the flavin-containing monooxygenase-3 system of leukocytes (Nooijen et al., 2011). Although the mechanism of zotepine-induced pancytopenia is unclear, zotepine might cause bone marrow suppression through similar mechanisms. Moreover, the decreased levels of vitamin B12 by zotepine might further negatively affect haematopoiesis. Importantly, although the patient was still on zotepine, the supplementation of cobalamin and folic acid could normalise the blood dyscrasia. This suggests that zotepine-associated vitamin B12 deficiency and pancytopenia can be reversed by zotepine discontinuation and managed with the supplementation of cobalamin and folic acid.

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