Letters to the Editor

Recognizing hypomania symptoms in the current expanses of depression in Japanese clinical practices

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IN 1991, FOR THE first time in psychiatric epidemiology, Angst and his group showed a prevalence of hypomania of about 4% among the young adult population on the basis of the Zurich cohort study (Switzerland).[1] Several other studies on hypomania in depressed patients were subsequently carried out in France (i.e., EPIMAN, EPIDEP and Bipolact study). These demonstrated clearly that hypomania symptoms were often unrecognized and under-evaluated by both subjects and clinicians. Some of the most interesting findings come from the Bipolact Surveys, national data obtained in 'real world' medical practice, which revealed rates of hypomania as high as around 62% in both recurrent depression samples (primary care and psychiatric settings) and 55% in resistant major depression.[2]

The high prevalence of hypomania found first in the report by Angst *et al*. has since been widely recognized in the clinical field. In 2005 the group therefore published the Hypomania Check List 32 (HCL-32), a questionnaire for the self-assessment of hypomania, which has rapidly spread to many countries.[3] This tool measures hypomania in a stable way across cultures.[4] The HCL-32 begins by assessing the current compared to the usual mood state; it then presents 32 statements of hypomania symptoms for self-checking (yes/no) within the last 4 weeks. The higher scores reflect more marked hypomanic states. The HCL-32 was demonstrated to have sensitivity (0.80) and specificity (0.51) at an optimal cut-off of 14 in a sample comprising predominantly outpatients with bipolar and unipolar in Europe, suggesting higher sensitivity but lower specificity for bipolar disorder, compared to the Mood Disorder Questionnaire.[3] The relative advantage is that subjects need only several minutes to complete this questionnaire.

In the evidence-based literature in Japan, on the other hand, the clinical reality of the heterogeneity of depressive disorders has been insufficiently investigated. Recently we translated Angst's HCL-32 Revised version (HCL-32 R1) into Japanese under the author's supervision.[5] This should prove a promising tool for identifying hypomanic components in patients presenting only depressive symptoms in clinical settings. For example, Rybakowski *et al*. confirmed an association between bipolarity and non-response to antidepressant drugs in patients with mood disorders, using the Polish version of the HCL-32.[6]

In modern Japanese society, increasing numbers of depressed subjects are being referred to psychiatric clinics. The use of the HCL-32 hypomania self-assessment scale may make clinicians/users more aware of hypomania symptoms in daily life. This will hopefully curb the growing easy reliance on the use of antidepressants and psychostimulants without clinical reflection and lead to the practice of appropriate bipolar psychopharmacology.

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Electroconvulsive therapy can improve psychotic symptoms in anti-NMDA-receptor encephalitis

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ANTI-*N*-METHYL-D-ASPARTATE (NMDA) RECEPTOR encephalitis has recently been described as paraneoplastic encephalitis often associated with ovarian teratoma.[1] This form of encephalitis is important to psychiatrists because of the possibility of misdiagnosis as schizophrenia. Tumor removal and immunotherapy are usually recommended for anti-NMDA-receptor encephalitis. Reports on the effectiveness of electroconvulsive therapy (ECT), however, are limited.[2,3]

We present here a case of anti-NMDA-receptor encephalitis accompanied by schizophrenia-like psychosis with catatonia. To our knowledge, this is the first report on the successful treatment of this encephalitis with ECT, unaccompanied by immunotherapy or tumor removal.

After recuperating from influenza, an 18-year-old Japanese man felt fatigue and vertigo. Five days later, he developed acute-onset behavioral abnormalities and personality change. Another 6 days later, he developed delusions and committed violence, and was admitted to hospital. At the first visit, he was found to be in a confusional state with catalepsy, stereotypy, convulsions, and involuntary movements of the tongue. Initial electroencephalography, brain magnetic resonance imaging, and cerebrospinal fluid (CSF) were normal. Full body computed tomography (CT) showed no malignant

neoplasm. A CSF sample for anti-NMDA antibody testing was obtained at the time of admission. The first attempt to treat him for catatonic schizophrenia with antipsychotics, lorazepam, and sodium valproate only reduced his confusional states. Therefore, ECT was carried out. ECT improved catatonia and psychosis, and confusional states gradually. After 13 ECT sessions and use of antipsychotics, the patient made a full recovery. He did not show any central hypoventilation in the course of the disease. After discharge we were informed that the anti-NMDA antibody in his CSF was positive. At 1-year follow-up the patient had fully recovered, and required no medication.

Without information on anti-NMDA-receptor antibody, we would have misdiagnosed the patient as having schizophrenia and passed over the encephalitis. Because treatment for anti-NMDA-receptor encephalitis differs from that of schizophrenia, the differential diagnosis is crucial. Pharmaceutical therapy for schizophrenia was not effective in the present case, but ECT ameliorated the psychotic symptoms.

The present finding suggests that ECT is an effective treatment option for catatonia and psychosis in anti-NMDA-receptor encephalitis. The current literature shows only a limited effect of ECT for anti-NMDA-receptor encephalitis: one patient made a full recovery after ECT but only in conjunction with methylprednisolone pulse therapy,[2] while another patient's symptoms were partially improved with ECT, but full recovery was attained only after tumor removal.[3] We do not fully understand the mechanism of ECT in anti-NMDA-receptor encephalitis. In the present case, it is possible that ECT temporarily attenuated the symptoms while encephalitis was improved in the natural course.[4] Recent studies, however, have shown that ECT modulates the glutamatergic synapses in animal models.[5] Thus, studying anti-NMDA-receptor encephalitis may lead to a better understanding of the function of NMDA receptors and ECT. Further studies are needed to confirm the present observation.

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Depressive state due to isolated adrenocorticotropic hormone deficiency underlies school refusal

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SCHOOL REFUSAL OCCURS in 1% of all school children and adolescents worldwide; it refers to a condition in which children refuse to attend school for reasons of emotional distress.[1] School refusal has deleterious effects on academic performance, family bonds and peer relationships.[2] In the current case, we diagnosed an adolescent boy who had school refusal with isolated adrenocorticotropic hormone (ACTH) deficiency (IAD), and we successfully treated him with exogenous steroids.

The boy lost his father at age 12, during the spring of his first year of middle school, and became severely depressed. He began to refuse to go to school 8 months later. He managed to graduate from middle school and attend high school. However, throughout high school, he was consistently absent from school for 3 months, from spring to summer, which seems like an anniversary effect of his father's death.

At age 19, he appeared to be suffering from a severe depressive state with anhedonia and apathy. He was diagnosed with recurrent depressive disorder (DSM-IV 296) with a seasonal pattern and started receiving standard treatment with paroxetine initially at 10 mg and then continuously at 40 mg for 8 weeks. However, this treatment failed to improve his symptoms. We decided to carry out laboratory testing to identify any physical abnormalities contributing to the patient's symptoms.

The results showed that his serum ACTH level was strikingly low (6.2 pg/mL, normal range: 8.2–54.8 pg/mL) and his serum cortisol level was also at the lower end of the normal range (5.2 g/dL, normal range: 4.6–19.4 g/dL), though hypoglycemia was not observed (110 mg/dL, normal range: 70–110 mg/dL). After more detailed examinations, including corticotrophin-releasing hormone stimulation test, insulin tolerance test and ACTH stimulation test, we diagnosed him with IAD and began hormone replacement therapy with oral administration of hydrocortisone 10–20 mg/day. His depressive symptoms were completely ameliorated within 1 week without adverse effects. In 2 weeks he returned to high school, enrolled in college, and then continued to attend school every day for subsequent years.

Generally, patients with IAD manifest non-specific symptoms, such as asthenia, anorexia and tendency to hypoglycemia. IAD may easily be confounded with major depressive disorder due to similar symptoms of fatigue, lethargy and other signs of adrenal dysfunction; however, patients with IAD fare relatively well during periods of low stress.[3] There was a seasonality in his depressive states from spring to summer, which seemed to be related to the anniversary of his father's death. Generally, cortisol-deficit symptoms worsen under stressful conditions because of a relative inability to increase cortisol in response to stress in individuals with IAD. In this case, the anniversary of his father's death might be a stressful event for him, leading to depressive symptoms due to the relative lack of cortisol in response to the strong stressor.

Our case suggests that, in treatment-resistant cases of depression, it may be helpful to conduct laboratory testing,

including assessment of serum level of ACTH and cortisol. Endocrine-psychiatric syndromes should be taken into consideration, especially if patients demonstrate certain symptoms like lack of motivation, depressed mood, or disturbance of biological periodicity. The patient and his mother gave the authors informed consent to publish this letter.

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Improvement in QTc prolongation induced by zotepine following a switch to perospirone

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TO OUR KNOWLEDGE, there have been only two reports concerning the effect of zotepine on the QT interval.[1,2] We herein report the findings of a case of zotepine-induced QTc prolongation in a Japanese patient with schizophrenia.

A 45-year-old woman was undergoing single-agent therapy for schizophrenia with a 200-mg intramuscular (i.m.) injection of haloperidol decanoate every 4 weeks. She received the i.m. injection of haloperidol decanoate 10 days before hospitalization. However, because her psychotic symptoms worsened, she was hospitalized on day 0. On the same day, electrocardiography showed a QTc of 419 msec at a heart rate (HR) of 64/min. We then started to switch the patient to 50 mg/day of zotepine. As a result of increasing the dosage of zotepine from 50 mg to 400 mg/day (on day 39), the patient's psychotic symptoms became stable. However, on day 61, electrocardiography showed a QTc of 483 msec at a HR of 98/min. Therefore, we started to switch the patient to 16 mg/day of perospirone on day 121. During the switch to perospirone treatment, her psychotic symptoms became unstable again. Therefore, the dosage of perospirone was increased from 16 mg to 32 mg daily on day 88, and then 48 mg/day on day 102. As a result of increasing the dosage of perospirone, the patient's psychotic symptoms became stable. On day 128, electrocardiography showed a QTc of 418 msec at a HR of 76/min. During the examinations, only benzodiazepines could be concomitantly used; zotepine and perospirone were administered once daily before sleep, and electrocardiographic measurements were conducted between 09.00 and 10.00 hours. The QT interval was corrected using Bazett's correction formula (QTc = QT/RR1/2). When electrocardiography was conducted at each time-point, biochemical examinations revealed no electrolyte abnormalities in the serum Na, K, Cl, or Mg levels, and no cardiac diseases, such as arrhythmia, or any other new physical disorders were observed. This patient provided written, informed consent.

One cross-sectional study revealed that zotepine did not affect QTc in Japanese patients with schizophrenia.[2] On the other hand, a dose-dependent effect of zotepine on QTc was also reported in a Han Chinese case.[1] The results of the current case are in line with those reported by Lin *et al*.[1] The QT interval can be affected by various factors, such as age, sex and drug–drug interactions. Hence, we believe that increased doses of zotepine should be given carefully, especially in patients who have other risk factors. In our case, a switch to perospirone from zotepine treatment normalized the QTc. However, the details regarding the correlation between perospirone and QTc prolongation still remain unclear. Further studies are needed to clarify the effect of zotepine or perospirone on QTc using longitudinal methods rather than with cross-sectional studies.

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Diphenhydramine overdose and serotonin syndrome

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I READ WITH INTEREST the case presented by Tanaka *et al*. recently published in your journal.[1] They reported, for the first time, a case of central anticholinergic syndrome due to diphenhydramine overdose that shared some clinical features of serotonin syndrome. They managed their case with intravenous drip infusion of fluids and oral administration of lorazepam. The patient's abnormal vital signs, myoclonus, hyperreflexia, and mental status returned to normal within 2–3 days. It can be suggested that administration of cyproheptadine could have improved the patient's condition earlier. As you know, there are seven serotonin receptor families (5-HT1 to 5-HT7), which are further subdivided into groups based on different activities in neural and peripheral organ systems.[2] As the authors themselves have also mentioned, serotonin

syndrome is thought to be due to excessive stimulation at certain central nervous system 5-HT receptors (i.e. 5-HT-2A, 5-HT-1A, and 5-HT-3).[3] Cyproheptadine is a first-generation, histamine-1 receptor-blocking agent with non-specific antagonist properties at 5HT-1A and 5HT-2A receptors.[4] It has been shown that patients with mild to moderate symptoms of serotonin syndrome that are not hyperthermic typically respond to this pharmacological agent within 30 min to 2 h of administration.[5,6]

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Hyperhidrosis under combination of zotepine and haloperidol alleviated by aripiprazole

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HYPERHIDROSIS IS A possible side-effect of antipsychotics. We report a case developing hyperhidrosis under combination of zotepine and haloperidol, in which the sweating subsided after switching from zotepine to aripiprazole.

Mrs C, a 55-year-old woman, was diagnosed as having schizophrenia at age 30 and diabetes mellitus at age 45. From 6 months before admission, because of refractory auditory hallucinations, the antipsychotics were gradually increased from zotepine 200 mg/day and haloperidol l5 mg/day; however her compliance was doubtful. After admission, zotepine 350 mg/day and haloperidol 15 mg/day were regularly administered. The concurrent medication included propranolol 60 mg/day, biperiden 6 mg/day, metformin 1000 mg/day, and glimepiride 2 mg/day. During the first 2 weeks of admission, excessive sweating was noticed. The sweating was generalized, with the most severe location in the trunk, and it was aggravated at night. The patient had no history of hyperhidrosis. The patient showed parkinsonism on neurological examination. Blood examination revealed fasting glucose 116 mg/dL and glycated hemoglobin A1c 7.3%, which were similar to her past data. Thyroid and adrenal functions were within normal limits. Antipsychotics-associated hyperhidrosis was suspected. During the third week of admission, we tapered zotepine to 200 mg/day and raised aripiprazole to 15–30 mg/day. The patient reported less sweating after that. There was no more evidence of excessive sweating at the end of the 6th week when we completely discontinued zotepine. Mrs C showed less auditory hallucination under a combination of aripiprazole and haloperidol, though mild rigidity could still be observed. Concurrent medications were not adjusted.

This is the first report demonstrating hyperhydrosis associated with a combination of zotepine and haloperidol. The hyperhidrosis of Mrs C had two possible mechanisms. The first was via the cholinergic pathway. A report by Richardson *et al*. states that sweating induced by clozapine is related to cholinergic effect and is reversible under biperiden.[1] But in our case, biperiden did not work in preventing hyperhidrosis. Second, depleted dopamine in hypothalamus influences thermoregulatory function. Mrs C received a high dose of zotepine and haloperidol. Her extrapyramidal syndrome implied low dopamine activity in nigrostriatal region, which is compatible with dopamine-related thermoregulatory disturbance.

Aripiprazole was prescribed when tapering zotepine. Under aripiprazole, the depleted dopamine may be corrected to a regular activating level due to its feature as a dopamine partial agonist. Aripiprazole has higher D2 affinity (Ki = 0.95 nM) than haloperidol (Ki = 2 nM) or zotepine (Ki = 25 nM).[2] Therefore, the D2 partial agonist property of aripiprazole can still work when combining with haloperidol. Aripiprazole is reported to alleviate antidepressant-induced excessive sweating by adjusting thermoregulatory function in the hypothalamus.[3]

Mrs C's blood glucose level was not significantly different to her previous data. Besides, the sweating alleviated without adjusting diabetic medication. We consider diabetes to be less likely to induce hyperhidrosis.

To summarize, hyperhidrosis associated with zotepine and haloperidol use in this case was possibly related to dopamine depletion, which was modified by aripiprazole. Clinicians should be prudent when prescribing zotepine in patients with concurrent haloperidol use.

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Sulpiride-associated torsade de pointes in a woman with bipolar disorder

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ANTIPSYCHOTIC AGENTS HAVE long been suspected to increase the risk of torsade de pointes (TdP) and subsequent sudden cardiac death.[1] Some cases of TdP induced by sulpiride at a high dose or in a poisoning condition have been reported. Herein, we report the first case of sulpiride-associated TdP in a patient receiving a therapeutic dosage.

A 60-year-old woman had suffered from bipolar disorder for decades. She had experienced recurrent manic and depressive episodes during the past few years and was stabilized by lithium 900 mg/day and sulpiride 800 mg/day for about 2 years. In addition, she had received medications to control hypertension, including amlodipine, atenolol and chlorthalidone. Unfortunately, she developed a sudden onset of syncope, which resulted in left tibial fracture. On arriving at the emergency room, an initial electrocardiogram revealed sinus bradycardia (53 b.p.m.) with multiple ectopic beats; QRS complex was wide with a duration of 138 msec and the QTc interval was measured up to 760 msec. She developed another episode of syncope with subsequent consciousness loss. Meanwhile, electrocardiogram monitoring demonstrated TdP. Magnesium sulfate 100 mg was given intravenously immediately. Blood tests were within normal limits, except severe hypokalemia with a serum potassium level of 2.7 mmol/L. Sulpiride and lithium were discontinued and the QT interval was gradually normalized.

Lithium and valproic acid were used concomitantly for the recurrent manic episodes during follow up with a good result. In the serial electrocardiogram follow up, the QT interval was no longer prolonged.

In this case, lithium was co-administered, so the possibility of TdP induced by this polypharmacy could not be ruled out. However, no lithium-induced TdP has been reported. Furthermore, lithium was used continuously after the event without causing QTc prolongation or TdP, so the role of lithium in this case would be minimal. Nevertheless, given no available lithium plasma level in this case, we could not completely rule out the addictive role of lithium toxicity in causing TdP.

Sulpiride has been reported to be associated with QTc prolongation,[2] possibly by interfering with the delayed rectifier potassium current. Nevertheless, there is a lack of sound evidence implicating sulpiride in the induction of TdP. The use of sulpiride in the therapeutic range is reasonable; however, when risk factors are present, evaluation and specific action should be taken to reduce the risk of TdP. Our patient had many risk factors for TdP: increasing age, female sex and hypokalemia.[3] The clinician should titrate the dosage to a lower level for patients carrying risk factors for TdP, particularly older patients with known heart disease.

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