Visual hallucinations and agitation in Alzheimer's disease due to memantine: report of three cases

Memantine, a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist, is currently the only drug proposed for the treatment of moderate to severe Alzheimer's disease.[1] It has been shown to have neuroprotective effects by inhibiting the excitotoxic effect of NMDA glutamate receptors.[2] Memantine has a tolerability profile similar to placebo.[1] However, the worsening of psychotic symptoms in patients with Lewy body dementia (LBD) treated with memantine has been recently reported.[3] We describe three patients with probable Alzheimer's disease who developed worsening or de novo visual hallucinations and agitation after memantine treatment.

Case reports

Patient 1 was a 65-year-old woman with a 2-year history of slowly progressive cognitive decline, affecting episodic memory, naming and executive-attentive skills. Functional abilities of daily living were impaired. Physical and neurological examination, routine blood tests and electrocardiogram (ECG) were normal. Magnetic resonance imaging (MRI) of the brain showed a bilateral frontotemporal atrophy. A diagnosis of probable Alzheimer's disease was made, and she was treated initially with rivastigmine, then 2 years later with donepezil (10 mg/day) for a further 2 years. Because the patient's Mini Mental State Examination (MMSE) score was 14/30 at 69 years, she was prescribed a combination treatment with memantine. Her other drugs included vitamin E supplements, citalopram and quetiapine for mild agitation. One week after the starting of memantine (5 mg/day), agitation increased in frequency and severity and she developed florid visual hallucinations, described as ''small animals going around the room''. A neurological examination showed a mild bradykinesia. Blood test, ECG, chest *x* ray and brain MRI were unremarkable. Memantine was discontinued, and she experienced immediate reduction of agitation and disappearance of the visual hallucinations. At a follow-up visit 3 months later, no other adverse effects were seen.

Patient 2 was a 75-year-old woman with a 5-year history of depressive symptoms, followed by slowly progressive cognitive decline affecting episodic memory, naming, visuoconstructional and executive skills in the past 2 years. Functional abilities of daily living were impaired, and moderate anxiety and depressive symptoms were present. Physical and neurological examination, blood tests and ECG were normal. Brain MRI showed bilateral atrophy and mild periventricular white matter lesions. The patient's drugs included atorvastatin and bisphosphonate. She was diagnosed with probable Alzheimer's disease and treated with donepezil (10 mg/day) for 3 years. As her MMSE score was 12/30, she was prescribed a combination therapy with memantine. Other drugs included paroxetine, trazodone, folic acid, vitamin E supplements, atorvastatin and bisphosphonate. After taking three doses of memantine (5 mg/day), she developed florid visual hallucinations, described as ''people looking at her through the windows''. Blood test, ECG, chest *x* ray and brain MRI were unremarkable. A neurological examination showed mild bradykinesia and rigidity. Memantine was discontinued, and within 24 h her visual hallucinations completely resolved. After 1 week, with the consent of the patient and her daughter, memantine was resumed and the visual hallucinations returned. Memantine was again discontinued and the visual hallucinations rapidly resolved. Over the next 6 months, no recurrence of the visual hallucinations was reported.

Patient 3 was a 73-year-old woman with a 3-year history of slowly progressive cognitive decline affecting episodic memory, naming and visuoconstructional skills. There was a concomitant impairment of functional abilities of daily living, occasional incontinence and mild apathetic symptoms. Physical and neurological examination, blood tests and ECG were normal. Brain MRI showed bilateral frontotemporal atrophy. She was diagnosed with probable Alzheimer's disease and started on rivastigmine treatment with a modest response. After 6 months, she was switched to donepezil with similar results. After further 6 months, she was administered galantamine treatment (progressively titrated up to 24 mg/day). After 2 years, she developed mild agitation and visual hallucinations, described as ''people coming out of the television screen''. As her MMSE was 12/30, she was prescribed a combination treatment with memantine. Other drugs included paroxetine, quetiapine and vitamin E supplements. One week after the starting of memantine (5 mg/day), the agitation, and in particular the visual hallucinations, worsened, to such an extent that relatives had to take her to hospital. At admission, blood test, ECG, chest *x* ray and brain MRI were unremarkable. A neurological examination showed mild gait disturbances. Memantine was immediately stopped and, within 48 h, agitation and visual hallucinations improved considerably. At a follow-up visit 3 months later, she reported mild agitation and infrequent mild visual hallucinations.

Discussion

We report three cases with probable Alzheimer's disease who developed worsening or de novo visual hallucinations and agitation after memantine treatment. The strict temporal relationship between the use of the drug and the onset or worsening of the symptoms, and the resolution once treatment was discontinued, suggests a causal link between the two phenomena. This hypothesis is strengthened by the fact that we were able to verify the recurrence of visual hallucinations after memantine administrationin in patient 2.

None of the clinical trials of memantine in monotherapy or combination therapy with cholinesterase inhibitors in patients with Alzheimer's disease reported the development of visual hallucinations or agitation as adverse effects.[1] However, the worsening of psychotic symptoms, including visual hallucinations, as a result of memantine treatment in patients with LBD has been described recently.[3] Memantine is structurally similar to amantadine, an influenza drug used for the treatment of Parkinson's disease, which has been reported to cause visual hallucinations in patients with Parkinson's disease.[4] Both drugs bind with low affinity to the ion channel phencyclidine site at the NMDA receptor.[2] Phencyclidine, an NMDA receptor antagonist with high affinity, induces psychotomimetic effects, including hallucinations, agitation and delusions.[2] The relative rapid off-rate (that is, the time taken for a drug to vacate a receptor binding site) of memantine is crucially important for its clinical tolerability.[2] Some patients with Alzheimer's disease could be susceptible to concomitant neurotransmitter and receptor imbalance, as proposed to occur in patients with LBD.[3] However, in the absence of pathological confirmation, our patients may represent those subjects with Alzheimer's disease with concomitant LBD pathology.[5] Because of the fact that all three patients were also receiving antidepressant drugs of the selective serotonin reuptake inhibitor class, another possible explanation is that a drug interaction between memantine and the serotonin reuptake inhibitors might have occurred, which could have increased the potential for inducing or worsening hallucinations and agitation. Further studies or case reports are required regarding the incidence of these side effects and the underlying mechanisms of action before definitive conclusions can be reached.

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Hemimacropsia after medial temporo-occipital infarction

Dysmetropsia is a disorder of visual perception characterised by an apparent modification of the size of perceived objects.[1–3] Objects can appear larger (macropsia) or smaller (micropsia) than their actual size. Dysmetropsia can result from retinal oedema causing a dislocation of the receptor cells and from lesions affecting other parts of extracerebral visual pathways. Transient micropsia can also result from epileptic seizure, migraine, infectious mononucleosis, the action of mescaline and other hallucinogenic drugs, and psychopathological phenomena.

Permanent dysmetropsia following focal cerebral lesions is rare. Most of the prior reports described hemimicropsia due to lesions mainly involving the lateral aspect of the visual association cortex.[1–3] However, reports of hemimacropsia following focal cerebral lesions have been extremely rare[1 4] and hemimacropsia following a focal vascular lesion has not been

described previously. We describe a patient with left hemimacropsia due to right medial temporo-occipital infarction.

Case report

A 64-year-old right-handed man with hypertension was admitted 4 days after a sudden onset of visual disturbance. He reported that objects in the left side of the visual fields appeared larger in size without distortion of the shape. On neurological examination, he was alert and fully oriented to time and space. His visual acuity was normal, but left homonymous upper quadrantanopsia was found on confrontation tests. He was able to recognise objects, and name colours and his family members. He was fluent and had no problems in comprehension, reading and writing. There was no evidence of visuospatial dysfunction in a cancellation task and line bisection test. He had no weakness or sensory deficit. Babinski sign was not elicited bilaterally. Humphrey perimetry showed left homonymous upper quadrantanopsia (fig 1A). To verify hemimacropsia, we performed size discrimination tasks. We instructed him to stare at the examiner's right eye with his right eye covered and then presented a circle of 1, 1.5 or 2 cm diameter in the nasal and temporal side of his left eye separately. After taking away the circle, we asked him to indicate a circle of the same size among circles of variable sizes ranging from 0.5 to 4 cm in diameter with binocular viewing. We repeated the same task with his left eye covered. He always selected a circle of larger size than the one presented when the circle appeared in the temporal field of the left eye and in the nasal field of the right eye. However, he was able to choose a circle of the same size when the circle was presented in the temporal field of the right eye or in the nasal field of the left eye.

MRI disclosed an infarction in the right medial temporo-occipital region, which corresponded to the medial aspect of Brodmann areas 17, 18 and 19 (fig 1B–E). The macropsia resolved completely 1 month after symptom onset, but left homonymous upper quadrantanopsia remained unchanged on follow-up perimetry.

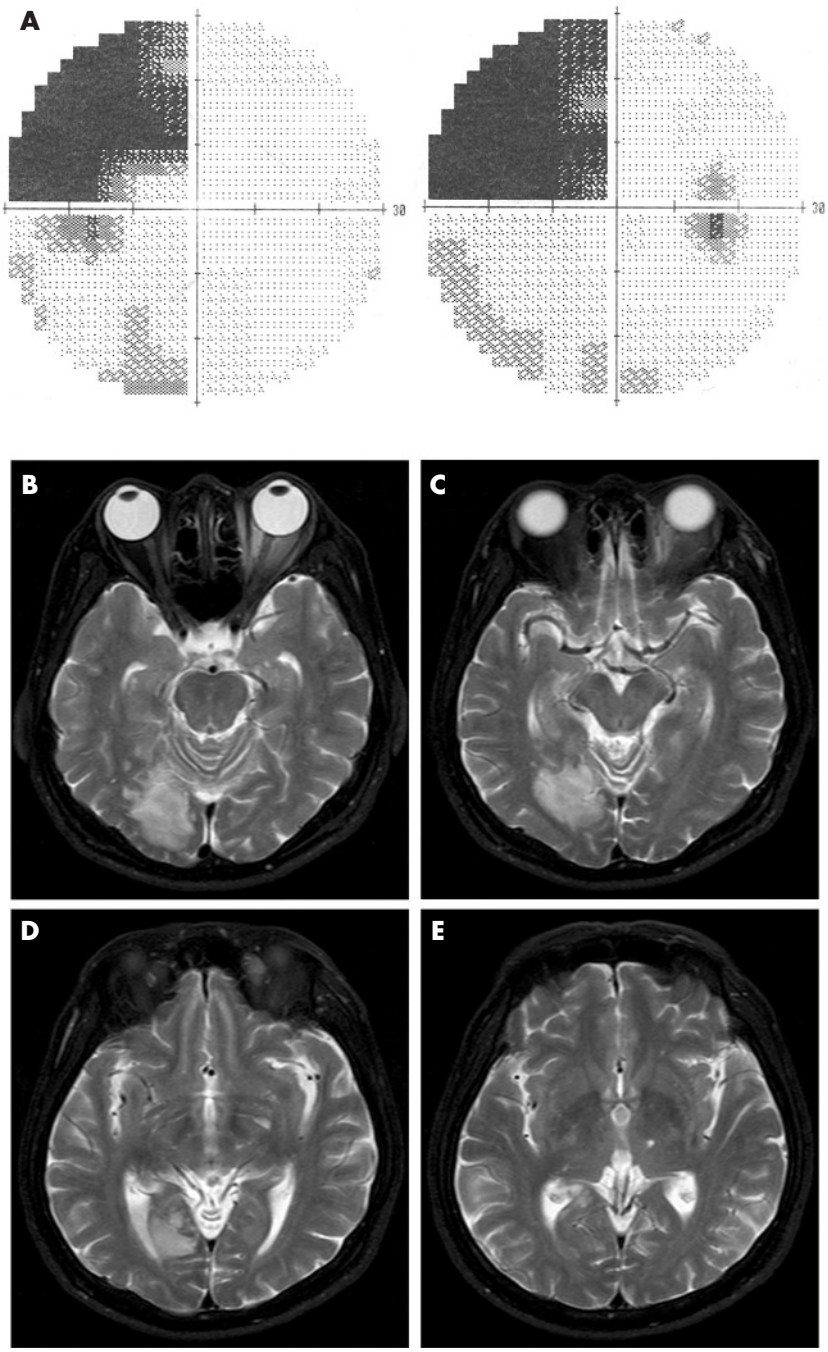

Figure 1 Humphrey perimetry shows left homonymous upper quadrantanopsia (A) and brain MRIs (B–E) show an infarction in right medial temporo-occipital lobe (Brodmann areas 17, 18 and 19).

Comment

Although precise anatomical details on the cerebral lesions responsible for dysmetropsia remain uncertain, hemimicropsia has mostly been reported in lesions involving the lateral aspect of the visual association cortex (Brodmann areas 18 and 19).[1–3]

The striate cortex is the source of two multisynaptic corticocortical pathways.[5] The occipitotemporal projection system is crucial for the visual identification of objects, whereas the occipitoparietal projection system is critical for the visual location of objects. Authors have argued that the prestriate areas are responsible for hemimicropsia, because the reported patients did not show any evidence of contralesional spatial neglect or a systematic bias in locating contralesional objects towards the ipsilesional side despite the lesions in the lateral aspect of the visual association cortex.[1–3]

On the other hand, the anatomical substrate and the pathophysiological mechanism of hemimacropsia have not been well described, and reports of hemimacropsia following focal cerebral lesions have been sparse.[1 4] Previously, a patient experienced right hemimacropsia immediately after excision of a tumour involving the inferior portion of the left occipital lobe,[1] and another experienced micropsia for objects presented in the left visual field due to a right occipital lesion from blunt head trauma, but the disorder reversed to macropsia under certain circumstances.[4]

Our patient showed left hemimacropsia and homonymous upper quadrantanopsia, without any other aspect of visual processing being affected. Brain MRI documented an infarction in the medial aspect of the right temporo-occipital lobe. Our case suggests that, unlike hemimicropsia, hemimacropsia may be associated with a lesion in the ventral portion of the occipitotemporal projection, including the lingual and fusiform gyri, which play a decisive role in the visual identification of objects by interconnecting the striate, prestriate and inferior temporal areas. Patients with hemimacropsia may have an anatomical localisation of the lesions in the medial aspect of the temporo-occipital lobe, whereas hemimicropsia usually results from lesions in the lateral aspect.

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Improvement in neuroleptic-induced akathisia with intravenous iron treatment in a patient with iron deficiency

Iron deficiency may play a role in the pathogenesis of drug-induced akathisia, but the evidence is conflicting.[1–3] There have been no reports of the effect of iron treatment in this condition. We report the case of a patient with iron deficiency whose akathisia had not responded to standard interventions but did respond dramatically to intravenous iron treatment.

A 68-year-old man with schizophrenia had been well controlled for 10 years on thioridazine 150 mg/day. His treatment was changed to respiridone 1 mg twice daily. Within 2 weeks, he had developed a severe sensation of inner restlessness and anxiety associated with increased leg movements and body rocking. No depressive or psychotic symptoms were noticed, although the patient was greatly distressed. Acute drug-induced akathisia was diagnosed.

No improvement in akathisia symptoms was noticed when the dose of respiridone was reduced or when respiridone was discontinued and thioridazine restarted. Therapeutic trials of alprazolam, benztropine and propranolol failed to alleviate his symptoms and led to side effects.

When seen in our clinic, the patient had had symptoms for >6 months. He reported a ''terrible feeling'' of restlessness and anxiety ''gnawing inside me'' each day. Symptoms were present throughout the day, with no worsening at night, and no limb paraesthesias were noticed. There was no personal or family history suggestive of restless legs syndrome (RLS). Neurological examination was normal apart from reduced facial expressiveness. The Barnes Akathisia Rating Scale (BARS), a well-validated scale of akathisia severity comprising objective and subjective components, was 11/14, which is consistent with severe akathisia.[2]

Electrolytes, serum urea, creatinine and glucose, thyroid function tests, erythrocyte sedimentation rate, C reactive protein, vitamin B_{12}, and folate levels were normal. Haemoglobin was 13.1 g% (abnormal in our laboratory <13 g%), transferrin saturation 12% (abnormal <15%), serum ferritin 36 μg/l (abnormal <12 μg/l), total iron-binding capacity 490 μg/l (abnormal >400 μg/l) and serum iron 520 μg/l (abnormal <600 μg/l). A diagnosis of iron deficiency was made on the basis of the abnormal transferrin saturation combined with a serum ferritin <50 μg/l.[4] Gastrointestinal examination was normal and serial tests for faecal occult blood were negative. He had a distant history of peptic ulcer disease. Dietary history showed inadequate intake of iron-containing foods. His dentition was poor. The patient refused endoscopic investigation of the intestinal tract. Screening tests for coeliac disease were negative.

Oral iron supplements caused unacceptable nausea and epigastric discomfort. The patient was given 400 mg intravenous ferrous sucrose in divided doses (100 mg in 100 ml normal saline on days 1 and 3, and 200 mg on day 5). On day 7, the patient reported that he felt normal for the first time in months. The BARS score was now 3/14 (corresponding to mild or questionable akathisia); haemoglobin was 13.8 g%, ferritin 52 μg/l and transferrin saturation 17%. Dietary advice was given to increase the intake of iron-containing food. Subsequently, he was able to tolerate 300 mg ferrous gluconate (containing 35 mg of elemental iron) every second day. Clinical (BARS score 3/14) and haematological (haemoglobin 13.7 g% and ferritin 68 μg/l) improvement were maintained on review at 5 months.

Both akathisia and RLS are characterised by motor restlessness and sleep disturbances, and RLS can be precipitated by dopamine-blocking drugs. There is convincing evidence that iron status is an important factor in the pathogenesis of RLS, and correction of iron deficiency improves symptoms in RLS.[5] The balance of evidence from previous studies does not suggest that iron deficiency plays a similarly critical role in the development of drug-induced akathisia in most patients. However, many studies either focused on serum iron,[1 2] which is not a good guide to iron status, or used an inappropriately low cut-off for normal serum ferritin.[4] Nevertheless, studies that examined ferritin levels reported that patients with akathisia had lower levels than controls without akathisia.[3]

Studies comparing blood tests with bone marrow examination have shown that serum ferritin at a cut-off of 50 μg/l is the best screening test for iron deficiency in patients with and without anaemia.[4] Furthermore, serum ferritin <50 μg/l has also proved useful for predicting responsiveness to iron supplementation in people with RLS.[5]

The patient in this report had several haematological indices suggestive of iron deficiency and several risk factors for iron deficiency. His serum ferritin of 36 μg/l is also consistent with mild iron deficiency. His haemoglobin level of 13.1 g% was at the low end of normality for a man. As a general rule, 8 mg of storage iron corresponds to 1 μg/l ferritin. Thus, in an iron replete person, 400 mg of intravenous iron would lead to a rise in serum ferritin of about 50 μg/l; the relatively small rise in ferritin levels in our patient suggests that the iron supplement was indeed used to correct a tissue deficiency in iron.

It is unlikely that this patient had an atypical RLS. No night-time worsening of symptoms (a necessary diagnostic feature in RLS) was noticed. The feeling of inner restlessness and body rocking are characteristic of acute drug-induced akathisia. It is not uncommon for akathisia, once provoked, to fail to resolve when the precipitating drug change is reversed.

The close temporal relationship between administration of intravenous iron and resolution of hitherto resistant symptoms in our patient suggests that iron deficiency can contribute to the development or persistence of akathisia in some patients. Iron repletion may be valuable in such cases, although this requires further evaluation. There are, of course, other potential benefits to treating and identifying the cause of iron deficiency. We suggest that haemoglobin, serum ferritin and transferrin saturation should be checked in patients with akathisia, and that patients with iron deficiency should be treated until haemoglobin is normal and serum ferritin is more than 50 μg/l. Although the use of intravenous iron formulations may facilitate examination of the potential effects of iron repletion on akathisia in future studies, biochemical improvement is usually seen within 2–4 weeks of starting oral iron supplements in patients with deficiency and this should remain the initial treatment.

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Guillain–Barré syndrome with antibodies to GD1a/GD1b complex

Recently, ganglioside complexes (GSCs) such as GD1a/GD1b, GD1a/GM1, GD1b/GT1b, GM1/GT1b, GQ1b/GM1 and GQ1b/GD1a have been