Figure 2 (A) Brain MRI carried out on day 2 of admission shows hyperintensity signal changes in the bilateral dorsal part of the striatum and adjacent corona radiata in T2-weighted and diffusion-weighted images. (B) Three months after the steroid pulse treatment, the area of hyperintensity signal in the corona radiata decreased in size as observed in T2-weighted images.

Discussion

Neurological evaluation showed that the symptoms of the patient were not accompanied by intellectual deterioration or neuropsychological abnormalities. Additionally, the patient was cooperative and well oriented to the copying tasks. These findings indicate that the smallness of the handwriting presented here corresponds to micrographia. The micrographia of the patient, however, is atypical compared with the common form of micrographia in Parkinson's disease, which is characterised by a spectacular shrinking in character size as the handwriting progresses.¹ This feature of Parkinson's disease is presumably attributed to the smallness of motor output and the use of visual feedback of a previous or an ongoing stroke recursively to programme the subsequent strokes during handwriting.² With regard to the micrographia presented here, the constant size of the character during the handwriting sequence suggests that the patient preserves the ability to use the feedback mechanism that provides the trial-by-trial adaptations of character size in handwriting.²

The micrographia in this patient was further characterised by an initial marked reduction in size. This feature is considered to be more prominent than that in patients with Parkinson's disease. Scolding and Lees³ showed that an isolated lesion in the parietal white matter caused micrographia, in which an initial reduction in the size of the handwriting was also noted. Strikingly, the MRI of this patient showed that the lesions affected mainly the corticostriatal white matter. Furthermore, the shrinkage of such lesions was consistent with the improvement in the symptom. Experimental data suggest that the functions of the corticostriatal pathway are associated with spatial attention⁴ and motor skill learning,⁵ which presumably maintain the quality of handwriting. Interestingly, the corticostriatal pathway is insidiously affected in patients with Parkinson's disease too.⁶ We therefore speculate that this disruption may contribute to aberrant kinesthetic processing in which the sensorimotor apparatus is "set"

small.⁷ This aberration may underlie the atypical micrographia of this patient. Taken together, these findings suggest that the disruption of the corticostriatal pathway is responsible for the initial reduction in the size of the handwriting.

Although the question of whether it is the dominant or non-dominant hemisphere that is principally implicated in this symptom remains elusive, our observations raise the possibility that the corticostriatal pathway contributes to the adjustment of the sensorimotor input in the control of elaborate movements such as handwriting.

T Ishihara, T Ozawa

Department of Neurology, Niigata University Brain Research Institute, Niigata, Japan

M Otsuki

School of Psychological Science, Health Sciences University of Hokkaido, Hokkaido, Japan

J Shimbo, K Tanaka, M Nishizawa

Department of Neurology, Niigata University Brain Research Institute

Correspondence to: Tetsutaro Ozawa, Department of Neurology, Niigata University Brain Research Institute, 1 Asahimachi, Niigata 951-8585, Japan; ozawa@bri.niigata-u.ac.jp

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Myoclonus as an acute complication of low-dose hydromorphone in multiple system atrophy

Myoclonus has been described as a neuro-excitatory side effect of high doses of opioids. It has been seen almost exclusively in patients receiving palliative care after long-term administration of opioids. Gradual accumulation of opioid metabolites has been thought to cause opioid-induced myoclonus.¹ Naloxone has usually been ineffective in resolving this condition. In this study, we present a case of severe generalised myoclonus after a patient with known multiple system atrophy received a low dose of intravenous hydromorphone. The generalised myoclonus reversed completely immediately after he received naloxone.

Case report

A 75-year-old man with a history of multiple system atrophy with parkinsonism was admitted to the Montreal General Hospital, Montreal, Canada, with a hip fracture. Drugs administered on admission were fludrocortisone, gliclazide, intravenous immune globulin (for bullous pemphigoid) and midodrine. He was not taking levodopa because of severe orthostatic hypotension. To treat his pain, 1 mg of intravenous hydromorphone was given over 20 min. About 35 min after receiving the hydromorphone infusion, the patient had decreased consciousness, severe generalised myoclonus and rigidity. The neurology service was consulted.

On examination, the patient was difficult to rouse. He inconsistently opened his eyes with sternal rub, and would occasionally localise sound. No oral response was evident, and he did not obey motor commands. His pupils were pinpoint. Motor examination showed generalised rigidity. Throughout the examination, there were continuous, extremely severe multifocal myoclonic jerks. The myoclonus occurred in all four limbs, the axial musculature and the face. Movements were continual and asynchronous, about 4–6 jerks/s. Stimulus sensitivity could not be assessed because of the high baseline frequency. Plantar reflexes were downgoing bilaterally.

Laboratory values showed normoglycaemia and normal serum biochemistry, including calcium levels and renal function. Despite the low dose given, an adverse reaction to hydromorphone was suspected, and 0.4 mg of naloxone, an opioid antagonist, was given. Within seconds of administration, his condition improved dramatically, with a complete reversal of the myoclonus and a return to normal consciousness. As the effects of the naloxone dissipated, the patient had a gradual reappearance of the myoclonus, but never at the same intensity. The symptoms resolved completely over the next 2 h. Acetaminophen without opioids was used for subsequent analgesia. A resting

electroencephalogram the next day showed mild to moderate diffuse cerebral dysfunction, but no epileptiform activity. On follow-up examination weeks later, no spontaneous or stimulus-sensitive myoclonus was observed.

Discussion

Myoclonus is a known manifestation of neuroexcitotoxicity in patients receiving long-term opioids. In palliative care settings, wherein patients are given long-term high-dose opioids, the incidence of opioid-induced myoclonus ranges from 2.7% to 11%.¹ With the exception of a single case report,² opioid-induced myoclonus has been described only in the setting of long-term and high-dose administration of opioids.¹ It has been hypothesised that neuroexcitotoxicity is secondary to a gradual accumulation of several morphine and hydromorphone metabolites in plasma and the CSF and is not due to the opioid itself.^{1,3} Animal and in vitro studies of opioid-induced myoclonus have almost unanimously implicated the build-up of neuroexcitotoxic opioid metabolites, such as morphine-3-glucuronide or hydromorphone-3-glucuronide.^{1,3} For this reason, periodic rotation of different types of opioids, which reduces CSF levels of individual metabolites, is usually the treatment of choice.¹

In contrast with previously reported cases, our patient developed severe neuroexcitotoxicity within a brief interval after the acute administration of a single dose of hydromorphone. This strongly suggests that in at least a subset of cases, neuroexcitotoxicity is not dependent only on accumulation of opioid metabolites but can be induced by the opioids themselves.

Controversy exists as to whether neuroexcitotoxicity of opioids is reversible with naloxone. Early studies suggested that the neuroexcitotoxicity of a morphine metabolite was inversely proportional to its affinity to the opioid receptor. Whereas certain in vitro and animal studies showed diminution or abolishment of neuroexcitotoxicity with the administration of naloxone,⁴ others found opioid antagonists to be ineffective at reducing experimentally induced neuroexcitotoxicity.⁵ Perhaps in cases where accumulation of opioid metabolites is responsible for neuroexcitotoxicity, naloxone may be incapable of reversing the side effect. On the other hand, our patient had a complete abolition of myoclonus with a single dose of naloxone, suggesting that in acute-onset cases naloxone may be of use.

It is interesting to note that our patient had multiple system atrophy. Myoclonus is often seen in multiple system atrophy and is thought to be cortical in origin. This is, however, generally mild and usually consists of infrequent axial, stimulus-sensitive myoclonic jerks. Our patient's underlying condition, however, may have led to a predisposition to such a strikingly unusual presentation of opioid-induced myoclonus.

This case report shows that, in contrast to previous studies, opioid-induced myoclonus can occur acutely and with administration of low doses. The acuity of its development suggests that myoclonus is not reliant on accumulation of metabolites but can be caused by the drug itself. Naloxone may be of use in acute-onset cases.

A Hofmann, N Tangri

Department of Internal Medicine, McGill University, Montreal, Quebec, Canada

A-L Lafontaine, R B Postuma

Department of Neurology, McGill University

Correspondence to: Ronald B Postuma, Department of Neurology, L7-305 Montreal General Hospital, 1650 Cedar Avenue, Montreal, Quebec, Canada H3G 1A4; ron.postuma@mcgill.ca

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Transient global amnesia after gastroscopy

Transient global amnesia (TGA) is an amnesic syndrome characterised by sudden-onset, clear-cut, anterograde amnesia during the episode, but otherwise normal neurological functions.¹ Episodes end within 24 h.¹ TGA may follow various precipitating events, such as emotional stress, contact with cold water, physical exercise or sexual intercourse.^{2,3} Medical action precipitating onset of TGA is reported to be coronary angiography or painful procedures, but reports of TGA after endoscopic procedures are few. We present three patients who developed TGA after gastroscopy.

Case reports

One morning, a 58-year-old woman, a nurse's aid, underwent gastroscopy at the hospital where she worked. After the operation, she immediately returned to work on a ward. A co-worker noticed she had amnesia because she was repeatedly asking, "Where do I bring this patient?" She was taken to the neurology department for examination. Her blood pressure was 140/70 mm Hg, and heart rate 68 beats/min. She demonstrated anterograde amnesia, the inability to learn new facts and repetitious questioning. She was unable to recall any of three objects after 5 min. No cranial nerve dysfunction was presented. Tendon reflexes in the four extremities were normal, as were muscle strength and sensory examination results. Cranial CT scan was negative, and an electroencephalogram (EEG) detected no epileptic abnormalities. Brain MRI diffusion-weighted images obtained during the episode were normal. Seven and a half hours after the onset of symptoms she was reoriented, but did not recall anything that happened during the episode.

A 59-year-old woman was taken by a nurse to the emergency room because of amnesia after gastroscopy. Her blood pressure was 150/90 mm Hg and heart rate 90 beats/min.

She was alert, but had had retrograde amnesia for several years as well as anterograde amnesia. She repetitively inquired, "Why do I stay here?" Her pupils were 3 mm in diameter and equal. She had no neurological deficits, except recent memory disturbances. Brain CT scan was normal. She was admitted for observation. Her EEG detected no epileptic discharges. She regained her memory within 15 h. Brain MRI diffusion-weighted images 5 days after onset showed no abnormal lesions.

A 65-year-old woman who had undergone gastroscopy at a hospital afterwards sat on a chair in the waiting room completely conscious. Her daughter asked her for the results of her procedure, but she could not remember what the doctor had told her. She was alert, but had anterograde amnesia and repeatedly asked the same questions. She regained her memory 8 h after onset, and was brought to our hospital 10 h later. On arrival, no neurological deficits were found, except the recent ameliorated memory disturbances already described. Brain MRI diffusion-weighted images and an EEG 12 days after onset were normal.

Clinical profiles of these three patients are given in table 1. A veteran endoscopist with more than 10 years of experience handled the endoscope. The patients were placed at the left lateral position during gastroscopy. Patients 2 and 3 had been premedicated with an intramuscular injection of scopolamine butylbromide (20 mg). All three patients received 8% topical pharyngeal lidocaine spray before undergoing endoscopy. None had had endoscopic polypectomy, nor a history of migraine, epilepsy or stroke.

Discussion

These three patients showed sudden amnesia after gastroscopy. The common clinical feature, typical of TGA, was the repeated asking of questions with retrograde and anterograde memory disturbance. The patients had no other neurological abnormality, and fulfilled the diagnostic criteria for TGA.¹ All of them had a gastroscopy history, and the endoscope had been handled by a veteran endoscopist. Their cases suggest that gastroscopy may have adverse effects resulting in TGA. Although scopolamine easily penetrates the blood-brain barrier and scopolamine intoxication can cause anterograde amnesia,⁴ these patients had no anti-cholinergic symptoms such as mydriasis, tachycardia, urinary retention or dry mouth. In addition, patient 1 had not received any anti-cholinergic agent before gastroscopy. Even without such agents, therefore, TGA may occur after gastroscopy. Autonomic function of these patients during gastroscopy could not be clearly evaluated. Autonomic dysfunction or emotional stress are, however, possible reasons for their TGA. Changes in autonomic nervous activity during endoscopy are reported to occur reflexively when an endoscope passes through the upper digestive tract, because of excessive parasympathetic tone, anxiety, premedication, discomfort or rapid gastric dilatation,⁵ and the memory disorder of TGA is speculated to be triggered by these factors. As shown here, gastroscopy may precipitate TGA. These atypical features of TGA indicate that further study is required to confirm the pathophysiological mechanism. TGA as a result of gastroscopy is rare, but doctors need to be aware of the possibility of amnesic events after this procedure.