LESSON OF THE MONTH

Idiopathic recurrent stupor: a warning

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A proposal that an endogenous benzodiazepine-like agent named endozepine-4 might be responsible for presentations of recurrent stupor has gained wide acceptance. A case of recurrent stupor over two decades is presented with many similarities to previous cases of ''endozepine stupor''. This case, however, was caused by exogenous benzodiazepine administration and serves as a warning to clinicians to beware of this diagnosis.

As clinicians we have been taught to always first exclude common causes before considering rare ones. Doctors, especially specialists, like to make exotic diagnoses as a part of the intellectual games we play. In the case to be presented, the clinicians were seduced by an obscure but plausible diagnosis when the clinical setting and test results should have raised their suspicions.

CASE HISTORY

A 71 year old man had a 16 year history of recurrent episodes of stupor and coma. Initially these attacks occurred every three to six months, but in recent years he had required up to seven hospital admissions a year. The first attack occurred when he was an inpatient at his local hospital for an unrelated medical problem and witnessed the suicide of a fellow patient; soon afterwards he lapsed into a coma from which he recovered spontaneously. Subsequent attacks often occurred in stressful situations—family disputes and medical consultations related to his condition were common precursors. Typically, he would develop a gradually deepening stupor over 20 minutes to several hours, often progressing to coma with a Glasgow coma scale score as low as 4. Hypoventilation (six to eight breaths a minute, occasionally in a Cheyne–Stokes pattern) and mild hypotension with bradycardia were common accompaniments. At times, medical attendants had noted loss of oculo-cephalic, corneal, and gag reflexes. His pupils were generally small but not pinpoint, and were reactive. He had never shown any convulsive movements, nor lost continence.

Several episodes of profound coma required intubation and mechanical ventilation. Impairment of consciousness would usually resolve over 12 to 36 hours, but occasionally recurred one or more times over a period of one to two weeks. Between attacks, the neurological examination was normal except for right sensorineural deafness.

Over the course of multiple episodes at several different hospitals, extensive investigations failed to reveal a cause. Routine haematology and biochemistry including thyroid function were normal. Blood lactate and ammonia levels were normal both during and between attacks. Urine immunoassays for opiates, ethanol, cocaine, benzodiazepines, barbiturates, and antidepressants were done on many occasions. These were usually negative, but on two occasions when a positive result for benzodiazepines was found this was thought to be caused by lorazepam prescribed by his local doctor in case stress was triggering the attacks. Electroencephalography (EEG) on several occasions was unremarkable. Computed tomography of the brain and four vessel angiography were normal. Examination of cerebrospinal fluid (CSF) pressure and content was normal. Later in the course of his illness, magnetic resonance imaging of the brain revealed a small right acoustic neuroma, which subsequently shrank with localised beam radiotherapy. The attack pattern did not change with this successful treatment and it was thought not to be relevant to his stupor episodes.

Finally, after nine years of such presentations, telemetric EEG monitoring during coma revealed low amplitude symmetrical beta activity of 16–18 Hz. Following the administration of 0.5 mg of flumazenil intravenously, the patient regained consciousness and medium voltage alpha activity at 8–9 Hz returned. A diagnosis of ''endozepine stupor'' was then made; this is a recently described syndrome of recurrent stupor caused by an increase of an endogenous benzodiazepine-like neuropeptide. The diagnosis was subsequently accepted by senior consultants in three other major medical centres during recurrent admissions for stupor over the next seven years. He was given intravenous flumazenil in doses up to 5 mg daily for periods of up to two weeks on several occasions.

Just before the last admission, one of us was informed that the patient's wife had confessed to surreptitious administration of lorazepam to her elderly mother during an admission to the local hospital for suspected stroke. The nursing staff had become suspicious when the patient's condition deteriorated after each visit by the daughter. She had initially denied administering the drug but, under threat of legal action, she confessed to having done so. When her husband was later admitted in stupor, urine gas chromatography mass spectrometry found a high level of oxazepam and when challenged his wife confessed to having given oxazepam and lorazepam to him over the period of his presentations. She often gave the tablets disguised in his tea or his food, but may also have openly given them to him on the pretext of ''calming him down''. She herself had at least a 15 year history of benzodiazepine dependence with multiple overdoses. She worked at the local hospital and had been constantly in attendance at her husband's presentations and throughout the course of his admissions. She agreed to undergo psychiatric treatment.

DISCUSSION

This case, which had the typical features reported in endozepine stupor, was eventually shown to be related to exogenous benzodiazepine administration. However, this possibility was completely overlooked by attending clinicians.

Presentation of a patient in stupor is a common diagnostic problem for emergency departments everywhere. Recurrent stupor is a less common disorder and has a wide differential diagnosis including epilepsy, sleep disorders, and hepatic, renal, or respiratory failure. Self administration of exogenous benzodiazepines needs always to be excluded. Rarer causes include migraine stupor, intermittent CSF obstruction, and a

variety of metabolic disorders. Endozepine stupor has recently been added to this list,[1] characterised as a syndrome of recurrent episodes of stupor or coma which are temporarily reversed by the benzodiazepine antagonist flumazenil given intravenously.[2] These episodes are thought to be caused by an increase in endozepine-4,[3] one of a group of regulatory peptides known as endozepines.[4]

Munchausen syndrome by proxy (MSP) is a syndrome in which caregivers deliberately invent, induce, or exaggerate psychological or physical symptoms in others.[5 6] It seems that the primary purpose for this superficially bizarre behaviour is internal gratification of the perpetrator. The vast majority of the reported cases involve the presentation of a child with the symptoms and a parent, most often reported as the mother, as the perpetrator. MSP involving adult victims is rare. We have found five such cases in published reports.[7–11] However, the clinical setting of a pleasant elderly country gentleman, always accompanied by his appropriately worried wife, gave no reason for us to suspect drug abuse. The test results, although on two occasions consistent with exogenous benzodiazepine administration, were accepted as being part of the exotic diagnosis of endozepine stupor. That the real diagnosis was the apparently unbelievable MSP in adults doubly conspired to confound us. In retrospect, the perpetrator took advantage of our vanity and we looked at the literature instead of the patient and, more particularly, his ever present partner.

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ECHO

Eating fats may not affect risk of stroke in men after all

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A long term prospective study has reported that eating fats—of whatever type—seems not to affect risk of ischaemic or haemorrhagic stroke in men, even though the same researchers earlier reported that omega 3 long chain fatty acids reduced the risk of ischaemic stroke. Clearly, more research is needed.

The men were healthcare professionals aged 40–75 in 1986 in the United States. Comprehensive data were obtained by validated questionnaires on their medical history, diet, and lifestyle, regularly updated over the following 14 years. When fatal or non-fatal strokes were reported a blinded physician assessed the risk factors from the medical notes. Nearly 44 000 men were studied, after exclusions for prior diagnosis of cardiovascular disease or diabetes mellitus, questionable energy intake, or incomplete data.

There were 725 cases of stroke—455 ischaemic, 125 haemorrhagic, 145 unknown—during follow up. Neither total fat nor type of fat affected risk of ischaemic or haemorrhagic stroke with data adjusted for known confounders. Long term effects, judged by comparing the highest fifth of intake with the lowest fifth in each subject, did not alter the risk for total fat or fats of different types—animal, vegetable, saturated, monounsaturated, polyunsaturated, *trans* unsaturated—or cholesterol. Furthermore, red meats, high fat dairy foods, nuts, and eggs had no effect.

Dietary fat intake is a big risk factor for heart disease but, apparently, not for stroke. Most of the evidence has not explored whether there might be any differences in risk between ischaemic and haemorrhagic strokes.

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