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CASE REPORT

Recognise malignant catatonia early: it is well treatable! A case report and review of literature

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Abstract

A 41-year-old man presented with reduced consciousness and severe autonomic dysregulation. Besides an increased creatine kinase of 978 U/l, no other abnormalities were found. After excluding infectious or autoimmune causes, drug withdrawal and serotonergic syndrome, malignant catatonia was suspected. Catatonia is a neuropsychological disorder, characterised by various movement disorders and the inability to react to external stimuli. A malignant subtype of catatonia is associated with life-threatening autonomic instability. The patient was not reactive to treatment with benzodiazepines. Electroconvulsive therapy (ECT) was commenced. After a total of 13 ECT treatments his catatonic state resolved, including the autonomic dysregulation. The exact pathophysiological mechanism of malignant catatonia is unknown. Dysregulation in cortical-subcortical circuits, neurotransmitters and synaptic transmission may play an important role.

Early recognition of malignant catatonia is essential. First-line treatment is lorazepam. In case of life-threatening conditions or no response to benzodiazepines, the patient should be treated with ECT.

Introduction

Catatonia is a neuropsychiatric, motor and behavioural syndrome with a variety of clinical manifestations, which can occur in the context of variable somatic or psychiatric disorders.[1] Malignant catatonia is a subtype of catatonia, characterised by rigidity, severe autonomic dysregulation and altered mental status. In ten prospective studies the mean incidence of catatonia in patients admitted to a psychiatric unit was 10%.[2] In fact, the incidence might probably be higher due to poor recognition, especially in non-psychiatric units. The incidence in the intensive care unit is unknown. Although not extensively studied, malignant catatonia, when treated, seems to have a favourable prognosis.

Here, we report a case of a male who developed malignant catatonia due to an unknown somatic cause. Potential physiological substrates and therapeutic recommendations are discussed.

Case

A 41-year-old man was seen at the emergency department because of agitation, fluctuating consciousness and hyperthermia. His neighbours had found him agitated with reduced consciousness. His medical history consisted of diabetes insipidus and epilepsy after a surgically removed dermoid cyst near the pituitary gland followed by radiation therapy, 31 years ago. His medication consisted of levetiracetam, valproic acid and desmopressin. The patient had no psychiatric history, however he regularly consumed cannabis and huge quantities of energy drinks. His family history was unknown.

Physical examination on the emergency ward revealed tachycardia, rigidity and a temperature of 41°C. Due to severe agitation, the patient was sedated with midazolam, received rocuronium and was intubated. Laboratory examinations revealed an increased creatine kinase (CK) of 978 U/l, increasing to 49,420 U/l three days later, a creatinine of 86 µmol/l, a C-reactive protein of 31 mg/l and a leukocyte count of 10.6 x 10^9/l. Chemical and immunological examination of the cerebrospinal fluid (CSF) revealed no abnormalities. An intoxication screening was positive for benzodiazepines (probably iatrogenic) and cannabis. The blood alcohol level was undetectable. Cerebral computed tomography revealed no other abnormalities than those due to previous neurosurgery.

The patient was transferred to the ICU. The differential diagnosis consisted of infectious or autoimmune meningoencephalitis, intoxication with an unknown substance, drug withdrawal,

serotonergic syndrome and neuroleptic malignant syndrome (NMS). He was treated with ceftriaxone, acyclovir and dexamethasone, which were stopped after the negative culture results of the CSF. Normothermia was induced with a circulating cold water blanket. Hyperhydration was initiated to prevent acute kidney injury by rhabdomyolysis.

A thorough diagnostic work up revealed no explanation for the patient's symptoms *(table 1)*. We assumed a cannabis or, theoretically, gamma-hydroxybutyric acid withdrawal, which we temporally treated with therapeutic cannabis and baclofen without any changes in his clinical condition. Since it has been described in patients taking valproic acid, serotonergic syndrome could not be excluded and therefore treatment with bromocriptine was initiated without any effect on consciousness, temperature or heart rate.

Table 1. Diagnostic tests

Test		Result
Toxicology screening	Cannabis	Negative
	Alcohol	Negative
	Benzodiazepines	Positive (probably iatrogenic)
	Heroin	Negative
Blood cultures		No growth
Cerebrospinal fluid	Herpes simplex virus	Negative
	Enterovirus	Negative
	Parechovirus	Negative
	Autoimmune serology	Negative
Nasopharyngeal swab	Legionella	Negative
	Mycoplasma	Negative
	Chlamydophila psittaci	Negative
	Human respiratory syncytial virus	Negative
	Rhinovirus	Negative
Blood serological tests	Human immunodeficiency virus	Negative
	Treponema pallidum	Negative
	Antinuclear antibodies	Negative
	Antineutrophil cytoplasmic antibodies	Negative
	Anti-thyroid peroxidase	Negative
MRI of the brain		No abnormalities other than those due to past surgery
Electroencephalography		No epileptiform discharges
FDG-PET		Increased FDG uptake in skeletal muscles

Hyperthermia persisted as well as the agitation when lowering the dose of sedatives. One month after admission, all sedatives were stopped to assess the mental and somatic condition of the patient. He became agitated, hypotensive, the CK increased from 500 U/l to more than 24,000 U/l and he developed acute kidney failure. We suspected malignant catatonia, therefore we administrated intravenous lorazepam up to 20 mg daily without any effect on the symptoms.

Given the lack of response to benzodiazepines, electroconvulsive therapy (ECT) was indicated. Since catatonia superposed on a chronic neurological condition has a lower response to ECT than when associated with other comorbidities, bilateral ECT, with high stimulus (started immediately with a stimulus of 100% instead of stimulus titration) and frequency (daily use) was recommended.[3]

After three ECT treatments the sedatives could be tapered, his temperature lowered and the CK levels decreased. After a total of 13 ECT treatments the patient became responsive to stimuli, able to communicate, his temperature normalised and the rigidity completely disappeared. After recovery no underlying psychiatric illness could be detected.

Discussion

This case report focuses on the recognition and treatment of malignant catatonia in an ICU patient in the absence of an underlying somatic or psychiatric illness at the time of admission.

Causes of malignant catatonia include: psychiatric, neurological and metabolic disorders, medication, toxins and malaria.[4] The literature reports more psychiatric than somatic studies regarding catatonia. In catatonic patients admitted to a psychiatric ward, Rosebush et al. found the following distribution of underlying illnesses: affective disorder 46%, schizophrenia 20%, schizoaffective disorder 6%, medical/neurological illnesses 16% and benzodiazepine withdrawal 4%.[5] ICU patients belong to the group at high risk of developing malignant catatonia since they have a high incidence of the previously mentioned risk factors. Despite this well-known risk there is no systematic assessment and/or report of malignant catatonia and its incidence within the ICU.

Several factors may have induced the catatonic condition in our patient: previous damage after brain surgery with secondary epilepsy, use of cannabis and energy drinks, possible electrolyte disturbances due to diabetes insipidus and drugs acting as a dopamine agonist (valproic acid). The diagnostic process took us almost a month. We were focused on a possible infectious or autoimmune cause of the hyperthermia and reduced consciousness, and failed to consider all possible diagnoses. So, we were waiting for culture results and serological tests without treating the true cause of patient's illness, resulting in a significant delay. Therefore we believe that awareness of this syndrome has to increase among intensivists.

Clinical diagnosis

Catatonia is generally acute in onset and the clinical features are heterogeneous. The pattern of symptoms and signs defines catatonia, but is not specific for this disorder. Catatonia is

defined on the basis of three or more of twelve symptoms listed in *table 2*. In DSM-5 catatonia is not seen as an independent diagnostic class. It is distinguished in three entities: as a specifier for schizophrenia, for major mood disorders and as a residual category of catatonia not otherwise specified.[1]

There are several subtypes of catatonia. Patients can exhibit signs of different subtypes concurrently and suffer different subtypes consecutively. Malignant catatonia is characterised by an altered mental status, rigidity and autonomic instability, including hyperthermia, hypertension, tachycardia and tachypnoea.

Table 2. Definition of catatonia

Catatonia in DSM-5: presence of three or more of the following
1. Catalepsy (passive induction of a posture held against gravity)
2. Waxy flexibility (maintenance of limbs and body in externally imposed positions)
3. Stupor (decrease in reactivity to the environment and in spontaneous movements)
4. Agitation
5. Mutism (no or very little verbal response)
6. Negativism (resistance to instructions or attempts to be moved, or movement in the opposite direction)
7. Posturing (spontaneous and active maintenance of a posture against gravity)
8. Mannerisms (odd caricature of normal actions)
9. Stereotypies (repetitive, abnormally frequent, non-goal directed movements)
10. Grimacing
11. Echolalia (automatic repetition of vocalisations)
12. Echopraxia (automatic repetition of movements)

Features of NMS may be impossible to distinguish from those of malignant catatonia. Both symptomatology and pathophysiology of NMS and malignant catatonia overlap. Several studies have tried to identify discriminating factors for both conditions, but all are limited by the absence of an external validation of the diagnosis.[6]

Serotonergic syndrome also shares a number of features, but can be distinguished by diarrhoea, flushing and myoclonic twitching. Many researchers believe that NMS and serotonergic syndrome represent drug-induced variants of malignant catatonia.[7,8].NMS is usually caused by dopamine receptor blocking agents and dopaminergic drugs, serotonergic syndrome by serotonergic agents.[9]

Recognition of catatonia is difficult due to the heterogonous presentation and different aetiology. Diagnostic criteria, defined by Taylor and Fink, are less applicable for the ICU setting where patients often meet criteria such as immobility and stupor, in the absence of catatonia.[10] The same applies to the modified Bush-Francis Catatonia Rating Scale. Recently Saddawi-Konefka et al. proposed an algorithmic approach to the diagnosis and management of catatonia in the ICU.[11] For the critically ill patient, this seems to be a more useful aid in diagnosing and treating malignant catatonia.

Pathophysiology

The exact pathophysiological mechanism of malignant catatonia is unknown. Neurotransmitters and synaptic transmission are presumed to play an important role in the aetiology of catatonia. The motor symptoms are presumed to be related to a deficient GABA-ergic state in the orbito-frontal cortex that disturbs the modulation to the basal ganglia 'top-down'. In NMS, a dopaminergic deficit in the basal ganglia may lead to a 'bottom-up' disturbance of the same circuit, although this may also play a role in catatonia. The GABA-ergic cortical dysfunction may explain the affective and behavioural disturbances in catatonia, which are not seen in NMS [12]. Postulating different mechanisms for catatonia, ECT would be more effective in 'top-down' variants of the syndrome [3]. Unfortunately in clinical practice these variants are indistinguishable.

The range of medical conditions and medications that can provoke catatonia is broad. In up to a quarter of patients with catatonia, this is due to a medical condition or psychoactive substance use.[13] Decreased density of GABA-A receptors in the left sensorimotor cortex was shown in akinetic catatonic patients.[14] The model of GABA dysfunction is underlined by the good response to lorazepam, a positive modulator of the benzodiazepine/GABA-A receptor complex and the tolerance of high-dose benzodiazepines without inducing sedation in catatonic patients. GABA dysfunction in the hypothalamus may account for the severe autonomic disturbances in malignant catatonia.[15] Disruption of the electrical discharges in the frontal lobes and the anterior limbic system[16] and changes in the neurotransmitter systems of dopamine, glutamate and serotonin[17] are also suggested to play a role in the pathophysiology of catatonia.

Prognosis

Complications of catatonia are mainly secondary to prolonged bed rest: venous thromboembolism, pressure ulcers, aspiration pneumonia, malnutrition and contractures. Malignant catatonia is potentially life-threatening due to hyperthermia and cardiopulmonary instability. Although previous studies reported mortality rates of 10-20% in malignant catatonia, a real estimation of the mortality rate in malignant catatonia is difficult. Delayed diagnosis lead to complications of critical illness and may increase mortality.

Treatment

Malignant catatonia necessitates admission to an ICU. Supportive measures are necessary and a probable underlying disorder should be identified and treated. Dopamine-antagonists should be avoided.

Benzodiazepines are the first choice treatment for catatonia. Restoration of consciousness five to ten minutes after administration of 1 to 2 mg of lorazepam intravenously

confirms the diagnosis of catatonia. No response to lorazepam does not rule out the diagnosis of catatonia, since 20% of the patients are unresponsive.[18]. In life-threatening conditions where immediate resolution of symptoms is needed or in case of no response to benzodiazepines ECT is warranted. Although randomised controlled evidence is lacking, the effectiveness of both lorazepam and ECT is well described.

ECT is effective in 80-100% of the patients with catatonia. [19-21] Although ECT is generally considered safe, risks are cardiovascular complications, dental or oral trauma, prolonged seizures and memory loss. The mechanism of action is unknown. It probably inhibits the propagation of abnormal electrical signals through cerebral synapses.[3] Predictors of a favourable response to ECT are: young age, high temperature, rapid start of the therapy, daily ECT procedure for the first week of treatment and longer seizure time. Patients with malignant catatonia are physically compromised. In the technical procedure of ECT it is therefore recommended to select bilateral stimulation, daily treatment for the first week, use of rocuronium in place of succinylcholine in order to minimise the risks of hyperkalaemia and caution in tapering of benzodiazepines before or during the ECT. Poor response is associated with an underlying chronic neurological condition, severe somatic and psychiatric comorbidities, delayed start of the ECT and previous treatment with dopamine agonists.[22-23] Most somatic treatments, inclusive anticoagulant therapy, may be carried on during the ECT. The duration of ECT treatment depends of the remission of symptoms. The response should be evaluated after every sixth session. Usually 12-20 sessions are needed.[3] The symptoms of catatonia may alleviate before the underlying disease is in remission.

Recommendations

1. Malignant catatonia should be suspected in all patients presenting with reduced consciousness and severe autonomic dysregulation. Early recognition is essential.
2. Information regarding the medical history, medication and substance abuse should be gathered as quickly as possible. Rapid investigations to determine the underlying illness and consultation of the neurologist and psychiatrist are recommended.
3. When malignant catatonia is suspected, 1-2 mg lorazepam should be given intravenously, even when the diagnostic procedures are ongoing, this may be repeated one hour after the first administration. With good response, treatment with benzodiazepines should be continued by gradually increasing the dose.
4. ECT is recommended in malignant catatonia unresponsive to benzodiazepines. ECT should be the first choice of treatment in malignant catatonia with life-threatening autonomic dysregulation.
5. Treatment for the underlying illness and prophylaxis of ICU-related comorbidities should be carried on during and after ECT treatment.

Disclosures

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