

Some patients with advanced malignancies also have reversible catatonia or limbic encephalitis

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Editorial

Abstract

Two potentially treatable disorders, paraneoplastic catatonia and paraneoplastic limbic encephalitis, may be hidden within the presentation of end stage cancer patients, because catatonia and limbic encephalitis usually feature severely altered mental status, confusion, anorexia, and minimal responsiveness that are also common with people dying of cancer. If catatonia and limbic encephalitis are correctly diagnosed and treated, there should be definite and dramatic improvement that would translate into better quality of life and perhaps even resumption of cancer therapy. This editorial reviews basic features of catatonia and limbic encephalitis, and then presents a strategy to systematically screen for these in end stage cancer patients who are about to enter hospice. A protocol is outlined that could be adapted for clinical practice or for designing clinical studies.

Keywords: Catatonia; Limbic Encephalitis; Anti NMDA-receptor Encephalitis

Introduction

Patients with advanced malignancies usually reach a state of anorexia and impairment that warrants hospice care. I present here the idea that at least a few of these end-stage patients also have catatonia or limbic encephalitis that if properly recognized could open the door for better palliative care and perhaps even resumption of active cancer treatment. My goal is to increase awareness of catatonia and limbic encephalitis among practicing oncologists and to encourage further studies by academic researchers.

Catatonia

Catatonia is a potentially correctable disorder with three cardinal features: anorexia, mutism and immobility.¹ In short, catatonic patients don't eat, talk or move. Associated features may include posturing, grimacing, echopraxia and echolalia (mimicking of examiners movements and speech), stereotypy (repetitive, non-goal directed activity), mannerisms (odd purposeful movements such as saluting or waving), rigidity, gegenhalten (automatic resistance to passive movement), mitgehen (arm raising in response to light touch of examiner's finger in spite of verbal instruction not to move), ambitendency (patients appear stuck in hesitating movements), waxy flexibility (holding limbs in bizarre positions after being placed by examiners) and autonomic abnormalities (abnormalities of pulse, blood pressure, respiratory rate or presence of diaphoresis).² Catatonic patients can have almost miraculous revivals after being given

parenteral or oral benzodiazepines, such as lorazepam or diazepam.¹ It seems counterintuitive that a sedative could awaken someone, but it is thought that direct stimulation of GABA receptors on basal ganglia spiny interneurons somehow disinhibits overactive inhibitory centers and unlocks the patient. Other medications reported to reverse catatonia include zolpidem, methylphenidate, topiramate, valproic acid, memantine and atypical anti-psychotic agents.³⁻¹⁰ Zolpidem is a common hypnotic that also stimulates GABA receptors; methylphenidate acts as a general central nervous system stimulant, elevating dopamine, serotonin and norepinephrine, and memantine is a noncompetitive antagonist of NMDA type glutamate receptors. The other agents produce "awakenings" either through indirect potentiation of the GABAergic spiny interneurons or through some other mechanism. Catatonia refractory to medications can usually be treated with electroconvulsive therapy (ECT).¹¹ Similar to methylphenidate, ECT is somehow activating enough centers to overcome excessive inhibitor tone in the basal ganglia.

Catatonia is often popularly conceived as a purely psychiatric disorder, as a subtype of schizophrenia or depression, but catatonia can also be caused by organic etiologies, including closed head injuries, multiple sclerosis, stroke, infections and cancer.¹ For example, two patients with catatonia from HIV encephalitis promptly recovered after a single dose of lorazepam, even while the underlying HIV

infection was unchanged.^{12,13} Similarly, intracranial masses can cause benzodiazepine-responsive catatonia. A patient with a pituitary adenoma had catatonia reversed by oral diazepam.¹⁴ The patient relapsed when diazepam was weaned and so she was ultimately maintained on diazepam long term to keep catatonic symptoms at bay.¹⁴ If catatonia were caused by mass effect, this means that diazepam could counteract catatonia while the mass effect remained present, as the patient did not have surgical resection. Granted this was a benign tumor, not a primary CNS malignancy or brain metastasis, but either of these could have the same mass effect as a pituitary adenoma. In a more direct proof of principle that cancer and reversible catatonia can co-exist, a young woman with stage IV breast cancer and a past history of schizophrenia developed catatonia secondary to leptomeningeal carcinomatosis.¹⁵ She did not respond satisfactorily to lorazepam, but did respond to ECT. She ultimately succumbed to the breast cancer, but thanks to recognition and treatment of her catatonia, she had three months when she was alert and interactive.¹⁵ As additional proof of principle, there is a case report of a 58-year-old woman with anaplastic lung cancer but no brain metastases that had catatonia partially responsive to clonazepam as part of a wider paraneoplastic encephalopathy.¹⁶

Limbic encephalitis

Limbic encephalitis is another potentially correctable condition that could easily be mistaken for merely the end stage of cancer. Limbic encephalitis is a complicated autoimmune disorder with widely variable neurological symptoms that can range from seizures, agitation, dementia and delirium to catatonic symptoms of anorexia, mutism and immobility.¹⁷⁻²⁰ Many, although not all cases of limbic encephalitis, are paraneoplastic, with the most common associated malignancies being breast and ovarian teratoma, along with small cell lung cancer, testicular cancer, Hodgkin's lymphoma, and rarely gastric malignancies.¹⁷⁻¹⁹ Diagnosis of paraneoplastic limbic encephalitis can be made via postmortem neuropathology showing inflammation in the temporal lobes and other limbic structures of the brain, but in clinical practice the diagnosis is made by fulfilling 4 specific criteria.¹⁷ First, there should be a clinical picture with seizures or other alterations in mental status, such as catatonic features.¹⁷ Second, there should be an interval of less than four years between the onset of symptoms and the tumor diagnosis.¹⁷ Third, there should be exclusion of other conditions, such as central nervous system infection, neurotoxicity from chemotherapy, mass effect of tumor or meningeal carcinomatosis.¹⁷ For the fourth criteria, one needs at least one of the following three conditions to be met: cerebrospinal fluid inflammatory changes but negative cytology; an MRI of the brain which shows temporal lobe imaging abnormalities, or an electroencephalogram showing epileptic activity in the temporal lobes.¹⁷ Limbic encephalitis is treated by immunosuppression with pulsed intravenous

methylprednisolone, intravenous immunoglobulin, plasmapheresis, rituximab, or cyclophosphamide.¹⁹

Patients with limbic encephalitis usually have antibodies against neuronal proteins and neurotransmitter receptors. For example, in one series thirty out of 50 patients (60%) had antibodies against neuronal nuclear proteins, and 20 were antibody-negative or had uncharacterized antibodies.¹⁷ Most of these neurooncology antibodies are markers of disease rather than a cause of pathology,¹⁸ but this is not the case for anti-NMDA receptor encephalitis, a subtype of limbic encephalitis first described in 2007 and receiving increasing attention in recent literature.^{21,22} Anti-NMDA receptor encephalitis is characterized by autoantibodies against NMDA glutamate receptors. Proper function of NMDA receptors is vital for learning, memory and other brain activities.²¹ It is thought the autoantibodies somehow disrupt function of the NMDA glutamate receptors to cause widespread brain dysfunction.²² Antibodies against GABA receptors, glycine receptors and non-NMDA glutamate receptors such as AMPA subtype probably also cause similar disruption of neuronal function.²²

Convergence of paraneoplastic catatonia and limbic encephalitis

Limbic encephalitis and catatonia may frequently overlap. For example, a patient with limbic encephalitis associated with recurrent metastatic seminoma actually presented with catatonia responsive to lorazepam but also to prednisone, intravenous immunoglobulin (IVIG) and plasmapheresis.²³ In that patient's case, catatonia and encephalitis recurred with tumor recurrence and resolved completely with treatment of the underlying malignancy.²³ It is thought that anti-NMDA receptor encephalitis has catatonia as the single most common clinical presentation, up to 50% of cases.²⁴ It may be that patients in those earlier reports of catatonia associated with malignancy actually had anti-NMDA receptor encephalitis; the case reports cited above in this paper were published before anti-NMDA receptor encephalitis had been recognized as a clinical entity. Note also that just as is true for catatonia, ECT can be effective as a primary treatment for limbic encephalitis if other treatments such as including steroids and immunosuppressive agents fail.^{25, 26}

Better detection of paraneoplastic catatonia and limbic encephalitis

The key question now is how to differentiate catatonia and limbic encephalitis from the ordinary anorexia and functional decline of end stage cancer and its treatment. It could be very difficult unless there were obvious giveaways like waxy flexibility or new onset seizures. Moving forward, we need a program of systematic brain imaging, standardized clinical

assessment for catatonia and limbic encephalitis, and screening for autoantibodies. Brain MRIs would help identify some cases of limbic encephalitis by finding temporal lobe abnormalities.¹⁷ PET scanning can also help pick up both occult catatonia and limbic encephalitis, but at this point one is looking for abnormalities rather than a specific pathognomonic pattern. For example, in 3 patients with anti-NMDA receptor encephalitis and catatonic features, fluorodeoxyglucose PET CT scans demonstrated hypermetabolism in the frontotemporoparietal regions and bilateral basal ganglia in the patient with mild catatonia, and spread of hypermetabolism to the thalamus and brainstem with more severe catatonia,²⁴ but the patient with lorazepam-responsive catatonia and limbic encephalitis secondary to a seminoma mentioned above had hypometabolism of the frontal cortex and the left temporal lobe,²³ and in a series of 6 patients with confirmed anti-NMDA receptor encephalitis, there was relative frontal and temporal glucose hypermetabolism associated with occipital hypometabolism.²⁷ Hypometabolism in various brain regions may represent the chronic phase of disease, whereas hypermetabolism is during acute onset of encephalitis,²⁸ but at this point, all we can say is that PET scans of patients with catatonia and limbic encephalitis will likely be abnormal. This quite imprecise but it still provides a powerful tool for diagnosis. Consider that most patients are already getting MRI and PET scanning for staging of cancer, so MRIs and fluorodeoxyglucose PET scans of the brain could be obtained specifically when patients present with prolonged obtundation which might represent catatonia or limbic encephalitis. In concert with the brain imaging and checking each patient for the 4 clinical criteria of limbic encephalitis, serological screening would help identify patients who have normal brain imaging but still do in fact have limbic encephalitis. In one series of 16 patients from India with limbic encephalitis, 4 of the patients had normal brain MRIs.²⁹ We want to be able capture those image negative patients and hopefully determine how they are different from patients with abnormal MRIs.

Proposed protocol

I describe here a protocol that could be incorporated into both established cancer treatment pathways and future clinical trials. This is intended as a starting point that practicing oncologists and academic researchers can use to design their own protocols before submitting any such protocols to appropriate oversight authorities for approval. For clinical practice or smaller studies, portions of the protocol could be omitted or abbreviated; the overarching goal is to be screening in some kind of systematic way for occult catatonia and limbic encephalitis in end stage cancer patients to the degree possible with available resources and other constraints.

1. The protocol would be intended for patients with

stage 3 or 4 malignancies who are hospice eligible due to persistently altered mental status and currently ineligible for further treatment who have either suspected catatonia with 3 cardinal features (immobility, mutism and anorexia)¹ or suspected limbic encephalitis by the 4 diagnostic criteria (compatible clinical picture, onset of symptoms < 4 years from tumor diagnosis, exclusion of other conditions and CSF or imaging data).¹⁷ With the expectation that many or most of the study enrollees would be severely obtunded at the time of entry into the study, informed consent would have to be obtained well in advance while patients are still competent, or alternatively consent could be obtained from family members.

2. Patients would have the option of dropping out at any time and returning to hospice status. Those who achieve significant recovery should have the option to receive renewed attempts at cancer therapy or alternatively, receive the same hospice benefits and services they were eligible for previously.
3. Each patient should get baseline brain MRIs, PET scans and functional status assessments such as the Karnofsky palliative performance scale.
4. Patients with catatonia should be rated according to the 23 item Bush-Francis Catatonia rating scale, with a score of 0-3 for presence or absence of excitement, immobility/stupor, mutism, staring, posturing/catalepsy, grimacing, echopraxia/echolalia, stereotypy, mannerisms, verbigeration, rigidity, negativism, waxy flexibility, withdrawal, impulsivity, autonomic obedience, midgehen, gegenhalten, ambidetendency, grasp reflex, perseveration, combativeness and autonomic abnormality.² Score on the Bush-Francis scale before and after treatment could then be measured.
5. All patients should be tested for serology with a comprehensive panel of autoantibodies, using as a model the work of Endres *et al.*: anti-NMDA receptor antibodies, antibodies against other neurotransmitter receptors (AMPA-1/2-R, GABA-B-R, VGKC-complex), antibodies against intracellular synaptic antigens (GAD, amphiphysin), and intracellular onconeural antigens (Yo, Hu, Ri, Cv2/CRMP5, Ma1, Ma2, SOX1), and anti-thyroid antibodies (anti-thyroid peroxidase antibodies, anti-thyroglobulin antibodies and thyroid-stimulating hormone receptor antibodies).³⁰
6. All patients with putative catatonia would be given a lorazepam challenge with one milligram of intravenous lorazepam. Those responding would be

placed on maintenance oral lorazepam at 1 mg three times a day for 4 weeks before gradually tapering. Patients not responding to lorazepam would then be challenged sequentially with 10 mg of oral zolpidem, oral memantine 5 mg twice a day, topiramate 25 mg twice a day, and valproic acid 500 mg twice day. Responders at any point would continue the successful agent and exit the protocol, to be re-evaluated for hospice services or resuming cancer treatment.

7. Patients with limbic encephalitis would be initiated on immunosuppressive therapy. These would include patients with positive serology but also those with negative serology but who fulfill the four clinical criteria for limbic encephalitis. A typical immunosuppressive regimen might be intravenous methylprednisolone at 1 gram daily for 3–5 days, with either intravenous immunoglobulin (IVIG) at 0.4–1 grams/kilogram daily for 3–5 days or plasmapheresis, followed by a tapering dose of oral prednisone.¹⁹ If patients do not respond to steroids with IVIG or plasmapheresis, cyclophosphamide and rituximab could then be tried.
8. Patients with catatonia who also have limbic encephalitis would only undergo immunosuppression if anti-catatonia drugs were not effective.
9. As the final phase of the protocol, those patients still obtunded after treatment for catatonia and/or limbic encephalitis would be challenged with oral methylphenidate, starting at 5 mg daily and escalating to 20 mg daily and could be offered a course of ECT if the methylphenidate was not effective. At one time there was a concern about doing ECT in patients with brain tumors, but subsequent case reports and patient series have shown that ECT is safe for patients with brain tumors, so even those with intracranial masses could be included in this proposed protocol.^{31,32} The only caveat is that in many countries there are negative public attitudes about ECT,³³ and so the idea of giving terminal cancer patients ECT will have to be broached very delicately to carefully selected patients, typically those who are highly motivated to advance cancer research irrespective of whether it helps their own survival.
10. Patients should have repeat brain imaging and serologies following treatment. For larger series of patients, it should be possible to estimate the incidence and prevalence of paraneoplastic catatonia and limbic encephalitis among all patients with particular types of cancers and to correlate

patterns on MRI and PET imaging with type of cancer, severity of symptoms and response to medications and ECT.

If a significant number patients with advanced malignancies do prove to have reversible catatonia or limbic encephalitis that would otherwise go unrecognized, this will have important implications for the practice of oncology. Even if patients are not usually curable, one should still achieve dramatic improvement in meaningful quality of life in the last stages of cancer. Furthermore, at least a few patients might then have sufficiently high palliative performance scores to resume active treatment of cancer. Given how hard we fight to give even a few months of improvement to patients with advanced cancer, we must not neglect the possibility that reversible catatonia and limbic encephalitis might lie hidden in the background of general end-stage decline. This idea is thus put forward for the use of oncologists and researchers world-wide, and new case reports and research studies should be published as quickly as possible.

Conflict of interest

The authors declare that they have no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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