

Mixed dementia and hyperactive delirium: a diagnostic challenge

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Accepted 17 April 2021

SUMMARY

It is well recognised that acute confusion or delirium complicates up to 10% of acute medical admissions. Disorientation in time and place with an impaired short-term memory and conscious level are the hallmarks of an acute confusion. In delirium, disorders of perception may produce restlessness and agitation. A similar state during the final days of life is termed 'terminal delirium'. Less than 10% of affected individuals will have a primary neurological disorder, for example, dementia, a neurodegenerative disease with varying aetiologies. Currently there are at least 50 million people globally suffering from dementia rendering it a global healthcare problem. Mixed dementia (MD) can be defined as a cognitive decline sufficient to impair independent functioning in daily life resulting from the coexistence of Alzheimer's disease (AD) and cerebrovascular pathology. MD occurs in patients with a neurodegenerative disorder, such as AD, Lewy body or Pick's disease and additionally cerebrovascular disease. The mechanistic synergisms between the coexisting pathologies affecting dementia risk, progression and the ultimate clinical manifestations remain elusive. Although AD can be diagnosed with a considerable degree of accuracy, the distinction between isolated AD, vascular dementia and MD, when both pathologies coexist in the same patient remains one of the most difficult diagnostic challenges because their clinical presentation can overlap. Neuropathological studies indicate that mixed vascular Alzheimer's dementia (MD) has a prevalence of 22% in the elderly. The authors present the case of a 78-year-old man with a diagnosis of MD presenting to the emergency department with delirium, a common but serious acute neuropsychiatric syndrome with the core features of inattention and global cognitive dysfunction. This case demonstrates the challenges in establishing a diagnosis in patients presenting with MD and shows that a cognitive assessment at presentation in a delirious state offers very little diagnostic information. It is therefore suggested to conduct a routine cognitive function examination on patients with dementia to anticipate new neurological signs and/or symptoms thus allowing earlier diagnosis and treatment. However, a baseline cognitive assessment when the patient was well, duration and nature of deterioration as well as collateral history will help differentiate delirium from an underlying dementia.



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To cite: Dunphy L,
Akin-Komolafe T,
Etheridge Z. *BMJ Case
Rep* 2021;14:e238542.
doi:10.1136/bcr-2020-
238542

terminal delirium is a variant that occurs during the final days of life. Most evidence-based medicine focuses on Alzheimer's disease (AD) and vascular dementia (VaD) as separate, uncomplicated clinical pathologies. It remains unclear on how to differentiate between these conditions as patients may present with permutations of the aforementioned. However, increasing evidence exists that demonstrates that in the older patient cohort, the brain lesions associated with each pathological process often occur together and that AD and VaD brain lesions interact in important ways to increase the likelihood of clinically significant cognitive decline.^{1,2} The term mixed dementia (MD) is often given to the coexistence of AD and VaD and its prevalence is likely to increase as the population ages. Admittedly, the differentiation between AD, VaD and MD is complicated by symptom overlap and the lack of well-defined diagnostic criteria to help establish the diagnosis. Despite advances in neuroimaging, MD remains a challenging clinical diagnosis to establish, however, controlling cardiovascular risk factors such as hypertension and hyperlipidaemia, likely represent important strategies for preventing or slowing its progression. Admittedly, the search for a single unifying diagnosis to explain signs and symptoms, also known as the 'Occam's razor rule', likely does not apply to the geriatric population, who are at risk of neurodegeneration from both AD and cerebrovascular disease.³

CASE PRESENTATION

A 78-year-old male UK resident with a diagnosis of mixed AD and VaD presented to the emergency department with a 5-day history of increased confusion, agitation and aggression. His carer reported his refusal to have personal care and a decreased appetite. He was referred to the Memory Clinic in 2011 when he developed cognitive problems. An MRI showed small areas of vascular damage with cerebral atrophy (figure 1). He commenced treatment with donepezil. His dementia was now severe with limited speech, comprehension and the inability to have a conversation. He had a lack of circadian rhythm impacting on the ability of his live-in carer and family to look after him. His functional baseline included the ability to dress himself and guidance required for a shower. He no longer recognised his children. He was registered blind due to hereditary retinal dystrophy. Three months prior to this presentation, he experienced a 'black-out' of uncertain aetiology. A subsequent 24-hour tape showed normal sinus rhythm. One month later, he had an episode of atrial fibrillation

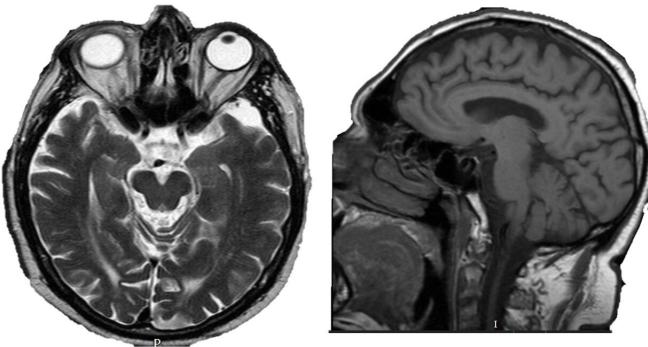


Figure 1 An MRI showed small areas of vascular damage with cerebral atrophy.

with a fast-ventricular response requiring direct current cardioversion. Six weeks later, he developed acute onset of central and epigastric pain. A 12 lead ECG showed sinus bradycardia with no ischaemic change. His troponin was normal. His transthoracic echocardiogram showed an ejection fraction of 55% with no significant valve disease. The 24-hour ECG showed sinus rhythm with episodes of sinus bradycardia (predominantly nocturnal). The heart rate profile was between 46 and 86 beats per minute (mean 60 beats per minute) and all intervals were within normal limits. He declined anticoagulation. His cardiac CT scan showed an average amount of coronary calcification for a man of his age (coronary calcification score 510, 50th percentile for age and gender). There was potentially flow-limiting stenosis within the proximal and mid-left anterior descending artery and also the distal dominant left circumflex. Due to his chest pain which likely represented angina, he commenced treatment with a low dose of bisoprolol (1.25 mg), glyceryl trinitrate spray and atorvastatin (40 mg once daily). There was a decline in his cognitive function since donepezil was stopped due to concerns about his chest pain. He developed complex partial seizures and commenced treatment with Keppra 1000 mg two times per day. As he could not tolerate this dose, it was reduced to 750 mg with the addition of sodium valproate which caused a rash. Hence, he was treated with carbamazepine titrated to 400 mg two times per day while his Keppra was reduced to 250 mg two times per day. One week later, he was admitted with confusion and hyponatraemia (Na^+ 112) with a plasma osmolality of 259. His carbamazepine was discontinued and lamotrigine commenced. His medications included levetiracetam liquid 500 mg mane and 750 mg nocte, flecainide 50 mg two times per day, lamotrigine 50 mg mane and 25 mg nocte, folic acid liquid 5 mg once daily, memantine 20 mg nocte, aspirin 75 mg once daily and timolol 0.75% applied to both eyes. He was a non-smoker and did not consume alcohol. He was independently mobile. Classical music helped to keep him calm. His observations were as follows: temperature 37.2°C, blood pressure 107/83 mm Hg, heart rate 63, respiratory rate 16 and oxygen saturation (SpO_2) 97% on air. His pulse was regular and heart sounds were normal. Respiratory examination confirmed bibasal crackles. His abdomen was soft and non-tender. Rectal examination was unremarkable with no evidence of faecal impaction. There was no peripheral oedema. He appeared restless and agitated, therefore, physical examination was challenging.

INVESTIGATIONS

His ECG showed sinus rhythm with a degree of ventricular conduction delay (QRS duration

Table 1 Laboratory investigations showed an elevated white cell count and CRP

Haematology	Biochemistry
Haemoglobin 141 g/L (118–148)	Sodium 133 mmol/L (133–146)
White blood cell count $11.70 \times 10^9/\text{L}$ (3.5–11)	Potassium 4.9 mmol/L (3.5–5.3)
Platelet count $190 \times 10^9/\text{L}$ (150–400)	Urea 12.1 mmol/L (1.0–7.8)
Mean cell volume 86 fl (80–100)	Creatinine 34 mmol/L (50–130)
Mean cell haemoglobin 30.9 pg (28–33)	Alkaline phosphatase 21 U/L (30–300)
Neutrophil count $359 \times 10^9/\text{L}$ (2–7.5)	Alanine transaminase 88 U/L (<35)
Monocyte count $1.15 \times 10^9/\text{L}$ (0.2–0.8)	Albumin 37 g/L (40–50)
Eosinophil count $0.05 \times 10^9/\text{L}$ (0.0–0.4)	Calcium 2.32 mmol/L (2.2–2.6)
Basophil count $0.04 \times 10^9/\text{L}$ (0.0–0.2)	
Clotting	CRP 220 mg/L (<5)
Prothrombin time 15.5 s (9–12)	
APTT 28.9 s (30–45)	

APTT, Activated partial thromboplastin time; CRP, C-reactive protein.

121 ms) but with no specific abnormality. His chest radiograph showed left-sided consolidation. Laboratory investigations including a full blood count, C-reactive protein (CRP), renal and liver function tests were requested (table 1). His blood cultures, urinalysis and point of care influenza swab were negative. His venous blood gas was unremarkable. A bladder scan showed that he was in urinary retention and a catheter was inserted. His glucose was in the normal range.

DIFFERENTIAL DIAGNOSIS

He was diagnosed with hyperactive delirium on a background of mixed AD and VaD. Laboratory investigations showed an elevated white cell count ($11.7 \times 10^9/\text{L}$) and CRP (220 ng/L) as well as an acute kidney injury (urea 12.1 mmol/L, creatinine 34 mmol/L) (table 1). His liver function tests and clotting were normal. A bladder scan confirmed the diagnosis of acute urinary retention and a catheter was inserted. As his physical examination revealed bibasal crackles and left-sided consolidation was evident on his chest radiograph, he was diagnosed with a community-acquired pneumonia, CURB-65 score of 3. He also developed fast atrial fibrillation, at a rate of 130 beats per minute and remained normotensive. He remained restless and agitated.

TREATMENT

As per the Trust's antimicrobial guidelines, he commenced treatment with Amoxicillin 1 g three times a day intravenously. His fast atrial fibrillation was rate controlled with digoxin and bisoprolol. His agitation was treated with haloperidol and lorazepam. He developed a maculopapular rash over 48–72 hours in the context of recent antimicrobial therapy on his trunk, limbs and his scalp (figures 2 and 3). There were no blisters or excoriation, or evidence of oral, ocular or genital involvement. The clinical diagnosis was of a drug exanthem and it remained unknown which antibiotic was the cause. Diprobase cream was applied two times per day to his skin. Elocon ointment was prescribed as required if his skin became itchy as it recovered and dried out. He was washed with dermol 500.

OUTCOME AND FOLLOW-UP

His bloods were monitored twice weekly. He became very agitated, confused and physically aggressive towards the nursing staff. He was pacing up and down the ward in a combative manner. He was reviewed by the old age psychiatry team. He



Figure 2 A maculopapular rash developed on his trunk, limbs and his scalp.

was prescribed haloperidol (0.5 mg doses not exceeding 3 mg/24 hours) as required (prn) for delirium and his memantine 20 mg once daily was continued. Long-term use of antipsychotics to manage the behavioural and psychological symptoms of dementia were advised once he recovered from his delirium.

Occupation and distraction with music and tactile objects including the 'twiddle muff' were provided by the old age psychiatry team. He developed increased restlessness and refused to eat. He pulled out his catheter causing urethral trauma. A Deprivation of Liberty Safeguards form was completed. He deteriorated clinically and it became apparent that he was in terminal delirium. Following discussion with his family, he was reviewed by the palliative care team and commenced a syringe driver with morphine 5 mg, midazolam 5 mg, hyoscine butyl bromide 60 mg and haloperidol 1.5 mg. He died 5 days following his admission, with his family at his bedside. This case demonstrates the inherent challenges in taking a history, performing a physical examination and investigations in patients with a diagnosis of MD presenting with acute onset of delirium. In addition, it demonstrates the importance of performing a delirium workup rather than diagnosing and treating dementia when in a state of delirium. Teasing out the other characteristics of an underlying dementia is nearly impossible unless the delirium resolves.

DISCUSSION

AD and VaD are the two most prevalent causes of dementia and it remains a diagnostic challenge to differentiate them from MD. Our patient also had delirium, a Latin term meaning 'going off the ploughed track' presenting as a transient, reversible syndrome that is acute, multifactorial and fluctuating, occurring in the setting of an acute medical condition or a medication adverse effect. Indeed, it is well documented that delirium has

adverse physical, cognitive and psychological consequences and is associated with an increased mortality and length of hospital stay. Delirium represents a serious complication in patients after anaesthesia and surgery and is predictive of mortality at 6 months in patients in intensive care unit (ICU). Terminal delirium, a form of the delirious state occurring during the final days of life, is not a Diagnostic and Statistical Manual of Mental Disorder's diagnosis and is often unrecognised in patients with multiple comorbidities or in those individuals requiring hospitalisation for exacerbation of a chronic condition. Dying is a complex process but early recognition of the dying phase can empower the patient and their families.

Dementia is a well-recognised risk factor for delirium, occurring in 66% of the geriatric population. Indeed, the occurrence of delirium may alter the clinical course of an underlying dementia with negative prognostic implications, including further functional and cognitive decline, increased rehospitalisation and death. Patients with hyperactive delirium demonstrate features of restlessness, as described in our case, agitation, hypervigilance, hallucinations and delusions. An alteration in the patient's behaviour is usually reported by a relative or friend rather than by the patient. It is important to check for disorientation and memory impairment with the mini-mental test, which is challenging in this patient cohort and not very helpful. The drug chart should be reviewed as the risk of drug-induced delirium is high especially in elderly hospitalised patients in whom polypharmacy, altered pharmacokinetics and underlying pathology all interact to cause delirium. Although the pathophysiological mechanisms underlying delirium remain to be fully elucidated, its aetiology is multifactorial. Medications acting on the cholinergic, γ -aminobutyric acid-mediated and monoaminergic neurotransmitter pathways are frequently involved. The patient should be assessed for an acute illness. Physical examination is required to exclude faecal impaction and urinary retention. The differential diagnosis of delirium is broad and includes a systemic disorder, drug toxicity, a central nervous system disorder or a malignancy (table 2). The National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) diagnostic criteria for VaD does not include a category for MD, recommending instead the term AD with cerebrovascular disease.⁴ Admittedly, there is a significant overlap between AD, VaD and synucleinopathies like Lewy body dementia. Pathological Parkinson's disease is present in 20% of patients with AD and 50% of cases of dementia with Lewy bodies are associated with AD pathology.⁵ MD prevalence rates vary widely from 2% to 60%.⁶ The brain lesions of AD include extracellular amyloid plaques and intracellular neurofibrillary tangles. Neuropsychiatric signs of VaD include apathy, emotional lability, lack of motivation and psychomotor retardation. Memory, language and praxis have more variability than AD. Individuals with a diagnosis of VaD present with more agitation (40% vs 14%), sleep disturbance (57% vs 32%), higher rates of depression (48% vs 20%) and aberrant motor behaviour (31% vs 13%) than those with AD. VaD can be differentiated from AD by the early onset of gait disturbance, falls, urinary problems, a temporal association following a stroke and the presence of ischaemic periventricular leukoencephalopathy. In MD, both pathologies can occur together and interact in several ways to increase the likelihood of a clinically significant cognitive decline. Indeed, autopsy series have suggested that a coexisting vascular pathology occurs in up to 8% of patients with AD.⁷ Once the acute delirium has resolved, then the workup for MD could be considered.



Figure 3 Image showing there were no blisters or excoriation. The clinical diagnosis was of a drug exanthem.

Table 2 The differential diagnosis and investigation of delirium

Differential diagnosis	Investigations
Systemic disorder	Check urine Blood cultures Laboratory investigations—white cell count, renal function, liver function, glucose, calcium, CRP, troponin Arterial blood gas ECG Chest radiograph
Sepsis is common	
Alcohol withdrawal	
Metabolic disorder	Consider magnesium, amylase, porphyrins, thiamine, vitamin B ₁₂ , folate, thyroid-stimulating hormone, free T4
► Hyperglycaemia or hypoglycaemia ► Vitamin deficiency ► Endocrine disease (thyroid/adrenal) ► Uraemia ► Hypercalcaemia is common	
Myocardial ischaemia	
Organ failure	
► Renal ► Respiratory ► Liver ► Cardiac	
Drug toxicity	Check prescribed medication Serum alcohol A drug screen
CNS disorder	Consider a CT scan with contrast Lumbar puncture Electroencephalogram Blood cultures CRP Syphilis and Lyme serology
► Dementia—Alzheimer's common ► CVA ► Intracranial bleed (SAH, subdural) ► Infection (encephalitis, meningitis) ► Trauma ► Malignancy ► Post-ictal: non-convulsive status ► Cerebral vasculitis (SLE/PAN)	
Malignancy	Chest radiograph CT head and chest Serum calcium

CNS, Central nervous system; CRP, C-reactive protein; CVA, cerebrovascular accident; SLE, systemic lupus erythematosus.

A criterion for the pathological diagnosis of mixed-vascular-alzheimer-dementia (MVAD), including the combination of autopsy-confirmed AD, with multiple lacunar infarcts in the cortex, basal ganglia, thalamus, hippocampus and white matter, with an infarcted volume of 30–50 mL has been proposed.⁸ The MVAD, as well as other dementias, start several years before the symptoms display. According to the vascular theory, cardiovascular disease such as hypertension and dyslipidaemia as well as diabetes mellitus can produce several vascular changes resulting in thickening of the capillary basal membrane and the accumulation of collagen in the vascular endothelium. These changes affect the cerebral microvasculature reducing the cerebral blood flow.⁹ Terminal delirium is a reliable predictor of impending death within a few days. Agitation makes communication difficult and intensifies families' frustrations and emotional stress. Glaser and Strauss' theories of 'context of awareness and dying' explain different patterns of onset and course of terminal delirium in dying patients.^{10 11}

The dementia workup should be completed for suspected VaD. Comorbidities including cardiac or cerebrovascular risk factors, diabetes and obstructive sleep apnoea raises the risk of VD. Smoking, passive inhalation of smoke, obesity and alcohol excess raises the VD risk. The association of the apolipoprotein E ε4 genotype with an increased risk for both AD and cardiovascular

disease further suggests a potential link.⁸ Amyloid deposition in cerebral blood vessels due to AD increases the risk for haemorrhagic strokes and subsequent VaD. Several epidemiological studies have suggested that age is the main risk factor followed by hypertension, hyperhomocysteinaemia and leukoaraiosis that are shown as hyperintensities on brain MRI.¹² These factors increase the risk of injury to cerebral blood vessels, leading to cerebrovascular disease which can manifest with cognitive defects exceeding those of normal ageing. There remains no consensus for the diagnosis of MVAD. However, the Alzheimer's Disease Diagnostic and Treatment Centres (ADTC), the NINDS-AIREN have proposed diagnostic criteria.¹³ According to the ADTC criteria, the diagnosis of MVAD requires the existence of a typical AD and closely related cerebrovascular disease. The International Society of Vascular Behavioural and Cognitive Disorders (VASCOG) states that a near temporal relationship, ideally 3 months, between a vascular event and the development of cognitive symptoms and signs must be present to suspect VD especially if previous imaging has been undertaken.¹⁴ Both medial temporal atrophy and large vessel disease contribute to global cognitive impairment and from a structural radiological perspective, medial temporal atrophy is generally considered to be the best surrogate marker of degenerative pathology in AD. Idiopathic normal pressure hydrocephalus may mimic VaD with its symptom triad of ataxia, urinary incontinence and dementia.

Delirium is diagnosed based on special tests such as 3D-CAM (Confusion Assessment Method) which can be completed in an average of 3 min and performs very well compared with an expert evaluation. In order to identify a CAM-positive delirium, the two essential features of 'acute onset and fluctuating course' and 'inattention' are required, in addition to 'disorganized thinking' or 'altered level of consciousness'. Furthermore, the CAM for Intensive Care Unit Patients Scale has been validated in medical and coronary ICU patients. The 4 As test can also be used to diagnose delirium in the geriatric cohort. It focuses on alertness, AMT4, attention and an acute change or a fluctuating course. In addition, a validated model of delirium prediction based on four criteria evaluated using specific scales, include illness severity (Acute Physiology and Chronic Health Evaluation Score), visual impairment (Snellen test), cognitive impairment (Mini-Mental State Evaluation Score) and serum urea:creatinine ratio. CT (CT) visualises established infarcts, whereas MRI enables its degree, location and extent to be assessed.

Once the diagnosis has been established, the main goal of delirium therapy is to identify important, potentially life-threatening, treatable, organic causes responsible for this syndrome. Serious agitation with delirium requires emergency pharmacological intervention. However, an organic cause must first be eliminated before titrating to effect. Neuroleptics such as haloperidol, a well-tolerated, easily titratable medication can be used for sedation. It has been shown that management of cognitive dysfunction, sleep deprivation, immobility, visual and hearing impairment as well as multimodal physiotherapy reduced the incidence of delirium in hospitalised elderly patients. Death anxiety or an apprehension generated by an awareness of oncoming death expressed by care workers, has an impact on a patient's emotional well-being. Currently, therapeutic guidelines suggest that treatment is symptomatic and offers only a modest clinical benefit once a patient has developed MVAD, without any modification of its evolution. Large trials focusing on the pharmacological management of VaD are lacking. Acetylcholinesterase inhibitor drugs such as donepezil, galantamine and rivastigmine as well as antideementia drugs such as memantine can be used to treat patients with AD and VaD.¹⁵ Galantamine

and memantine have shown therapeutic benefits for both cognitive and functional outcomes and randomised controlled trials have shown that donepezil has treatment benefits for patients with mild to moderate AD and VaD.^{16–19} Cholinesterase inhibitors have also shown reproducible beneficial effects on cognitive and functional outcomes in patients with MD.²⁰ Secondary prevention is necessary to prevent the development of acute or recurrent stroke and to reduce the progression of cerebral vascular-related changes. The Perindopril Protection Against Recurrent Stroke Study showed that active treatment with an ACE inhibitor, given alone or in combination with a diuretic, was associated with a reduced dementia risk and cognitive decline in patients with recurrent stroke.²¹ Lifestyle modification factors including regular exercise and a healthy diet with a low consumption of red meat is advised to reduce the risk of developing AD. Further prospective studies and randomised controlled trials are required to further delineate and enhance our understanding of MVAD.

Most individuals have some idea of how they want to live their life, however, a large proportion have not communicated their end-of-life decision to family. The majority of family members do not recognise the terminal nature of dementia and fail to conceptualise between dementia and impending death. Shared communication with family may enhance their understanding of the dementia trajectory and the types of decisions that need to be made. Treatment should be provided for reversible causes of delirium, as in our case, hyperactive delirium was managed with intravenous antibiotics, while maintaining a balance between somnolence and control of agitated symptoms. This case demonstrates the impact of terminal delirium and the support that geriatricians and palliative care physicians provide patients and their families during the advanced stages of the disease. This case also highlights the importance of advance care planning, addressing emotional distress and symptom

burden as well as developing the appropriate treatment regimen for a delirious patient.

Contributors LD wrote the case report. TA-K was involved in the literature review. ZE edited the paper.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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Learning points

- This case demonstrates the challenges in establishing a diagnosis in patients with a diagnosis of mixed dementia. It highlights the importance of minimising cardiovascular risk factors such as hypertension and hypercholesterolaemia. An ECG should be performed to exclude cardiac pathology.
- Individuals with dementia with Lewy bodies can present with episodic reduced consciousness but this is not found in Alzheimer's. A trial of antiepileptic therapy may be required even if the diagnosis is not confirmed (the long-term antiepileptic side effects are much less of a concern in this patient cohort as their life expectancy is short).
- A cognitive assessment at presentation in a delirious state offers very little diagnostic information. A baseline cognitive assessment when the patient was well, duration and nature of deterioration and collateral history will help differentiate delirium from an underlying dementia.

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