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Original Article

The use of cerebral imaging for investigating delirium aetiology

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ABSTRACT

Background: This study aims to investigate the frequency and patterns of use of cerebral imaging in delirium and to describe pathological changes associated with delirium using computed tomography (CT) and magnetic resonance imaging (MRI).
Methods: This retrospective observational study included patients with delirium admitted to a tertiary hospital (The Royal Melbourne Hospital, Australia) between January 2015 and August 2016. Data on cerebral imaging was collected and positive imaging findings were defined as: Acute or subacute infarct, haemorrhage, abscess, neoplasm, vasculitis, posterior reversible encephalopathy syndrome, encephalitis, acute demyelination, or fat embolism.
Results: There were 1653 (5% of 32,725) patients with delirium (median age 80 years, inter-quartile range 71–86, 54% male). Thirty-three percent (N = 538) had cerebral imaging (CT only: N = 457, MRI only: N = 10, both: N = 71). In 11% (N = 57) of patients, CT brain scans were positive. MRI brain was completed in 17 patients with a positive CT (17/57), changing the diagnosis in two cases. Fifty-four patients with negative CT scans also had MRI brain; 33% (N = 18) of these were positive. Younger patients were more likely to have MRI compared to CT brain scan. Patients admitted to a neurology unit were more likely to have cerebral imaging.
Conclusion: Use of CT brain was common in delirium patients, with an 11% rate of positive findings. Fewer patients had MRI brain scans, which added diagnostic information in some cases. Future studies are needed to define the significance of cerebral imaging in delirium management and establish guidelines for its use.

1. Introduction

Delirium is a condition that affects up to 60% of frail elderly patients admitted to hospital [1]. It occurs in the setting of a complex interplay between predisposing and precipitating factors, which can include intracranial events [2]. Cerebral imaging is one of the tools used to investigate the aetiology of delirium. Current delirium guidelines recommend investigation with cerebral computed tomography (CT) if there is a history of falls or head injury, if the patient is taking therapeutic anticoagulation, or if there are focal neurological deficits or evidence of raised intracranial pressure [3–7].

The yield of pathological findings on CT brain ranges between 3 and 45% for hospitalized patients with delirium, with studies having varying definitions of positive imaging results [6,8–13]. The use of cerebral magnetic resonance imaging (MRI) as diagnostic tool in delirium has not yet been compared to CT brain. In studies including intensive care unit patients who have had a CT or MRI brain for any indication, MRI was found to have an increased sensitivity compared to CT for acute stroke, neoplasms, infections, [14] and cerebral venous thrombosis [15]. Furthermore, MRI brain is supported in the literature as being more sensitive than CT in cases of encephalopathy due to hypoxia, sepsis, uraemia, hyperammonaemia, glucose and sodium abnormalities, hepatic encephalopathy, Wernicke's encephalopathy, autoimmune encephalopathy and herpes simplex encephalitis [16]. Acute stroke is a particularly important precipitant of delirium, with the incidence of delirium in acute stroke reported as around 26% [17].

Since MRI brain has been shown to be superior to CT in detecting several diseases that can precipitate delirium, the aim of this study is to investigate the frequency and patterns of use of cerebral imaging (CT and MRI) in delirium in a tertiary hospital, and to describe and compare the pathological changes detected by these imaging modalities.

2. Methods

The cross-sectional retrospective cohort included all patients admitted to an adult tertiary hospital (the Royal Melbourne Hospital,

Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging

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Australia) from January 2015 to August 2016 diagnosed with delirium either at or during admission. Patients were selected by use of the “International Statistical Classification of Diseases and Related Health Problems, version 10” (ICD-10) code for delirium or disorientation: F05 (delirium, not induced by alcohol and other psychoactive substances), R41.0 (disorientation, unspecified), F05.8 (other delirium), and F05.9 (delirium, unspecified). Patients with delirium due to drug use or withdrawal or related to psychiatric illness were excluded from the cohort. To identify the reason for CT or MRI brain, the clinical notes section of the radiology request was reviewed. Patients were excluded if delirium was not documented in the medical records prior to the neuroimaging request (i.e. imaging was performed for an indication other than delirium) or the medical record was missing or not accessible electronically.

The following variables were recorded for all patients: age, sex, admitting unit (neurology, non-neurology medical or surgical unit), primary language spoken, co-existent dementia, discharge to residential care and death during admission.

Data was collected on CT and MRI brain scans requested during each patient's admission. The MRI protocol was recorded as either diffusion weighted imaging (DWI), structural imaging (using T1/T2 weighting), or both. Images had been reported by consultant radiologists or supervised trainees in radiology as per the hospital's usual practice. Pathological changes identified by CT or MRI brain were considered “positive” as possible delirium aetiology in the case of documentation of acute or subacute infarct, haemorrhage, abscess, neoplasm, vasculitis, posterior reversible encephalopathy syndrome, encephalitis, acute demyelination, or fat embolism in the radiology report.

2.1. Statistical analysis

Patient characteristics were analysed by group of patients dependent on the imaging technique (having had CT brain, MRI brain, both CT and MRI brain, or no imaging). Pearson's Chi-squared test was used to assess associations between categorical variables. Characteristics found to be statistically significant in the univariate analysis were tested in a multivariate analysis using logistic regression with two models; one model comparing CT or MRI brain with no imaging, and another comparing MRI and CT brain. An odds ratio (OR) and confidence interval (CI) were calculated. Statistical analysis was performed using Stata, version 14.1 (StataCorp, College Station, TX, USA). A two-sided alpha value of < 0.05 was assumed to indicate statistical significance.

3. Results

Of the 32,725 patients admitted during the timeframe of the study, 1965 patients had a diagnosis of delirium. Three hundred and twelve patients were excluded from detailed analysis due to imaging requested for an indication other than delirium (N = 277), non-available medical record (N = 13) and duplicates of the same admission (N = 22) leaving 1653 patients. Thirty-three per cent (N = 538) of patients with delirium had cerebral imaging (CT only: N = 457, MRI only: N = 10, both: N = 71). The use of cerebral imaging in the cohort is summarized in Fig. 1 and Table 1.

Eleven per cent (N = 57/528) of CT brain scans were positive; diagnoses included haemorrhage (N = 23), infarct (N = 18), possible neoplasm (N = 15) and posterior reversible encephalopathy syndrome (N = 1).

The MRI brain protocols included 51 structural MRIs with T1/T2 weighted images, 21 DWI sequences, and 9 with both structural and DWI protocols. MRI brain was completed in 17 patients with a positive CT (17/57), of which 16 used a structural protocol and one used a DWI protocol. In two cases of possible neoplasms on CT brain, the pathological change reported was different on the structural MRI (one reported as an abscess and another as an infarct). The remainder (N = 15) MRI brain scans reported the same pathological change as CT brain.

Fifty-four cases with negative CT brain scans also had MRI (29 structural, 18 DWI, 7 both); 33% (N = 18) of these were positive. Pathological changes detected by MRI brain but undetected by CT included ischaemic stroke (N = 11), haemorrhage (N = 3), neoplasm (N = 2), fat embolism (N = 1) and encephalitis (N = 1). Of these positive MRI scans, there were 9 structural protocols, 7 DWI, and 2 both. Of patients who had MRI brain only (6 structural, 2 DWI, 2 both), 3 were positive (two diagnoses of infarct in DWI protocols and one diagnosis of vasculitis in the structural protocol).

Pathological changes detected on MRI and CT brain were most commonly in multiple intra-cerebral areas. Further detail on locations of pathological changes can be found in Supplementary Table 1.

Table 2 lists patient characteristics according to the method of cerebral imaging and Table 3 provides results of the multivariate analysis. Patients with delirium admitted to a neurology unit were more likely to have a CT brain compared to patients admitted to other units. Patients who received CT or MRI brain scanning were less likely to be discharged to residential care (neurology admission: OR 3.06; CI 1.77–5.29, discharge to residential care: OR 0.42; CI 0.26–0.66) compared to patients who received no imaging. There was no significant difference in the remaining patient characteristics (age, sex, English speaking status, admission to a medical compared to surgical unit, death during admission, or co-existent dementia) between patients who received CT or MRI brain compared to patients who received no imaging. Older patients with delirium were less likely to have an MRI compared to CT brain (OR 0.96; CI 0.95–0.97). Patients with delirium admitted to a neurology unit were more likely to have an MRI brain compared to CT brain (OR 6.86; CI 3.16–14.93). Patients who had dementia were more likely to have an MRI compared to CT brain (OR 2.63, CI 1.34–5.16). There was no significant difference in sex, English speaking status, admission to a medical compared to surgical unit, death during admission, or discharge to residential care between patients who received MRI brain compared to patients who received CT brain.

4. Discussion

CT brain was requested in nearly one third of patients with delirium, of which 11% were positive. The most common diagnosis detected by CT brain was haemorrhage. MRI brain was requested in 5% of cases. Where MRI brain followed negative CT, 33% of scans were positive. Patients with delirium were more likely to receive cerebral imaging (CT or MRI brain) compared to no imaging if they were admitted to a neurology unit. Patients with delirium were more likely to have MRI compared to CT brain if they were younger, had dementia, or were admitted to a neurology unit.

The rate of positive findings in CT brain scanning is comparable to previous literature in hospitalized patients with delirium, although this figure varied (3–45%) in previous studies depending on the patient population and outcome definition [6,8–13]. This study included all patients with delirium, whereas some studies only included delirium patients with falls, head trauma and neurological deficits [8] or excluded patients with head trauma [11]. Also, this study's outcome definition excluded chronic pathology (such as chronic small vessel ischaemia) whereas some previous studies incorporated all abnormal findings on CT brain and therefore had a relatively high rate of abnormal findings, 45% in one study [12]. There is little previous research to compare with regarding the rate of positive findings for MRI brain detected in this study. Two previous studies included both CT and MRI brain in delirium investigation, with a rate of positive findings of 14% [7] and 32% [13], however there was no comparison between CT and MRI brain findings regarding rate of positive findings or pathological findings on each type of imaging. One case series of eight patients in the

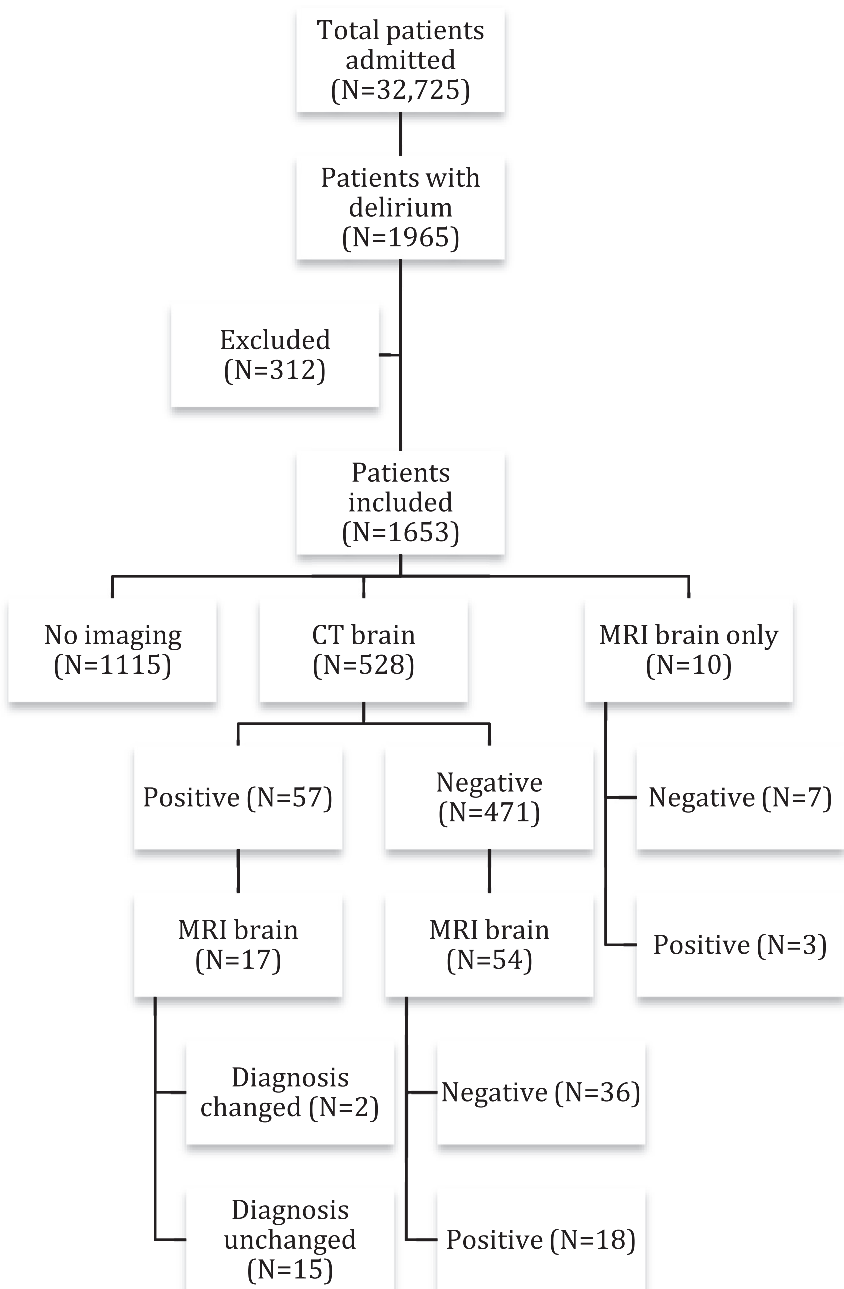

Fig. 1. Use of CT and MRI brain in delirium patients.
CT: computed tomography, MRI: magnetic resonance imaging.

Table 1
Use of cerebral imaging in delirium investigation.

Imaging modality requested	N = 1653
CT brain, n (%)	457 (28)
MRI brain, n (%)	10 (1)
Both CT and MRI brain, n (%)	71 (4)
No cerebral imaging, n (%)	1115 (67)

MRI: magnetic resonance imaging, CT: computed tomography.

intensive care unit concluded that MRI (performed for a variety of indications) did not alter the treatment course. However, it did not specifically study delirium patients and the DWI modality was not included [18]. Algethami et al. [14] retrospectively explored the value of MRI brain in intensive care unit patients, regardless of indication for MRI scanning. Similar to this study, they identified that MRI brain revealed additional pathological changes that were undetected by CT brain, most of which were ischaemic lesions. The rate of lesions in their study was higher (CT 71% and MRI 95%), with 63% of MRI brain scans identifying lesions missed by CT brain. The higher rate of positive findings compared to this study may be due to differing definitions of relevant lesions. In this study, the most common pathological change that was detected by MRI brain but undetected by CT was ischaemic stroke. MRI also detected neoplasms and changes suggestive of infections despite a negative CT brain. This can be explained by an increased sensitivity of MRI compared to CT brain in detecting these changes [14]. The DWI modality, which is sensitive for detecting ischaemia, may be an important additional investigation in patients with unexplained delirium and is quicker and therefore likely to be more feasible in patients with delirium than a structural MRI using T1/T2 weighted sequences [19].

Table 2
Characteristics of delirium patients according to method of cerebral imaging.

Characteristic	CT brain[a] N = 457	MRI brain[b] N = 10	CT and MRI brain N = 71	No imaging N = 1115	p
Age ≥ 65 (yes/no), n (%)	387 (85)	5 (50)	48 (68)	954 (86)	< 0.001
Male, n (%)	259 (57)	3 (30)	36 (51)	600 (54)	0.273
Dementia, n (%)	75 (16)	5 (50)	14 (19)	177 (16)	0.029
Non-English speaking, n (%)	129 (28)	0 (0)	12 (17)	326 (29)	0.029
Neurology admitting unit, n (%)	20 (28)	5 (50)	12 (17)	22 (2)	< 0.001
Died during admission, n (%)	38 (8)	1 (10)	4 (6)	123 (11)	0.236
Discharge to residential care, n (%)[c]	22 (5)	0 (0)	2 (3)	117 (10)	0.001

CT: computed tomography, MRI: magnetic resonance imaging.
[a] CT brain alone.
[b] MRI brain alone.
[c] Per cent of patients that survived (N = 1487).

Table 3
Multivariate analysis of characteristics of delirium patients according to cerebral imaging.

Characteristic	CT or MRI brain vs no imaging, OR (CI)	MRI vs CT brain[a], OR (CI)
Age (years),	0.99 (0.98–1.00)	0.96 (0.95–0.97)
Dementia (yes/no)	1.32 (0.98–1.77)	2.63 (1.34–5.16)
Non-English speaking (yes/no)	0.88 (0.69–1.14)	0.50 (0.24–1.04)
Neurology admitting unit (yes/no)	3.06 (1.77–5.29)	6.86 (3.16–14.93)
Discharge to residential care (yes/no)	0.42 (0.26–0.66)	0.65 (0.14–2.92)

CT: computed tomography, MRI: magnetic resonance imaging, OR: Odds Ratio, CI: Confidence Interval.
[a] MRI with or without CT vs CT brain alone.

Patients admitted to the neurology unit were more likely to receive a CT or MRI brain compared to patients admitted to other units. The association between admission to a neurology unit and receiving a CT or MRI brain has not been explored in previous literature. The association between elderly patients being less likely to receive MRI brain scanning may be explained by the fact that delirium is more common in hospitalized older people [20]. It is therefore possible that clinicians may utilise imaging as part of the diagnostic work-up for younger people with delirium.

The prevalence of delirium on admission and incidence during admission was 5%, which is lower than has been previously reported (around 29–64% in elderly patients admitted to the medical wards) [1]. This finding may be due to under-recognition or under-documentation of delirium in either the medical record or the ICD-10 coding system. Previous literature found that ICD-10 coding for delirium in the hospital database underestimates delirium when compared to bedside diagnosis using the confusion assessment method (CAM) [21]. The proportion of patients receiving cerebral imaging (30%) was comparable to previous studies, with the rate of use of cerebral imaging ranging between 24 and 41% in studies in the emergency department [12,22].

The pathological findings in this study for both CT and MRI brain were most commonly in multiple intra-cerebral areas. Studies on brain imaging changes associated with delirium implicate the frontal, right sided parietal and their associated subcortical regions in the development of delirium [23]. Abnormalities in the basal ganglia and caudate nucleus have been associated with a predisposition to developing delirium [24,25]. Further study is required into whether acute lesions in certain locations, rather than chronic abnormalities, precipitate delirium.

The strengths of this study include that it is the first study to describe pathological changes detected by both CT and MRI brain in the investigation of delirium aetiology. Previous studies on neuroimaging in delirium did not compare findings between CT and MRI brain [7,13]. Also, a clear definition of 'positive' imaging results was used, focusing on precipitating causes of delirium and excluding chronic changes such as chronic small vessel ischaemia. The limitations of the study are due to its retrospective design, with patients having already been selected for certain brain imaging modalities. It is therefore beyond the scope of the study to comment on the superiority of MRI compared to CT brain in delirium investigation. Several factors may have resulted in confounding and require consideration in future study, including comorbidity burden, medications, presenting clinical features and patterns of imaging use across different health services. Another limitation is that the inclusion criteria were based on clinician documentation of delirium rather than a standardized criterion, such as the Diagnostic And Statistical Manual of Mental Disorders (DSM-V) or Confusion Assessment Method. It is possible that some cases of aphasia due to stroke where misdiagnosed as delirium prior to requesting neuroimaging. The outcome measure was also subjective in that where the radiology report stated a "possible" diagnosis, it was considered 'positive' from the perspective of the study. Furthermore, due to the multifactorial nature of delirium aetiology, it is difficult to define a solitary precipitating factor, particularly with the smaller lesions detected in this study, such as small volume metastatic disease or small infarcts. Another limitation is that due to the small sample size of patients receiving MRI brain scanning, this study did not analyse which factors increased the likelihood of positive imaging findings.

This study encourages further research into which patients should be selected for imaging, and whether imaging in delirium leads to a change in management and clinical outcome for delirium patients. MRI brain better detects several disease processes that can explain delirium and this study suggests its utility may be advantageous in delirium cases. However, it is important to study this in more detail, as MRI brain scanning is a lengthier and more costly process than CT brain. Furthermore, patients may also require sedation for MRI, with its associated risks of complications.

5. Conclusions

The use of imaging may improve the diagnosis of the underlying aetiology in selected cases of unexplained delirium. MRI brain may assist, particularly in cases of undetected ischaemic stroke. Future work is needed to address the utility of imaging in delirium in diagnosing the underlying cause of delirium or changes that may reflect a higher vulnerability to delirium.

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Competing interests

The authors have no competing interests to declare.

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