

CLINICAL OBSERVATION

Advanced carotid artery disease associated with recurring delirium followed by dementia

N. Nagaratnam¹, S.A. Nagaratnam²¹ Sydney Medical School (Westmead), The University of Sydney, Sydney, Australia; ² Westmead Hospital, Westmead, NSW Australia

Background: delirium and dementia have been defined as different entities in the literature. Knowledge of the relationship between delirium and dementia which are the major causes of cognitive impairment in the elderly is scanty. There has not been any convincing demonstration of altered cognitive function to chronic cerebral ischemia associated with asymptomatic carotid artery disease and remains a concept which is continuously being debated.

Case presentation: a 79-year-old man with severe asymptomatic carotid artery disease presented with acute delirium. This was followed by three other episodes over a period of 32 months. He was cognitively and functionally normal prior to the first episode and in between the episodes of delirium. Following the fourth episode he exhibited significant cognitive and functional deterioration consistent with dementia. CT scan had shown a small focal hypodense lesion in the right region following the first episode. A duplex scan of the carotid arteries had shown extensive disease of both common carotids and internal carotid arteries. It is surmised that the dementia that followed was the result of a chronic cerebral ischemia resulting from the bilateral carotid artery disease.

Conclusions: if the true role of occlusive carotid artery disease and progressive cognitive decline is acknowledged then early endarterectomy may forestall the disaster. However the optimal treatment choice remains unclear.

Key words: Carotid artery stenosis, Chronic cerebral ischemia, Delirium, Dementia, Carotid endarterectomy, Carotid artery stenting

BACKGROUND

Knowledge of the relationship between delirium and dementia which are the major causes of cognitive impairment in the elderly is scanty. There is growing evidence that delirium occurs across various types of dementia (Alzheimer's diseases, vascular dementia, dementia with Lewy bodies and Parkinson's disease with dementia) and that they overlap, notably in dementia with Lewy bodies¹. Studies relating to the association between carotid atherosclerosis and dementia are meagre². It has also been documented that cognitive decline

often occur in patients with severe carotid stenosis without clinical evidence of stroke or TIA^{3,4}. However, the mechanisms linking altered cognitive function and severe carotid artery disease without symptomatic cerebrovascular events remains less distinct and remains a concept which is continues to be debated. High grade carotid stenosis has been shown to be associated with reduced brain blood perfusion⁵. The likely mechanism of cognitive impairment with advanced carotid disease includes cerebral embolization and chronic hypoperfusion^{3,4}.

■ Received: November 29, 2016 - Accepted: August 28, 2017

■ Correspondence: Nages Nagaratnam, Sydney Medical School (Westmead), The University of Sydney, Darcy Rd, Westmead NSW 2145, Sydney, Australia – E-mail: nages@nagaratnam.net

CASE PRESENTATION

A 78-year-old right-handed man presented with acute confusion. He had had a flu-like illness one week prior to this. His wife who was the informant said that normally a talkative person he had become unusually quiet. He had been in good health and was not on any medication. There was no past history of strokes, TIAs, mental illness or chronic alcoholism and his cognitive state was normal. The vital signs were normal and general physical examination was unremarkable other than for bilateral carotid bruits. He was inattentive, easily distracted by external stimuli and was disorientated in all spheres person, place and time. His recent memory and immediate recall were impaired. There were no focal or lateralizing signs. Routine laboratory (haematological and biochemical) tests were normal. A computed tomography (CT) scan of the brain on day 2 revealed no abnormality. The electrocardiogram was normal. A Duplex scan of the carotid arteries revealed more than 80% stenosis of the right internal carotid artery and narrowing of the right common carotid artery. On the left side there was 60-80% stenosis of the internal carotid artery and tight stenosis of the left common carotid artery. The symptoms fluctuated day by day and on day 7 he began to improve and was discharged to his home on day 10. When seen a week later at the Outpatients his mental state was normal on the Mini-Mental State Examination (26/30)(MMSE). A repeat scan of the brain showed a small hypodense area in the right parietal region consistent with a cerebral infarction. In view of the extent of the disease surgical intervention was not offered to the patient. He was commenced on dipyridamole and aspirin. On subsequent follow-ups there was no evidence of cognitive deficits as measured by the MMSE.

The second admission to hospital was 13 months later with acute confusion and was discharged 16 days later. The CT scan showed no new changes. The laboratory investigations were normal including arterial blood gases and blood cultures. He remained well other than for numbness of the left arm which lasted for a day. Surgical intervention was offered but his wife and he declined.

When reviewed three months later his scores on the MMSE was normal and he was functioning normally. Seven months later he was re-admitted to hospital with acute confusion and remained in hospital for 27 days. The CT scan of the brain was normal but for the old hypodense area in the right parietal region. His MMSE score two weeks later was 26/30. Twelve months later he was admitted to hospital for the fourth time and was extremely confused and remained so during the entire stay in hospital for 45 days. He was now dependant for basic self-care and performed poorly on formal memory

tests. His spouse too had noted the marked deterioration. The findings were consistent with a dementing illness and he had to be institutionalised.

DISCUSSION

Our patient presented with four documented episodes of acute delirium (syn: acute confusional state, acute organic syndrome), duration of which varied from 10 to 45 days over a period of 32 months. In between the episodes, psychometric testing revealed no significant cognitive or memory deficits nor was there any functional impairment. He had severe bilateral occlusive carotid artery disease involving both the internal as well as the common carotid arteries bilaterally. A doubtful TIA occurred during the second episode. The CT scan had shown a small hypodense area in the parietal region of the right cerebral hemisphere with the first episode.

Most patients with acute delirium suffer from reversible toxic, metabolic or infectious disorder and the confusion is caused by a physiological disturbance rather than by structural brain damage. The pathological mechanisms of acute delirium remain unclear and the current view is that they are caused by the disruption of the neurotransmitters, inflammation and acute stress which may all contribute to the disorder. The final common pathway of acute delirium is regarded as a cholinergic deficit combined with dopaminergic hyperactivity⁶. Interaction between the neurotransmitters such as serotonin or noradrenaline with the cholinergic and dopaminergic systems may play a role⁶. Physical stressful events giving rise to increased cortical secretion of cytokines may have a role and some cytokines can influence the activity of the neurotransmitters and these mechanisms can interact⁷. According to MacLulich et al.⁸ there are two categories of triggers, namely "direct brain insults" and "aberrant stress responses".

Acute delirium has been reported following focal lesions in the right hemisphere in the territories of the middle cerebral and posterior cerebral arteries and could involve either the cortex or subcortical regions. In both medical and psychiatric literature acute delirium and dementia have been considered as two different disorders. Clinical characteristics and risk factors of acute delirium are different in dementia and non-dementia elderly patients⁹. Acute delirium may be more persistent than generally believed¹⁰ as in our patient. It is generally assumed that the symptoms resolve in 1-2 weeks after appropriate diagnosis and treatment. Distinguishing this from dementia can be difficult. Knowledge of the relationship between acute delirium and dementia, which are the major causes of cognitive impairment in the elderly, is scanty.

In most instances the MMSE has been used as in our patient to stratify the severity of cognitive impairment and dementia. It is requisite that the clinician to look for causes in dementia more so potentially reversible causes such as thyroid disorders, B12 deficiency, normal pressure hydrocephalus among others although the actual reversibility is low. Majority of the patients screened with dementia do not require extensive tests and the testing should be guided by the history and physical examination. Our patient's history, presentation and train of events did not suggest any potentially reversible cause.

It is well documented that occlusion of the carotid arteries could cause dementia either by multifocal infarction or less commonly by haemodynamic mechanism¹¹ although perfusion insufficiency had been difficult to document as a cause of dementia. It is interesting to speculate that the recurrent episodes of delirium in our patient may be the result of micro-emboli from the diseased carotid arteries resulting in small cerebral infarcts. Trans Doppler ultrasonography has demonstrated high intensity transient signals in patients with symptomatic carotid stenosis and they may present in the territories of the arteries with TIA attacks rather than cerebral infarction¹². Alternately prolonged hypoxia due to slow flow secondary to bilateral carotid stenosis could result in neuronal death resulting in ischaemic dementia/vascular dementia. The term vascular cognitive impairment is now the preferred term for vascular dementia for it embraces the complex interactions between vascular risk factors, cerebrovascular disease etiology and cellular changes with the brain and cognition¹³. It has been reported that the greatest risk of dementia are in individuals in the upper quintile of carotid intima medial thickness or bilateral carotid plaques¹.

Although cognitive impairment increases with age some elderly have normal cognitive function whereas others exhibit marked deterioration. However the explanation of the relationship between carotid artery stenosis and cognitive functioning remains unclear and the effect of carotid interventions on cognitive function is not fully understood⁴. Symptomatic and asymptomatic carotid stenosis may be an independent factor for cognitive impairment^{3,4}. It is well known that there is substantial overlap between cerebrovascular disease and Alzheimer's disease and hence coexisting Alzheimer's pathology cannot be ruled out.

In asymptomatic patients there is no evidence to support prophylactic endarterectomy or stenting to prevent cognitive decline⁴. Two of the operated patients studied by Gibbs et al.¹⁴ did not show any cognitive improvement but according to Tatemichi et al.¹¹ delayed neuronal attrition could continue in spite of correcting the cerebral blood flow. In a subgroup of patients in

their 80s the mortality rate was 10.8% following CAS and was attributed to severity of the lesion, calcification, aortic arch elongation, tortuosity and great vessel origin stenosis together with perioperative stroke/myocardial infarction¹⁵. Age is a risk factor for carotid endarterectomy (CEA) especially in those 80 years and over. Moreover our patient had extensive disease involving the common carotids as well, carrying a high risk. Furthermore, it is generally believed that there are no convincing grounds at present to support the prophylactic carotid endarterectomy or carotid stenting with the intention of preventing cognitive decline in otherwise asymptomatic patients⁴ thus posing a problem as to the advisability of any surgical intervention in our patient.

There are some limitations to this study which warrant comment. Firstly imaging with CT perfusion and MRI would have been better at evaluating vascular damage rather than the CT scan. Secondly, the MMSE was used to estimate cognitive function and no other psychometric testing was done. MMSE scores range from 0 to 30 with a score of 24 and above taken as normal function. Although MMSE does not differentiate among specific cognitive functions it is broad and global. Nevertheless we believe this case adds to the concept that severe carotid disease predisposes to delirium and the eventual development of dementia.

References

- 1 Morandi A, Davis D, Bellelli G, et al. *The diagnosis of delirium superimposed on dementia: an emerging challenge*. J Am Med Dir Assoc 2017;18:12-8.
- 2 Wendell CR, Waldenstein SR, Ferrucci LF, et al. *Carotid atherosclerosis and prospective risk of dementia*. Stroke 2012;43:23319-24.
- 3 Dutra AP. *Cognitive function and carotid stenosis: review of the literature*. Dementia Neuropsychologica 2012;6:127-30.
- 4 Martinić-Popović I, Lovrenčić A, Demarin V. *Advanced asymptomatic carotid artery disease and cognitive impairment: an understated link?* Stroke Res Treat 2012, Article ID981416 (<http://dx.doi.org/10.1155/2012/981416>).
- 5 Alexandrov AV. *The Spencer's curve: clinical implications of a classic haemodynamic model*. J Neuroimaging 2007;17:6-10.
- 6 Lorenzi S, Fusgen I, Nouchlar S. *Acute confusional states in the elderly. Diagnosis and treatment*. Dtsch Arztebl Int 2012;109:398-9.
- 7 van der Mast RC. *Pathology of delirium*. J Geriatr Psychiatry Neurol 1998;11:138-45.
- 8 MacLulich AM, Ferguson KJ, Miller T, et al. *Unravelling the pathophysiology of delirium: a focus on the role of aberrant stress responses*. J Psychosom Res 2008;65:225-38.
- 9 Margiotta A, Blanchetti A, Ranien P, et al. *Clinical characteristics and risk factors of demented and not*

- demented elderly medical inpatients.* J Nutr Health Aging 2006;10:535-9.
- ¹⁰ Levekoff SE, Evans DA, Liptzin B, et al. *Delirium: the occurrence and prevalence of symptoms among elderly hospitalised patients.* Arch Intern Med 1992;152:334-40.
- ¹¹ Tatemichi TK, Desmond DW, Prohovnik I, et al. *Dementia associated with bilateral carotid occlusions: Neuropsychological and haemodynamic cause after extracranial to intracranial surgery.* J Neurol Neurosurg Psychiatry 1995;58:633-56.
- ¹² Foretza AM, Babikian VL, Hyde C, et al. *Effect of time on cerebrovascular symptoms in the prevalence of microemboli in patients with cervical carotid stenosis.* Stroke 1996;27:687-90.
- ¹³ Erkinjuntti T, Gauthier S. *The concept of vascular cognitive impairment.* Front Neurol Neurosci 2009;24:79-85.
- ¹⁴ Gibb JM, Prackowisk RSJ, Legg NJ. *Regional cerebral blood flow and oxygen metabolism in dementia due to vascular disease.* Gerontology 1986;32:84-8.
- ¹⁵ Lam RC, Lin SC, De Robertis B, et al. *The impact of increasing age on anatomic factors affecting carotid angioplasty and stenting.* J Vasc Surg 2007;45:875-80.