Neuropsychiatric patterns in cerebral amyloid angiopathy and psychiatric presentations

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Abstract

Cerebral amyloid angiopathy(CAA) is diagnosed in various settings including stroke units, memory clinics and geriatric psychiatry. CAA is observed in community dwelling populations as well (Vernooij et al 2008). Clinical presentations including neuropsychiatric presentations were described in the last two decades. Various neuropsychological manifestations have been described which include impairment in perceptual speed, episodic memory, semantic memory, attention and executive function and global cognitive impairment. Neuropsychological manifestations included a new manifestation of high impulsivity, in addition to organic personality change, and depression. This study focuses on neuropsychological impairments and psychiatric manifestations observed in CAA patients and discusses the possibility of a neuropsychological profile for CAA.

Background

Cerebral amyloid angiopathy (CAA) is a neurovascular disease characterized by b-amyloid fibrils deposited in the walls of cerebral blood vessels (Biffi & Greenberg 2011). A contemporary systematic overview paper which collectively studied the results of four population- based pathological studies concerning the link between the presence of CAA (of any severity) and dementia found that 55-59% of patients suffering from dementia suffered from CAA as well, while a CAA prevalence of only 28–38% was determined in patients without dementia (Keage et al.,2009). CAA micro bleeds are believed to occur in greater than 30% of adults over the age of 70, and are potentially even more prevalent given the amount of symptomatic individuals with micro bleeds (Viswanathan et al 2011). CAA is diagnosed in various settings including stroke units, memory clinics and geriatric psychiatry. CAA is observed in community dwelling populations as well (Vernooij et al 2008). Risk factors in the development of CAA include age (Vinters 1987) and a genetic facto, apolipoprotein E alleles (Verghese et al 2011). Clinical presentations including neuropsychiatric presentations were described in last two decades. These include symptomatic intracerebral haemorrhage, cognitive impairment and dementia, rapidly progressive cognitive and neurological decline and transient neurological symptoms (Chaaridimou et al 2012) Various neuropsychological manifestations have been described which include impairment in perceptual speed, episodic memory (Arvanitakis et al. 2011), semantic memory, attention and executive function and global cognitive impairment (Boyle et al 2015). Cognitive disorders in CAA patients were frequent, in numerous domains. Patients exhibited significant deficits in language, processing speed and executive and memory functions compared to the control group, but were not different on attention and praxis domains. Studies showed that naming was the most impaired process, as in the deep group, followed by executive and processing speed (Planton et al 2017). This pattern of frontal cognitive dysfunction was already highlighted in the CAA population by Xiong et al 2106.

In clinical settings modified the Boston criteria allow for probable or possible CAA diagnosis or exclusion of diagnosis of CAA (Figure 1). The Modified Boston criteria were proposed in 2010 in order to incorporate cortical superficial siderosis into the radiological diagnosis of probable CAA (Linn et al). They comprise of combined clinical, imaging and pathological parameters, and are based upon the original Boston criteria (Knudson 2001). The Modified Boston criteria for diagnosis of 'probable CAA' was pathologically validated in 2010, and compared to the Boston criteria had an increase in sensitivity (95%, 95% confidence interval (CI) 76% to 99%) with only a modest decrease in specificity (81%, 95% CI 62% to 93%)

CAA is mainly a neurological illness, possibly may present with psychiatric symptoms. Currently there are no studies that address the psychiatric manifestations of CAA in a systematic way. We report a case series describing three cases with neuropsychiatric manifestations presented to a geriatric psychiatric unit.

Figure 1 Modified Boston criteria for cerebral amyloid angiopathy.

The criteria are very similar to the original Boston criteria,(Knudson et al 2001) divided into four tiers (Linn et all):

Definite CAA

- *full post-mortem examination reveals lobar, cortical, or cortical/subcortical haemorrhage and pathological evidence of severe cerebral amyloid angiopathy*

probable CAA with supporting pathological evidence

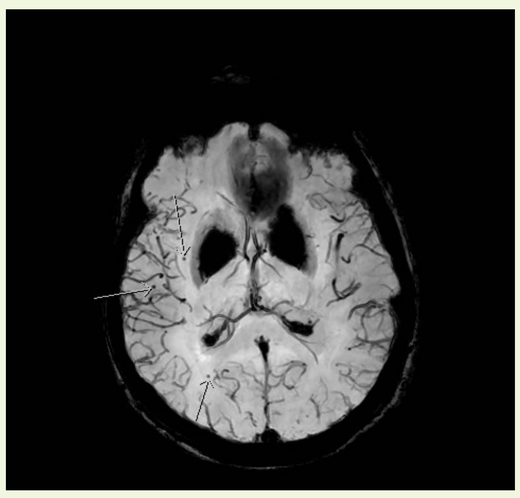
- *clinical data and pathological tissue (evacuated haematoma or cortical biopsy specimen) demonstrate a haemorrhage as mentioned above and some degree of vascular amyloid deposition*
- *doesn't have to be post-mortem*

probable CAA

- *pathological confirmation not required*
- *patient 55 years or older*
- *appropriate clinical history*
- *MRI findings demonstrate*
  - *multiple haemorrhages restricted to lobar, cortical, or corticosubcortical regions (cerebellar haemorrhages allowed) of varying sizes/ages without another cause, or*
  - *a single lobar, cortical, or corticosubcortical haemorrhage and focal (three or less sulci) or disseminated (more than three sulci) cortical superficial siderosis without another cause*

possible CAA

- *patient 55 years or older*
- *appropriate clinical history*
- *MRI findings demonstrate*
  - *a single lobar, cortical, or corticosubcortical haemorrhage without another cause, or*
  - *focal or disseminated cortical superficial siderosis without another cause*



	Neuropsychiatric presentation	Neuropsychological findings
Case 1	Cognitive impairment Focal temporal lob seizures Depression	Poor concentration
Case 2	Depression Organic personality change	Poor cognitive flexibility, decreased processing speed, impaired free recall and impaired executive function Accentuation of poor impulse control.
Case 3	Delirium Cognitive impairment	Apathy Impaired memory Impaired executive function

Cases

Case 1

A 77 year old male with a background of paroxysmal atrial fibrillation had presented with headache, drowsiness and left visual inattention. His computerised tomographic (CT) head scan showed a multifocal right temporal lobe acute intra parenchymal haemorrhage with 4 mm of midline shift and 6 mm of right uncal herniation. An Magnetic resonant imaging (MRI) brain scan two months later showed a right temporal lobe residual haematoma with a background evidence of amyloid angiopathy on susceptibility sequence with confluent hyper intensity in the periventricular white matter of both occipital lobes on T2/FLAIR. On follow up he developed temporal lobe focal seizures. There was also evidence of a cognitive decline [Addenbrooke's cognitive examination (ACE III) - 71/100]. He was referred to a psychiatrist for depression, anhedonia and poor sleep with little response to citalopram. There were no frank delusions or hallucinations and past psychiatric history was unremarkable. As there was only partial control of seizures on Leviteracetam and the potential for this agent to contribute to low mood this was cross-titrated with carbamazepine and eventually stopped. Additionally, citalopram was switched to mirtazapine. Following this depression markedly improved and seizures abated.

Case 2

A 74 year old female with a background history of hypertension, ischemic heart disease and possible subcortical degeneration presented with feeling low in mood, tiredness inability to cope with recent stressful situations. She gave a long standing history of depression and was on citalopram at the time of presentation. Collateral information from her husband and two daughters suggested changes in her personality for last three to four years. Her notable changes include high struggling to manage time, became irritable and argumentative for trivial reasons, ruminates on past issue, difficult to 'stop' thinking. She had issues with urinary incontinence for five years and gait was wide based, unsteady and veering to left. Mental state examination showed low mood, no delusions or hallucinations and judgment was intact. She scored 90/100 in ACE III. On neuropsychological testing her attention and concentration were below expectations as is her processing speed. There was a significant decline in impulse control and cognitive flexibility. The pattern of results also indicates that she struggles to freely recall unstructured information and becomes overwhelmed with complex tasks. Qualitative information suggests that pre-morbidly, she showed behaviours indicative of impulse control difficulties, however, the degree of change here suggests a clear decline in executive function which has exacerbated these longstanding traits. MRI scan on two separate occasions one year apart showed multiple bilateral foci of susceptibility in the cerebral cortex suggestive of amyloid angiopathy. No significant generalised or focal parenchymal atrophy and the hippocampi bilaterally appear normal. MRI also showed moderate small vessel ischaemic disease in the deep cerebral white matter. She is stabilized on with Mirtazapine 45 mg, Quetiapine 100 mg and Clonazepam. She showed improvement in impulsivity sleep and appetite. She is euthymic with no somatic complaints.

Case 3

An 80 year old female with a background of mastectomy for breast cancer and Hashimoto thyroiditis (on levothyroxine) but no previous psychiatric history presented with intermittent confusion and fixed false beliefs, and auditory and visual hallucinations complicated by anxiety and agitation. This culminated in an attempt to jump out of a moving car. Following admission to a psychiatric unit she was diagnosed with delirium secondary to a urinary tract infection. A brain CT showed extensive presumed physiological calcification within the basal ganglia and cerebellum and mild small vessel white matter ischaemic change. ACE III score was 78/100 on admission but improved to 86/100 just before discharge. Three weeks later she was readmitted to hospital when her symptoms recurred. A repeat CT scan did not indicate new changes. A lumbar puncture revealed no growth with normal protein and glucose levels. An MRI brain revealed punctate foci of susceptibility within the cerebral hemispheres peripherally in keeping with cerebral amyloid angiopathy. There were also areas of susceptibility within the basal ganglia and cerebellum in keeping with calcification seen on CT. ACE III was 83/100 and 79/100 three months later. She was treated with a small dose of Risperidone and discharged home after her symptoms improved. On follow up she developed further episodes of intermittent confusion with decline in memory and apathy. She died suddenly about six months after discharge.

Discussion

In our case series we could not demonstrate histopathological confirmation of CAA. However these cases all meet the modified Boston radiological criteria for probable CAA (Figure 1). MRI findings in these cases (see figure 2) all include multiple old haemorrhages or varying size within lobar, cortical, or subcortical regions. Case (label here) demonstrated an evolving subacute intraparenchymal macrohaemorrhage within the right temporal lobe. Case (different label here) demonstrates superficial siderosis. No alternative cause of haemorrhage identified. Our study also highlights the importance of MRI scanning in psychogeriatric population.

Psychiatric presentations are uncommon in CAA. Report of these three cases show the importance of looking for CAA in psychiatry settings. Psychiatrists need to be aware of CAA, particularly in older population. In our cases two cases had depression but it is difficult to ascribe causality in these cases due to multiple problems in these cases. The spectrum of clinical symptomatology is mainly neurological as well as cognitive decline (Attems J et.al 2011). Due to CAA being a chronic progressive illness of the central nervous system, the development of slight psychiatric symptoms during the disease progression is conceivable, especially in the first stages of CAA, which do not bear the typical, impressive clinical signs of intra cerebral bleeding or other neurological symptoms such as epileptic seizures. Cognitive impairment and dementia were reported. In case 2 she developed organic personality change in last four years. There are no attributable reasons for her personality change other than CAA. Though a theoretical possibility of personality change is mentioned in literature there are limited reports available (Gahr et al 2012). A case was reported in hereditary form CAA with personality change (Biffi et al 2011.). Our case is a sporadic one. Taking into account that dementia and neurodegeneration are frequently associated with behavioural problems and/or personality change (Hope and Keene, 1996; Klugmann et al., 2009) it seems plausible that CAA may cause these clinical syndromes as well, although this connection has not yet been studied in a systematic way.

Neuropsychological manifestations (Table 1) in our series include cognitive impairment, organic personality change, depression, focal temporal lob seizure and delirium. A direct causality cannot be ascribed in these cases, but it is possible that CAA may have caused or contributed to current presentations. Other neuropsychological issues demonstrated in these cases include accentuation of poor impulse control, impaired concentration, poor cognitive flexibility, processing speed, impaired free recall, executive function and apathy. All these disturbances were described in previous studies (Gahr et al 2012; Charidimou 2011; Boyle et al 2015), though there are no reports on organic personality change in sporadic cases or accentuation of poor impulse control.

Conclusion

The clinical spectrum of CAA continues to grow. Despite remarkable recent interest, CAA remains under-recognised by neurologists and stroke physicians (Charidimou et al 2013) At present an awareness needs to be created among psychiatrists to recognise cerebral amyloid angiopathy as a possible cause of psychiatric presentations. More insight is needed in demonstrating psychopathology and its relation to CAA. Case control studies are needed to delineate psychiatric manifestations are part of CAA. In addition long-term follow-up studies with repeated imaging will increase insight in the clinical meaning of these situations in CAA over time.

Waitemata District Health Board

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