

Iatrogenic cerebral amyloid angiopathy secondary to cadaveric lyophilised dural graft in childhood: a case in New Zealand

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Iatrogenic cerebral amyloid angiopathy (iCAA), attributed to pathological amyloid-beta ($A\beta$) seed transmission, is an emerging clinical phenomenon. We believe this is the first case identified in New Zealand.

Case

A 43-year-old man with a long-standing history of focal epilepsy presented with increasing seizure frequency, cognitive decline and behavioural changes.

He was born in the early 1980s with aplasia cutis congenita, which caused a defect in the scalp near the vertex, exposing the underlying dura. In the first weeks of life the dura deteriorated, necessitating surgical procedures to resect non-viable herniated brain tissue and to close the dural defect. The dura was repaired with lyophilised cadaveric dura. This had resulted in a left hemiparesis, mild intellectual disability and focal epilepsy. He had been clinically stable for many years, and until recently had been living independently and working full-time. There was no family history of cerebral amyloid angiopathy.

For around 3 months prior to hospital admission, he experienced increased seizures despite adjustments to antiseizure medication, and mood and cognitive changes. On assessment, he was disorientated and inattentive, anxious and expressing paranoid thoughts. His left hemiparesis was worse than his baseline, and there were frequent bouts of left-sided face, arm and leg twitching, suggestive of focal seizures.

Brain magnetic resonance imaging showed multiple bilateral periventricular and deep white matter hyperintense foci on T2 fluid-attenuated inversion recovery imaging (Figure 1), as well as numerous bilateral microhaemorrhages in a peripheral distribution on susceptibility-weighted imaging (Figure 2), in addition to

long-standing post-surgical changes seen (Figure 3).

Given the appearance of cortical microbleeds, and the history of exposure to cadaveric dural tissue, we considered iCAA and performed cerebrospinal fluid (CSF) testing (Table 1). This showed decreased CSF $A\beta$, which is indicative of amyloid deposition in the central nervous system. This supports a diagnosis of probable iCAA. The patient was discharged from hospital on an adjusted antiseizure medication regimen with acceptable seizure control, and improvements in paranoia. Unfortunately, there has not been a significant cognitive or functional improvement, and he requires hospital-level care. The patient and his family have been counselled about the risk of future intracranial bleeding.

Discussion

Cerebral amyloid angiopathy (CAA) is a disease characterised by deposition of $A\beta$ proteins in the cerebral vessels, causing intracranial bleeding, ischaemia and progressive cognitive decline. Like Alzheimer's disease, it is strongly associated with ageing, and diagnostic criteria for sporadic CAA requires age over 50.¹ Our patient's imaging and clinical phenotype mimics CAA, but at an unexpectedly early age. Although the absence of family history does not fully exclude genetic causes, it makes this much less likely. His neurosurgical history involving cadaveric-derived product led us to consider an iatrogenic cause.

iCAA occurs due to seeding of pathological $A\beta$ proteins into brain tissue from a human-derived graft, and has been described as a distinct clinical subtype of CAA.^{2,3} Evidence to suggest transmission of $A\beta$ protein between humans was first identified in 2016, when evidence of amyloid deposition was unexpectedly found in the brains of those exposed to cadaveric brain tissue.⁴ The ability of $A\beta$ proteins to seed was later confirmed

in laboratory conditions.⁵ Subsequently, there have been around 50 cases of iCAA reported in the literature.^{2,3}

The onset of clinical symptoms in our patient was four decades after exposure to cadaveric dural tissue. This is similar to other reported cases, with delays of between 25 and 46 years reported.² Though iCAA and CAA share similar clinical and radiological presentation, there are some differences. The earlier onset in iCAA is likely explained by the early age at which patients are initially exposed to abnormal A β protein. In reported iCAA cases, more affected patients were males and there was no correlation with ApoE ϵ 2 and ϵ 4 alleles in contrast with sporadic CAA.^{2,3} In addition, seizures and rapidly progressing cognitive impairment as presenting symptoms have been described in iCAA, which is a feature more commonly seen in the inflammatory form of CAA.²

Cadaveric lyophilised dural grafts are one of the commonest reported causes of iCAA, and were used in neurosurgical procedures in

New Zealand in the 1980s. Usage ceased when they were recognised as a cause of iatrogenic Creutzfeldt–Jakob disease, the best known example of seeding of abnormal proteins causing a neurodegenerative condition. Overseas, the condition has recently gained public attention with media coverage.⁶ It is unknown how many patients in New Zealand received cadaveric dural grafts as no registry was kept. To our knowledge, this is the first reported case of iCAA in New Zealand; however, the long delay from exposure to symptoms means it is possible more cases of iCAA will be seen in New Zealand.

Conclusion

This case highlights the importance of considering iCAA in younger patients with suggestive imaging and a history of dural graft use. Due to the long delay from exposure to symptoms, the exposure may not be immediately evident without looking into old case notes.

Table 1: Cerebrospinal fluid (CSF) results.

CSF test, unit	Results	Reference range
Protein, g/L	0.62	0.15–0.40
White cell, $\times 10^6$ /L	1	<5
Abeta1-42, ng/L	211	>1,030
P-tau181, ng/L	25.2	≤ 27
Total-tau, ng/L	201	≤ 300
Total-tau/abeta1-42 ratio	0.95	≤ 0.28
Neurofilament light (NfL), ng/L	330	≤ 85

Figure 1: Axial T2 fluid-attenuated inversion recovery imaging demonstrates multiple bilateral periventricular and deep white matter hyperintense foci.

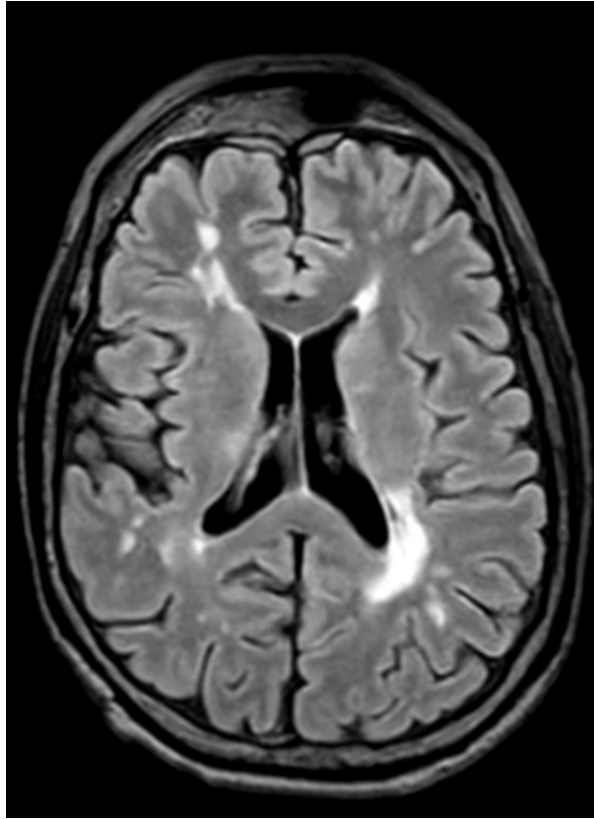


Figure 2: Susceptibility-weighted imaging demonstrates numerous bilateral microhaemorrhages in a peripheral distribution.

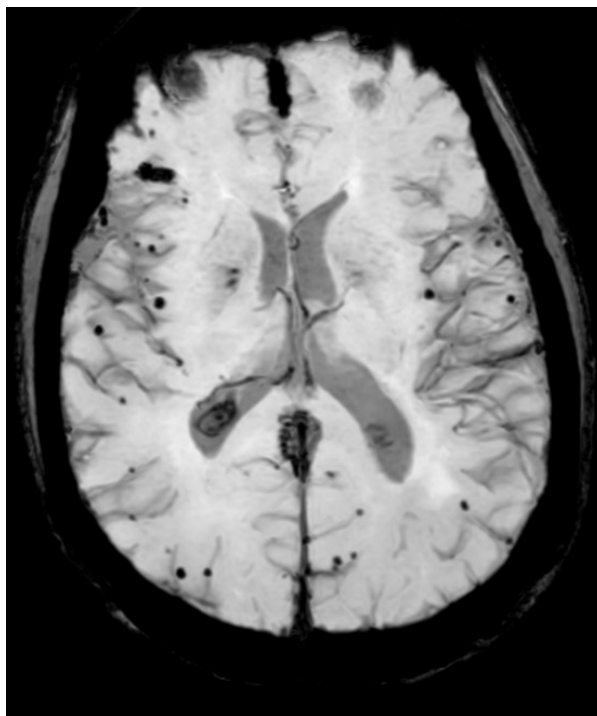


Figure 3: Sagittal T1-weighted brain magnetic resonance imaging shows right superior frontal lobe cystic encephalomalacia with overlying skull and scalp defect.



COMPETING INTERESTS

SB participates on the Pharmac Neurology Specialist Advisory Committee and is secretary for the Neurological Association New Zealand.

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