Title: The role of amyloid PET in diagnosing possible transmissible cerebral amyloid angiopathy in young adults with a history of neurosurgery: a case series

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Short title: Amyloid PET in transmissible CAA

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ABSTRACT

Background

Cerebral amyloid angiopathy (CAA) is a common cause of cerebrovascular disease in the elderly. There is accumulating evidence suggestive of transmissibility of β-amyloid resulting in amyloid pathology at younger age. According to the Boston criteria, defining CAA in patients <55 years requires histological evidence which may hamper diagnosis. We explored the role of amyloid PET in the diagnosis of possible transmissible CAA in young adults.

Cases

We report four young adults (<55 years) presenting with clinical and neuroimaging features suggestive of CAA but without genetic evidence of hereditary CAA explaining the young onset. A common factor in all cases was a medical history of neurosurgery during childhood. All patients underwent amyloid PET to support the diagnosis of an amyloid-related pathology and the result was positive in all four.

Conclusion

Combining the clinical presentation and imaging findings of the four cases, we postulate transmissible CAA as the possible diagnosis. Further epidemiological studies are required to gain more insight in the prevalence of this novel entity. Amyloid PET may be a useful, non-invasive tool in these analyses especially since pathological evidence will be lacking in most of these studies.

INTRODUCTION

Cerebral amyloid angiopathy (CAA) is caused by deposition of β-amyloid in the media and adventitia of small cortical and leptomeningeal blood vessels. This may induce both hemorrhages and ischemia in the tissue around the amyloid-loaded vessels leading to a broad spectrum of radiological and clinical presentations. Neuroimaging may reveal microbleeds, intracerebral hemorrhage, superficial siderosis, lacunar infarcts and white matter hyperintensities. Patients can be asymptomatic or present with ischemic or hemorrhagic stroke, transient focal neurological episodes and/or cognitive decline[1].

CAA is mostly a sporadic condition and is associated with ageing (prevalence in 65-74y: 2.3-22.8%, 75-84y: 8.0-38%; >85y: 12.1-100%)[2]. Non-hereditary CAA is therefore rare in younger patients as reflected in the Boston criteria which state that in patients below 55 years histopathological evidence is required[3–5]. This hampers diagnosing CAA in younger patients with clinical and radiological characteristics of this underlying disease in whom tissue analysis is lacking.

Recently transmissibility of β-amyloid has been suggested following inoculation of β-amyloid through treatment with cadaveric growth hormone, dural grafts and even neurosurgical procedures resulting in CAA decades later[6–10].

We report four patients with a history of neurosurgery during childhood presenting with cerebrovascular disease reminiscent of CAA below 55 years and without mutations or duplications in amyloid precursor protein (APP) or presenilin-1 (PSEN1) and without mutations in presenilin-2 (PSEN2). Moreover, no human tissue was implanted during the neurosurgical procedure in either of the patients. We performed ^{11}C-Pittsburgh Compound B (PiB) Positron Emission Tomography (PET) to assess amyloid burden which may support the diagnosis of CAA.

CASES

CASE 1

This 32-year-old man with a medical history of neurosurgery at the age of three months for a congenital meningo-encephalocele presented with a spontaneous nontraumatic intracerebral hemorrhage (ICH) in the left thalamus with intraventricular extension (shown in Fig. 1A). There was mild arterial hypertension. Magnetic resonance imaging (MRI) did not reveal a vascular malformation. Five months later he suffered a second ICH in the right parietal region (shown in Fig. 1B). Cerebral digital subtraction angiography was unremarkable. Family history was negative for ICH and genetic testing for mutations or duplications in APP, PSEN1 and PSEN2 was negative. Apolipoprotein E (APOE) genotype was E3/E3. ^{11}C-PiB PET showed increased tracer uptake bilaterally in the prefrontal and anterior temporal cortex and in the right parietal cortex (shown in Fig. 2A).

CASE 2

This 47-year-old male patient was diagnosed with a posttraumatic frontal network syndrome related to a head trauma as infant requiring a neurosurgical intervention at the age of one. At the age of 50 he consulted a neurologist with symptoms of (presumably drug induced) parkinsonism and MRI revealed pronounced white matter disease and superficial siderosis (shown in Fig. 1C-D). He had no cardiovascular risk factors, no familial history of ICH. Genetic testing (Notch3, collagen type 4 (COL4)A1/A2, APP, PSEN1/2) was negative. Alfa-galactosidase A activity was normal. ^{11}C-PiB PET revealed increased amyloid uptake in the frontal, parietal and temporal lobes bilaterally (shown in Fig. 2B).

CASE 3

This male patient, previously described by Jaunmuktane[9], was born with a meningioma which was resected at the age of one. At the age of 31, he presented with ICH in the resection cavity (shown in Fig. 1E). His only cardiovascular risk factor was hypertension. Hematoma evacuation was performed because of neurological worsening and tissue biopsy was compatible with CAA. ^{11}C-PiB PET showed an increased amyloid load in the frontal, parietal and occipital cortices (shown in Fig. 2C). Genetic testing for APP, PSEN1 and PSEN2 was normal. APOE genotype was E2/E3. At the age of 35 and 37, he experienced a second and third ICH (shown in Fig. 1F).

CASE 4

At the age of 32 and 37 this man suffered lacunar infarcts and neuroimaging revealed a recent ischemic lesion twice as well as old white matter hyperintensities and evidence of microbleeds and superficial siderosis (shown in Fig. 1G-H). He had neonatal neurosurgical treatment for a lumbosacral meningomyelocoele. His only cardiovascular risk factor was hypercholesterolemia. Testing for Notch3, COL4A1/A2 and alfa-galactosidase activity was negative. ^{11}C-PiB PET showed widespread amyloid accumulation throughout the entire neocortex (shown in Fig. 2D). Genetic testing for APP, PSEN1 and PSEN2 was negative.

The summary of the neuroimaging findings of the four cases can be found in table 1.

AMYLOID IMAGING

All four patients underwent ^{11}C-PiB PET/CT (computed tomography) imaging as part of their clinical work up to assess the possibility of an amyloid-related pathology. Images were acquired 40-60 minutes post injection of 308±22 MBq ^{11}C-PiB (Siemens Biograph PET/CT). Amyloid positivity was assessed both on visual read by a certified nuclear medicine physician

(KVL) as well as semiquantitatively. For the semiquantitative assessment, an in house available dataset of amyloid negative healthy volunteers (19 subjects, 65-75 years) was used as control population. First, ^{11}C-PiB images were preprocessed using PMOD software (v3.902, PMOD technologies, Zurich, Switzerland): motion correction, summation and spatial normalization to MNI (Montreal Neurological Institute) space. Standardized uptake value ratio (SUVR) parametric images were calculated with pons (automated anatomical labeling atlas) as reference region. Then we performed voxelwise comparisons of the individual patients to the set of healthy volunteers with Statistical Parametric Mapping (SPM12; UCLvSPM12, London, UK). We used 8mm smoothed SUVR images and applied an explicit grey matter mask ($p_{heigth,FWE\text{-}corrected} < 0.05$, extent threshold >50 voxels(2x2x2mm)).
Both on visual read as well as according to the semiquantitative approach, the amyloid images of all four patients were classified as amyloid positive (figure 2).

For quantification of amyloid PET, both cerebellum and pons have been used as reference region. Because the cerebellum may be affected by amyloid pathology in CAA, we chose to use the pons as reference region since this area is unaffected in CAA.

DISCUSSION

We report four patients with young onset of cerebrovascular disease who underwent cranial or spinal neurosurgery in early childhood. Amyloid PET showed increased binding suggestive of underlying amyloid pathology. Although this does not provide definite proof of CAA, we tentatively diagnosed these patients with transmissible amyloid pathology resulting in the clinical presentations of CAA. We excluded the presence of the most frequent genetic causes for early onset amyloid pathology (APP, PSEN1 and PSEN2), but acknowledged as a

limitation that more rare mutations like ITM2B (Integral Membrane Protein 2A or BRI2) and CST3 (cystatin 3) were not tested.

Amyloid pathology is believed to be rare in young adults and this is reflected in almost absent amyloid tracer binding in younger individuals (<10% below 50y)[11]. Therefore, amyloid PET is almost never investigated in young adults and we did not have access to a ^{11}C-PiB PET database of young healthy volunteers. For this study we selected healthy volunteers in the youngest age category of our database. This is a limitation since a more optimal control population would have been unselected individuals in the same age range. However since amyloid tracer binding increases with aging, comparing the patients to a slightly older population could be considered a rather conservative approach to identify amyloid pathology on PET.

Amyloid PET is not capable of differentiating between fibrillary amyloid plaques (as seen in Alzheimer disease (AD)), and vascular amyloid (the pathological hallmark in CAA)[12], but the clinical presentation of these patients favored a diagnosis of CAA and not AD. In view of the well-established cross-validation of amyloid tracers with anatomopathological amyloid burden[13–15], it is plausible to assume these patients have underlying amyloid pathology although pathologically confirmed in only one case. Three out of four patients (case 2-4) fulfilled the modified Boston criteria for probable CAA (except for the age criterion). An alternative cause for the superficial siderosis could be head trauma (case 2) or neurosurgery itself, but that would not explain the findings on amyloid PET. Case 1 initially presented with basal ganglia hemorrhage arguing against a diagnosis of CAA. However, the lobar location of the recurrent ICH and microbleeds in addition to the findings on amyloid PET are supportive of a diagnosis of CAA.

Transmissibility of β-amyloid was described in experimental animal models and in humans following tissue transferal in patients treated with cadaveric pituitary growth hormone or undergoing dura mater transplantation[7–9]. Reports of amyloid transmission through neurosurgical procedures without tissue transplants are rare[9,10]. Our cases however may support this route of transmission as no human nor cadaveric materials were used.

We believe that in patients presenting with clinical symptoms suggestive of CAA at relatively young age and a history of neurosurgery, (transmissible) CAA should be a differential diagnosis. Since histopathological evidence is often not obtainable we suggest amyloid PET as important diagnostic tool in these patients, as it is very well cross-validated with anatomopathological amyloid burden[13–15]. It may be considered if CSF analysis of β-amyloid may be equally suitable, but as we did not have CSF samples available, we could not address this question.

The prevalence of amyloid transmission following neurosurgery is unknown and also the pathophysiological mechanism involved remains poorly understood. Since there is no evidence in literature derived from larger/representative cohorts of subjects who underwent neurosurgery during childhood owing a higher risk of developing CAA as compared to subjects without previous neurosurgery, our hypothesis could be considered speculative. However the existing numbers of cases should urge clinicians to obtain more data to determine the magnitude of transmissible amyloid pathology in patients who underwent neurosurgery, probably at young age. To gain more insights in the prevalence of this condition epidemiological or case-control studies are required. However, histological conclusive evidence to support the diagnosis of CAA will not be possible since a tissue

diagnosis will not be feasible. Amyloid PET may therefore provide an important alternative diagnostic tool in these studies.

CONCLUSION

The clinical presentations of these four cases suggest that non-hereditary CAA is not limited to elderly patients, but may present at younger age in patients with a history of neurosurgery. We suggest amyloid PET as a valuable non-invasive technique to assess amyloid status in the absence of histopathological proof to provide patients with the most likely diagnosis and to explore the prevalence of this rather poorly understood disorder in larger epidemiological studies.

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Not applicable.

Statement of Ethics

The study was approved by the local ethics committee and we obtained written informed consent for publication from all individuals (or relatives).

Disclosure of conflict of interest and funding

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Contributors

LM, KVL and RL designed the study concept. JD and RL were responsible for patient selection, RV acquired data of healthy volunteers. LM, DVW and KVL were responsible for the image processing and analysis. All authors contributed to the interpretation of the data. LM and RL drafted the manuscript, DVW, RV, JD en KVL critically revised the intellectual content of the manuscript.

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Figure legends

Fig. 1: **A:** Non-contrast head CT of case 1: first spontaneous nontraumatic intracerebral hemorrhage (ICH). **B:** Non-contrast head CT of case 1: second ICH. **C:** Gradient echo MRI of case 2: superficial siderosis. **D:** T2-FLAIR (fluid attenuation recovery) MRI of case 2: white matter hyperintensities. **E:** Non-contrast head CT of case 3: first ICH. **F:** Non-contrast head CT of case 3: third ICH. **G:** Gradient echo MRI of case 4: superficial siderosis. **H:** T2-FLAIR of case 4: white matter hyperintensities.

Fig. 2. **A-D:** Rendered statistical parametric maps of the 4 individual patients SUVR ^{11}C-PiB-PET (using pons as reference region) to 19 amyloid-negative healthy volunteers. Significant clusters are shown in yellow-red ($p_{height,FWE\text{-}corrected} < 0.05$, extent threshold > 50 voxels (2x2x2mm)). Top row: superior and inferior view, second row: anterior and posterior view, third row: medial view of left hemisphere, medial view of right hemisphere, fourth row: lateral view of right hemisphere, lateral view of left hemisphere. **A:** case 1, $SUVR_{maximum\ voxel}$ = 1.26 (vs 0.53 in healthy volunteers) **B:** case 2, $SUVR_{maximum\ voxel}$ = 1.43 (vs 0.59 in healthy volunteers) **C:** case 3, $SUVR_{maximum\ voxel}$ = 1.21 (vs 0.64 in healthy volunteers) **D:** case 4, $SUVR_{maximum\ voxel}$ = 1.19 (vs 0.49 in healthy volunteers). $SUVR_{maximum\ voxel}$ represents the intensity value (in SUVR) at the most significant voxel.

Table legends

Table 1: Summary of neuroimaging findings of the four patients. ICH: intracerebral hemorrhage; (number) = amount of ICHs. *: Fazekas scale; deep white matter component.