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Amyloid Imaging with AV45 (^{18}F-florbetapir) in a Cognitively Normal AβPP Duplication Carrier

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Abstract. We report the case of a 62-year-old asymptomatic carrier of *AβPP* gene duplication. He was investigated by MRI and the amyloid ligand ^{18}F-AV45, and compared to Alzheimer's disease patients ($n = 11$) and healthy controls ($n = 11$). The neuropsychological examination was normal. Cortical thickness and AV45 retention were comparable to Alzheimer's disease patients. *AβPP* duplication was diagnosed because cerebral amyloid angiopathy and Alzheimer's disease pathology were found on the neuropathological examination of his youngest brother, who died at 42 from intracerebral hemorrhage. This is the first description of a pre-symptomatic *AβPP* duplication carrier over 60, despite widespread cerebral amyloid angiopathy, "Alzheimer's like" atrophy, and amyloid deposition.

Keywords: *AβPP* duplication, Alzheimer's disease, amyloid, AV45 PET, cerebral amyloid angiopathy, genetics, MRI

INTRODUCTION

Mutations in the gene encoding the amyloid-β protein precursor (*AβPP*) have been found to cause autosomal dominant amyloid-β (Aβ)-related cerebral amyloid angiopathy (CAA) and early onset

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Alzheimer's disease (EOAD), by increased production and deposition of amyloid proteins [1]. Duplications of *AβPP* remain rare in autosomal dominant CAA, exceptional in EOAD without CAA [2, 3], and unknown in sporadic forms of CAA [4]. Patients with *AβPP* duplication may present with different phenotypes such as EOAD, intracerebral hemorrhage (ICH), Lewy body dementia (LBD), or seizures [2, 3, 5–10]. Remes et al. have shown that Pittsburgh Compound B (^{11}C-PiB) Position emission tomography (PET) examination is a useful tool for detecting *in vivo* amyloid accumulation in patients with *AβPP* gene duplication [11].

Here we report the case of a man with CAA due to *AβPP* duplication, who remained asymptomatic at 62 years of age. He underwent a multimodal imaging assessment including amyloid imaging with the novel AV45 ligand. His youngest brother died from an ICH at age 42. A neuropathological examination was performed.

CASE STUDY

II.1, a 62 year-old man (level of education = 11), contacted our team regarding his familial history.

One of his brothers (II.2) and his father (I.1) both died at the age of 54 from ICH. Cognitive decline was diagnosed respectively one year and two years before their deaths (Fig. 1).

In addition, his youngest brother II.4 (41 years old, level of education = 11), was admitted to our department for an ICH related to CAA diagnosed on routine MRI scan according to the Boston criteria [12]. Four months after ICH, II.4's Mini Mental State Examination score was 27/30 and memory functions were normal; only executive impairment was observed (Table 1). II.4 developed seizures and recurrent brain hemorrhages and died at age 42. The microscopic brain examination postmortem found severe CAA associated with amyloid plaques localized in the neocortices and Ammon's horn. A few neurofibrillary tangles, stained by anti-tau antibodies, were seen in the frontal cortex. Immunohistochemistry revealed that vessel deposits and plaques were stained by anti-Aβ_{40} and anti-Aβ_{42} antibodies (Fig. 2). These features confirmed Aβ-related CAA together with topographically restricted Alzheimer-type lesions [13]. Genetic testing was performed according to the possible familial CAA history. No mutations were found in the *AβPP* gene. Then a quantitative multiplex PCR of short fluorescent fragments (QMPSF) was performed on *AβPP* and neighboring genes, and found a 9.7 ± 3.4 Mb-long duplication, including complete duplication of the *AβPP* gene.

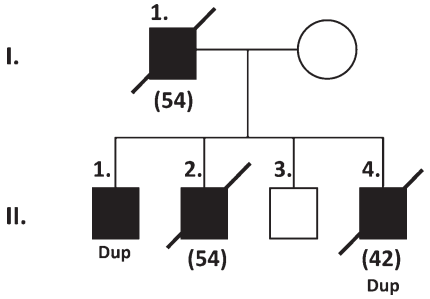

Fig. 1. Pedigree of family. Black filled squares indicate probands with CAA. Crossed out squares indicate deceased individuals. Age at death is indicated in brackets. Confirmed presence of *AβPP* duplication is indicated by "Dup".

II.1 had neither somatic nor neuropsychological complaints. His relatives did not report any cognitive or behavioral change. A first neuropsychological examination was normal (M0, Table 1). He underwent a first clinical MRI scan that showed numerous cortical and subcortical micro-bleeds on T2* images (BOMBS total score: 403 [14]) (Fig. 3A). Few white matter hyperintensities were observed on FLAIR images. QMPSF found the same *AβPP* gene duplication as for II.4. Therefore, II.1 appeared to be a clinically asymptomatic carrier of *AβPP* duplication.

Fourteen months later, he underwent a further comprehensive neuropsychological assessment, 3DT1 structural MRI scan (3T Philips) and florbetapir (^{18}F-AV45) PET (Truepoint Siemens) in a research study (NIMAD, EudraCT 2008-002727-87A, AFSSAPS A90605-58) approved by the Ethics Committee. PET images were acquired for 20 minutes, 50 minutes after injection of 385MBq of AV45 [15–17]. Eleven pre-demential AD patients [18] (mean age: 72.1 ± 4.8, level of education: 12.1 ± 2.8) and 11 healthy elderly controls (mean age: 68 ± 3.6, level of education: 13.5 ± 3.8) were recruited and underwent the same imaging protocol. II.1, the AD patients, and the control subjects gave their informed consent.

From 3DT1 MRI scans, cortical thickness was measured for all subjects using software previously described [19]. Mean values and standard deviations were obtained in all Brodmann's areas (BA) for the AD patients and the elderly control groups. II.1 was compared to each of them using Z-scores. PET images were whole-brain normalized using AVID's template (http://www.avidrp.com/) and smoothed ($10 \times 10 \times 10$ mm). Mean and standard deviation

Table 1
Neuropsychological assessment results for II.1 at M = 0 and M = 14, his brother II.4, the group of 11 sporadic pre-demential AD patients, and the group of 11 healthy controls

	II.4	II.1 M0	II.1 M14	AD patients ($n = 11$) Mean scores	HC ($n = 11$) Mean scores
Global functioning					
MMSE	27	NA	24	25	28.5
Memory functions					
Free recall					
RL/RI-16, sum of three free recall	**27 (−1.6)**	32 (0.5)	27 (−0.7)	**9.0 (−2.9)**	32.6 (0.5)
RL/RI-16, delayed free recall	**10 (−2.2)**	12 (−0.1)	10 (−0.8)	**3.1 (−3.4)**	12.9 (0.9)
Rey memory, score	20 (−0.5)	28 (1.2)	17 (−1.2)	**8.3 (−2.8)**	19.0 (−0.6)
Cued recall					
RL/RI-16, sum of three total recall	46	42	41	**24.1**	46.7
RL/RI-16, delayed total recall	16 (0.3)	15 (−0.9)	15 (−0.9)	**8.6 (−5.6)**	15.8 (0.4)
Recognition					
RL/RI-16, recognition score	16 (0.2)	**14 (−2.4)**	16 (0.4)	**13.3 (−4.9)**	16 (0.6)
Executive					
Mental processing speed					
TMT A, time	30 (0.9)	47 (0.3)	51 (0.2)	55 (−0.4)	33.5 (0.7)
Verbal working memory					
WAIS-III digit span, forward	6 (0.2)	5 (−0.9)	5 (−0.9)	5.5 (−0.4)	5.5 (−0.4)
WAIS-III digit span, backward	5 (0.6)	4 (−0.5)	3 (−1.4)	3.8 (−0.4)	4.5 (0.1)
Initiation					
Verbal fluency, letter (P)	22 (0.3)	17 (−0.4)	17 (−0.4)	21.2 (0.1)	22.8 (0.3)
Verbal fluency, Animal category	**15 (−2.4)**	17 (−1.3)	**16 (−1.5)**	22.5 (−0.7)	35.5 (0.8)
Planification					
Rey copy	34 (1.1)	36 (2.2)	35 (1.7)	34.4 (1.3)	34.7 (1.5)
Flexibility					
TMT B, time	133 (−1.3)	120 (0.3)	199 (−0.7)	161.5 (−0.6)	87.4 (0.7)
TMT B, errors	**1 (−1.5)**	1 (−0.6)	1 (−0.6)	0.6 (−0.1)	0.4 (0)
TMT, subtraction score (B errors – A errors)	**1 (−1.5)**	1 (−0.8)	1 (−0.8)	0.6 (−0.6)	0.4 (−0.1)
Attention					
TMT A, errors	0 (0.3)	0 (0.3)	0 (0.3)	0 (0.2)	0 (0.2)

Abbreviations : M0, Month 0; M14, Month 14; AD, Alzheimer's disease; HC, Healthy controls; NA, Not Available; MMSE, Mini Mental State Examination; RL/RI-16, Free recall/Cued Recall-16, a French equivalent of the Free and Cued Selective Reminding test; TMT, Trail Making Test; WAIS-III, Wechsler Adult Intelligence Scale-III. () indicates standard deviation according to the published norms of the test. Bold values indicate scores below −1.5 standard deviations according to the norms of the tests.

images were obtained for both the AD patients and the control groups, using Statistical Parametric Mapping software (SPM8). II.1 was compared to both groups using Z-scores. All Z-scores below −2 or above 2 were considered as significant.

II.1 remained complaint-free and his relatives did not notice any cognitive or behavioral change. The second cognitive evaluation was normal despite a slight decrease on raw scores (M14, Table 1).

Regarding the structural imaging data, II.1's cortex was thinner than those of controls in numerous locations: right orbito-frontal regions [BA11 (Z = −2.1), BA12 (Z = −2.0)], temporal lobe bilaterally [right: BA34 (Z = −4.9), BA27 (Z = −4.5), BA28 (Z = −3.4), BA20 (Z = −3.0), BA36 (Z = −2.5), BA35 (Z = −2.5); left: BA20 (Z = −2.1), BA36 (Z = −2.1), BA48 (Z = −2.1)], right posterior dorsal cingular cortex [BA31 (Z = −2.1)], and somatosensorial cortex bilaterally [right BA02 (Z = −2.2); left BA05 (Z = −2.3)] (Fig. 3B). We found no thickness difference between II.1 and the AD group.

On visual assessment, AV45 uptake was marked in II.1's cortex (Fig. 3C). Compared to the controls, II.1 had widespread higher cortical retention in the frontal lobes (right: Z = 2.2; left: Z = 3.6), the parietal lobes (right: Z = 5.2; left: Z = 5), the temporal lobes (right: Z = 4.6; left: Z = 6.4), the occipital lobes (right: Z = 3.3; left: Z = 5.4), the anterior cingulate (right: Z = 2.6; left: Z = 3.1), the precuneus/posterior cingulate (right: Z = 6.8; left: Z = 10.3), the striatum (right: Z = 2.2; left: Z = 2.5), the cerebellum (right: Z = 3.1; left: Z = 3.8) (Fig. 3D). No Z-score below −2 was found. When compared to the AD group, II.1 showed isolated increased uptake in the right frontal lobe (Z = 2.7). No Z-score below −2 was observed.

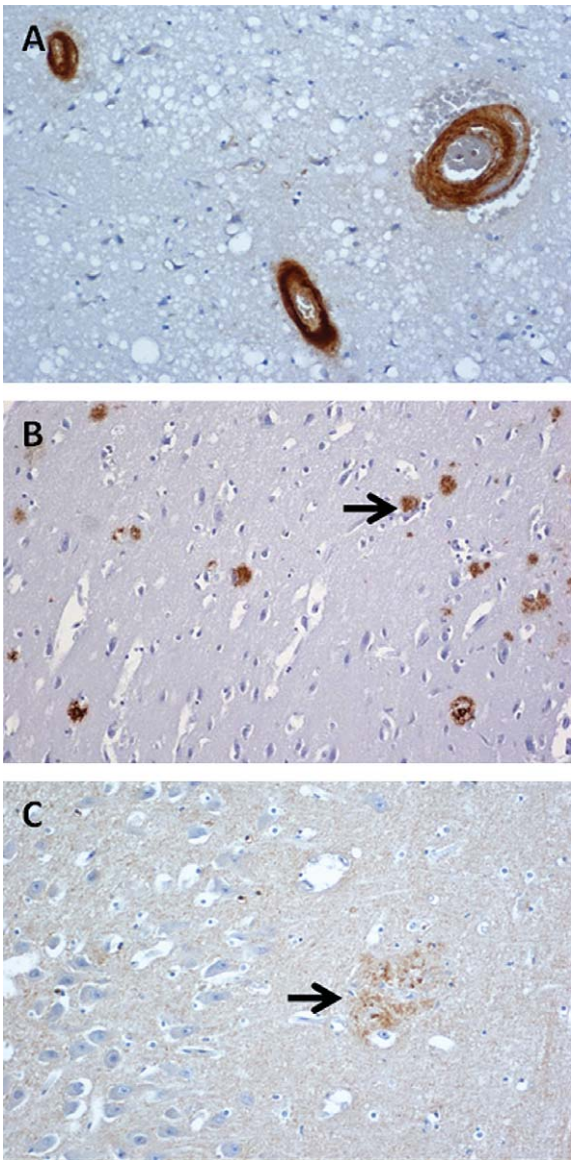

Fig. 2. Brain examination of II.4. A) Vessel walls stained by anti-$A\beta_{40}$ antibody (frontal cortex, ×200); B) Plaques (black arrow) stained by anti-$A\beta_{40}$ antibody (temporal cortex, ×200); C) Plaques (black arrow) stained by anti-tau antibody (hippocampus, ×200).

Twelve months after this assessment, II.1 developed complex bilateral visual seizures sometimes secondarily generalized. At this time, he still had no neuropsychological complaint and was rigorously autonomous in his daily life.

DISCUSSION

We report the case of an *AβPP* duplication carrier who remained asymptomatic after the age of 60.

AβPP duplication was initially reported in five families and all the probands showed either AD dementia or dementia associated with ICH before the age of 60 [5, 6]. In these families, the neuropathological examination was the same as in our case II.4. Guyant-Marechal et al. have described different phenotypes of *AβPP* duplication. These included AD, ICH with dementia, seizures with microbleeds, and LBD [8]. Sleegers et al. described a four-generation pedigree with diagnosis of AD, AD and CAA, or LBD [7]. Kasuga et al. investigated two patients with dementia associated with CAA and AD [3]. McNaughton et al. described 5 patients with cognitive impairment and seizures [9]. To the best of our knowledge, II.1 is the first asymptomatic *AβPP* duplication carrier above the age of 60 to be described. The first clinical symptoms in genetic forms of AD usually occur early in the lifetime. Though this absence of symptoms in II.1 could be explained by cognitive reserve, it is hardly plausible since he had a low level of education.

On MRI examination, II.1 showed a fronto-temporo-parietal atrophy compared to a group of controls, and did not differ from sporadic pre-demential AD patients. The method used for cortical thickness measurement appeared to be efficient to discriminate AD subjects from controls [19], suggesting II.1 could be a presymptomatic AD patient. II.1 presented no cardiovascular risk factor as potential cause of brain hemorrhages. Moreover, localizations were typical for CAA.

Amyloid imaging of 2 *AβPP* gene duplication carriers has been performed in only one study using PiB, showing an increased PiB retention in the striatum and in the posterior cingulate for both patients [11]. This striatal retention has also been described in other genetic causes of AD [20, 21]. In our study, we found a higher striatal and posterior cingulate/precuneus AV45 uptake compared to the healthy controls but no difference was found compared to the AD patients group in these regions. In our case, the pattern of amyloid deposition did not differ from classic AD.

Previous studies have shown that *in vivo* amyloid PET is a powerful tool to assess amyloid location, not only in AD [22] but also in sporadic CAA. Johnson et al. suggested that a negative PiB was incompatible with a CAA diagnosis [12, 23]. The binding distribution seems to be different between AD and CAA patients, with higher lobar neocortical PiB uptake in the occipital lobes of patients with CAA [24]. In a recent study, Yates et al. showed that healthy asymptomatic controls with lobar microbleeds had higher PiB uptake than controls without micro-hemorrhage [25]. Our study is the first so far to investigate an

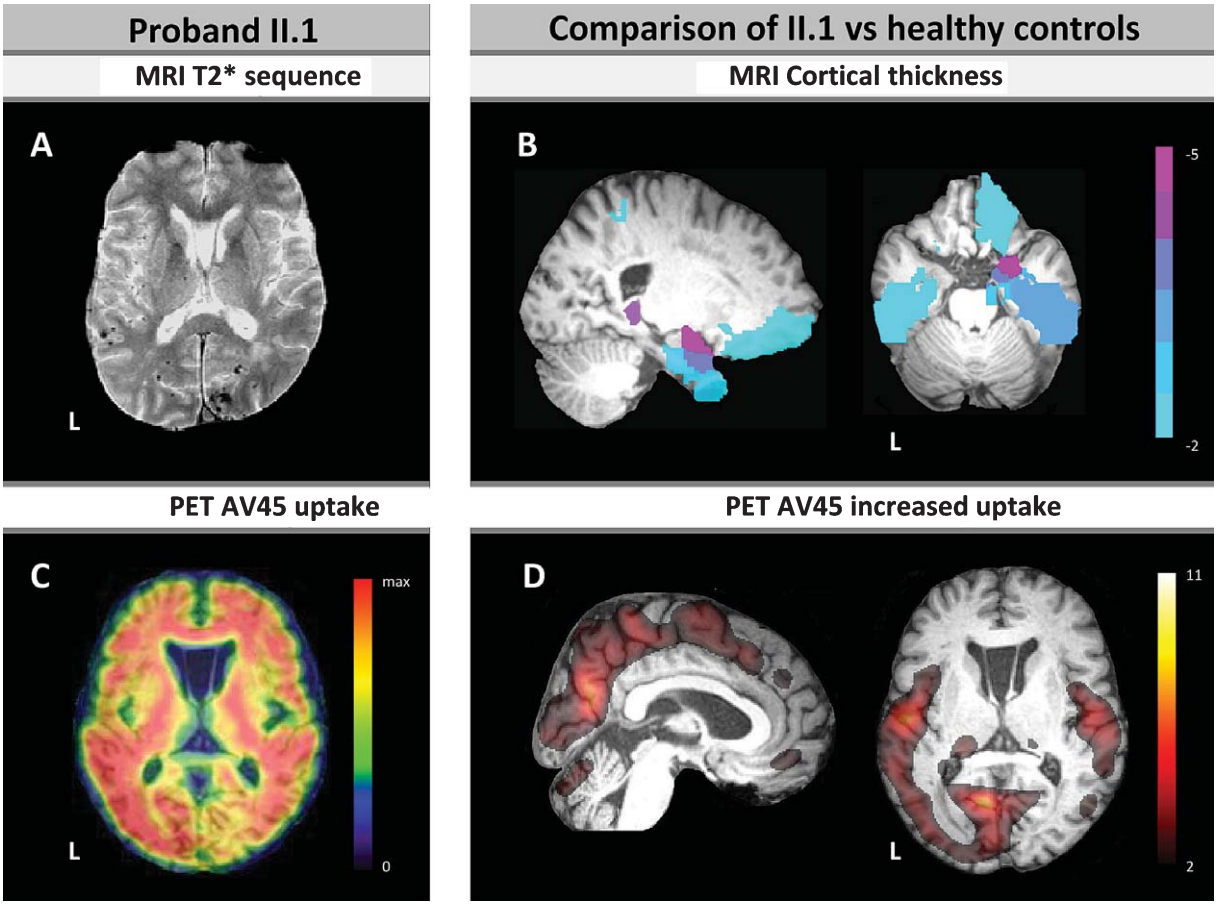

Fig. 3. MRI and AV45-PET imaging. II.1's MRI T2* sequence (A) and AV45–PETscan examination (C). Comparison between II.1 and elderly healthy controls ($n = 11$) for cortical thickness (B) and AV45 uptake (D). II.1's cortical atrophy below −2 standard deviations and his amyloid higher retention above 2 standard deviations are shown. L = Left side.

asymptomatic patient with CAA/AD using the novel AV45 amyloid ligand. This ligand seems to have a good affinity for the amyloid protein as reported in a recent study assessing AD patients before their death with neuropathological confirmation [17]. We report here the case of AV45 uptake in CAA patient.

It has been shown that typical CAA pathology is often found in AD [26]. We can therefore wonder whether amyloid binding studies in AD are specific to diffuse Aβ, plaques, or vascular Aβ. In the case of II.1, AV45 probably bounds both vascular Aβ and plaques, and both $A\beta_{40}$ and $A\beta_{42}$. In an *in vitro* study, Lockhart et al. demonstrated that PiB bound both diffuse Aβ deposits and CAA [27]. They concluded on a low PiB specificity for AD pathology, for both diagnosis and monitoring of progression. Combining amyloid imaging and improved MRI sequences may help to discriminate the amyloid pathologies [28].

Our case illustrates morphological and molecular changes in an asymptomatic patient. Recent studies have shown that, in AD, amyloid deposition starts well before the first symptoms [29, 30] and remains stable throughout the disease [31]. The use of AV45 imaging therefore seems to be a useful tool for *in-vivo* detection of amyloid accumulation in the earliest stages of the disease.

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