β-Amyloid may accumulate in the human brain after focal bacterial infection: a ^{18}F-flutemetamol positron emission tomography study

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Running title: β-Amyloid in human brain after bacterial brain abscess

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Abbreviations used: ADC: apparent diffusion coefficient, CT: computed tomography, DWI: diffusion-weighted imaging, MRI: magnetic resonance imaging, PET: positron emission tomography

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β-Amyloid may accumulate in the human brain after focal bacterial infection: a ^{18}F-flutemetamol positron emission tomography study

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Background and purpose: β-Amyloid formation has been suggested to form part of the brain's response to bacterial infection. This hypothesis has been based on experimental animal studies and autopsy studies in humans. We asked if β-amyloid accumulates locally around a bacterial brain abscess in living human patients. Further, because brain abscess patients may suffer from chronic cognitive symptoms after abscess treatment, we also asked if a brain abscess precipitates accumulation of β-amyloid in the neocortex in a manner that could explain abscess-related cognitive complaints.

Methods: In a prospective study, we investigated 17 brain abscess patients (age 24-72 years) with ^{18}F-flutemetamol positron emission tomography on one occasion 1-10 months after brain abscess treatment to visualize β-amyloid accumulation.

Results: ^{18}F-flutemetamol uptake was reduced in the edematous brain tissue that surrounded the abscess remains. On this background of reduced ^{18}F-flutemetamol signal, three out of 17 patients showed a distinctly increased ^{18}F-flutemetamol uptake in the tissue immediately surrounding the abscess remains, suggesting accumulation of β-amyloid. These three patients underwent ^{18}F-flutemetamol positron emission tomography significantly earlier after neurosurgical treatment (p=0.042), and they had larger abscesses (p=0.027) than the rest of the patients. All 17 patients suffered from mental fatigue or some subjective cognitive symptom, such as attention difficulties or memory problems, but in none of the patients was there an increase in neocortical ^{18}F-flutemetamol signal.

Conclusion: β-Amyloid may accumulate locally around the abscess remains in some patients with brain abscess.

Keywords: β-amyloid, brain abscess, ^{18}F-flutemetamol-positron emission tomography

Introduction

β-Amyloid accumulation in the neocortex is an important feature of Alzheimer's disease pathology.[1-3] A physiological function of β-amyloid has been difficult to establish, but recent studies have pointed to an antimicrobial effect of the peptide, which has led to the concept of β-amyloid formation as part of the brain's antimicrobial response.[4] A link between Alzheimer's disease and bacterial infection has been suspected from post mortem findings in brains of patients with the disease.[5-7] Further, β-amyloid accumulation has been seen in transgenic mice that were highly prone to Alzheimer-like neuropathology, when their brains were inoculated with bacteria[8] or herpes virus.[9] However, so far β-amyloid accumulation after bacterial brain infection has not been addressed in living human patients.

A focal bacterial brain infection may lead to the formation of an abscess, a cavity within the brain parenchyma filled with pus.[10] The pus contains multiple neuroactive compounds at toxic levels, e.g. ammonia, glutamate, trace metals, and cytokines.[11-14] Neurologic symptoms depend on the localization of the abscess in the brain, and may include motor and sensory deficits and seizures.[10] Longstanding cognitive dysfunction after brain abscess has also been reported.[15]

Because of the possible role of β-amyloid in the brain's antibacterial response[4,8] and its role in the cognitive dysfunction of Alzheimer's disease,[2,3] we investigated whether β-amyloid had accumulated locally around the brain abscess and/or globally in the neocortex in patients who experienced cognitive symptoms after brain abscess. To visualize β-amyloid accumulation we performed ^{18}F-flutemetamol positron emission tomography (PET), which is increasingly being used to detect accumulation of β-amyloid in the brains of Alzheimer's disease patients.[16-18]

Methods

Patients and treatment

The study was approved by The Regional Committees for Medical and Health Research Ethics of Norway (Approval # 2018/1081 and 256/2014). Patients were recruited consecutively from February 2018 to January 2020 from the Department of Neurosurgery, Oslo University Hospital, Oslo, Norway. Nineteen patients underwent treatment for bacterial brain abscess in the study period. Seventeen patients agreed to participate in the study and gave informed, written consent. None of the patients had shown signs of cognitive decline prior to their brain abscess, and all patients agreed personally to take part in the study. The

study conformed with the Declaration of Helsinki.[19] The included patients consisted of seven women and ten men 24-72 years old. Fifteen patients underwent neurosurgical evacuation of the brain abscess pus followed by antibiotic treatment. Two patients, who had brain abscesses subsequent to endocarditis, received antibiotic treatment only.

Pus evacuation was performed as a minimally invasive neurosurgical procedure. Under general anesthesia a small skin incision was made, a burr hole <1 cm in diameter was made in the cranium, followed by stereotactic frameless puncture of the abscess and aspiration of the pus through a cannula 2 mm in diameter. The abscess cavity was rinsed once with saline before the skin incision was closed. The abscess capsule was not removed. Surgery was followed by intravenous, and later oral, antibiotic treatment for 4-6 weeks. MRI was performed every 14 days with diffusion-weighted images (DWI) and apparent diffusion coefficient (ADC) mapping. Antibiotic treatment was discontinued when the patients showed good clinical response with respect to the infection and MRI indicated successful treatment of the abscess (reduced size, decreased signal intensity on DWI combined with increased ADC values).

All brain abscess pus samples were transported to the Oslo University Hospital microbiology laboratory immediately after aspiration and analyzed by light microscopy following Gram and acridine orange staining. Samples underwent culture (aerobic and anaerobic, *Actinomyces* and *Nocardia* culture), and they underwent direct 16S ribosomal DNA polymerase chain reaction amplification and sequencing. Blood culture (in the case of endocarditis) was performed using the BD BACTEC^{TM} system (Becton, Dickinson & Co, Franklin Lakes, New Jersey, USA) followed by matrix-assisted laser desorption/ionization-time of flight (Maldi-TOF) mass spectrometry.

MRI and ^{18}F-flutemetamol-PET

All patients underwent 1.5 Tesla contrast-enhanced MRI with DWI and ADC mapping prior to neurosurgical treatment to ascertain the presence of an abscess, its location within the brain, the volume of the abscess cavity, and whether the abscess affected the neocortex. Abscess volume was calculated with the ellipsoid formula: $4/3 \times \pi \times r_x \times r_y \times r_z$. Neocortical involvement was defined as the abscess wall being within 4 mm of neocortical grey matter; in all cases this proximity entailed the neocortex being involved in the edema that surrounded the abscess.

^{18}F-flutemetamol-PET was performed on one occasion 1-10 months after neurosurgery to shed light on the cognitive symptoms of the patients as they were presented on follow-up to a neuropsychologist or neurologist. Also, the timing of the PET investigation was influenced by the feasibility of conducting the investigation (e.g. availability of ^{18}F-flutemetamol or the PET scanner itself). Patients were given ^{18}F-flutemetamol, 188-198 MBq, as an intravenous injection, and PET was performed after 80-100 minutes. PET-CT images were acquired on three different scanners (GE Discovery MI, GE Discovery 690, or Siemens Biograph mCT). A low-dose CT scan was performed for attenuation correction and anatomical information followed by PET acquisition for 20 minutes. Different reconstruction algorithms, matrix sizes and slice thicknesses were applied according to each scanner. The PET images were visually classified as positive or negative with Siemens SyngoVia (VB30, Siemens Healthineers, Erlangen, Germany) by three nuclear medicine physicians/radiologists with experience in ^{18}F-flutemetamol PET classifications (M-ER, EGM, and JPC). ^{18}F-flutemetamol uptake was assessed according to the validated image reader program.[20] In addition, the neocortical ^{18}F-flutemetamol signal was semi-quantified automatically with Cortex ID suite (AW server, GE Medical Systems), using the pons as reference.[16] In the absence of pathological β-amyloid deposition, the neocortical ^{18}F-flutemetamol signal should be <62% of the pons signal according to a study in elderly patients.[16]

The ^{18}F-flutemetamol signal in the brain tissue surrounding the abscess remains was evaluated visually only. For this evaluation, PET images were compared to previous MRIs and/or contrast-enhanced CTs to visualize the abscess remains, and in some cases PET was co-registered with MRI. MRI was not done on the same day as PET; the two imaging modalities were performed 2 days to 9 months apart.

Data presentation and statistics

Data are given as individual values in the tables. Neocortical ^{18}F-flutemetamol-PET data are given as mean ± SD values, and correlations are given as Pearson's coefficients. Group differences were analyzed with the Mann-Whitney U test, Student's *t*-test, or the Fisher exact test, as appropriate.

Results

Patient characteristics and MRI findings

Duration of brain abscess symptoms (headache, motor symptoms, speech problems, visual difficulties, etc.) prior to surgery ranged from 2 days to 3 months (Table 1). In 11 out of the 17 patients a condition predisposing to the brain abscess was identified, including middle ear infection, dental infection, endocarditis, atrial septal defect, craniofacial resection for paranasal cancer, and retained shrapnel in the brain after penetrating head injury. In all patients a microbial diagnosis was made (Table 1). The abscesses were located in any of the cerebral lobes or in the basal ganglia. Volumes ranged from <0.3 to 42 cm^3. All abscesses affected mainly white matter, and 13 involved the overlying neocortex in the sense that the abscess wall was within 4 mm of neocortical grey matter, as could be seen on MRI prior to surgery and during the first 1-2 months after surgery (Fig. 1a-c).

^{18}F-flutemetamol-PET findings in the brain tissue surrounding the abscess remains

Patients underwent ^{18}F-flutemetamol PET 1-10 months after initial treatment for brain abscess to shed light on their cognitive symptoms. All patients complained of some degree of mental fatigability or cognitive dysfunction, such as attention difficulties or memory problems (individual data not given).

^{18}F-Flutemetamol uptake was reduced in the edematous brain tissue that surrounded the abscess remains (Fig. 1d-f). On this background of reduced ^{18}F-flutemetamol signal, three patients showed a distinctly increased ^{18}F-flutemetamol uptake in the tissue immediately surrounding the abscess remains (Fig. 1d-f; Table 2). In the 14 remaining patients PET did not show increased ^{18}F-flutemetamol signal, including two patients who did not undergo pus evacuation. The three patients with ^{18}F-flutemetamol uptake around the abscess remains underwent PET at a statistically earlier time point than the rest of the patients ($p=0.042$; Mann-Whitney U test), and their abscesses were significantly larger ($p=0.027$). The three ^{18}F-flutemetamol-positive patients also had the shortest interval between their PET investigation and MRI ($p=0.013$), suggesting that this interval could be of importance for the detection of a ^{18}F-flutemetamol signal around the abscess remains. Other parameters, such as microbial findings, length of symptoms prior to surgery, or time from surgery to ^{18}F-flutemetamol PET, did not distinguish these three patients from the rest of the group. The three ^{18}F-flutemetamol-positive patients underwent PET investigation on one each of three different

PET scanners used (see Methods). In none of the 17 patients did we observe ^{18}F-flutemetamol signal corresponding to the track of the cannula used to evacuate the pus.

^{18}F-flutemetamol-PET findings in the neocortex

None of the 17 patients had ^{18}F-flutemetamol signal in the neocortex that indicated pathological accumulation of β-amyloid according to validated visual evaluation.[20] Also, when the ^{18}F-flutemetamol-PET images were semi-quantified with Cortex ID suite, were results deemed normal, meaning that the signal from neocortex was <62% of that from pons (Table 2).[16] The neocortical ^{18}F-flutemetamol signal was not statistically different if the abscess involved the neocortex or not (46±4% vs. 48±5%; p=0.55; N=13 and 5 abscesses, respectively). Nor was there a correlation between neocortical ^{18}F-flutemetamol signal on the one hand and time from abscess treatment until PET investigation (r=0.23; p=0.4), abscess size (r=0.20; p=0.4), or age of the patient (r= -0.16; p=0.6) on the other.

Discussion

β-Amyloid may accumulate locally around a brain abscess

Our findings show that β-amyloid may accumulate locally around the remains of a bacterial brain abscess. In three out of 17 patients there was a distinct signal from the β-amyloid ligand ^{18}F-flutemetamol in the tissue immediately surrounding the brain abscess remains, suggesting accumulation of β-amyloid. Animal studies have indicated that β-amyloid formation is part of the brain's antimicrobial response.[8,9] The present finding of β-amyloid accumulation around the remains of bacterial brain abscesses provides support for the notion that β-amyloid formation is part of the antimicrobial response also in the human brain. We did, however, fail to detect local β-amyloid accumulation in 14 out of 17 patients. Several factors may have contributed to this. First, a time factor may have been important: the three patients with increased ^{18}F-flutemetamol signal in the tissue surrounding the abscess remains underwent PET significantly earlier than the rest of the patients This may suggest that early investigation could have detected more cases with increased perilesional ^{18}F-flutemetamol signal. Second, the size of the abscesses may have played a role: the abscesses that caused increased ^{18}F-flutemetamol signal were among the largest in the sample. The relatively poor spatial resolution of PET images makes larger structures easier to detect than smaller ones (partial

volume effect). Therefore, we may have missed increased ^{18}F-flutemetamol signal around some of the smaller abscess remains. Third, ^{18}F-flutemetamol binds to the fibrillary plaque form of β-amyloid,[21] whereas the antibacterial activity of β-amyloid depends on its soluble oligomeric, non-fibrillary form.[8] Therefore, the lack of ^{18}F-flutemetamol signal in most of the patients in the present study may have been due to removal of soluble oligomeric β-amyloid before it reached the fibrillary stage. β-Amyloid fibrillation probably occurs on a time scale of minutes,[22] which would allow time for soluble oligomeric β-amyloid to disperse in the extracellular fluid of the brain. However, whether the increased ^{18}F-flutemetamol signal that we saw in three patients is stable over time remains a question for longitudinal studies.

Some sources of error may have contributed to the increased ^{18}F-flutemetamol signal in the three patients that were deemed to have β-amyloid accumulation around their abscess remains. First, the increased ^{18}F-flutemetamol signal could have been due to the white matter being compressed around the abscess remains, leading to a higher density of binding sites for ^{18}F-flutemetamol. Second, increased perfusion around the abscess remains could have led to greater delivery of ^{18}F-flutemetamol to these regions. Third, it is possible that the collapse of the abscess cavity during surgical evacuation of the pus could have led to the tissue surrounding the abscess being stimulated, mechanically or otherwise, to produce β-amyloid.

β-Amyloid accumulation does not explain early cognitive symptoms after brain abscess

Brain abscess patients have been shown to suffer from cognitive difficulties years after treatment.[15] Therefore, we investigated whether the brain infection in our patients had caused neocortical β-amyloid accumulation, similar to what is seen in Alzheimer's disease.[2,3] Indirect evidence in favor of β-amyloid accumulation (in the form of reduced cerebrospinal fluid levels of β-amyloid) during bacterial meningitis was reported in one study.[23] Further, the innate immune response, which is highly active in a bacterial brain infection,[10,14] is believed to be an important aspect of Alzheimer's disease development.[24] The patients in the present study complained of cognitive symptoms or mental fatigue. Even so, we did not detect neocortical β-amyloid accumulation in our patients as evaluated with ^{18}F-flutemetamol PET, suggesting that cognitive symptoms in the first months following treatment are caused by factors other than β-amyloid accumulation, such as neurotoxic substances from pus, inflammation, perilesional edema and the destruction of brain tissue inherent in abscess formation.[10-14]

Longer term studies of brain abscess patients are needed to see whether β-amyloid accumulation may occur at a later stage than evaluated in the present report.

Limitations

A limitation of the present study was the time lag between ^{18}F-flutemetamol PET imaging and morphologic brain imaging (see Methods section), which could make it difficult to correctly identify the localization of the ^{18}F-flutemetamol signal. This is so because the abscess capsule may shrink with time, and the edema may resolve, causing morphological changes. Another potential limitation was the classification of ^{18}F-flutemetamol PET findings in the neocortex as 'normal': ^{18}F-flutemetamol PET normality criteria are based on findings in elderly, non-demented subjects;[16,20] it is not known whether younger persons, of whom there were several in the present study, have a different threshold for pathologic ^{18}F-flutemetamol uptake. Lastly, we did not investigate the genetic susceptibility to Alzheimer pathology in our patients, a factor that theoretically could be of importance for the tendency for β-amyloid to accumulate in bacterially infected brain tissue.[25,26]

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Data availability statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

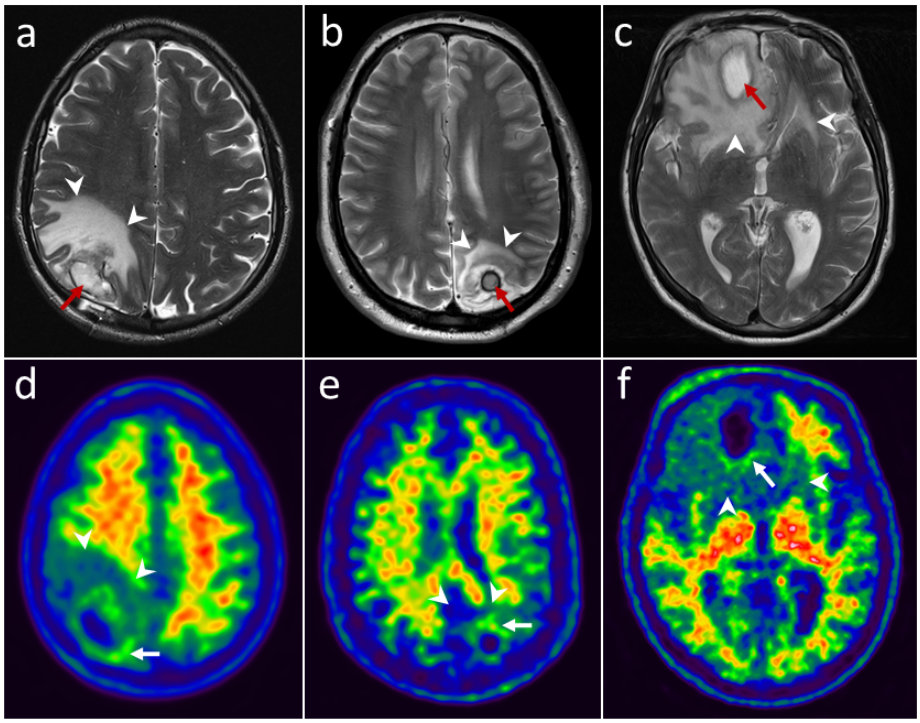

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Table 1. Clinical data, abscess localization, and microbiological results in brain abscess patients.

Patient sex and age (yrs)	Pre-surgery symptoms and their duration	Abscess localization	Microbial identification
M60†	Ataxia L. leg, 4 days	R. frontal lobe	*Staph. aureus* *E. cloacae*
M24	Headache, fever, 1 week	L. occipital lobe	*S. intermedius* *G. morbillorum* *H. parainfluenzae*
F32	Speech problems, 7 days	L. temporal lobe	*A. aphrophilus*
M64	Headache, seizures, 2 days	L. frontal lobe	*S. intermedius*
M27	Visual dysfunction, seizure, 2-3 weeks	R. parieto-occipital	*S.intermedius*
M70‡	Visual dysfunction, 1 month	R. occipital lobe	*S. oralis*
F59	Headache, quadrant anopsia, 2 days	R. occipital lobe	*S. intermedius*
M25	Headache, nausea, neck stiffness, 5 days	R. frontal lobe	*C. amalonaticus*
F70	Fatigue, weakness R. leg, 2 months	L. fronto-parietal	*S. intermedius*
M60†	Fever, fatigue, 1 month	L. striatum	*Staph. aureus* *E. cloacae*
M72	Weakness R. arm/leg, 6 days	L. temporal lobe + L. basal ganglia	*S. intermedius*
F54	Headache, nausea, photophobia, 14 days	L. temporo-occipital lobe	*S. intermedius*
F62	Fatigue, seizure, weakness R. side, 3 weeks	L. frontal lobe	*S. intermedius* *A. aphrophilus* *F. nucleatum*
F61	Somnolence, 5 days	Deep WM R. temporal lobe	*S. pneumoniae*
M48‡	Fever, endocarditis, 1 month	Both frontal and both occipital lobes	*Staph. aureus*
M68	Speech problems, 7 days	L. temporal lobe	*S. pneumoniae*
M58	Headache, fever, 3-4 days	R. striatum	*S. intermedius*
F43	Paresthesia L. side of body, headache, focal seizures, 3 months	R parietal lobe	*S. intermedius*

Seventeen brain abscess patients underwent pus evacuation and antibiotic treatment (N=15), or antibiotic treatment alone (N=2). The table gives the patients' sex (M: male, F: female) and age (years) at surgery †: This patient had a brain abscess in his left striatum, followed 5 months later by an abscess in his right frontal lobe and therefore appears twice in the table. ‡: These patients did not undergo pus evacuation, but received antibiotic treatment only. Abbreviations: L: left, R: right, *A: Aggregibacter, C: Citrobacter, E: Enterobacter, F: Fusobacterium, G: Gemella, H: Haemophilus, S*: *Streptococcus, Staph: Staphylococcus.*

Table 2. ^{18}F-flutemetamol PET results in brain abscess patients.

Patient sex and age (yrs)	Time from abscess surgery to PET	Abscess volume	^{18}F-flutemetamol around abscess?	Neocortical ^{18}F-flutemetamol signal (% of pons signal)
M60†	12 days	13 cm^3	Yes	50+
M24	1 month	36 cm^3	Yes	54+
F32	1.3 month	2.2 cm^3	No	43+
M64	1.3 month	0.62 cm^3	No	49+
M27	2 months	40 cm^3	Yes	42+
M70‡	2 months	2.6 cm^3	No	40+
F59	2 months	5.0 cm^3	No	46+
M25	2 months	0.99 cm^3	No	46-
F70	3 months	2.4 cm^3	No	44-
M60†	4.5 months	5,6 cm^3	No	50-
M72	5 months	6.6 cm^3	No	46+
F54	6 months	4.8 cm^3	No	49+
F62	6 months	6.8 cm^3	No	45+
F61	8 months	42 cm^3	No	46+
M48‡,§	8 months	9.7 cm^3	No	53+
M68	9 months	3. 5 cm^3	No	44-
M58	10 months	15 cm^3	No	56-
F43	10 months	12 cm^3	No	42+

Seventeen brain abscess patients underwent ^{18}F-flutemetamol PET to shed light on their subjective cognitive problems after brain abscess. The first column gives the sex (M: male, F: female) and age (years) at surgery. PET was done 1-10 months after initial treatment (second column). The third and

fourth columns give the volumes of the abscesses and whether there was an increased ^{18}F-flutemetamol signal in the tissue surrounding the abscess remains. The rightmost column shows neocortical ^{18}F-flutemetamol signal in percent of the signal from pons; all results were <62% of the pons signal, which is considered normal (Thurfjell et al., 2014). †: This patient had a brain abscess in his left striatum, followed 5 months later by an abscess in his right frontal lobe and therefore appears twice in the table. ‡: These patients did not undergo pus evacuation, but received antibiotic treatment only. §: This patient had 5 abscesses, one that was 9.7 cm^3 and four that were <0.3 cm^3.

+: abscess affected neocortex, meaning that the abscess was < 4mm from neocortex; -: abscess did not involve neocortex.