Functional neuroinflammatory- and serotonergic imaging in Alzheimer's disease
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CHAPTER THREE
COBALT AS AN INFLAMMATORY TRACER IN ALZHEIMER’S DISEASE
SUMMARY

Introduction: Inflammatory mechanisms contribute to the pathophysiology in senile dementia of the Alzheimer type (sDAT). Previous studies showed that $^{57}$Co SPECT is able to visualise inflammatory lesions, probably by means of the final common pathway of the Ca$^{2+}$-homeostasis disturbance in both neuronal degeneration and inflammation. The aim of this study was (1) to detect $^{57}$Co SPECT changes in sDAT patients, (2) correlate these findings with conventional neuroimaging techniques and neuropsychological testing (NPT), and (3) compare $^{57}$Co SPECT findings in sDAT patients with other types of dementia.

Patients and methods: Six patients suffering from probable sDAT were included and compared with 4 patients suffering from other types of dementia. All patients had a MRI-scan, NPT, $^{57}$Co and a $^{99m}$Tc-ECD SPECT scan. Perfusion SPECT images were semiquantitatively evaluated by comparison with an age-matched normal database while $^{57}$Co SPECT scans were assessed qualitatively.

Results and conclusions: MRI and $^{99m}$Tc-ECD SPECT scans yielded conclusive results as to the exclusion of other pathologies and confirmation of diagnosis. Using visual analysis, $^{57}$Co SPECT scans were not able to show any regional raised uptake, irrespective of the disorder, depth or extent of the perfusion defects, presence of atrophy on MRI, or the results of NPT.
INTRODUCTION

In most industrialised countries, senile dementia of the Alzheimer type (sDAT), a primary degenerative disease of the brain, either alone or in combination with other illnesses, accounts for about 70% of dementia cases. The typical course in sDAT is one of progressive decline with an average survival of 8 to 10 years. The most characteristic feature is progressive memory impairment, predominantly loss of short-term memory. However, other cognitive dysfunctions or behavioral symptoms, as well as changes in the neurological status (especially late sDAT) are important [1].

Pathophysiologically, sDAT is characterised by dense and neuritic amyloid plaques, cerebral intraneuronal neurofibrillary tangles (NFT), neuronal and synaptic loss and deficits in neurotransmitter functions [2]. However, over the last years, it has become clear that inflammatory mechanisms may contribute to the neurodegenerative process in sDAT. Indeed, epidemiological data from about 20 studies have shown the protective and progression-retarding effect of non-steroidal anti-inflammatory drugs (NSAIDs) which would reduce the prevalence by 50% of sDAT in people who regularly take these drugs for various reasons [3]. As such, Breitner et al. concluded from twin studies that the use of NSAIDs could delay the onset of sDAT by 5 to 7 years [4]. As for treatment, there is only one double-blind placebo-controlled clinical trial showing this same progression-retarding effect [5].

Visualising this inflammation with positron emission tomography (PET) or single photon emission computed tomography (SPECT) would be of interest, firstly for clarifying the underlying pathophysiology, secondly for selecting subgroups of patients that are more eligible for anti-inflammatory treatment and finally, for monitoring patients during trials with anti-inflammatory agents.

Both in vivo and in vitro experiments have shown that Ca\(^{2+}\) accumulates in the (ir)reversibly damaged nerve cell body and degenerating axons, this through a passive influx due to a shortage of ATP following ischemia, resulting in the disappearance of the membrane potential, and through neuronal and glial uptake by divalent cation-permeable kainate-activated non-NMDA glutamate receptor-operated channels in the membrane [6-11]. \(^{57}\)Co (SPECT) and \(^{55}\)Co (PET), both as Ca\(^{2+}\)-analogues, reflect Ca\(^{2+}\)-influx in ischaemically or neurotoxically damaged cerebral tissue. In this way, both \(^{57}\)Co SPECT and \(^{55}\)Co PET have been shown capable of visualising focal neurodegenerative changes, reactive gliosis, endangered brain tissue and/or ongoing neuronal tissue decay including inflammatory lesions in various brain diseases e.g. multiple sclerosis, trauma, tumours, and stroke [12-18]. Moreover, the time sequence of the \(^{55}\)Co-load seems to correlate well with cell death and glial proliferation in the ipsilateral thalamus following supratentorial ischaemic stroke in an experimental rat stroke model [19]. The visualisation of these inflammatory processes in sDAT can be expected to occur by means of the final common pathway of the Ca\(^{2+}\)-homeostasis-disturbance in both neuronal degeneration and inflammation [20-24].

A previous study by Oosterink et al. with PET and \(^{55}\)Co suggested that this technique could generate additional specific information, which cannot be obtained with conventional neuroimaging techniques
like perfusion and $^{18}$FDG PET [25]. The objectives of this study were (1) to visualise inflammation \textit{in vivo} in sDAT patients by detecting $^{57}$Co SPECT changes and investigate whether $^{57}$Co SPECT can generate additional information which cannot be obtained with conventional neuroimaging techniques or neuropsychological testing (NPT); (2) to search for a possible correlation of findings with data obtained from MRI, perfusion SPECT, and NPT; and (3) to compare findings in sDAT patients with patients suffering from vascular dementia (VaD) and frontal lobe-type dementia (FLD).
PATIENTS AND METHODS

Patients
The study was approved by the medical ethics committee and all patients gave informed (proxy-)consent. Six patients suffering from probable sDAT (mean age 79 ± 7 yrs; range 68 to 87 yrs) according to the NINCDS-ADRDA criteria were included [26]. As controls, 3 VaD patients (mean age 67 ± 5 yrs) according to the NINDS-AIREN criteria and one FLD patient (75 yrs) according to the criteria suggested by Gustafson et al. were included [27, 28].

Methods

Magnetic Resonance Imaging
All patients had a MRI scan (1.5 Tesla, Siemens, Erlangen, Germany). After the administration of Gadolinium, 5 mm axial slices were scanned with proton-density-, T₂- and T₁-weighting. Subsequently, the head was scanned with a 3D-MPRAGE sequence yielding 128 sagittal T₁-weighted images with a thickness of 1.25 mm. From the MPRAGE series, axial, sagittal, and coronal planes were reconstructed. The images were hard copied and then viewed to assess global/regional atrophy, white matter lesions (periventricular, frontoparietal, occipital, and temporal), and the presence of infarcts.

Neuropsychological testing
Patients underwent the following battery: mini mental state examination (MMSE; N=10), Rey auditory verbal learning test for verbal learning and memory (AVLT; N=9), Trail making test for attention, sequencing, mental flexibility, and visual search and motor function (TMT, N=7), Controlled Oral Word Association Task for semantic and syntactic verbal fluency (COWAT, N=8), and the Money Road map test for spatial orientation (MRMT, N=8). Not all tests could be performed in every patient due to non-compliance.

$^{57}$Co SPECT scan
$^{57}$Co was purchased from Amersham (Amersham Cygne, Eindhoven, the Netherlands). Approximately 37 MBq (1 mCi) of $^{57}$Co was injected. The patient was scanned on a triple-headed gamma camera (Toshiba GCA-9300A, Dutoit Medical, Wijnegem, Belgium) equipped with low energy, high-resolution parallel hole collimators (FWHM 9.5 mm), 15 ± 10 hours (range 3 to 24) after injection, in the same session as the $^{99m}$Tc-ECD SPECT scan, enabling image registration. Images were acquired in a 128×128 matrix with a step angle of 6, frame time of 90 seconds, and a 1.25 zoom. Images were reconstructed with filtered backprojection (FBP, Butterworth filter 0.9 cycles/cm, order 8). Uniform attenuation correction was performed ($\mu$=0.09), no scatter correction was applied. A visual qualitative assessment of the $^{57}$Co SPECT images was made.

$^{99m}$Tc-ECD SPECT scan
Nine patients underwent a $^{99m}$Tc-ECD SPECT scan, after the injection of 925 MBq $^{99m}$Tc-ECD (ethyl cysteinate dimer; DuPont Pharmaceuticals Ltd., Belgium). Images were acquired in a 128×128 matrix with a frame time of 60 seconds, a step angle of 6, and a 1.25 zoom. Images were reconstructed with FBP (Butterworth filter 0.9 cycles/cm, order 8). Uniform attenuation correction was performed ($\mu$=0.09), without scatter correction. Perfusion SPECT images were automatically fitted and realigned into Talairach co-ordinates where 26 cortical, 6 subcortical, 2 cerebellar, and one pons 3D-volumes of interest were assessed semiquantitatively (normalisation total number of counts) (Brass software, Nuclear Diagnostics, Sweden). Comparison was done to a database consisting of 20 healthy controls (mean age 70.4 ± 6.2 yrs) [29]. Mean counts per voxel were averaged in the sDAT group to assess a group perfusion deficit. A hypoperfusion in a specific region was considered as
significant when the uptake was less than the averaged uptake for the healthy volunteers minus two times the SD for that specific region.
RESULTS
Age, pathology, MMSE-score, the presence of cerebral infarcts on MRI and the perfusion defects are presented in Table 1. Age was inversely correlated with the relative perfusion in the left temporal lobe, temporal atrophy, the MMSE-score and the number of hyop erfused regions \((p = 0.04,\) Pearson correlation; \(p = 0.01, p = 0.02,\) and \(p = 0.02,\) Spearman correlation coefficient) respectively.

<table>
<thead>
<tr>
<th>Age</th>
<th>Pathology</th>
<th>MMSE</th>
<th>Infarcts on MRI</th>
<th>Significant perfusion defects</th>
</tr>
</thead>
<tbody>
<tr>
<td>75</td>
<td>sDAT</td>
<td>12</td>
<td>(-)</td>
<td>L and R temporal superior, medial inferior, and parietal inferior region</td>
</tr>
<tr>
<td>68</td>
<td>sDAT</td>
<td>19</td>
<td>(-)</td>
<td>L prefrontal and superior frontal region; posterior cingulate gyrus</td>
</tr>
<tr>
<td>84</td>
<td>sDAT</td>
<td>16</td>
<td>(+)</td>
<td>L temporal superior and parietal inferior region; cerebellum</td>
</tr>
<tr>
<td>83</td>
<td>sDAT</td>
<td>0</td>
<td>(-)</td>
<td>L temporal superior region</td>
</tr>
<tr>
<td>87</td>
<td>sDAT</td>
<td>10</td>
<td>(-)</td>
<td>L lateral frontal, temporal medial inferior, and parietal inferior region</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>R lateral frontal and temporal anterior region</td>
</tr>
<tr>
<td>77</td>
<td>sDAT</td>
<td>22</td>
<td>(-)</td>
<td>R prefrontal region and posterior cingulate gyrus; thalamus</td>
</tr>
<tr>
<td>68</td>
<td>VaD</td>
<td>17</td>
<td>(+)</td>
<td>Not performed</td>
</tr>
<tr>
<td>71</td>
<td>VaD</td>
<td>18</td>
<td>(+)</td>
<td>R lateral/superior frontal, temporal medial inferior, and parietal superior region</td>
</tr>
<tr>
<td>61</td>
<td>VaD</td>
<td>24</td>
<td>(+)</td>
<td>R temporal anterior region, cerebellum</td>
</tr>
<tr>
<td>75</td>
<td>FLD</td>
<td>17</td>
<td>(-)</td>
<td>L lateral frontal and R prefrontal region</td>
</tr>
</tbody>
</table>

sDAT = senile dementia of the Alzheimer type; VaD = vascular dementia; FLD = frontal lobe-type dementia

Table 1: Age, pathology, MMSE-score, presence of infarcts on MRI and the significant perfusion defects detected on the $^{99m}$Tc-ECD SPECT scans
**Structural imaging**

MRI scans yielded conclusive results as to the exclusion of other pathologies and the confirmation of diagnosis. One patient had a lenticulostriate infarct but was however classified as a sDAT patient. No significant correlation was found between the rCBF deficits and the regional atrophy rating scores derived from the MRI scans. Vascular dementia patients had more white matter lesions than sDAT patients (10.5 vs. 2.2 ml) did, whereas the periventricular hyperintensities did not differ between groups. The total amount of periventricular white matter hyperintensities correlated significantly with the memory performance on the AVLT and the MMSE score (p = 0.02 and 0.03 respectively; Spearman correlation coefficient).

**57Co SPECT scans**

By visual analysis, 57Co SPECT scans were unable to show any regional raised uptake (and in this way inflammatory lesions), irrespective of the disorder, depth or extent of the associate lesions on the perfusion images or MRI, and irrespective of the results of the NPT.

**Perfusion SPECT - Neuropsychological testing**

Perfusion SPECT scans in sDAT patients showed significant deficits in the anterior, superior and inferior mesiotemporal region, the inferior parietal region, the orbitofrontal, prefrontal, superior frontal and lateral frontal region, the posterior cingulate gyrus, the caput caudate nucleus, thalamus, and the cerebellum. A group perfusion defect for the sDAT patients was found in the left inferior parietal and the right temporal anterior region. The FLD patient showed perfusion deficits in the left lateral frontal and the right prefrontal region. The VaD patients showed mixed defects in the frontal, temporal and parietal lobes but also in the cerebellar region. The MMSE-score correlated significantly with the relative left temporal perfusion (p = 0.002, Pearson correlation coefficient). Results of the spatial orientation task correlated significantly with the relative perfusion in the right lateral frontal, right medial temporal and the right parietal region (p = 0.03, 0.005, and 0.03; Pearson correlation coefficient).
DISCUSSION

Neuroinflammatory imaging

Scintigraphic visualisation of inflammation has previously been done with Ga$^{67}$, radiolabelled leukocytes, nanocolloid and human immunoglobulins [30]. The application of these techniques in sDAT for the visualisation of the inflammatory process would pose several difficulties. Indeed, despite repeated efforts by several laboratories, neutrophil invasion has until now not yet been documented in sDAT and a consistent lymphocytic or immunoglobulin involvement appears to lack [31]. The absence of these phenomena makes the application of the former mentioned techniques inadequate. As such, the aim of the present study was to visualise inflammatory lesions in sDAT patients with $^{57}$Co SPECT and compare this with findings in patients suffering from other types of dementia. Inflammation as a pathogenic mechanism has been described to a lesser extent for VaD but not for FLD [32]. The evidence of inflammation in the group of frontotemporal dementia patients is to our knowledge limited to one study where some cases of Pick’s disease were found to exhibit a neuronal expression of class II major histocompatibility complex with a dramatic microglial response suggesting an inflammatory process [33].

Limitations of the study

The limitations of $^{57}$Co SPECT are manifold. Due to the long physical half-life of 270 days, only a limited dose can be injected which is responsible for the low count rate and the resulting low statistics. Moreover, whether $^{57}$Co visualises specific aspects of neuronal damage or blood-brain barrier integrity is still uncertain. To what extent $^{57}$Co really visualises calcium-mediated processes (in vitro and more importantly in vivo), and therefore resembles identical molecular uptake mechanisms, has yet to be determined, although the cerebral uptake of intravenously administered radioactive $^{45}$Ca and $^{60}$Co in neuronal damage is highly similar [7]. Finally, the exact cellular site of accumulation of radioactivity is, as yet, not known. As for inflammatory imaging, however, it is interesting to note that calcium may also accumulate in activated leukocytes and that both for $^{55}$Co and $^{57}$Co, only 12% of the total fraction is in its free form where the remainder is bound to leukocytes or plasma proteins [34-36].

Perfusion SPECT and sDAT

The role of perfusion SPECT in dementia, both for clinical (early diagnosis and follow-up) and research objectives has been well described in literature, even in the very early stages of the disease [37]. As such, the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology evaluated the use of perfusion SPECT for sDAT as established to support the clinical diagnosis with a sensitivity of up to 95% [38]. Perfusion defects in sDAT patients have been mainly described in the posterior temporal and parietal lobe region, in concordance with the group perfusion defect in the temporal and parietal region found in this series. The frontal association cortex is said to be mostly unaffected until late in the course of the disease, however, this is contested by several SPECT and PET studies [38-40]. In this way, none of the dementia diseases can be identified with certainty by any characteristic topography of regional cerebral blood flow deficits, with an incidence of an exclusive or predominant bilateral reduction of perfusion tracer uptake in the
temporoparietal cortex ranging in literature from 26 to 100% [37, 41-43]. As such, group comparisons provide less information due to the heterogeneity of the disease (different stages and progression patterns), as already pointed out by Waldemar et al. [37].

**Perfusion SPECT and other types of dementia, correlation with neuropsychological tests**

The frontal perfusion defects found in the FLD patient is in agreement with the finding of Risberg et al. where bilateral frontal or frontotemporal defects were found in 25 out of 26 autopsy-verified cases of frontal lobe degeneration of the non-Alzheimer type [44]. Moreover, Pickut et al. identified bifrontal hypoperfusion as the most powerful predictor of clinical classification of sDAT versus FLD on perfusion SPECT [45]. The defects in the cerebellar region in the VaD patient are probably caused by functional diachisis related to deafferentiation, where metabolic findings in any specific brain region represent complex relationships between a local and remote pathology. [46, 47]. The significant correlation between the orientation task and parietal perfusion confirms previous reports of this parietal hypoperfusion being associated with deficits in visuospatial function whereas a correlation between the MMSE-score and the relative temporal lobe perfusion was also described by O’Brien et al. [48] and Waldemar et al. [49].

**MRI and sDAT**

Not or only a partial correlation (right parietal region) was found between the rCBF deficits and the regional atrophy rating scores or the number of white matter lesions found on MRI. This is in agreement with studies performed by Eagger et al. and Waldemar et al. which indicates firstly that the hypoperfusion really reflects a reduced metabolism per gram brain tissue and secondly is not caused by a deafferentiation from underlying white matter hyperintensities [40, 50, 51]. The relationship between periventricular hyperintensities and cognitive functions as indicated in this study was already pointed out by Harrel at al [52]. Also, VaD patients having significantly more white matter lesions but not periventricular hyperintensities compared to sDAT patients, was previously indicated by Bowen et al. [53]. Although MRI is useful in the workout of patients with dementia since it shows the presence of space-occupying lesions, ventricular dilatation, cerebral atrophy, widening of sulci or infarcts, this technique is not of particular value in the direct diagnosis of sDAT, although promising results have been made with volumetric measurements of the (para)hippocampal and amygdala region [54].

**Conclusions**

In conclusion, $^{57}$Co SPECT scans are not able to show any regional raised uptake and in this way ongoing tissue decay or inflammation, irrespective of the type of dementia, the depth or extent of perfusion defects, the presence of atrophy on MRI, or the results of NPT.
REFERENCES


