Current Radiopharmaceuticals, 2017, *10*, 115-122

RESEARCH ARTICLE

Experiences with 99mTc-HMPAO in a Diagnostic Pathway for Violent Patients with Schizophrenic Spectrum Disorders

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ARTICLE HISTORY

Received: March 29, 2017
Revised: June 13, 2017
Accepted: June 14, 2017

DOI:
10.2174/1874471010666170621122221

Abstract: ***Background and Objective*:** In a security ward we assessed the diagnostic contribution of single photon scintigraphy [SPECT] in our diagnostic pathway for patients with serious mental disease and a history of violence.

***Methods*:** Twenty patients were examined between 2012 and 2015 and the findings compared to those in nine patients with the same diagnosis, but no history of violence.

***Results*:** All violent patients had areas with reduced accumulation of ^{99m}Tc-HMPAO frontally and in the temporal lobe, in the non-violent group only two patients demonstrated these findings.

***Conclusion*:** Traditionally, low accumulation of the tracer in SPECT is related to reduced perfusion of brain tissue. We discuss our findings in the light of other possible pathophysiological mechanisms.

Keywords: SPECT, Schizophrenia spectrum disorder, brain perfusion, violence, forensic psychiatry.

1. INTRODUCTION

Our department is a regional security ward serving a total population of 290000 with 16 beds in a non-university hospital. The patients are admitted either after court sentences or according to paragraph 3.3 in the Norwegian act of mental health law. In the Norwegian legal system, a violent perpetrator with serious mental diseases is sentenced to care rather than prison. As the diagnosis often marks the divide between these two legal options; treatment or jail, our diagnoses and therapy suggestions should be as evidence-based as possible. Thus, our hospital developed in 2011 a clinical pathway for psychotic and violent patients in a high-security ward to ensure as correct diagnoses as possible. This pathway has later been adjusted in concurrence with published guidelines from The Norwegian Directorate of Health and a list of tests and procedures were recommended [1].

In addition, we locally included single photon spectrometry [SPECT]. Given the rapid progresses in brain imaging, we were unsure whether such imaging would be helpful in the individual evaluation of our patients. CT, MR and SPECT are readily available, relatively cheap and without serious side effects. However, the established MR-methods are mainly applied to exclude tumours and bleeding. More sophisticated procedures like functional MR, diffusion tensor imaging, magnetic resonance spectroscopy are delivering very promising results, but are valid mostly on group levels. These examinations require additional equipment and insights in physics and application of statistical models that are not readily available in non-university, rural clinics. SPECT provides three-dimensional information on brain perfusion and metabolic status of brain tissue [2] and is available in our clinic. The links between the pathophysiology in individual psychiatric disease and the scintigraphy findings remain speculative.

Many researchers have applied SPECT in the studies of patients with schizophrenia [3-8]. Most studies imply that reduced retention of the radioactive compound is related to reduced circulation and thus use the term “hypo perfusion”. However, as several researchers have pointed out, other mechanisms, both biochemical and metabolic, may be involved as well [3]. We continue to use the term “hypo perfusion” when citing others who have applied it. Furthermore, we omit a comparison with “normal “population that is available in our software NeuroGam®, [GE Medical System, Segami Corp., Columbia, MD, USA] as this contain a very limited number of individuals which in our opinion do not encompass the interperson variability in a normal population. Thus, our results are mainly based on the description given by the specialist in nuclear medicine based on the normalized, primary registrations. Ideally, given a representative normal population for comparison, more statistical methods would have been available.

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Table 1. Technical details of SPECT examination.

Camera	**Discovery NM/CT GE**
Collimator	LEHR (Low Energy High Resolution)
Tracer	99m Tc – HMPAO (Ceretec, GE)
Dose	750 MBq (+/- 50 MBq)
Matrix/zoom	128 x 128/i.5
Total angular range/View angle	360O/3O
Step	120
Step and shoot	30 seconds
Exposure	33 minutes 03 Seconds
Time to exposure	Between five and sixty minutes
Normalization and reconstruction	Xeleris version 3.1
Program	Brain SpectR
Filter	Butterworth
Reconstruction	OSEM/MLEM
Attenuation	Chang order 0

Violence by patients with schizophrenia is estimated to occur with twice the incidence of that in the general population, however, combined with substance abuse and psychosis an eight-fold risk increase is estimated [9]. Wake *et al*. [10] found significant bilateral temporal hypoperfusion in patients with first episode schizophrenia and Wahlund [11] pointed out that it would be useful to focus on the limbic system and to investigate which parts of the frontal lobes and cerebral networks that are of interest in the pathological SPECT. Anckarsäter found similar results, which consisted over years [12, 13] and consider that frontotemporal hypo-activity to be a trait rather than a state in violent perpetrators. Interestingly, in his study diagnoses of personality disorders were made, but not of schizophrenia.

The aim of this study was to assess the value of adding routine SPECT to our diagnostic work-up in violent patients with suspected schizophrenia spectrum disorders. All diagnostic procedures were performed in consenting cooperation with the patient.

2. METHODS

2.1. Patients

All patients with psychosis and a history of serious violence that were examined and treated in our ward between 2012 and 2015 were included. Additionally, in the same time period, patients with a diagnosis of schizophrenia but without any history of violence who were treated in other wards and had been examined with SPECT were included in the study. The diagnoses of schizophrenia were made in accordance with the ICD-10 criteria based on observations and at least evaluation with the Positive and Negative Syndrome Scale [PANSS)] [14] and Structured Clinical Interview for DSM-IV Axis I Disorders [SCID-I] [15]. In two patients the diagnosis remained uncertain in spite of years of observation and they were not included the study. Duration of disease was calculated as the time from the first remission to psychiatric care to the date of the SPECT examination.

All patients with a violent history were additionally examined with HCR-20, version 3, risk assessment scheme [16]. The test closest to the SPECT scan was taken for evaluation. The HCR-20 scores were grouped into high [>30], moderate [between 20 and 29], and low [below 20]. We have only included violent episodes that were undisputable, and directed towards others, thus, minor in-house episodes are not included. The non-violent group was diagnosed according to the same ICD-10 criteria but had no records of violent behavior. The treatment histories of the patients were taken from the hospital records.

2.2. SPECT

For Brain scintigraphy we used 750MBq, 99mTc-HMPAO SPECT. Patients were prepared according to hospital routine and told to avoid caffeine and alcohol prior to the examination. The patients were instructed to keep eyes closed and were observed for thirty minutes in solitude before and after the procedure. A specialist in nuclear medicine evaluated the primary images. The data were then fitted in a normalization process using both the cerebellum and the whole brain. Since the examinations were stretched over time with different interpretations reviewing the images, we re-evaluated all SPECT examinations in a second round using the old recordings but repeated the normalization and evaluation process. There were no major differences between the two assessments. The technical details of the SPECT instrument/procedure are given in Table **1**.

2.3. MR

MR caput was performed on almost all patients. The patients had been without substance abuse at least eight weeks before performing imaging procedures. For MR we used a 1.5 Tesla Siemens Symphony® [Siemens Healthcare, Erlangen, Germany] and a standardized protokoll including Axial T2 SE [Spin Echo], Sagittal T1 TSE [Turbo Spin Echo], Epi diffusion/ADC [Apparent Diffusion Coefficient] and Coronal FLAIR [Fluid Attenuated Inversion Recovery]. An experienced neuroradiologist evaluated the examinations.

2.4. Illicit Drugs/Alcohol

Our guidelines demand that patients should be drug-free and observed at least 6 months before a diagnosis of schizophrenia is made. Frequent urinary analyses to detect illicit drugs are made. Thus, none of our patients were influenced by or had used illicit drugs at the time of investigation. Their history on alcohol and illicit substances use were taken from the hospital records, in retrospect.

2.3. Ethics

The study was performed within the regulation for quality assessment [Act of 2 July, 1999, No. 64], The Health Personnel Act, §26.]. This implies that all data that were temporarily stored and later deleted under the control of Data Protection Official: Norwegian Social Science Data Services [NSD], project number 38986. NSD is a Limited Company owned by the Ministry of Education and Research [+4755582117] [personvernombudet@nsd.no]. The local research department in the hospital approved the protocol. No additional data to those already in the hospital files were collected. The analyses were performed on non-identifiable data. All patients consented orally to the procedures and they were presented the results of the examinations both individually and in group meetings.

2.4. Statistics

For comparison of the SPECT findings in violent versus non-violent patients Fishers test was used. A p- value <0.05 was considered significant.

3. RESULTS

A total of 29 inpatients, 20 patients with a history of violence from the forensic unit and 9 non-violent patients from other wards fulfilled the ICD-10 criteria for schizophrenic spectrum disorder. Average age was 32 years, range 18-78 and the length of the stay varied from one to twelve years. Of the twenty violent patients in the forensic unit, eight were sentenced by court to mandatory treatment, [murder with knife/ axe, stabbing or arson] and 12 were admitted because other type of violence [paragraph 3.3 in the Norwegian Act of Mental Health Law].

The timespan from their first contact with a mental health specialist till SPECT-examinations varied significantly in the two groups. In the violent group it was (mean, SD) 82.2±71.5 months, in the non-violence group significantly shorter; 25.6±22.9 months.

The PANSS scores for the whole group was in sum (mean± SD, (range) 76±21.2, (11-112), positive scores 21.0±10.1, (7-36) negative scores 21.6±6.6, (7-37) and PANSS general 38±12.0, (16-61). There was no difference between the violent and the non-violent group.

Prior, chronic substance abuse was documented in 23 of 29 patients [79%]. Preferred substances were alcohol, cannabis, and/or amphetamine. In the violence group, 16 of 20 patients [80 %], and in the group without violence in 7 of 9 [77 %] patients had been abusing drugs. The record showed that all started their substance abuse before the age of 18 with a debut age ranged from 13 -18 years.

In the violence group the mean HCR-20 score was 27.7 range (11- 39). Sixteen patients scored higher than 20 and eight higher than 30 points. One patient displayed a low score and data were missing in four patients. All patients were treated with psychopharmacological drugs. One patient received Zuklopentixol the others were treated with second generation drugs. However, the information on patient compliance are not available so estimation of chlorpromazine equivalents were not performed.

Neither CT nor MR revealed pathological findings in any patients. Among the patients with violence and schizophrenia [n=20] we found that all patients with HCR-20 above 20 had a pathological SPECT pattern in their left temporal lobe. Of these, 12 patients showed bilateral reduced perfusion temporally, and 11 also had frontally hypoperfused areas. In the non-violent group, only two patients had pathological SPECT results (Table **2**). The difference between the groups was significant (p=0.04, Fischer exact). One typical result is shown in Fig. (**1**). Here pathological emission is seen in the frontal, temporal and even occipital lobe. For comparison, the mean area values for the patient are compared to mean values in the standard, normal population and deviates more than two SD in these areas (Fig. **1**).

Because of the poor response with antipsycotic (zuclopenthixol and klozapine) in four of the patients in the violence group, we performed a second SPECT and three of them had progression of their pathological findings. The changes progressed in temporal, parietal and frontal areas.

4. DISCUSSION

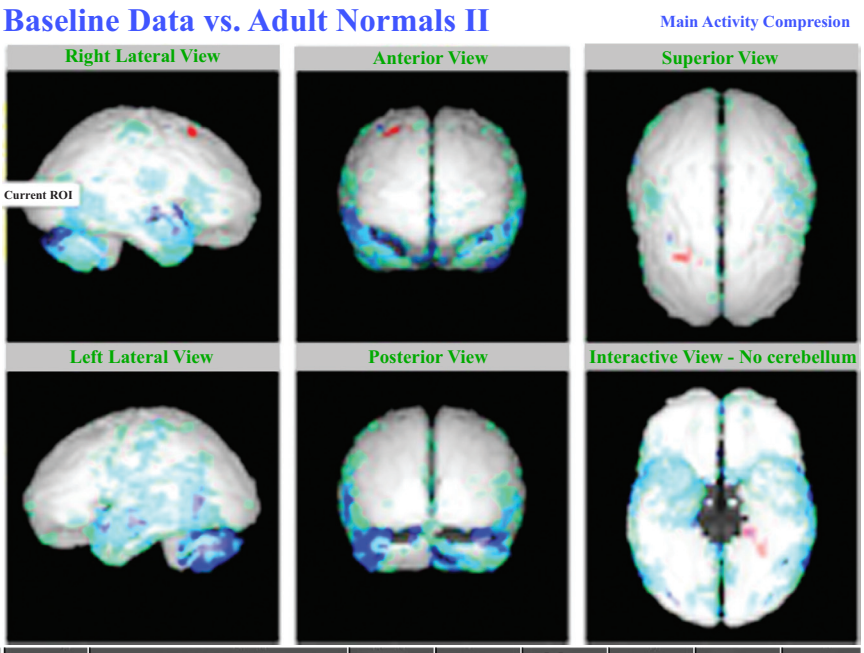
The main finding in our study is that a majority of patients with schizophrenia and violence had, hypo-perfused areas on their SPECT examination. The main affected areas were in the prefrontal and medial temporal lobe. The group without violence had significantly less areas of "hypoperfusion" on their scans. The latter group had the same symptom load estimated from the PANSS, but a significant shorter duration of disease than the former which may contribute to this difference. Achieving such alliances that the patients voluntary perform SPECT, MR or PANSS, sometimes while still paranoid and psychotic, has been time consuming and challenging. Both the symptoms, the patients' often negative attitude to the confinement and also legal processes prolong the time needed to achieve a correct diagnosis, in some this takes 12-18 months. In early studies of patients with first-episode of schizophrenia [10] volumes

Table 2. Localization of pathological SPECT findings in violent and non-violent patients with schizophrenia.

		POS/NEG	FRONTAL	TEMPORAL	PARIETAL	OCCIPITAL
Violent Patients	1	POS	-	Left	Left	Right
	2	POS	-	Left	-	-
	3	POS	Left	Left	Left	Bilateral
	4	POS	Bilateral	-	Bilateral	-
	5	POS	-	Bilateral	-	-
	6	POS	Left	Bilateral	-	-
	7	POS	-	Bilateral	-	Bilateral
	8	POS	Bilateral	Left	Bilateral	Bilateral
	9	POS	-	Bilateral	Left	-
	10	POS	Bilateral	Bilateral	Bilateral	-
	11	POS	Bilateral	Bilateral	Left	-
	12	POS	-	Bilateral	-	Bilateral
	13	POS	Bilateral	Left	-	-
	14	POS	Bilateral	Bilateral	Bilateral	Left
	15	POS	-	Left	-	Right
	16	POS	-	Left	-	-
	17	POS	Bilateral	Bilateral	Bilateral	Bilateral
	18	POS	-	Bilateral	Right	-
	19	POS	Bilateral	Bilateral	Bilateral	Bilateral
	20	POS	Bilateral	Bilateral	Bilateral	-
Non-violent Patients	1	POS	-	Left	-	-
	2	NEG	-	-	-	-
	3	NEG	-	-	-	-
	4	NEG	-	-	-	-
	5	NEG	-	-	-	-
	6	POS	-	-	-	Bilateral
	7	NEG	-	-	-	-
	8	POS	Bilateral	Bilateral	Bilateral	Bilateral
	9	NEG	-	-	-	-

were not significantly decreased in comparison with control subjects, which may indicate that the duration of disease may be important.

The relationship between frontal and temporal lobes of the brain and violent and aggressive behaviour has been previously recognized [12]. More recent work done both in the resting state and during cognitive tasks suggests that multiple regions are involved in schizophrenia [17]. It is acknowledged that cerebral structures are changed in patients with schizophrenic disorders. In our study, MR did not contribute to any increased differentiation between the patients. In an ENIGMA-study [18], several subcortical brain structures [amygdala, hippocampus] had deviant sizes compared to the control mean. These changes on group levels are not readily transformed into objective findings in single patients. The lack of congruency between MR and SPECT in our experience may represent different mechanisms. MR was performed with a 1.5 Tesla magnet and newer 3 T might have revealed other structural changes. Also, the fact that three of the patients with the most pathological SPECT had normal F-FDG PET examinations during the preparation for this paper rises several questions. Seidenwurm [19] found in a



ROI #	ROI Label	# Elts	Volume	Max	Min	Mean	St. dev.
0	Caudate Nucleus - Left	975	3 ml	0.6 sd	-5.0 sd	-2.1 sd	1.2 sd
1	Caudate Nucleus - Right	975	3 ml	0.8 sd	-5.0 sd	-2.3 sd	1.1 sd
2	Cerebellum - Left	14470	53 ml	3.4 sd	-5.0 sd	-2.1 sd	2.2 sd
Current ROI	Cerebellum - Right	14470	53 ml	2.0 sd	-5.0 sd	-2.5 sd	1.9 sd
4	Cerebral Cortex - Left	127354	474 ml	3.8 sd	-5.0 sd	-1.9 sd	1.6 sd
5	Cerebral Cortex - Right	127354	474 ml	4.7 sd	-5.0 sd	-1.8 sd	1.5 sd
6	Entire Brain	371172	1382 ml	4.7 sd	-5.0 sd	-1.8 sd	1.6 sd
7	Entire Cerebrum	332575	1238 ml	4.7 sd	-5.0 sd	-1.7 sd	1.5 sd
8	Frontal Lobe - Left	59798	222 ml	2.5 sd	-5.0 sd	-1.5 sd	1.2 sd
9	Frontal Lobe - Right	59798	222 ml	4.7 sd	-5.0 sd	-1.4 sd	1.3 sd
10	Occipital Lobe - Left	12482	46 ml	1.8 sd	-5.0 sd	-1.7 sd	1.4 sd
11	Occipital Lobe - Right	12482	46 ml	2.7 sd	-5.0 sd	-1.6 sd	1.3 sd
12	Parietal Lobe - Left	25766	95 ml	1.4 sd	-5.0 sd	-1.8 sd	1.4 sd
13	Parietal Lobe - Right	25766	95 ml	1.9 sd	-5.0 sd	-1.5 sd	1.2 sd
14	Putamen - Left	1668	6 ml	2.7 sd	-2.9 sd	0.2 sd	1.1 sd
15	Putamen - Right	1668	6 ml	3.0 sd	-2.0 sd	0.4 sd	0.8 sd
16	Temporal Lobe - Left	20953	78 ml	3.5 sd	-5.0 sd	-2.3 sd	1.8 sd
17	Temporal Lobe - Right	20953	78 ml	2.0 sd	-5.0 sd	-2.4 sd	1.6 sd
18	Thalamus - Left	1487	5 ml	1.0 sd	-3.7 sd	-1.0 sd	0.9 sd
19	Thalamus - Right	1487	5 ml	2.8 sd	-3.2 sd	-0.2 sd	1.1 sd

Fig. (1). The pictures show changed emittion in the frontal, temporal and occipital parts compared to the normal population. As can be seen in the table the differences are more than two standard deviations.

selected population of seven violent subjects that FDG-PET scans showed metabolic abnormalities in the temporal lobes. These abnormalities correlated with limbic abnormalities seen at electrophysiological and neuropsychiatric evaluation, but not with the MR-findings.

In a more recent, MR-based paper Palijan TZ 2010 [20] suggested that violence occurred as a disruption of a balance between impulsive aggression mediated by the limbic structures and the control of this drive by the frontal region. The hippocampus is contained in the temporal lobe and projects to the prefrontal cortex via strong monosynaptic glutamatergic projections [21]. Spaletta [22] found reduced prefrontal regional blood flow with SPECT during Wisconsin card sorting task. In a review of structural changes Pridmore *et al*. 2005 [23] cited three studies using SPECT in violent patients, which "strongly suggests dysfunction of particular frontal and temporal lobe structures in psychopathy". However, there were difficulties selecting homogeneous index cases and appropriate control groups.

In its infancy SPECT was shown to correlate well with other methods for cerebral blood flow examinations [2, 3] However, reservations were made that this only had validity when no other diseases were present.

Already Jaquir-Sarlin [24] speculated that additional mechanisms related to the disease, the metabolism and cellu-

lar uptake of HMPAO may be involved. This has been shown for infectious diseases like Herpes-encephalitis [25]. Studies into the uptake of HMPAO show that the extracellular redox-potential influence the cellular uptake of the tracer and this depend on the extracellular glutamat content. Also, this fits with the findings that cytotoxic kynurenin metabolites influences glutathione as one main regulator of intercellar redox-potentials [26, 27]. Other factors, however, also have been proposed to play a role in flow-independent accumulation of 99mTc-HMPAO, including changes in oxidoreductive state [24], metabolic alterations [26], and formation of a complex with proteins in subcellular organelles. Zerarka [27] showed that astrozytes retained HMPAO and this may influence the SPECT scans. Ôngür in 1998 [28] suggested that the reduced retention was linked to inflammatory processes in the glia. The realization of the role played by glutathion and the metabotropic glutamat receptor GRM3 [29] lead to the suggestion by Muguruza to apply agonist in the therapy [30]. This gene, together with the glial glutamat transporter EAAT2 may prove of interest in understanding he complex process of HMPAO retention in brain tissue. Thus, if the proposed notion that a low grade inflammatory process is present in schizophrenia [31], this may contribute to HMPAO retention that is independent of blood-flow factors.

The relationship between frontal and temporal lobes of the brain and violent and aggressive behaviour has been previously recognized [32]. More recent work done both in the resting state and during cognitive tasks suggest that multiple regions are involved in schizophrenia [13]. Furthermore, it has been shown that the connection between the medial temporal lobe and its subcortical structures and the prefrontal cortex is affected in several psychiatric diseases [33]. The areas with pathological HMPAO-retention in our study would indicate pathological processes in these areas.

In our patients the violent group had significantly longer disease duration than the non-violent group. They also showed more pathological retention pattern, indicating that the duration of disease is of importance for our findings. However, longer disease duration also indicate a longer consumption of drugs. Etchebehere [34] found cortical hypoperfusion among male patients depending on multiple drugs. Honea [35] showed that the structural changes in drug/alcohol users depended on their antipsychotic medication. Drug use/abuse may be as an important factor as the disease itself in contributing to the pathology described in the SPECT examinations.

There are few studies which describe brain SPECT perfusion changes in adolescent drug dependency [35]. In one study with sixteen male patients dependent of multiple drugs [36] cortical hypo-perfusion occurred in 7/16 patients [44%]. There was a significant inverse correlation between the number of regions with reduced retention and the patient's age and with the age when the drug dependence began. There was also a tendency towards an inverse correlation between regions of hypo-perfusion and the duration of the drug dependence. Recently, Del Bene found changed volumes of amygdala, hippocampus and thalamus [17] in violent non-psychotic participants on MR-examinations and concluded that the association between amygdala reduction and violence is mediated by substance abuse.

CONCLUSION

We can only conclude that in patients with a long-standing disease and treatment, who have committed serious violence towards other and have a long-standing history of violence, SPECT reveals multiple pathological patterns that are not present in non-violent patients with the same diagnosis. The exact mechanisms behind the retained HMPAO in these patients remains unclear, however, pure changes in flow may not be the full answer. Emerging research [37, 38] may indicate that abnormal dorsolateral prefrontal cortex and disrupted fronto-temporal integration are probable models for behaviour deficits in schizophrenia. Both frontal, occipital and temporal areas are affected in our study. Also, the link between inflammatory changes and HMPAO-uptake require more research as several mechanisms are involved [39]. We hypothesize that the presence of abnormal findings in these locations, combined with progressive schizophrenic disease and/ or illicit drugs, may increase the risk for violence.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was performed within the regulation for quality assessment [Act of 2 July, 1999, No. 64], The Health Personnel Act, §26.]. This implies that all data that were temporarily stored and later deleted under the control of Data Protection Official: Norwegian Social Science Data Services [NSD], project number 38986. NSD is a Limited Company owned by the Ministry of Education and Research [+4755582117] [personvernombudet@nsd.no]. The local research department in the hospital approved the protocol. No additional data to those already in the hospital files were collected. The analyses were performed on non-identifiable data.

HUMAN AND ANIMAL RIGHTS

No Animals were used for studies that are base of this research. All patients consented orally to the procedures and they were presented the results of the examinations both individually and in group meetings and agreed to publication.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

Declared none.

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