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# Tc-99m HMPAO BRAIN SPECT IN PATIENTS WITH ALUMINUM INTOXICATION AND NEUROTOXICITY OCCURING DUE TO LONG TERM HEMODIALYSIS

## UZUN DÖNEM HEMODİYALİZE BAĞLI ALÜMİNYUM İNTOKSİKASYONU VE NÖROTOKSİSİTESi GELİŞEN HASTALARDA Tc-99m HMPAO BEYİN SPECTİ

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**ÖZET**

*Bu çalışmada uzun dönem hemodiyaliz tedavisine bağlı alüminyum intoksikasyonu (Al) ve nörotoksisitesi (AN) gelişen hastalara Tc-99m HMPAO beyin perfüzyon SPECT yapıldı.AN'nin ana sebebi beyin gri cevherinde Alüminyum birikmesi olduğundan böyle hastalarda meydana gelebilen beyin perfüzyon bozukluğunu saptamak ve lokalize etmek amaçlandı.Dokuz Al'HJki AN'li ve on sağlıklı kontrol çalışmaya alındı ve hepsine Tc-99m HMPAO beyin SPECT yapıldı.Bütün vakalara nörolojik, psikolojik muayene ve nöropsikolojik test uygulandı. Bilgisayarlı tomografi (BT) ve Elektroensefolografi (EEG) çekilip serum alüminyum seviyeleri ölçüldü. Bütün hastaların bazal Alüminyum seviyeleri normalin üstündeydi ve BT bulguları normaldi. AN'li bir hastada patolojik ve patagnomonik EEG tespit edildi. Semikantitatif beyin SPECT analizinde iki hastada çok sayıda bölgesel perfüzyon azalması,üç hastada çok sayıda bölgede perfüzyon artması saptandı.Diğer beş hastada ise sadece az sayıda bölgesel perfüzyon bozuklukları gözlendi.Toplam onaltı bölgede düşük perfüzyon, ellialtı bölgede ise yüksek perfüzyon tespit edildi. Bu bulgulara bağlı olarak Tc-99m beyin perfüzyon SPECT'in AN'de meydana gelen nöropsikolojik bozuklukların bir kısmım açıklamada yardımcı olacağını düşünmekteyiz.*

**Anahtar kelimeler: Tc-99m HMPAO, Beyin SPECT, Alüminyum İntoksikasyonu, Alüminyum Nörotoksisitesi**

**SUMMARY**

*In this study, Tc-99m Hexamethylpropyleneamine oxime (HMPAO) brain perfusion single photon emission computed tomography (SPECT) was performed in patients with aluminum intoxication (AI) and expectable aluminum neurotoxicity (AN) occuring due to the treatment with long term hemodialysis. Because accumulation of aluminum in brain gray matter is the main cause of AN, we would like to determine if there is any detonation in brain perfusion and to localize the perfusion abnormalities in patients with AN and AI. Nine patients with AI, 2 with AN and 10 control subjects were included in the study. Tc-99m HMPAO brain SPECT were performed in all patients and control subjects. All patients were evaluated by neurological andpsycological examination and neuropsycological testing. Computerized tomography (CT) and Electroencephalography (EEG) were performed and serum aluminum levels were measured in all patients. Basal aluminium levels of the patients were above normal value. CT findings were normal in all patients. Pathologic and pathognomonic EEG was found in one patient with AN. In semiquantitative brain analysis, multiple regional decreased brain perfusion abnormalities were detected in 2 patients and multiple regional increased perfusion in 3 patients. Regional perfusion abnormalities were also observed in the other 5 patients but only in a few regions. Total 16 regions were hypo-perfused and 56 regions were hyper-perfused.*

*We think that Tc-99m HMPAO brain perfusion SPECT study may help to explain the pathogenesis of some neuropsicological findings of AN.*

**Key words: Tc-99m HMPAO, Brain SPECT, Aluminum Intoxication, Aluminum Neurotoxicity**

## INTRODUCTION

Aluminum intoxication (AI) is a complication of long term hemodialysis treatment. It is a multisystemic disorder affecting brain, bone, soft tissue and hemopoietic system. Aluminum Neurotoxicity (AN) (Dialysis Dementia or Dialysis Encephalopathy) is the part of this multisystemic disorder. It may manifest with various neurological findings including speech and motor disturbance, auditory and visual hallucinations, personality change, impaired memory, dementia and

seizures (1-2). Clinical and electroencephalographic (EEG) findings supported by evidence of aluminum loading may some help for the diagnosis. Computerized tomography (CT) may show nonspesific cortical atrophy,none of these tests are spesific for the diagnosis of AN.

Tc-99m Hexamethylpropyleneamine oxime (HMPAO) is a brain perfusion imaging agent and it is used widely for the evaluation of brain perfusion in various diseases (3-4). Because aluminum accumulates in the gray matter of the brain in patients with AN, it may effect brain perfusion and uptake of brain perfusion seeking radiopharmaceuticals in the brain. Therefore,the aim of this study was to evaluate the brain perfusion changes with Tc-99m HMPAO brain perfusion SPECT.

## MATERIAL AND METHODS

Nine patients with AI and two with AN occuring due to long term hemodialysis were included in the study (9 F, 2 M, aged 25 to 71 years, mean age 504.1). The diagnosis of AI was based on the basal serum aluminum levels and that after deferoxamine treatment. Seven patients had been given deferoxamine therapy 3 months before the SPECT study, but serum aluminum levels of these patients were still high during the SPECT study. Four of the patients did not receive any medication. Patients underwent detailed neurological and pyscological tests ( Cornel Index Test, Beck Depression Inventory, Brief Psychiatric Rating Scale) and CT,EEG examinations. In addition , ten healthy volunteers (4 F, 6 M, aged 28 to 46 years, mean age 372 year) were also included in the study. Serum aluminum levels were measured by atomic absorbtion spectrophotometry (normal leveKlO microgram/lt). Tc-99m HMPAO brain perfusion SPECT was performed in all patients and control subjects before hemodialysis therapy. The study protocol had been approved by the ethics committee of our institution and informed consent was obtained from all patients Semiquantitative SPECT analysis was performed by applying performed templates to transaxial SPECT slices, parallel to the OML. Three templates were used, based on a standardized brain atlas delinating anatomic structures at approximately 4,6 and 7 cm above the OML (8). Region of interest (ROIs) were placed on right and left frontal, superior temporal, middle temporal, occipital, basal ganglia, thalamus and hemisphere (global) in the transaxial brain slice 4 cm above OML, frontal, parietal, occipital and hemisphere in 6 and 7cm above OML in according to these templates. The rCBF ratio was calculated for each ROI using the average number of counts divided by maximal cerebellar uptake and was used for the statistical comparison with control subjects. Uptake ratios were compared between all patients and controls by means of the Mann-Whitney U test. P values less than 0.05 are indicated as significant. In addition, to determine individual abnormalities, tracer uptake ratios of each region of each patient less than 2 SD of the mean uptake ratios of the same region of control group were accepted to be consistent with hypoperfusion and more than 2 SD hyperperfusion.

## RESULTS

Clinical and laboratory findings of patients are shown in Table 1 and other blood biochemistry results in Table 2. All patients' basal serum aluminum levels were high during the study. Duration of hemodialysis was ranging from 4 to 10 years and duration of biochemically determined AI from 1 to 9 months. Six patients were anemic (htc<35%). Five patients have been giving eryhtropoietin treatment for anemia.

Two patients had pathologic neuro-psycological findings including cognitive functional disorder, visual and hearing hallucinations, myoclonic jerks, dispraxia and these patients were diagnosed as expectable AN in according to increased serum aluminum level and neuro-psycologyical findings. Pathologic and pathognomonic EEG findings (slow waves and spike activity) were found in one of the these two patients with AN( Patient 5) . CT was normal in these two patients. The neurological and psycological examinations of patients with AI was normal. In neuropsycological testing, only adjustment problems were found in these patients. No pathologic findings were found by EEG in all of these patients and CT was normal.

In visual analysis of the SPECT slices, we couldn't observe any gross abnormality. There was only mildly inhomogeneous activity distribution in cortical and subcortical areas in some patients. In the semiquantitative analysis of the brain SPECT images; regional hypoperfusion were detected in 5 patients in 17 regions. Most of the lesions were found in two patients Patient 9; 6 regions ( R frontal, bilateral temporal, R basal ganglion and R thalamus) and R global , patient 10; 7 regions ( bilateral temporal, R frontal, R parietal) and R global. Regional hypoperfusion was detected only two regions in a patient ( Patient 1 ;R temporal and R parieto occipital) and in one region in the other two patients( Patients 2 and 7; R temporal region). In these two patients there was also hyperperfused regions. We found regional hyperperfusion in 7 patients in 56 regions. Most of the lesions were found in three patients ( Patient 4; 14 regions and bilateral global, Patient 8; 16 regions and bilateral global , patient 11; 17 regions and bilateral global ). In group analysis, no significant differences were found between all patients and control subjects.

**Table 1.** Clinical and laboratory findings of patients

| No | ID | Age | Sex | Al Dur. (month) | H Dur. (year) | Ther. | Basal All level microgr/lt | Neurologic Findings | EEC | CT |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | NA | 46 | F | 7 | 10 | + | 50 | - | N | N |
| 2 | HB | 67 | M | 7 | 9 | + | 230 | AN:Cognitive tune. impairment,dispraxia, speech disorder | N | N |
| 3 | MU | 45 | F | 8 | 6 | + | **41** | - | N | N |
| 4 | SB | 50 | F | 8 | 7 | + | 119 | - | N | N |
| 5 | HAO | 41 | F | 9 | 9 | + | 272 | AN:Cognitive rune.impairment, Myoclonic jerk, hallucination.dispraxia. | Slow waves and Spike activity | N |
| 6 | BT | 67 | F | 8 | 8 | + | **230** | - | N | N |
| 7 | SP | 44 | F | 8 | 9 | + | 90 | - | N | N |
| 8 | AS | 48 | F | 8 | **10** | | **160** | - | N | N |
| 9 | RB | 53 | M | 1 | 4 | | **100** | - | N | N |
| 10 | ST | 71 | F | 6 | **10** | | **111** | - | N | N |
| 11 | NY | 25 | F | 7 | 9 | | 114 | - | N | N |

AI: Aluminum Intoxication, AN: Aluminum Neurotoxicity, H:Hemodialysis, Ther.:Theraphy, Dur.: Duration.

**Table 2.** Blood biochemistry results of the patients

| No | Urea mg/dl (15-45) | Creatinin mg/dl (0.7-1.4) | Na mEq/1 (135-145) | K mEq/1 (3.5-5) | Ca mg/dl (8.6-10.2) | P mg/dl (2.5-5) | AP U/L (80-310) | Htc % E | PTH pg/ml (9-55) |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 74 | 4.5 | **141** | 3.2 | 10.6 | 3.7 | 128 | 34, E- | 913 |
| 2 | 160 | 8.2 | 134 | 5.3 | 10.2 | 4.2 | 143 | 26 E+ | 17.4 |
| 3 | 141 | 7.1 | 140 | 4.5 | 9.6 | 7.7 | 220 | 35 E+ | 59.5 |
| 4 | 140 | 9.4 | 138 | 4.6 | 9.8 | 6.9 | 223 | 45 E- | 350 |
| 5 | 136 | 10.1 | 140 | 4.5 | 8.7 | 3.7 | 21.9 | 37 E- | 1.3 |
| 6 | 130 | 7.2 | 137 | 4.4 | 10.1 | 5.8 | 232 | 45 E- | 289 |
| 7 | 149 | 9.2 | 135 | 5.1 | 9.5 | 6.9 | 186 | 38 E- | 524 |
| 8 | 133 | 6.9 | 138 | 5.2 | 11.6 | 6 | 132 | 32 E- | 200 |
| 9 | 106 | 6.8 | 141 | 5.2 | 9.8 | 5.1 | 148 | 31 E+ | 117 |
| 10 | 133 | 6.9 | 143 | 4.1 | 10.3 | 72 | 334 | 30 E+ | 100 |
| 11 | 152 | 10.1 | 142 | 4.6 | 8.6 | 4.7 | 174 | 34 E+ | 83.6 |

E: Eryhtropoietin treatment

**Table 3.** Uptake ratios of 11 patients

4 cm above the OML

| N | RF | LF | RST | LST | RMT | LMT | RO | LO | RBG | LBG | RT | LT | RG | LG |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 85 | 88 | 86* | 94 | 90 | 89 | 96 | 95 | 88 | 83 | 87 | 84 | 89 | 91 |
| 2 | 99[A] | 99[A] | 85* | 85 | 93 | 97[A] | 91 | 80 | 100 | 90 | 95 | 90 | 92 | 90 |
| 3 | 84 | 77 | 88 | 82 | 84 | 80 | 93 | 83 | 85 | 81 | 85 | 81 | 87 | 80 |
| 4 | 103[A] | 95 | 110[A] | 105[A] | 102[A] | 97[A] | 111[A] | 112 | 108[A] | 100 | 107[A;] | 100 | 106[A] | 102[A] |
| 5 | 82 | 84 | 87 | 95 | 85 | 95[A] | 96 | 93 | 92 | 99 | 91 | 99 | 87 | 91 |
| 6 | 92 | 89 | 91 | 86 | 93 | 96[A] | 99 | - 97 | 99 | 98 | 98 | 98 | 93 | 92 |
| 7 | 87 | 83 | 82* | 89 | 90 | 87 | 103[A] | 99 | 94 | 93 | 93 | 92 | 90 | 90 |
| 8 | 98[A] | 99[A] | 109[A] | 101[A] | 109[A] | 110[A] | 100 | 105 | 99 | 105[A] | 100[A] | 109[A] | 104[A] | 103[A] |
| 9 | 79* | 80 | 71* | 69* | 79* | 78 | 90 | 97 | 82* | 84 | 82* | 83 | 79* | 81 |
| 10 | 82 | 80 | 81* | 77* | 82* | 75* | 87 | 83 | 83 | 87 | 83 | 87 | 83* | 78 |
| 11 | 101[A] | 90 | 109[A] | 82 | 99[A] | 102[A] | 107[A] | 100 | 106[A] | 131[A] | 109[A] | 108[A] | 104[A] | 93 |

6 cm above the OML

| N | RF | LF | RP | LP | RO | LO | RG | LG |
|---|---|---|---|---|---|---|---|---|
| 1 | 86 | 89 | 86 | 87 | 92 | 92 | 88 | 89 |
| 2 | 91 | 88 | 95 | 90 | 96 | 90 | 94 | 89 |
| 3 | 84 | 79 | 85 | 78 | 93 | 90 | 87 | 82 |
| 4 | 100[A] | 94 | 102[A] | 99[A] | 112[A] | 111[A] | 108[A] | 101[A] |
| 5 | 87 | 88 | 98[A] | 98[A] | 99 | 101 | 92 | 95 |
| 6 | 85 | 86 | 87 | 86 | 101 | 101 | 91 | 91 |
| 7 | 89 | 84 | 82 | 81 | 89 | 88 | 86 | 84 |
| 8 | 99[A] | 98[A] | 111[A] | 110[A] | 108[A] | 104[A] | 106[A] | 10 4[A] |
| 9 | 82 | 84 | 76 | 76 | 91 | 92 | 83 | 82 |
| 10 | 74* | 75 | 77 | 82 | 87 | 88 | 79* | 81 |
| 11 | 112[A] | 108[A] | 98[A] | 93[A] | 104[A] | 103[A] | 104[A] | 101 |

7 cm above the OML

| RF | LF | RP | LP | RPO | LPO | RG | LG |
|---|---|---|---|---|---|---|---|
| 87 | 91 | 82 | 92 | 75* | 80 | 81 | 87 |
| 93 | 90 | 90 | 96 | 94 | 96 | 92 | 94 |
| 89 | 81 | 85 | 84 | 86 | 86 | 86 | 83 |
| 10.1 | 95 | 102 | 98 | 114 | 98. | 106[A] | 97 |
| 92 | 89 | 99 | 97 | 101 | 96 | 97 | 94 |
| 94 | 88 | 91 | 88 | 99 | 96 | 94 | 90 |
| 84 | 84 | 86 | 81 | 81 | 81 | 83 | 82 |
| 97 | 98 | 99 | 99 | 111[A] | 100 | 102[A] | 99 |
| 90 | 87 | 87 | 85 | 90 | 92 | 89 | 88 |
| 71* | 80 | 73* | 84 | 82 | 84 | 75 | 82 |
| 101 | 100 | 99 | 104[A] | 102[A] | 89 | 100[A] | 102[A] |

F: Frontal, P: Parietal, T: Temporal, ST: Superior Temporal, MT: Middle Temporal, O: Occipital, PO:Parieto-occipital, BG: Basal Ganglion, T: Thalamus, G: Global, R: Right, L: Left, *: Hypo-perfused regions, [A]: hyper-perfused regions

**DISCUSSION**

In addition to uremic encephalopathy , a number of other CNS disorders or abnormalities such as metabolic encephalopathies, intoxications, hypertensive encephalopathies or dialysis disequilibrium syndrome cause central nervous system dysfunction in patients on hemodialysis. AI is a complication of long term hemodialyis. AI occur by dialyzing the patient with dialyzate prepared with aluminum-contaminated water. AI is a multisystemic disorder including AN , osteomalacia, proximal myopathy, and microcytic anemia (1-2). AN is a progressive, frequently fatal, neurological disorder seen in patients on hemodialysis. Aluminum has been found markedly elevated in brain gray matter of patients with AN. The disease is characterized by intermittent speech and motor disturbances, seizures, auditory and visual hallucinations, impaired memory. The disorder is progressive and global dementia and death are the usual outcome. Serum aluminum levels increase a few fold of basal levels after deferoxamine infusion. Although EEG seems useful labarotory test supporting the diagnosis of AN, EEG patterns may be seen in other metabolic encephalopathies. The CT scan may appear normal or show only mild cortical atrophy. Because AN is a frequently fatal disorder, it is extremely important to diagnose AN in the early period and to start proper treatment regimen.Aluminum is neurotoxic and may also play a role in the development of Alzheimer's disease(AD). An association between dialysis encephalopathy and AD has been suggested due to presence of neurofibrillary tangles and alteration of the conformation of calmodulin in both disorders. But the role of aluminum in the pathogenesis of AD has remained controversial (9,10).

Although some radionuclide brain perfusion studies have been performed in hemodialysis patients, as a best of our knowledge, there is no report about radionuclide brain perfusion studies in patients with AI and AN due to long term hemodialysis (1**1,12).**

When we looked through the our results; regional hypoperfusions were found in five of the patients but mostly in two patients. One of these patients' old age may be an possible explanation of multiple regional decreased perfusion due to cortical atrophy. But when we compared these two patients with the others, these two patients had not been treated with deferoxamine to decrease aluminum level. Deferoxamine theraphy before the study may effect the results. Four of our patients had not been treated with deferoxamine and 7 patients had been treated before the study but serum aluminum level of these patients were still high during the study. The cause of multiple brain perfusion abnormalities in our two patients may be due to effect of aluminum on brain perfusion. In these two patients we detected bilateral temporal hypoperfusion in addition to one sided hypoperfused regions. The other patient in whom we detected right temporal hypoperfusion had AN (patient 2) and very high blood aluminum level although treatment. There was bilateral or unilateral temporal hypoperfusion in our five patients. We think because aluminum is suspected as a possible factor in the pathogenesis of Alzheimer's disease, our results may be significant to support this suggestion. Also, our findings may be a possible explanation of demential findings of AN or dialysis dementia.

In our study we also found multiple regional hyperperfusion in 7 of the 11 patients but mostly in three patients. Also two of this three patients had not been treated to decrease blood aluminum level. Increased cerebral blood flow was reported in several studies in patients on hemodialysis due to anemia. But cerebral blood flow was returned to normal level with the erythropoietin treatment of anemia in this studies (13,14). Hemotacrite is known to influence cerebral blood flow. Carbondioxide is well known for its powerful vasodilatory action. Also hyperdinamic blood circulation has been described in hemodialysis patients. In our study we found no correlation among hyper-perfusion and anemia. Increased brain perfusion is also a finding of epilepsy during ictal period. Seizure is a finding of aluminum neurotoxicity. In our patients we didn't observed epilepsy during our study. In addition to multiple regional cortical hyperperfusion, we found bilateral thalamic hyperperfusion in two patients and unilateral thalamic hyperperfusion in a patient. Thalamus is considered in the pathogenesis of absence seizure. The cause of multiple regional hyperperfusion in some of our patients may be due to absence seizure, but we have no EEG findings of these patients during the study to support this finding. Also we think increased brain perfusion due to seizure or anemia in patients with AN may mask the hypoperfused regions which we expect to see in patients with dialysis dementia, because of aluminum accumulation in gray matter.

In visual analysis of our study there was only mild inhomogeneous activity distribution in cerebral cortex and subcortical structures in some patients which may be seen sometimes in normal people. We think semiquantitative analysis of data is more helpful than visual analysis. In statistical group analysis we couldn't find any difference between patients and controls. Because some uptake ratios are less than 2 SD of normal ratio and some are more than 2 SD of normal ratio in multiple regions , mean ratio was found normal.

Although our patients mean age seems higher than the control group , there was only three patients in patients group that increasing the mean ratio.

Because aluminum is neurotoxic and it localizes in brain gray matter and causes various neurological findings with high fatality ratio, further studies with radionuclide brain perfusion agents in this population may help to explain the pathogenesis of various neurological findings of AN.

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