# Positron Emission Tomography Reveals Bilateral Reductions of Dopamine Transporter in Unilateral Parkinson's Disease

## *UNILATERAL (TEK TARAFLI) PARKINSON HASTALIĞINDA, DOPAMİN TAŞIYICILARININ ÇİFT TARAFLI AZALIŞININ PET İLE GÖSTERİLMESİ*

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**Summary**

*Positron emission tomography (PET) with dopaminergic neuromarlcers initially with 18F-fluoroDOPA and, more recently, by 11C-WIN 35,428, has shown great promise for biochemical differentiation ofPD early in the course of the illness. The purpose of this study was to quantify the reduction in 11C-WIN 35,428 binding in the basal ganglia corresponding to the asymptomatic side to provide information that may be helpful in the future for the presymptomatic diagnosis ofPD. 11C-W1N 35,428 binding in seven patients with early PD, affecting the left limbs in five, and the right limbs in two (mean symptom duration of 3.6 years and mean age 54±8 years) were compared with a group of seven normal subjects (mean age 55±9 yers).The preliminary data demonstrate decreased [11CJ-WIN 35,428 binding in the bazal ganglia both contralateral to the clinically asymptomatic side and in the ipsilateral side in patients with heini-/)arkinsonism (p<0.05). The reduction in [11CJ-WIN 35,428 binding contralateral to the symptomatic side were 64%, 47% and 23%> in the posterior putamen, anterior putamen and caudate nucleus, respectively. On the clinically silent side, the percent reduction was 51%, 28% and 18%, respectively.Interestingly, when the affected side was compared to the unaffected side of the same individual, significant differences were observed in the anterior putamen (p<0.01), but not in the posterior putamen (p=0.08), suggesting that a significant overlap exists between affected and clinically unaffected regions. These findings indicate that presymptomatic diagnosis of PD by using PET is possible and this early dopaminergic terminal loss may be biochemically measured in the brain. In the future such a test could be used to provide an earlier diagnosis than is possible by clinical means, thus leading to prompt institution of neuroprotective therapy.*

Key Words: Unilateral Parkinson disease. Dopamine transporters, PET

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**Özet**

*18F-fhıoroDOPA ve son yıllarda da 11C-JVIN 35,428 kullanarak pozitron emisyon tomografi (PET) ile dopaminerjik yolakların görüntülenmesi, Parkinson hastalığının erken ve ayırıcı tanısında önemli ölçüde yarar sağlayan bir yöntemdir. Bu çalışmanın amacı, hemiparkinsonlu olgularda asemptomatik bazal gangliada 11C-W1N 35,428, tutulumunu ölçüm-lenıe yolu ile presemptomatik dopamin transport proteini kaybını görüntüleme ve gelecekte erken dönemde nöroprotektif tedavinin başlanması açısından preklinik dönemde PD saptamanın mümkün olup olamayacağını araştırmak idi.Bu amaçla seınptomatik ve asemptomatik bazal ganglia spesifik 11C-WIN 35,428 bağlanma oranları 7 hemiparkinsonlu olgu (ortalama semptom süresi 3.6yıl, ortalama yas 54±8 yıl) ile 7 kontrol olgusunda (ortalama yaş 55±9 yıl) PET uygulanarak karşılaştırıldı. Hemiparkinson olgularında klinik semptom gözlenmeyen tarafı kontrol eden striatal yapılarda spesifik 11C-WIN 35,428 bağlanma oranlarının kontrol gurubunda saptanan değerlerden belirgin olarak düşük olduğu gözlendi (p<0.05). Bu azalma seınptomatik taraf için posterior putamen, anterior putamen ve nukleus kaudatıısta sırası ile 64%), 47%, and 23%> oranında iken asemptomatik taraf için yine sırası ile 51%, 28% and 18%, oranında idi. Seınptomatik ve asemptomatik tarafın putamen ve nukleus kaudatus spesifik 11C-WIN 35,428 bağlanma oranları birbiri ile karşılaştırıldığında anterior putamende sağ ve sol arasında belirgin fark saptanırken (p<0.01), posterior putamen bağlanma oranları arasında anlamlı bir fark gözlenmemesi (p=0.()8), klinik olarak etkilenen ve etkilenmeyen tarafı kontrol eden posterior putamen bölgesinde biyokimyasal olarak benzer düzeyde dopamin transport proteini kaybı olduğunu ortaya koydu. Bu sonuçlar PET ile parkinson hastalığının presemptomatik tanısının mümkün olabileceğini ve erken dönemde dopaminerjik terminal kaybının beyinde biyokimyasal o/arak ölçümlenebileceğini göstermektedir. Gelecekte bu yöntemle klinik yaklaşımdan daha önce tanıya giderek erken dönemde nöroprote/dif therapiye haşlamak mümkün olabilir.*

**Anahtar Kelimeler:** Tek taraflı Parkinson hastalığı, Dopamin taşıyıcıları, PET

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Positron emission tomography (PET) has shown great promise for biochemical differentiation of PD early in the course of the illness; indeed,

there is the potential for prc-clinical discrimination. The hallmark of PD is degeneration of dopaminergic neurons in the substantia nigra and a corresponding loss of dopamine-containing nerve terminals in the basal ganglia. PET has been shown to delineate selective patterns of disruption of dopaminergic ncuromarkers initially with 18F-fluoroDOPA (1) (2) (3) and, more recently, by 11C-WIN 35,428, a ligand for the dopamine transporter (4).

As risk factors for idiopathic PD are identified in the future, and in particular for familial PD, the issue of screening for presymptomatic PD may become more important in the context of instituting early neuroprotective therapy. Thus, PET imaging of the dopamine transporter could play an important role. The problem of detecting early loss of dopaminergic cell function may be aided by the study of patients with hcmi-PD since the basal ganglia have not lost dopaminergic function to an extent sufficient to produce symptoms on both sides. In patients with hemi-Parkinson's disease (stage I), 11C-WIN 35,428 binding may be reduced in the basal ganglia corresponding to the asymptomatic side of the body, in addition to the already present loss of dopamine-containing nerve terminals corresponding to the symptomatic side. Therefore, the purpose of this study was to quantify the reduction in 11C-WIN 35,428 binding in the basal ganglia corresponding to the asymptomatic side to provide information that may be helpful in the future for the presymptomatic diagnosis of PD.

## Materials and Methods

### Patients

Seven patients with early PD affecting the left limbs in five and the right limbs in two, with mean symptom duration of 3.6 years and mean age 54 + 8 years, were compared with a group of seven normal subjects, mean age 55 + 9 yrs. Patients were clinically assessed by a single observer at 12 hrs after stopping their medication using the Unified Parkinson's disease (UPDRS) and Hoelin and Yahr (H&Y) rating scales. Patient characteristics are shown in Table 1. A11 controls had a normal neurological examination without evidence of rest tremor, rigidity or bradykinesia. A11 subjects provided informed consent and patients agreed to withdraw medications prior to the performance of the imaging protocol. Patients were studied following withdrawal of antiparkinsonian medications for a minimum of 12 hours prior to PET scanning.

### PET Acquisition

Imaging parameters were identical to those described previously (4). Briefly, a limited CT scan was performed to identify an imaging plane passing through the center of the head of the caudate nucleus, parallel to the glabellar-inion line. Tins imaging plane was registered in an individually fitted thermoplastic mask which the subjects wore during the imaging protocol, allowing the standardization of imaging planes between subjects. PET imaging was performed after the i.v. administration of approximately 20 mCi [11CJ-WIN 35,428 (mean specific activity, 6600 mCi/umole), synthesized as previously described (5). Twenty five scans of increasing duration (0.5 to 8 min) were then obtained over 90 min in a GE 4096 plus scanner. Throughout the acquisition the gantry and bed positions were continuously monitored and adjusted to ensure accurate positioning on the mask alignment line. A 10-minute transmission scan using a 68Ge source was performed prior to each study for subsequent attenuation correction. Images were reconstructed using ramped filtered back projection and smoothed with a 9 point neighborhood averaging filter to a final resolution of approximately 9 mm FWHM.

### ROI Analysis

Paired 4 x 4 pixel regions of interest (8 mm square ROI) were drawn on four summed (34 - 82 min) and smoothed PET images in each hemisphere using the coregistered CT as a guide. Eight regions of interest were placed throughout the cerebellar cortex in the lowest summed PET slice. Two consecutive summed images were used to cover a greater extent of the striatum. On each of these two summed images, and in each hemisphere, one region of interest was placed in the caudate and two in the putamen; the first one in the anterior putamen and the second one more posteriorly. To quantify [11CJ-WIN 35,428 binding, we computed the (region - cerebellum) / cerebellum ratio (Rcb), as previously described (4), where cerebellum represents non-specific binding.

Statistical analyses were performed on the (region-cerebellum)/cerebellnm ratios using a 2-tailed paired t-test for intra-subject comparisons, and using analysis of variance (Anova with post-hoc t-tests and Bonferroni correction) for group comparisons.

## Results

The preliminary data from stage 1 PD (hemiparkinson group) (Figure 1) demonstrate decreased [11C]-WIN 35,428 binding in the basal ganglia both contralateral to the clinically asymptomatic side and in the ipsilateral side. The decrease was greatest in the posterior putamen. Differences in [11CJ-WIN 35,428 binding between controls and the clinically unaffected side of the stage 1 PD reached statistically significant levels (ANOVA, $p<0.05$ ) in anterior and posterior putamen. Our results with [11CJ-WIN 35,428 in stage 1 PD patients show a 64%, 47% and 23% reduction in the posterior putamen, anterior putamen and caudate nucleus, respectively.

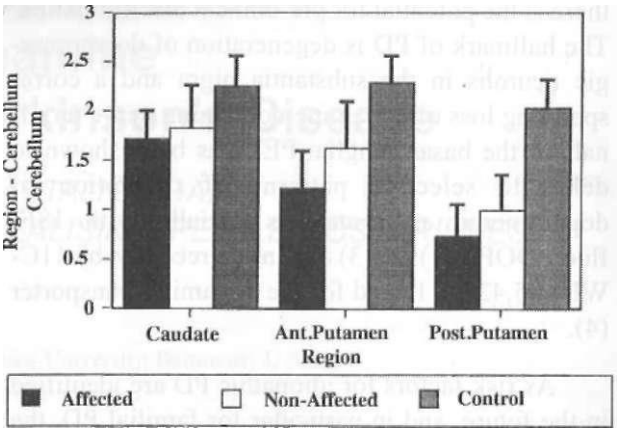


**Figure 1.** [11CJ-WIN 35,428 binding in stage 1 PD and normal controls. Affected corresponds to the basal ganglia contralateral to the symptomatic side of the body and non-affected corresponds to the asymptomatic side.

On the clinically silent side, the percent reduction was 51%, 28% and 18%, respectively. Interestingly, when the affected side was compared

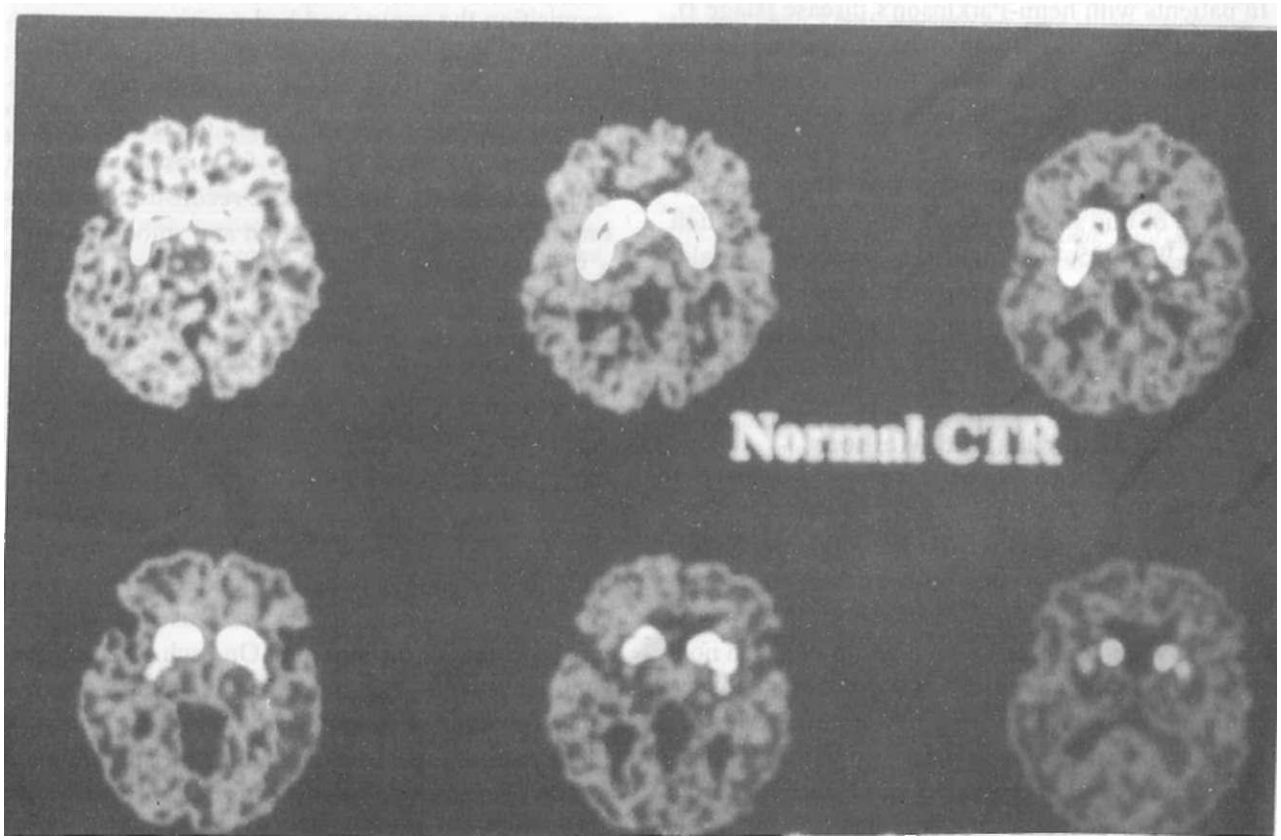


**Figure 2.** The comparison of the [I ICj-WIN 35,428 PET images in a patient with left hemi-PD (lower panel) with an age matched healthy control (upper panel). These images show significant reductions in DAT binding throughout the right and left putamen in the presence of left-sided symptoms.

to the unaffected side of the same individual (paired ttests, two tailed), significant differences were observed in the anterior putamen ($p<0.01$), but not in the posterior putamen ($p=0.08$), suggesting that a significant overlap exists between affected and clinically unaffected regions. In Figure 2, PET images of a healthy control and stage 1 PD patient are shown.

Previous data from this laboratory have shown that the specific binding in stage 2 PD patients with mild bilateral PD had a marked reduction in [11C]-WIN 35,428 binding in the basal ganglia, providing a clear visual and quantitative discrimination from normal controls. The cerebellum functioned as an appropriate region for nonspecific binding. In controls, the (region-cerebellum)/ccrebellum ratio varied around 3 in the striatum. Although we have recently developed the Patlak method for analysis of [11CJ-WIN 35,428 binding, the pattern and magnitude of change is similar to that of the ratio method.

## Discussion

An important finding of this study was that, in Stg 1-PD, there is significant reduction of DAT in the striatum contralateral to the asymptomatic side before the patients develop overt clinical features on that side. Similar to the previous PET findings obtained by 18F-fluoroDOPA, our findings with [11C]-WIN 35,428 show the greatest reduction in posterior putamen and the smallest reduction in the head of the caudate nucleus in patients with PD. This is likely due to the more rapid loss of ventrolateral substantia nigra cells that project primarily to the posterior putamen, whereas the rostral and medial cells project primarily to the caudate nucleus.

This data support previously reported postmortem findings suggesting that nigral cell loss may be over 50% by the time patients present with symptoms and clinical parkinsonism does not develop until approximately 80% of striatal dopamine is lost (6-9). Unfortunately, there arc no reported studies of postmortem nigral cell counts on newly diagnosed, idiopathic Stg 1 PD to directly assess this issue. The reason for the overt unilateral clinical features in the presence of significant bilateral DAT loss in Stg 1 PD still remains to be investigated. One explanation is that, at early stages of PD, there may be adaptive processes to counterbalance the nigral dopaminergic cell loss, until a critical treshold is reached where these adaptive mechanisms are no more effective for compensation. One such possible mechanism may be the increased synthesis and release of dopamine from residual midbrain dopaminergic neurons. Another compensatory mechanism may be increased turnover of the dopamine in the synapse with corresponding adjustments in synaptic enzyme activity (10). This has been demonstrated in animal studies by producing partial or unilateral midbrain lesions which have resulted in increased dopamine content and turnover in the remaining dopaminergic nerve terminals (11). In this regard, postmortem studies of patients with PD suggest that among various dopaminergic markers, striatal dopamine levels are most effected .While these levels correlate well with the tyrosine hydroxylase (TH) activity, there is lesser reduction of dopa decarboxylase (AADC) activity.Therefore, it has been suggested that in the early stage of nigrostriatal dopaminergic neuronal degeneration, AADC levels may be less susceptible to neurodegenerative influences than is TH synthesis or, alternatively, AADC synthesis may be more aggressively uprcgulated. Thus, in PD patients with moderate reductions of dopamine, dopa decarboxylase activity, as estimated by [18FJ-FDOPA PET may overestimate residual endogenous pre-synaptic dopamine terminal density function.

Consistent with this hypothesis is the evidence from PET findings reporting apparent wide differences in side to side putamen 18F-FDOPA uptake in unilateral PD, with ipsilateral putamen function often normal (12). [18FJ-FDOPA PET shows the activity of AADC (13) and is not a direct measure of the pre-synaptic dopaminergic nerve terminal content while [18F]-FDOPA Ki may be directly proportional to the number of the intact dopaminergic cells in substantia nigra (14). On the other hand, a SPECT imaging of the dopamine transporter performed in hemi-PD patients using 123I-B-CIT (15) showed that the mean striatal uptake of B-CIT contralateral to the asymptomatic side was reduced by 38%. Thus, both PET and SPECT studies using tracers labelling the dopamine transporter show significant reductions in DAT binding in putamen contralateral and ipsilateral to the symptom side in patients with hemi-PD.

In this regard, while pre-synaptic markers such as DAT may reflect the density of pre-synaptic dopaminergic, nerve terminals in PD (16) (17), [18FJ-FDOPA may represent the metabolism and turnover of the dopamine in the synapse. It would be desirable to cany out a study that would compare 18F-fluoroDOPA and [11CJ-WIN 35428 as tracers for measurement of changes in the dopaminergic system in PD. Such a comparative study may allow direct comparison of the two tracers with respect to, for example, sensitivity and specificity or the relationship to clinical symptoms. Then perhaps, in the same individual, different levels of reduction in the tracer uptake representing these two functions may be observed where reductions in dopamine turnover and therefore [18F]-FDOPA uptake would be different than the reductions in dopamine transporter.

An interesting observation in this study was the overlap in individual striatal binding (Rcb) values between patients with stage 1 and stage 2 PD as well as the overlap between the "symptomatic" and "asymptomatic" striatum in putamen and caudate regions. Thus, the levels of dopaminergic nerve terminal loss necessary to cause symptoms seems to be variable among patients, possibly due to these secondary adaptive mechanisms, with some subjects showing a higher level of compensatory change in the presence of higher levels of dopamine terminal degeneration than others.

On the other hand, this overlap perhaps would not be observed in later stages of the PD since a great amount of the dopaminergic nerve terminal densities would already be lost. Then an exponential relationship between the stage of PD and dopamine terminal degeneration would be true with a high rate of dopaminergic denervation in early stages versus a relatively slower rate of denervation in later stages of PD. This issue would best be clarified in longitudinal studies by comparing the loss of DAT in patient groups in different stages of PD over a period of time by a series of PET scans. This will again require robust and reproducible analysis methods such as statistical parametric mapping (SPM) in an observer independent manner. Furthermore, using SPM analysis, symptom measures such as tremor, rigidity and bradykinesia may also be covaricd throughout the time elapsed together with the tracer specific binding to follow up the changes in dopaminergic denervation.

**Conclusion:** The purpose of this study was the early biochemical identification of dopamine neuronal loss in hemi-PD by the use of [11CJ-WTN 35,428 and PET. These findings indicate that early >. diagnosis of PD by using PET is possible and presymptomatic dopaminergic teiininal loss may be biochemically measured in the brain. In the future such a test could be used to provide an earlier diagnosis than is possible by clinical means, thus leading to prompt institution of neuroprotective therapy. This would likely lead to an improvement in quality of life and perhaps life span, as well.

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