# Clinical and Imaging Data in Essential Tremor with Parkinsonian Features

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## Background

- Multiple clinical, genetic, histological and neuroimaging studies suggest overlap between essential tremor (ET) and Parkinson's disease (PD) [1].
- Mild parkinsonian features (rest tremor, bradykinesia, rigidity) can be observed in some ET patients.
- DaTscan (GE Healthcare, Princeton, NJ), or I123-ioflupane SPECT, has been recommended as a tool to image dopamine transporter (DAT) and to assist in differentiating between ET and PD in clinically uncertain cases.
- Mild presynaptic dopaminergic deficit in ET patients was reported by some studies utilizing DAT imaging [2]; although the majority of previous studies revealed no difference in DAT imaging between ET and healthy controls [3].
- This study was designed to analyze demographic, clinical and DAT imaging data in patients with ET with or without parkinsonian features.

## Methods

- 20 patients with ET with and without parkinsonian features, and 11 healthy volunteers were enrolled.
- All study subjects were examined by a movement disorders neurologist and divided into 4 groups:
  1) healthy controls, HC (no tremor or parkinsonian features),
  2) pure ET (no parkinsonian features),
  3) ET with parkinsonian features, ET-p (1 parkinsonian feature or 2 subtle parkinsonian features not sufficient for the clinical diagnosis of PD),
  4) ET with concomitant PD, ET+PD (2 or more clear parkinsonian features when clinical presentation meets diagnostic criteria for PD). ET preceded PD onset by at least 5 years.
- All study subjects underwent smell test (University of Pennsylvania Smell Identification Test, UPSIT) and DaTscan imaging.
- Tremor severity in ET patients was graded according to TETRAS (The Essential Tremor Rating Assessment Scale).
- Severity of PD was graded according to MDS UPDRS (Movement Disorders Society Unified Parkinson's Disease Rating Scale).
- DaTscan images were visually analyzed by a nuclear medicine physician and interpreted as normal or abnormal.
- By using a semi-automated software DaTQUANT, quantitative measurements of striatal binding ratios (SBR) were obtained in the following Volume of Interests (VOIs): Caudate, Putamen, Anterior Putamen, Posterior Putamen, Striatum and Background. Quantitative image analysis was performed by a radiologist (Dr. Wu) blinded to the study subjects' clinical data and to the results of visual image interpretation.
- Statistical analysis and comparison of demographic, clinical and imaging characteristics was performed among all groups of study subjects.

## Results

**Table 1. Demographic and clinical data of the study subjects**

| | HC (N=11) | ET pure (N=7) | ET-p (N=5) | ET+PD (N=7) |
|---|---|---|---|---|
| **Age, yrs Mean, SD (range)** | 62.9, SD 10.3 (36 – 73) | 61.1, SD 9.1 (45 – 75) | 61.2, SD 6.6 (49 – 69) | 58.7, SD 6.9 (49 – 67) |
| **Gender** | 5 F, 6 M | 2 F, 5 M | 3 F, 2 M | 2 F, 5 M |
| **Family history of ET** | 2 | 5 | 2 | 6 |
| **Family history of PD** | 0 | 1 | 0 | 2 |
| **Age at ET onset, yrs Mean, SD (range)** | n/a | 29.3, SD 15.2 (11 – 48) | 43.2, SD 14.7 (21 – 60) | 27.5, SD 11.9 (19 – 49) |
| **Duration of ET, yrs Mean, SD (range)** | n/a | 31.9, SD 15.4 (9 – 41) | 20.0, SD 10.5 (2 – 31) | 31.1, SD 8.9 (17 – 45) |
| **Onset, bilateral (b/l) or unilateral** | n/a | Uni (N=4), b/l (N=2), b/l but asymmetric (N=1) | b/l (N=3), b/l but asymmetric (N=2) | Uni (N=5), b/l but asymmetric (N=2) |
| **UPSIT score, max 40 Mean, SD (range)** | 35.1, SD 2.02 (32 – 38) | 33.7, SD 2.0 (31 – 37) | 30.4, SD 3.2 (25 – 32) | 18.4, SD 7.1 (8 – 24) |
| **TETRAS, max 68 Mean, SD (range)** | n/a | 19.6, SD 7.8 (8.5 – 34.5) | 24.8, SD 12.9 (12 – 45.5) | 21.4, SD 8.3 (8.5 – 31) |
| **MDS UPDRS motor Mean, SD (range)** | n/a | n/a | 18.2, SD 9.6 (10 – 29) | 34.4, SD 18.3 (12 – 67) |

## Results, continued

- All healthy controls and all ET patients had normal DaTscan as determined by visual image analysis.
- 7 out of 8 patients with clinical diagnosis ET+PD had reduced striatal radioligand uptake suggestive of presynaptic dopaminergic deficit. One patient with Klinefelter syndrome, clinical diagnosis ET+PD (action tremor since childhood, rest tremor, generalized bradykinesia and mild rigidity) had normal DaTscan. This subject was excluded from statistical analysis.
- Quantitative DaTscan image analysis revealed no statistically significant difference in the SBRs among HC, pure ET and ET-p groups in all VOIs (Table 2).
- Among all ET patients, SBRs were slightly lower in ET-p subjects than in pure ET subjects in all VOIs (p-value 0.56 / 0.71 for right / left striatum) (Box 1).
- ET subjects had slightly higher SBRs than HCs in all VOIs except caudate nuclei where SBRs was equal or even lower than in HC (p-value 0.96 / 0.74 for right / left side) (Box 2a). Putamen-to-Caudate ratio was also slightly higher in ET than in HC (p-value 0.29 / 0.04 for right / left side) (Box 2b).
- Patients with ET+PD had predominantly decreased SBRs in posterior caudate (p-value 0.000008 / 0.0007 for right / left side) (Box 3a) and slightly lower Putamen-to-Caudate ratio than HCs (p-value 0.1 / 0.27 for right / left side) (Box 3b).

**Table 2. DaTscan imaging data in study subjects**

Box 1

| Mean, SD (range) | HC | ET all | ET pure | ET-p | ET+PD |
|---|---|---|---|---|---|
| **Striatum, R** | 1.64, SD 0.28 (1.27 – 2.12) | 1.7, SD 0.32 (1.04 – 2.14) | 1.75, SD 0.27 (1.31 – 2.12) | 1.63, SD 0.4 (1.04 – 2.14) | 0.78, SD 0.2 (0.56 – 1.1) |
| **Striatum, L** | 1.64, SD 0.27 (1.25 - 2.13) | 1.7, SD 0.35 (0.98 - 2.17) | 1.73, SD 0.31 (1.2 - 2.08) | 1.64, SD 0.44 (0.98 - 2.17) | 0.79, SD 0.41 (0.48 - 1.69) |
| **Put, R** | 1.52, SD 0.26 (1.09 - 1.93) | 1.61, SD 0.33 (0.98 - 2.05) | 1.68, SD 0.26 (1.25 - 2.02) | 1.5, SD 0.41 (0.98 - 2.05) | 0.63, SD 0.22 (0.4 - 1.0) |
| **Put, L** | 1.5, SD 0.25 (1.03 - 1.93) | 1.61, SD 0.34 (0.89 - 2.03) | 1.67, SD 0.28 (1.13 - 1.98) | 1.54, SD 0.43 (0.89 - 2.03) | 0.66, SD 0.41 (0.41 - 1.57) |
| **Anterior Put, R** | 1.66, SD 0.29 (1.24 - 2.19) | 1.75, SD 0.34 (1.08 - 2.2) | 1.82, SD 0.27 (1.34 -2.17) | 1.64, SD 0.42 (1.08 - 2.2) | 0.73, SD 0.22 (0.51 - 1.12) |
| **Anterior Put, L** | 1.7, SD 0.27 (1.24 - 2.25) | 1.75, SD 0.38 (0.93 - 2.26) | 1.81, SD 0.29 (1.26 - 2.15) | 1.67, SD 0.5 (0.93 - 2.26) | 0.78, SD 0.47 (0.46 - 1.81) |
| **Posterior Put, R** | 1.08, SD 0.24 (0.61 - 1.47) | 1.2, SD 0.31 (0.68 - 1.62) | 1.26, SD 0.24 (0.96 - 1.53) | 1.1, SD 0.4 (0.68 - 1.62) | 0.33, SD 0.22 (0.07 - 0.64) |
| **Posterior Put, L** | 0.97, SD 0.25 (0.47 - 1.41) | 1.26, SD 0.24 (0.8 - 1.53) | 1.29, SD 0.25 (0.81 - 1.53) | 1.21, SD 0.24 (0.8 - 1.43) | 0.37, SD 0.29 (0.1 - 0.95) |
| **Caud, R** | 1.84, SD 0.35 (1.48 - 2.47) | 1.85, SD 0.34 (1.14 - 2.29) | 1.86, SD 0.3 (1.41 - 2.29) | 1.84, SD 0.42 (1.14 - 2.29) | 1.03, SD 0.25 (0.72 - 1.31) |
| **Caud, L** | 1.9, SD 0.34 (1.5 - 2.51) | 1.85, SD 0.41 (1.13 - 2.42) | 1.86, SD 0.4 (1.31 - 2.27) | 1.83, SD 0.47 (1.13 - 2.42) | 1.01, SD 0.44 (0.6 - 1.91) |
| **Put/Caud R** | 0.89, SD 0.06 (0.8 - 0.99) | 0.92, SD 0.07 (0.8 - 1.08) | 0.94, SD 0.06 (0.9 - 1.08) | 0.88, SD 0.06 (0.8 - 0.93) | 0.81, SD 0.1 (0.67 - 0.98) |
| **Put/Caud L** | 0.86, SD 0.07 (0.76 - 0.97) | 0.92, SD 0.06 (0.88 - 1.07) | 0.94, SD 0.07 (0.88 - 1.07) | 0.9, SD 0.03 (0.88 - 0.95) | 0.82, SD 0.07 (0.69 - 0.9) |
| **Put Asymmetry ratio** | 0.02, SD 0.02 (0 - 0.06) | 0.03, SD 0.02 (0 - 0.05) | 0.03, SD 0.02 (0 - 0.05) | 0.03, SD 0.02 (0.01 - 0.05) | 0.11, SD 0.08 (0.04 - 0.25) |
| **Caud Asymmetry ratio** | 0.04, SD 0.03 (0 - 0.1) | 0.03, SD 0.03 (0 - 0.09) | 0.04, SD 0.03 (0.01 - 0.09) | 0.02, SD 0.03 (0 - 0.06) | 0.11, SD 0.08 (0.01 - 0.25) |

Box 2a

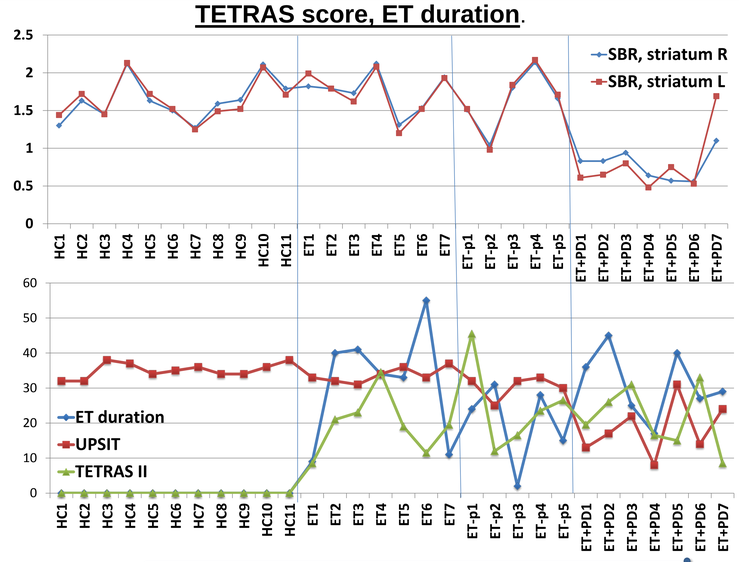
Box 2b

- UPSIT score was lower in ET group than in HC (p-value 0.02). ET+PD group demonstrated the lowest UPSIT score.
- There was strong correlation between UPSIT score and SBRs in all study subjects (Pearson correlation coefficient 0.76 and 0.77 for the right and left side respectively) (Figure 1).
- There was weak correlation between SBRs and ET duration (Pearson correlation coefficient -0.23 and -0.26), and no correlation between SBRs and tremor severity as measured by TETRAS (Pearson correlation coefficient 0.07 and -0.05) (Figure 1).

*Poster available for download.*

## Results, continued

**Figure 1. Correlation between striatal binding ratio (SBR), UPSIT, TETRAS score, ET duration.**




Box 3a

Box 3b

## Discussion

- Subpopulation of patients with ET and parkinsonian symptoms includes patients with a combination of ET and PD (ET+PD) and ET with parkinsonian features but without evidence of presynaptic dopaminergic deficit (ET-p).
- DAT imaging in ET+PD group is not different from pure PD patients with predominant and asymmetric dopaminergic deficit in posterior putamen followed by involvement of other VOIs in striatum as disease progresses.
- Parkinsonian features in ET patients do not seem to be related to underlying dopaminergic deficit as measured by DAT imaging. On the other hand, motor symptoms in PD usually manifest only after loss of about 50% of dopamine-containing neurons in the substantia nigra that would reflect in abnormal DAT imaging. Therefore, pathophysiology of parkinsonian features in ET might be different from PD.
- Our study results demonstrate relative dopaminergic deficit in caudate nuclei in ET patients as opposed to predominantly putaminal dopaminergic deficit observed in PD patients, similar to previously reported data [4].

## Conclusions

- Pathophysiology of parkinsonian features in ET is unclear and might be different from pathophysiology of PD.
- Dopaminergic hypofunction in caudate nuclei might be implicated in pathophysiology of ET and especially ET with parkinsonian features; however this hypothesis requires further investigation.

## References

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## Acknowledgements

1. GE Healthcare, Princeton, NJ – study sponsor
2. Ying Wu, MD; Center for Advanced Imaging ,Radiology Department, NorthShore University HealthSystem, Evanston, IL – quantitative DaTscan image analysis.