



INFLUENCE OF SEMIQUANTIFICATION IN DATSCANTM STUDIES FOR DIAGNOSIS OF PARKINSONIAN SYNDROMES

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Abstract

Healthy controls reference values (RV) of DaTScanTM and its semi-quantification (SQ) adapted to Infanta Cristina's Hospital in Badajoz were created. It was used a sample of 120 DaTScanTM tests divided into 4 groups with $n = 30$. The first one of healthy controls (GI) was used for calculation of RV. It was applied a semiautomatic method for segmentation and posterior calculi of the specific uptake ratios (SUR), respectively: Left and Right Caudate Nucleus/Occipital (A) and (B); Left and Right Putamen/Occipital (C) and (D); Striatum/Occipital (E); Left and Right Striatum/Occipital (F) and (G); Putamen/Caudate Nucleus (H). The second and third groups (healthy group (GIH) and pathological group (GIIP)) were compared to GI for validation proposes. Control charts and ROC curves (ROCC) were obtained. The fourth group of randomized patients was used to evaluate the ability of SQ classification and it was compared with the physician evaluation. Sensibility (S), Specificity (SP), Positive (PPV) and Negative (NPV) predictive values were calculated. RV ($\bar{x} \pm \delta$): A (2.60±0.40); B (2.57±0.36); C (2.29±0.36); D (2.31±0.35); E (2.44±0.35); F (2.44±0.37); G (2.44±0.34); H (0.89±0.07). The GIH values are above the RV and the GIIP group below the RV. The AUC, S and SP values for each SUR obtained by ROCC were: A (0.805; 0.765; 0.846); B (0.787; 0.711; 0.864); C (0.907; 0.853; 0.962); D (0.933; 0.930; 0.933); E (0.884; 0.871; 0.897); F (0.860; 0.800; 0.920); G (0.868; 0.844; 0.893); H (0.866; 0.732; 1.00). Were obtained results for PPV=0.466; NPV=1; S=1 and SP=0.65. The SQ combined with the visual analysis is a good method to detect healthy patients.

1. INTRODUCTION

Parkinsonian Syndromes (PS) are a group of neurodegenerative diseases characterized by the functional loss of neurons and dopaminergic terminations in the *substantia nigra*. Parkinson Disease (PD) belongs to this group and it is the second most common movement disorder (it afflicts 1-2% of the population), being thereby of great importance the capability of distinguish between PS and other pathologies with similar symptoms but with different origin and physiopathology. [1, 2]

Single Photon Emission Computed Tomography (SPECT) with ¹²³I-FP-CIT – DaTScanTM – is used for assessment by imaging of the *Striatum*, allowing the evaluation of the presynaptic dopaminergic system, in which Dopamine Transporters (DaT) are responsible for the release and reabsorption of dopamine in to the synapse, for this to be stored or degraded [2-5].

Therefor DaTScanTM is used in differentiation between essential tremor and PS [1-6]. *Tolosa E. et al.*, reported the sensibility of 77% and specificity of 100% in this differentiation, being aware that this diminution of DaT only occurs in PS this differentiation is important for the following therapeutic management [7, 8].

In DaTScanTM exams with a healthy image standard imaging it is characterized by the visualization of portions of the *Striatum Body* (SB), with the shape similar to two symmetric comas. In pathologic exams there is a diminishing of the uptake in the SB, in the early stage of these diseases this starts to be noticeable in the Putamen and in later stages this starts to occur also in the caudate. This uptake changes can be symmetric or asymmetric [1, 7].

In the clinic work is usual the evaluation of these exams for diagnostic purpose being performed only by visual assessment, although this evaluation is subjective, complex and dependent of the operator experience, it is also influenced by high levels of variability intra and operator [7-9].

In order to improve the diagnosis process, several methods of SQ of the ¹²³I-FP-CIT uptake in the interest brain structures have being developed [8, 10]. To apply these methods in DaTScanTM studies, there are drawn Region of Interest (RoI) and ratios between different regions: Specific uptake ratios (SUR) are calculated between regions of specific uptake (in the *Striatum*) and other regions of nonspecific uptake that correspond to the background, and are regions with a low density of DaT (for example in the occipital region) and symmetry ratios (SR) between regions of specific uptake [5-8, 11]. By using the different uptake values of the segmented regions the rations are calculated, for the SUR is expressed in the equation (1).

$$SUR = \frac{\bar{x} \text{ Striatum counts} - \bar{x} \text{ background counts}}{\bar{x} \text{ background counts}} \quad (1)$$

The segmentation process in this process can be by manual, automatic or semiautomatic methods [11]. The manual method is the most currently used in the clinical practice although the automatic method being the most reproducible [10, 11].

In the segmentation process by with semiautomatic RoI, these are automatically

generated, and after they are manually adjusted, diminishing the variability intra and inter operator when compared with the fully manual method [9-11].

The reproducibility of the SQ increases when its values are compared with the Reference Uptake Ratios of the same age class. The low utilization of the SQ in the clinical practice, is due to the necessity of its values to be adjusted to the population where it is being applied, and also to the exam protocol of each Nuclear Medicine Department. There are also many factors that can create bias in the process of implementation of the Reference Values (RV), and it is also a process that takes much time [5, 7-12].

The purpose of the study is the creation and validation of RV obtained by recurring to SQ of DaTScanTM studies, as complement to the visual assessment, in order to increase the accuracy diagnosis of the PS in DaTScanTM exams.

2. METHODOLOGY

The present study was developed in the three stages following presented: creation of a Data Base with healthy controls for the determination of the RV of each Uptake Ratio (UR); the validation of the obtained RV by comparison with studies between healthy controls with ratios obtained in patients with PS; and the third stage the assessment of the influence of the SQ of the DaTScanTM, through the comparison of the results of diagnostic classification by applying the RV with the previous diagnosis performed by a clinic trained physician, without recurring to SQ.

2.1. Sample Selection

A sample of 120 DaTScanTM studies was collected, the subjects of the sample had ages between 60 and 75 years, and were people with indication for undergoing DaTScanTM exam, and were in the database of the XelerisTM workstation in Infanta Cristina's Hospital, in Badajoz.

The first 90 studies were selected by convenience sampling, and divided into three groups with 30 elements; this separation was made by the classification of the exams clinical reports by Nuclear Medicine and Neurologist Physicians: Group I (GI) – Healthy control group, these exams had a normal uptake imaging, and this group was used for obtention of the RV; Group IIP (GIIP) – Pathologic group that presented a pathologic uptake imaging, suggestive of PS and Group IIS (GIIS) – healthy group, these exams were of subjects with normal uptake. Both GIIP and GIIS were used in the validation of the obtained RV.

In the last phase of the study was used random sampling for the selection of 30 DaTScanTM studies of the same age range than the ones of the created RV, also from studies of the department workstation database. This sample was the Group III (GIII), it was guaranteed that this group didn't include repeated studies from the previously created groups.

2.2. Exams protocol

All studies were acquired by *EANM guidelines* suggested protocol, and with the same acquisition conditions. For the acquisition of the exams the patients were in supine position and had the head immobilized with a head support, to restrict movement. The exams were acquired 4 hours after the Intravenous administration of 185 MBq of ¹²³I-FP-CIT.

All the SPECT Studies performed using parallel-hole, low energy, and high resolution collimator; the rotation radius was minor than 15 cm, matrix of 128x128 pixels, and zoom of 1.25, circular acquisition orbits of 360 ° in mode *step and shoot*, the Energy peak of 159 keV±10%, 64 projections with 30 seconds each [5,10].

For the image reconstruction and processing of the *DaTScan™ studies of GI, GII and GIII*, each study was processed three times in the workstation *Xeleris™*, by the same operator, to eliminate any interference of interoperator variability. All data were reconstructed by Filtered Back Projection (FBP), it was used Butterworth filter (cutoff frequency of 0.4 cycles per pixel and power was 10), the ramp filter applied was quantitative, the color map applied was GE Color.[10]

It was created a summed image of three transaxial slices that comprehend the totality of the Striatum tissue. It was determined the average counts of the Left and Right Caudate (LC and RC), left and right putamen (LP and RP) and of the occipital (OC) regions respectively. This was achieved by using the semi-automated Rols presented in the figure 1[5, 10].

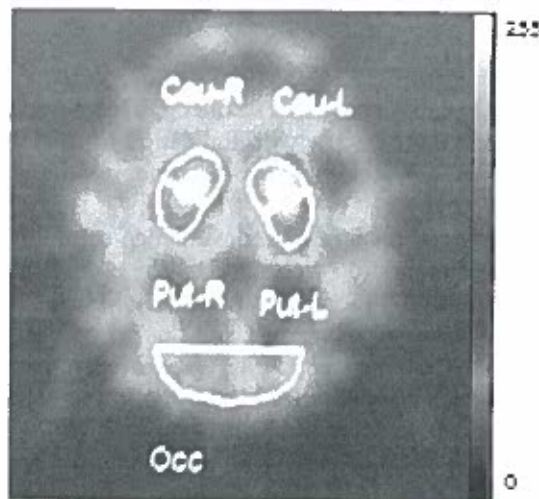


Figure 1: Summed image of three transaxial slices containing the striatum, and the semiautomatic used Rols in LC, RC, LP, RP and OC.

2.3. Reference Values Uptake Ratios

After the assessment and exclusion of outliers through the dispersion diagram, it was calculated the average \pm standard deviation ($\bar{x} \pm \delta$) of the UR (both the SUR and symmetry ratios (SR)) to obtain the RV of the healthy controls of Infanta Cristina's Hospital.

There were calculated RV for each of the UR of each study, presented in the table 1.

Table 1: Expressions for ratios calculation for SQ of the in the *DatScan™* studies, and code of the expression.

| Uptake Ratio | | Short form | Code |
|---|---|----------------------------------|------|
| <u>Caudate</u> <u>Occipital</u> | $\frac{\text{Left Caudate}}{\text{Occipital}}$ | $\frac{LC}{Oc}$ | A |
| | $\frac{\text{Right Caudate}}{\text{Occipital}}$ | $\frac{RC}{Oc}$ | B |
| <u>Putamen</u> <u>Occipital</u> | $\frac{\text{Left Putamen}}{\text{Occipital}}$ | $\frac{LP}{Oc}$ | C |
| | $\frac{\text{Right Putamen}}{\text{Occipital}}$ | $\frac{RP}{Oc}$ | D |
| <u>Striatum</u> <u>Occipital</u> | $\frac{\text{Right Putamen} + \text{Left Putamen} + \text{Right Caudate} + \text{left Caudate}}{4 \text{ Occipital}}$ | $\frac{RP + LP + RC + LC}{4 Oc}$ | E |
| <u>Left Striatum</u> <u>Occipital</u> | $\frac{\text{Left Putamen} + \text{Left Caudate}}{2 \text{ Occipital}}$ | $\frac{LP + LC}{2 Oc}$ | F |
| <u>Right Striatum</u> <u>Occipital</u> | $\frac{\text{Right Putamen} + \text{Right Caudate}}{2 \text{ Occipital}}$ | $\frac{RP + RC}{2 Oc}$ | G |
| <u>Putamen</u> <u>Caudate</u> | $\frac{\text{Right Putamen} + \text{Left Putamen}}{\text{Right Caudate} + \text{Left Caudate}}$ | $\frac{RP + LP}{RC + LC}$ | H |

2.4. Validation of the Reference values

To validation of the RV, after assessment of the normal distribution of the samples GIII and GIIP were created control charts, with the distribution of the values of the ratios with the codes name from A to H presented in the table 1, using the RV as standard [13, 14].

The control charts were analyzed by a different, method, for more restrict classification, it was considered healthy all values which the SUR were higher than the lower value of standard deviation, and always that in the symmetry UR, this was preserved and fitted the limit ($\bar{x} \pm \delta$).

This analysis considers what from a clinic point of view makes sense in a way of increasing the rigor of the established RV. From the analysis of the control charts, to assess the sensibility and specificity of the study, were created Receiver Operating Characteristics (ROC) curves [15, 16].

2.5. Assessment of the influence of the SQ in the classification of *DaTScan*TM studies

After calculation of the UR of the GIII, and by comparison of the UR from A to H, obtained with the created RV, each study was classified as pathologic or non-pathologic. This classification was after compared with the diagnosis that the Nuclear Medicine Physician (realized only with visual assessment of the *DaTScan*TM studies) and with the results of the neurologic reports with the evolution of the last five years, always that this information was available. From this comparison were calculated the sensibility, specificity, Positive Predictive Value (PPV) and Negative Predictive Value (NPV) [14, 17, 18].

3. RESULTS

The RV created from the SQ of the Healthy control group, are presented as ($\bar{x} \pm \delta$), in the table 2. The UR A (2.60 ± 0.40) and B (2.57 ± 0.36) are about the caudate dopaminergic uptake, the UR C (2.29 ± 0.36) and D (2.31 ± 0.35) of the putamen right and left respectively. The UR E is the one that measures the totality of all the Striatum and it value is (2.44 ± 0.35). The UR F (2.44 ± 0.37), G (2.44 ± 0.34) and H (0.89 ± 0.07) are UR of symmetry.

Table 2: Reference Values ($\bar{x} \pm \delta$) obtained for the SUR A-H through the SQ of GI.

| UR | Reference Value ($\bar{x} \pm \delta$) |
|----|--|
| A | 2.60 ± 0.40 |
| B | 2.57 ± 0.36 |
| C | 2.29 ± 0.36 |
| D | 2.31 ± 0.35 |
| E | 2.44 ± 0.35 |
| F | 2.44 ± 0.37 |
| G | 2.44 ± 0.34 |
| H | 0.89 ± 0.07 |

In the control charts of all the Uptake ratios calculated, obtained for validation of the RV previously calculated, only the UR C of the GIIP did not presented one normal distribution ($p=0,004$). The control charts allow the global visualization of the distribution of the UR of the subjects in the groups GIIH and GIIP, when compared with the established RV.

The limit ($\bar{x} - \delta$) of each RV of the UR were considered the value that allow to distinguish a pathologic *DaTScan*TM from a healthy one. The UR from A to H corresponding to the GIIH places above the RV ($\bar{x} - \delta$) and in the GIIP it occurred the opposite. In the UR A and B that correspond to the caudate uptake is the UR that presents the bigger quantity of subjects of the GIIP above the average of the RV.

The UR H that corresponds to a Symmetry UR is one that also presents many subjects of the GIIP above the average, nevertheless it does not present any subject of the GIIH below that limit. The UR D is the one that presents better concordance with the theoretical assumed knowledge.

Through the analysis of the control charts, was verified that 93% of the patients of the GIIH were above the limit ($x - \delta$) of the UR and 80% of the patients that belong to the GIIP were below the same limit, for corresponding to clinical pathologic patients.

The results of the Area Under the Curve (AUC) obtained by the ROC curves of standard error, sensibility and specificity of the UR from A to H is in the figure 2. The AUC range is between 0 and 1. In this study the AUC values are comprehended between 0.787 UR B and 0.933 UR D, and the standard error range from 0.037 UR D and 0.062 UR B. The UR A is the one that presents lower value is of 0.84. The UR D of 0.930 is the one that present higher value of specificity, being the UR B 0.711, the one which presents the lower value.

Table 3: Results AUC, Standard Error, Specificity and Sensibility of the curves ROC of the UR A to H.

| | A | B | C | D | E | F | G | H |
|----------------|-------|-------|-------|-------|-------|-------|-------|-------|
| AUC | 0.805 | 0.787 | 0.907 | 0.933 | 0.884 | 0.860 | 0.868 | 0.866 |
| Standard Error | 0.059 | 0.062 | 0.042 | 0.037 | 0.048 | 0.051 | 0.051 | 0.046 |
| Specificity | 0.765 | 0.711 | 0.853 | 0.930 | 0.871 | 0.800 | 0.844 | 0.732 |
| Sensibility | 0.846 | 0.864 | 0.962 | 0.933 | 0.897 | 0.920 | 0.893 | 1.000 |

In the tables 4 and 5 are presented the concordance values between the medical report and the diagnosis performed having SQ for basis, with the sensibility values (1.000); specificity (0.652), PPV (0.467) and NPV (1.000) of the RV of the UR A to H. The sensibility is elevated, and consequently an NPV also high. On the other side the specificity is not so elevated, to which 5 corresponds a lower PPV. The elevated NPV indicates that all the subjects classified as healthy (n=15), having by support the RV of the UR from A to H,

correspond to healthy subjects also classified as healthy by the medical reports that are being used as reference [19, 20].

The lower PPV indicates that from the 15 that our classifier classified as pathologic only 7 were classified as pathologic by the physician's reports.

Table 4: Sensibility, Specificity, PPV and NPV of the RV of the UR C to H, compared to physician's diagnosis by Visual assessment.

| | |
|-------------|-------|
| Sensibility | 1,00 |
| Specificity | 0,652 |
| PPV | 0,467 |
| NPV | 1,00 |

Table 5: Classification of positive or negative to the presence of PS, by comparing classification by the RV limit implementation and the visual assessment by the physician.

| | Pathologic | Yes | No | Total |
|-------|------------|-----|----|-------|
| Test | Positive | 7 | 8 | 15 |
| | Negative | 0 | 15 | 15 |
| Total | | 7 | 23 | 30 |

4. DISCUSSION

About the RV calculated for the GI, the UR from A-B, C-D and F-G are similar, as they correspond to the homologs symmetric structure of the striatum. The UR F and G present an average value between the caudate and the left and right putamen respectively.

The UR C and D correspond to putamen uptake. This is the first structure to suffer degeneration in pathologic cases [5, 10]. The present study corroborates this.

The AUC values presented in the table 3 more elevated are relatives to the UR C (0.907) and D (0.933), corresponding also to the lower values of the obtained standard error. Through the SQ analysis of these two UR exist 90.7% and 93.3% probability, respectively; of a pathologic study present a lower uptake value than a healthy study [15, 16, 21-23]. This result needs further investigation, for understanding the reason for the asymmetry, or if it is a random probabilistic value. Although this value these two UR are considered an excellent tool for separating the pathologic form the non-pathologic subjects [15, 21-23]. These UR have also very high values of specificity and sensibility.

The UR E, F, G and H present as AUC values 0.884, 0.860, 0.868 and 0.866, respectively; being also useful for separation of the groups [16, 21-23].

In this group the UR E is the best indicator, because it accounts for total of the specific uptake, being the summed value of the UR F and G.

The UR G presents a AUC value slightly higher to the UR F, for the same reason of the difference between UR C and D.

The UR H is the one with better value of sensibility (1.000), being an excellent parameter for detecting pathologic subjects [16].

The UR A and B account the uptake of the left and right caudate, the caudate is the last structure of the *Striatum* to suffer diminishing of the uptake [5, 10]. Thereby these are the UR with lower value of AUC of 0.805 and 0.787, respectively.

In the last stage of the study only the UR C to H were taken in to consideration, for the subject's classification, for being the best discriminating ratios between pathologic and healthy. It was possible to verify the high NPV and consequently the high sensibility (1.000) of the created RF, as is presented in the tables 4 and 5. These results confirm the high capability of the SQ for detecting pathology between the subjects that are positive to the presence of the disease [16, 21]. The concordance level between the two techniques was of 100%, in this detection.

The specificity is lower, the proportion of truly healthy subjects between the ones that were considered non pathologic is lower [16], in this study it were considered 8 subjects as pathologic, that the reference clinical reports classified as healthy. These results can be explained by the SQ being able of detect pathologic changes prior to the visual assessment, but further investigations are required, with the following of the patients and extern validation by other techniques, to confirm this hypothesis. The majority of patients had no information with a 5 years follow up; this could have provided more certainty about the evolution of the patient, to confirm which classification was more accurate. The method with only one limit below the standard deviation that was used could also influenced the results and have influence in this parameters.

5. CONCLUSION

From this study we can conclude that the SQ, with the RV established for Infanta Cristina's Hospital in the *DaTScanTM* studies, is precise and accurate in the classification of subjects with suspected PS, being able of use for complementing visual assessment.

In the future it would be interesting to confirm is the differences between SQ classification and the visual assessment classification could be due to an earlier detection by the SQ technique.

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