


De l'utilisation des données de séries de cas à la conception de projet de recherche

L'exemple de la maladie de Parkinson


M. Vaillant, N. Sauvageot, N. Diederich



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Plan

- Collaboration
- séries de cas
 - Matériels et méthodes
 - Résultats
- études prospectives
 - Matériels et méthodes
 - Résultats
- Conclusion



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Etudes de séries de cas

- Etude 1: Syndrome de l'apnée du sommeil chez les personnes atteints de la maladie de Parkinson
- Etude 2: Destructuration progressive du sommeil chez les personnes atteints de la maladie de Parkinson

Collecte des données

- 57 Patients vus en consultation au CHL
- Sélection de 49 patients parkinsoniens idiopathiques, non déments
- Polysomnographie au laboratoire du sommeil (électroencéphalographie, électro-oculographie, électromyographie, suivi de la respiration et électrocardiographie)
- Hoehn-Yarr, Epworth sleepiness scale

Méthodologies

- Etude 1:
 - Cas-témoins, 49 cas vs 49 témoins
 - Appariement sur âge, sexe, ahi → en classes
- Etude 2:
 - Observationnelle, 46 patients (3 patients ayant secondairement développé une démence)



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Syndrome de l'apnée du sommeil chez les personnes atteints de la maladie de Parkinson

- Hypothèse:

Le syndrome d'apnée du sommeil serait la cause du fractionnement du sommeil de patients parkinsoniens dans le cas où l'étude montrerait des répercussions identiques chez un groupe de témoins non parkinsoniens



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Syndrome de l'apnée du sommeil chez les personnes atteints de la maladie de Parkinson

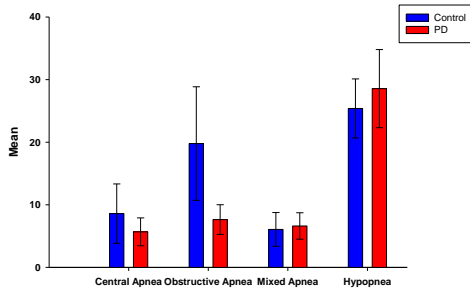
- Sex ratio:38/11 dans les 2 groupes
- Age: 64.9 (9.5) ans dans le groupe PD et 61.3 (15.1) ans dans le groupe témoin.
- AHI : 9.1 (13.2) dans le groupe PD et 10.9 (17.1) dans le groupe témoin.
- Les patients du groupe parkinsonnien avaient:
 - une durée de la maladie de 7.5 (5.2) ans
 - un score de Hoehn-Yahr de 2.4 (0.8)
 - un score d'Epworth de 8.5 (4.8)
 - un dosage de levodopa de 495.9 (293.5) mg
 - un dosage d'agoniste dopaminergiques (exprimé en équivalents pergolide) de 1.2 (1.4) mg.

Syndrome de l'apnée du sommeil chez les personnes atteints de la maladie de Parkinson

- 43% du groupe Parkinson vs 24% du groupe témoin présente un SAS
- Déclin de la saturation moyenne et minimale en oxygène moins faible du groupe Parkinson
- Différence de saturation minimale en oxygène maintenue dans le groupe Parkinson avec AHI>15

Syndrome de l'apnée du sommeil chez les personnes atteints de la maladie de Parkinson

- Ratio des apnées obstructives, centrales et mixtes identique dans le groupe Parkinson
- Apnées obstructives prévalentes chez les témoins



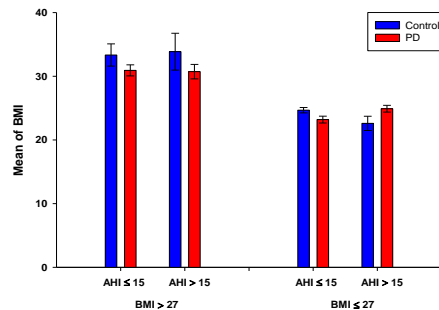
The Apnea-Hypopnea Index (AHI) components in 49 PD patients and 49 controls

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Syndrome de l'apnée du sommeil chez les personnes atteints de la maladie de Parkinson

- Avec BMI > 27:
 - Saturation moyenne en oxygène similaire
 - Apnées obstructives et centrales similaires

Comparison of the mean BMI value between the PD patients and the controls, with subgroup analysis considering AHI ≤ 15 vs AHI > 15 and BMI ≤ 27 vs BMI > 27 (error bars= standard error).



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Sleep Apnea Syndrome in Parkinson's Disease. A Case–Control Study in 49 Patients

Nico J. Diederich, MD,^{1,2*} Michel Vaillant, MS, MPH,³ Mike Leischen, MPH,³
Giovanna Mancuso, PhD,⁴ Serge Golinval, MD,⁵ Romain Nati, MD,^{2,5} and Marc Schlessler, MD^{2,5}

¹Department of Neuroscience, Centre Hospitalier de Luxembourg

²Interdisciplinary Sleep Laboratory, Centre Hospitalier de Luxembourg

³Service d'Epidémiologie et de Transfert de Technologies, CRP Santé, Luxembourg

⁴Health Research Consulting, Luxembourg

⁵Department of Internal Medicine, Centre Hospitalier de Luxembourg

Abstract: In PD, the impact of nocturnal respiration on sleep continuity and architecture has not been systematically investigated by polysomnography (PSG). We performed a case–control study with retrospective analysis of PSG data of 49 PD patients. After classifying the PD patients according to their apnea/hypopnea index (AHI), they were matched with 49 controls in terms of age, gender, and AHI. There were 21 PD patients (43%) who had sleep apnea syndrome (SAS), classified as mild (AHI, 5–15) in 10 patients, moderate (AHI, >15–30) in 4 patients, and severe (AHI, > 30) in 7 patients. PD patients had more deep sleep ($P = 0.02$) and more nocturnal awakenings ($P < 0.001$) than the controls. Their body mass index (BMI) was lower ($P = 0.04$), and they maintained a more favorable respiratory profile, with higher mean and minimal oxygen saturation values ($P = 0.006$ and 0.01 ,

respectively). These differences were preserved when only considering PD patients with AHI > 15. PD patients had less obstructive sleep apneas ($P = 0.035$), independently from the factor AHI. Only the respiratory changes of 4 PD patients with BMI > 27 and AHI > 15 (8%) approximated those seen in the controls. At an early or middle stage of the disease, non-obese PD patients frequently have AHI values suggesting SAS, however, without the oxygen desaturation profile of SAS. Longitudinal studies of patients with such "abortive" SAS are warranted to establish if this finding reflects benign nocturnal respiratory muscle dyskinesia or constitutes a precursor sign of dysautonomia in PD. © 2005 Movement Disorder Society

Key words: sleep apnea syndrome; polysomnography; excessive daytime sleepiness; Parkinson's disease

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Syndrome de l'apnée du sommeil chez les personnes atteints de la maladie de Parkinson

DISCUSSION

This study was not designed to produce epidemiological data on the frequency of SAS in PD; nevertheless, the calculated frequency of 43% may roughly reflect reality, as the data were obtained from unselected ambulatory PD patients. SAS has been found by others in 40% of patients with parkinsonism.^{2,9} In contrast, only

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Méthodologies

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Déstructuration progressive du sommeil chez les personnes atteintes de la maladie de Parkinson

- Hypothèse:

La perte de l'architecture physiologique du sommeil serait progressive avec une durée de maladie plus longue et en lien avec la progression des troubles moteurs et l'augmentation du traitement dopaminergique



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The sleep complaints, as registered in the medical records and indicated by the patients at the three last visits before the PSG, were grouped into four major syndromal matrices (M):

- (a) complaints suggestive of REM sleep behavior disorder (M-RBD);
 - (b) hallucinations (M-H);
 - (c) complaints about excessive daytime sleepiness, sleep attacks or an Epworth sleepiness score ≥ 10 (M-EDS);
 - (d) complaints about insomnia, poor subjective sleep quality, frequent awakenings (M-I).
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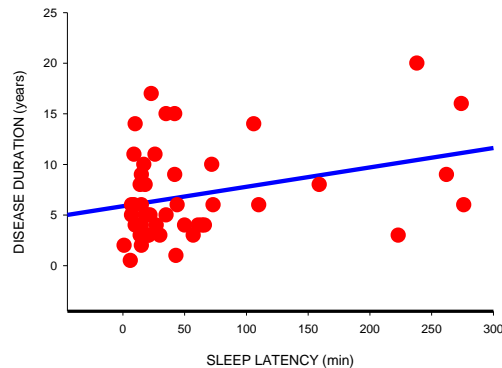
Déstructuration progressive du sommeil chez les personnes atteintes de la maladie de Parkinson

- Sex ratio: 36/10
- Age: 64.26 (9.4) ans
- Durée de la maladie de 7.0 (4.6) ans
- Score de Hoehn-Yahr de 2.3 (0.8)
- Score d'Epworth de 8.5 (4.8)
- 85% se plaignaient de leur sommeil
- M-RBD, M-H, M-EDS, M-I

Déstructuration progressive du sommeil chez les personnes atteints de la maladie de Parkinson

Corrélation avec durée de la maladie:

- + latence
- Efficience
- temps total
- REM
- sommeil profond



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Déstructuration progressive du sommeil chez les personnes atteints de la maladie de Parkinson

- Les patients avec M-RBD avaient une fréquence élevée de RBD [64% vs. 20%; $P=0.010$] mais un taux similaire de sommeil REM que les patients sans M-RBD.
- Les patients avec M-H seulement montraient plus fréquemment des microréveils [49.1 (20.1) vs. 27.2 (17.1); $P=0.008$] que ceux sans M-H.
- Les patients avec des symptômes d'EDS seulement avaient un BMI supérieur aux patients sans symptômes d'EDS [23.9 (3.8) vs. 26.7 (4.5), $P=0.0295$].

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Original article

Progressive sleep ‘destructuring’ in Parkinson’s disease. A polysomnographic study in 46 patients[☆]

Nico J. Diederich^{a,b,*,}, Michel Vaillant^c, Giovanna Mancuso^d, Peter Lyen^b, Jo Tiete^b^aDepartment of Neuroscience, Centre Hospitalier de Luxembourg, 4, rue Barblé, L-1210 Luxembourg, Luxembourg^bInterdisciplinary Sleep Laboratory, Centre Hospitalier de Luxembourg, Luxembourg, Luxembourg^cService d’Epidémiologie et de Transfert de Technologies, CRP-Santé, Luxembourg, Luxembourg^dHealth Research Consulting, Luxembourg, Luxembourg

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Abstract

Background: Sleep abnormalities in Parkinson’s disease (PD) are frequent, but it is unknown whether or not there is *progressive* loss of physiological sleep architecture or what the causes could be.


Methods: Retrospective review of medical records and polysomnographic data from 46 non-demented PD patients.

Results: Sleep latency was correlated with disease duration ($F_{1,44}=4.87$, $P=0.03$). Total sleep time ($F_{1,44}=8.54$, $P=0.005$), deep sleep time ($F_{1,44}=4.06$, $P=0.05$), REM sleep time ($F_{1,44}=9.15$, $P=0.004$) and sleep efficiency (SE) ($F_{1,44}=10.20$, $P=0.003$) were inversely correlated with disease duration. The same sleep parameters were independent from the degree of motor impairment, dosage of the dopaminergic medications, and age. Subjective sleep complaints could only partially predict abnormalities in polysomnographic (PSG) studies.

Conclusion: In PD nocturnal sleep ‘destructuring’ is linked to disease duration and evolves independently from other major disease parameters.

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Keywords: Parkinson’s disease; Sleep architecture; Polysomnography; REM sleep behavior disorder; Excessive daytime sleepiness




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Sommeil à ondes lentes et traitement dopaminergique dans la maladie de parkinson

- Hypothèse:

Le syndrome d’apnées du sommeil serait la cause du fractionnement du sommeil de patients parkinsoniens dans le cas où l’étude montrerait des répercussions identiques chez un groupe de témoins non parkinsoniens



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Slow wave sleep and dopaminergic treatment in Parkinson's disease: a polysomnographic study

Diederich NJ, Paolini V, Vaillant M. Slow wave sleep and dopaminergic treatment in Parkinson's disease: a polysomnographic study.

Acta Neurol Scand 2009; 120: 308–313.

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Background – In Parkinson's disease (PD), there is entanglement of disease-inherent and treatment-induced sleep abnormalities. So far, there has been no study specifically investigating the influence of diurnal dopaminergic medication (DM) on nocturnal slow wave sleep (SWS). **Methods** – Polysomnographic analysis in 62 PD patients. **Results** – PD patients had a sleep efficiency of $70 \pm 17\%$ and an SWS amount of $16 \pm 11\%$. Linear regression analysis showed no significant correlation between the amounts of SWS and DM. However, patients with a medium DM dosage (300–600 mg of levodopa equivalents) preserved a SWS percentage $> 25\%$ ($p = 0.035$, χ^2 test) more frequently than patients with higher or smaller DM. The DM dosage had no effect on other main sleep parameters. Psychotropic comedication had no effect on SWS percentage. In contrast, SWS amount was inversely correlated with both disease duration and age. It was independent of rapid eye movement sleep amount. The natural female bonus effect on SWS amount was absent in women with PD. **Conclusion** – Diurnal dopaminergic treatment has no major impact on SWS in PD, which, however, decreases with disease duration. Disease-dependent, but treatment-independent decrease in SWS suggests primary degeneration of sleep-regulating systems in PD.

N. J. Diederich¹, V. Paolini², M. Vaillant²

¹Department of Neurosciences, Centre Hospitalier de Luxembourg, Luxembourg City, Luxembourg; ²Center for Health Studies, Clinical Epidemiology, CRP-Santé, Luxembourg City, Luxembourg

Key words: Parkinson's disease; polysomnography; slow wave sleep

Nico J. Diederich, Department of Neurosciences, Centre Hospitalier de Luxembourg, 5, rue Barblé, L-1210 Luxembourg
Tel: +352 44119627
Fax: +352 44114020
e-mail: didierich@cpt.lu

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Influence sympathique dans la réduction de la variabilité de la fréquence cardiaque durant le sommeil dans la maladie de parkinson

- Hypothèse:

Les patients idiopathiques montreraient une réduction des composants de la variabilité de la fréquence cardiaque sous influence sympathique durant le sommeil. Ce phénomène serait particulièrement prononcé durant le sommeil REM qui est normalement caractérisé par une excitation et une instabilité cardiovasculaires.

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- Acquisition du signal – polysomnographie
- Algorithme de filtrage des données
- Analyse des « time domain measures of variability » : SDRR, SDSD, pNN50 pour chaque stade de sommeil
- Analyse des « frequency domain measures »: LF et HF



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RESEARCH ARTICLE

Reduced Sympathetically Driven Heart Rate Variability During Sleep in Parkinson's Disease: A Case-Control Polysomnography-Based Study

Nicolas Sauvageot, M. STAT¹, Michel Vaillant, PHD¹, Nico J. Diederich, MD^{2*}

¹Centre de Recherche Publique Santé, Centre d'Etudes en Santé, Strassen, Luxembourg

²Department of Neurosciences and Interdisciplinary Sleep Laboratory, Centre Hospitalier de Luxembourg, Luxembourg-City, Luxembourg

ABSTRACT:

Objectives: To study heart rate variability during nocturnal sleep in idiopathic Parkinson's disease.

Methods: Retrospective study, using part of the data set accumulated in an earlier study, in which polysomnography was performed in 35 idiopathic Parkinson's disease patients under their usual medication and in 35 nonidiopathic Parkinson's disease controls, matched for age, gender, and amount of apneas/hypopneas per hour. R-R intervals were calculated separately for NREM and REM sleep stages. R-R variability was analyzed for time and frequency domains. Selected variables considered were high frequency band (0.15–0.40 Hz) influenced by parasympathetic input and low frequency band (0.04–0.15 Hz) influenced by sympathetic input. Both frequency bands were considered in normalized units (low frequency and high frequency normalized units). Low frequency/

high frequency ratio was calculated as an estimate of sympathicovagal balance.

Results: All respiratory and sleep stage characteristics were similar in both groups. Low frequency normalized unit was reduced in idiopathic Parkinson's disease patients, both for NREM and REM sleep ($P = 0.005$). Low frequency/high frequency was smaller in idiopathic Parkinson's disease for both sleep portions ($P = 0.02$).

Conclusions: Idiopathic Parkinson's disease patients show reduced sympathetic influence on heart rate variability in both NREM and REM sleep stages. We speculate that these findings are a consequence of the postganglionic noradrenergic cardiac denervation found in idiopathic Parkinson's disease patients.

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Key Words: heart rate variability; Parkinson; sleep; MIBG-SPECT; dysautonomia





Niveaux de preuve et forces des Recommandations

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Niveaux de preuve scientifique	Niveau de preuve
Grands essais comparatifs randomisés avec résultats méthodologiquement indiscutables.	PROUVE
Petits essais comparatifs randomisés et grands essais avec résultats incertains. Essais comparatifs non randomisés avec groupe contrôle contemporain, suivis de cohortes. Essais comparatifs non randomisés avec groupes contrôles historiques, études cas-témoin.	PROBABLE
Pas de groupe contrôle, essais contrôlés sur des critères intermédiaires, séries de patients, consensus professionnels, opinions d'experts.	ACCEPTÉ

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Etude Prospective

- ***Frequency and Evolution of Non Motor Signs in Early Parkinson's Disease. A Prospective Case-Control Study***
- ***Appel FNR PROVIE (2003)***
- ***Appel FNR PROVIE II (2006)***

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Frequency and Evolution of Non Motor Signs in Early Parkinson's Disease. A Prospective Case-Control Study

- Hypothèse :
un ou plusieurs symptômes de la maladie de parkinson pourrait avoir suffisamment de pouvoir discriminant pour identifier les patients atteints et ceux souffrant de déficits liés à l'âge sans utiliser la polysomnographie



Frequency and Evolution of Non Motor Signs in Early Parkinson's Disease. A Prospective Case-Control Study

- Etude à recrutement prospectif
- Design Cas – Témoins
- 30 patients non-déments, < 3 ans de syndromes moteurs, vs 30 témoins
- 6 clusters (Hyposmie, anomalies du sommeil, dysautonomie, déficits visuels, signes frontaux, dépression) évalués par 1 à 3 critères ou échelles

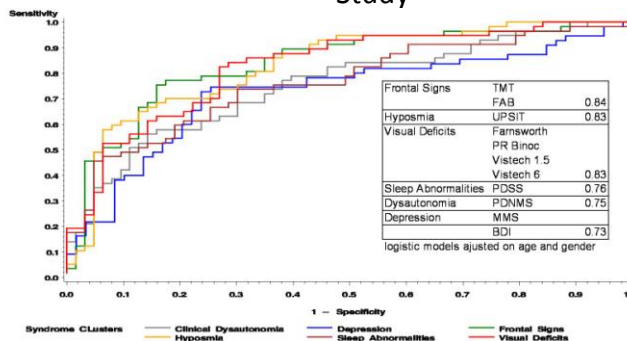


Frequency and Evolution of Non Motor Signs in Early Parkinson's Disease. A Prospective Case-Control Study

- Age : PD: 64 +/-12 vs Controls: 64 +/- 9 (n.s.)
- Gender (female): PD 47% vs Controls 63% (n.s.)
- PD patients:
 - mUPDRS: 8 +/- 5
 - Levodopa: 2 +/- 0.5mg
 - DA agonist: 0.8 +/- 1.7 mg

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Frequency and Evolution of Non Motor Signs in Early Parkinson's Disease. A Prospective Case-Control Study



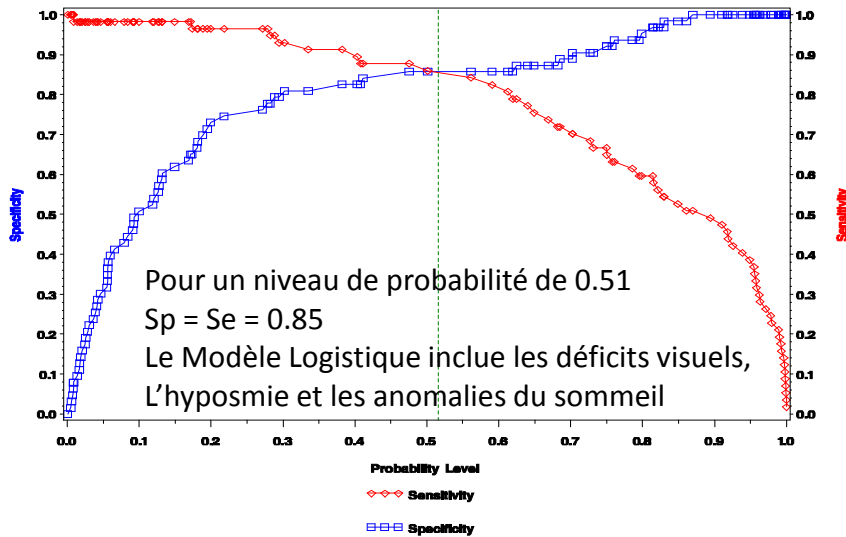
...further « unfolding » the visual DC

	Odds Ratio	95% Wald Confidence Limits		p-value
gender	0.57	0.262	1.243	0.724
age	0.986	0.948	1.025	0.157
Farnsworth total score	1.011	1.004	1.017	0.0005

Sp=Se=0.65

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Frequency and Evolution of Non Motor Signs in Early Parkinson's Disease. A Prospective Case-Control Study



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Frequency and Evolution of Non Motor Signs in Early Parkinson's Disease. A Prospective Case-Control Study

- 1^{ère} Version (etude Pilote): December 12, 2008
- Reviewer: *Overall, this is a very well-written and thoughtful paper on an important topic. The main limitation [...] is the sample size. I have only minor comments.[...]*
- Editor: *The paper is very interesting but due to the small no of patients and controls all results are at risk to be at variance. [...] **would give a much better answer to your interesting questions and hypothesis.***
- Version acceptée : November 17, 2009

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Discriminative Power of Different Nonmotor Signs in Early Parkinson's Disease. A Case–Control Study

Nico J. Diederich, MD,^{1,2*} Vannina Pieri, PhD,¹ Géraldine Hipp, PhD,¹ Olivier Rufra, RN,²
Sara Blyth,¹ and Michel Vaillant, MPH³

¹Department of Neurosciences, Centre Hospitalier de Luxembourg, Luxembourg-City, Luxembourg

²Interdisciplinary Sleep Laboratory, Centre Hospitalier de Luxembourg, Luxembourg-City, Luxembourg

³Centre of Health Studies, Clinical Epidemiology, CRP Santé, Luxembourg-City, Luxembourg

Abstract: The objective of this study was to evaluate the discriminative power of different nonmotor signs for early diagnosis of Parkinson's disease (PD). Thirty patients with PD with ≤ 3 years of disease duration were compared with 30 healthy controls. Six deficit domains (DD) were defined: hyposmia, sleep abnormalities, dysautonomia, visual deficits, executive dysfunction, and depression. Plotting of Receiver operating characteristic (ROC) curves and exact conditional logistic modeling, followed by manual stepwise descending procedure were used to identify a model for nonmotor signs that detects early PD. Patients with PD and controls did not differ in terms of age, gender, and educational level. Several DD discriminated patients with PD from healthy controls.

Visual deficits showed the largest area under the ROC curve (0.83), followed by hyposmia (0.81) and dysautonomia (0.80). When combining the DD visual deficits and dysautonomia, the best residual model was obtained; it maximized both sensitivity and specificity for PD at a level of 0.77. At an early disease stage, several nonmotor domains were already able to discriminate patients with PD from healthy controls. Visual deficits had the best discriminatory power. Being brief and inexpensive, visual tests should be further investigated in larger cohorts as potential screening tool for early PD. © 2010 Movement Disorder Society

Key words: Parkinson's disease; nonmotor signs; visual deficits; REM sleep atonia; hyposmia

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Myocardial MIBG scintigraphy: a useful clinical tool?

A retrospective study in 50 parkinsonian patients

Ines Fröhlich · Nico J. Diederich · Wilfried Pilloy ·
Michel Vaillant

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Abstract Meta-iodobenzylguanidine scintigraphy (MIBG scintigraphy) shows reduced uptake in idiopathic Parkinson's disease (IPD), idiopathic REM sleep behavior disorder (IRBD) and Lewy body dementia (LBD), but not in other parkinsonian or dementia syndromes. We retrospectively reevaluated 50 patients. Concordance rate between last clinical diagnosis and scintigraphy diagnosis was only given in two-thirds of the patients. Confounding factors were: decreasing heart/mediastinum ratio (HMR) with progressive age, higher HMR in women and possibly interference with antihypertensive medication. Standardization of the methods and precise clinical guidelines are warranted for better clinical use.


Keywords Myocardial scintigraphy ·
Idiopathic Parkinson disease

REM sleep behavior disorder (IRBD) and Lewy body dementia (LBD) [1, 2]. This probably reflects cardiac sympathetic denervation due to degeneration of postganglionic sympathetic fibers [3, 4]. In contrast, the cardiac uptake is normal in parkinsonian syndromes due to taupathy and other dementia syndromes [5–8]. Notably, this diagnostic tool is easily applicable, the radioactive compound rather cheap in comparison to other ligands and the patients do not need to withdraw from the current antiparkinsonian medications. Therefore, it has been proposed as a diagnostic tool for differentiation of parkinsonian and dementia syndromes at the early stages [9–11]. Despite these promising characteristics, usefulness of routine application outside selected research cohorts has not yet been proven. Therefore, the purpose of the present study

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Conclusion

- séries de cas:
 - Exploration de question de recherche
 - Financement difficile
- Etudes prospectives
 - Réflexion sur la question de recherche et design de l'étude
 - Niveau de preuve
 - Accès aux appels d'offres



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Merci


Centre de Compétences en Méthodologie et Statistiques

Michel.vaillant@crp-sante.lu

Nicolas.sauvageot@crp-sante.lu

Centre Hospitalier de Luxembourg

Diederich.nico@chl.lu



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