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Reproducibility, Accuracy, and Predictors of Accuracy for the Detection of Coronary Atherosclerotic Plaque Composition by Computed Tomography: An Ex Vivo Comparison to Intravascular Ultrasound.


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PURPOSE.: To determine the reproducibility, accuracy, and predictors of accuracy of computed tomography (CT) angiography to detect and characterize coronary atherosclerotic plaque as compared with intravascular ultrasound. METHODS.: Ten ex vivo human coronary arteries were imaged in a moving phantom by dual-source CT (collimation: 0.6 mm, reconstructed slice thickness: 0.4 mm) and intravascular ultrasound (IVUS). Coregistered cross-sections were assessed at 0.4 mm intervals for the presence and composition of atherosclerotic plaque (noncalcified, mixed, and calcified) on CT and IVUS by independent readers to determine reader agreement and diagnostic accuracy. Quantitative measurements of lumen and plaque area, plaque eccentricity, and intimal thickness on IVUS were used to determine predictors for the detection of noncalcified plaque by CT.

RESULTS.: Within 1002 coregistered cross-sections, the interobserver agreement to detect plaque on CT was K = 0.48, K = 0.42, and K = 1.00 for noncalcified, mixed, and calcified plaque, respectively. The sensitivity and specificity of CT was 57% out of 84% for noncalcified, 32% of 92% for mixed, and 56% of 93% for calcified plaque when compared with IVUS, respectively. Misclassification occurred in 68% of mixed and 43% of noncalcified plaques. The odds of detecting noncalcified plaque in CT independently increased by 56% (95% CI: 47%-77%, P < 0.0001) with every 0.1 mm increase in maximum intimal thickness as measured by IVUS. Detection rate for noncalcified plaques was poor for plaques <1 mm (36%) but excellent for plaques >1 mm maximal intimal thickness (90%). CONCLUSION.: Reader agreement and diagnostic accuracy for the detection of coronary atherosclerotic plaque vary with plaque composition. Intimal thickness independently predicts detection of noncalcified plaque by CT with excellent sensitivity for >1 mm thick plaques.
Nuclear imaging has used initially anatomic and volumetric technologies as CT or MRI. In recent years new dimensions of non-invasive studies, as PET, have shown a higher utility in the effectiveness of the treatment. The evaluation of need must be done according to a principle of Horizontal Equity, equal treatment for equal need and of a principle of Vertical Equity, Different treatment, at regional level, according to each hospital level. The evaluation of need has been made according to the Potential Demand by Potential User Groups: diabetes, type 2, (50 years and more); screening colorectal (50 years and more); morbidity by cancer; surgery of lung cancer; cardiology; heart surgery; acute chest pain in the emergency department. In a Macro Perspective need has been evaluated using the Population Estimations for 2007, at municipality level. Relatively to Lisbon and Porto data at locality level has been used, from the 2001 Census. According to Campos, J.R. (2007), in 2006, it existed 1 PET by 1 million inhabitants and after that date 2 more were created (Quadrantes and Hospital ad Luz), belonging to the private sector. Mores 15 PET are needed in the NHS, 1 PET for about 504128 inhabitants. According to The Potential Demand perspective 18 new PET are needed, 15 from the public sector. The private sector will cover progressively the demand. Dorado and Albertino (2002), in Spain, mention that the introduction of this new technique in our Health System must be done slowly due to the cost and complexity. In Portugal exists already 6 PET and this applies also. As a first priority the intervention in Oncology in the IPO (Coimbra). A priority must be given to the University Hospitals of Santa Maria and São João. The Central Hospitals of Viseu and VilaReal/Régua must have also 1 PET. A priority must be given to the interior in order to avoid transports of patients and families. In fourth place the HC Central Lisbon must have also 1 PET, which will go to the New Hospital of Todos-os-Santos. The Hospital Garcia de Orta must have also 1 PET, what will avoid the patients from the Setubal district to come to Lisbon. The HC of Coimbra and the HC of Ocidental Lisbon must have 1 PET in order to cover the population of the Centre Region and of Lisbon Region. The HC of VN de Gaia, the Hospital Pedro Hispano, Matosinhos, and the Hospital of Guimarães, must have 1 PET due to the population density of the North Region. The New Central Hospitals of Evora and Faro must also have 1 PET and the New Hospital of Braga. The estimation of diabetes, type 2, has been made using the minimum prevalence of 3%. The prevention of cardiac illness in the population of 50 years need with diabetes, type 2, must be done with PET annual examinations in the Hospital, referred by the family doctor in the health centre. The screening colorectal has not a tradition in Portugal. Sun L et al (2008) mention that according to criteria of specificity, sensibility and precision PET/CT presents higher advantages in the colorectal screening. It has been estimated that it must be done in 10% of the adults of 50 years and more with annual examinations in the Hospital, referred by the family doctor in the health centre. The use of PET in cancer treatment must be done only in the cancer of mama; cancer colorectal; cancer of esofagus; cancer of head and neck; lung cancer; linfoïma; melanoma; and Solitary Pulmonary Nodules; cancer of thyroid; cancer cervical . Those types of cancer are 46,7 % of total cancer mortality. The use of PET in cardiology in CAD is also important. If the prevalence of CAD is less than 70% PET has a lower value per QALY. The number foreseen of examinations is of about 3114 examinations/ year. The application of Pet in acute chest pain makes that the localization of PET must be done near the Emergency Department. Mowatt, G. et al. (2008) conclude that, based in some studies of Acute Chest Pain there is an evidence of prognostic that the use of 64-slice CT has influence in the way as patients are treated, what gives origin to a reduction in some inpatient care and avoids the development of invasive CAD.
underlying mechanisms. Objective: We sought to track the fate of injected human CD34(+) cells in the hearts of severe combined immune deficiency (SCID) mice after experimental MI and to determine the mechanisms of action. Methods and Results: We used multimodality molecular imaging to track the fate of injected human CD34(+) cells in the hearts of SCID mice after experimental MI, and used selective antibody blocking to determine the mechanisms of action. Bioluminescence imaging showed that injected CD34(+) cells survived in the hearts for longer than 12 months. The PET signal from the injected cells was detected in the wall of the left ventricle. Cardiac MRI showed that left ventricular ejection fraction was significantly improved in the treated mice compared to the control mice for up to 52 weeks (P<0.05). Furthermore, treatment with anti-alpha4beta1 showed that generation of human-derived cardiomyocytes was inhibited, whereas anti-vascular endothelial growth factor (VEGF) treatment blocked the production of human-derived endothelial cells. However, the improvement in cardiac function was abolished only in the anti-VEGF, but not anti-alpha4beta1, treated group. Conclusions: Angiogenesis and/or paracrine effect, but not myogenesis, is responsible for functional improvement following CD34(+) cells therapy.

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Epicardial adipose tissue volume and coronary artery calcium to predict myocardial ischemia on positron emission tomography-computed tomography studies.


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BACKGROUND: There appears to be an association of epicardial adipose tissue (EAT) with coronary artery disease (CAD) and its risk factors. EAT is assumed to influence CAD development by altering vasomotor tone and via toxic paracrine effects. The relationship of EAT to myocardial perfusion has not been studied. METHODS: Quantification of EAT and CAC was performed on positron emission tomography/computed tomography (PET/CT) studies in 45 subjects (77% intermediate pre-test probability of CAD) with mild-moderate myocardial ischemia (5-14% perfusion defect, n = 23), severe ischemia (>15% defect, n = 22) and a control group with no ischemia matched for CAD risk factors (n = 52). RESULTS: EAT volume showed a better correlation with myocardial ischemia than total CAC (r = .47 vs r = .28, P < .01). EAT volume increased significantly from the control group to subjects with mild-moderate and severe ischemia (96.9, 124.5, and 143.9 cm(3), P < .01 for both ischemia groups vs controls). Total mean CAC was significantly higher in the severe ischemia group (676.3) than in control group (229.4) (P < .01). Multivariable logistic regression analyses showed that EAT volume was, but CAC was not, a significant predictor of ischemia after adjustment for age, sex, body mass index, and each other. EAT volume was a better predictor of ischemia than total CAC [area under the curve (AUC)= .764 vs .6291, P = .04]. The combination of EAT + CAC (AUC = .7694) did not improve over EAT volume alone (P = .57). CONCLUSIONS: In this study, EAT volume assessed by CT was an independent predictor of ischemia on PET, and outperformed CAC score in a CAD naïve population at intermediate pre-test probability of disease.


Perceived usefulness of cardiac computed tomography as assessed by referring physicians and its effect on patient management.


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Despite the growing use of computed tomographic angiography (CTA), the effect on patient management is less clear. We sought to determine the perceived usefulness of the results provided by CTA and to assess whether and how it influences patient management. Comprehensive prospective data were collected from 184 consecutive patients who presented for clinical CTA for the evaluation of coronary artery disease from March to July 2008. In addition, a detailed survey was sent to each referring physician for each patient examined to assess whether they found the results of the CTA useful and whether it had any influence on subsequent patient management. Of 184 CTA examinations, which had been ordered by 82 different providers, 108 surveys (59%) were completed by 53 different physicians. No significant differences were found in either the patient or provider characteristics for the completed versus noncompleted surveys. Of the 184 CTA examinations, the severity of coronary disease detected by CTA was severe for 26%, mild to moderate in 47%, and not present in 27% of the patients. Clinicians considered the test results to be useful in virtually all cases and thought the results led to significant risk recalculation in 58% of the patients.
If CTA had not been available, the clinicians indicated that they would have ordered an invasive test for 46% of the patients and noninvasive tests for 32%. After CTA, changes in medical therapies were made for 31%, invasive angiography was planned for 19%, and noninvasive testing was scheduled for 6% of the patients. In conclusion, of 53 different referring clinicians from different medical specialties, CTA was considered to almost always be useful; however, the effect on subsequent medical management was more variable.

Feasibility of FDG imaging of the coronary arteries: comparison between acute coronary syndrome and stable angina.

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OBJECTIVES: This study tested the hypothesis that fluorodeoxyglucose (FDG) uptake within the ascending aorta and left main coronary artery (LM), measured using positron emission tomography (PET), is greater in patients with recent acute coronary syndrome (ACS) than in patients with stable angina. BACKGROUND: Inflammation is known to play an important role in atherosclerosis. Positron emission tomography imaging with (18)F-FDG provides a measure of plaque inflammation. METHODS: Twenty-five patients (mean age 57.9 +/- 9.8 years, 72% male, 10 ACS, and 15 stable angina) underwent cardiac computed tomographic angiography and PET imaging with (18)F-FDG after invasive angiography. Images were coregistered, and FDG uptake was measured at locations of interest for calculation of target-to-background ratios (TBR). Additionally, FDG uptake was measured at the site of the lesion deemed clinically responsible for the presenting syndrome (culprit) by virtue of locating the stent deployed to treat the syndrome. RESULTS: The FDG uptake was higher in the ACS versus the stable angina groups in the ascending aorta (median [interquartile ranges] TBR 3.30 [2.69 to 4.12] vs. 2.43 [2.00 to 2.86], p = 0.02), as well as the LM (2.48 [2.30 to 2.93] vs. 2.00 [1.71 to 2.44], p = 0.03, respectively). The TBR was greater for culprit lesions associated with ACS than for lesions stented for stable coronary syndromes (2.61 vs. 1.74, p = 0.02). Furthermore, the TBR in the stented lesions (in ACS and stable angina groups) correlated with C-reactive protein (r = 0.58, p = 0.04). CONCLUSIONS: This study shows that in patients with recent ACS, FDG accumulation is increased both within the culprit lesion as well as in the ascending aorta and LM. This observation suggests inflammatory activity within atherosclerotic plaques in acute coronary syndromes and supports intensification of efforts to refine PET methods for molecular imaging of coronary plaques.

An abbreviated hyperinsulinemic-euglycemic clamp results in similar myocardial glucose utilization in both diabetic and non-diabetic patients with ischemic cardiomyopathy.

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BACKGROUND: Positron emission tomography (PET) with insulin-stimulated (18)F-2-deoxyglucose (FDG) uptake is the gold standard for myocardial viability. However, insulin stimulation is infrequently performed due to time and inconvenience. We therefore assessed the clinical applicability of an abbreviated hyperinsulinemic-euglycemic clamp. METHODS AND RESULTS: Dynamic FDG PET was performed in 50 patients with ischemic cardiomyopathy (ejection fraction: .30 +/- .10) using an abbreviated hyperinsulinemic-euglycemic clamp with separate Non-Diabetic (n = 26) and Diabetic (n = 24) protocols (American Society of Nuclear Cardiology guidelines), and supplemental potassium. In regions with normal resting perfusion ((13)N-ammonia uptake >/=80% maximal segment), there were no differences in either maximal (Non-Diabetic: .60 +/- .17 mumol/min/g, P = .93) or mean rates of myocardial glucose uptake (MGU) (Non-Diabetic: .52 +/- .18 vs Diabetic: .52 +/- .14 mumol/min/g, P = .63) between the protocols. Multivariate analysis showed that diastolic blood pressure alone (maximal MGU, r (2) = .20, P = .001) or with NYHA Heart Failure Class (mean MGU, r (2) = .25, P = .003) could account for some of the variability in normal-region MGU. Potassium supplementation safely attenuated the decline in plasma levels. CONCLUSIONS: This abbreviated hyperinsulinemic-euglycemic clamp produced similar MGU values in normal resting myocardium in non-diabetic and diabetic subjects, which are no different than published rates with a standard insulin clamp. Thus, this abbreviated approach is sufficient to overcome myocardial insulin resistance.
Assessment of myocardial perfusion and function with PET and PET/CT.

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Technetium-99m-sestamibi redistribution after exercise stress test identified by a novel cardiac gamma camera: two case reports.

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Single photon emission computer tomography (SPECT) myocardial perfusion imaging (MPI) employing technetium-99m (Tc-99m)-based imaging tracers is the mainstay of nuclear cardiology for the detection of myocardial ischemia. Current guidelines for same day rest/stress Tc-99m-sestamibi SPECT MPI recommend image acquisition 15-60 minutes after the stress testing. A novel sensitive SPECT imaging technique, D-SPECT, allows fast acquisition of images and captures rapid changes in radiotracer distribution. Here we report 2 cases of SPECT MPI in patients with angiographically confirmed coronary artery disease (CAD) where Tc-99m-sestamibi exhibited marked redistribution between early (6-8 min) and late (60-70 min) post-stress imaging leading to an underestimation of the extent and severity of ischemia on late images. These observations suggest that early imaging maybe more sensitive for CAD detection. Fast SPECT imaging techniques, such as D-SPECT, will facilitate similar studies in the future as they will allow fast image acquisition at several time points after the stress test.

18F-FDG PET imaging of myocardial viability in an experienced center with access to 18F-FDG and integration with clinical management teams: the Ottawa-FIVE substudy of the PARR 2 trial.


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Comment in:

(18)F-FDG PET may assist decision making in ischemic cardiomyopathy. The PET and Recovery Following Revascularization (PARR 2) trial demonstrated a trend toward beneficial outcomes with PET-assisted management. The substudy of PARR 2 that we call Ottawa-FIVE, described here, was a post hoc analysis to determine the benefit of PET in a center with experience, ready access to (18)F-FDG, and integration with clinical teams. METHODS: Included were patients with left ventricular dysfunction and suspected coronary artery disease being considered for revascularization. The patients had been randomized in PARR 2 to PET-assisted management (group 1) or standard care (group 2) and had been enrolled in Ottawa after August 1, 2002 (the date that on-site (18)F-FDG was initiated) (n = 111). The primary outcome was the composite endpoint of cardiac death, myocardial infarction, or cardiac rehospitalization within 1 y. Data were compared with the rest of PARR 2 (PET-assisted management [group 3] or standard care [group 4]). RESULTS: In the Ottawa-FIVE subgroup of PARR 2, the cumulative proportion of patients experiencing the composite event was 19% (group 1), versus 41% (group 2). Multivariable Cox proportional hazards regression showed a benefit for the PET-assisted strategy (hazard ratio, 0.34; 95% confidence interval, 0.16-0.72; P = 0.005). Compared with other patients in PARR 2, Ottawa-FIVE patients had a lower ejection fraction (25% +/- 7% vs. 27% +/- 8%, P = 0.04), were more often female (22% vs. 13%, P = 0.006), tended to be older (64 +/- 10 y vs. 62 +/- 10 y, P = 0.07), and had less
previous coronary artery bypass grafting (13% vs. 21%, P = 0.07). For patients in the rest of PARR 2, there was no significant difference in events between groups 3 and 4. The observed effect of (18)F-FDG PET-assisted management in the 4 groups in the context of adjusted survival curves demonstrated a significant interaction (P = 0.016). Comparisons of the 2 arms in Ottawa-FIVE to the 2 arms in the rest of PARR 2 demonstrated a trend toward significance (standard care, P = 0.145; PET-assisted management, P = 0.057). CONCLUSION: In this post hoc group analysis, a significant reduction in cardiac events was observed in patients with (18)F-FDG PET-assisted management, compared with patients who received standard care. The results suggest that outcome may be benefited using (18)F-FDG PET in an experienced center with ready access to (18)F-FDG and integration with imaging, heart failure, and revascularization teams.

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**PET/CT challenge for the non-invasive diagnosis of coronary artery disease.**

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This review will focus on the clinical potential of PET/CT for the characterization of cardiovascular diseases. We describe the technical challenges of combining instrumentation with very different imaging performance and discuss the clinical applications in the field of cardiology.

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**Cardiac PET-CT: advanced hybrid imaging for the detection of coronary artery disease.**


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Hybrid imaging of positron emission tomography (PET) together with computed tomography (CT) is rapidly emerging. In cardiology, this new advanced hybrid imaging modality allows quantification of cardiac perfusion in combination with assessment of coronary anatomy within a single scanning session of less than 45 minutes. The near-simultaneous anatomical evaluation of coronary arteries using CT and corresponding functional status using PET provides a wealth of complementary information in patients who are being evaluated for (suspected) coronary artery disease, and could help guide clinical patient management in a novel manner. Clinical experience gained with this recently introduced advanced hybrid imaging tool, however, is still limited and its implementation into daily clinical practice remains largely unchartered territory. This review discusses principles of perfusion PET, its diagnostic accuracy, and potential clinical applications of cardiac PET-CT in patients with ischaemic heart disease. (Neth Heart J 2010;18:90-8.).

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*[Positron emission tomography 2008 in Germany - results of the query and current status]*

*[Article in German]*

Kotzerke J, Oehme L, Lindner O, Hellwig D; Arbeitsausschuss PET der DGN.

Collaborators (15)


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AIM: The working group on positron emission tomography (PET) of the DGN (German Society of Nuclear Medicine) initiated this first survey to collect and analyse information on the practise of PET in Germany in the year 2008. METHODS: A questionnaire was sent to PET performing facilities (medical practices, hospitals, university hospitals and others) for retrospective data acquisition. Details regarding the equipment and examination procedures were examined as well as indications and number of studies. In addition, the role of PET within the diagnostic process was evaluated. RESULTS: Responses from 65 sites were analysed. Their technical equipment consisted of 77 PET scanners (40 of them were combined PET/CT devices). About 63500 PET studies had been performed with 86% in the field of oncology, 8% in neurology and 3% in cardiology. The radiotracers were labelled with 18F in 91% of the studies, whereas 68Ga was used in 4% and 11C in 3%. The analyses revealed lung tumours as the most investigated tumour entity, followed by malignant lymphoma, tumours of the gastro-intestinal tract and prostate cancer (about 14000, 6000, 5000 and 2000). Corresponding to the new scanners and software procedures, the number of studies with attenuation correction by CT was high (68%) and nearly all studies were reconstructed iteratively (99%). The PET images were analysed quantitatively in the majority of cases (91%). The clinical reports, which included image documentation for the greater part, were posted regularly within 3 days. However, in 70% of the sites electronic transfer possibilities were used additionally to speed up the diagnostic process. The high standard of quality was demonstrated by the fact, that 40 facilities were engaged in a tumour board. Further on, one third of the physicians had gained a PET certification awarded by the DGN. CONCLUSION: Relative to the high general standard of diagnostic instrumentation in Germany, PET is less established, in particular when compared with other industrialised countries such as USA and Switzerland.


Trends in PET scanner ownership and leasing by nonradiologist physicians.

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PURPOSE: The aim of this study was to examine growth trends in ownership or leasing of private-office PET scanners by nonradiologist physicians. MATERIALS AND METHODS: The Medicare Part B Physician/Supplier Procedure Summary Master Files for 2002 through 2007 were used to collect the following data for each PET-related Current Procedural Terminology(R) code: 1) annual procedure volume, 2) places of service for the procedures, and 3) specialties of the physicians filing the claims. To determine ownership or leasing, only technical and global claims that occurred in the nonhospital, private-office setting were included in the study. Professional component-only claims were not included. Procedure volume and growth trends were compared between radiologists and other specialties. RESULTS: Between 2002 and 2007, radiologist-owned Medicare PET scans increased by 259%, whereas nonradiologist-owned or nonradiologist-leased scans grew by 737%. Five specialty groups accounted for 95% of all nonradiologist PET volume in 2007: internal medicine subspecialties (28,324 studies in 2007), medical oncology (14,320 studies), cardiology (13,724 studies), radiation oncology (9,563 studies), and primary care (2,398 studies). In 2002, of all Medicare PET examinations performed on units owned or leased by physicians, the share for nonradiologists was 13%; their share rose to 24% in 2007. CONCLUSION: Although a large percentage of PET scans in private offices are done by radiologists, the growth rate among nonradiologists was far higher between 2002 and 2007 (259% for the former, 737% for the latter). The disproportionately rapid growth of PET scans performed on units owned by nonradiologists raises concern about self-referral at a time when policymakers are struggling to contain costs and reduce radiation exposure.


Diagnosis of myocardial viability by fluorodeoxyglucose distribution at the border zone of a low uptake region.


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PURPOSE: In cardiac 2-[F-18]fluoro-2-deoxy-D-glucose (FDG)-positron emission tomography (PET) examination, interpretation of myocardial viability in the low uptake region (LUR) has been difficult without additional perfusion imaging. We evaluated distribution patterns of FDG at the border zone of the LUR in the cardiac FDG-PET and established a novel parameter for diagnosing myocardial viability and for discriminating the LUR of normal variants. MATERIALS AND METHODS: Cardiac FDG-PET was performed in patients with a myocardial ischemic event (n = 22) and in healthy volunteers (n = 22). Whether the myocardium was not a viable myocardium (not-VM) or an ischemic but viable myocardium (isch-VM) was defined by an echocardiogram under a low dose of dobutamine infusion as the gold standard. FDG images were displayed as gray scaled-bull's
eye mappings. FDG-plot profiles for LUR (= true ischemic region in the patients or normal variant region in healthy subjects) were calculated. Maximal values of FDG change at the LUR border zone (a steepness index; S(max) scale/pixel) were compared among not-VM, isch-VM, and normal myocardium. RESULTS: S(max) was significantly higher for n-VM compared to those with isch-VM or normal myocardium (ANOVA). A cut-off value of 0.30 in Smax demonstrated 100% sensitivity and 83% specificity for diagnosing n-VM and isch-VM. S(max) less than 0.23 discriminated LUR in normal myocardium from the LUR in patients with both n-VM and isch-VM with a 94% sensitivity and a 93% specificity. CONCLUSION: S(max) of the LUR in cardiac FDG-PET is a simple and useful parameter to diagnose n-VM and isch-VM, as well as to discriminate the LUR of normal variants.


Alterations of pre- and postsynaptic noradrenergic signaling in a rat model of adriamycin-induced cardiotoxicity.


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Comment in:


BACKGROUND: Altered sympathetic nervous system signaling is known to play a role in the cardiotoxicity of the anthracycline chemotherapeutic agents, but the interaction of pre- and postsynaptic function is not well understood. METHODS AND RESULTS: Our aim was to study the noradrenergic signaling in an established rat model of adriamycin cardiotoxicity (15 mg/kg administered i.p. over 2 weeks) using radiotracers having potential applicability for imaging with positron emission tomography (PET). Ex vivo biodistribution was performed 1 and 3 weeks post-adriamycin treatment with the noradrenaline analogue [(11)C]meta-hydroxyephedrine ([(11)C]HED), beta-adrenergic receptor antagonist [(3)H]CGP12177, and phosphodiesterase-4 inhibitor (R)-(11)C)rolipram. Cardiac function (echocardiographic parameters) and heart/body weight ratio were not affected. Myocardial retention of [(11)C]HED, [(3)H]CGP12177, and (R)-(11)C)rolipram were unchanged 1 week post-adriamycin. Compared to controls, 3 weeks post-treatment [(3)H]CGP12177 uptake decreased (left ventricle free wall and septum; P < 0.05), while [(11)C]HED and (R)-(11)C)rolipram uptake were unaffected. Following acute increase in myocardial noradrenaline levels with desipramine treatment, (R)-(11)C)rolipram retention increased in the left atrium, right ventricle, left ventricle free wall and septum (P < 0.05) in vehicle-, but not adriamycin-treated animals. CONCLUSION: Our results suggest that adriamycin-induced toxicity exhibits no change in presynaptic noradrenaline uptake, but decreased beta-adrenergic receptors in cardiac tissues, supporting a role for PET imaging of noradrenaline signaling in the study of anthracycline cardiotoxicity.

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OBJECTIVE: Perivascular fat through the secretion of paracrine and pro-inflammatory mediators may play a role in obesity-mediated vascular disease. We sought to examine associations between adipose tissue depots immediately surrounding the thoracic aorta, metabolic risk factors, and vascular calcification. METHODS: In participants free of cardiovascular disease (CVD) from the Framingham Heart Study Offspring cohort who underwent computed tomography (n=1067, mean age 59 years, 56.1% women), thoracic peri-aortic fat depots were quantified. Visceral abdominal tissue (VAT) and calcification of the thoracic and abdominal aorta were also measured. RESULTS: Peri-aortic fat depots were correlated with body mass index, waist circumference (WC), VAT (all p<0.0001), hypertension (p=0.007), low HDL (p<0.0001), serum triglycerides (p<0.0001), impaired fasting glucose (p=0.005), and diabetes (p=0.02). These associations generally remained significant after adjustment for BMI and WC (all p-values<0.05), but not after VAT adjustment. Thoracic aortic fat was associated with thoracic calcification in models containing VAT (OR 1.31, 95% CI 1.01-1.71, p=0.04), but was not significant after adjustment for CVD risk factors (OR 1.16, 95% CI 0.88-1.51, p=0.30). Thoracic aortic fat, however, was associated with abdominal aortic calcification (OR 1.48, 95% CI 1.11-1.98, p=0.008) and coronary artery calcification (OR 1.47, 95% CI 1.09-1.98, p=0.001) even in models including CVD.
PET-Cardiology

risk factors and VAT. CONCLUSIONS: Thoracic peri-aortic fat is associated with measures of adiposity, metabolic risk factors, and coronary and abdominal aortic calcification.


Assessment of myocardial perfusion by positron emission tomography in patients with end-stage coronary artery disease treated with percutaneous myocardial revascularization.


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BACKGROUND: Reportedly, patients with persistent refractory angina due to end-stage coronary artery disease (CAD) not amenable to traditional revascularization techniques have experienced symptomatic relief following laser revascularization, either surgical transmyocardial revascularization (TMR) or percutaneous myocardial revascularization (PMR). In spite of several hypotheses (i.e., channel patency, placebo effect, denervation, neoangiogenesis), the mechanism of action and the benefit remains controversial. METHODS: A prospective trial utilizing positron emission tomography (PET) was conducted as an attempt to correlate quantified myocardial blood flow (MBF) to clinical improvement following PMR. Thirteen consecutive patients with angina class > II in spite of maximal medical treatment underwent PMR with a holmium:yttrium-aluminum-garnet (Ho:YAG) laser. MBF at rest and under hyperemia was assessed by [(13)N]ammonia PET at baseline, 3 and 6 months following PMR. RESULTS: Mean angina class and exercise tolerance time improved at 6 months compared with baseline (P < 0.001). The clinical results were accompanied with an improvement in hyperemic MBF (P = 0.05) and a reduction in minimal coronary resistance (MCR; P < 0.05) in PMR-treated segments. Opposite effects, reduced hyperemic MBF and increased MCR, were observed in nontreated segments. The increase in MCR in nontreated segments revealed the favorable therapeutic impact achieved in PMR-treated segments. CONCLUSION: The results of this trial utilizing a quantitative technique to quantify myocardial perfusion link clinical improvement post-PMR to neoangiogenesis and consistently improved microcirculation.


Reduced regional myocardial perfusion reserve is associated with impaired contractile performance in idiopathic dilated cardiomyopathy.


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Background. In idiopathic dilated cardiomyopathy (IDC) an imbalance between myocardial oxygen consumption and supply has been postulated. Subclinical myocardial ischaemia may contribute to progressive deterioration of left ventricular function. The relation between regional myocardial perfusion reserve (MPR) and contractile performance was investigated. Methods. Patients with newly diagnosed IDC underwent positron emission tomography (PET) scanning using both (13)N-ammonia as a perfusion tracer (baseline and dipyridamole stress), and (18)F-fluorodeoxyglucose viability tracer and a dobutamine stress MRI. MPR (assessed by PET) as well as wall motion score (WMS, assessed by MRI) were evaluated in a 17-segment model. Results. Twenty-two patients were included (age 49 +/- 11 years; 15 males, LVEF 33 +/- 10%). With MRI, a total of 305 segments could be analysed. Wall motion abnormalities at rest were present in 127 (35.5%) segments and in 103 (29.9%) during dobutamine stress. Twenty-one segments deteriorated during stress and 43 improved. MPR was significantly higher in those segments that improved, compared with those that did not change or were impaired during stress (1.87 +/- 0.04 vs. 1.56 +/- 0.07 p<0.01). Conclusion. Signs of regional ischaemia were clearly present in IDC patients. Ischaemic regions displayed impaired contractility during stress. This suggests that impaired oxygen supply contributes to cardiac dysfunction in IDC. (Neth Heart J 2009;17:470-4.).
Combined PET/MR imaging--technology and applications.

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The combination of PET and MR in one imaging device has certain advantages over conventional imaging modalities. These include: no additional radiation dose from the MR, superior soft tissue contrast and a multitude of tracers for PET. Certain technical challenges exist when designing a PET/MR system. On the one hand these stem from the presence of the strong MR magnetic field and the addition of PET components to the MR system. Different approaches are presented to overcome these technical obstacles ranging from long optical fibers to systems that use semiconductor light detectors for photon counting. The applications of combined PET/MR are profound in the field of oncology and allow imaging of the four main processes in cancer formation: apoptosis resistance, angiogenesis, proliferation and metastasis. PET/MR has also many clinical and research applications in neurology and cardiology. Alternative techniques such as image fusion, hyperpolarized imaging, 17O imaging and whole body diffusion are discussed in respect to their relevance regarding PET/MR. Simultaneous multifunctional and anatomical imaging using PET/MR has a great potential to impact biomedical imaging in research and clinic.

Determinants of myocardial energetics and efficiency in symptomatic hypertrophic cardiomyopathy.

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PURPOSE: Next to hypertrophy, hypertrophic cardiomyopathy (HCM) is characterized by alterations in myocardial energetics. A small number of studies have shown that myocardial external efficiency (MEE), defined by external work (EW) in relation to myocardial oxidative metabolism (MVO(2)), is reduced. The present study was conducted to identify determinants of MEE in patients with HCM by use of dynamic positron emission tomography (PET) and cardiovascular magnetic resonance imaging (CMR).

METHODS: Twenty patients with HCM (12 men, mean age: 55.2 ± 13.9 years) and 11 healthy controls (7 men, mean age: 48.1 ± 10 years) were studied with [(11)C]acetate PET to assess MVO(2). CMR was performed to determine left ventricular (LV) volumes and mass (LVM). Univariate and multivariate analyses were employed to determine independent predictors of myocardial efficiency. RESULTS: Between study groups, MVO(2) (controls: 0.12 ± 0.04 ml x min(-1) x g(-1), HCM: 0.13 ± 0.05 ml x min(-1) x g(-1), p = 0.64) and EW (controls: 9,139 ± 2,484 mmHg x ml, HCM: 9,368 ± 2,907 mmHg x ml, p = 0.83) were comparable, whereas LVM was significantly higher (controls: 99 ± 21 g, HCM: 200 ± 76 g, p < 0.001) and MEE was decreased in HCM patients (controls: 35 ± 8%, HCM: 21 ± 10%, p < 0.001). MEE was related to stroke volume (SV), LV outflow tract gradient, NH(2)-terminal pro-brain natriuretic peptide (NT-proBNP) and serum free fatty acid levels (all p < 0.05). Multivariate analysis revealed that SV (ss = 0.74, p < 0.001) and LVM (ss = -0.43, p = 0.013) were independently related to MEE. CONCLUSION: HCM is characterized by unaltered MVO(2), impaired EW generation per gram of myocardial tissue and subsequent deteriorated myocardial efficiency. Mechanical external efficiency could independently be predicted by SV and LVM.

Cardiac CT angiography--radiation dose-how effective are we in reducing radiation dose from cardiac CT angiography?

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Comment on:
PET imaging in pediatric neuroradiology: current and future applications.

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Molecular imaging with positron emitting tomography (PET) is widely accepted as an essential part of the diagnosis and evaluation of neoplastic and non-neoplastic disease processes. PET has expanded its role from the research domain into clinical application for oncology, cardiology and neuropsychiatry. More recently, PET is being used as a clinical molecular imaging tool in pediatric neuroimaging. PET is considered an accurate and noninvasive method to study brain activity and to understand pediatric neurological disease processes. In this review, specific examples of the clinical use of PET are given with respect to pediatric neuroimaging. The current use of co-registration of PET with MR imaging is exemplified in regard to pediatric epilepsy. The current use of PET/CT in the evaluation of head and neck lymphoma and pediatric brain tumors is also reviewed. Emerging technologies including PET/MRI and neuroreceptor imaging are discussed.

Direct comparison of rest and adenosine stress myocardial perfusion CT with rest and stress SPECT.


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INTRODUCTION: We have recently described a technique for assessing myocardial perfusion using adenosine-mediated stress imaging (CTP) with dual source computed tomography. SPECT myocardial perfusion imaging (SPECT-MPI) is a widely utilized and extensively validated method for assessing myocardial perfusion. The aim of this study was to determine the level of agreement between CTP and SPECT-MPI at rest and under stress on a per-segment, per-vessel, and per-patient basis. METHODS: Forty-seven consecutive patients underwent CTP and SPECT-MPI. Perfusion images were interpreted using the 17 segment AHA model and were scored on a 0 (normal) to 3 (abnormal) scale. Summed rest and stress scores were calculated for each vascular territory and patient by adding corresponding segmental scores. RESULTS: On a per-segment basis (n = 799), CTP and SPECT-MPI demonstrated excellent correlation: Goodman-Kruskall gamma = .59 (P < .0001) for stress and .75 (P < .0001) for rest. On a per-vessel basis (n = 141), CTP and SPECT-MPI summed scores demonstrated good correlation: Pearson r = .56 (P < .0001) for stress and .66 (P < .0001) for rest. On a per-patient basis (n = 47), CTP and SPECT-MPI demonstrated good correlation: Pearson r = .60 (P < .0001) for stress and .76 (P < .0001) for rest. CONCLUSIONS: CTP compares favorably with SPECT-MPI for detection, extent, and severity of myocardial perfusion defects at rest and stress.

Arteriogenesis induced by intramyocardial recombinant adeno-associated virus vector encoding human CD151 cDNA gene transfer in swines with coronary artery occlusion


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OBJECTIVE: To investigate the efficacy of CD151 gene delivery in promoting blood perfusion in swines after myocardial infarction. METHODS: Swines received coronary artery ligation and intramyocardial injection with rAAV-CD151, rAAV-anti-CD151 or rAAV-GFP. Eight weeks after vector injection, Western blot, immunostaining and 13N-labeled NH3 PET were performed to detect gene expression and biological effects of various treatments. RESULTS: High level of CD151 protein expression was detected in the rAAV-CD151 group. The capillary density in the rAAV-CD151 group [(83.8 +/- 6.7) n/mm2] was significantly higher than that in the control group [(33.2 +/- 4.5) n/mm2] and rAAV-GFP group [(41.6 +/- 5.6) n/mm2] (all P<0.05); the arteriole density in the rAAV-CD151 group [(16.4 +/- 2.5) n/mm2] was also higher than that in the control group [(6.6 +/- 2.3) n/mm2] and the rAAV-GFP group [(8.4 +/- 1.6) n/mm2] (all P<0.05). However, the lowest capillary density and arteriole density were evidenced in rAAV-anti-CD151 group. Myocardial blood perfusion was significantly increased in rAAV-CD151 group and significantly reduced in rAAV-anti-CD151 group (all P<0.05 vs. control). CONCLUSION: Intramyocardial injection of rAAV-CD151 could enhance the myocardial express of CD151 protein, increase capillary and arteriole densities and improve blood perfusion in swine with myocardial infarction.


In vivo assessment of myocardial glucose uptake by positron emission tomography in adults with the PRKAG2 cardiac syndrome.

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BACKGROUND: The PRKAG2 cardiac syndrome is an inherited metabolic disease of the heart characterized by excessive myocardial glycogen deposition. The biochemical alterations associated with this condition remain controversial and have not previously been studied in affected humans. METHODS AND RESULTS: Positron emission tomography (PET) imaging was used to quantitatively assess myocardial glucose uptake (MGU) in 6 adult subjects with the PRKAG2 cardiac syndrome and 6 healthy, matched control subjects using the glucose analogue (18)F-Fluoro-2-deoxyglucose (FDG). Studies were performed under a euglycemic hyperinsulinemic clamp to ensure stable blood glucose levels. Rubidium-82 perfusion scans were performed to ensure that myocardial differences in myocardial glucose uptake were not the result of significant myocardial scar. In adult patients with phenotypic expression of disease, the median myocardial glucose uptake of the left ventricle was 0.18 mumol/min/g (interquartile range, 0.14, 0.24), compared with 0.40 mumol/min/g (interquartile range, 0.30 to 0.45) in the control group (P=0.01). The median blood glucose during FDG-PET imaging was 4.72 mmol/L (interquartile range, 4.32 to 4.97) in the PRKAG2 group and 4.38 mmol/L (interquartile range, 3.90, 4.79) in the control group (P=NS). The significant decrease observed in myocardial glucose uptake in affected patients occurred in the absence of significant myocardial scar. CONCLUSIONS: The PRKAG2 cardiac syndrome is associated with a reduction of glucose uptake in adult patients affected with this genetic condition. In this pilot study, (18)F-FDG-PET imaging is a useful tool to assess alterations in myocardial glucose transport in this inherited metabolic disease and provide insight into the biochemical pathophysiology of the diseased state.


Novel O-[(11)C]methylated derivatives of candesartan as angiotensin II AT(1) receptor imaging ligands: radiosynthesis and ex vivo evaluation in rats.

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[(11)C]Methyl-candesartan and its desethyl derivative ([(11)C]TH4) were developed as potential radiotracers for imaging angiotensin II (Ang II) type 1 (AT(1)) receptors. These compounds were synthesized via methylation of tetrazole-protected candesartan using [(11)C]methyl iodide followed by deprotection through HCl hydrolysis at 65 degrees C to produce [(11)C]methyl-candesartan, and 90 degrees C for [(11)C]TH4. Ex vivo biodistribution and competition studies were carried out for both [(11)C]methyl-candesartan and [(11)C]TH4 to assess tissue retention time course and binding selectivity. Besides the liver, [(11)C]methyl-candesartan and [(11)C]TH4 displayed highest tissue retention in the AT(1) receptor-rich renal cortex and outer medulla. At tracer doses 15 min post-injection, [(11)C]methyl-candesartan demonstrated higher specific binding proportion for AT(1) receptors, and selectivity for AT(1) over Ang II AT(2), Mas, beta-adrenergic, and alpha(2)-adrenergic receptors in rat
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Kidneys compared to [(11)C]TH4. This study indicates that [(11)C]methyl-candesartan has potential for in vivo imaging renal AT(1) receptors selectively using positron emission tomography.

Severe ventricular arrhythmias in a patient with cardiac sarcoidosis: insights from MRI and PET imaging and importance of early corticosteroid therapy.

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Right and left ventricular uptake with Rb-82 PET myocardial perfusion imaging: markers of left main or 3 vessel disease.

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BACKGROUND: Relative myocardial perfusion imaging may underestimate severity of coronary disease (CAD), particularly in cases of balanced ischemia. Can quantification of peak left (LV) and right (RV) ventricular Rb-82 uptake measurements identify patients with left main or 3 vessel disease? METHODS: Patients (N = 169) who underwent Rb-82 PET MPI and coronary angiography were categorized as having no significant coronary stenosis (n = 60), 1 or 2 vessel disease (n = 81), or left main disease/3 vessel disease (n = 28), based on angiography. Maximal LV and RV ventricular myocardial Rb-82 uptake was measured during stress and rest. RESULTS: Failure to augment LV uptake by ≥8500 Bq/cc at stress, predicted left main or 3 vessel disease with a sensitivity of 93% and specificity of 61% (area under curve = 0.83). A >10% increase in RV:LV uptake ratios with stress over rest was 93% specific (area under curve = 0.74) for left main or 3 vessel disease. These indices incrementally predicted left main or 3 vessel disease compared to models including age, gender, cardiac risk factors, and summed stress and difference scores. CONCLUSION: Quantifying maximal rest and stress LV and RV uptake with PET myocardial perfusion imaging may independently and incrementally identify patients with left main or 3 vessel disease.

Serial noninvasive in vivo positron emission tomographic tracking of percutaneously intramyocardially injected autologous porcine mesenchymal stem cells modified for transgene reporter gene expression.

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BACKGROUND: Porcine bone marrow-derived mesenchymal stem cells (MSCs) were stably transfected with a lentiviral vector for transgene expression of the trifusion protein renilla luciferase, red fluorescent protein and herpes simplex truncated thymidine kinase (LV-RL-RFP-tTK; positron emission tomography [PET] reporter gene) for in vivo noninvasive tracking of the intramyocardially delivered MSC fate. METHODS AND RESULTS: A closed-chest, reperfused myocardial infarction was created in farm pigs. Sixteen days after myocardial infarction, LV-RL-RFP-tTK-MSCs were injected intramyocardially using electromechanical mapping guidance in the infarct border zone (n=7). PET-computed tomographic metabolic and perfusion imaging was performed after an intravenous injection of 10 mCi [18F]-FHBG and 13N-ammonia PET at 30+/-2 hours and 7 days after LV-RL-RFP-tTK-MSC treatment. Fusion imaging of the [18F]-FHBG PET-computed tomography with MRI was used to determine the myocardial location of the injected LV-RL-RFP-tTK-MSCs. Seven days after injections, [18F]-FHBG PET showed a decreased cardiac uptake with a mild increased pericardial and pleura uptake in the treated animals, which was confirmed by the measurement of luciferase activity. At 10 days, infarct size by MRI in the LV-RL-RFP-tTK-MSC-treated animals was smaller than controls (n=7) (23.3+/-1.5% versus 30.2+/-3.5%, P<0.005). The presence of the LV-RL-RFP-tTK-
MSCs (5.8+/−1.1% of the injected cells) in the myocardium 10 days after intramyocardial delivery was confirmed histologically. CONCLUSIONS: Reporter gene imaging enables the tracking of the persistence of viable LV-RL-RFP-rTK-MSC in the peri-infarcted porcine myocardium at 10 days after delivery using clinical PET scanners.


Giant cell arteritis as a cardiovascular entity.

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Abstract
Giant cell arteritis (GCA) is a relatively infrequent disorder that is underdiagnosed and little appraised in the field of general cardiology. However, it is important to be familiar with the clinical picture of this disease, especially because of the risk of developing fatal aortic aneurysms. If the disease is suspected after a thorough history and clinical examination combined with laboratory investigation, the diagnosis can be confirmed with (18)F-2-deoxy-glucose positron emission tomographic (FDG-PET) imaging. Early recognition of giant cell arteritis followed by prompt treatment with glucocorticosteroids will decrease the risk of developing large-vessel complications. (Neth Heart J 2009;17:281-3.).


Cardiomyopathy of uncertain etiology: Complementary role of multimodality imaging with cardiac MRI and 18FDG PET.

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Increasing benefit from revascularization is associated with increasing amounts of myocardial hibernation: a substudy of the PARR-2 trial.

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Comment in:
JACC Cardiovasc Imaging. 2009 Sep;2(9):1069-71.

OBJECTIVES: We sought to determine: 1) whether F-18-fluorodeoxyglucose (FDG) positron emission tomography (PET) parameters identify high-risk patients who gain benefit from revascularization; 2) whether there is a cut point for such benefit; and 3) predictors of outcome in patients with severe left ventricular (LV) dysfunction due to coronary artery disease. BACKGROUND: Patients with ischemic LV dysfunction might benefit from revascularization but not without risk. The FDG PET imaging can detect viable myocardium that recovers after revascularization. In the PARR-2 (PET and Recovery Following Revascularization-2) trial, FDG PET imaging showed a nonsignificant trend for improved outcome compared with standard care. Understanding the predictors of outcome from this prospective trial should help better identify patients at risk and which patients most benefit from revascularization. METHODS: This post hoc analysis included 182 patients with left ventricular ejection fraction (LVEF) <35% and coronary artery disease, being considered for revascularization work-up, and randomized to the PET
arm of PARR-2. The primary outcome was a composite of cardiac death, myocardial infarction, or cardiac repeat hospital stay at 1 year. RESULTS: There is an interaction between PET mismatch and protocol revascularization such that higher mismatch, when combined with revascularization, yields fewer primary outcome events (p = 0.02). On the basis of adjusted Cox modeling, with reduced mismatch (<7%), the risk is not significantly different with or without revascularization. As mismatch increases above this mark, risk is reduced with revascularization. Increasing creatinine (for a 10-mumol/l increase: hazard ratio: 1.03, 95% confidence interval: 1.01 to 1.06, p = 0.010) is also associated with increased risk, whereas decreasing LVEF (for a 2% decrease: hazard ratio: 1.08, 95% confidence interval: 0.99 to 1.18, p = 0.087) trends toward an association with increased risk. CONCLUSIONS: In this post hoc analysis, patients with ischemic cardiomyopathy with larger amounts of mismatch have improved outcome with revascularization. Renal function was also an independent predictor of outcome. The FDG PET seems to define high-risk patients that gain benefit from revascularization. (PET and Recovery Following Revascularization [PARR 2]; NCT00385242).


Diffuse involvement of the heart and great vessels in primary cardiac lymphoma.

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Primary cardiac lymphoma (PCL) is an extremely rare disorder. In this report, a 57-year-old male with diffuse large B-cell lymphoma involving the heart and great vessels is presented. Trans-thoracic echocardiography was the first modality used to establish the diagnosis. Fluorine-18-fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT) showed diffuse increased metabolic activity of the heart walls and hypermetabolic lesions occupying cardiac chambers in some areas. The patient underwent systemic chemotherapy, and after 13 days, a marked regression of the tumour mass was evident based on echocardiographic examination. After completing six R-CHOP chemotherapy treatments, PET imaging was planned to control the residual mass, but the patient was intubated due to pneumonia that developed after the sixth chemotherapy session and subsequently died due to sepsis.


Recent advances in cardiac PET and PET/CT myocardial perfusion imaging.

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BACKGROUND: In 2005, 80% of cardiovascular disease (CVD) deaths occurred in low- to middle-income countries (i.e., developing nations). Cardiovascular imaging, such as myocardial perfusion SPECT, is one method that may be applied to detect and foster improved detection of at-risk patients. This document will review the availability and utilization for nuclear cardiology procedures worldwide and propose strategies to devise regional centers of excellence to achieve quality imaging around the world. Methods: As a means to establish the current state of nuclear cardiology, International Atomic Energy Agency member and non-member states were queried as to annual utilization of nuclear cardiology procedures. Other sources for imaging statistics included data from medical societies (American Society of Nuclear Cardiology, European Society of Cardiology, and the European Association of Nuclear Medicine) and nuclear cardiology working groups within several nations. Utilization was calculated by dividing annual procedural volume by 2007 population statistics (/100,000) and categorized as high (>1,000/100,000), moderate-high (250-999/100,000), moderate (100-249/100,000), low-moderate (50-9/100,000) and low (<50/100,000). RESULTS: High nuclear cardiology utilization was reported in the United States, Canada, and Israel. Most Western European countries, Australia, and Japan reported moderate-high utilization. With the exception of Argentina, Brazil, Colombia and Uruguay, South America had low usage. This was also noted across Eastern Europe, Russia, and Asia. Utilization patterns generally mirrored each country's gross domestic product. However, nuclear cardiology utilization was higher for developing countries neighboring moderate-high “user” countries (e.g., Algeria and Egypt); perhaps the result of accessible high-quality training programs.
J Am Coll Cardiol. 2009 Sep 15;54(12):1072-84.

Adenosine-induced stress myocardial perfusion imaging using dual-source cardiac computed tomography.


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Comment in:

OBJECTIVES: This study sought to determine the feasibility of performing a comprehensive cardiac computed tomographic (CT) examination incorporating stress and rest myocardial perfusion imaging together with coronary computed tomography angiography (CTA). BACKGROUND: Although cardiac CT can identify coronary stenosis, very little data exist on the ability to detect stress-induced myocardial perfusion defects in humans. METHODS: Thirty-four patients who had a nuclear stress test and invasive angiography were included in the study. Dual-source computed tomography (DSCT) was performed as follows: 1) stress CT: contrast-enhanced scan during adenosine infusion; 2) rest CT: contrast-enhanced scan using prospective triggering; and 3) delayed scan: acquired 7 min after rest CT. Images for CTA, computed tomography perfusion (CTP), and single-photon emission computed tomography (SPECT) were each read by 2 independent blinded readers. RESULTS: The DSCT protocol was successfully completed for 33 of 34 subjects (average age 61.4 +/- 10.7 years; 82% male; body mass index 30.4 +/- 5 kg/m(2)) with an average radiation dose of 12.7 mSv. On a per-vessel basis, CTP alone had a sensitivity of 79% and a specificity of 80% for the detection of stenosis >=50%, whereas SPECT myocardial perfusion imaging had a sensitivity of 67% and a specificity of 83%. For the detection of vessels with > or =50% stenosis with a corresponding SPECT perfusion abnormality, CTP had a sensitivity of 93% and a specificity of 74%. The CTA during adenosine infusion had a per-vessel sensitivity of 96%, specificity of 73%, and negative predictive value of 98% for the detection of stenosis > or =70%. CONCLUSIONS: Adenosine stress CT can identify stress-induced myocardial perfusion defects with diagnostic accuracy comparable to SPECT, with similar radiation dose and with the advantage of providing information on coronary stenosis.


Extracorporeal cardiac shock wave therapy ameliorates clinical symptoms and improves regional myocardial blood flow in a patient with severe coronary artery disease and refractory angina.

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Different therapeutic options are being used for chronic coronary artery disease (CAD). We report about a 51-year-old female with CAD and refractory angina pectoris despite maximally tolerated medical therapy and after both percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG). The patient received cardiac shock wave therapy (CSWT) over a period of 6 month. There was no arrhythmia during or after treatment; enzyme levels were normal at all times. PET imaging showed a substantial improvement of myocardial stress perfusion. Since the patient reported that she now was fully capable to deal with her everyday life, further treatment options were postponed. Our case report suggests that ultrasound-guided CSWT is able to improve symptoms and perfusion in ischemic myocardium.
The case for myocardial ischemia in hypertrophic cardiomyopathy.

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Since its original description 50 years ago, myocardial ischemia has been a recognized but underappreciated aspect of the pathophysiology of hypertrophic cardiomyopathy (HCM). Nevertheless, the assessment of myocardial ischemia is still not part of routine clinical diagnostic or management strategies. Morphologic abnormalities of the intramural coronary arterioles represent the primary morphologic substrate for microvascular dysfunction and its functional consequence—that is, blunted myocardial blood flow (MBF) during stress. Recently, a number of studies using contemporary cardiovascular imaging modalities such as positron emission tomography (PET) and cardiovascular magnetic resonance (CMR) have led to an enhanced understanding of the role that myocardial ischemia and its sequelae fibrosis play on clinical outcome. In this regard, studies with PET have shown that HCM patients have impaired MBF after dipyridamole infusion and that this blunted MBF is a powerful independent predictor of cardiovascular mortality and adverse LV remodeling associated with LV systolic dysfunction. Stress CMR with late gadolinium enhancement (LGE) has also shown that MBF is reduced in relation to magnitude of wall thickness and in those LV segments occupied by LGE (i.e., fibrosis). These CMR observations show an association between ischemia, myocardial fibrosis, and LV remodeling, providing support that abnormal MBF caused by microvascular dysfunction is responsible for myocardial ischemia-mediated myocyte death, and ultimately replacement fibrosis. Efforts should now focus on detecting myocardial ischemia before adverse LV remodeling begins, so that interventional treatment strategies can be initiated earlier in the clinical course to mitigate ischemia and beneficially alter the natural history of HCM. 2009 by the American College of Cardiology Foundation.

Nuclear cardiology and heart failure.

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The prevalence of heart failure in the adult population is increasing. It varies between 1% and 2%, although it mainly affects elderly people (6-10% of people over the age of 65 years will develop heart failure). The syndrome of heart failure arises as a consequence of an abnormality in cardiac structure, function, rhythm, or conduction. Coronary artery disease is the leading cause of heart failure and it accounts for this disorder in 60-70% of all patients affected. Nuclear techniques provide unique information on left ventricular function and perfusion by gated-single photon emission tomography (SPECT). Myocardial viability can be assessed by both SPECT and PET imaging. Finally, autonomic dysfunction has been shown to increase the risk of death in patients with heart disease and this may be applicable to all patients with cardiac disease regardless of aetiology. MIBG scanning has a very promising prognostic value in patients with heart failure.

Current status of vulnerable plaque detection.

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Critical coronary stenoses have been shown to contribute to only a minority of acute coronary syndromes (ACS) and sudden cardiac death. Autopsy studies have identified a subgroup of high-risk patients with disrupted vulnerable plaque and modest stenosis. Consequently, a clinical need exists to develop methods to identify these plaques prospectively before disruption and clinical expression of disease. Recent advances in invasive and noninvasive imaging techniques have shown the potential to identify these high-risk plaques. The anatomical characteristics of the vulnerable plaque such as thin cap fibroatheroma and lipid pool can be identified with angioscopy, high frequency intravascular ultrasound, intravascular MRI, and optical coherence.
tomography. Efforts have also been made to recognize active inflammation in high-risk plaques using intravascular thermography. Plaque chemical composition by measuring electromagnetic radiation using spectroscopy is also an emerging technology to detect vulnerable plaques. Noninvasive imaging with MRI, CT, and PET also holds the potential to differentiate between low and high-risk plaques. However, at present none of these imaging modalities are able to detect vulnerable plaque neither has been shown to definitively predict outcome. Nevertheless in contrast, there has been a parallel development in the physiological assessment of advanced atherosclerotic coronary artery disease. Thus recent trials using fractional flow reserve in patients with modest non flow-limiting stenoses have shown that deferral of PCI with optimal medical therapy in these patients is superior to coronary intervention. Further trials are needed to provide more information regarding the natural history of high-risk but non flow-limiting plaque to establish patient-specific targeted therapy and to refine plaque stabilizing strategies in the future.


Ischemic patterns assessed by positron emission tomography predict adverse outcome in patients with idiopathic dilated cardiomyopathy.


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BACKGROUND: Although patients with idiopathic dilated cardiomyopathy (DCM) have no coronary artery disease, regional impairment of myocardial perfusion combined with preserved metabolism has been found using positron emission tomography (PET). Our aim was to assess the prognostic relevance of PET-mismatch between stress myocardial perfusion and glucose uptake on clinical outcome in DCM. METHODS: In 24 patients with DCM who underwent both myocardial perfusion and metabolism PET scanning, “mismatch” was assessed and the association with clinical outcome (hospitalization, mortality, and heart transplantation) was investigated. RESULTS:Mismatch was found in 16 patients (66.7%). Univariate analysis showed that the presence of mismatch was associated with adverse outcome (P = 0.03). After adjustment for sex and age, the association remained significant with an adjusted relative risk of 10.4 (95% CI 1.1-103; P = 0.04) for death, heart transplant, or hospitalization. Univariate analysis also showed that a higher extent of mismatch was significantly associated with adverse outcome (P = 0.02). After adjusting for sex and age, the association remained significant with an adjusted relative risk of 6.5 [95% CI 1.2-36; P = 0.03] for death, heart transplantation, or hospitalization. CONCLUSION: PET stress perfusion-metabolism mismatch, indicative for ischemia, is frequently found in DCM patients and related to a poorer outcome.

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Left atrial volume and index by multi-detector computed tomography: Comprehensive analysis from predictors of enlargement to predictive value for acute coronary syndrome (ROMICAT study).


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OBJECTIVES: We aimed to identify the predictors of left atrial (LA) enlargement by multi-detector computed tomography (CT) and determine its association and predictive value for acute coronary syndrome (ACS). BACKGROUND: LA enlargement is associated with myocardial ischemia and coronary artery disease (CAD) and is a strong predictor for cardiovascular events. These studies were performed primarily with echocardiography. With the rise of cardiac CT, LA volume can be readily measured. METHODS: In 377 emergency department patients with chest pain, we performed 64-slice CT for coronary artery assessment. We derived LA volumes (LAV(max), LAV(min)) and indices (LAVI(max), LAVI(min)) using a threshold-based volumetric method. RESULTS: Subjects, with cardiac risk factors or CAD by CT, had larger LA (ΔLAV(max) 9.1ml, p=0.004; ΔLAV(min) 8.1ml, p=0.001; ΔLAVI(max) 3.3ml/m2, p=0.03; ΔLAVI(min) 3.4ml/m2, p=0.006) than controls. Predictors of LA enlargement were related to risk factors for diastolic dysfunction. ACS risk was greater in patients with top quartile LAVI(max) (odds ratio [OR] 3.4, p=0.02) and LAVI(min) (OR 4.7, p=0.01) than lowest quartile, but not when indexed. Similarly, the predictive values of LA volumes were incrementally better when added to CT finding of indeterminate stenosis (LAVI(max)): C statistic 0.62 to 0.70, p=0.046; LAVI(min): C statistic 0.65 to 0.73, p=0.008), but not when indexed. CONCLUSIONS: Risk factors related to diastolic dysfunction are independent predictors of LA enlargement. LA enlargement by
volumes are associated with a 3-5 fold increase risk for ACS and have incremental value for predicting ACS when added to the CT finding of indeterminate stenosis.


CD151 gene delivery after myocardial infarction promotes functional neovascularization and activates FAK signaling.


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Abstract
Our previous studies showed that tetraspanin CD151 promotes neovascularization in rat hindlimb and myocardial ischemia models. This study is to assess whether CD151 induces arteriogenesis and promotes functional neovascularization in a pig myocardial infarction model, and to determine the signaling pathways involved. CD151 cDNA and antiCD151 sequence were constructed into a recombinant adeno-associated virus (rAAV) vector. All 26 pigs used either were subjected to coronary artery ligation or did not undergo surgery. Eight wks after viral administration, the expression of CD151 protein was measured by Western blot. The densities of capillaries and arterioles were determined using immunohistochemistry. Regional myocardial perfusion and other myocardial functions were evaluated by (13)N-labeled NH(3) positron emission computed tomography ((13)N-NH(3) PET) and echocardiography. Western blot was performed for assessing the signaling mechanisms. Overexpression of CD151 markedly increased the densities of capillaries and arterioles, significantly enhanced the regional myocardial perfusion, reduced myocardial ischemia, and improved the myocardial contraction, wall motion, and wall thickness. Conversely, antiCD151 gene delivery reversed the above changes. In addition, CD151 activated focal adhesion kinase (FAK), extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinase (JNK), phosphatidylinositol-3 kinase (PI3K), protein kinase B (Akt), and endothelial nitric-oxide synthase (eNOS), and increased nitric oxide (NO) level. These findings demonstrate a robust role of CD151 in inducing and/or upregulating neovascularization. CD151-dependent neovascularization correlates with the activations of FAK, mitogen activated protein kinases (MAPKs), and PI3K signaling, suggesting that CD151 may promote neovascularization via MAPKs and PI3K pathways.


Cardiac risk - coronary calcium scoring for all?

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Association between regional cerebral blood flow during hypoglycemia and genetic and phenotypic traits of the renin-angiotensin system.

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The risk of severe hypoglycemia in patients with type I diabetes and high basal activity in the renin-angiotensin system (RAS) is significantly higher than in patients with low basal RAS activity. In healthy men, we tested the hypothesis that differences in spontaneous RAS activity are associated with differences in cerebral activity responses during mild hypoglycemia. A total of 10 healthy men with high and 10 with low spontaneous RAS activity were selected. An H(2)(15)O-PET (H(2)(15)O-positron emission tomography) study was conducted with a series of six scans, i.e., two during normoglycemia, two during hypoglycemia, and two after hypoglycemia. The mean plasma glucose concentration was similar in both the groups (i.e., 2.1 mmol/L (s.d.: 0.4)
in the low RAS group and 2.2 mmol/L (s.d.: 0.4) in the high RAS group (P=0.47). The high RAS group has lower cerebral activity in the frontal area and a higher cerebral activity in the entorhinal area that expanded to include the parahippocampal gyrus after hypoglycemia. Our findings suggest that the high RAS group to a lesser extent than the low RAS group activates areas involving executive function that may explain the correlation between high basal RAS activity and risk of severe hypoglycemia in type I diabetes.
Objective and quantitative evaluation of motor function in a monkey model of Parkinson's disease.

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Monkeys treated with 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine (MPTP) are currently the best animal model for Parkinson's disease (PD) and have been widely used for physiological and pharmacological investigations. However, objective and quantitative assessments have not been established for grading their motor behaviors. In order to develop a method for an unbiased evaluation, we performed a video-based assessment, used qualitative rating scales, and carried out an in vivo investigation of dopamine (DA) transporter binding in systemically MPTP-treated monkeys. The video-based analysis of spontaneous movement clearly demonstrated a significant correlation with the qualitative rating score. The assessment of DA transporter (DAT) function by [11C]-CFT PET showed that, when compared with normal animals, the MPTP-treated animals exhibited decreased CFT binding in the bilateral striatum, particularly in the dorsal part in the putamen and caudate. Among the MPTP-treated monkeys, an unbiased PET analysis revealed a significant correlation between CFT binding in the midbrain and qualitative rating scores or the amount of spontaneous movements. These results indicate that a video-based analysis can be a reliable tool for an objective and quantitative evaluation of motor dysfunction of MPTP-treated monkeys, and furthermore, that DAT function in the midbrain may also be important for the evaluation.


Autopsy as gold standard in FDG-PET studies in dementia.

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Positron emission tomography (PET) imaging with F18-fluorodeoxyglucose (FDG) is increasingly used as an adjunct to clinical evaluation in the diagnosis of dementia. Considering that most FDG-PET studies in dementia use clinical diagnosis as gold standard and that clinical diagnosis is approximately 80% sensitive or accurate, we aim to review the evidence-based data on the diagnostic accuracy of brain FDG-PET in dementia when cerebral autopsy is used as gold standard. We searched the PubMed and Medline databases for dementia-related articles that correlate histopathological diagnosis at autopsy with FDG-PET imaging and found 47 articles among which there were only 5 studies of 20 patients or more. We were able to conclude that sensitivity and specificity of FDG-PET for Alzheimer's disease are good, but more studies using histopathological diagnosis at autopsy as gold standard are needed in order to evaluate what FDG-PET truly adds to premortem diagnostic accuracy in dementia.

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Mitochondrial matters of the brain: the role in Huntington’s disease.

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Even before the discovery of the mutant htt gene as the cause of Huntington’s Disease (HD), abnormal energy metabolism and mitochondrial dysfunction had been suggested as a possible pathogenic mechanism in HD. These initial investigations described defects in energy metabolism using Positron Emission Tomography (PET) and Nuclear Magnetic Resonance (NMR) Spectroscopy in symptomatic and pre-symptomatic HD patients. Concurrently, 3-nitropropionic acid, a mitochondrial complex II inhibitor, was found to replicate many of the pathological and clinical features of HD when administered to animals. Subsequently, reductions in mitochondrial respiratory chain enzyme activities in HD brain and muscle, HD mice models and cellular HD models were discovered and confirmed impaired mitochondrial function as an important component of pathogenesis. A unifying hypothesis linking chronic ATP depletion, oxidative stress and mitochondrial dysfunction culminated in the “slow excitotoxic theory” of HD pathogenesis. More recently, the localization of mutant htt within mitochondria and the association between transcriptional dysregulation caused by impaired PGC-1alpha activity with abnormal mitochondrial biogenesis and function has provided further links with additional potential pathogenic mechanisms.
PET - Neurology

Arch Neurol. 2010 May;67(5):596-605.
Fluorodeoxyglucose F18 positron emission tomography in progressive apraxia of speech and primary progressive aphasia variants.

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OBJECTIVES: To determine patterns of hypometabolism on fluorodeoxyglucose F18 positron emission tomography (FDG-PET) in patients with progressive apraxia of speech (PAS) and primary progressive aphasia (PPA) variants and to use these patterns to further refine current classification. DESIGN: We identified all patients who had FDG-PET and PAS or PPA who were evaluated by an expert speech-language pathologist. Patterns of hypometabolism were independently classified by 2 raters blinded to clinical data. Three speech-language pathologists reclassified all patients into 1 of 7 operationally defined categories of PAS and PPA blinded to FDG-PET data. SETTING: Tertiary care medical center. PATIENTS: Twenty-four patients with PAS or PPA and FDG-PET. MAIN OUTCOME MEASURE: Fluorodeoxyglucose F18 PET hypometabolic pattern. RESULTS: Of the 24 patients in the study, 9 had nonfluent speech output; 14, fluent speech; and 1 was unclassifiable. Twenty-one patients showed FDG hypometabolism; the remaining 3 did not. Among the patients showing hypometabolism, 8 had a prerolandic pattern of which 7 had nonfluent speech including progressive nonfluent aphasia (n = 3), PAS (n = 1), and mixed nonfluent aphasia/apraxia of speech (n = 3); the other patient had PPA unclassifiable. The remaining 13 had a postrolandic pattern, all with fluent speech (P < .001), including logopenic progressive aphasia (n = 6), progressive fluent aphasia (n = 6), and semantic dementia (n = 1). Patterns of hypometabolism differed between the nonfluent variants and between the fluent variants, including progressive fluent aphasia. CONCLUSION: Patterns of FDG-PET hypometabolism support the clinical categorizations of fluency, the distinction of apraxia of speech from progressive nonfluent aphasia, and the designation of a progressive fluent aphasia category.

[Rapidly progressive parkinsonism that developed one year after ventriculoperitoneal shunting for idiopathic aqueductal stenosis: a case report]
[Article in Japanese]
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A 46-year-old woman was diagnosed with having idiopathic aqueductal stenosis for which she underwent ventriculoperitoneal (V-P) shunting. One year after the surgery, she developed acute parkinsonism and sylvian aqueduct syndrome. Brain magnetic resonance imaging (MRI) did not reveal any signs of hydrocephalus and fluorodopa positron emission tomography (PET) did not reveal any decrease in accumulation of fluorodopa at the striatum. On admission, the Unified Parkinson Disease Rating Scale (UPDRS) (Part III) score was 30 points. The preliminary diagnosis was parkinsonism associated with V-P shunting: therefore, the levodopa dosage was increased from 200 mg/day to 600 mg/day. Thereafter, the symptoms of parkinsonism and the sylvian aqueduct syndrome markedly improved, and the UPDRS (Part III) score decreased. If such a patient presents without signs of hydrocephalus or shunt malfunction, dopaminergic medication should be used as the initial treatment.

Neurobiol Aging. 2010 May 4. [Epub ahead of print]

Integrating ADNI results into Alzheimer's disease drug development programs.
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Abstract

The Alzheimer's Disease Neuroimaging Initiative (ADNI) is providing critical new information on biomarkers in cognitively normal elderly, persons with mild cognitive impairment (MCI), and patients with mild Alzheimer's disease (AD). The data provide insights into the progression of the pathology of AD over time, assist in understanding which biomarkers might be most useful in clinical trials, and facilitate development of disease-modifying treatments. ADNI results are intended to support new AD treatment development; this report considers how ADNI information can be integrated in AD drug development programs. Cerebrospinal fluid (CSF) amyloid beta protein (Abeta) measures can be used in Phase I studies to detect any short term effects on Abeta levels in the CSF. Phase II studies may benefit most from biomarker measures that can inform decisions about Phase III. CSF Abeta levels, CSF total tau and phospho-tau measures, fluorodeoxyglucose positron emission tomography (FDG PET), Pittsburgh Compound B (PIB) amyloid imaging, or magnetic resonance imaging (MRI) may be employed to select patients in enriched trials or as outcomes for specific disease-modifying interventions. Use of biomarkers may allow Phase II trials to be conducted more efficiently with smaller populations of patients or shorter treatment times. New drug applications (NDAs) may include biomarker outcomes of phase III trials. ADNI patients are highly educated and are nearly all of Caucasian ethnicity limiting the generalizability of the results to other populations commonly included in global clinical trials. ADNI has inspired or

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collaborates with biomarker investigations worldwide and together these studies will provide biomarker information that can reduce development times and costs, improve drug safety, optimize drug efficacy, and bring new treatments to patients with or at risk for AD.


Noninvasive imaging of endogenous neural stem cell mobilization in vivo using positron emission tomography.

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Neural stem cells reside in two major niches in the adult brain [i.e., the subventricular zone (SVZ) and the dentate gyrus of the hippocampus]. Insults to the brain such as cerebral ischemia result in a physiological mobilization of endogenous neural stem cells. Since recent studies showed that pharmacological stimulation can be used to expand the endogenous neural stem cell niche, hope has been raised to enhance the brain’s own regenerative capacity. For the evaluation of such novel therapeutic approaches, longitudinal and intraindividual monitoring of the endogenous neural stem cell niche would be required. However, to date no conclusive imaging technique has been established. We used positron emission tomography (PET) and the radiotracer 3'-deoxy-3'-(18)F]fluoro-l-thymidine ([18]F)FLT) that enables imaging and measuring of proliferation to noninvasively detect endogenous neural stem cells in the normal and diseased adult rat brain in vivo. This method indeed visualized neural stem cell niches in the living rat brain, identified as increased ([18]F)FLT-binding in the SVZ and the hippocampus. Focal cerebral ischemia and subsequent damage of the blood-brain barrier did not interfere with the capability of ([18]F)FLT-PET to visualize neural stem cell mobilization. Moreover, ([18]F)FLT-PET allowed for an in vivo quantification of increased neural stem cell mobilization caused by pharmacological stimulation or by focal cerebral ischemia. The data suggest that noninvasive longitudinal monitoring and quantification of endogenous neural stem cell activation in the brain is feasible and that ([18]F)FLT-PET could be used to monitor the effects of drugs aimed at expanding the neural stem cell niche.


Cerebral cortical and subcortical cholinergic deficits in parkinsonian syndromes.

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OBJECTIVES: Cholinergic projections to cerebral cortical and subcortical regions are decreased in Parkinson disease (PD), but not evaluated in the parkinsonian syndromes of multiple system atrophy (MSA-P) and progressive supranuclear palsy (PSP). We studied cholinergic innervation in these disorders as compared to age-appropriate normal control subjects. METHODS: We used PET with [(11)C]PMP to measure acetylcholinesterase (AChE) activity in multiple cerebral cortical and subcortical regions. We studied 22 normal controls, 12 patients with PD, 13 patients with MSA-P, and 4 patients with PSP. RESULTS: We found significantly decreased AChE activity in most cerebral cortical regions in PD and MSA-P, and a similar but nonsignificant decrease in PSP. No differences were found between PD and MSA-P. Significantly decreased AChE activity was found in PD in striatum, cerebellum, and thalamus, with a marginally significant decrease in mesencephalon and no change in pons. Significantly greater declines in AChE activity in all subcortical regions were seen in MSA-P and PSP vs in PD. Decreased AChE activity in brainstem and cerebellum of all 3 disorders correlated with disturbances of balance and gait. CONCLUSIONS: Cerebral cortical cholinergic activity is decreased to a similar level in Parkinson disease (PD), parkinsonian syndromes of multiple system atrophy (MSA-P), and progressive supranuclear palsy (PSP) as compared to normal controls. Subcortical cholinergic activity is significantly more decreased in MSA-P and PSP than in PD. The more substantial decrease reflects greater impairment in the pontine cholinergic group, which is important in motor activity, particularly gait. These differences may account for the greater gait disturbances in the early stages of MSA-P and PSP than in PD.

Lung Cancer. 2010 Apr 27. [Epub ahead of print]

Prognostic value of SUVmax measurements obtained by FDG-PET in patients with non-small cell lung cancer receiving chemotherapy.

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Fluorodeoxyglucose (FDG) uptake has been shown to correlate well with tumor proliferation rates. In patients with non-small cell lung cancer (NSCLC) receiving chemotherapy, we analyzed the relationships between the maximum standardized uptake value (SUVmax) obtained by FDG positron emission tomography (FDG-PET) and other clinical factors, and examined whether or not SUVmax could predict progression-free survival (PFS) and/or overall survival (OS). This retrospective study involved 62 consecutive NSCLC patients (35 male and 27 female: median age, 65 years). All patients underwent FDG-PET examination before treatment. As the first-line treatment, the patients received chemotherapy with (n=15) or without (n=47) radiotherapy. Survival curves were obtained by the Kaplan-Meier method, and differences in survival between subgroups were analyzed by the log-rank test and the Cox proportional hazards model. Significant correlations were observed between SUVmax and gender (P=0.006), histology (P<0.001), smoking status (P=0.049), stage (P=0.015), and treatment modality (P=0.008), but not other factors, including age (P=0.402) and performance status (P=0.421). The median SUVmax was 5.1 (25-75th percentile: 3.45-7.0) in patients with adenocarcinoma and 8.3 (25-75th percentile: 6.9-9.9) in those with other types of NSCLC. Adenocarcinomas showed significantly lower SUVmax than the other tumor types (P<0.001). Cox analysis adjusting for possible confounding factors, including gender, smoking status, histology and stage, demonstrated that the hazard ratios increased as the SUVmax increased in terms of both PFS (P=0.008) and OS (P=0.045), indicating that SUVmax predicts outcome independently of other clinical factors, such as histology and stage. Our findings indicate that FDG-PET examination can provide information useful for prognostication in NSCLC.

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Deep brain stimulation in cluster headache: hypothalamus or midbrain tegmentum?

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Abstract

Functional and structural neuroimaging studies have provided pivotal insights into the pathophysiology of trigeminal autonomic cephalalgias (TACs), particularly cluster headache (CH). Functional imaging studies using positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) in TACs have reported activation of the posterior hypothalamus. A structural neuroimaging study using voxel-based morphometry in CH reported increased volume of the hypothalamic gray, although another larger study failed to reproduce this finding. These studies in CH prompted the use of stereotactic stimulation of the target point identified by functional and structural neuroimaging. The precise anatomical localization of the deep brain stimulation (DBS) target places it at the midbrain tegmentum rather than the posterior hypothalamus. A comparison of the PET and fMRI studies in TACs reveals that the diencephalic/mesencephalic activation is more postero-inferior in the PET studies, straddling the hypothalamus and midbrain tegmentum, whereas the activation is centered on the hypothalamus in the higher spatial resolution fMRI studies. To optimize the outcomes from DBS, it is likely that patients will need to be studied individually using functional imaging techniques that have high spatial and temporal resolution to enable targeting of the appropriate locus with stereotactic stimulation.

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[Acute hemiplegia and hemianesthesia together with decreased tendon reflexes mimicking acute stroke representing a conversion disorder]

[Article in Hebrew]

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Acute hemiplegia and hemianesthesia is commonly caused by obstruction of major cortical arteries. Such a presentation secondary to a conversion reaction is very rare, especially in the pediatric age group. The authors report an adolescent presenting with acute complete left-sided hemiplegia and sensory loss together with decreased tendon reflexes mimicking an acute arterial stroke. Examination revealed Hoover's sign was present and the patient was oblivious to his stern neurological state. Movement of his paralytic limbs was observed during sleep. Cortical and spinal CT, cortical MRI, motor and somatosensory evoked potentials and a PET study were all normal. As such, the diagnosis of psychogenic hemiplegia was established, apparently within a period that the patient had experienced severe emotional stress while questioning his gender identity. After three days, the adolescent began to move the paralytic limbs along gradual resolution of sensory deficit, leading to complete clinical recovering within two months. Although extremely rare, a conversion reaction should be taken into account in children presenting with acute hemiplegia and anaesthesia, even accompanied with decreased tendon reflexes, when the patient is oblivious to his alleged grave state, and when clinical observations such as Hoover's sign remain intact, substantiated by normal extensive radiological and...
neurophysiological investigation. Intact motor evoked potentials serve as a key for the diagnosis of psychogenic hemiplegia and, should therefore be performed in suspected cases.

Clin Neurol Neurosurg. 2010 Apr 12. [Epub ahead of print]

**Spinal myoclonus in the periscapular muscles after mastectomy assessed by FDG-PET.**


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We describe a 64-year-old woman who developed spinal myoclonus around the left scapula after long thoracic nerve injury by mastectomy. Involuntary muscle twitching was semi-rhythmic, and ultrasonography identified contraction of the serratus anterior, teres major, and rhomboid muscles. FDG-PET imaging revealed markedly increased glucose uptake only in the serratus anterior. Lidocaine injection into this muscle resulted in complete cessation of the involuntary movement, and then she was successfully treated with botulinum toxin type A. These findings raise the possibility that the myoclonus was primarily caused by ectopic firing of the injured long thoracic nerve, then spreading to adjacent muscles possibly via a central mechanism mediated by group Ia afferents. The new imaging tools, such as FDG-PET and ultrasonography, were useful to determine the therapeutic target muscle.

Clin Neurol Neurosurg. 2010 Apr 12. [Epub ahead of print]

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Department of Neurology, Graduate School of Medicine, Chiba University, Inohana 1-8-1, Chuo-ku, Chiba 260-8670, Japan.

We describe a 64-year-old woman who developed spinal myoclonus around the left scapula after long thoracic nerve injury by mastectomy. Involuntary muscle twitching was semi-rhythmic, and ultrasonography identified contraction of the serratus anterior, teres major, and rhomboid muscles. FDG-PET imaging revealed markedly increased glucose uptake only in the serratus anterior. Lidocaine injection into this muscle resulted in complete cessation of the involuntary movement, and then she was successfully treated with botulinum toxin type A. These findings raise the possibility that the myoclonus was primarily caused by ectopic firing of the injured long thoracic nerve, then spreading to adjacent muscles possibly via a central mechanism mediated by group Ia afferents. The new imaging tools, such as FDG-PET and ultrasonography, were useful to determine the therapeutic target muscle.


**Comparing fludeoxyglucose F18-PET assessment of regional cerebral glucose metabolism and [11C]dihydrotetrabenazine-PET in evaluation of early dementia and mild cognitive impairment.**

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OBJECTIVE: To compare assessment of regional cerebral metabolic changes with [(11)C]dihydrotetrabenazine (DTBZ)-positron emission tomography (PET) measurement of regional cerebral blood flow (K(1)) and fludeoxyglucose F18 (FDG)-PET measurement of regional cerebral glucose uptake (CMR(glc)) in a clinically representative sample of subjects with mild dementia and mild cognitive impairment (MCI). DESIGN: [(11)C]Dihydrotetrabenazine-PET K(1) and FDG-PET CMR(glc) measurements were performed. SETTING: University-based cognitive disorders clinic. PARTICIPANTS: Fifty subjects with either mild dementia (Mini-Mental State Examination score > or = 18) or MCI. Their results were compared with those of 80 normal control subjects. MAIN OUTCOME MEASURES: The DTBZ-PET regional K(1) and FDG-PET CMR(glc) measurements were compared with standard correlation analysis. The overall patterns of DTBZ-PET K(1) and FDG-PET CMR(glc) deficits were assessed with stereotaxic surface projections (SSPs) of parametric images. RESULTS: The DTBZ-PET regional K(1) and FDG-PET CMR(glc) measurements were highly correlated, both within and between subjects. The SSP maps of deficits in DTBZ-PET regional K(1) and FDG-PET CMR(glc) measurements were markedly similar. The DTBZ-PET K(1) SSP maps exhibited a mild decrease in sensitivity relative to FDG-PET CMR(glc) maps. CONCLUSIONS: Both DTBZ-PET K(1) and FDG-PET CMR(glc) measurements provide comparable information in assessment of regional cerebral metabolic
deficits in mild dementia and MCI. Blood flow measures can assess regional cerebral metabolism deficits accurately in mild dementia and MCI. Blood flow assessments of regional cerebral metabolic deficits can be combined with tracer binding results to improve utility of PET imaging in mild dementia and MCI.

Epilepsia. 2010 Apr 2. [Epub ahead of print]

The topography and significance of extratemporal hypometabolism in refractory mesial temporal lobe epilepsy examined by FDG-PET.

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Abstract

Summary Purpose: This study aims to map the temporal and extratemporal 18-fluorodeoxyglucose positron emission tomography (FDG-PET)-defined hypometabolism in mesial temporal lobe epilepsy (MTLE). We hypothesize that quantitative analysis will reveal extensive extratemporal glucose hypometabolism (EH), that the EH is related to seizure propagation beyond the temporal lobe, hypometabolism restricted to one temporal lobe predicts a good outcome following surgery, and EH predicts a poor outcome. Methods: Sixty-four patients were studied who had undergone temporal lobectomy for intractable MTLE and had at least 2 years of postoperative follow-up. Spatial preprocessing and statistical analysis on preoperative interictal FDG-PET using statistical parametric mapping (SPM 2) identified significant regions of hypometabolism compared to normal controls. The predictors of outcome were determined by univariable and multiple logistic regression analyses. Results: EH was common and widespread, occurring most frequently in the ipsilateral insula and frontal lobe. The extent of EH was not significantly associated with age of onset or the duration of epilepsy. Presence of secondarily generalized tonic–clonic seizures (SGTCS) was associated with a larger extent of remote hypometabolism (RH, p < 0.005). Multiple logistic regression analysis identified the extent of RH and the age at surgery as independent predictors of seizure outcome. Discussion: Our results indicate that RH in MTLE is associated with a poorer surgical outcome, especially if seen in the contralateral hemisphere. The extent of RH relates to SGTCS but not to duration of epilepsy.


[Localization of epileptic foci in frontal lobe epilepsy and its surgical therapy]

[Article in Chinese]


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OBJECTIVE: To analyze the clinical data and pre-operative examination results of frontal lobe epilepsy and combine with intra-operative intracranial electrical record in order to localize epileptic foci and to direct surgical therapy. METHODS: Preoperative EEG record and MRI scan were performed in 23 patients with refractory frontal lobe epilepsy. Among them, 17 patients received interictal 18F-FDG-PET-CT, 11 received MEG examination, 2 received functional MRI, 10 received surgical operation and intra-operative intracranial electrical record. RESULTS: The positive predictive value of clinical features of epileptic seizure, interictal EEG, ictal EEG, MRI and PET-CT were 56.52%, 56.52%, 60.87%, 54.55% and 94.12% respectively. Their consistent results helped to confirm the epileptogenic zone. MEG was more accurate than EEG. ECoE and VEEG monitoring was significant for operative guidance. CONCLUSION: A series of examinations is necessary for the diagnosis of epileptogenic zone of frontal lobe epilepsy. The surgical outcome is related to the accuracy of epileptic foci localization and the removal of epileptogenic zone.

Clin Neurol Neurosurg. 2010 Mar 26. [Epub ahead of print]

Acute behavioural change in a young woman evolving towards cerebellar syndrome.

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Symptomatic paraneoplastic neurological syndromes are rare manifestations of cancers. Recently, a new type of encephalitis associated with antibodies against NMDA-glutamate receptors (A-NMDAR) was defined. The patients, usually young women,
present with acute onset of psychiatric symptoms and decreased consciousness. We describe the case of a patient who presented with acute onset of delirium alternating with sub-comatose state. Blood analyses were within normal range. Lumbar puncture showed lymphocytic pleiocytosis. Brain gadolinium injected MRI, brain and full body PET scans were normal. Investigations led to suspect a paraneoplastic syndrome and a right ovarian teratoma and A-NMDAR were found and the teratoma removed. The remaining sequellae included a cerebellar syndrome seldom described before. As cerebellar and cortical neurons share the same excitatory pathway through NMDA-glutamate receptors, the cerebellar function impairment observed in our patient could be explained by a disabling action on glutamate NMDAR by the A-NMDAR

Neurotoxicology. 2010 Mar 24. [Epub ahead of print]

Carbon monoxide poisoning-induced nigrostriatal dopaminergic dysfunction detected using positron emission tomography (PET).

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Abstract

A malfunctioning heater caused a severe carbon monoxide (CO) intoxication leading to unconsciousness and predominantly right-sided extrapyramidal syndrome in a 29-year-old man. Follow-up included thorough clinical monitoring, and brain MRI and PET studies. Nine days after the poisoning, brain MRI showed symmetrical necrosis in the globus pallidi, but no abnormality was found in the substantia nigra. In addition, white matter periventricular lesions were seen. In a control scan 14 months later the white matter changes had subsided but small necrotic lesions were still noted bilaterally in the globus pallidi. A 6-[(18)F]fluoro-l-dopa PET examination performed 5 weeks after the intoxication revealed impaired presynaptic dopaminergic function in the left putamen whereas in the right putamen the dopaminergic activity was within normal limits. [(11)C]raclopride PET imaging 4 months after the poisoning showed no abnormality in postsynaptic D2 binding in the striatum. Clinically, the parkinsonian symptoms resolved 1.5 years after the poisoning. The final outcome of the recovery was excellent, and the patient returned to work. This is the first case reported where unilateral presynaptic, dopaminergic hypofunction in putamen could be confirmed with fluoro-l-dopa PET imaging on a patient with extrapyramidal syndrome caused by CO poisoning. Our results emphasize that CO intoxication can lead to striatal dopaminergic hypofunction, and that PET is a sensitive tool in evaluating extrapyramidal system after sudden neurotoxic insult. Copyright © 2010 Elsevier Inc. All rights reserved.


Biomarkers: Parkinson disease with dementia and dementia with Lewy bodies.

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Dementia is a common feature in Parkinson disease (PD), the time of onset determining how patients are classified. Those patients where dementia develops prior to Parkinsonism or during the first year of disease are designated as having dementia with Lewy bodies (DLB). In those where dementia develops over a year after the onset of motor signs, the condition is known as Parkinson’s disease with dementia (PDD). While this seems at first sight to be a definitive way to distinguish these conditions, reality is rather different. The overlap between them is considerable, and there is much uncertainty associated with patients who have both motor symptoms and early cognitive impairment. The diagnosis is still based on medical history and clinical evaluation. It is not even certain that they can be accurately distinguished at autopsy. For this reason, the data concerning these entities have been reviewed, to examine various markers employed or measured in clinical, neuropathological, neuroimaging, and biochemical investigations. The concept of PDD and DLB being separate conditions is comparatively new, and the most promising tools with which to separate them at present are cerebrospinal fluid (CSF) markers and positron emission tomography (PET) scanning that indicate increased amyloid-beta burden in DLB compared to PDD. However as yet there are no markers that unequivocally distinguish between PDD and DLB.
Comparison of neuropsychological and FDG-PET findings between early- versus late-onset mild cognitive impairment: A five-year longitudinal study.

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AIMS: Our purpose was to investigate differences in neuropsychological characteristics and glucose metabolism between early-onset mild cognitive impairment (EOMCI) and late onset MCI (LOMCI) patients and to determine if the baseline differences are predictive of conversion to dementia. METHODS: We enrolled 28 patients with MCI (12 EOMCI, 16 LOMCI) and 2 age-matched control groups. At the end of a 5-year follow-up, we compared the baseline neuropsychological and PET data between converters and nonconverters. RESULTS: The EOMCI patients obtained significantly higher scores in verbal recall and word fluency tests than the LOMCI patients. The EOMCI group, compared to the young controls, demonstrated hypometabolism in brain regions vulnerable in mild Alzheimer's disease. Converters were significantly more impaired in the delayed verbal recall test than nonconverters (p = 0.028) and tended to be more impaired in the semantic word fluency test (p = 0.084). The baseline PET scan of the converters demonstrated severer hypometabolism in frontal areas than that of the nonconverters both in the EOMCI and LOMCI groups. CONCLUSION: Our study suggests that EOMCI patients may differ from LOMCI in the patterns of cognitive deficits and glucose hypometabolism. In addition, baseline neuropsychological and FDG-PET findings suggest that MCI patients with poor memory or frontal dysfunction are at greater risk of conversion to dementia.

Neural correlates of forgiveness for moral transgressions involving deception.

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We used positron emission tomography (PET) to investigate the neural mechanisms underlying the willingness to forgive another person's moral transgression involving deception. During scanning, 12 subjects were asked to judge the forgivability of a perpetrator's moral transgression. These transgressions were described by four kinds of scenarios composed of a combination of two factors: the attitude of the perpetrator (dishonest or honest) and the severity of the moral transgression (serious or minor). Behavioral data showed that both the perpetrator's dishonesty and the seriousness of the scenario decreased the subjects' willingness to forgive the moral transgression. Neuroimaging data revealed that, relative to honest responses, a perpetrator's dishonest responses were associated with right ventromedial prefrontal activity, which possibly reflects the subjects' identification of the perpetrator's deception. The opposite comparison did not show significant activation. Moreover, a comparison of serious scenarios with minor scenarios did not reveal significant activation. Instead, minor scenarios, relative to serious scenarios, evoked activity in the right middle frontal gyrus and the right caudate nucleus, possibly reflecting increased demand on frontal control system function. Further analysis revealed that the left ventromedial prefrontal cortex showed a significant interaction between the two factors, indicating that this region functions as a mediator of the two factors, modulating judgments regarding the forgivability of moral transgressions. Taken together, these findings suggest that the ventromedial prefrontal cortex plays a key role in the forgiveness of moral transgressions involving deception.


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Dopaminergic depletion in the nigrostriatal system is the neurochemical hallmark of Parkinson's disease (PD). Although numerous efforts have been made to determine the evolution of dopaminergic depletion in PD, "in vivo" data concerning the stages of this process are still scarce. We evaluated 6-[18F]-fluoro-L-DOPA ((18)F-DOPA) and 11C-(+)-alpha-dihydrotetrabenazine ((11)C-DTBZ) using PET in a model of chronically MPTP-induced parkinsonism in non-human primates. Methods: Sixty-seven cynomolgus monkeys (Macaca fascicularis) were included in the study. Progressive parkinsonism was
induced by repeated administration of small doses of MPTP (iv) over several months. Animals were classified as controls, asymptomatic, recovered (having exhibited parkinsonian features transiently) and stable parkinsonian, according to their motor status. Analysis of striatal dopaminergic activity was conducted by regions of interest (ROI) and statistical parametric mapping (SPM) over normalized parametric images. Results: A progressive loss of striatal uptake was evident among groups for both radiotracers, which correlated significantly with the clinical motor status. Changes occurred earlier, i.e. in the less affected stages, with (11)C-DTBZ. Similar results were achieved by ROI and SPM analysis. Uptake was similar with both radiotracers for the asymptomatic and recovered groups. Conclusions: Serial assessment with (18)F-DOPA and (11)C-DTBZ PETs provides an effective approach to evaluate evolution of dopaminergic depletion in monkeys with MPTP-induced parkinsonism. This approach could be useful to perform studies aiming to test the effect of early therapeutic intervention and putative neuroprotective treatments.


Effects of Age on the Glucose Metabolic Changes in Mild Cognitive Impairment.


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Abstract
BACKGROUND AND PURPOSE: Decreased glucose metabolism in the temporal and parietal lobes on FDG-PET is recognized as an early imaging marker for the AD pathology. Our objective was to investigate the effects of age on FDG-PET findings in aMCI. MATERIALS AND METHODS: Twenty-five patients with aMCI at 55-86 years of age (median = 73 years) and 25 age- and sex-matched CN subjects underwent FDG-PET. SPM5 was used to compare the FDG uptake in patients in aMCI-old (>73 years) and aMCI-young (<=<73 years) groups with CN subjects. The findings in the aMCI-old patients were independently validated in a separate cohort of 10 aMCI and 13 CN subjects older than 73 years of age. RESULTS: The pattern of decreased glucose metabolism and gray matter atrophy in the medial temporal, posterior cingulate, precuneus, lateral parietal, and temporal lobes in aMCI-young subjects was consistent with the typical pattern observed in AD. The pattern of glucose metabolic changes in aMCI-old subjects was different, predominantly involving the frontal lobes and the left parietal lobe. Gray matter atrophy in aMCI-old subjects was less pronounced than that in the aMCI-young subjects, involving the hippocampus and the basal forebrain in both hemispheres CONCLUSIONS: Pathologic heterogeneity may be underlying the absence of AD-like glucose metabolic changes in older compared with younger patients with aMCI. This may be an important consideration for the clinical use of temporoparietal hypometabolism on FDG-PET as a marker for early diagnosis of AD in aMCI.


Comparative analysis of brain structure, metabolism, and cognition in myotonic dystrophy 1 and 2.


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Comment in:


OBJECTIVE: Myotonic dystrophy type 1 and 2 (DM1/DM2) are multisystemic diseases with common cognitive deficits beside the cardinal muscular symptoms. We performed a comprehensive analysis of cerebral abnormalities to compare the neuropsychological deficits with findings in different imaging methods in the same cohort of patients. METHODS: Neuropsychological investigations, structural cerebral MRI including brain parenchymal fraction (BPF) and voxel-based morphometry (VBM), and (18)F-deoxy-glucose PET (FDG-PET) were performed in patients (20 DM1 and 9 DM2) and matched healthy controls, and analyzed using statistical parametric mapping (SPM2). RESULTS: DM1 and DM2 patients showed typical neuropsychological deficits with a pronounced impairment of nonverbal episodic memory. Both patient groups showed a reduction of the global gray matter (measured by BPF), which could be localized to the frontal and parietal lobes by VBM. Interestingly, VBM revealed a bilateral hippocampal volume reduction that was correlated specifically to both a clinical score and episodic memory deficits. VBM also revealed a pronounced change of thalamic gray matter. White matter lesions were found in >50% of patients and their extent was correlated to psychomotor speed. FDG-PET revealed a frontotemporal hypometabolism, independent of the decrease in cortical gray matter. All abnormalities were similar in both patient groups but more pronounced for DM1. CONCLUSIONS: Our results suggest that 1) some of the characteristic cognitive deficits of these
patients are linked to specific structural cerebral changes, 2) decreases in gray matter and metabolism are independent processes, and 3) the widespread brain abnormalities are more pronounced in DM1.


Epidural and foramen-ovale electrodes in the diagnostic evaluation of patients considered for epilepsy surgery.

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PURPOSE: To evaluate the clinical utility of epidural and foramen-ovale recordings and associated morbidity in the pre-surgical evaluation of epilepsy. METHODS: We retrospectively analysed 59 epilepsy patients, who underwent recordings with epidural (n = 59) and foramen-ovale electrodes (n = 46) as part of their pre-surgical evaluation between 1990-1999. The epidural and foramen-ovale evaluation was based on the results of the non-invasive EEG-video recordings in patients, in whom non-invasive evaluation failed to localise seizure onset (75%, 44 patients) or where EEG, and imaging studies were discrepant (25%, 15 patients) but allowed a testable hypothesis on the seizure onset zone. RESULTS: Most patients (n = 57) were evaluated between 1990-1994. Only two patients were evaluated later. The results of the epidural (n = 559) and foramen-ovale (n = 83) electrode recordings allowed us to proceed to resective epilepsy surgery in 31% (n = 18) and to exclude further invasive evaluation in 15% (n = 9) of the patients. In 49% (n = 29) of the patients the results guided further invasive recordings using subdural and/or depth electrodes. For only three patients no additional information was gained by the electrode recordings. Temporary morbidity included local infection (epidural; n = 1) and facial pain (foramen ovale; n = 1) but no permanent complication occurred. DISCUSSION: Epidural and foramen-ovale electrodes have almost been abandoned in recent years, most likely because of the improvement of neuroimaging techniques such as MRI, PET and ictal SPECT. However, in selected patients, epidural electrodes and foramen-ovale electrodes are either useful as a measure to avoid invasive evaluation or serve to guide invasive evaluation.


[Positron emission tomography 2008 in Germany - results of the query and current status]

[Article in German]

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AIM: The working group on positron emission tomography (PET) of the DGN (German Society of Nuclear Medicine) initiated this first survey to collect and analyse information on the practise of PET in Germany in the year 2008. METHODS: A questionnaire was sent to PET performing facilities (medical practices, hospitals, university hospitals and others) for retrospective data acquisition. Details regarding the equipment and examination procedures were examined as well as indications and number of studies. In addition, the role of PET within the diagnostic process was evaluated. RESULTS: Responses from 65 sites were analysed. Their technical equipment consisted of 77 PET scanners (40 of them were combined PET/CT devices). About 63500 PET studies had been performed with 86% in the field of oncology, 8% in neurology and 3% in cardiology. The radionuclides were labelled with 18F in 91% of the studies, whereas 68Ga was used in 4% and 11C in 3%. The analyses revealed lung tumours as the most investigated tumour entity, followed by malignant lymphoma, tumours of the gastro-intestinal tract and prostate cancer (about 14000, 6000, 5000 and 2000). Corresponding to the new scanners and software procedures, the number of studies with attenuation correction by CT was high (68%) and nearly all studies were reconstructed iteratively (99%). The PET images were analysed quantitatively in the majority of cases (91%). The clinical reports, which included image documentation for the greater part, were posted regularly within 3 days. However, in 70% of the sites electronic transfer possibilities were used additionally to speed up the diagnostic process. The high standard of quality was demonstrated by the fact, that 40 facilities were engaged in a tumour board. Further on, one third of the physicians had gained a PET certification awarded by the DGN. CONCLUSION: Relative to the high general standard of diagnostic instrumentation in Germany, PET is less established, in particular when compared with other industrialised countries such as USA and Switzerland.
Cerebral Blood Flow Measurement by PET in Hypertensive Subjects as a Marker of Cognitive Decline.

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Recent epidemiological studies have shown that hypertension is a significant risk factor for Alzheimer's disease (AD). Cerebral small vessel disease (CSVD) including silent cerebral infarction and white matter lesions could represent hypertensive target organ damages in the brain and may be reliable predictors for incident dementia. However, there have been few measures to classify those patients with CSVD who are at high risk for cognitive decline and dementia. Although cerebral hypoperfusion is central to the vascular hypothesis of AD, there have been no studies linking cerebral blood flow (CBF) and future cognitive decline. Using positron emission tomography, we have demonstrated a moderate association between CBF under baseline conditions and cognitive decline during a 3-year follow-up study in 27 hypertensive patients ($r=0.53$, $P=0.003$). Findings from randomized clinical trials together with our results suggest that the preservation or improvement of CBF by anti-hypertensive treatment might be effective for the prevention of cognitive decline and dementia, especially in hypertensive patients with CSVD.

Neurotransmitter changes in dementia with Lewy bodies and Parkinson disease dementia in vivo.


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Objective: Although Parkinson disease with dementia (PDD) and dementia with Lewy bodies (DLB) show a wide clinical and neuropathologic overlap, they are differentiated according to the order and latency of cognitive and motor symptom appearance. Whether both are distinct disease entities is an ongoing controversy. Therefore, we directly compared patients with DLB and PDD with multitracer PET. METHODS: PET with (18)fluorodopa (FDOPA), N-(11)C-methyl-4-piperidyl acetate (MP4A), and (18)fluorodeoxyglucose (FDG) was performed in 8 patients with PDD, 6 patients with DLB, and 9 patients with PD without dementia vs age-matched controls. Data were analyzed with voxel-based statistical parametric mapping and region of interest-based statistics. RESULTS: We found a reduced FDOPA uptake in the striatum and in limbic and associative prefrontal areas in all patient groups. Patients with PDD and patients with DLB showed a severe MP4A and FDG binding reduction in the neocortex with increasing signal diminution from frontal to occipital regions. Significant differences between PDD and DLB were not found in any of the radioligands used. Patients with PD without dementia had a mild cholinergic deficit and no FDG reductions vs controls. CONCLUSIONS: Patients with dementia with Lewy bodies and Parkinson disease dementia share the same dopaminergic and cholinergic deficit profile in the brain and seem to represent 2 sides of the same coin in a continuum of Lewy body diseases. Cholinergic deficits seem to be crucial for the development of dementia in addition to motor symptoms. The spatial congruence of cholinergic deficits and energy hypometabolism argues for cortical deafferentation due to the degeneration of projection fibers from the basal forebrain.

Utility of positron emission tomography for tumour surveillance in children with neurofibromatosis type 1.

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Purpose: There is little consensus regarding optimal surveillance of optic pathway glioma (OPG) and plexiform neurofibroma (PNF) in childhood neurofibromatosis type 1 (NF1). (18)F-2-Fluoro-2-deoxy-D-glucose (FDG) positron emission tomography and computed tomography (PET/CT) is employed in the surveillance of adult PNFs; but its utility has neither been specifically studied in children with PNFs nor in children with OPG. METHODS: Review of PET/CT studies was performed in NF1 children with OPG or PNF. FDG-avidity of tumours was semi-quantitatively analysed and graded by calculating the maximum standardised uptake value (SUV(max)) [grade 1: <3 (low), grade 2: >3-<4 (intermediate), grade 3: >4 (intense)]. RESULTS:
Eighteen children (ten girls; median age: 8.5-years) had PET/CT. Nineteen OPGs were imaged. The SUV(max) could be measured in 16. Ten were grade 1 and three each were grade 2 and grade 3. FDG-avidity reduced from grade 3 to grade 1 in two symptomatic OPGs following chemotherapy and this was associated with clinical improvement. PET/CT diagnosed symptomatic OPGs with a sensitivity of 0.625 [95% confidence interval (CI): 0.259-0.897] and specificity of 0.875 (95% CI: 0.466-0.993). Sixteen PNFs were imaged. Twelve were grade 1 and two each were grade 2 and grade 3. The two grade 3 PNFs were confirmed malignant peripheral nerve sheath tumours. PET/CT diagnosed malignant transformation with a sensitivity of 1.0 (95% CI: 0.197-1.0) and specificity of 0.857 (95% CI: 0.561-0.974). CONCLUSION: PET/CT may contribute useful information to the surveillance of OPG in childhood NF1-particularly to identify progressive, symptomatic tumours. As in adults, PET/CT is useful for the detection of malignant transformation in PNFs in children with NF1.

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Imrovement of non-paraneoplastic voltage-gated potassium channel antibody-associated limbic encephalitis without immunosuppressive therapy.

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We describe a 61-year-old patient with clinical evidence of limbic encephalitis who improved with anticonvulsant treatment only, that is, without the use of immunosuppressive agents. Three years following occurrence of anosmia, increasing memory deficits, and emotional disturbances, he presented with new-onset temporal lobe epilepsy, with antibodies binding to neuronal voltage-gated potassium channels and bitemporal hypometabolism on FDG-PET scan; the MRI scan was normal. This is most likely a case of spontaneous remission, illustrating that immunosuppressive therapy might be suspended in milder courses of limbic encephalitis. It remains open whether treatment with anticonvulsant drugs played an additional beneficiary role through the direct suppression of seizures or, additionally, through indirect immunomodulatory side effects.

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THE LEFT TEMPORAL POLE IS IMPORTANT FOR RETRIEVING WORDS FOR UNIQUE CONCRETE ENTITIES.

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BACKGROUND: The neuroanatomical basis of lexical retrieval has been studied intensively. The current review focuses on the special case of proper nouns. AIMS: This article reviews a program of research that has used both lesion-deficit and functional imaging (PET) approaches to investigate the neuroanatomical basis for lexical retrieval of proper nouns. In lesion-deficit studies, we found that damage to the left temporal polar (TP) region leads to reliable and specific impairments in naming famous persons (e.g., "George Clooney") and famous landmarks (e.g., "Golden Gate Bridge"). In functional imaging studies, we found that when participants name famous persons and landmarks, they produce specific activation (increases in regional cerebral blood flow) in the left TP region. MAIN CONTRIBUTION: These findings converge with lesion and functional imaging data from other laboratories to support the idea that the left TP region is important for the retrieval of names for unique concrete entities, persons and landmarks being typical examples of such categories of entities. CONCLUSIONS: We have interpreted these results within a theoretical framework that suggests that left TP contains convergence regions that operate as intermediaries between conceptual knowledge retrieval and lexical retrieval for classes of unique concrete entities.


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BACKGROUND AND PURPOSE: Gd-enhancement provides essential information in the assessment of brain tumors. However, enhancement does not always correlate with histology or disease activity, especially in the setting of current therapies. Our aim
was to compare FDG-PET scans to ADC maps and Gd-enhanced MR images in patients with glial neoplasms to assess whether DWI might offer information not available on routine MR imaging sequences and whether such findings have prognostic significance. MATERIALS AND METHODS: Institutional review board approval was obtained for this retrospective review, which was conducted in full compliance with HIPAA regulations. Twenty-one patients (11 men and 10 women) with glial tumors underwent FDG-PET and MR imaging, including ADC and Gd-enhancement. Subjectively, regions of interest were drawn around the following areas: 1) increased FDG uptake, 2) decreased signal intensity on ADC maps, and 3) Gd-enhancement. Objectively, FDG-PET and MR images were co-registered, and pixel-by-pixel comparison of ADC to PET values was made for all regions of interest. Correlation coefficients (r values) were calculated for each region of interest. Percentage overlap between regions of interest was calculated for each case. RESULTS: Subjective evaluation showed 60% of patients with excellent or good correlation between ADC maps and FDG-PET. Pixel-by-pixel comparison demonstrated r values that ranged from -0.72 to -0.21. There was significantly greater overlap between decreased ADC and increased FDG-PET uptake (67.1 +/- 15.5%) versus overlap between Gd-enhancement and increased FDG-PET uptake (54.4 +/- 27.5%) (P < .05). ADC overlap was greater with increased FDG-PET than with Gd-enhancement in 8/9 cases. Survival data revealed that the presence of restricted diffusion on ADC correlated with patient survival (P < .0001). CONCLUSIONS: ADC maps in patients with brain tumors provide unique information that is analogous to FDG-PET. There is a greater overlap between ADC and FDG-PET compared with Gd-enhancement. ADC maps can serve to approximate tumor grade and predict survival.


Epilepsy duration impacts on brain glucose metabolism in temporal lobe epilepsy: results of voxel-based mapping.

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OBJECTIVE: [(18)F]Fluorodeoxyglucose positron emission tomography ([(18)F]FDG-PET) is a valuable method for detecting focal brain dysfunction associated with epilepsy. Evidence suggests that a progressive decrease in [(18)F]FDG uptake occurs in the epileptogenic cortex with an increase in the duration of epilepsy. In this study, our aim was to use statistical parametric mapping (SPM) to test the validity of this relationship in a retrospective study of patients with temporal lobe epilepsy (TLE). METHODS: [(18)F]FDG-PET scans of 46 adult patients with pharmacoresistant unilateral TLE (25 RTLE and 21 LTEL) were subjected to SPM analysis. RESULTS: Forty-six patients were diagnosed with nonlesional TLE, 16 of whom had hippocampal sclerosis (HS). The average duration of epilepsy was 17.4 +/- 12.3 years (3-46 years), <5 years in 10 patients and >or=10 years in 30 patients. Visual analysis of [(18)F]FDG-PET images, hypometabolism was unilateral and reported in lateral and mesial structures of the epileptogenic temporal cortex in addition to the ipsilateral fusiform and middle occipital gyrus. Subsequent analysis revealed that temporal lobe hypometabolism was present only in patients with longer epilepsy duration (>or=10 years) in parahippocampal gyrus, uncus, and middle and superior temporal gyrus (P < 0.05 corrected). Epilepsy duration was inversely correlated with decreased glucose uptake in the inferior temporal gyrus, hippocampus, and parahippocampal gyrus of the epileptogenic temporal cortex (P < 0.05). Age at seizure onset did not affect the correlation between epilepsy duration and glucose uptake except in the inferior temporal gyrus (P < 0.05). CONCLUSION: Voxel-based mapping supports the assertion that glucose hypometabolism of the epileptogenic temporal lobe cortex and other neighboring cortical regions increases with longer epilepsy duration in TLE. (c) 2009 Elsevier Inc. All rights reserved.


11C-PIB binding is increased in patients with cerebral amyloid angiopathy-related hemorrhage.


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BACKGROUND: The in vivo diagnosis of cerebral amyloid angiopathy (CAA) is inferred from clinical and structural imaging features. (11)C-Pittsburgh compound B (PIB) is a PET ligand that binds to beta-amyloid in extracellular plaques and vessel walls. We hypothesized that patients with a clinical diagnosis of CAA-related hemorrhage (CAAH) have increased (11)C-PIB uptake and that the pattern differs from Alzheimer disease (AD). METHODOLOGY: Patients with CAAH based on established clinical criteria were studied using (11)C-PIB PET and were compared with age-matched controls and patients with AD. Distribution volume ratio (DVR) parametric maps were created using the cerebellar cortex as a reference region. RESULTS: Twelve patients with CAAH of mean age 73.9 (range 58-93) years were compared with 22 normal controls and 13 patients with AD of mean age 71.8 (59-83) and 73.8 (56-90) years, respectively. CAAH PIB median DVR binding was higher in cortical regions (1.69, interquartile range 1.44-1.97) compared with controls (1.32, 1.21-1.44, p = 0.002) but lower than AD (2.04, 1.93-
2.26, p = 0.004). The occipital-global uptake ratio was lower among patients with AD than among patients with CAAH (p = 0.008), and the frontal-global uptake ratio was higher (p = 0.012). CONCLUSION: (11)C-Pittsburgh compound B (PIB) binding is moderately increased in most patients with probable cerebral amyloid angiopathy (CAA)-related intracerebral hemorrhage. The distribution may differ from that seen in Alzheimer disease. (11)C-PIB PET may assist in the in vivo diagnosis of CAA and serve as a surrogate marker for future therapeutic studies.


Noninvasive testing, early surgery, and seizure freedom in tuberous sclerosis complex.


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BACKGROUND: The unambiguous identification of the epileptogenic tubers in individuals with tuberous sclerosis complex (TSC) can be challenging. We assessed whether magnetic source imaging (MSI) and coregistration of (18)fluorodeoxyglucose PET (FDG-PET) with MRI could improve the identification of the epileptogenic regions noninvasively in children with TSC. METHODS: In addition to standard presurgical evaluation, 28 children with intractable epilepsy from TSC referred from 2000 to 2007 had MSI and FDG-PET/MRI coregistration without extraoperative intracranial EEG. RESULTS: Based on the concordance of test results, 18 patients with TSC (64%) underwent surgical resection, with the final resection zone confirmed by intraoperative electrocorticography. Twelve patients are seizure free postoperatively (67%), with an average follow-up of 4.1 years. Younger age at surgery and shorter seizure duration were associated with postoperative seizure freedom. Conversely, older age and longer seizure duration were linked with continued seizures postoperatively or prevented surgery because of nonlateralizing or bilateral independent epileptogenic zones. Complete removal of presurgery MSI dipole clusters correlated with postoperative seizure freedom. CONCLUSIONS: Magnetic source imaging and (18)fluorodeoxyglucose PET/MRI coregistration noninvasively localized the epileptogenic zones in many children with intractable epilepsy from tuberous sclerosis complex (TSC), with 67% seizure free postoperatively. Seizure freedom after surgery correlated with younger age and shorter seizure duration. These findings support the concept that early epilepsy surgery is associated with seizure freedom in children with TSC and intractable epilepsy.


Wakefulness and loss of awareness: brain and brainstem interaction in the vegetative state.


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OBJECTIVE: The ascending reticular activating system (ARAS) modulates circadian wakefulness, which is preserved in a persistent vegetative state (PVS). Its metabolism is preserved. Impairment of metabolism in the polymodal associative cortices (i.e., precuneus) is characteristic of PVS where awareness is abolished. Because the interaction of these 2 structures allows conscious sensory perception, our hypothesis was that an impaired functional connectivity between them participates in the loss of conscious perception. METHODS: (15)O-radiolabeled water PET measurement of regional cerebral blood flow (rCBF) was performed at rest and during a propriocceptive stimulation. Ten patients in PVS and 10 controls were compared in a cross-sectional study. The functional connectivity from the primary sensorimotor cortex (S1M1) and the ARAS in both groups was also investigated. RESULTS: Compared with controls, patients showed significantly less rCBF in posterior medial cortices (precuneus) and higher rCBF in ARAS at rest. During stimulation, bilateral Brodmann area 40 was less activated and not functionally correlated to S1M1 in PVS as it was in controls. Precuneus showed a lesser degree of deactivation in patients. Finally, ARAS whose activity was functionally correlated to that of the precuneus in controls was not in PVS. CONCLUSIONS: Global neuronal workspace theory predicts that damage to long-distance white matter tracts should impair access to conscious perception. During persistent vegetative state, we identified a hypermetabolism in the ascending reticular activating system (ARAS) and impaired functional connectivity between the ARAS and the precuneus. This result emphasizes the functional link between cortices and brainstem in the genesis of perceptual awareness and strengthens the hypothesis that consciousness is based on a widespread neural network.
Association of anosmia with autonomic failure in Parkinson disease.

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BACKGROUND: Olfactory dysfunction and autonomic failure are gaining recognition as nonmotor manifestations of Parkinson disease (PD). This observational study assessed whether in PD anosmia and autonomic failure are related to each other or to neuroimaging evidence of striatal dopamine deficiency. METHODS: Olfactory function was assessed by the University of Pennsylvania Smell Identification Test (UPSIT) in 23 patients with sporadic PD. Baroreflex-cardiovagal gain was quantified from the relationship between cardiac interbeat interval and systolic pressure during the Valsalva maneuver and baroreflex-sympathoneural function by responses of systolic pressure to the Valsalva maneuver and of hemodynamics and plasma norepinephrine (NE) and dihydroxyphenylglycol (DHPG) levels to orthostasis. 6-(18)F]Fluorodopamine PET and plasma and skeletal muscle microdialysate NE and DHPG were used to indicate cardiac and extracardiac noradrenergic innervation and brain 6-(18)F]fluorodopa PET to indicate striatal dopaminergic innervation. Parkinsonism was assessed by UPDRS scores.

RESULTS: Compared to patients with PD and normal to moderately decreased sense of smell, patients with anosmic PD had lower mean baroreflex-cardiovagal gain (p = 0.04), larger falls in systolic pressure during the Valsalva maneuver and orthostasis (p = 0.04, p = 0.02), smaller orthostatic increments in plasma NE and DHPG (p = 0.003, p = 0.03), lower cardiac septal:hepatic and renal cortical:hepatic ratios of 6-(18)F]fluorodopamine-derived radioactivity (p = 0.01, p = 0.06), and lower microdialysate NE and DHPG (p = 0.01; p = 0.006). Neither clinical severity of parkinsonism nor the putamen:occipital cortex ratio of 6-(18)F]fluorodopa-derived radioactivity was related to the UPSIT category. CONCLUSIONS: In Parkinson disease, anosmia is associated with baroreflex failure and cardiac and organ-selective extracardiac noradrenergic denervation, independently of parkinsonism or striatal dopaminergic denervation.
modeling. Linear compartmental pharmacokinetic models of increasing complexity were tested on the tumor tissue data. Four suitable models were applied and compared using the Bayesian information criterion (BIC). Model 1 consisted of an instantaneously equilibrating space, followed by a unidirectional trap. Models 2a and 2b contained a reversible space between the instantaneously equilibrating space and the trap, into which metabolites were excluded (2a) or allowed (2b). Model 3 built on model 2b with the addition of a second reversible space preceding the unidirectional trap and from which metabolites were excluded. RESULTS: The half-life of the (18)F-FDHT in blood was between 6 and 7 min. As a consequence, the uptake of (18)F-FDHT in prostate cancer lesions reached a plateau within 20 min as the blood-borne activity was consumed. Radiolabeled metabolites were shown not to bind to ARs in in vitro studies with CWR22 cells. Model 1 produced reasonable and robust fits for all datasets and was judged best by the BIC for 16 of 26 tumor scans. Models 2a, 2b, and 3 were judged best in 7, 2, and 1 cases, respectively. CONCLUSION: Our study explores the clinical potential of using (18)F-FDHT PET to estimate free AR concentration. This process involved the estimation of a net uptake parameter such as the k(trap) of model 1 that could serve as a surrogate measure of AR expression in metastatic prostate cancer. Our initial studies suggest that a simple body mass-normalized standardized uptake value correlates reasonably well to model-based k(trap) estimates, which we surmise may be proportional to AR expression. Validation studies to test this hypothesis are underway.


Effects of emotion and reward motivation on neural correlates of episodic memory encoding: a PET study.


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It is known that emotion and reward motivation promote long-term memory formation. It remains unclear, however, how and where emotion and reward are integrated during episodic memory encoding. In the present study, subjects were engaged in intentional encoding of photographs under four different conditions that were made by combining two factors (emotional valence, negative or neutral; and monetary reward value, high or low) for subsequent successful recognition) during H2 15O positron emission tomography (PET) scanning. As for recognition performance, we found significant main effects of emotional valence (negative>neutral) and reward value (high value>low value), without an interaction between the two factors. Imaging data showed that the left amygdala was activated during the encoding conditions of negative pictures relative to neutral pictures, and the left orbitofrontal cortex was activated during the encoding conditions of high reward pictures relative to low reward pictures. In addition, conjunction analysis of these two main effects detected right hippocampal activation. Although we could not find correlations between recognition performance and activity of these three regions, we speculate that the right hippocampus may integrate the effects of emotion (processed in the amygdala) and monetary reward (processed in the orbitofrontal cortex) on episodic memory encoding. 2010 Elsevier Ireland Ltd and the Japan Neuroscience Society.


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The hallmark clinical symptom of early Alzheimer's disease (AD) is episodic memory impairment. Recent functional imaging studies suggest that memory function is subserved by a set of distributed networks, which include both the medial temporal lobe (MTL) system and the set of cortical regions collectively referred to as the default network. Specific regions of the default network, in particular, the postero medial cortices, including the precuneus and posterior cingulate, are selectively vulnerable to early amyloid deposition in AD. These regions are also thought to play a key role in both memory encoding and retrieval, and are strongly functionally connected to the MTL. Multiple functional magnetic resonance imaging (fMRI) studies during memory tasks have revealed alterations in these networks in patients with clinical AD. Similar functional abnormalities have been detected in subjects at-risk for AD, including those with genetic risk and older individuals with mild cognitive impairment. Recently, we and other groups have found evidence of functional alterations in these memory networks even among cognitively intact older individuals with occult amyloid pathology, detected by PET amyloid imaging. Taken together, these findings suggest that the pathophysiological process of AD exerts specific deleterious effects on these distributed memory circuits, even prior to clinical manifestations of significant memory impairment. Interestingly, some of the functional alterations seen in prodromal AD subjects have taken the form of increases in activity relative to baseline, rather than a loss of activity. It remains unclear whether these increases in fMRI activity may be compensatory to maintain memory performance in the setting of early AD pathology or instead, represent evidence of excitotoxicity and impending neuronal failure. Recent studies have also revealed disruption of the intrinsic connectivity of these networks observable even during the resting state in early AD and asymptomatic individuals with
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high amyloid burden. Research is ongoing to determine if these early network alterations will serve as sensitive predictors of clinical decline, and eventually, as markers of pharmacological response to potential disease-modifying treatments for AD.


Beta-amyloid burden in the temporal neocortex is related to hippocampal atrophy in elderly subjects without dementia.


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Abstract

OBJECTIVE: To investigate whether global and regional beta-amyloid (Abeta) burden as measured with 11C Pittsburgh compound B (PIB) PET is associated with hippocampal atrophy characterized using MRI in healthy controls and patients with amnestic mild cognitive impairment (aMCI) or Alzheimer disease (AD). METHODS: Ninety-two elderly healthy controls, 32 subjects with aMCI, and 35 patients with AD were imaged using 11C-PIB PET and MRI. Hippocampal volume was measured and PIB standardized uptake value ratio was extracted after partial volume correction within 41 regions of interest. Global, regional, and voxel-based correlations between PIB and hippocampal volume were computed for each group. RESULTS: In healthy control participants with elevated neocortex PIB retention, significant correlation was found between PIB retention in the inferior temporal region and hippocampal volume using both region-based and voxel-based approaches. No correlation was found in any other group. CONCLUSIONS: The strong correlation between hippocampal atrophy and beta-amyloid (Abeta) burden in the Pittsburgh compound B-positive healthy control group suggests that Abeta deposition in the inferior temporal neocortex is related to hippocampal synaptic and neuronal degeneration.


Positron emission tomography-computed tomography in paraneoplastic neurologic disorders: systematic analysis and review.


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OBJECTIVE: To evaluate the cancer detection rate of whole-body positron emission tomography-computed tomography (PET-CT) in a paraneoplastic neurologic context. DESIGN: Retrospective medical record review. SETTING: Mayo Clinic, Rochester, Minnesota. PATIENTS: Fifty-six consecutive patients with clinically suspected paraneoplastic neurologic disorders who underwent PET-CT after negative standard evaluations, including CT. MAIN OUTCOME MEASURE: Rate of cancer detection. RESULTS: Abnormalities suggestive of cancer were detected using PET-CT in 22 patients (39%); 10 patients (18%) had cancer confirmed histologically. Cancers detected (limited stage in 9 of 10 patients and extratruncal in 4) were as follows: 2 thyroid papillary cell carcinomas, 3 solitary lymph nodes with unknown primary (2 adenocarcinomas and 1 small cell carcinoma), 1 tonsil squamous cell carcinoma, 3 lung carcinomas (1 adenocarcinoma, 1 small cell, and 1 squamous cell), and 1 colon adenocarcinoma. Detection of a well-characterized neuronal nuclear or cytoplasmic paraneoplastic autoantibody was associated with a successful PET-CT-directed cancer search (P < .001). Detection of limited-stage cancer facilitated early initiation of oncologic treatments and immunotherapy; cancer remission was reported in 7 patients, and sustained improvements in neurologic symptoms were reported in 5 (median follow-up, 11 months; range, 2-48 months). Combined data from 2 previous studies using conventional PET alone (123 patients) revealed that 28% of patients had a PET abnormality suggestive of cancer and that 12% had a cancer diagnosis. CONCLUSION: In a paraneoplastic neurologic context, PET-CT improves the detection of cancers when other screening test results are negative, particularly in the setting of seropositivity for a neuronal nuclear or cytoplasmic autoantibody marker of cancer.


Clinical experience with miglustat therapy in pediatric patients with Niemann-Pick disease type C: a case series.


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Niemann-Pick disease type C (NP-C) is an inherited neurovisceral lysosomal lipid storage disease characterized by progressive neurological deterioration. Different clinical forms have been defined based on patient age at onset: perinatal, early-infantile (EI), late-infantile (Li), juvenile and adult. We evaluated the efficacy and tolerability of miglustat in 16 symptomatic NP-C patients, with comparative reference to one neurologically asymptomatic, untreated patient. All patients were categorized according to age at neurological disease onset, and were assessed using a standardized clinical assessment protocol: disability and cognitive function scales, positron emission tomography (PET), and biochemical markers. PET and disability scale evaluations indicated that cerebral hypometabolism and neurological symptoms were stabilized during treatment in juvenile-onset NP-C patients. EI and Li NP-C patients, who had higher disease severity at baseline (treatment start), showed increased disability scores and progressive cerebral hypometabolism during follow up. Similarly, while cognitive scale scores remained relatively stable in patients with juvenile NP-C, cognition deteriorated in EL and Li patients. Plasma chitotriosidase (ChT) activity was lower in the juvenile NP-C subgroup than in EL and Li patients, and generally increased in patients who discontinued treatment. Plasma CCL18/PARC and ChT activities indicated greater macrophagic activity in EL and Li patients versus juveniles. Miglustat was generally well tolerated; frequent adverse events included diarrhea and flatulence, which were managed effectively by dietary modification and loperamide. Overall, miglustat appeared to stabilize neurological status in juvenile-onset NP-C patients, but therapeutic benefits appeared smaller among younger patients who were at a more advanced stage of disease at baseline.


OBJECTIVE: To investigate the specificity of in vivo amyloid imaging with [(11)C]-Pittsburgh Compound B (PIB) in Parkinson disease dementia (PDD). METHODS: We performed detailed neuropathologic examination for 3 individuals with PDD who had PIB PET imaging within 15 months of death. RESULTS: We observed elevated cortical uptake of [(11)C]-PIB on in vivo PET imaging in 2 of the 3 cases. At autopsy, all 3 individuals had abundant cortical Lewy bodies (Braak PD stage 6), and were classified as low-probability Alzheimer disease (AD) based on NIA-Reagan criteria. The 2 PIB-positive individuals had abundant diffuse Abeta plaques but only sparse neuritic plaques and intermediate neurofibrillary tangle pathology. The PIB-negative individual had rare diffuse plaques, no neuritic plaques, and low neurofibrillary tangle burden. CONCLUSIONS: [(11)C]-Pittsburgh Compound B (PIB) PET is specific for fibrillar Abeta molecular pathology but not for pathologic diagnosis of comorbid Alzheimer disease in individuals with Parkinson disease dementia. The ability to specifically identify fibrillar Abeta amyloid in the setting of alpha-synucleinopathy makes [(11)C]-PIB PET a valuable tool for prospectively evaluating how the presence of Abeta amyloid influences the clinical course of dementia in patients with Lewy body disorders.
Multimodal microglia imaging of fiber tracts in acute subcortical stroke.


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OBJECTIVE: Case series with (11)C-PK11195 and positron emission tomography (PET) in stroke patients suggest that activated microglia may be detected in remote brain regions with fiber tract connections to the lesion site as an indicator of poststroke neuroinflammation. However, the specificity of these imaging findings remains to be demonstrated. METHODS: In a prospective controlled study, we measured microglia activity using (11)C-PK11195-PET along the pyramidal tract, as defined by diffusion tensor imaging, in 21 patients with first-time acute subcortical ischemia within 2 weeks of stroke. Uptake ratios (affected vs unaffected side) were determined for a set of standardized volumes of interest along the pyramidal tracts (PT). Uptake ratios from patients in whom the PT was affected were compared with those in whom the PT was not affected. Uptake ratios were related to motor deficit and lesion size according to correlation analyses. RESULTS: Increased uptake ratios were only found in patients in whom the PT was affected by stroke. In the affected hemisphere, uptake was increased at the level of pons, midbrain, and internal capsule, but not in the oval center. The extent of remote microglia activation was independent of infarct size or clinical measures of stroke severity. INTERPRETATION: A specific activation of microglia was only found in patients in whom the PT was affected by the stroke and only caudal (anterograde) to the lesion; no activation was found in the retrograde direction or in those patients in whom the PT was not affected. These findings were independent of infarct size and may represent changes secondary to early Wallerian degeneration.


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OBJECTIVE: To evaluate associations of [(11)C]Pittsburgh compound B (PIB) and [(18)F]FDDNP with impairment in specific cognitive domains over the broader spectrum comprising cognitively normal elderly subjects, patients with mild cognitive impairment (MCI), and patients with Alzheimer disease (AD). METHODS: Twelve patients with AD, 13 patients with MCI, and 15 cognitively normal elderly subjects were included. Paired [(11)C]PIB and [(18)F]FDDNP PET scans were performed in all subjects; Binding potential (BP(ND)) was calculated using parametric images of BP(ND) for global, frontal, parietal, and temporal cortex; medial temporal lobe; and posterior cingulate. Cognitive functions were assessed using a battery of neuropsychological tests. Linear regression analyses were used to assess associations of [(11)C]PIB and [(18)F]FDDNP binding with cognitive measures. RESULTS: Adjusted for age, sex, and [(18)F]FDDNP binding, higher global [(11)C]PIB binding was associated with lower scores on the Mini-Mental State Examination, immediate and delayed recall of the Rey Auditory Verbal Learning Task part B. Conversely, higher [(18)F]FDDNP binding was independently associated with lower scores on immediate recall of the RAVLT. After additional adjustment for diagnosis, higher [(11)C]PIB binding remained independently associated with delayed recall (standardized beta = -0.39, p = 0.01), whereas higher [(18)F]FDDNP binding remained independently associated with immediate recall (standardized beta = -0.32, p = 0.03). When regional binding was assessed using stepwise models, both increased frontal [(11)C]PIB and temporal [(18)F]FDDNP binding were associated with memory, whereas increased parietal [(11)C]PIB binding was associated with nonmemory functions. CONCLUSION: Increased [(18)F]FDDNP binding is specifically associated with impairment of episodic memory, whereas increased [(11)C]Pittsburgh compound B binding is associated with impairment in a broader range of cognitive functions.

Differences in hippocampal metabolism between amnestic and non-amnestic MCI subjects: automated FDG-PET image analysis.


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AIM: The aim of this study was to assess whether 18F-fluorodeoxyglucose positron emission tomography differentiates amnestic (aMCI) from single-non-amnestic mild cognitive impairment (snaMCI) with executive dysfunction. METHODS: Sixteen aMCI subjects (62% females, age 75±4-8 years) and 14 snaMCI subjects (71% females, age 74±1-6 years) underwent [18F]FDG-PET and clinical follow-up. Comparisons between MCI subgroups and with seven cognitively normal elderly subjects were performed using SPM2. RESULTS: At baseline aMCI and snaMCI exhibited a similar pattern of hypometabolism, mostly in the posterior cingu late gyrus, as compared with controls. In the comparison between the MCI subtypes, the aMCI subjects showed reduced metabolism in the medial temporal lobes (MTL) (hippocampus, fusiform gyrus and amygdala). At follow-up 12 aMCI developed Alzheimer’s disease (AD), while snaMCI had a heterogeneous course, including five subjects who developed Lewy body dementia. CONCLUSIONS: The patterns of altered brain metabolism in aMCI and snaMCI subjects compared to controls are similar and do not provide evidence for making clinical distinctions between them. Comparison between the two MCI subtypes showed MTL hypometabolism in aMCI subjects, possibly reflecting the fact that most had prodromal AD.

Minocycline 1-year therapy in multiple-system-atrophy: effect on clinical symptoms and [(11)C](R)-PK11195 PET (MEMSA-trial).


The aim of the study was to investigate the efficacy of the antibiotic minocycline as a drug treatment in patients with Multiple-System-Atrophy Parkinson-type (MSA-P). Sixty-three patients were randomized to minocycline 200 mg/d (n = 32) or a matching placebo (n = 31). The primary outcome variable was the change in the value of the motor score of the Unified Multiple-System-Atrophy Rating-Scale (UMSARSII) from baseline to 48 weeks. Secondary outcome variables included subscores and individual Parkinsonian symptoms as determined by the UMSARS and the Unified-Parkinson’s-Disease Rating-Scale (UPDRS). Health-related quality of life (HrQoL) was assessed using the EQ-5D and SF-12. "Progression rate" was assumed to be reflected in the change in motor function over 48 weeks. At 24 weeks and 48 weeks of follow-up, there was a significant deterioration in motor scores in both groups, but neither the change in UMSARSII nor in UPDRSIII differed significantly between treatment groups, i.e. "progression rate" was considered to be similar in both treatment arms. HrQoL did not differ among the two treatment arms. In a small subgroup of patients (n = 8; minocycline = 3, placebo = 5)([11]C)(R)-PK11195-PET was performed. The three patients in the minocycline group had an attenuated mean increase in microglial activation as compared to the placebo group (P = 0.07) and in two of them individually showed decreased [(11)C](R)-PK11195 binding actually decreased. These preliminary PET-data suggest that minocycline may interfere with microglial activation. The relevance of this observation requires further investigation. This prospective, 48 week, randomized, double-blind, multinational study failed to show a clinical effect of minocycline on symptom severity as assessed by clinical motor function.

Impaired verbal memory in Parkinson disease: relationship to prefrontal dysfunction and somatosensory discrimination.

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OBJECTIVE: To study the neurocognitive profile and its relationship to prefrontal dysfunction in non-demented Parkinson's disease (PD) with deficient haptic perception. METHODS: Twelve right-handed patients with PD and 12 healthy control subjects underwent thorough neuropsychological testing including Rey complex figure, Rey auditory verbal and figural learning test, figural and verbal fluency, and Stroop test. Test scores reflecting significant differences between patients and healthy subjects were correlated with the individual expression coefficients of one principal component, obtained in a principal component analysis of an oxygen-15-labeled water PET study exploring somatosensory discrimination that differentiated between the two groups and involved prefrontal cortices. RESULTS: We found significantly decreased total scores for the verbal learning trials and verbal delayed free recall in PD patients compared with normal volunteers. Further analysis of these parameters using Spearman’s ranking correlation showed a significantly negative correlation of deficient verbal recall with expression coefficients of the principal component whose image showed a subcortical-cortical network, including right dorsolateral-prefrontal cortex, in PD patients. CONCLUSION: PD patients with disrupted right dorsolateral prefrontal cortex function and associated diminished somatosensory discrimination are impaired also in verbal memory functions. A negative correlation between delayed verbal free recall and PET activation in a network including the prefrontal cortices suggests that verbal cues and accordingly declarative memory processes may be operative in PD during activities that demand sustained attention such as somatosensory
discrimination. Verbal cues may be compensatory in nature and help to non-specifically enhance focused attention in the presence of a functionally disrupted prefrontal cortex.

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Cerebrospinal fluid metabolite and nigrostriatal dopaminergic function in Parkinson's disease.


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Abstract

Ishibashi K, Kanemaru K, Saito Y, Murayama S, Oda K, Ishiwata K, Mizusawa H, Ishii K. Cerebrospinal fluid metabolite and nigrostriatal dopaminergic function in Parkinson's disease. Acta Neurol Scand: DOI: 10.1111/j.1600-0404.2009.01255.x. (c) 2009 The Authors Journal compilation (c) 2009 Blackwell Munksgaard. Objectives - To evaluate the association between cerebrospinal fluid (CSF) homovanillic acid (HVA) concentrations and nigrostriatal dopaminergic function assessed by positron emission tomography (PET) imaging with carbon-11-labeled 2beta-carbomethoxy-3beta-(4-fluorophenyl)tropane ((11)C-CFT), which can measure the dopamine transporter (DAT) density, in Parkinson's disease (PD). Methods - (11)C-CFT PET scans and CSF examinations were performed on 21 patients with PD, and six patients with non-parkinsonian syndromes (NPS) as a control group. Results - In the PD group, CSF HVA concentrations were significantly correlated with the striatal uptake of (11)C-CFT (r = 0.76, P < 0.01). However, in the NPS group, two indices were within the normal range. Conclusions - In PD, CSF HVA concentrations may be an additional surrogate marker for estimating the remaining nigrostriatal dopaminergic function in case that DAT imaging is unavailable.


EEG-fMRI: adding to standard evaluations of patients with nonlesional frontal lobe epilepsy.


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OBJECTIVE: In patients with nonlesional frontal lobe epilepsy (FLE), the delineation of the epileptogenic zone is difficult. Therefore these patients are often not considered for surgery due to an unclear seizure focus. The aim of this study was to investigate whether EEG-fMRI can add useful information in the preoperative evaluation of these patients. METHODS: Nine nonlesional FLE patients were studied with EEG-fMRI using a 3 T scanner. Spike-related blood oxygen level dependent (BOLD) signal changes were compared to the topography of the spikes and to PET and SPECT results if available. The structural MRIs were reviewed for subtle abnormalities in areas that showed BOLD responses. For operated patients, postoperative resection and histology were compared to BOLD responses. RESULTS: Concordance between spike localization and positive BOLD response was found in 8 patients. PET and SPECT investigations corresponded with BOLD signal changes in 6 of 7 investigations. In 2 cases, reviewing the structural MRI guided by EEG-fMRI data resulted in considering a suspicious deep sulcus. Two patients were operated. In 1, the resected cortex corresponded with the suspicious sulcus and fMRI results and histology showed cortical dysplasia. In another, histology revealed an extended microdysgenesis not visible on structural MRI. EEG-fMRI had shown activation just adjacent to the resected pathologic area. CONCLUSIONS: Our study provides different types of support (topography, concordance with PET and SPECT, structural peculiarities, postoperative histology) that EEG-fMRI may help to delineate the epileptic focus in patients with nonlesional frontal lobe epilepsy, a challenging group in the preoperative evaluation.


Hanja (Ideogram) alexia and agraphia in patients with semantic dementia.


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Posterior fusiform gyrus (BA 37) is responsible for Hanja (ideogram) alexia in stroke patients. Patients with semantic dementia (SD) have lesions in the basal temporal area. The close proximity in these two lesions and the fact that reading ideograms requires holistic processing as is necessary in recognition of objects, suggests a possibility that ideogram alexia/agraphia may occur in patients with SD. We established and carried out Hanja and Hangul (phonogram) reading/writing tasks on six SD patients and nine Alzheimer's disease (AD) patients as control to see if these two patient groups show dissociation in the two sets
of tests. SPM analysis was performed on the SD patients' PET images to look for any dysfunctions in the posterior fusiform gyrus. The SD patients manifested Hanja alexia/agraphia whereas Hangul reading/writing ability was relatively preserved. There were group differences between SD and AD in the Hanja tasks but not in the Hangul tasks. The SPM analysis revealed no hypometabolism in the posterior fusiform gyrus, but only in the middle and the anterior part of the temporal gyrus. Dysfunction in the middle temporal gyrus (BA 21) may have disrupted the temporal lobe connections preventing the function of the posterior fusiform gyrus.

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**Competition between 11C-raclopride and endogenous dopamine in Parkinson's disease.**

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OBJECTIVE: The aim of this study was to understand whether the increase in 11C-raclopride binding in the striatum of patients with Parkinson's disease (PD) is associated with the depletion of endogenous dopamine. METHODS: Positron emission tomography (PET) scans of the two dopamine D2 receptor ligands, 11C-raclopride and 11C-N-methylspiperone (11C-NMSP), and the dopamine transporter ligand, 11C-2beta-carbomethoxy-3beta-(4-fluorophenyl)-tropane, were performed on five patients with PD and seven controls. The binding of each tracer was calculated by using a (region-cerebellum)/cerebellum ratio in the caudate, anterior putamen, and posterior putamen. RESULTS: In patients with PD, the 11C-raclopride to 11C-NMSP ratios in the posterior putamen, which was the subregion of the striatum with the lowest binding of 11C-2beta-carbomethoxy-3beta-(4-fluorophenyl)-tropane, were the largest among all three subregions of the striatum. In controls, the 11C-raclopride to 11C-NMSP ratios in all three subregions of the striatum were within a constant range. CONCLUSION: In patients with PD, the kinetic difference between 11C-raclopride and 11C-NMSP was found prominently in the posterior putamen, in which presynaptic degeneration occurred most profoundly. Therefore, we concluded that the increase in 11C-raclopride binding in the striatum of patients with PD was strongly associated with the depletion of endogenous dopamine. 11C-NMSP can be chosen in the place of 11C-raclopride in cases in which it may be essential to eliminate the influence of endogenous dopamine.

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**Zolpidem-induced sleepwalking, sleep related eating disorder, and sleep-driving: fluorine-18-fluoro deoxyglucose positron emission tomography analysis, and a literature review of other unexpected clinical effects of zolpidem.**

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**Abstract**

Zolpidem is a hypnotic which acts at the GABA receptor and is indicated for short-term insomnia. Sleep related disorders including somnambulism, sleep related eating and sleep-driving have been reported with zolpidem. A 51-year-old insomniac who used zolpidem 10 mg nightly starting at 44 years of age is described. A few weeks after starting zolpidem she began walking, eating, and had one episode of driving while asleep. Episodes of sleep related eating, sleepwalking, and sleeptalking occurred 3 nights per week, 1 to 2 h after sleep onset. After her evaluation, the patient's zolpidem was gradually discontinued, and all sleep related activities immediately ceased. An 18F-FDG-PET was obtained 2 months after discontinuation of zolpidem. The following day, FDG was administered 1 h after oral administration of 10 mg zolpidem, and then a second PET was performed. We report the results and a review of the literature regarding other unintended effects seen with zolpidem use.

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**Subthalamic nucleus stimulation in Parkinson disease induces apathy: a PET study.**


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OBJECTIVE: Apathy may be induced by subthalamic nucleus deep brain stimulation (STN-DBS) in Parkinson disease (PD). We therefore wished to test the hypothesis that apathy induced by STN-DBS correlates with changes in glucose metabolism, using
(18)FDG-PET. METHODS: Twelve patients with PD were assessed 3 months before (M-3) and 3 months after (M+3) STN-DBS with (18)FDG-PET and the Apathy Evaluation Scale. RESULTS: Apathy had significantly worsened at M+3 after STN-DBS. Positive correlations were observed between this variation in apathy scores and changes in glucose metabolism, especially in the right frontal middle gyrus (Brodmann area [BA] 10) and right inferior frontal gyrus (BA 46 and BA 47). Negative correlations between the two were observed in the right posterior cingulate gyrus (BA 31) and left medial frontal lobe (BA 9). CONCLUSION: These preliminary results confirm the role of the subthalamic nucleus in associative and limbic circuitry in humans and suggest that it is a key basal ganglia structure in motivation circuitry.


History of falls in Parkinson disease is associated with reduced cholinergic activity.

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OBJECTIVE: To investigate the relationships between history of falls and cholinergic vs dopaminergic denervation in patients with Parkinson disease (PD). BACKGROUND: There is a need to explore nondopaminergic mechanisms of gait control as the majority of motor impairments associated with falls in PD are resistant to dopaminergic treatment. Alterations in cholinergic neurotransmission in PD may be implicated because of evidence that gait control depends on cholinergic system-mediated higher-level cortical and subcortical processing, including pedunculopontine nucleus (PPN) function. METHODS: In this cross-sectional study, 44 patients with PD (Hoehn & Yahr stages I-III) without dementia and 15 control subjects underwent a clinical assessment and [(11)C]methyl-4-piperidinyl propionate (PMP) acetylcholinesterase (AChE) and [(11)C]dihydrotetrabenazine (DTBZ) vesicular monoamine transporter type 2 (VMAT2) brain PET imaging. RESULTS: Seventeen patients (38.6%) reported a history of falls and 27 patients had no falls. Analysis of covariance of the cortical AChE hydrolysis rates demonstrated reduced cortical AChE in the PD fallers group (-12.3%) followed by the PD nonfallers (-6.6%) compared to control subjects (F = 7.22, p = 0.0004). Thalamic AChE activity was lower only in the PD fallers group (-11.8%; F = 4.36, p = 0.008). There was no significant difference in nigrostriatal dopaminergic activity between PD fallers and nonfallers. CONCLUSIONS: Unlike nigrostriatal dopaminergic denervation, cholinergic hypofunction is associated with fall status in Parkinson disease (PD). Thalamic AChE activity in part represents cholinergic output of the pedunculopontine nucleus (PPN), a key node for gait control. Our results are consistent with other data indicating that PPN degeneration is a major factor leading to impaired postural control and gait dysfunction in PD.


PET studies of cerebral metabolism in Parkinson disease.

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A defect in cerebral energy production due to dysfunction of the mitochondrial electron transport system (ETS) has been postulated to be important in the pathogenesis of Parkinson Disease (PD). However, direct in vivo measurements of cerebral mitochondrial function are scant and inconsistent. We directly investigated cerebral mitochondrial function in vivo with positron emission tomography (PET) in 12 patients with early, never-medicated PD and 12 age-matched normal controls by combined measurements of the cerebral metabolic rate of oxygen (CMRO(2)) and the cerebral metabolic rate of glucose (CMRglc). Instead of the decrease in CMRO(2) and CMRglc molar ratio characteristic of defects in mitochondrial oxidative metabolism, there was a statistically significant 24% general increase in CMRO(2) and no change in CMRglc. Since PD symptoms were already manifest, reduced oxidative activity of the mitochondrial ETS cannot be a primary mechanism of neuronal death in early PD. This increase in metabolism could reflect the increased energy requirements of an injured brain or an uncoupling of ATP production from oxidation in the terminal stage of oxidative phosphorylation. Which is the case in early PD and whether these metabolic abnormalities are important in the pathogenesis of PD will require further study.
Susac syndrome: a case report and PET imaging findings.

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We describe the case of a twenty-year-old woman with subacute encephalopathy, who subsequently developed hearing loss and ophthalmapathy. The clinical triad and typical findings on magnetic resonance imaging and cerebrospinal fluid analysis led to the diagnosis of Susac syndrome. Brain positron emission tomography showed abnormalities which are comparable with other types of central nervous system vasculitis, and distinct from those found in multiple sclerosis.

Clinical syndromes associated with posterior atrophy: early age at onset AD spectrum.


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OBJECTIVE: Posterior cortical atrophy (PCA) and logopenic progressive aphasia (LPA) are clinical syndromes associated with posterior brain atrophy. We compared PCA and LPA to each other and to an age-matched group of patients with early age at onset of Alzheimer disease (EO-AD). We hypothesized that these 3 syndromes are part of a single clinical and biologic continuum. METHODS: Voxel-based morphometry (VBM) was used to assess atrophy in 14 PCA, 10 LPA, and 16 EO-AD patients compared to 65 healthy controls. Genetic analysis for APOE was conducted in 30 patients and 44 controls. Four patients came to autopsy. An additional 14 were studied with the beta-amyloid specific PET with tracer (11)C-labeled Pittsburgh Compound-B (PIB). RESULTS: VBM results demonstrated that, compared to controls, each patient group showed a large area of overlapping atrophy in bilateral parietal, occipital, precuneus, posterior cingulate, posterior temporal, and hippocampal regions. Surrounding this common area, group-specific atrophy was found in small, symptom-specific regions for each group: the right ventral-occipital and superior parietal regions in PCA, the left middle and superior temporal gyri in LPA, and the prefrontal cortex in EO-AD. APOE epsilon4 frequency was higher in all patient groups compared to controls. Four PCA, 5 LPA, and 8 EO-AD patients showed evidence of cortical amyloid at pathology (n = 3) or on PIB-PET (n = 14). CONCLUSIONS: Logopenic progressive aphasia and posterior cortical atrophy showed largely overlapping anatomic and biologic features with early age at onset of Alzheimer disease, suggesting that these clinical syndromes represent the spectrum of clinical manifestation of the nontypical form of Alzheimer disease that presents at an early age.

Late-onset choreoathetotic syndrome following heart surgery.


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Choreoathetotic syndromes are frequently observed in children after congenital cardiopathy surgery. To report the case of an adult patient who developed a choreoathetotic syndrome after cardiac operation, probably related to a transitory hypometabolism of basal ganglia. A 52-year-old patient underwent heart surgery under circulatory arrest and deep hypothermia, for type III dissecting thoracic aorta aneurysm. Two weeks later she developed an acute choreic syndrome. The positron emission tomography using fluorodeoxyglucose (FDGC-PET) showed a bilateral hypometabolism of basal ganglia. After haloperidol administration, choreic syndrome improved and 6 months later FDGC-PET was normal. Choreoathetosis has been described as a rare complication after heart surgery. The authors suggest that this movement disorder may be related to hypothermia that can induce a reversible basal ganglia metabolic damage.
**Temporal limbic activation by intracranial electrical stimulation.**

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BACKGROUND: To evaluate the results of intracranial electrical stimulation (ICES) as a pre-surgical tool in order to select the side of the operation in bitemporal lobe epilepsy (BTLE) patients who underwent depth electrode (DE) implantation.

METHODS: We reviewed the files of 77 medically intractable BTLE patients who underwent ICES with positive results through implanted DEs and then were under surgical treatment. One year or more after surgery, we evaluated the outcome. ICES was performed through: 1) Square-wave bipolar stimulation with symmetrical pulses of 60 Hz for 0.5 ms was delivered by a constant current Nuclear Chicago stimulator; 2) An initial intensity of 0.5 mA, and subsequently progressively stronger currents at 1-2 and occasionally 3 or 4 mA; 3) The duration of a single stimulation was usually 5 seconds; 4) The volume of tissue effectively stimulated did not exceed 5 mm. RESULTS: We obtained habitual auras or seizures (clinical responses, CRs) in 74 patients and after-discharges, ADs in 61 of them, according to Engel's classification for post surgery outcomes. If CRs or ADs were obtained by stimulation of only one temporal lobe the result of epilepsy surgery tended to be better (Engel classes I or II) when the resection took place in the same side of positive responses to ICES (CRs: chi2 4.74 and p=0.0295; ADs: chi2 7.57 and p=0.0059). CONCLUSION: In addition to other methods (PET, MRI and neuropsychology) presurgical ICES can provide useful data in the process of identifying the temporal lobe to be targeted for resection in BTLE patients.

Nonparametric Residue Analysis of Dynamic PET Data With Application to Cerebral FDG Studies in Normals.


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Kinetic analysis is used to extract metabolic information from dynamic positron emission tomography (PET) uptake data. The theory of indicator dilutions, developed in the seminal work of Meier and Zierler (1954), provides a probabilistic framework for representation of PET tracer uptake data in terms of a convolution between an arterial input function and a tissue residue. The residue is a scaled survival function associated with tracer residence in the tissue. Nonparametric inference for the residue, a deconvolution problem, provides a novel approach to kinetic analysis-critically one that is not reliant on specific compartmental modeling assumptions. A practical computational technique based on regularized cubic B-spline approximation of the residence time distribution is proposed. Nonparametric residue analysis allows formal statistical evaluation of specific parametric models to be considered. This analysis needs to properly account for the increased flexibility of the nonparametric estimator. The methodology is illustrated using data from a series of cerebral studies with PET and fluorodeoxyglucose (FDG) in normal subjects. Comparisons are made between key functionals of the residue, tracer flux, flow, etc., resulting from a parametric (the standard two-compartment of Phelps et al. 1979) and a nonparametric analysis. Strong statistical evidence against the compartment model is found. Primarily these differences relate to the representation of the early temporal structure of the tracer residence-largely a function of the vascular supply network. There are convincing physiological arguments against the representations implied by the compartmental approach but this is the first time that a rigorous statistical confirmation using PET data has been reported. The compartmental analysis produces suspect values for flow but, notably, the impact on the metabolic flux, though statistically significant, is limited to deviations on the order of 3%-4%. The general advantage of the nonparametric residue analysis is the ability to provide a valid kinetic quantitation in the context of studies where there may be heterogeneity or other uncertainty about the accuracy of a compartmental model approximation of the tissue residue.
Safety and tolerability of putaminal AADC gene therapy for Parkinson disease.


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BACKGROUND: In Parkinson disease (PD), the benefit of levodopa therapy becomes less marked over time, perhaps because degeneration of nigrostriatal neurons causes progressive loss of aromatic l-amino acid decarboxylase (AADC), the enzyme that converts levodopa into dopamine. In a primate model of PD, intrastratal infusion of an adeno-associated viral type 2 vector containing the human AADC gene (AAV-hAADC) results in robust response to low-dose levodopa without the side effects associated with higher doses. These data prompted a clinical trial. METHODS: Patients with moderately advanced PD received bilateral intraputaminal infusion of AAV-hAADC vector. Low-dose and high-dose cohorts (5 patients in each) were studied using standardized clinical rating scales at baseline and 6 months. PET scans using the AADC tracer [(18)F]fluoro-L-m-tyrosine (FMT) were performed as a measure of gene expression. RESULTS: The gene therapy was well tolerated, but 1 symptomatic and 2 asymptomatic intracranial hemorrhages followed the operative procedure. Total and motor rating scales improved in both cohorts. Motor diaries also showed increased on-time and reduced off-time without increased "on" time dyskinesia. At 6 months, FMT PET showed a 30% increase of putaminal uptake in the low-dose cohort and a 75% increase in the high-dose cohort. CONCLUSION: This study provides class IV evidence that bilateral intrastriatal infusion of adeno-associated viral type 2 vector containing the human AADC gene improves mean scores on the Unified Parkinson's Disease Rating Scale by approximately 30% in the on and off states, but the surgical procedure may be associated with an increased risk of intracranial hemorrhage and self-limited headache.
Acute limbic encephalitis and glutamic acid decarboxylase antibodies: a reality?


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Limbic encephalitis (LE) associated with glutamic acid decarboxylase antibodies (GAD-Ab) is rare. We describe a 30-year-old male with acute LE and GAD-Ab, with follow-up during 2 years of cognitive status including verbal episodic memory, number of seizures recorded by high-resolution video-EEG, brain MRI, 2-[18F]-fluoro-2-deoxyglucose PET and GAD-Ab titres. Treatment with corticosteroids, IV immunoglobulins, immunosuppressors and antiepileptic drugs resulted in improved memory status, disappearance of seizures and decreased GAD-Ab titres. Review of the other cases of literature and this case is in favour of the existence of autoimmune LE associated with GAD-Ab and supports the link between memory, temporal seizures and possibly GAD-Ab titres.

"All that spikes is not fits", mistaking the woods for the trees: the interictal spikes--an "EEG chameleon" in the interface disorders of brain and mind: a critical review.

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Recent research into mammalian cortical neurophysiology, after 6 decades of Berger's seminal work on electroencephalography, has shifted the older concept of interictal epileptiform activity (IEA) away from that of a mere electrographic graphoelement of relevance to diagnostic implications in epilepsy. Instead, accumulating information has stressed the neuropsychological implications, cognitive and/or behavioral consequence of these electrophysiological events, which are the phenotypic expression of aberrations of actual biophysical cellular function. We feel that this review is germane to neuropsychiatry, however, a rather neglected area of research. There is a great scope for brain-behavior-EEG research in the future that can be complemented by other techniques of "neurobehavioral electrophysiology". This review does not address the "pearls, perils and pitfalls" in the use of EEG in epilepsy, but critically and systematically reappraises the published electroencephalographic correlates of human behavior. We reiterate that epileptiform and other paroxysmal EEG dysrhythmias unrelated to clinical seizures do have neuropsychological, cognitive and/or behavioral implications as seen in the various neuropsychiatric and neurobehavioral disorders discussed in this article. IEA and EEG dysrhythmias should neither be ignored as irrelevant nor automatically attributed to epilepsy. The relevance of these EEG aberrations in the disorders of the brain-mind interface extend beyond epilepsy, and may be an electrophysiological endophenotype of aberrant neuronal behavior indicative of underlying morpho-functional brain abnormalities. Magnetoencephalography (MEG), data fusion models (EEG-MRI-BOLD), transcranial magnetic stimulation (TMS), evoked potentials (EP); intracranial electrophysiology, and EEG neurofeedback complemented by current functional neuroimaging techniques (fMRI and PET) would certainly help in further understanding the broader relationship between brain and behavior.


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Animal and functional imaging studies had identified cortical structures such as the parieto-insular vestibular cortex, the retrolimbic cortex, or the anterior cingulate cortex belonging to a vestibular cortical network. Basic animal studies revealed that endorphins might be important transmitters involved in cerebral vestibular processing. The aim of the present study was therefore to analyse whether the opioid system is involved in vestibular neurotransmission of humans or not. Changes in opioid receptor availability during caloric air stimulation of the right ear were studied with [(18)F] Fluoroethyl-diprenorphine ([18F]FEDPN) PET scans in 10 right-handed healthy volunteers and compared to a control condition. Decrease in receptor availability to [(18)F]FEDPN during vestibular stimulation in comparison to the control condition was significant at the right posterior insular
cortex and the postcentral region indicating more endogenous opioidergic binding in these regions during stimulation. These data give evidence that the opioidergic system plays a role in the right hemispheric dominance of the vestibular cortical system in right-handers.


**Fluorodeoxyglucose positron emission tomography (FDG-PET) is useful in the diagnosis of neurosarcoidosis.**

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A 45-year-old man presented with a progressive transverse spinal cord syndrome. MRI scanning revealed bitemporal and multiple spinal lesions with significant enhancement after gadolinium administration mimicking an acute disseminated encephalomyelitis. CSF analyses showed a lymphocytic pleocytosis. After treatment with high dose steroids clinical improvement was observed with a secondary decline shortly thereafter. MRI rescanning showed no remarkable alterations of the lesions. Further diagnostic work-up included a fluorodeoxyglucose positron emission tomography (FDG-PET) of the whole body to search for occult inflammation or neoplasia. The FDG-PET showed hypermetabolic foci corresponding to the lesions on MRI and additionally increased uptake in mediastinal and pulmonary hilar lymph nodes. A mediastinal lymph node was biopsied. Pathology was consistent with the diagnosis of sarcoidosis. The usual diagnostic tools to evaluate a sarcoidosis, such as serum angiotensin converting enzyme (ACE) and computed tomography of the chest were performed initially and revealed no pathological results. Therefore, in this case FDG-PET was crucial for the diagnostic work-up leading to an accessible inflammatory lesion outside the CNS for biopsy and the final diagnosis of sarcoidosis.

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**Primary central nervous system lymphoma.**

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Abstract

PURPOSE OF REVIEW: This review will summarize recent advances in the understanding and treatment of primary central nervous system lymphoma (PCNSL). RECENT FINDINGS: The molecular and genetic characteristics that distinguish PCNSL are beginning to be elucidated. New tools such as flow cytometry and PET are improving the diagnosis and management of PCNSL. Although the current standard of care is high-dose methotrexate-based chemotherapy alone or in combination with whole brain radiotherapy, multiple questions remain regarding the optimal treatment of PCNSL, in general, and unusual variants of PCNSL. SUMMARY: Although recent advances have improved our understanding of PCNSL, the need for additional collaborative research is critical.


**Does hippocampal FDG-PET asymmetry predict verbal memory dysfunction after left temporal lobectomy?**

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The primary aim of this study was to determine whether hippocampal asymmetries in fluorodeoxyglucose (FDG) uptake on preoperative PET scans would predict post-temporal lobectomy verbal memory (VM) decline in patients with left temporal lobe epilepsy. A quantitative asymmetry index (AI) of uptake values within a hippocampal region of interest (ROH) was defined by an automated technique. No statistically significant effect of the hippocampal AI on the outcome measure, the pre- to postsurgical change in Logical Memory Percent Retention, was evident. Post hoc analyses revealed that AIs of the superior and inferior temporal gyri approached significance, however, with relatively greater left-sided preoperative metabolism predicting better VM outcomes. This finding suggests reorganization of function and/or retained function of remaining tissue. Although hippocampal FDG-PET asymmetries did not significantly predict changes in VM, the predictive value of neocortical AIs should be further explored. Automated ROI parcellation provides a feasible tool for use in such investigations.


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OBJECTIVE: In Alzheimer disease (AD), the accumulation pattern of beta-amyloid over time and its relationship with dementia severity are unclear. We investigated the brain uptake of the amyloid ligand (11)C-labeled Pittsburgh compound B ([11C]PIB) and volumetric brain changes over a 2-year follow-up in patients with AD and in aged healthy controls. METHODS: Fourteen patients with AD (mean age 72 years, SD 6.6) and 13 healthy controls (mean age 68 years, SD 5.4) were examined at baseline and after 2 years (patients with AD: mean 2.0 years, SD 0.2; controls: mean 2.1 years, SD 0.6) with [11C]PIB PET, MRI, and neuropsychological assessments. [11C]PIB uptake was analyzed with a voxel-based statistical method (SPM), and quantitative data were obtained with automated region-of-interest analysis. MRI data were analyzed with voxel-wise tensor-based morphometry. RESULTS: The [11C]PIB uptake of the patients with AD did not increase significantly during follow-up when compared with that of the controls. MRI showed progressive brain volume change in the patients with AD, e.g., in the hippocampal region, temporal cortex, and precuneus (p < 0.05). The mean Mini-Mental State Examination score of the patients with AD declined from 24.3 (SD 3.1) at baseline to 21.6 (SD 3.9) at follow-up (p = 0.009). Cognitive decline was also evident in other neuropsychological test results. Baseline neocortical [11C]PIB uptake ratios predicted subsequent volumetric brain changes in the controls (r = 0.725, p = 0.005). CONCLUSIONS: The results suggest no (or only little) increase in [11C]labeled Pittsburgh compound B ([11C]PIB) uptake during 2 years of Alzheimer disease progression, despite advancing brain atrophy and declining cognitive performance. Nevertheless, changes in [11C]PIB uptake during a longer follow-up cannot be excluded. High cortical [11C]PIB uptake may predict ongoing brain atrophy in cognitively normal individuals.

Autoimmune polyendocrine syndrome type I and brain calcinosis.

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Autoimmune polyendocrine syndrome (APS) is a rare disorder. One of the possible associated endocrinopathies in APS is hypoparathyroidism. We describe brain calcifications secondary to hypoparathyroidism in family members with APS and compare clinical manifestations, the extent of brain calcifications on CT scans and the result of PET-FDG scans. We found extensive brain calcifications and striatal hypometabolism in PET-FDG scan in the only symptomatic member of the family, which supports the assumption that extensive brain calcification and the presence of hypometabolism in PET-FDG scan are likely to be found in symptomatic patients with brain calcifications. Copyright 2009 Elsevier Ltd. All rights reserved.

Acquired cognitive dysfunction with focal sleep spiking activity.

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The syndrome of continuous spike-waves during slow sleep (CSWS) is considered an epileptic encephalopathy in which the epileptiform abnormalities may contribute to progressive cognitive dysfunction. The characteristic electroencephalographic feature of the syndrome occurs during non-REM sleep, and takes the form of continuous bilateral and diffuse slow spike-waves that persist through all slow sleep stages. Using a case study design including clinical, neuropsychological, electroencephalographic, and positron emission tomography with 18F-fluorodeoxyglucose (PET-FDG) investigations, we describe the clinical and electroencephalographic findings in two patients who presented with nonsymptomatic epilepsy with unilateral spike-waves during sleep. Both patients presented with a left unilateral motor neglect of the upper limb that was
associated with unilateral CSWS activity over the right hemisphere, predominantly in the centrottemporal region. PET-FDG studies during the active phase of CSWS showed right centrottemporal hypermetabolism in both cases. After treatment, a regression of the CSWS activity and an improvement of the cerebral FDG pattern were paralleled by a remission of the motor neglect. These cases demonstrate that the electroencephalographic pattern of CSWS in nonsymptomatic epilepsies is not necessarily diffuse and bilateral, and that focal unilateral CSWS activity can be associated with focal neuropsychological deficits. These findings add further evidence that the spectrum of clinical conditions associated with the electroencephalographic pattern of CSWS can include different forms of acquired cognitive disturbances that may be focal in nature.