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Striatal Dopamine Transporter and D2 Receptor Status in Patients under Treatment with Amisulpride: A [Tc-99m]TRODAT-1 and [I-123]IBZM Study

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Objectives: The atypical neuroleptic amisulpride is a highly specific dopamine D2/D3 receptor antagonist without substantial affinity to D1 and serotonergic HT2 receptors. Depending on dosage, amisulpride may be effectively used for treatment of positive and negative symptoms of schizophrenia. Aim of the study was to assess the degree of dopamine D2 receptor occupancy under high dose treatment and to investigate potential effects on the dopamine transporter.
Methods: 13 schizophrenic patients (8 males, 5 females, age 19 – 63 yrs, DSM IV) were injected with 740 MBq [Tc-99m]TRODAT-1 and 60 minutes later with 185 MBq [I-123]IBZM. SPECT scans were acquired 3 hrs after the first injection using a Picker Prism 3000 XP gamma camera. Striatal uptake was assessed by calculating the ratio of specific (ROI-background) to nondisplaceable (background) activity. All findings were compared to three normal age matched controls, who were simultaneously scanned. These controls did not show statistically significant differences to larger control groups for [Tc-99m]TRODAT-1 (n = 9) and [I-123]IBZM (n = 10).
Results: Amisulpride treated schizophrenic patients (average dose: 685 mg) presented with markedly decreased binding of [I-123]IBZM to the D2 receptors (0.16 ± 0.05 vs. 0.95 ± 0.11, p<0,001). The binding of [Tc-99m]TRODAT-1 to the DAT was found to be slightly decreased with a mean of 0.84 ± 0.10 (controls 1.28 ± 0.14, p<0.01). A weak correlation was found between D2 receptor occupancy and blood levels of amisulpride (r=-0.52, p=0.069) as well as between D2 receptor occupancy and extrapyramidal side effects (r=0.6, p=0.03).
Conclusion: The results of our study suggest that high dose treatment with amisulpride leads to a 71 – 94 % decrease in D2 receptor binding and reduces the availability of the DAT. The degree of D2 blockade is similar to the one of haloperidol, whereas the DAT effect may be caused by competition of the radiopharmaceutical with increased levels of dopamine within the synaptic cleft.

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Brain SPECT study of common ground between hypothyroidism and depression

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Aim: Hypothyroid patients often present with neuropsychiatric features similar to those of major depression (MDD). Extensive hypoperfusion has been found in hypothyroidism, and reduced regional cerebral blood flow (rCBF) in frontal and limbic areas is characteristic of MDD. In this study, a comparison between rCBF in hypothyroidism, MDD and normal subjects is used to investigate the presence of a pattern of rCBF deficits corresponding to the depressive symptoms common to hypothyroidism and MDD.
Materials and Methods: Ten hypothyroid (9 females, mean age 45.9 years), 10 depressed (9 females, mean age 48.7) and 10 healthy subjects (9 females, mean age 49.7) were studied. Hamilton Rating Scale for Depression (HAM-D) scores were 10+/-5.6 and 30.2+/-10.2 for hypothyroid and MDD patients, respectively. Serum TSH levels were 15.1+/-2.9 and 1.6+/-0.8 mU/L for hypothyroid and MDD patients, respectively. All participants underwent HMPAO brain SPECT while medication free. Statistical Parametric Mapping was used for comparisons between the three study groups.
Results: When comparing hypothyroid patients to controls, decreased rCBF was seen in occipital lobes (R>L), posterior cingulate, right mid temporal and cuneus areas. In MDD, we observed reduced rCBF relative to controls in frontal areas, specifically in the fronto-parietal lobe and superior mid-frontal gyri, as well as in the left inferior/mid occipital gyri, and increased rCBF was seen in the right fusiform/inferior temporal gyrus. Comparison between hypothyroid and MDD patients showed reduced rCBF in the same extensive brain regions as seen in the comparison between hypothyroid patients and controls, but with the following additional areas: right precentral gyrus, pons and midbrain. In contrast, reduced rCBF in left pre- and post-central gyri was only found when comparing hypothyroid patients to healthy subjects. rCBF was higher in hypothyroid than in MDD patients in left mid-frontal gyrus.
Conclusion: Cerebral perfusion in hypothyroidism is strikingly reduced relative to MDD, much like the difference between hypothyroid and healthy subjects. Yet, certain regions with reduced rCBF, such as parts of the occipital cortex, are found in both hypothyroidism and MDD, and may be involved in depressive symptoms observed in hypothyroidism. On the other hand, decreased rCBF in mid-frontal gyrus found only in MDD patients, relative to both healthy and hypothyroid patients, points to a region uniquely involved in MDD symptomatology. This study exemplifies a strategy for elucidating brain regions underlying the depressive component of hypothyroidism.

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Regional cerebral blood flow correlates with neuropsychological function in Tourette syndrome

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Objectives: The literature to date has suggested that intellectual ability is normally distributed in Tourette syndrome (TS). However, patients with TS have significant discrepancies between their verbal and nonverbal abilities. Specific cognitive deficits in TS include visuomotor integration problems, impaired fine motor skill, and executive dysfunction. The presence of a learning disability or cognitive deficit may lead to a greater obstacle for patients with TS than the tic disorder itself. It would be important that patients with TS will be evaluated to having neuropsychological difficulties as soon as possible. The aim of this study was to evaluate the correlation between the clinical severity and neuropsychological impairment (especially memory deficit) of patients with TS and rCBF abnormalities.
Methods: The assessment included neurological, psychiatrical examination (Yale Scale [YS], staging of the severity of disease), CT/MRI, and a specific test of explicit and implicit memory (Probabilistic Classification Learning test, PCL). ^{99m}Tc-HMPAO-SPECT studies were carried out with a standard technique for each patient. The data were analyzed visually and by a special ROIs program. RCBF results were correlated to the results of the PCL test and the Yale scale.
Results: The SPECT measurements showed significant (p<0.05) decrease of rCBF in patients with YS>40 in the temporal medial and lateral regions, and also in the cerebellum, compared to the patients with YS<40. Also, an increase of rCBF was observed in the left striatal, temporal medial and lateral regions, compared to the contralateral homologous regions (p<0.05). The YS (disease severity) demonstrated significant (p<0.05) and strong correlation with the rCBF in the right temporal region (r= -0.83) and in the thalamus (r= -0.69). The performance in the explicit memory test showed significant (p<0.05) and strong correlation with the perfusion in both temporopolar (r= 0.9) and left temporomedial region (r=0.92).
Conclusion: RCBF SPECT proved to be concordant with disease severity (measured by YS) and neuropsychological findings. There was a strong correlation between the PCL test (memory deficit) and rCBF data. The functional neuroimaging data obtained by rCBF SPECT might be useful for the objective evaluation of TS. Additionally, these studies may help to understand the basic mechanisms and pathophysiology of the disease, by revealing the relation between the impairment of the underlying functional networks (BGTC) and disease severity. Further rCBF studies may reveal important clues to the neuroanatomic substrates of neuropsychological impairment of patients with TS.

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Value of Nucleus Caudatus and Thalamus SPECT rCBF in discriminating among Alzheimer Disease, Unipolar Depression and normal individuals

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Aim: Basal ganglia and thalamus play a central role, via the cortico-basal ganglia-thalamus-cortical loop, in the processing of the neuronal signal from and to the cerebral cortex. Metabolic alterations in the neocortex, causing proportional regional cerebral blood flow (rCBF) changes, affect neuronal signal also in such structures. The aim of this study was to investigate the possibility of using the rCBF of the central structures in discriminating Alzheimer Disease (AD) and Unipolar Depression (UNI) patients from normal controls (CTR).
Materials and Methods: 47 AD patients, 70 UNI patients and 66 CTR were included in the study. rCBF was assessed by 99m-Tc-HMPAO and using a three-headed gamma camera. A standardised brain atlas was used to define volumes of interest corresponding to nc. caudatus, putamen and thalamus. Analysis of variance (ANOVA) was used to test the significance of the differences in flow and data were covariated for age. Receiver Operating Characteristic (ROC) curves were implemented to evaluate the ability of the rCBF in the different structures to discriminate between the groups.
Results: ANOVA showed a significant overall rCBF group difference (p<0.001). As compared to CTR, rCBF in nc. caudatus and thalamus decreased in AD and increased in UNI. The blood flow in putamen was significantly increased only in the CTR/UNI comparison (p<0.001). Thalamus blood flow significantly differed in the CTR/AD (p<0.02) and CTR/UNI (p< 0.001) comparisons. Nc. caudatus blood flow significantly discriminated all three groups (CTR/AD:p<0.001; CTR/UNI: p<0.001; AD/UNI:p<0.01). According to ROC curves, nc. caudatus correctly categorised 74% of the individuals in the CTR-AD group pair and 72% in the CRT-UNI group pair.
Conclusions: The blood flow in nc. caudatus and thalamus reflected corresponding changes in cortical regions in both AD and UNI. The decreased perfusion in the temporo-parietal cortex of the AD patients and the increased blood flow in the fronto-temporal cortex of the UNI patients were concomitant in nc. caudatus and thalamus. This is consistent with the anatomical path of the cortico-basal ganglia-thalamus-cortical loop projecting the fronto-temporo-parietal association cortex fibres in a segregated manner to nc. caudatus and thalamus. The putamen receives fibres mainly from motor and pre-motor cortices not involved in AD.

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Classification of early and severe Alzheimer Disease. Differences in accuracy basing the analysis of SPECT CBF data on either hippocampus, temporo-parietal lobes or factorial analysis

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Aim: Hippocampus and temporo-parietal regional cerebral blood flow (rCBF) reductions are well known to be specific of early (eAD) and severe Alzheimer Disease (AD). The specificity and the sensitivity of SPECT rCBF in discriminating the two stages of the disease vary across different investigations. The aim of this study is to develop a new method to increase the accuracy in the classification of eAD and AD.
Materials and Methods: Twenty eAD and 21 controls (CTR), and 15 AD and 13 further CTR were included in the study. The two group pairs were age-matched and rCBF was assessed by 99m-Tc-HMPAO and using a three-headed gamma camera. Regions were identified and signal intensity was evaluated by a standardised brain atlas. Hippocampus, temporal and parietal lobes and four factors, derived from a previous principal components analysis, and whose rCBF was proven to significantly differ between groups, were considered for data analysis. These four factors were functionally connected clusters of Brodmann areas belonging to the temporo-parietal lobes (n=3) and to central structures (n=1) and were analysed together. The accuracy of the classification of eAD, AD and CTR utilising the K-means clustering method was separately tested for each group pair and for each region.
Results: In AD/CTR evaluation, hippocampus uptake could correctly classify the 82.1% of the subjects, while the accuracy of both temporo-parietal lobes and the four joint factors was 96.4%. When the correct classification to eAD/CTR groups was tested, the accuracy of 99m-Tc-HMPAO uptake intensity in discriminating the groups was 85.4% for hippocampus, 80.5% for temporo-parietal lobes and 87.8% for the four joint factors.
Conclusion: Utilising separately sensitive regions (hippocampus), lobes (temporo-parietal) and functionally connected regions in classifying eAD and AD yielded different results. Severe AD was better classified by data from lobes and from the functionally connected regions affected by the disease. Early AD was classified with higher accuracy by hippocampus and the functionally connected regions in temporo-parietal lobes and central structures. Such differences are consistent with the progression of the disease which is supposed to start in the medial temporal lobe and spread through the temporo-parietal cortex. The proposed method adds information mainly in the early stage of the disease.

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Regional cerebral blood flow and metabolic abnormalities as predictors of response to bilateral anterior capsulotomy for obsessive-compulsive disorder

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Objectives: Earlier single photon emission tomography (SPECT) and positron emission tomography (PET) studies of patients with obsessive-compulsive disorder (OCD) have demonstrated abnormal regional cerebral blood flow (rCBF) and cerebral glucose metabolic (rCGlM) pattern in the orbitofrontal-basal ganglia-thalamo-cortical circuits (OBgThC). OCD is characterized by intrusive, repetitive thoughts and/or behaviors that cause marked distress. In case of a severe, and medically and/or psychotherapeutically intractable disease surgical therapy remains the only possible solution. The purpose of this study was to evaluate rCBF and rCGlM correlates as potential predictors of treatment response to bilateral anterior capsulotomy. We performed rCBF SPECT and rCGlM PET studies in 5 patients with severe, intractable OCD before and after (3, 6 and 12 months) surgical therapy.
Methods: The assessment included neurological, psychiatrical examination, CT, MRI, and neuropsychological evaluation. ^{99m}Tc-HMPAO-SPECT and ^{18}F-FDG-PET studies were carried out with a standard technique for each patient. The data were analyzed visually and by a special region of interests (ROIs) program. The rCBF SPECT and glucose metabolic PET results were compared to clinical and neuropsychological findings.
Results: The SPECT and PET measurements showed significant ($p<0.05$) rCBF and metabolic abnormalities in caudate nuclei, thalamus, cingular and orbitofrontal cortex. There was a marked, but individually variable rCBF and rCGlM pattern before and after surgery. Additionally, the preoperative and postoperative rCBF and rCGlM results proved to be concordant with clinical and neuropsychological findings.
Conclusion: Both SPECT and PET (before and after surgery) proved to be concordant with clinical and neuropsychological findings. However, rCGlM PET measurements had a higher sensitivity. Patients with higher preoperative rCBF and rCGlM rates of OBgThC circuits were associated with a better postoperative outcome. RCBF SPECT and glucose metabolic PET seems to be helpful in the evaluation and follow-up of patients with intractable OCD. Additionally, the methods might be useful in presurgical selection of candidates for surgery. The results argue for the further evaluation of neurosurgery for the treatment of severe and intractable OCD.

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OTHER CLINICAL SCIENCE: THYROID 1

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Pretreatment with a single, low dose of recombinant human thyrotropin (rhTSH) allows dose reduction of radioiodine therapy in patients with nontoxic, nodular goiter

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In patients with nontoxic, nodular goiter radioiodine (131-I) therapy results in a mean reduction in thyroid volume of approximately 40% after 1 year. We have demonstrated that pretreatment with a single, low dose of rhTSH doubles 24-h radioactive iodine uptake (RAIU) in these patients. We have now studied the efficacy of therapy with a reduced dose of radioiodine after pretreatment with rhTSH. 22 patients (18 women and 4 men; age 60±9 yr, mean±SD) with a nontoxic, nodular goiter received 131-I therapy 24 h after im administration of 0.01 (n=12) or 0.03 mg (n=10) rhTSH. The therapeutic dose of 131-I was aimed at 100 mCi/g thyroid tissue retained at 24 h and adjusted to the rhTSH-induced increase in 24-h RAIU, determined in a diagnostic study using a tracer dose of 131-I. In the diagnostic study 24-h RAIU increased by a factor of 1.9±0.5 (from 27±8% to 50±11%) in the 0.01 mg and by a factor of 2.4±0.4 (from 22±4% to 54±9%) in the 0.03 mg rhTSH group. The therapeutic doses of 131-I were reduced accordingly with factors of 1.9±0.5 and 2.4±0.4 respectively and were 39.4±16.8 mCi (0.01 mg rhTSH) and 22.8±5.7 mCi (0.03 mg rhTSH). Before and 1 year after therapy thyroid volume and the smallest cross-sectional area of the tracheal lumen (SCAT) were measured with MRI. During the year of follow-up serum TSH, FT4 and TSH-receptor-antibodies (TRAb) were measured at regular intervals. Thyroid volume before therapy was 143±54 cm^3 (range 70-209 cm^3) in the 0.01 mg and 103±44 cm^3 (range 44-172 cm^3) in the 0.03 mg rhTSH group. One year after treatment thyroid volume was 91±41 cm^3 (range 50-170 cm^3) and 62±35 cm^3 (range 23-127 cm^3) respectively. Thyroid volume reduction was 35±14% (0.01 mg rhTSH) and 41±12% (0.03 mg rhTSH). In both groups SCAT increased significantly. TRAbs were negative in all patients before therapy and became positive in 4 patients. Hyperthyroidism developed in 3 of these 4 patients between 23 and 25 weeks after therapy. Hypothyroidism was observed in 8 patients (0.01 mg rhTSH n=4, 0.03 mg rhTSH n=4). In conclusion, in patients with nontoxic, nodular goiter pretreatment with a single, low dose of rhTSH allowed approximately 50 to 60% reduction of the therapeutic dose of radioiodine without compromising the efficacy of thyroid volume reduction. Further studies are needed whether treatment with larger doses of rhTSH and/or 131-I results in larger thyroid volume reduction in these patients.

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Incidence of radiation-induced Graves`disease in patients treated with radioiodine for functional thyroid autonomy after introduction of a high sensitivity TSH-receptor antibody assay

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Objectives: Autoimmune hyperthyroidism may occur several months after radioiodine treatment for functional thyroid autonomy. Exacerbation of preexisting subclinical Graves`disease has been held responsible for this phenomon. Determination of TSH-receptor antibodies (TRAb) using solubilized porcine epithelial cell membranes is insensitive and failed in these patients before radioiodine therapy. A new assay, using the hTSH-receptor as an antigen, showed a high sensitivity for the detection of TRAb. After introduction of this assay the incidence of radiation-induced Graves`disease should be reduced.
Methods: Two collectives of pts treated for functional thyroid autonomy by radioiodine were investigated retrospectively. Between 11/1993 and 03/1997 1428 pts and between 01/2001 and 06/2001 1286 pts were treated with radioiodine. The new Dynotest TRAK human assay (Brahms, Germany) was introduced in our clinic in 01/2000. The radiation dose delivered to the thyroid in multifocal autonomy (MFA) or disseminated autonomy (DISA) varied from 150 to 300 Gy (k=18.5) in the first collective, and from 150 to 250 Gy (k=25) in the second collective, depending on the ^{99m}Tc-pertechnetate uptake in the thyroid (TcTUs) under TSH-suppression (<0.1µU/ml). TRAb assay was negative and no endocrine ophthalmopathy was observed in any pt at the time of radioiodine therapy. All pts underwent at least one control examination 4 - 8 months later.
Results: Using a low sensitivity assay for exclusion of TRAb (sensitivity about 80 %, as reported in literature), 15 (1.1 %) of 1428 pts treated for functional thyreoid autonomy developed radiation-induced Graves`disease 8.4 (4 - 13) months after radioiodine therapy. Increasing the sensitivity of the TRAb assay to about 99 % (as reported in literature) resulted in 18 (1.3 %) of 1286 pts with Graves`disease induced by radioiodine 8.7 (7 - 13) months later. Elevated serum anti-TPO levels were seen before radioiodine therapy in 73 % of the pts in collective I and in 39 % of the pts in collective II.
Conclusion: Introduction of a high sensitivity TRAb assay did not reduce the incidence of autoimmune hyperthyroidism occurring late after radioiodine treatment for functional thyroid autonomy. Hence, hypothesis of preexisting subclinical Graves`disease becoming manifest disease by radiation may not be valid. However, a preexisting autoimmune thyroiditis is more frequent in these pts which may be related to an individual iodine supply.