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Interventional brain SPECT—A review

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Brain SPECT with HMPAO or ECD has—due to its short accumulation period—a rather high time resolution of approx. 60 sec. Compared to isopropyl amphetamine (I-123) and FDG-PET, shortlasting interventions may be evaluated by SPECT. Usually, a two-step approach is used, injecting one third of the dose under baseline conditions and two thirds during intervention. The first study is then subtracted from the second study, resulting in a "difference" image which allows to calculate the effect of the intervention. These interventional procedures may include drug, mechanical, and mental intervention as well as ictal, blood pressure and receptor intervention. Moreover, the difference of pCO_2 after hyperventilation or hypoventilation may also be used as a stimulus. The above mentioned procedures are described in detail.

BRAIN IMAGING with HMPAO or ECD has gained widespread clinical application in epilepsy, psychiatry and cerebrovascular diseases[1–5] as resolution could be improved by using dedicated SPECT systems (triple head gamma camera, annular crystal). However, the sensitivity may be considerably improved by the application of interventional techniques. Pharmacological intervention includes the injection of diamox or barbiturates (WADA test) as well as the reduction of medication, especially in epilepsy. Mechanical intervention requires the balloon occlusion or manual compression of the carotid artery (MATAS test). This procedure may also be combined with the application of diamox to increase the perfusion difference between normal and low flow areas. For the evaluation of brain function, mental intervention may be useful. The stimuli include accoustical, visual and motoric challenge. Above that, the speech areas may be identified by language stimulation. The prefrontal functions can be stimulated using the Wisconsin Card Sorting Test, especially in patients with psychiatric diseases. During sleep, circumscribed hypoperfusions may be detected in sleep apnea and narcolepsy. The CO_2-intervention allows the evaluation of the cerebrovascular (perfusion) reserve by raising pCO_2 by hypoventilation as well as hyperventilation (decreasing pCO_2). The ictal intervention is the most common procedure for the proof of epileptic foci. The ictal/interictal switch allows a localization of a focus in more than 90% which is extremely useful in patients considered candidates for temporal lobectomy. Above that, D2-receptor scintigraphy using IBZM may be performed before and after application of D2 agonists or antagonists. This procedure allows to calculate a basal ganglia/frontal cortex ratio which is equivalent to the binding of "cold" receptor drugs.

The here mentioned procedures will be described in detail in this review:

DRUG INTERVENTION

Diamox

Autoregulation of the cerebral blood flow (CBF) plays an important role especially in cerebrovascular disease.[6] The degree of arterial occlusion does not correlate well with the hemodynamic condition of the affected brain areas, as the collateral circulation is only poorly evidenced by sonography. The evaluation of the cerebrovascular

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reserve capacity in stroke patients may have a major impact on the management of CVD. For estimating the reserve capacity, the correlation of CBF and blood volume were used. However, positioning problems lead to a degradation of the results. Since many years now, the diamox test is used for estimating the perfusion reserve. For this test, at first a baseline study using HMPAO or ECD is obtained. After completion of the SPECT study, 1 g acetazolamide (diamox) is injected intravenously. A second SPECT study (split dose technique) is acquired 10–20 min. after the injection of diamox. Both investigations are performed with the patients head strictly immobilized for 1 h. Subtraction of the first from the second SPECT data results in rCBF (stress) images during acetazolamide-induced vasodilation. Usually, in not-compensated CVD, the diamox test leads to hypoperfusion in brain areas supplied by stenotic vessels. Pavics et al.[6] reported on 29 patients (3 controls and 26 stroke patients) who all had transcranial Doppler sonography studies. The sensitivity of rCBF SPECT increased from 62 to 77% after diamox provocation in stroke patients. In patients with a reversible neurological deficit, the sensitivity increased from 50 to 71%. Additionally, under diamox-induced hypoperfusion of brain areas, transient crossed cerebellar diaschisis was observed.

Neuroleptics

In patients with schizophrenia or major depression, a hypoperfusion of the frontal and/or temporal lobe has been reported.[3] The application of therapeutic drugs like haloperidol leads to normal perfusion in these brain areas.[7] These findings were well correlated to the symptoms.[7]

Drug reduction

In patients with epilepsy and equivocal interictal brain SPECT studies, the antiepileptic medication was reduced to provoke a focus. Six out of 10 patients with seizures showed a change of perfusion at the site of an epileptic focus.[8] However, as ictal SPECT (see later) was superior, this procedure is no longer used, at least in our department. Also, the application of anexate (arteficial ictal study) did not yield promising results.

WADA Test

Brain SPECT during WADA test was first described in 1987.[9] For this procedure, the sodium amytal was injected first. Two–5 min. later, HMPAO was given intravenously during hemianesthesia of one hemisphere. The most prominent result was that perfusion during hemianesthesia was much more pronounced in the left (dominant) hemisphere than in the subdominant hemisphere, at least in right handed subjects. Moreover, transient crossed cerebellar diaschisis was observed. The results give rise to the assumption that the dominant hemisphere is much more vulnerable to anesthesia that the subdominant hemisphere.

MECHANICAL INTERVENTION

The MATAS test[10] requires the occlusion of the internal carotid artery (left or right). It is used to predict the outcome after permanent intraoperative occlusion of the internal carotid artery. If no sufficient collateral circulation is present, hypoperfusion of the respective hemisphere is observed.[11] During the last years, this procedure was improved by preoperative temporary balloon occlusion of the internal carotid artery.[11,12] Recent results published by Lorberboym et al.[12] gave evidence that patients with symmetric cerebral perfusion measured by HMPAO SPECT still had a high long-term complication rate following carotid sacrifice. The scan findings in these patients were not predictive of the outcome. Patients with asymmetric cerebral perfusion had alternative therapeutic approach to carotid sacrifice and had good surgical outcome. On the contrary, our own results gave evidence that the MATAS test using HMPAO and the balloon occlusion was well in agreement with the postoperative outcome.[11]

MENTAL INTERVENTION

Acoustic, visual and motor activation

Acoustic stimulation was first described in patients with schizophrenia having auditory hallucinations.[13] Studies performed during the hallucinogenic stimulus showed right or left sided temporal lobe hyperperfusion. Motor activation may be achieved by asking the patient to do certain movements, especially with his finger. This leads to circumscribed increased perfusion in the respective cortical areas. Visual stimulation by asking the patient to look at a complex scene or flickering light causes hyperactivation of the visual cortex. These studies were used clinically in patients with certain diseases of the visual pathways. A baseline study may be needed to quantitatively evaluate the activation differences. For this purpose, usually a split dose technique (one third of the dose for the baseline study, two thirds of the dose for the activation study) is applied. The patient is then investigated in the same position. A subtraction image (activation minus baseline study) allows to delineate the activated brain areas.

Language activation

Despite of the importance to activate syntactic knowledge in relating words, functional imaging studies on language mainly have focussed on processing of isolated words rather than sentences.[14]

Former brain lesion studies suggest a different processing of semantic and syntactic structures. In an ethical committee-approved study, 9 right handed male volunteers (age 23 to 46 years) were investigated by high resolution SPECT using Tc-99m ECD as a tracer.[15] The stimulus was to listen either to content words (semantic

condition) or to short phrases containing no lexical, but only grammatical information (syntactic condition). Following the resting acquisition after intravenous injection of ECD, stimulation was performed either with the semantic stimulus or the syntactic set binaurally over a period of 5 1/2 minutes. The second dose was slowly injected during this period, thus representing the cerebral perfusion pattern during stimulation. The SPECT results were evaluated both semiquantitatively and visually. Quantitative data were related to the baseline set by calculating the percent increase or decrease of counts per voxel normalized to the whole brain activity in the stimulation study. Thus, each subject served as its own control.

Different activation patterns were observed when comparing the two conditions. Hyperperfusion under syntactical stimulation (n = 4) was seen in the following areas: All 4 superior temporal gyrus (1 left, 3 right), 2 inferior frontal gyrus (1 left, 1 right) and 3 insula (2 left, 1 right). Moreover, 2 subjects had hyperperfusion within the gyrus postcentralis (1 left, 1 right). During semantic stimulation (n = 5), 4 subjects had hyperperfusion of the medius frontal gyrus (2 left, 2 right), 2 of the superior frontal gyrus, the precentral gyrus and the medius temporal gyrus (each 1 left, 1 both sides), 3 of the right postcentral gyrus, 3 of the insula (1 left, 2 both sides), and 3 of the cuneus (1 right, 2 both sides).

The results of the syntactic stimulation agree well with experiments demonstrating disabled syntactic processing following lesions of Broca's area and the insula and suggesting the insula to be relevant in syntactic process. The semantic stimulation reflects involvement of both hemispheres, more prominent on the right side. The hyperperfused regions are not primary language areas. These findings are consistent with other studies using PET or SPECT which report activation outside these areas and conclude that semantic processes may be distributed over a network of brain regions. Further studies have to be done to evaluate the handedness or sex differences. Probably, these studies may prove useful in the rehabilitation of aphasia.

Wisconsin Card Sorting Test

The Wisconsin Card Sorting Test was applied in human volunteers as well as in depressed and schizophrenic patients. This test was used to evaluate the stimulation of prefrontal cortical areas with regard to the supposed pathophysiology of the two diseases. Studies in human volunteers (n = 16) showed that right or left sided activation may occur. The same test was applied in a group of depressed (n = 26) and schizophrenic (n = 7) patients. In depressed patients, the Wisconsin Card Sorting Test did not show activation of prefrontal areas in 15 out of 26 patients. In schizophrenics, the same was true for 2 out of 7 patients. One of the clinical benefits might be to subgroup patients with psychiatric disorders.

Sleep

Five patients with sleep apnea and 4 patients with narcolepsy underwent brain SPECT using HMPAO under awake condition and during sleep.[16] The most prominent finding was a hypoperfusion of the left temporal lobe during sleep, whereas the right temporal lobe did not show significant differences. These data suggest that during sleep the right temporal lobe remains activated.

CO_2-INTERVENTION

As mentioned before, the CO_2 pressure may be used to evaluate the cerebrovascular reserve. For this purpose, the patient may breath CO_2. However, complications were observed using this method. We used hyperventilation in patients with epilepsy and equivocal interictal brain SPECT. After a base-line study, the patient was asked to hyperventilate for a couple of minutes. During hyperventilation and low pCO_2, HMPAO was injected intravenously. In 4 out of 10 patients a change of the scintigraphic results was observed. It was speculated that hyperventilation leads to an increased contrast between normal brain tissue and a seizure focus as the focus should not have autoregulation mechanisms.[8] However, the results were discouraging with respect to ictal brain SPECT studies.

ICTAL INTERVENTION

Overall sensitivity of interictal rCBF SPECT is 75%, with 69% for low resolution systems and 84% for high resolution systems.[17] This sensitivity may be as high as 90–95%[1,2] when ictal studies are performed. For this purpose, HMPAO or ECD is injected during video and EEG monitoring. The tracer has to be injected intravenously promptly after onset of the seizure, following the first seconds after onset of the symptoms or EEG discharge. Especially in temporal lobe epilepsy, excellent results were obtained. Furthermore, in frontal lobe epilepsy causing major clinical problems, a focus could be delineated in more than 75%.[17] In many cases, the comparison of baseline scan and ictal scan is necessary as the ictal changes may be very distinct.

BLOOD PRESSURE INTERVENTION

In patients with a complete stroke, therapeutic strategies are still controversially discussed. One of the therapeutic aims is an improvement of the perfusion in the stroke areas. For this purpose, the blood pressure may be elevated to increase the perfusion pressure of the tissue. On the other hand, an increased risk of a rupture of blood vessels has to be considered under high arterial blood pressure. Here, brain SPECT may also be helpful by

comparing the SPECT results under low and high pressure conditions. If the rCBF is increased during hyperperfusion, this kind of therapy should be maintained. However, results in a larger group of patients have not yet been published.

RECEPTOR INTERVENTION

Since many years, brain SPECT using I-123 IBZM is used for imaging the striatal D2-dopamine receptors. As the blood level does not correlate with the receptor occupation after application of D2-antagonists or agonists, it seems highly desirable to evaluate receptor binding in patients under respective therapy. In a recently published study by Klemm et al.,[18] 56 patients with schizophrenia, including 14 with schizoaffective disorder and one with schizophreni-form disorder, were evaluated. Fourteen patients were neuroleptic free. SPECT was performed 90–120 min. after intravenous injection of IBZM. Subsequent semiquantitative estimation of D2-receptor binding was done with the use of the basal ganglia (striatum/frontal cortex) ratio. Clinical symptoms were rated with a positive and negative symptom scale and the Hamilton depression rating scale. The striatum/frontal cortex ratios in patients taking typical neuroleptics were significantly lower than those in the neuroleptic free subjects. Patients on atypical neuroleptics (clozapine, remoxipride) did not significantly differ from the neuroleptic-free patients. For atypical antipsychotics, a dose dependent relationship with striatal D2-receptor binding could not be demonstrated. The ratios were not significantly correlated with clinical symptoms or with duration of the illness. These results indicate that IBZM-SPECT is useful for semiquantitative imaging of striatal D2-dopamine receptors and for estimating their blockade by neuroleptics thus improving drug monitoring in psychiatric patients. Furthermore, the findings suggest a complex relationship between the antipsychotic effect of atypical neuroleptics and D2-receptor blockade.[18] Similar results were obtained by Brücke et al.[19]

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