Doctoral thesis

Curriculum Vitae

Personalia

Patrick Santens,

Born on November 2nd, 1965.

Education :
Medical training at the Ghent University from 1983-1990.
MD in 1990, graduated with greatest distinction
Training in Neurology 1990-1995 at the Ghent University Hospital.
Certified neurologist since 1995
Doctoral thesis on 23/4/2002 on "Positron emission tomography of the brain in degenerative dementias : clinical applications and development of new tracer molecules".

Actual position :
Supervisor of consultation for cognitive disorders
Supervisor of consultation for movement disorders
Coordinator of movement disorder surgery in Ghent University Hospital
Co-supervisor of general neurology clinic Ghent University Hospital

Publication list :
Author and co-author of over 50 papers in national and international journals
Received a grant from Ghent University for research on PET in dementia in 1995
Past member of the Advisory board of the International Alzheimer's research foundation
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Positron emission tomography of the brain in degenerative dementias : clinical applications and development of new tracers

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Positron emission tomography (PET) of the brain allows in vivo visualization of numerous physiologic, metabolic and neuropharmacologic parameters by means of adequately selected tracers. Alterations of cerebral metabolism in Alzheimer's disease (AD), the most frequent cause of dementia, were reported in many studies. They suggested a decrease of metabolism in the parietal and temporal cortical areas as being the characteristic pattern of AD. For several reasons, however, the value of PET of the cerebral metabolism in the diagnosis of AD remains unclear :

- in most studies pathological confirmation of diagnosis is lacking
- many studies have reported on small series, with a possibility of selection bias
- patients in different stages of the disease have been included
- the disease itself is heterogeneous
- the validity cannot be calculated in the absence of data on prior probability of disease
- different techniques and data-analysis have been used

Studies of neuroreceptors by means of PET and selected ligands are difficult and hence sparse. Small series have been reported with ligands for the evaluation of central and peripheral benzodiazepine receptors, nicotine receptors, acetylcholinesterase.

Our study had two aims :

1. In an attempt to find more specific ligands for the in vivo research on AD, we studied two tracers, which, from a theoretical point of view, were potentially useful.

^{11}C-methoxyprogabidic acid (^{11}C-MPGA) is derived from a registerd drug with agonist activity on both $GABA_A$ and $GABA_B$ receptors. Biodistribution and dosimetry were evaluated in human and in animal studies. The use of the tracer was considered safe enough for further testing, but unfortunately the brain uptake of the tracer was low throughout the experiments, in contrast to the uptake in the intestinal organs. This is probably the consequence of limited passage through the blood-brain-barrier. Replacement studies demonstrated that specific binding was far too limited to be of use for further evaluation of the tracer.

^{11}C-donepezil is a labeled analogue of a well-known inhibitor of acetylcholinesterase used in the treatment of AD. From animal experiments it is concluded that the tracer uptake in brain does not parallel the measured cholinesterase activity. Hence this tracer cannot be used for further studies of the brain by means of PET. The reason for the discrepancy is unclear, but the reversible nature of the binding of the molecule to the enzyme might be a possible explanation.

2. In an attempt to evaluate the role of PET of cerebral metabolism in the differential diagnosis of AD, a number of clinical applications were studied.

The cerebral oxygen metabolism was studied in a small group of patients with progressive supranuclear palsy. As opposed to earlier studies, no frontal hypometabolism could be detected. Rather a temporoparietal pattern was found. This might be a consequence of co-morbidity with AD.

Regional cerebral glucose metabolism was compared between a small group of patients with frontotemporal dementia and a group of AD patients during the initial diagnostic phase. The classical patterns of hypometabolism in frontotemporal and parietotemporal cortex, respectively, were found. Parietal hypometabolism best differentiated the two groups, as it only appeared in AD. Semi-quantification based on different reference regions yielded highly discrepant results, the sensorimotor cortex being the most reliable reference region.

The contribution of paraclinical testing in the early diagnosis of corticobasal degeneration was retrospectively studied. Only functional imaging demonstrated characteristic abnormalities in the early stages of the disease in all patients, as opposed to oculography, structural neuroimaging

and neuropsychology. Our results suggest that functional neuroimaging may be of use in the early diagnosis of this disorder.

The description of focal neurodegenerative disorders, such as progressive dysarthria and posterior cortical atrophy, contributes to the discussion on the correlation of neurocognitive alterations and patterns of hypometabolism. This correlation is probably stronger than the correlation of either one of these two with pathology. PET of cerebral metabolism is therefore useful in making a diagnosis on an anatomical level.

These results are subject to many criticisms, the major ones being the small numbers of subjects studied and the lack of pathological verification. This, taken together with the above mentioned criticisms on earlier studies, emphasizes the need to prospectively enroll larger samples, which should be followed up longitudinally, up to the final stage of pathological confirmation. Only this kind of study would allow an estimation of the ecological validity.

PET still has an important potential in the future research on dementias. PET is a useful tool for further scientific research on new tracers, which in a later stage can be of clinical use, eventually even for SPECT studies, which necessitate less logistical burden. The value of PET in identifying asymptomatic persons with a risk of developing dementia is also to be further explored. This would allow the evaluation of potential neuroprotective agents in a selected group of patients. Limited research on this subject has suggested that PET is superior to volumetric measurements of vulnerable brain areas such as the medial temporal lobe structures. Future studies should further explore these possibilities.

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