PET Scan in Practice for CHI

- Basics, strength and weakness -

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Topics in today's presentation

1. Basics
   – Mechanisms of PET-Imaging
   – What is special on DOPA as PET-tracer?

2. 10 years experience: - role of DOPA/PET in CHI

3. Limits and Weaknesses of DOPA-PET in CHI

“The truth is rarely pure and never simple.”

Oscar Wilde
18F-DOPA-PET in CHI


- Superior performance compared to older localisation methods (PVS, Calc.-stimulation)
  - Non-invasive, faster
  - Less radiation than PVS
  - Higher sensitivity + specificity
The Berlin way

Creation of:

- high resolution PET-scans with a spatial resolution of 2 mm
- high resolution enhanced 3-phase CT-images (64 lines)
- serial scans after 20, 30 and 40 minutes

Chronology:

- First investigation at DTZ: 19\textsuperscript{th} of December 2003
- Total number of investigations: about 175 (in collaboration with Charité)

In collaboration with:

Diagnostisch Therapeutisches Zentrum am Frankfurter Tor (DTZ)
Nuklearmedizin · Strahlentherapie
PET

= **Positron-Emission-Tomography**
  – High spatial resolution (1 – 3 mm)
  – Visualization of metabolic processes
  – "true" 3D-imaging

*Image of a diagram showing the process of PET imaging.*
What do we expect from the DOPA-PET?

- Just Differentiation?
- Added value for the surgeon?
  - Image guided surgery, Potential reduction of surgical trauma

Localization is the key to differentiated therapy

- Focal $\rightarrow$ surgery with possible cure
- Diffuse $\rightarrow$ long-term therapy, limited surgical possibilities
Added value of PET-imaging?

• Tracer metabolism is the key to understand PET images
  – $^{18}$F-Glucose-PET shows where sugar is burned in the body (malignant tumors, inflammation)
  
  – $^{18}$F-DOPA is successful in visualization of CHI…(?)

• …but why…?

• is there a metabolic link between DOPA and Insulin?
Dopamine regulates Insulin-secretion

- Highly-specific dopamine transporter in human beta-cells (VMAT2)
- Same amount of dopamine and insulin in the secretory vesicles
- Dopamine is secreted together with insulin
- Dopamine reduces insulin-secretion of surrounding beta-cells
- Neurotransmitter-like mode of action

> DOPA-content is linked to insulin secretion…!
"Hey - I'm doing the job..."

- Without attenuation too much insulin would be released (always behind the blood sugar) resulting in hypoglycaemias
- Blunting of secretion curve by paracrine regulation.

Dopamine is the way β-cells tell their neighbourhood that they are active ("Hey - I'm doing the job...")

→ relevant effect on blood sugar (and PET images?)
Limits of DOPA-PET: Giant foci

3 patients in Berlin…
DOPA-PET is specific in focal CHI

- A diagnosis of a focal $^{18}$F-DOPA-Pet is true in 95 – 98% of surgical treated patients
- Only few false-positive PET focal diagnoses
  - Focal CHI, 3 mo.
  - Non-focal CHI, 4 mo.
Sensitivity is moderate – good

- Focal CHI has been found in up to 20% of surgically treated patients with non-focal-PET result
  - Histology available in only a small part of patients with non-focal-PET results
  - Those receiving surgical therapy were selected by individual criteria based on experience of PET examiner and paediatrician.
  - Individual differences of tracer metabolism
3D-Reconstruction in focal form
Known problems in identifying a focus

• Very small foci
• Very large foci (might be seen as diffuse)
• "Hidden behind other DOPA-accumulating structures"
  – Kidneys
  – Gallbladder
• Very low DOPA-uptake
Importance of DOPA metabolism in CHI

- Variable intensity of focus enhancement
  - Some patients show very low enhancement

**If you don't see it... – doesn't mean it isn't there**

6 mo. old CHI patient

Prior DOPA-PET scan: "showed nearly no uptake in the pancreas"

- Extreme weak uptake of tracer on re-examination
- Maximum sensitivity showed a **small focus** in corpus.
  - Very special DOPA-metabolism in this patient
Position and size of focal lesions?

• Size and position of focal lesions are accurate in 71 – 88% (Treglia, Pediatr. Radiol 2012)
  – Different surgical strategies in different places
  – PET pictures and situation in the operation theatre not always identical
  – No established technique of image-guided CHI surgery

Localization of the focus using intersection points between confluens and focus
Intermediate or mosaic forms of CHI?

- Objective histologic criteria missing
- No data on sensitivity or specificity available
- **All** PET-pictures are altered electronically:

Diffuse CHI?  
4 wk. old boy, CHI  
Intermediate or multifocal CHI?

Same patient – pictures taken with 10 min. time difference
Lasting $^{18}$F-DOPA PET Uptake after Clinical Remission of the Focal Form of Congenital Hyperinsulinism

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Horm Res Paediatr 2011;76:286–290

Fig. 1. $^{18}$F-DOPA PET scans taken at age 8 months (left) and again at 1 year and 10 months (right). Upper panels show coronal images of abdominal PET scans and lower panels show fused axial PET/CT images. The maximal standardized uptake values for these lesions were 5.0 (left) and 6.8 (right), respectively.
Conclusion(s) $^{18}$F-DOPA-PET/CT

- Very good specificity (95 – 98%),
- Good sensitivity (67 – 96%)
  - more false-negative than false-positive results
- Specific problems of $^{18}$F-DOPA-PET/CT:
  - Tracer uptake differences
  - Imaging of tracer uptake without clinical relevance
  - "Missing" of giant foci
- Risk of over-interpretation by the examiners.
  - Age pattern, digital alteration of images

$^{18}$F-DOPA-PET/CT is not perfect – but it is the best we have
Your questions... ????
Dopamine in nerve-cells

• Dopamine is a known neurotransmitter
• 80% of dopamine is inside vesicles
• Dopamine-receptors on cells to transmit signals
• Free dopamine is fast degraded
Auto-/Paracrine regulation durch Dopamin

Glukose → GLUT2 → Glukose-6-phosphat → Glucokinase → Metabolismus → ATP/ADP → K⁺/K⁺-ATPase

Glukosedehydrogenase → NADPH → Glukose-6-phosphat → Glucokinase → Metabolismus → ATP/ADP → K⁺/K⁺-ATPase

Insulin-Sekretgranula → Exozytose → Insulin = Insuline

Dopamin = Dopamine

\[ \text{VMAT 2 = Dopamine transporter} \]

\[ \text{Reduces insuline secretion} \]
so much left to do...