Remission in Non-Operated Patients with Diffuse Disease and Long-Term Conservative Treatment.

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Underlying pathomechanisms of Congenital Hyperinsulinism can have many different faces ...

- Dysregulated insulin secretion mostly uncoupled from the blood glucose concentration
- Inadequate high insulin concentration in turn:
  - Leads to hypoglycemia
  - Blocks the generation of alternate energy substrates
- Threshold for hypoglycemia to cause brain damage is unknown

* Figure from Glaser, Benjamin (2011): Lessons in human biology from a monogenic pancreatic β cell disease. In: *J. Clin. Invest.* 121 (10), S. 3821–3825
Therapeutic options: main strategy according to the underlying histopathology

Background: Rapid diagnosis and consequent therapeutic actions are crucial in order to prevent recurrent episodes of hypoglycemia and long-term damages.

<table>
<thead>
<tr>
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<th>Diffuse form</th>
<th>Focal form</th>
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<tbody>
<tr>
<td>Former times</td>
<td>Surgical treatment</td>
<td>Surgical treatment</td>
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<tr>
<td>Nowadays</td>
<td>Pharmacological treatment ?</td>
<td>Surgical or pharmacological treatment</td>
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* Pictures from: Hardy, Olga T.; Hernandez-Pampaloni, Miguel; Saffer, Janet R.; Suchi, Mariko; Ruchelli, Eduardo; Zhuang, Hongming et al. (2007): Diagnosis and localization of focal congenital hyperinsulinism by 18F-fluorodopa PET scan. In: *J. Pediatr.* 150 (2), S. 140–145.

Increased risk of diabetes due to an endogenous pancreatic insufficiency caused by pancreatectomy.

Serves both the principles of
1) **Nonmaleficence**
2) **Beneficence**
Present data elucidating the probability of remission

Already in the late 90s, an Israeli team examined the probability of remission in non-operated patients under long-term conservative treatment. Findings were interpreted in dependence on the presumed underlying histopathology. *

- **22 patients**
  - 9 x focal form
    - 8 x early remission after 16 +/- 6.2 months
  - 13 x diffuse form
    - only 4 x late remission after 15 - 107 months

Within the focal lesions, high rates of programmed cell death of β-cells could be detected.

⇒ possible explanation for the apparent self-limiting character of focal forms

In 2011, Banerjee and colleagues from Manchester tried to identify prognostic factors for the probability of remission:

**Positive correlation:**
- responsiveness to diazoxide
- absence of identified gene mutations

**No correlation:**
- initial glucose requirement
- birth weight

Comparison of therapeutic approaches in clinical practice

**Definition of remission:** no occurrence of symptomatic hypoglycemia with normal food intake after cessation of all pharmacological treatment.

**Pharmacological treatment** mainly diazoxide as a first step and, if diazoxide fails: octreotide and its analogs.

**Surgical intervention**, especially a near-total pancreatectomy in case of a diffuse form, must be well considered with regards to long-term effects. It may be a helpful device if a focal form is confirmed by a PET-Scan of the pancreas.

Some facts and figures from Düsseldorf describing the remission

Banerjee 2011
average: 101 days for remission
range: 6 days to 7.5 years

25th perc.  75th perc.
30 days    300 days

Odds-Ratio ≈ 3.519

* Data were analysed by means of IBM® SPSS® Statistics for Windows, Version 20.0 (IBM Corporation, Armonk, New York). The p-value of the Odds-Ratio was determined using the Mantel–Haenszel test.
Case report of a non-operated patient with diffuse disease and long-term pharmacological treatment

Case presentation
- male infant „U.K.“ born at 37+2 gestational weeks by caesarean sectio
- second child from consanguineous parents
- 5.320 g weight, 54 cm length → macrosomic
- first postpartal glucose measurement revealed a very low level of 29 mg/dl
  → glucose infusion started

Investigation
- during hypoglycemic episodes, elevated insulin concentrations were found
- at the same time, ketone bodies were undetectable
- defect of the β-oxidation was excluded
  ⇒ characteristic for Congenital Hyperinsulinism

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<tr>
<th>Glukose</th>
<th>Insulin</th>
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<tr>
<td>27 mg/dl</td>
<td>107 mU/l</td>
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<tr>
<td>35 mg/dl</td>
<td>61 mU/l</td>
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Genetic analysis: homozygous KCNJ11 mutation
  → $K_{ATP}$-channelopathy
  → diffuse form

Patient U.K.
Case report of a non-operated patient with diffuse disease and long-term pharmacological treatment

**Therapy**
- as the patient did not show any satisfactory response to diazoxide, octreotide was given subcutaneously
- under drug therapy combined with frequent feedings every 3 hours, the blood glucose level stabilised progressively

**Birth**
Start of octreotide therapy

0 1 2 3 4 5 6 7 8

Time bar of U.K. with age in years

4 years old
Change from octreotide to lanreotide

6 years old
Last injection of lanreotide

7 years old
Evaluation of the fasting tolerance in remission

BMI \(\approx 23.4\) (> 3 SD)

⇒ peripheral insulin resistance may have contributed to the entrance into remission
Structured review on conservative treatment

- We have a good chance for successful longterm treatment
- Lack of clinical studies
- Medline (ab 1947) und Embase (ab1988)
- 1261 patients with congenital hyperinsulinism
  → 619 patients with longterm treatment
  → Side effects for 1039 treatments reported

Aim
- Dosage, duration of treatment, side effects
  → Improved care and counselling (patients, physicians)
Conclusion

Data concerning the remission which have been found in an isolated population of Ashkenazi Jews in Isreal can also be relevant for European patient collectives.

Compared with Manchester, the Düsseldorf patient collective enters later into remission which might be a consequence of a different definition of congenital and transient hyperinsulinism.

Reported cases of diffuse diseases entering late into remission are useful arguments for a long-term conservative treatment.

Although based on just a small number of cases, treatment with octreotide is associated with a high probability of remission in our patients and is therefore a resonable alternative to surgical intervention if diazoxide fails to elevate blood glucose concentration sufficiently.

The probability of remission remains difficult to predict. Identification of prognostic factors and causative mechanisms should be objectives of future research projects.
Thanks a lot for your attention.

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