CLINICAL STUDY

Long-term follow-up of 114 patients with congenital hyperinsulinism

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Abstract

Background: The term congenital hyperinsulinism (CHI) comprises a group of different genetic disorders with the common finding of recurrent episodes of hyperinsulinemic hypoglycemia.

Objective: To evaluate the clinical presentation, diagnostic criteria, treatment and long-term follow-up in a large cohort of CHI patients.

Patients: The data from 114 patients from different hospitals were obtained by a detailed questionnaire. Patients presented neonatally (65%), during infancy (28%) or during childhood (7%).

Results: In 20 of 74 (27%) patients with neonatal onset birth weight was greatly increased (group with standard deviation scores (SDS) > 2.0) with a mean SDS of 3.2. Twenty-nine percent of neonatal-onset vs 69% of infancy/childhood-onset patients responded to diazoxide and diet or to a carbohydrate-enriched diet alone. Therefore, we observed a high rate of pancreatic surgery performed in the neonatal-onset group (70%) compared with the infancy/childhood-onset group (28%). Partial (3%), subtotal (37%) or near total (15%) pancreatectomy was performed. After pancreatic surgery there appeared a high risk of persistent hypoglycemia (40%). Immediately post-surgery or with a latency of several years insulin-dependent diabetes mellitus was observed in operated patients (27%). General outcome was poor with a high degree of psychomotor or mental retardation (44%) or epilepsy (25%). An unfavorable outcome correlated with infancy-onset manifestation ($\chi^2 = 6.1$, $P = 0.01$).

Conclusions: The high degree of developmental delay, in particular in infancy-onset patients emphasizes the need for a change in treatment strategies to improve the unfavorable outcome. Evaluation of treatment alternatives should take the high risk of developing diabetes mellitus into account.

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Introduction

Congenital hyperinsulinism (CHI) is the most common cause for recurrent episodes of hypoglycemia in early childhood (1). Different underlying genetic defects have been described during the previous years (2, 3). Germline mutations are known for the sulfonylurea receptor gene and the Kir6.2 gene affecting the function of the β-cell KATP-channel, as well as for the genes of glutamate dehydrogenase and glucokinase resulting in overactivity of these enzymes. Whereas germline mutations affecting all pancreatic β-cells result in so called ‘diffuse’ disease, somatic recessive disorder is caused by loss of maternal alleles of the imprinted region 11p15 in pancreatic lesions with ‘focal’ adenomatous hyperplasia, and usually a germline mutation on the paternal allele. However, management of patients with CHI still mainly depends on clinical parameters (4, 5). Results from mutational analyses are usually not available when important clinical decisions regarding conservative or surgical treatment have to be made, especially in patients non-responding to diazoxide. However, neither subtotal (80–94% resection) nor near total (>$95%$ resection) pancreatectomy are always sufficient to ensure post-operative euglycemia (6–10). Today, it is known that this might be due to the presence of overlooked focal lesions, especially localized in the head of the pancreas. Besides this, undirected extensive pancreatic resection is associated with a high risk of developing diabetes mellitus (11, 12). An alternative drug for long-term treatment is long-acting somatostatin (octreotide) in addition to a carbohydrate-enriched diet and frequent feedings (13). In this heterogeneous group the choice between surgical and non-surgical treatment for an individual patient is still crucial.

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We conducted a retrospective study that was larger in the number of cases and wider in age groups than most previous studies performed so far. We evaluated the course of 114 patients with CHI with respect to clinical manifestation, diagnostic criteria, management and outcome. These data are discussed with special respect to their impact on recently proposed management strategies (9, 14, 15), including pancreatic venous sampling and intra-operative histology of the pancreas in order to identify focal pancreatic lesions.

Materials and methods

This study was based on the German database on congenital hyperinsulinism located at the Clinic of General Pediatrics, University Children’s Hospital in Düsseldorf, Germany. At present, data from 114 patients (54 females and 60 males) with persistent hyperinsulinism are registered. The patients’ origins are from Germany (91), Turkey (14), Austria (3), The Netherlands (3), Russia (1), Bulgaria (1), and Rumania (1). All metabolic and endocrinologic pediatric centers for CHI participated in this study. Thus, the obtained data are representative for Germany. Whenever possible the data were collected, by one of the authors, based on the medical records and were updated in co-operation with the patients’ parents or the local treating physician. All data were obtained as a cross-sectional profile during the last 4 years by a questionnaire including detailed information on clinical symptoms, laboratory results, diagnostic and therapeutic procedures as well as follow-up findings. Neurologic and mental outcome were assessed by the physicians in charge of each patient usually in co-operation with a pediatric neurologist and psychologist, and were subdivided into three grades: normal, mild or severely abnormal. Neurologic outcome expresses the presence or absence of neurologic abnormalities, such as abnormal reflexes and tone, and represents the degree of motor development. Severely abnormal development was defined as severe abnormality of tone and movement leading to functional impairment and/or a delay in motor development. A mildly abnormal neurologic outcome was defined as a moderate abnormality of tone and movement leading to only minor functional impairment or a minor developmental delay. The mental outcome reflects the intellectual development of the child, as measured by psychological testing and the degree of schooling.

We included patients born between 1975 and 2002. The mean age at the time of analysis was 14 years with a median age of about 11 years. Patients with transient neonatal hyperinsulinism with a spontaneous resolution within the first 3 months of life were not included in this study.

Statistical analysis

The χ² test and Fisher exact test were used to test for the association between categorical variables, and the unpaired t-test was used to assess differences between groups. The results of t-tests were confirmed using the Mann-Whitney test for data that were not normally distributed. Binary logistic regression was used to determine factors predicting neurological outcome. Analyses were performed using SigmaStat version 2.0 (SPSS Inc., Chicago, IL, USA).

Results

Age at onset and presenting symptoms

Patients were attributed to one of three categories related to their onset of clinical symptoms. Those patients with neonatal onset \((n = 74)\) became symptomatic usually within the first 48 h after birth (Table 1). Main symptoms included seizures followed

<table>
<thead>
<tr>
<th>Table 1 Onset of clinical symptoms: different age groups.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Neonatal manifestation</strong> ((n = 74))</td>
</tr>
<tr>
<td>Age of first symptoms</td>
</tr>
<tr>
<td>Median</td>
</tr>
<tr>
<td>Range</td>
</tr>
<tr>
<td>Clinical symptoms</td>
</tr>
<tr>
<td>Seizure</td>
</tr>
<tr>
<td>Apnea</td>
</tr>
<tr>
<td>Hypotonia</td>
</tr>
<tr>
<td>Tremors</td>
</tr>
<tr>
<td>Cyanosis</td>
</tr>
<tr>
<td>Irregular respiration</td>
</tr>
<tr>
<td>Lethargy/changes in level of consciousness</td>
</tr>
<tr>
<td>Sweating</td>
</tr>
<tr>
<td>Poor sucking</td>
</tr>
<tr>
<td>Irritability</td>
</tr>
<tr>
<td>Bradycardia</td>
</tr>
</tbody>
</table>
by lethargy, hypotonia, apnea and tremor (Table 1). Other patients were diagnosed by routine glucose screening for macrosomia or because of prematurity. Patients with infancy onset (1–12 months, \( n = 32 \)) and childhood-onset patients (>12 months, \( n = 8 \)) usually became symptomatic with a hypoglycemic seizure.

### Parameters at birth

Mean gestational age was 38 weeks (with a range of 27 to 42 weeks) and mean birth weight for this gestational age was 3670 g (Fig. 1). There was a bimodal pattern in distribution of birth weight with a subset (27%) of patients with neonatal onset presenting with a birth weight >2.0 SDS (standard deviation scores) and a mean birth weight SDS of 3.2 (Table 2). The ratio for weight and length SDS was about 1.15 in patients with a birth weight >2.0 SDS. Whereas 85% of patients with high birth weight underwent surgery, the rate was 67% for the normal birth weight group (Table 2). However, we did not find significant differences with regard to treatment or neurological outcome between the groups of patients with normal birth weight and macrosomia (Table 2). In patients with neonatal onset the SDS of length and weight at birth were higher than for subjects with manifestation in infancy or childhood \((P = 0.016, P = 0.093 \text{ respectively})\) (Fig. 2).

We did not find any differences with respect to the rate of psychomotor or mental retardation in later life, whether symptomatic hypoglycemia occurred on the first day of life or later during the first week. In addition, we observed a highly increased rate of premature births (20%; 99% confidence interval \((CI_{99}) = 10.5–29.5\)) which is significantly different from the normal population rate of about 5–7%. Reasons for prematurity included a pathological cardiotocogram, preeclampsia, twin gestation or placenta praevia.

### Diagnosis

For the neonatal-onset group diagnosis was usually based on carbohydrate requirement to prevent hypoglycemia (17.6 mg/kg/min; range 12–28). Furthermore, a clearly measurable insulin (>5 mU/l) during hypoglycemia (<2.6 mmol/l) was found for all documented cases (Table 3). The lowest documented glucose concentration was significantly lower in

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**Table 2** Comparison of neonatal onset patients with very high birth weight (>2.0 SDS) and the normal birth weight group.

<table>
<thead>
<tr>
<th>Birth weight</th>
<th>Mean birth weight (g)</th>
<th>Mean gestational age (weeks)</th>
<th>Mean SDS birth weight</th>
<th>Response to diazoxide</th>
<th>Operated patients</th>
<th>Re-operation*</th>
<th>Insulin-dependent diabetes mellitus*</th>
<th>Psychomotor or mental retardation</th>
<th>Epilepsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;2.0 SDS</td>
<td>4676</td>
<td>38.0</td>
<td>3.15</td>
<td>15%</td>
<td>85%</td>
<td>38%</td>
<td>43%</td>
<td>35%</td>
<td>20%</td>
</tr>
<tr>
<td>≤2.0 SDS</td>
<td>3385</td>
<td>38.2</td>
<td>0.25</td>
<td>31%</td>
<td>67%</td>
<td>30%</td>
<td>27%</td>
<td>33%</td>
<td>22%</td>
</tr>
</tbody>
</table>

* The percentages for re-operation rate and insulin-dependent diabetes are based on the operated patients.
the neonatal-onset patients compared with infancy/childhood-onset patients ($P < 0.001$).

**Treatment**

After diagnosis a therapeutic trial with diazoxide was usually introduced. A total number of 47 patients responded to diazoxide (up to 15 mg/kg/day) and were long-term treated with this drug. Severe side effects were not observed. In one patient, diazoxide was discontinued due to sinus tachycardia, in another two patients it was discontinued due to recurrent rush or severe anaphylactic reaction. Transient disturbances of serum electrolytes or edema were observed frequently. The patients who did not respond to diazoxide were usually operated patients. Only two patients were on a long-term treatment with octreotide. In the group of patients with neonatal onset and pancreatic surgery the time of surgery was highly variable: 40% (21) of the patients were operated on within the first 2 months of life but 25% (13) of the patients were operated on as late as after 6 months of age (Fig. 3). Furthermore, various amounts of pancreatic tissue were removed during initial surgery (Fig. 4): a small part of the organ confined to a focal adenomatous hyperplasia, 80–94% of the pancreas (subtotal resection), or >95% of the pancreas (near total resection). Only 27% of all operated patients achieved stable long-term euglycemia after surgery without the need of further surgery or the development of hyperglycemia. In patients with subtotal pancreatectomy, the need for re-operation was similar as in patients who initially had a near-total pancreatectomy (Table 4).

**Outcome**

In general, a high frequency (44%) of neurodevelopmental retardation was observed (Table 5). A broad differentiation into two groups revealed severe retardation in 18% and mild retardation in 26% of patients. Furthermore, 25% of all patients suffered from epilepsy. There was a higher incidence of mental retardation in the group of patients with infancy onset compared with the neonatal-onset group ($\chi^2 = 6.1$, degrees of freedom = 1, $P = 0.01$). For further analyses, patients were divided into a group with psychomotor or mental retardation and a group with normal development/normal intelligence (Table 6). Birth weight or lowest documented glucose concentration were not significantly different for both groups. Lack of euglycemia after pancreatic surgery was a risk
factor for mental retardation (CI 90% = 1.34–48.1; Fisher exact test: \( P = 0.04 \)).

All cases of insulin-dependent diabetes mellitus have occurred so far in the group of operated patients and in patients with neonatal onset of hyperinsulinism. The incidence of diabetes mellitus was particularly high after re-operation due to persistent hyperinsulinemic hypoglycemia (71%). Insulin-dependent diabetes mellitus occurred most often either in the first year after pancreatectomy or between the age of 12 and 16 years. In seven patients diabetes mellitus was recognised before puberty and in 10 patients during puberty. In the group of operated patients without apparent diabetes mellitus the mean follow-up time was 6.6 years; one patient had finished puberty, two patients were at the end of puberty.

In general, in the course of treatment all patients showed a tendency to normalization of their body weight and length (Fig. 5). Apparently, neither long-term octreotide treatment (\( n = 2 \)) nor a potential exocrine pancreatic insufficiency (\( n = 24 \) precautionarily substituted with pancreatic enzymes) had a major influence on growth.

### Discussion

In this study we performed a retrospective analysis of clinical and laboratory data and evaluated clinical presentation, diagnostic criteria, therapeutic approaches as well as outcome in 114 patients with CHI. Analysis focused on the characterization of the clinical phenotype of this heterogeneous disease and an evaluation of the factors predisposing for developmental delay. Patients may present during pregnancy with macrosomia and we found a significantly increased birth weight in the patients with neonatal onset of hyperinsulinism but not in patients with infancy or childhood onset. Insulin is known to promote anabolism in the fetus and an increased mean birth weight can be explained by prenatal hyperinsulinism and an unlimited fuel supply by the mother.

Of note, distribution of birth weight of the patients with neonatal onset was not only shifted to a higher mean birth weight, but a bimodal pattern of distribution was also evident with a second peak for patients presenting with a high birth weight > 2.0 SDS and a mean SDS of 3.15. It seems likely that this increased birth weight in such affected patients reflects severe prenatal hyperinsulinism caused by \( K_{ATP} \) channel defects. However, compared with the remaining neonatal patients no increased severity could be demonstrated with respect to clinical course or outcome. The marked differences in birth weights might be caused by different rates of glucose crossing the placenta by facilitated diffusion along a concentration gradient between maternal and fetal plasma. Macrosomia was only a finding during the neonatal period and the first months of life. After adequate treatment a general tendency to normalization of weight as well as length was observed. The mean data revealed a normal distribution in percentile ranges at the time of the last clinical visit.

Diagnosis in neonatal-onset patients is usually established by a high carbohydrate (> 15 mg/kg/min) intake to prevent hypoglycemia (5). In our group of patients glucose requirements ranged from 12 to 28 mg/kg/min indicating that a level > 12 mg/kg/min
is already highly suspicious for hyperinsulinism. In addition, further blood tests were performed during hypoglycemia. It was further observed that in all tested individuals insulin was clearly measurable at the time of hypoglycemia. Once the diagnosis was confirmed, the first choice of treatment is diazoxide since this drug is orally administered and therefore suitable for long-term treatment. We found an adequate response to diazoxide and/or a carbohydrate-rich diet in 29% of the neonatal-onset group and in 69% of the patients with post-neonatal manifestation. This rate is higher for the patients with neonatal onset compared with a French cohort of patients, where only 16% of neonates responded to diazoxide (9, 15, 16). Nevertheless, even in diazoxide-responsive patients, further diagnostic procedures to identify a focal lesion have to be considered, since only enucleation of a focal lesion will really cure these patients (17). However, this recommendation does not include patients with moderate hyperammonemia who are highly suspicious for a hyperinsulinism/hyperammonemia syndrome (18) caused by germline mutations in Table 4 Operative treatment in CHI patients.

<table>
<thead>
<tr>
<th>Pancreatectomy</th>
<th>Initial operation</th>
<th>Re-operation</th>
<th>Insulin-dependent diabetes mellitus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partial (focal lesion)</td>
<td>3</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Subtotal (80–94%)</td>
<td>43</td>
<td>12</td>
<td>12*</td>
</tr>
<tr>
<td>Near-total (≥95%)</td>
<td>17</td>
<td>5</td>
<td>5</td>
</tr>
</tbody>
</table>

* 10 of 12 after re-operation.

Table 5 Management and outcome in patients with respect to onset of symptoms.

<table>
<thead>
<tr>
<th></th>
<th>Neonatal (n = 74)</th>
<th>Infantile (n = 32)</th>
<th>Childhood (n = 8)</th>
<th>Total (n = 114)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Operative treatment</td>
<td>70%</td>
<td>25%</td>
<td>38%</td>
<td>55%</td>
</tr>
<tr>
<td>Non-surgical treatment</td>
<td>30%</td>
<td>75%</td>
<td>62%</td>
<td>45%</td>
</tr>
<tr>
<td>Neuro-developmental retardation</td>
<td>34%</td>
<td>63%</td>
<td>50%</td>
<td>44%</td>
</tr>
<tr>
<td>Mild</td>
<td>20%</td>
<td>40%</td>
<td>25%</td>
<td>26%</td>
</tr>
<tr>
<td>Severe</td>
<td>14%</td>
<td>23%</td>
<td>25%</td>
<td>18%</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>22%</td>
<td>27%</td>
<td>50%</td>
<td>25%</td>
</tr>
</tbody>
</table>

Table 6 Relationship of different clinical features, psychomotor retardation and normal psychomotor development.

<table>
<thead>
<tr>
<th></th>
<th>Psychomotor or mental retardation</th>
<th>Normal psychomotor development</th>
<th>Odds ratio and 95% confidence interval</th>
<th>Statistical significance (P) of differences between psychomotor retardation and normal development group (by t-test/Mann–Whitney test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonatal onset</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (%)</td>
<td>36.7</td>
<td>66.1</td>
<td>3.38 (1.37–8.34)</td>
<td></td>
</tr>
<tr>
<td>No (%)</td>
<td>63.3</td>
<td>33.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Response to diazoxide</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (%)</td>
<td>34.3</td>
<td>49.2</td>
<td>1.86 (0.79–4.35)</td>
<td></td>
</tr>
<tr>
<td>No (%)</td>
<td>65.7</td>
<td>50.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Operative treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (%)</td>
<td>51.2</td>
<td>54.9</td>
<td>1.16 (0.54–2.51)</td>
<td></td>
</tr>
<tr>
<td>No (%)</td>
<td>48.8</td>
<td>45.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extent of pancreatectomy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subtotal (%)</td>
<td>88.2</td>
<td>67.6</td>
<td>0.28 (0.05–1.44)</td>
<td></td>
</tr>
<tr>
<td>Near total (%)</td>
<td>11.8</td>
<td>32.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postoperative euglycemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (%)</td>
<td>5.0</td>
<td>29.7</td>
<td>8.04 (0.65–67.66)</td>
<td></td>
</tr>
<tr>
<td>No (%)</td>
<td>95.0</td>
<td>70.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Re-operation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (%)</td>
<td>23.8</td>
<td>30.8</td>
<td>1.4 (0.42–7.78)</td>
<td>0.91</td>
</tr>
<tr>
<td>No (%)</td>
<td>76.2</td>
<td>69.2</td>
<td></td>
<td>0.27</td>
</tr>
<tr>
<td>Birth weight (SDS ± S.E.M.)</td>
<td>0.87 ± 0.28</td>
<td>0.83 ± 0.22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lowest documented glucose concentration (mmol/l; median)</td>
<td>1.43</td>
<td>1.43</td>
<td></td>
<td></td>
</tr>
<tr>
<td>First operation (day of life; mean ± S.E.M.)</td>
<td>360 ± 98</td>
<td>115 ± 19</td>
<td></td>
<td>0.10</td>
</tr>
</tbody>
</table>
recently developed management recommendation by
in adequate management will be achieved by the
improve-
difficulty of achieving euglycemia by pancreatic surgery
missed by blind pancreatic resections, and the general
glycemia. The main reasons might include the fact
which also did not always result in eliminating hypo-
surgery. The consequence was a high rate of re-surgery,
yielding euglycemia in only 27% of patients after initial
success of pancreatic surgery was not satisfactory,
thermore, we do not know the real incidence of focal
lesions in our patient group since there was a lack of
histological differentiation between focal or dif-
performed without prior investigation localizing a
local lesion, e.g. by pancreatic venous sampling. Fur-
more, we do not know the real incidence of focal
lesions in our patient group since there was a lack of
a clear histological differentiation between focal or dif-
fuse forms in some cases. Probably the ‘blind’ pancrea-
tic resections are one of the reasons why the overall
success of pancreatic surgery was not satisfactory,
yielding euglycemia in only 27% of patients after initial
surgery. The consequence was a high rate of re-surgery,
which also did not always result in eliminating hypo-
glycemia. The main reasons might include the fact
that focal lesions in the head of the pancreas may be
missed by blind pancreatic resections, and the general
difficulty of achieving euglycemia by pancreatic surgery
in patients with diffuse pancreatic disease. An improve-
ment in adequate management will be achieved by the
recently developed management recommendation by
the ENRHI (European Network of Research in Hyperin-
sulinism) which proposes pancreatic venous sampling
prior to surgery (4, 15, 23, 24). If no focal lesion is
found during this procedure and a diffuse disease is
likely, long-term octreotide treatment has to be con-
sidered, especially since after near total pancreatectomy
or recurrent operations the risk of developing insulin-
dependent diabetes mellitus is known to be greatly
increased, especially after puberty (11, 12). At present,
the overall incidence of insulin-dependent diabetes is
about 27% for all operated patients after a mean
follow-up period of 11 years. This rate is expected to
increase noticeably with time, since most of the non-
diabetic patients have not completed puberty. Diabetes
mellitus was particularly high after re-operation
(71%). Of note, diabetes has so far occurred only in
the group of neonatal-onset patients. This might be
due to several factors: many fewer patients with post-neonatal onset were operated on; the extent of
pancreatectomy was smaller; and the severity of hyperinsulinism may influence the rate of apoptosis
of pancreatic β-cells. At the time of analysis only one
of the patients with post-neonatal onset had completed puberty. The rate of diabetes might be
reduced in future by improved acceptance and success
of alternative octreotide treatment. This might be facili-
tated by the use of s.c. pumping systems with continu-
os application of the drug and lack of recurrent
s.c. injections.

Finally, but most important the mental outcome in
our patients showed a high degree of psychomotor or
mental retardation. This rate was particularly increased
in patients with infancy onset which is different from
the patients reported by the French group where
mental retardation occurred especially after neonatal
onset of hyperinsulinism (25). Differences in the
groups of patients in both studies may have contributed
to these results. Patients presented here are from all
kinds of different hospitals all over Germany, whereas
in the French study patients are from one single
center in Paris with a great reputation for the treatment
of hyperinsulinism. Therefore, in the French report
more severe cases from the whole of France and even
Europe might have been included. In addition, we
found patients with a syndromal type of disease
presenting during infancy, and one major symptom of
these patients included severe mental retardation (26).
These findings suggest that mental retardation might
not always be primarily and exclusively caused by
hyperinsulinism. Another study performed in Argentina
reported neurological impairment in 10 of 26 children
with CHI (27), whereas a study from Greece which
followed up 13 CHI patients reported a good neurologi-
cal outcome without any psychomotor retardation (28).
The latter patients were mostly treated with drugs and
only in two of 15 patients was pancreatectomy per-
formed. This patient group probably represents a milder clinical phenotype.

GLUD1. Blood ammonia concentrations were not
systematically screened in our patients, but we recently
reported mutational analysis data of 14 patients
from seven families with hyperinsulinism/hyperammon-
emia syndrome (19). This condition seems not to be
associated with focal pancreatic disease (20, 21).
In most patients non-responding to diazoxide, pan-
creatic surgery was performed. Only in two of them
was an initial long-term treatment with the long-acting
somatostatin analog, octreotide, initiated. Combination
drug regimens were only used in single patients. In rare
cases diazoxide, chlorothiazide, octreotide or nifedepin
were used in combination. However, no representative
data about the success of such combinations are
available. Only two patients with a mild clinical form
responded to nifedepin (22). Therefore, in more than
half of all patients a pancreatic resection was per-
formed. Since this follow-up study represents a time
period over the last two decades surgery was usually
performed without prior investigation localizing a
focal lesion, e.g. by pancreatic venous sampling. Fur-
more, we do not know the real incidence of focal
lesions in our patient group since there was a lack of
a clear histological differentiation between focal or dif-
fuse forms in some cases. Probably the ‘blind’ pancrea-
tic resections are one of the reasons why the overall
success of pancreatic surgery was not satisfactory,
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missed by blind pancreatic resections, and the general
difficulty of achieving euglycemia by pancreatic surgery
in patients with diffuse pancreatic disease. An improve-
ment in adequate management will be achieved by the
recently developed management recommendation by

Figure 5 Weight development with weight percentiles at birth and
at the last visit. Patients are divided into percentile (Pc) groups.
Lines indicate the changes over time.
It is well known already that transient neonatal hypoglycemia or rare episodes of hypoglycemia of other causes are associated with neurodevelopmental deficits (29, 30). However, it is still surprising that despite early treatment in specialized units some patients with CHI develop severe mental deficits (25). Next to the problems that still exist in completely preventing episodes of hypoglycemia, a general influence of the underlying defect on the central nervous system function cannot be completely excluded. Mutational analyses are not available for most of our patients, but at least one protein that has been shown to be involved in the etiology of hyperinsulinism, the sulfonlurea receptor, is also present in the brain and dysfunction might contribute to the clinical course, in particular with respect to seizure disorders (31, 32).

In conclusion, our data show neurodevelopmental deficits in 44% of the patients, lack of euglycemia after pancreatic surgery in 73% of operated patients and a diabetes rate of 27% which is expected to increase with time. However, the long-acting somatostatin analog, octreotide, was rarely used and also the preparative localizing of focal pancreatic lesions was barely realized. Furthermore, in the acute episode after initial manifestation even in individuals suffering from severe hyperinsulinism, normal glucose concentration can be achieved today by continuous carbohydrate supply and the use of glucagon or somatostatin. Therefore, improvement in the outcome of CHI patients might be achieved in future by increasing the awareness of the disease to achieve an early diagnosis, followed by an adequate treatment with definition of the anatomical lesion (focal or diffuse) prior to surgery and restriction of pancreatectomy to the minimal region necessary in the case of a focal lesion. Further substantial medical progress in the understanding and management of this heterogeneous disease now requires long-term prospective multidisciplinary international trials.

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