Forty patients with persistent, non-focal congenital hyperinsulinism: Urgent need for new treatment modalities

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BACKGROUND

Congenital hyperinsulinism (CHI) may be divided in focal, diffuse and atypical CHI. While focal CHI is cured surgically, non-focal CHI is a much greater challenge to manage. We aimed to review the medical and surgical treatment of non-focal CHI in a consecutive cohort of patients at one international CHI center, to evaluate the need for improved treatment options.

SUBJECTS AND METHODS

Retrospective evaluation of the treatment and outcome of a cohort of 40 patients with non-focal, persistent CHI admitted to the International Hyperinsulinism Center, Denmark from January 2000 to May 2017. The patients were referred from Denmark, Norway, Sweden, Latvia, Russia, Ukraine, Kazakhstan, Belarus and Greenland. In case of no surgery, diffuse CHI was defined by genetics and/or 18F-DOPA PET/CT. Problematic treatment status at last follow-up was defined as lack of hypoglycemia control, severe medical side effects, tube feeding, or diabetes.

RESULTS

• Baseline
  Mutations found: 52.5% (n = 21), TABLE 1
  55% could not be managed with medical monotherapy (diazoxide or octreotide).
  Severe potential side effects to medication: 15%

• Surgery
  Surgically treated: 43% (n = 17). Extend of pancreatic resection median 90%, range 66%-98%
  Early post-surgical complications: 5.9% (n = 1)
  Surgically treated patients had more frequently \( K_{ATP} \)-channel mutations \((p = 0.013)\), highly severe disease \((p = 0.025)\) and clinical onset <30 days of age \((p = 0.004)\).

• Follow-up
  Follow-up median (range) age: 5.3 (0.3-31.3) years
  Patients receiving treatment at last-follow up: 80% (n = 32), including 12/17 (71%) with surgery.
  Diabetes post-surgically: n = 1 (98% pancreatic resection).
  Problematic treatment status: 17.5% (n = 7). FIGURE 1
  Clinical remission: 20% (n = 8) (conservative, n=3, surgical, n=5)

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CONCLUSION

Persistent, non-focal CHI remains difficult to manage. Neurological impairment in 30% suggests a frequent failure of prompt and adequate treatment. A high rate of problematic treatment status at follow-up demonstrates an urgent need for new medical treatment modalities.

TABLE 1: Mutations and histology in non-focal CHI

<table>
<thead>
<tr>
<th>Mutations</th>
<th>All</th>
<th>Surgery</th>
<th>No surgery</th>
<th>Predicted diffuse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Homozygous</td>
<td>18</td>
<td>12</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Compound heterozygous</td>
<td>9</td>
<td>8</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Heterozygous</td>
<td>8</td>
<td>3</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Paternal</td>
<td>4</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Maternal</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>De novo</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>GU1-1</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NU2-1</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11p15UPD</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>19</td>
<td>1</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>40</td>
<td>13</td>
<td>4</td>
<td>8</td>
</tr>
</tbody>
</table>

* by genetics and/or 18-DOPA

FIGURE 1: Treatment status at last follow-up

Problematic: lack of hypoglycemia control, severe medical side effects, tube feeding, or diabetes.

FIGURE 2: Patients with neurological impairment at last follow-up

Neurological impairment: presence of psychomotor retardation, epilepsy, cerebral palsy or blindness.