One year r-GH therapy influence on blood gamma-amino-butyric acid, serotonin, dopamine and IGF-1 in 15 growth-hormone deficient children

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Graphical Abstract
**Abstract:**

**Aim:** To quantify the effect of 1 year r-GH therapy on blood gamma-amino-butyric acid (GABA), serotonin (5-HT), dopamine (DA) and IGF-1 in 15 growth hormone (GH) deficient children.

**Research design and methods:** This retrospective study included 8 boys (7-14 years) and 7 girls (7-14 years) with clinically established GH deficit and under GH replacement therapy. In 2016 they were quantified for GABA, DA, 5-HT and IGF-1. After 1 year again of GH therapy they were once more tested for the same parameters using analytical methods.

**Results:** Median plasma parameters in 8 boys pre- vs. post-GH therapy was: GABA: 59.44 vs. 105.83ng/mL; 5-HT: 269.66 vs. 196.55ng/mL; DA: 46.66 vs. 91.5pg/mL; IGF-1: 367.38 vs. 445.5ng/mL. The same parameters were tested in 7 girls as median pre- vs. post-GH therapy: GABA: 45 vs. 96ng/mL; 5-HT: 215 vs. 200ng/mL; DA: 40 vs. 60pg/mL; IGF-1: 284 vs. 420ng/mL. We established statistical significant differences in boys group pre- and post-treatment in: plasma GABA (P<0.001), serum 5-HT (P<0.01), plasma DA (P<0.02), serum IGF-1 (P=0.02). In girls group we calculated statistical significant differences in plasma GABA pre- vs. post-therapy (P<0.001) and in plasma DA pre- vs. post-therapy (P>0.02).

**Conclusions:** In fact replacement GH-therapy improved GABA/5-HT, GABA/DA, GABA/IGF-1, 5-HT/IGF-1 correlations in boys group. In girls group we estimated improved correlations between GABA/DA, 5-HT/DA, 5-HT/IGF-1. These observations could be translated in general improvement of health state in growth deficient children under GH-therapy.

**Key words:** GH deficient children, GH replacement therapy, gamma-amino-butyric acid (GABA), serotonin (5-HT), dopamine (DA)
Introduction

• GH secretion from the pituitary is under neural control from the hypothalamus through at least three hypophysiotropic factors: GHRH, somatostatin (SRIF) and Ghrelin.
• GHRH and SRIF release are controlled by a complex neuronal network, in which α-adrenergic, dopaminergic and serotonergic signals stimulate GH secretion.
• Growth hormone (GH) is essential for body growth during childhood and continues to stimulate anabolic processes in adults.
• GH exerts its anabolic effects largely indirectly via stimulation of insulin-like growth factor-1 (IGF1) production.
• Components of the GH–IGF1 axis make an important contribution to the development, function, and proliferation of different tissues.
The aim of the present study was to get information concerning the effects of one-year r-GH replacement therapy in 2 groups of children (8 boys and 7 girls) on blood markers by quantification: gaba aminobutyric acid (GABA), serotonin (5-HT), dopamine (DA) and IGF-1 before and after treatment.
Results and discussion

- This retrospective study included 8 boys (7-14 years) and 7 girls (7-14) with clinically established GH deficit and under GH replacement therapy.
- In 2016 they were quantified for plasma GABA, DA and serum 5-HT, IGF-1.
- After 1 year GH therapy (2017) they were again tested for the same parameters using analytical methods.
- All subjects collected in the morning at 9 am (after an overnight fasting, free of drugs) 2 samples of plasma (into EDTA vacutainers) and a sample of total blood.
After centrifugation, plasma and serum samples were aliquotted and stored at -20°C until assayed.

Plasma GABA, DA and serum 5-HT were evaluated by research Elisa methods.

Serum IGF-1 was evaluated by a chemiluminescent method.

Statistical processing of data was done using MedCalc Software version 14.8.1.
Range, medians, statistical significance, percentage increase/decrease for all 4 parameters were established both in boys and girls group before and after r-GH replacement therapy (Table 1,2; Fig.1,2,3).

- Median GABA in boys before and after treatment: 59.44 vs. 105.83 had a percentage increase of 77% (P<0.001).
- Median GABA in girls before and after treatment: 45 vs. 96 had a percentage increase of 113% (P<0.001).
- Median 5-HT in boys before and after treatment: 269.66 vs. 196.55 had a percentage decrease of 27% (P<0.01).
- Median 5-HT in girls before and after treatment: 215 vs. 200 had a percentage decrease of 7% (NS).
- Median DA in boys before and after treatment: 46.66 vs. 97.94 had a percentage increase of 110% (P < 0.02)
- Median DA in girls before and after treatment: 40 vs. 60 had a percentage increase of 50% (P > 0.02)
- Median IGF-1 in boys before and after treatment: 364.50 vs. 442.27 had a percentage increase of 21% (P = 0.02)
- Median IGF-1 in girls before and after treatment: 284 vs. 420 had a percentage increase of 47% (NS)
• Pearson coefficients between the 4 parameters in boys/girls are shown in Table 2.
• Good correlation coefficients were calculated in boys before and after treatment for GABA (R=0.77); 5-HT (R=0.66); IGF-1 (0.95).
• In girls, good correlation coefficients were established before and after treatment for 5-HT (0.71); DA (R=0.73); IGF-1 (0.66).
• Our selected group of GH deficient children (8 boys and 7 girls) after one-year of rh-GH replacement therapy showed a remarkable percentage increase in GABA values both in boys and girls together with an increase in DA values and IGF-1 values in both selected groups
• These results are in line with new data from the literature
• The GH-releasing effect of GABA in humans may occur through activation of dopaminergic pathways; GABA would activate DA release at a site inside the blood-brain barrier (BBB)
• Both hormones GH and IGF-1 stimulated linear growth
• GABAB receptors are involved in cognitive processes and in animal experiments has been reported to reverse age-related impairments of learning and memory functions
• GABAB receptors are expressed in the pituitary and have been suggested to be involved in regulation of GH release
• Furthermore, activation of GABAB receptors has been shown to protect neurons from apoptosis via a transactivation of the IGF-IR
• IGF1-independent actions mediated through GH receptor are the proliferation of chondrocyte stem cells at bone growth plate or direct stimulation of neural stem cells to proliferate
• The growth hormone insulin-like growth factor-1 system induces neurogenesis and increases brain plasticity
• GH is essential for growth but also modulates protein, lipid and carbohydrate metabolism
• Replacement therapy with GH has beneficial effects on body composition, bone turnover, cardiovascular risk factors and quality of life
Conclusions

- The major role of growth hormone (GH) during childhood is to promote bone growth and linear growth, but GH continues to have important metabolic actions throughout life.
- The growth hormone insulin-like growth factor-1 system induces neurogenesis and increases brain plasticity.
- Our biochemical study showed an improvement of GABA/DA/IGF-1 axis after one year of rh-GH therapy in a selected group of GH deficient children with a direct impact on bone growth and linear growth and on both mental and emotional well-being.
Bibliography

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Table 1 - Range/median of GABA, 5-HT, DA, IGF-1 in 15 children GH-deficient before and after 1 year GH replacement therapy

<table>
<thead>
<tr>
<th>15 SUBJECTS 8 BOYS/7 GIRLS</th>
<th>GABA Median/ Range</th>
<th>5-HT Median/ Range</th>
<th>DA Median/ Range</th>
<th>IGF1 Median/ Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>BOYS Before treatment</td>
<td>59.44 37-105</td>
<td>269.66 158-385</td>
<td>46.66 24-70</td>
<td>364.50 84-643</td>
</tr>
<tr>
<td>After treatment</td>
<td>105.83 46-183</td>
<td>196.55 131-273</td>
<td>97.94 58-205</td>
<td>442.27 135-747</td>
</tr>
<tr>
<td>T-TEST</td>
<td>P &lt; 0.001</td>
<td>P &lt; 0.01</td>
<td>P &lt; 0.02</td>
<td>P = 0.02</td>
</tr>
<tr>
<td>GIRLS Before treatment</td>
<td>45 37-63</td>
<td>215 66-553</td>
<td>40 20-91</td>
<td>284 196-511</td>
</tr>
<tr>
<td>After treatment</td>
<td>96 74-118</td>
<td>200 83-361</td>
<td>60 35-80</td>
<td>420 249-558</td>
</tr>
<tr>
<td>T-TEST</td>
<td>P &lt; 0.001</td>
<td>NS</td>
<td>P &gt; 0.02</td>
<td>NS</td>
</tr>
</tbody>
</table>
**Table 2- Percentage increase/decrease of the 4 parameters after rh-GH therapy and correlation coefficients between parameters before and after therapy**

<table>
<thead>
<tr>
<th>SUBJECTS</th>
<th>GABA</th>
<th>5-HT</th>
<th>DA</th>
<th>IGF-1</th>
</tr>
</thead>
<tbody>
<tr>
<td>8 Boys Before- rh-GH</td>
<td>59.44</td>
<td>269.66</td>
<td>46.66</td>
<td>364.5</td>
</tr>
<tr>
<td>After- rh-GH</td>
<td>105.83</td>
<td>196.55</td>
<td>97.94</td>
<td>442.27</td>
</tr>
<tr>
<td>% Increase</td>
<td>77</td>
<td>-</td>
<td>110</td>
<td>21</td>
</tr>
<tr>
<td>% Decrease</td>
<td>-</td>
<td>27</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Pearson coefficient</td>
<td>0.80</td>
<td>0.66</td>
<td>-0.36</td>
<td>0.95</td>
</tr>
<tr>
<td>7 Girls Before- rh-GH</td>
<td>45</td>
<td>215</td>
<td>40</td>
<td>284</td>
</tr>
<tr>
<td>After rh-GH</td>
<td>96</td>
<td>200</td>
<td>60</td>
<td>420</td>
</tr>
<tr>
<td>% Increase</td>
<td>113</td>
<td>-</td>
<td>50</td>
<td>47</td>
</tr>
<tr>
<td>% Decrease</td>
<td>-</td>
<td>7</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Pearson coefficient</td>
<td>-0.31</td>
<td>0.71</td>
<td>0.73</td>
<td>0.66</td>
</tr>
</tbody>
</table>
Fig. 1-Median values in 8 boys GH deficient before and after 1-year rh-GH replacement therapy
Fig. 2-Median values in 7 girls GH deficient before and after 1-year rh-GH replacement therapy.
FIG. 3 - Percentage increase/decrease of the evaluated parameters after rh-GH replacement therapy in the examined subjects

- 5HT: Girls = 7, Boys = 28
- IGF1: Girls = 22, Boys = 47
- DA: Girls = 50, Boys = 106
- GABA: Girls = 113, Boys = 72