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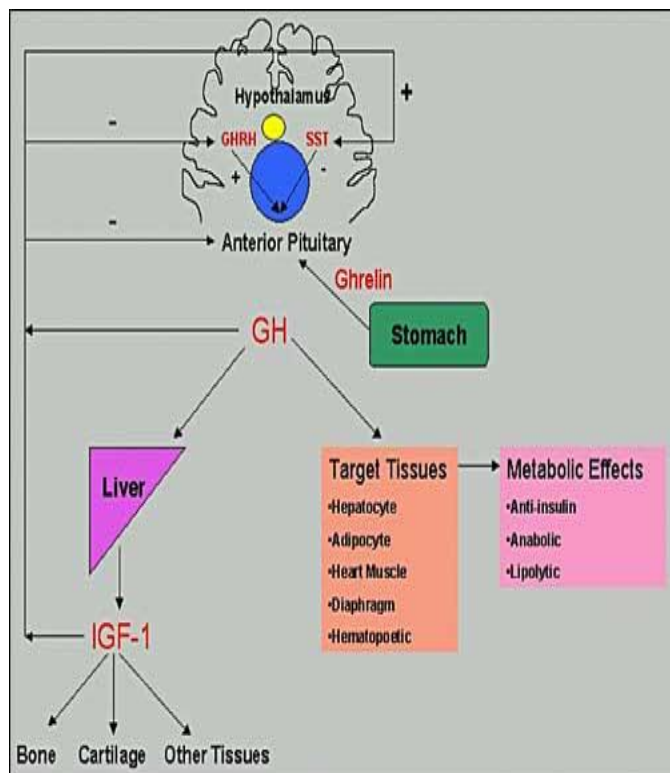
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# One year r-GH therapy influence on blood gamma-amino-butyric acid, serotonin, dopamine and IGF-1 in 15 growth-hormone deficient children

## Graphical Abstract



**GABA/DA/IGF1 >>**



**rh - GH**



## 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 (7-14years) and 7 girls (7-14years) 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  $\alpha$ -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(8boys and 7girls)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 (7-14years) 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 aliquoted 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 *Table2***
- **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

- Yuzuru Kato et al., Regulation of human GH secretion and its disorders ; *Internal Medicine* 41:7-13, 2002
- Rozario KS, Lloyd C, Ryan F. Gh and Igf-1 Physiology in Childhood. [Updated 2015 Nov 20]. In: De Groot LJ, Chrousos G, Dungan K, et al., editors. *Endotext* [Internet])
- M.P.Kawa et al, The Impact of Growth Hormone Therapy on the Apoptosis Assessment in CD34+ Hematopoietic Cells from Children with Growth Hormone Deficiency, *Int J Mol Sci.* 2017 Jan; 18(1): 111
- Hao Zhang et al. The Effect and Mechanism of Growth Hormone Replacement on Cognitive Function in Rats with Traumatic Brain Injury *PLOS ONE* | 2014 | Volume 9 | Issue 9
- Receptors and Sites of Synthesis and Storage of  $\gamma$ -Aminobutyric Acid in Human Pituitary Glands and in Growth Hormone Adenomas Katrin End, Katia Gamel-Didelon et al. *Am J Clin Pathol* 2005;124:550-558
- Devesa J, Devesa P, Reimunde P. Growth hormone [revisited] *MedClin(Barc)* 2009doi:10.1016/j.medcli.2009.10.017.
- A.Gronbladh 2013. Growth hormone and anabolic androgenic steroids: effects on neurochemistry and cognition-Digital comprehensive summaries of Uppsala dissertations from the Faculty of Pharmacy 175.73pp



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

<b>15 SUBJECTS 8 BOYS/ 7 GIRLS</b>	<b>GABA Median/ Range</b>	<b>5-HT Median/ Range</b>	<b>DA Median/ Range</b>	<b>IGF1 Median/ Range</b>
<b>BOYS Before treatment</b>	<b>59.44 37-105</b>	<b>269.66 158-385</b>	<b>46.66 24-70</b>	<b>364.50 84-643</b>
<b>After treatment</b>	<b>105.83 46-183</b>	<b>196.55 131-273</b>	<b>97.94 58-205</b>	<b>442.27 135-747</b>
<b>T-TEST</b>	<b>P &lt; 0.001</b>	<b>P &lt; 0.01</b>	<b>P &lt; 0.02</b>	<b>P = 0.02</b>
<b>GIRLS Before treatment</b>	<b>45 37-63</b>	<b>215 66-553</b>	<b>40 20-91</b>	<b>284 196-511</b>
<b>After treatment</b>	<b>96 74-118</b>	<b>200 83-361</b>	<b>60 35-80</b>	<b>420 249-558</b>
<b>T-TEST</b>	<b>P &lt; 0.001</b>	<b>NS</b>	<b>P &gt; 0.02</b>	<b>NS</b>



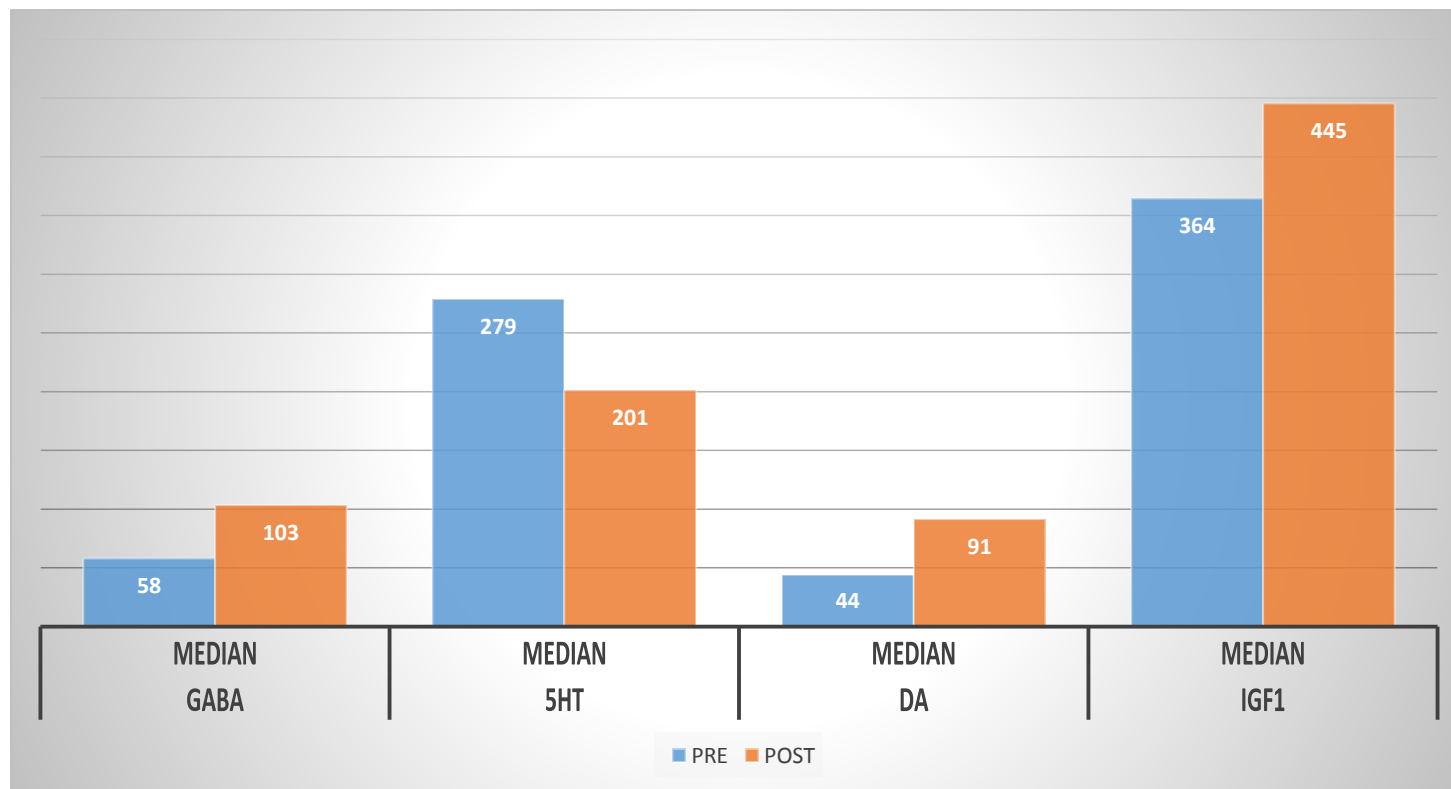


**Table 2- Percentage increase/decrease of the 4 parameters after rh-GH therapy and correlation coefficients between parameters before and after therapy**

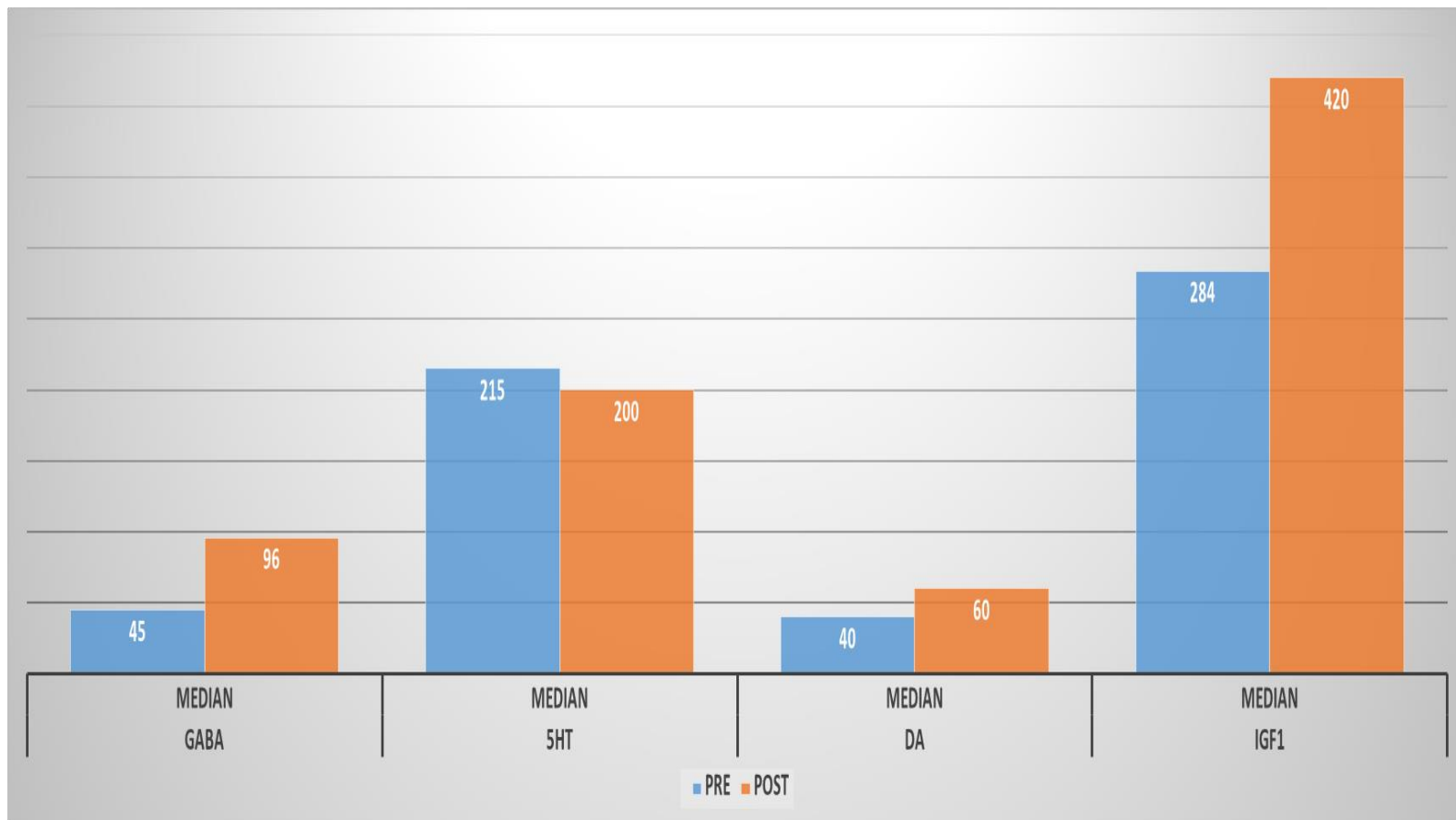
SUBJECTS	GABA	5-HT	DA	IGF-1
8 Boys Before- rh-GH	59,44	269,66	46,66	364.5
After- rh-GH	105.83	196,55	97,94	442.27
% Increase	77	-	110	21
% Decrease	-	27	-	-
Pearson coefficient	0.80	0.66	- 0.36	0.95
7 Girls Before- rh-GH	45	215	40	284
After rh-GH	96	200	60	420
% Increase	113	-	50	47
% Decrease	-	7	-	-
Pearson coefficient	- 0.31	0.71	0.73	0.66



**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**

