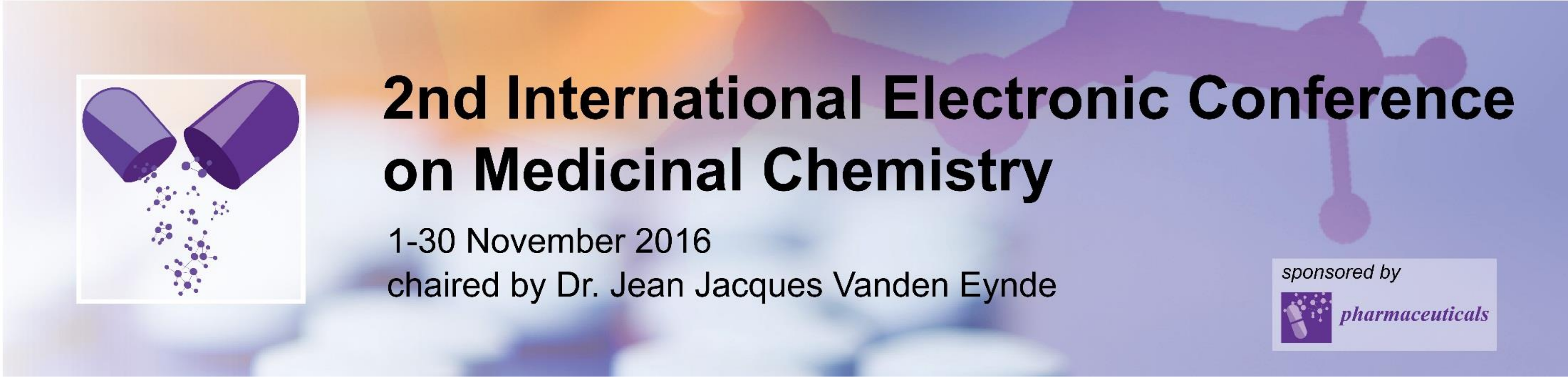

Plasma neurotransmitters variation in growth hormone deficient children under rh-GH replacement therapy. Preliminary data

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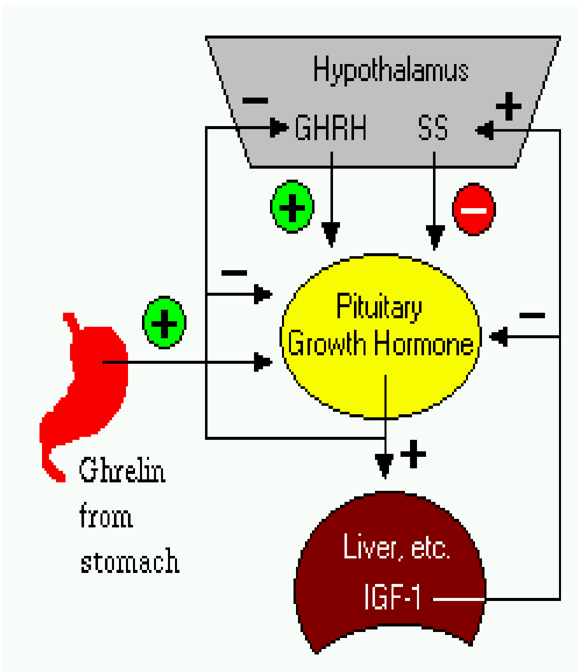
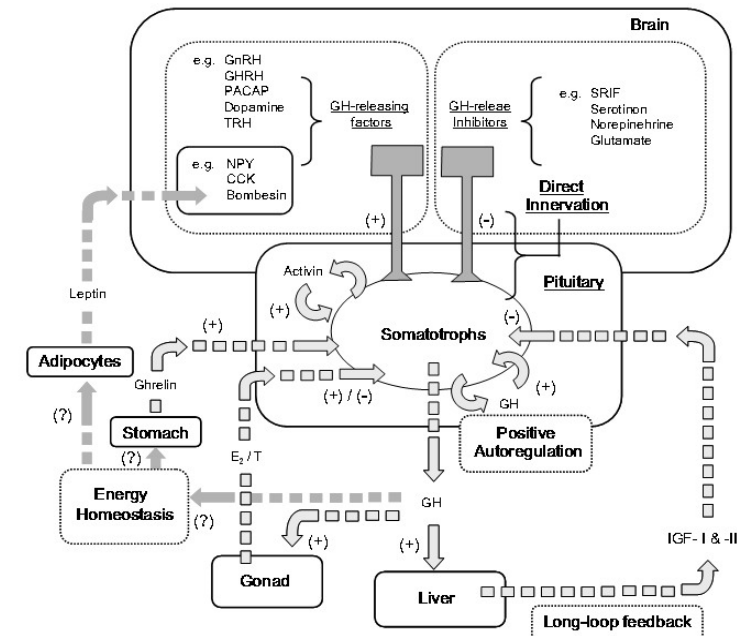




Abstract

Aim: To evaluate the impact of rh-GH replacement therapy on neurotransmitters: gamma - amino butyric acid (GABA), dopamine (DA) and serotonin (5-HT) in growth hormone deficient children
Research design and methods: This retrospective study included 30 subjects with growth hormone deficit clinically established: 20 boys (5-14 years) and 10 girls (6-14 years). All of them underwent GH replacement therapy from 9 months - 10.6 years. rh - GH dose varied in all subjects from 0.6-1.9 mg/day based on detailed clinical and anthropometric data. In 2015, all subjects in different phases of treatment were tested for plasma: GABA, DA, 5-HT and IGF-1
Results: Median plasma GABA in boys vs girls was: 50.5 vs 46 ng/mL; median plasma DA in boys vs girls was: 43.34 vs 29.4 pg/mL; median 5-HT in boys vs girls was: 227.5 vs 208.7 ng/mL and median IGF-1 in boys vs girls was: 334 vs 357.25.7ng/mL. We established a statistically significant difference in plasma GABA and in DA values in boys vs. girls. High multiple regression coefficients were established between age and IGF-1, DA, GABA or between IGF1 and 5-HT, DA, GABA in boys vs. girls
Conclusion: This study established a link between brain neurotransmitters and the height gain in GH-deficient children under replacement therapy in different phases of treatment.

***Key words**: GH-deficient children; rh-GH replacement therapy;* gamma - amino butyric acid; dopamine; serotonin*; insulin growth factor-1*

Introduction

- Early detection of abnormal growth, identification of the underlying cause and appropriate treatment of the medical condition are important issues for children with short stature
- Growth hormone (GH) therapy is widely used in GH deficient children and also in non- GH deficient short stature cases who have findings conforming to certain indications
- Efficacy of GH therapy has been shown in a multitude of short and long term studies
- Age at onset of GH therapy is the most important factor for a successful treatment outcome (*S. M. Shalet et al. Endocrine Reviews 1998; 19(2):203-223)*

Introduction

- In the multitude of brain neurotransmitters: catecholamines and acetylcholine play a major role in the control of neurosecretory GH-releasing hormone (GHRH) and somatostatin (SS)-producing neurons and hence GH secretion
- The episodic secretion of growth hormone (GH) depends on the rhythmic alternation in the hypothalamic release of GHRH and somatostatin (SS) into the hypophyseal portal system
- In turn, GH appears to maintain this rhythm by stimulating SS and inhibiting GHRH secretion
- Central adrenergic pathways, by modulating SS secretion, seem to be the final mediator for most stimuli, including other neurotransmitters (*H. J. Schneider et al. Eur J of Endocrinol 2003;149:377-392; J Ayuk et al. Postgrad Med J 2006;82:24-30)*

Introduction

- The diagnosis of classic GH deficiency should be made on the basis of peak GH
- The definition of GH neurosecretory dysfunction implies pituitary GH secretory abnormalities that may result from "abnormalities" in GH-RH or GH inhibiting hormone (somatostatin)
- These problems could be secondary to defects in neurotransmitters that regulate GH secretion via GH - RH - ergic and somatostatinergic neuronal pathways
- The aim of this study was to evaluate by indirect assessment, the impact of the rh-GH replacement therapy on the neurotransmitters: gamma - amino butyric acid (GABA), dopamine (DA) and serotonin (5-HT) in growth hormone deficient children

Results and discussion

- Our study (2016) enrolled 30 children (10 girls aged: 6-14 years and 20 boys aged: 5-14 years) clinically identified as GH-deficient after a detailed anamnesis, anthropometric measurements and different dynamic tests
- All of them received different doses of replacement therapy at the start of therapy and they were followed over time
- All subjects collected in the morning at 9 am(after an overnight fasting, free of drugs) a sample of plasma (into EDTA vacutainer) and a sample of total blood
- After centrifugation, plasma and serum samples were aliquoted and stored at -20°C until assayed
- Plasma GABA, plasma DA, 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 8.0.0.1

Results and discussion

- Means and standard errors were calculated for all 4 tested parameters and different correlation coefficients were established (*Table1*)
- T-test showed significant differences between boys and girls concerning GABA and DA means
- Interesting correlation coefficients were established in boys group between: GABA/DA and between: age/IGF-1
- In girls group the best correlation coefficients were established between: GABA/DA and also between: age/IGF-1 (*Table1*)
- We calculated by linear regression, high multiple coefficients in the boys group between: age/IGF-1 (R=0.93); age/GABA (R=0.90); age/DA (R=0.85)
- In girls group we found good multiple regression coefficients between: age/5-HT (R=0.57) and between: 5-HT/DA(R=0.62)

Results and discussion

- In Fig. 1 and 2 we showed GH-dose variation depending on height and weight in both groups of patients: boys/girls
- In Fig. 3 we showed blood concentration variation of neurotransmitters and IGF-1 in different phases of GH-treatment in girls group
- In Fig. 4 it was presented blood variation of neurotransmitters in 20 GH-deficient boys depending on age, under different doses of rh-GH at different stages of treatment
- Our preliminary data underlined an interesting link between: GABA/DA and age/IGF-1 in both groups of GH-deficient patients
- We can not neglect negative correlations between GABA/5-HT; DA/IGF-1 and 5-HT/IGF-1 in girls GH-deficient group (Table. 1)

Results and discussion

Table 1- Blood GABA, DA, 5-HT and IGF-1 in 20 boys vs. 10 girls GH-deficient

Patients	GABA ng/mL Mean ± SEM	DA pg/mL Mean± SEM	5-HT ng/mL Mean± SEM	IGF-1 ng/mL Mean± SEM
20 boys	52.5 ± 4.24	39.4 ± 3.98	295.3 ± 24.77	204.75 ± 31.96
10 girls	43.42 ± 2.89	28.02 ± 3.37	257.43 ± 45.15	379.22 ± 37.02
T-test	P = 0.05	P = 0.01	NS	NS
Correlation coefficient 20 boys	GABA/DA: 0.405			Age/IGF-1: 0.629
Correlation coefficient 10 girls	GABA/DA: 0.63 GABA/5-HT: 0.49	DA/IGF-1: -0.52	5-HT/IGF-1:-0.49	Age/IGF-1: 0.84

Fig.1 - Daily dose,height and weight in 10 GH-deficient girls in different phases of treatment

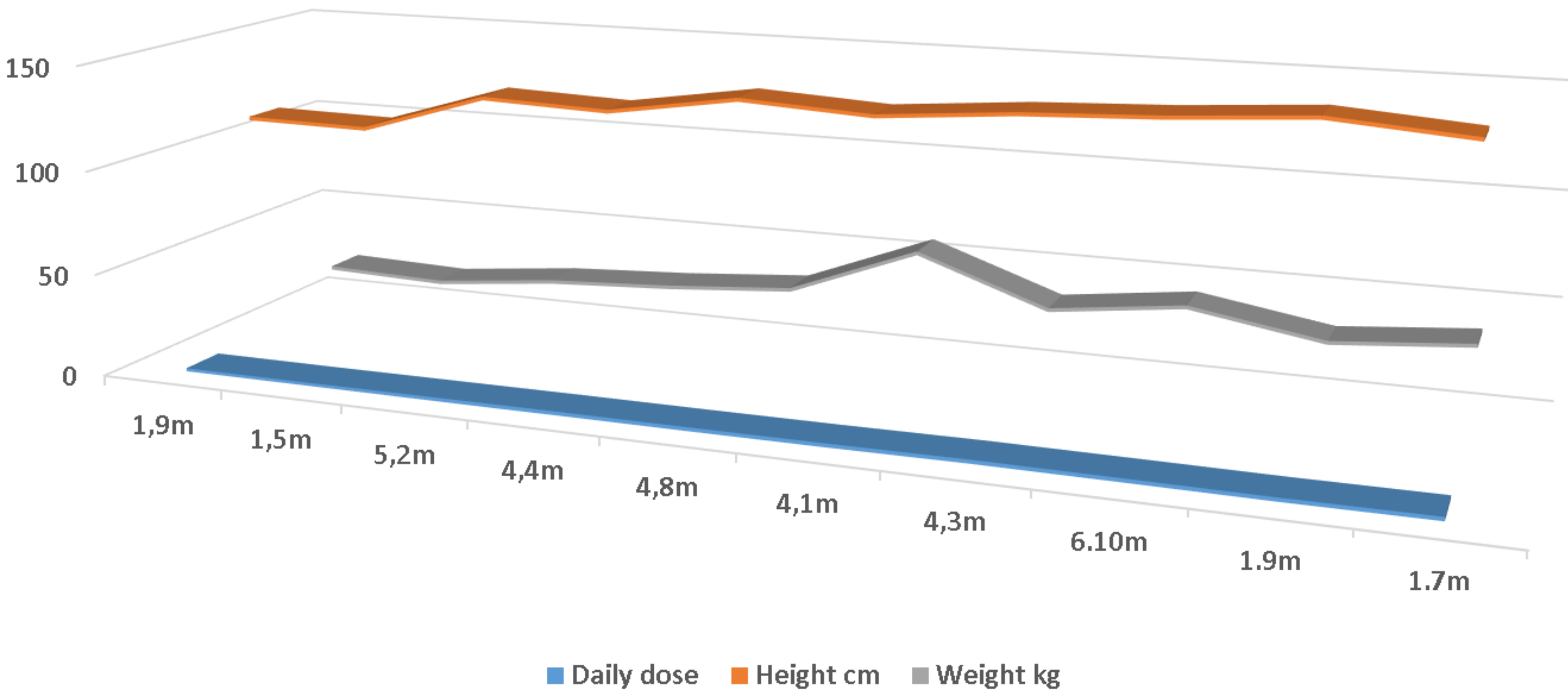


Fig.2 - Daily dose, height and weight in 20 GH-deficient boys in different phases of treatment

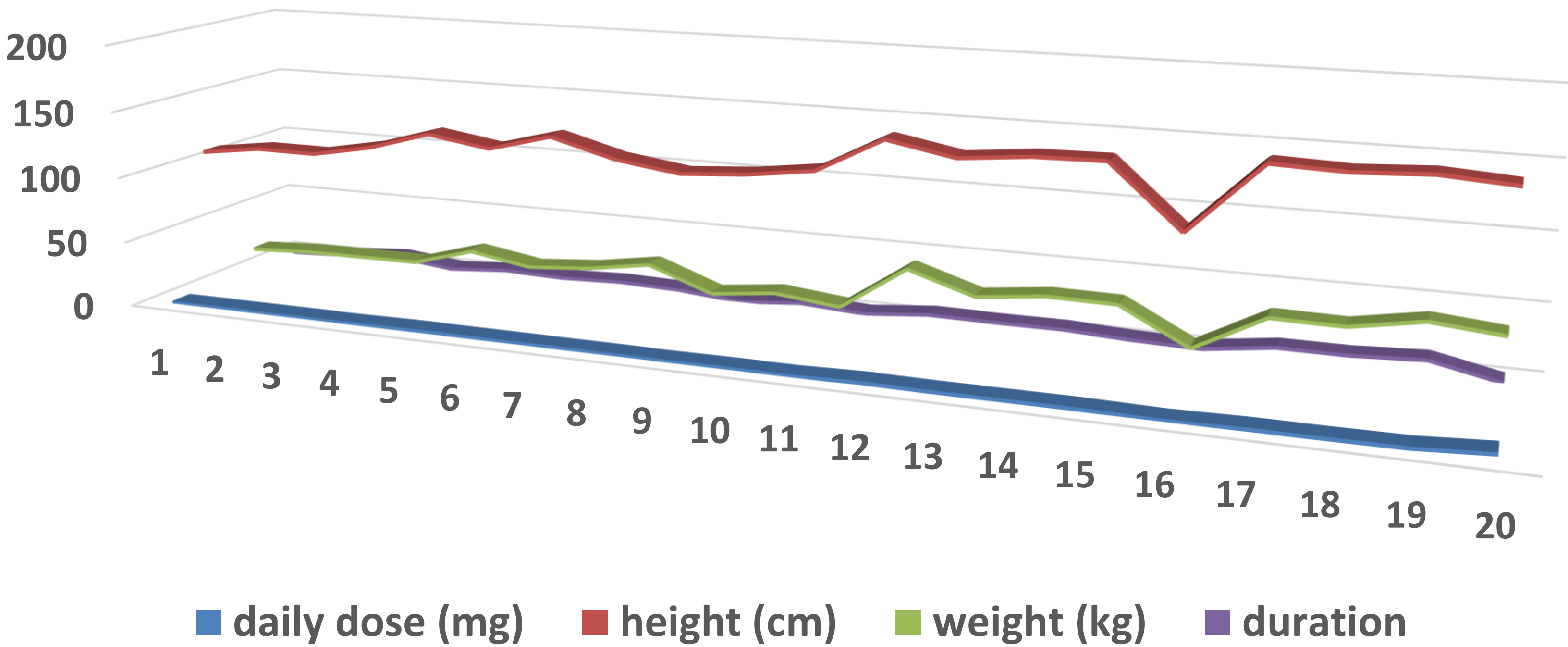


Fig .3 - Neurotransmitters and IGF-1 blood variation in 10 girls GH-deficient depending on the duration of treatment

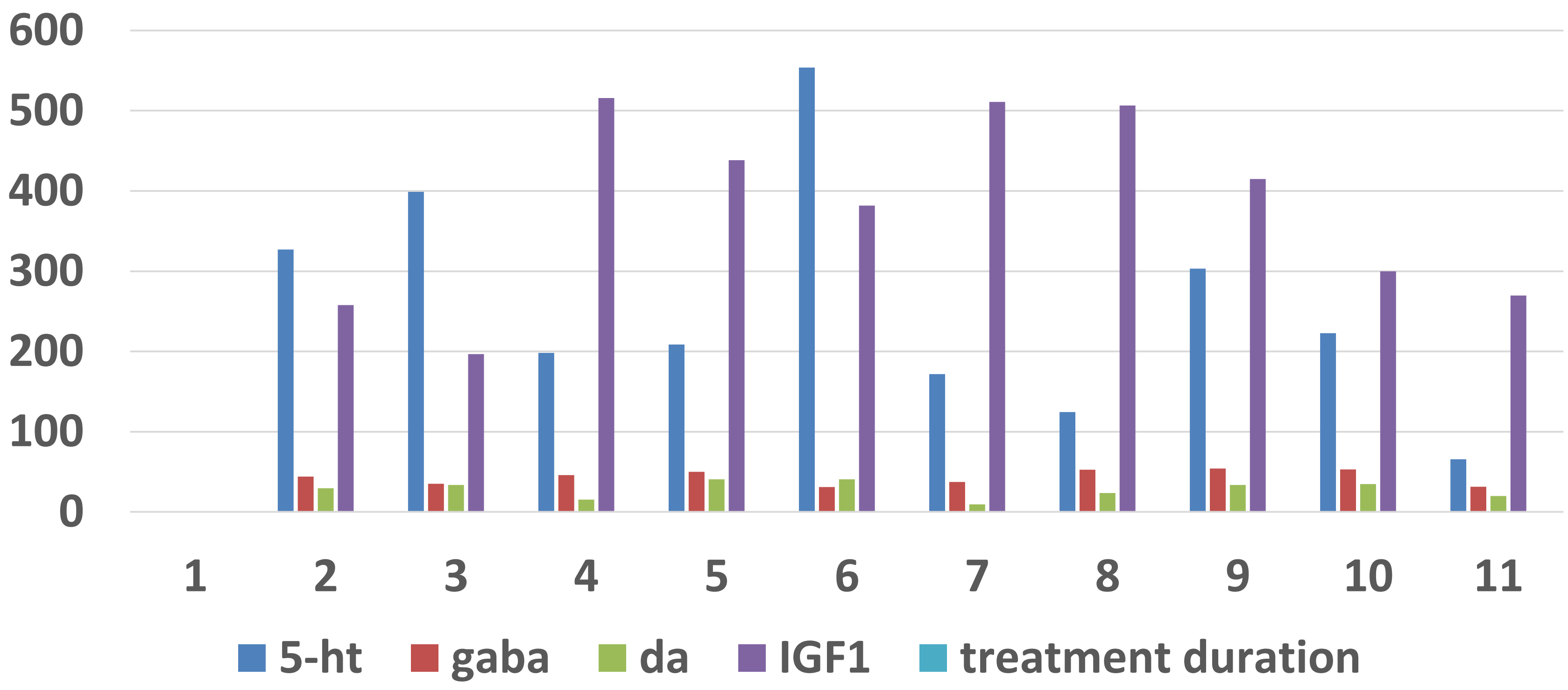
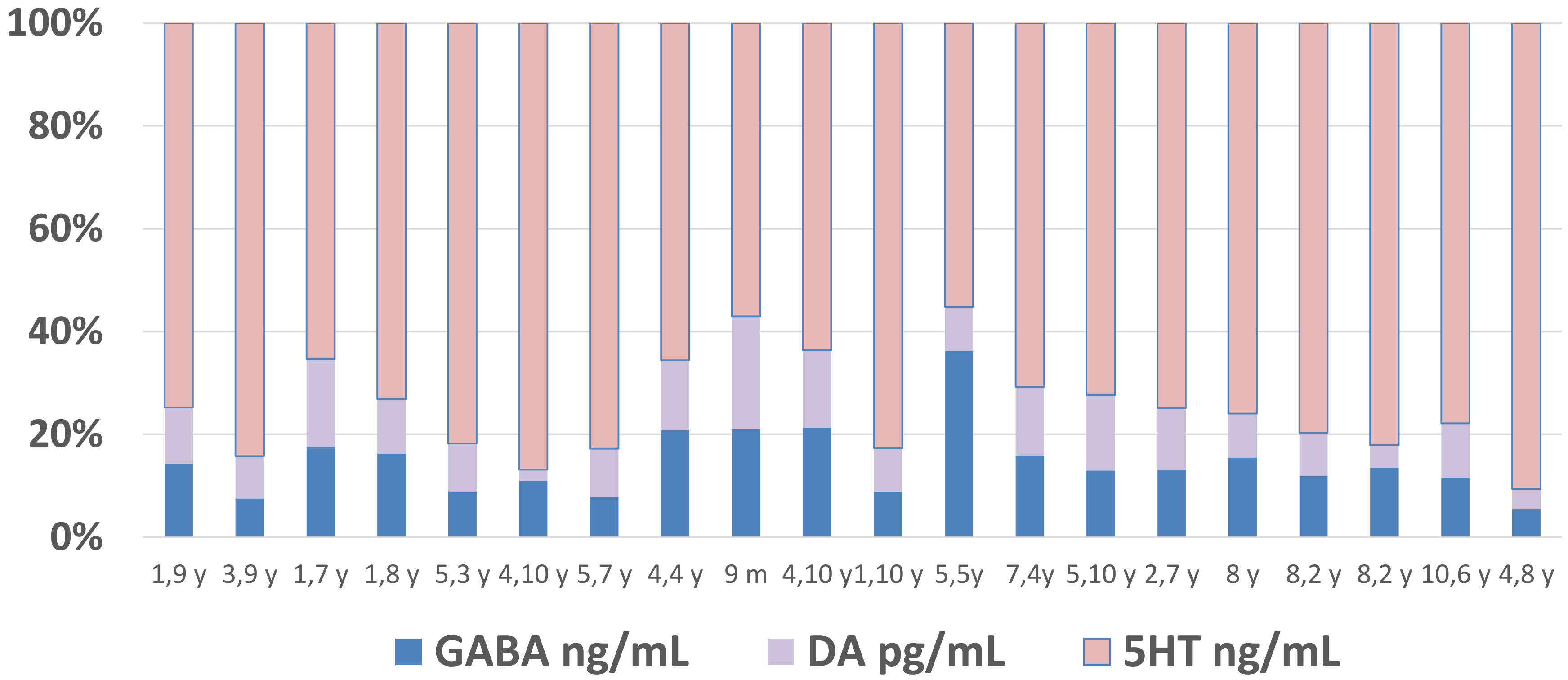


Fig.4-Blood variation of neurotransmitters in 20 GH-deficient boys depending on age,in different doses of rh-GH at different stages of treatment



Conclusions

- We think it is too early to draw conclusions about the inter-relationship between neurotransmitters and GH replacement therapy in our study group
- This study deserves to be continued to follow the same patients after another year of rh-GH treatment and testing the same markers: neurotransmitters and IGF-1
- In the future, comparison with our preliminary results can highlight some conclusions concerning the positive influence of rh-GH treatment on neurotransmitter systems with immediate effect in the development and growth.

Acknowledgements

This study was approved by the Ethical Commission of our Institute in 2016