Model for Quantitative Evaluation of Enzyme Replacement Treatment

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Summary: Gaucher disease is the most frequent lysosomal disorder. Its enzyme replacement treatment was the new progress of modern biotechnology, successfully used in the last years. The evaluation of optimal dose of each patient is important due to health and economical reasons. The enzyme replacement is the most expensive treatment. It must be held continuously and without interruption. Since 2001, the enzyme replacement therapy with Cerezyme*Genzyme was formally introduced in Bulgaria, but after some time it was interrupted for 1–2 months. The dose of the patients was not optimal. The aim of our work is to find a mathematical model for quantitative evaluation of ERT of Gaucher disease. The model applies a kind of software called "Statistika 6" via the input of the individual data of 5-year-old children having the Gaucher disease treated with Cerezyme. The output results of the model gave possibilities for quantitative evaluation of the individual trends in the development of the disease of each child and its correlation. On the basis of this results, we might recommend suitable changes in ERT.

1. INTRODUCTION

Gaucher disease is the most frequent lysosomal disease. The enzyme replacement treatment is a new biotechnology used with success around the world last year. The method was introduced in Bulgaria by B. Radeva in 1994. Since 2001 the treatment with Cerezyme/Gerezyme is formally registered for use [1-3]. This is one of the most expensive biotechnologies and the price of the drug is higher. The treatment with ERT must be continuous and without interruption. The patient needs optimal doses of Cerezyme. But during the treatment in the period 2001-2006, it has been interrupted several times for 1–2 months, and the doses have been deleted.

The aim of our work is to find a mathematical model for quantitative evaluation of ERT of patients with Gaucher disease.

2. MATERIALS AND METHODS

The patients R.V.T (P.1) and K.P.D (P.2) were diagnosed and treated with ERT since 2001–2006 in Clinical Genetics Dept. of the

University Children's Hospital, Sofia. Twice per month, patients received infusion with Cerezyme/Genzyme in different doses. RVT, 4 flacons x200 Uniinfusion per infusion (16 mg·kg⁻¹) and K.P.D.5 flacons x200 Units per infusion (25 mg·kg⁻¹). Before and during the treatment biomarkers were used for monitoring the complete blood count: haemoglobin, leucocytes, platelets, the measure of liver and spleen, and acid phosphatase and chitotriosidase.

With methods for investigation on time series, the model applies the Origin 6 [5] and Statistika 6 [4] software programs with their input being the individual data of children with Gaucher disease for quantitative evaluation the individual tendency in the development of the disease of each child and its correlation. On the basis of these results, we were able to recommend suitable changes in ERT.

3. RESULTS

The results showed a positive tendency of decreasing of spleen dynamics in the first patient. Spleen = 6879.8 – 3.429*year and correlation R^2 = -0.9310 (Fig. 1).
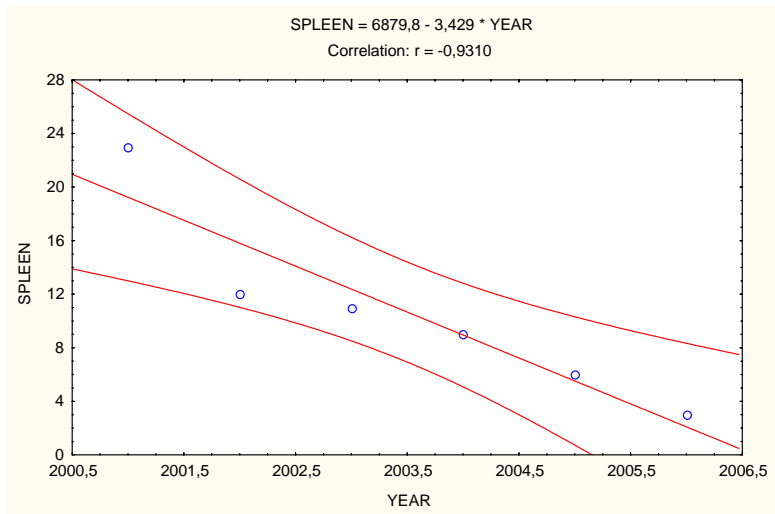

Fig. 1 Tendency of the spleen dynamics

Similar dynamics were exhibited for the liver. Liver = 2921.6 – 1.457*year and correlation R^2 = -0.8723 (Fig. 2).
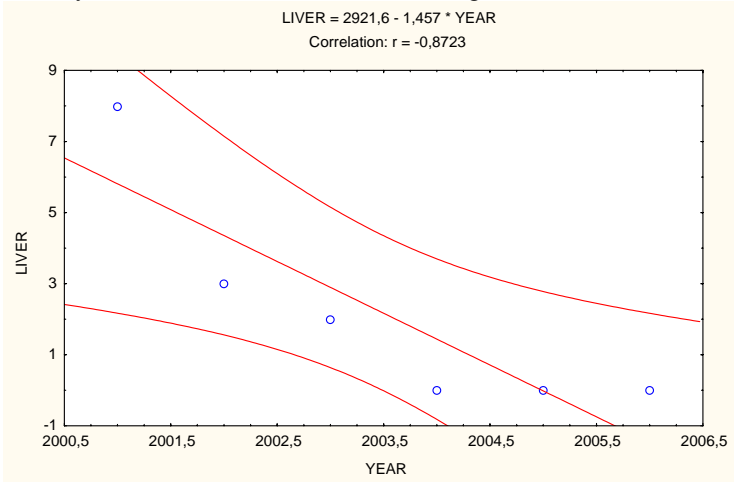

Fig. 2 Tendency of the liver dynamics

Haemoglobin showed a positive tendency of increasing of level dynamics. Haemoglobin = -1511 + 76000*year and correlation R^2=0.893 (Fig. 3).
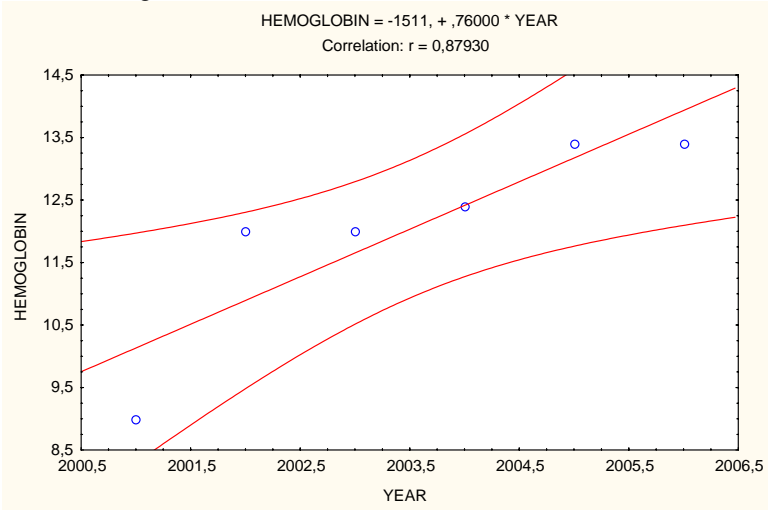

Fig. 3 Tendency of the haemoglobin dynamics

Platelets of the first patient also showed a positive tendency of dynamics. Platelets = -146E2+7.3143*year and $R^2 = 0.82267$ (Fig. 4).
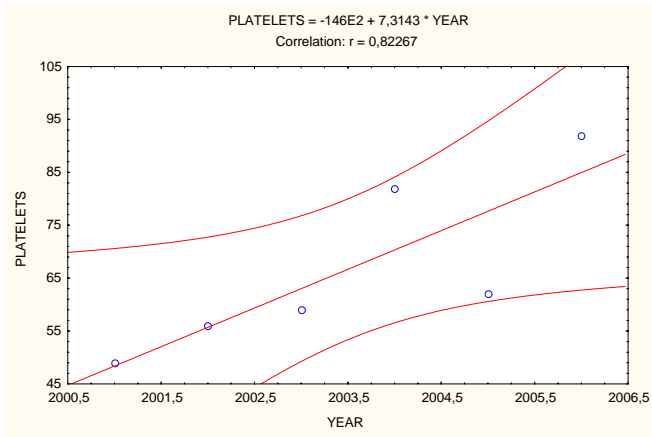

Fig. 4 Tendency of the platelets dynamics

The first patient had a positive tendency of leukocytes dynamics. leukocytes = -207.6 + 10571*year and with lower correlation $R^2 = 0.22903$ (Fig. 5).
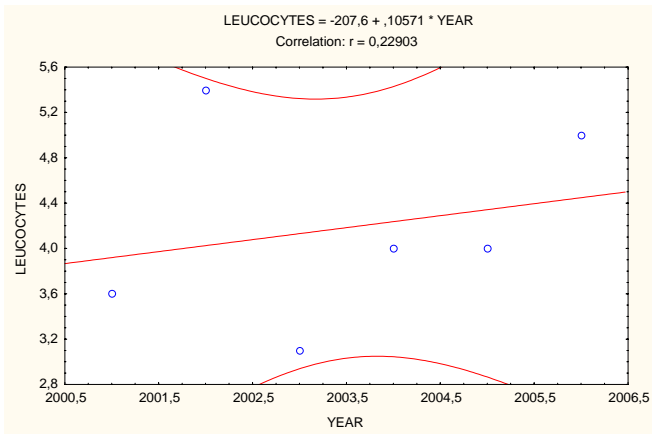

Fig. 5 Tendency of the leucocytes dynamics

The second patient showed a positive tendency of decreasing the spleen dynamics. Spleen = 3512.6 – 1.743*year and correlation $R^2 = -0.7054$ (Fig. 6)
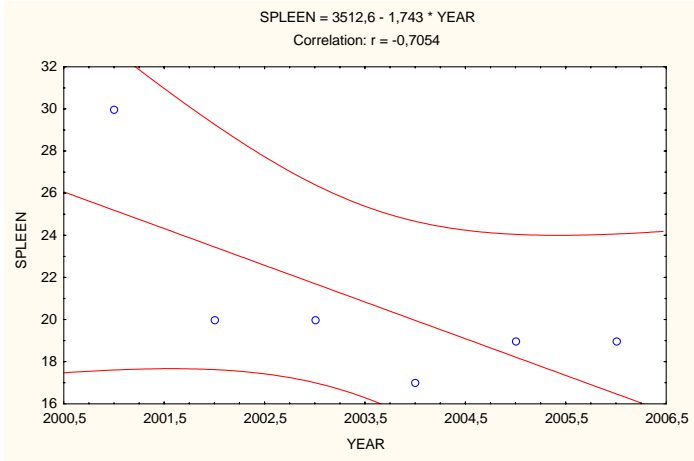

Fig. 6 Tendency of the spleen dynamics

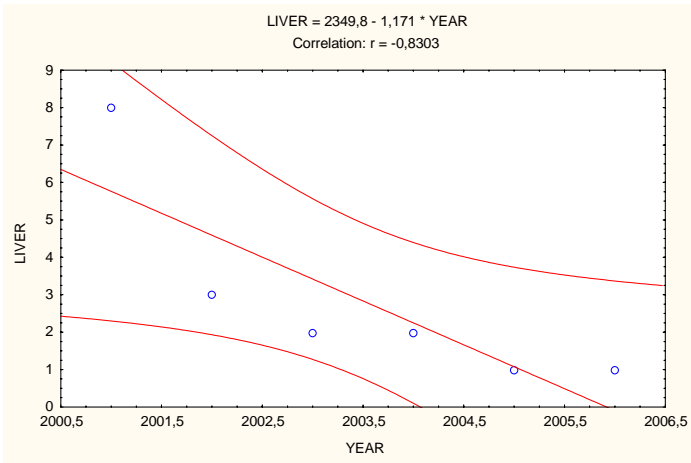Liver = 2349 – 1.171*year and correlation $R^2 = -0.8303$ (Fig. 7).

Fig. 7 Tendency of the liver dynamics

An increasing tendency of haemoglobin was found in the second patient: haemoglobin = 2335+1.1714*year. Correlation R^2=0.94601 (Fig. 8) and an increasing tendency of platelets dynamics: platelets = 8496 + 4.2571*year. Correlation R^2=+0.61198 (Fig. 9).
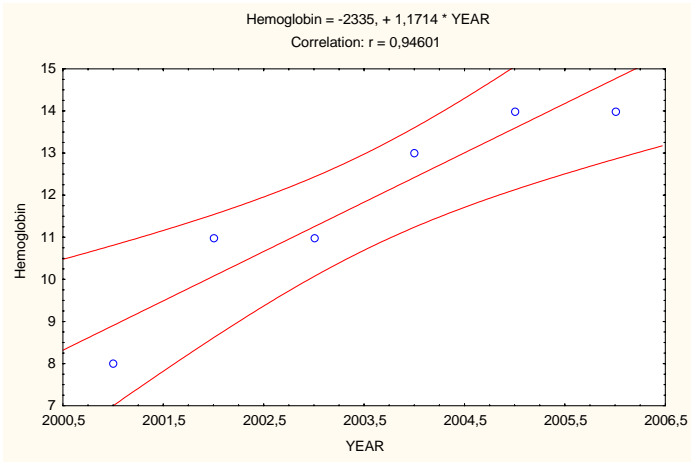

Fig. 8 Tendency of the haemoglobin dynamics
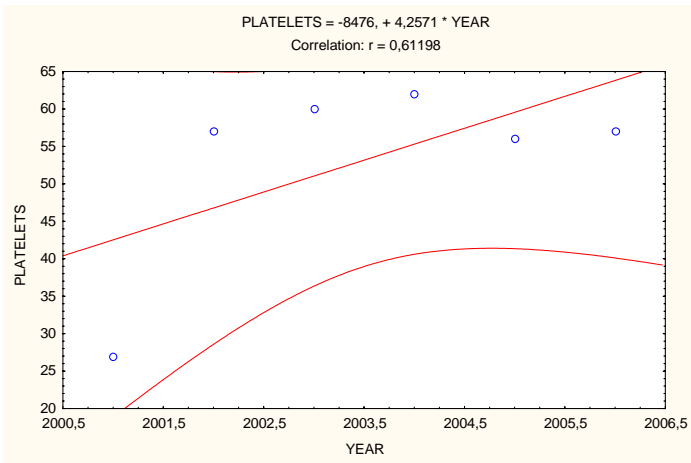

Fig. 9 Tendency of the platelets dynamics

The tendency of leukocytes dynamics was flat:
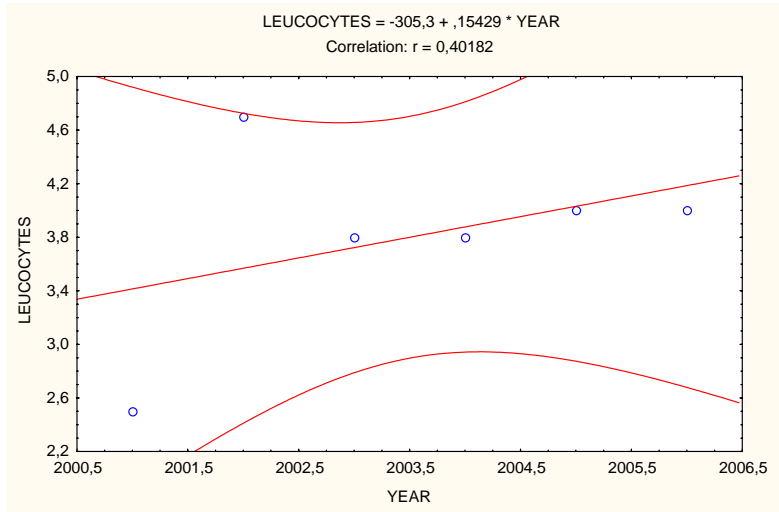leukocytes = -305.3 + 0.15429*year. Correlation R^2 = 0.4082
(Fig. 10)

Fig. 10 Tendency of the leucocytes dynamics

4. DISCUSSION

A model was created for the quantitative evaluation of the results of ERT with Cerezyme*Genzyme on the basis of the investigation dynamics of biomarkers of children with Gaucher disease during a treatment with ERT with Cerezyme*Genzyme. Its gave us better and easier comparison of the received results. In the first patient there were higher correlation between liver, spleen, haemoglobin and platelets, than in the second one. But the correlation R^2 of these biomarkers were above 0.5, which implies a significant tendency. This confirmed again the effect of ERT with recombinant enzyme Cerezyme.

It was clear that the second patient needed more enzyme to receive better results. It was recommended to increase his doses. The dynamics of leukocytes of the first patient were under 0.3 – this is un significant tendency because their absolute levels were normal. The

second patient showed a moderate tendency of leukocytes dynamics, above 0.3 (modarate tendency).

5. CONCLUSION

The developed model for quantitative evaluation, based on the method of investigation of time series, gave possibilities for longitudinal evaluation of the individual tendency of evolution of the disease. On the basis of received data, it was possible to make a precise decision about the correction of the individual doses. This approach will improve the quality of life of the patients and yield a positive economical effect.

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