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ORIGINAL ARTICLE

Neural network models – a novel tool for predicting the efficacy of growth hormone (GH) therapy in children with short stature

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Abstract

INTRODUCTION: The leading method for prediction of growth hormone (GH) therapy effectiveness are multiple linear regression (MLR) models. Best of our knowledge, we are the first to apply artificial neural networks (ANN) to solve this problem. For ANN there is no necessity to assume the functions linking independent and dependent variables.
The aim of study is to compare ANN and MLR models of GH therapy effectiveness.
MATERIAL AND METHODS: Analysis comprised the data of 245 GH-deficient children (170 boys) treated with GH up to final height (FH). Independent variables included: patients' height, pre-treatment height velocity, chronological age, bone age, gender, pubertal status, parental heights, GH peak in 2 stimulation tests, IGF-I concentration. The output variable was FH.
RESULTS: For testing dataset, MLR model predicted FH SDS with average error (RMSE) 0.64 SD, explaining 34.3% of its variability; ANN model derived on the same pre-processed data predicted FH SDS with RMSE 0.60 SD, explaining 42.0% of its variability; ANN model derived on raw data predicted FH with RMSE 3.9 cm (0.63 SD), explaining 78.7% of its variability.
CONCLUSION: ANN seem to be valuable tool in prediction of GH treatment effectiveness, especially since they can be applied to raw clinical data.

INTRODUCTION

Growth hormone (GH) deficiency (GHD) is the main indication for recombinant human GH (rhGH) therapy in children with short stature. As rhGH therapy is long-term and quite expensive, the prediction of growth response to treatment is very important for identifying the patients who should benefit during the therapy. The most important goal of treatment is to attain normal final height (FH). The diagnostic criteria of GHD are still the matter of discussion. Despite the fact that GHD has recently been defined as secondary insulin-like growth factor-I (IGF-I) deficiency (Wit *et al.* 2007; Savage *et al.* 2010) and GH assessment after pharmacological stimulation has important limitations (including arbitrarily established cut-off level for normal and decreased GH peak, independent from patient's age and the kind of test, poor reproducibility of test results), GH stimulation tests remain the main tool in diagnosing GHD (Richmond & Rogol 2010). On the other hand, the interpretation of IGF-I concentration depends on patient's age and gender and should take into account other than GHD possible causes of IGF-I deficiency. Moreover, in recent years, the effectiveness of rhGH therapy has been documented in children with normal GH peak in stimulation tests, diagnosed with idiopathic short stature (ISS) (Cohen *et al.* 2008). Regardless of the importance of documenting decreased GH and/or IGF-I secretion for the diagnosis of GHD, it seems particularly important to identify the patients who may benefit during rhGH therapy. The need for creating and improving the models of growth response to rhGH therapy has been strongly recommended (Ranke 2010). The published models are based either on the information available before rhGH therapy onset or include the data on rhGH therapy effectiveness in previous years for predicting growth response in subsequent years (Ranke 2010; Ranke *et al.* 2003; Carel *et al.* 2002; Schonau *et al.* 2001). Up to now, the created models are based on the multiple linear or non-linear regression that requires a number of presuppositions that must be met. Namely, the character of dependencies (mathematical functions) linking independent and dependent variables (input and output data) must be known *a priori*, input variables should not be correlated, the residuals, *i.*e. the differences between expected (real) and calculated values should fulfil some conditions. Thus the researcher has to determine the set of uncorrelated variables used for creating model. For this purpose, some data require conversion to standard deviation scores (for instance, all the auxological indices that correlate with age), other – if log-normally distributed – should be transformed to logarithms, *etc*. This step of creating model is quite laborious and requires having adequate reference data for many variables. Even after performing all the necessary transformations, the model may be not optimal, as the real dependencies linking different variables are very complex, often non-linear or even not defined. The created model must be tested on a set of new data (testing group).

In present study, we propose artificial neural networks (ANN) modelling as a novel tool for prediction of growth response to rhGH therapy in children with GHD. In contrary to multiple linear regression (MLR), ANN enable modelling complex, non-linear dependencies between variables, with no need to fulfil any statistical assumptions concerning the data and with no previous knowledge about the character of relations between input and output data.

Neural networks are sophisticated, biologically inspired computational systems, considered one of the leading tools of machine learning or even artificial intelligence. Their development is based on modelling structure and – what seems to be even more important – communication of neurons. The simplest way to create network is to form layers of neurons and introduce all possible connections between neurons from neighbouring layers, while avoiding connections between neurons belonging to the same layer. The very important part of neural modelling is learning – the process in which ANN model is derived. Before the models are built, the database is divided into three sets. First – learning set – is used directly to train the network, second – validation set – to control learning by checking the quality of results, third – testing set – to control the networks performance on new, completely independent data. In present study, supervised learning was used, in which dataset of input variables is presented to the network with correct answers. Previously, ANN have been used to solve many problems, among them medical (Yardimci 2009). However, best of our knowledge, we are the first who tried to apply ANN for creating models of the efficacy of rhGH therapy in children.

The mathematical and statistical issues concerning application of ANN for prediction the response to rhGH therapy have been described more specifically in previous paper of our research group (Smyczyńska *et al.* 2015).

MATERIAL AND METHODS

Patients' cohort, input and output data and their pre-processing

The models were derived on data collected from 245 patients (170 boys, 75 girls) treated with rhGH due to isolated GHD. At therapy onset 103 of patients were prepubertal, while the remaining 142 entered puberty before treatment. The initial dose of rhGH was 0.18±0.02 mg/kg/week (mean±SD) and remained relatively stable during the therapy duration. All the patients were treated no shorter than 2 years, up to fulfilling the criteria of therapy withdrawal, *i.e.*: height velocity (HV) below 3 cm/year and/or bone age (BA) over 16 years for boys and 14 years for girls. The patients were observed up to the attainment of FH. The data for creating models were collected during routine diagnosis

before treatment and at rhGH therapy withdrawal. The variables used in the models were limited to the information obtained directly during diagnostics and the attained FH. Children with concomitant chronic diseases, including multiple pituitary hormone deficiency, genetic syndromes, malnutrition, as well as ones with acquired GHD (brain tumours, injuries, cranial irradiation, *etc*.) were excluded from the study.

The studies on rhGH therapy effectiveness were approved by the Committee of Ethics of Scientific Research in Polish Mother's Memorial Hospital – Research Institute in Lodz.

The input variables obtained at rhGH therapy onset, chosen to create models, are listed below:

1. Patient's chronological age (**CA**).
2. Patient's height (**H [cm]**) and height standard deviation score (**H SDS**) for chronological age (CA) and sex at rhGH therapy onset. All the patients were measured by Harpenden stadiometer and their height was converted to SDS, according to the normative data for Polish children (Palczewska & Niedzwiecka 2001),
3. Patient's height velocity (**HV**), calculated on the basis of 2 measurements, performed by pediatric endocrinologists form our research group in the time interval at least 6 months.
4. Patient's bone age (**BA)**, assessed on the ground of radiogram of non-dominant hand and wrist, according to Greulich-Pyle's standards (Greulich & Pyle 1993) and **BA/CA** ratio.
5. Patient's **gender**. This variable is qualitative and must be transformed to a numerical value, *e.g.* 0 for males and 1 for females (the order of assignment is arbitrary and has no influence on the model correctness).
6. Pubertal status (**PUB**)– the qualitative variable, transformed to numerical values: 1 – for prepubertal children, 2 – for pubertal ones.
7. Heights of mother (**hm**) and father (**hf**) **[cm]** and transformed to **hmSDS** and **hfSDS**, respectively.
8. **GH peak [ng/ml]** in 2 stimulation tests and converted to natural logarithms (**lnGH**); the following test were performed: with clonidine 0.15 mg/m^2 orally and with glucagon 30 μg/kg *i.m*. (not exceeding 1.0 mg). The cut-off value for the diagnosis of GHD is GH peak in stimulation tests 10.0 ng/ml, however some patients with IGF-I deficiency (IGF-I SDS for age and sex below –2.0) were qualified to rhGH therapy despite normal GH peak in stimulation tests, as diagnosed with neurosecretory dysfunction of GH secretion or GH bioinactivity (primary IGF-I deficiency was excluded in each case by significant IGF-I increase in generation test). Concentrations of GH were measured by hGH IMMULITE, DPC assay, calibrated to WHO IRP 98/574 standard.
9. Serum concentration of **IGF-I [ng/ml]** and **IGF-I SDS** for age and sex, calculated according to the reference data of Elmlinger *et al.* (2004), assuming the log-normal distribution of IGF-I concentrations. Serum IGF-I concentrations were assessed by IMMULITE, DPC assay, calibrated to WHO NIBSC 1st IRR 87/518 standard.

The output variable was either patient's **FH** (for the model constructed on raw (unprocessed) data) or **FH SDS** (for the models derived from pre-processed data).

The detailed characteristics of the whole cohort of patients is presented in Table 1.

Models' derivation and quality measures

MLR model

In MLR models, the main assumption is that all the functions linking independent and dependent variables are linear. The initial set of input variables included all the auxological and hormonal data, pre-processed for elimination age-related correlations: patients' gender, CA, H SDS, HV before treatment, BA/CA, hmSDS, hfSDS, GH peak in 2 stimulation tests expressed as lnGH, IGF-I SDS, pubertal status. The data of 195 patients (learning group and validation group from ANN model, see below) were used for creating model, the remaining 50 ones constituted the testing group. During creating model, the statistically insignificant variables are subsequently eliminated. The final model was presented as linear function of multiple variables with coefficients related to the strength of influence of particular variables on prediction result. The last step was the analysis of residuals.

The commonly used measures for the assessment of models quality are root mean square error (RMSE) and coefficient of determination (R^2) often interpreted as

Tab. 1. Statistical characteristics of the whole patients' cohort and its division into particular sets (the values presented are mean±SD).

	All patients	Learning set	Validation set	Testing set
CA [years]	13.1±2.0	13.2±2.1	12.8±2.0	13.1±2.0
H [cm]	139.7±10.9	140.1±10.7	137.6±11.0	140.5±11.5
H SDS	–2.75±0.60	–2.74±0.61	–2.85±0.67	–2.65±0.49
HV [cm/year]	3.9±1.3	3.9±1.2	3.8±1.3	4.4±1.2
BA [years]	10.6±2.2	10.7±2.2	10.1±2.1	10.6±2.2
BA/CA	0.82±0.09	0.82±0.10	0.80±0.09	0.82±0.08
hm [cm]	159.4±5.1	159.5±5.1	158.4±5.7	160.0±4.3
hmSDS	–1.00±0.84	–0.98±0.84	–1.16±0.94	–0.90±0.70
hf [cm]	172.5±6.6	171.9±6.5	173.4±6.0	173.5±7.3
hfSDS	–0.92±1.03	–1.01±1.02	–0.79±0.93	–0.76±1.14
GH peak [ng/ml]	9.0±5.6	8.5±5.6	9.4±5.6	10.1±5.4
IGF-I [ng/m]	158.5±78.5	159.5±79.8	149.0±74.1	164.1±79.0
IGF-I SDS	–1.96±1.28	–2.01±1.28	–1.95±1.38	–1.79±1.18
FH [cm]	166.3±8.4	166.5±8.1	164.6±9.0	167.2±8.5
FH SDS	–1.30±0.80	–1.31±0.79	–1.33±0.85	–1.21±0.79

the amount of variability in data that is explained by model. These indices are calculated as follows:

$$RMSE = \sqrt{\frac{\sum_{i=1}^{n} \left(y_i - y_{di}\right)^2}{n}}$$

where y_i is predicted value and y_{di} is known correct value of patient FH SDS and n is number of patients taken into account in calculation.

$$R^2 = 1 - \frac{\sum_{i=1}^{n} \left(y_i - y_{di}\right)^2}{\sum_{i=1}^{n} \left(y_{di} - y_m\right)^2}$$

where y_m is average of patients' FH SDS. Actually, there exist simpler, equivalent formulas for calculating R^2 in MLR, however only the above, general formulation is acceptable for ANN.

ANN model

Among many available types of ANN, we have chosen to use multilayer perceptron (MLP), in which each neuron processes data in two stages. Firstly, each of neurons inputs x_i is multiplied by its weight coefficient w_i, then they are summed, what can be mathematically expressed as:

$$s = \sum_{i=0}^{n} w_i \cdot x_i$$

Secondly, the above sum is passed to the activation function, which in MLP is a logistic one, namely:

$$y = \frac{1}{1 + e^{-\beta \cdot s}}$$

This function approaches 0 for low values of s and is limited by 1 for high s.

The architecture of our MLP networks is described in following way:

MLP: number (Nº) of inputs: Nº of input neurons – Nº of neurons in 1st hidden layer – Nº of neurons in 2nd hidden layer (if applicable) – Nº of output neurons: Nº of outputs.

All ANN models were derived in *STATISTICA Neural Networks PL* with the use of automatic creator that allows analysis of numerous networks with different architecture in short time. Moreover, during the learning process the insignificant inputs could be automatically eliminated.

In our models, the three sets contained following number of cases:

- learning set: 150 (108 boys, 42girls),
- validation set: 45 (26 boys, 19 girls),
- testing set: 50 (36 boys, 14 girls), the same as for MLR model.

The detailed data concerning the subgroups (sets) of patients are presented in Table 1.

The models were created for unprocessed data, including patients' gender, CA [years], H [cm], HV [cm/year], BA [years], mh [cm], fh [cm], GH peak [ng/ml], IGF-I [ng/ml], pubertal status and for pre-processed data, including the same input variables as MLR model.

Before being introduced to models, all the parameters were automatically normalized by minimax transform, what is a common practice in neural network modelling.

The quality of models was checked by calculating RMSE and R^2 (as for MLR model). Both RMSE and R^2 were calculated for each subset of data separately.

RESULTS

MLR model

In MLR model, all the included parameters, except for patient's gender and GH peak in stimulation tests were statistically significant. The derived model has a form of following equation:

FH SDS = 0.78085 + 0.14616*CA + 0.62813*HSDS – 0.08506*HV – 0.166892*BA/CA + 0.14464*hmSDS + 0.09910*hfSDS – 0.13399*IGF-I SDS – 0.38533*PUB

For this model, RMSE for FH SDS is 0.58 SD (that corresponds to 3.6 cm of FH) for the dataset used for creating model and 0.64 SD (4.0 cm) for testing dataset, while R^2 is 47.2% and 34.3%, respectively.

Finally, the normal distribution of residuals was confirmed by Shapiro-Wilk test.

ANN models

The best ANN model, based on pre-processed input data (the same as for MLR model), has a form of MLP:7:7-8-1:1 and qualified as redundant variables (automatically eliminated from the model): patients' gender, GH peak in stimulation tests and pubertal status. The network is presented in Figure 1. In this model, RMSE of prediction of FH SDS is 0.59 SD (that corresponds to 3.7 cm of FH) for learning group, 0.63 SD (3.9 cm) for validation group and 0.60 SD (3.7 cm) for testing group, while R^2 is 43.0% for learning group, 43.1% for validation group and 42.0% for testing group.

The best model created on unprocessed data has a form of MLP:7:7-9-1:1. This model qualified as redundant variables: pre-treatment HV, GH peak in stimulation tests and pubertal status. The model is presented in Figure 2. In this model, RMSE of prediction of the attained FH is 3.8 cm (0.62 SD of FH SDS) for learning group and 3.9 cm (0.63 SD) for both validation group and testing group, while R^2 is 77.7% for learning group, 80.7% for validation group and 78.7% for testing group.

DISCUSSION

Most of prediction models for the treatment of GHD was derived either for prediction of response to rhGH therapy in first year of treatment (Südfeld *et al.* 2000)

and in subsequent years of therapy on prepubertal children (Ranke *et al.* 1999), or for prediction of total pubertal growth (Ranke *et al.* 2003). Only few models were dedicated for prediction of the attained FH (Carel *et al.* 2002; de Ridder *et al.* 2007).

In MLR models for prediction of FH SDS of children with isolated GHD or multiple pituitary hormone deficiency (MPHD), presented by de Ridder *et al.* (2007), only the information available at the start of rhGH treatment was included, while the models were derived for prepubertal and pubertal children separately. The significant variables in prepubertal group were: patients' H SDS at therapy onset, target height SDS (TH SDS), GH peak in stimulation tests (expressed as lnGH), gender, the kind of hormonal disorders (isolated GHD or MPHD) and BA. Interestingly, in the quoted study, for children who were pubertal at therapy onset, only 3 variables proved to be significant: H SDS before treatment, TH SDS and BA delay.

The first task undertaken in present study was quite similar, however in our study only the data of patients with isolated GHD were taken into account. Besides, pre-treatment HV and IGF-I SDS were included as additional independent variables during creating model. In our model the data of both parents were analysed separately, however they were both significant. Thus it seems that the information provided by TH SDS may be equivalent for hmSDS and hfSDS. Finally, in current study, one model was created for both prepubertal and pubertal children. In our model, the prediction error for testing group was smaller than that obtained by de Ridder *et al.* (2007) for prepubertal and pubertal children (0.58 SD vs. 0.83 and 0.84 SD, respectively), however our model explained less variability of FH SDS (34.2% vs. 37% and 41%, respectively). It seems that the accuracy of prediction could be improved by implementation of the data on IGF-I secretion and pretreatment HV. The worse ability to explain the variability of FH SDS in our model may be explained by the fact that other variables are most important in prepubertal and pubertal period, while in one model for both groups these differences cannot be accounted. The last but not least information that should be underlined is the fact that neither in de Ridder's model for pubertal children (de Ridder *et al.* 2007) nor in our MLR model, GH peak in stimulation tests a significant variable.

The best ANN model derived on pre-processed data was more accurate and explained more variability of FH SDS than MLR model, created for the same input data. For testing group the accuracy of ANN model was 0.60 SD, while for MRL model it was 0.64 SD; the models explained 42.0% and. 34.3% of variability of FH SDS, respectively. Better ability of ANN model to explain the variability of FH SDS arises from the possibility of reconstruction of complex, non-linear functions linking input and output variables, that is impossible in MLR model. Unfortunately, ANN model gives only a final result of prediction, with no direct insight into the

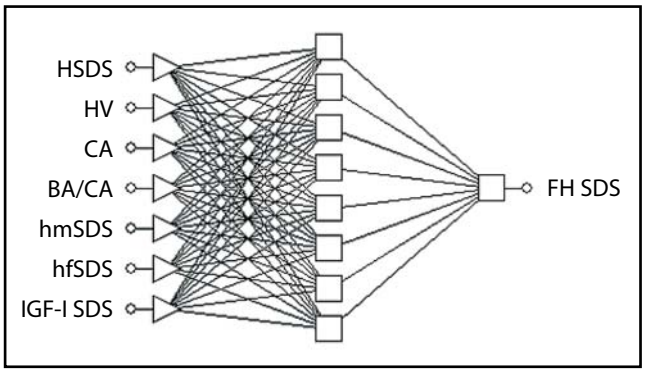

Fig. 1. ANN model of prediction of FH SDS based on pre-processed data.

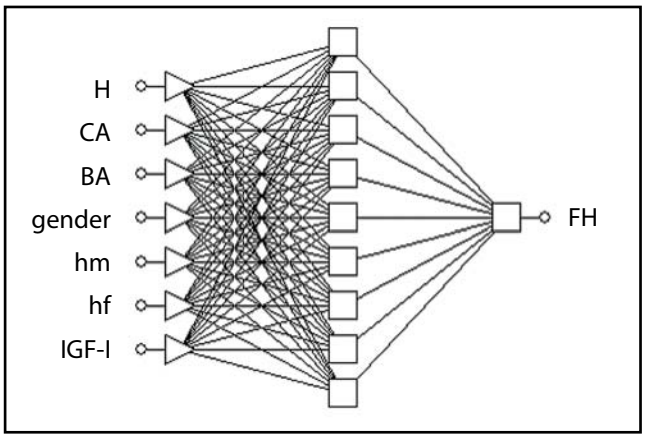

Fig. 2. ANN model of prediction of FH based on unprocessed (raw) data.

predictive strength of particular input variables. Both models eliminated patients' gender as a redundant variable, ANN model additionally eliminated pubertal status. These findings may be explained by the fact that numerous variables were expressed as the values of SDS for age and gender, as well as by a strong dependence of pubertal stage on patient's age.

Finally, similarly as MLR model, ANN models also eliminated GH peak in stimulation tests as a redundant variable. Conversely, all the models included IGF-I or IGF-I SDS as significant variables. The problem of selection of predictors of the response to rhGH therapy has been widely described by Ranke and Lindberg (2009) as a complex but well-established process. With respect to introducing IGF-I levels into the models, the authors presented the statement that it is difficult, however IGF-I may be an important growth predictor, directly related to growth disorders.

As it was previously mentioned, the main advantage of ANN models should be sought not only in no necessity to assume the functions linking input and output data but also in the possibility of including the unprocessed data to the model. The second ANN model in current study was derived on raw data, obtained directly from measurements, with no need for calculating SDS

or log-transforming the laboratory values due to their log-normal distribution. This model has slightly lower accuracy in FH prediction than ANN model with pre-processed data, namely: RMSE was 3.9 cm (0.63 SD) for the model on unprocessed data, while 0.60 SD (3.7 cm) for the model on pre-processed data. Nevertheless, the difference of 0.2 cm seems to be clinically insignificant. It should be stressed that, for new data, the model with unprocessed data explained much more variability of the attained FH than one with pre-processed data (78.6% vs. 42.0%, respectively). This difference may be probably explained by the ability of ANN models to find very complicated non-linear relationships (mathematical functions), linking independent and dependent variables, even if they were previously not defined or remained unknown. Unfortunately, this detailed "knowledge" acquired by ANN, constituting a basis to create modes, is not directly available for the researcher.

The results presented here are – to some extend – preliminary, as the main goal of current study was to verify, if ANN may be useful in creating such models. We are convinced that the answer for this question is positive. Further studies are planned on ANN application in modelling the effectiveness of rhGH therapy in children and on the predictors of rhGH therapy efficacy, especially on the predictive value of the assessment of GH peak in stimulation tests.

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