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Artificial neural networks for prediction final height in children with growth hormone deficiency

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Abstract. Mathematical models predicting final height (FH) and its standard deviation score (SDS) for children with growth hormone deficiency is an important tool for clinicians to manage treatment process. Previously developed models do not have enough accuracy or not good enough for practical use. We used 5 binary and 7 continuous predictors available at the time of diagnosis and start of therapy and developed multiple linear regression (MLR) models and artificial neural networks (ANN). The sample included 121 patients of Endocrinology Research Center (Moscow, Russia) who were under observation in 1978-2016 and reached the final height. All of them received growth hormone replacement therapy at least for 3 years. MLR models had poor quality. The best ANN predicting FH has RMSE 4.8 cm and explains 71.3% of variance, and 10 predictors are used. The best ANN for predicting FH SDS explains 50% of variance and has RMSE 0.749 SDS, and 12 predictors are used. It seems promising to increase the sample and improve the ANN models.

Keywords: Artificial Neural Network, Regression, Prediction, Final Height, Growth Hormone Deficiency, Children.

1 Introduction

Growth hormone deficiency (GHD) is a medical condition caused by problems arising in the pituitary gland, in which it does not produce enough growth hormone. This hormone is a polypeptide which stimulates growth and cell reproduction. A disease is caused by a violation in synthesis, secretion, regulation and its biological effects. Since 1985, injecting recombinant human growth hormone (rhGH) is the recognized method for normalizing growth rate and physical development of a child, the evidence of its efficacy is high.

Several mathematical models were developed to estimate height of patients with GHD, most models were derived by multiple regression analysis. Two models predict growth response during the

1st year of therapy and are based on few dozens of cases [1, 2]. Another model estimates the height velocity during pubertal period [3]. Three models estimate final height (FH) and standard deviation score (SDS) of FH [4-6], however one of them [4] uses specific predictors available only during treatment period. One more problem is that most of prediction models use some specific that are not available in routine clinical practice, such as average knee-heel length, urinary level of deoxypyridinoline and so on. Models by Ridder et al. [5] and Smyczynska et al. [6] use predictors available at the time of diagnosis and start of therapy, but the former model has only 37% of explained variance. The models presented in [6] are based on 245 cases and use multiple linear regression (MLR) and artificial neural networks (ANN). For testing dataset, MLR model predicted FH SDS with root mean square 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. So ANN demonstrated to be valuable tool to develop prediction models. The same conclusion was proposed in [7] as the result of applying different mathematical approaches (logit-regression, ANN and logical statistical methods) to pattern recognition in clinical medicine. The difficulties of medical data processing are limited numbers of cases, mixed types of data (qualitative and quantitative) and a lot of outliers and missing data. ANN seems to be one of the most powerful instruments in such situations.

The aim of our research was to develop mathematical models predicting FH and FH SDS using individual patients' data available at the time of diagnosis and start of therapy.

2 Materials and Methods

One hundred forty-one patients of Endocrinology Research Center (Moscow, Russia) in 1978-2016 achieved final height. One hundred eighteen cases were collected prospectively and 23 retrospectively. All patients were treated by rhGH in daily dose of 0,033 mg/kg at least for 3 years.

The input variables obtained at therapy onset include 5 binary and 7 continuous. The binary variables are:

1. Patient's gender (male/female),
2. Family history of short stature (yes/no),
3. Patient's pubertal status (prepubertal/pubertal),
4. Form of the disease (isolated growth hormone deficiency (IGHD)/multiple pituitary hormone deficiency (MPHD)) based on laboratory tests,
5. Predicted regularity of rhGH therapy (yes/no).

The continuous variables are:

6. Patient's chronological age (CA) (days),
7. Birth height SDS was calculated using Prader references,
8. Patient's height SDS (H SDS) for chronological age (CA) and sex at rhGH therapy onset was calculated it with Auxology software (Munich Auxology Project),
9. Patient's bone age (BA) assessed on radiogram of non-dominant hand and wrist, according to Greulich-Pyle's standards,
10. BA/CA ratio,
11. SDS of parental-adjusted height (PAH) based on Tanner formula for genetically predicted height = (father's height + mother's height ±13): 2 ±7 for boys and girls, respectively,
12. Growth hormone peak [ng/ml] in stimulation clinical test.

FH was fixed if height velocity was <2 cm per year over at least 9 months and a chronological age >16 years for boys/ >14 years for girls and/or bone age >14 years
in boys/13 years in girls.

FH SDS was calculated using Auxology software.

Results of mutation analysis of the relevant gene panel (ARNT2, GH1, GHRH, GHRHR, GHSR, GLI2, HESX1, LHX3, LHX4, OTX2, PAX6, POU1F1, PROP1, SHH, SOX2, SOX3) were not included as they were available only for 98 patients.

Statistica software v.13 (StatSoft, Inc., USA) was used for statistical analysis and ANN development. Different topologies were tested including linear and Bayesian networks, radial basis functions and 3- and 4-layer perceptrons. RMSE and explained variance R2 (%) were the main characteristics of models' quality.

3 Results

The descriptive statistics of the sample is presented in Table 1.

Table 1. Basic characteristics of patients who achieved final height.

Characteristics	N	N (%) or Medians (quartiles)
Sex (m/f)	141	90/51 (64% / 36%)
Age at diagnosis, years	140	9.61 (6.81; 12.91)
Pubertal status (prepub/pub)	140	114/26 (81% / 19%)
Form of disease (IGHD/MPHD)	141	35/106 (25% / 75%)
Family history (yes, no)	141	31/110 (22% / 78%)
rhGH therapy regularity (yes/no)	141	99/42 (70% / 30%)
Final height, cm		
boys	90	171 (165; 176)
girls	51	158 (154; 162)
Patients who did not achieve social norm of final height	32	
boys ≤ 165 cm		19 (21%)
girls ≤ 154 cm		13 (25%)

The impact of individual predictors to FH and FH SDS was estimated using Mann- Whitney test and non-parametric Spearman correlation analysis. After Bonferroni adjustment for multiple comparisons the FH was associated with sex, therapy regularity, PAH SDS, and H SDS. FH SDS was associated with therapy regularity, PAH SDS, H SDS, and BA. Only 121 patients (86%) have complete records on predictor set, so we had to exclude 20 cases from further multivariate analysis. Two multiple linear regression models for FH and FH SDS were developed using 7 continuous predictors and forward stepwise procedures. Both models were statistically significant and included 3 and 4 predictors for FH and FH SDS prediction, respectively. However, they had rather small explained variance (27% and 26%) and not acceptable RMSE (7.8 cm and -0.93 SDS). ANN were more effective. We used two types of predictor sets:

- full sets of predictors with further application of genetic algorithm,
- short sets of predictors which had individual impacts on outcomes.

The initial sample was randomly divided into training and testing samples with 7:3 ratio (85 and 36 cases, respectively). There were no control sample because of small total amount of cases, and also because the errors on testing and control samples are usually very similar.

Three and four-layer perceptrons appeared to be the most effective topologies among tested ones. Main results of modelling are presented in Table 2.

Table 2. Characteristics of artificial neural networks predicting final height and its standard deviation score in 121 children with growth hormone deficiency.

	Predicting FH		Predicting FH SDS	
Predictors	Selected by genetic algorithm	Short set	Selected by genetic algorithm	Short set
No. of predictors	10	4	12	4
Topology	MLP (3) 10:10-6-1:1	MLP (3) 4:4-4-1:1	MLP (4) 12:12-13-9-1:1	MLP (3) 4:4-10-1:1
RMSE				
total	4.816 cm	5.546 cm	0.749 SDS	0.823 SDS
training	4.903 cm	5.495 cm	0.760 SDS	0.840 SDS
testing	4.604 cm	5.664 cm	0.725 SDS	0.784 SDS
R^2				
total	71.3%	62.0%	50.0%	43.7%
training	68.3%	60.1%	47.5%	35.7%
testing	77.1%	65.5%	50.7%	59.8%
Correlation				
total	0.856	0.784	0.695	0.577
training	0.838	0.766	0.669	0.509
testing	0.879	0.830	0.714	0.709

The sets of variables selected by genetic algorithms provided better results than short sets of variables. Then, models for predicting FH had better performance comparing with the models predicting FH SDS. The best ANN had RMSE about 4.8 cm and explained 71.3% of variance. Figure 1 shows scatterplot of target and modelled FH for both training and testing samples. The non-parametric Spearman correlation is 0.856.

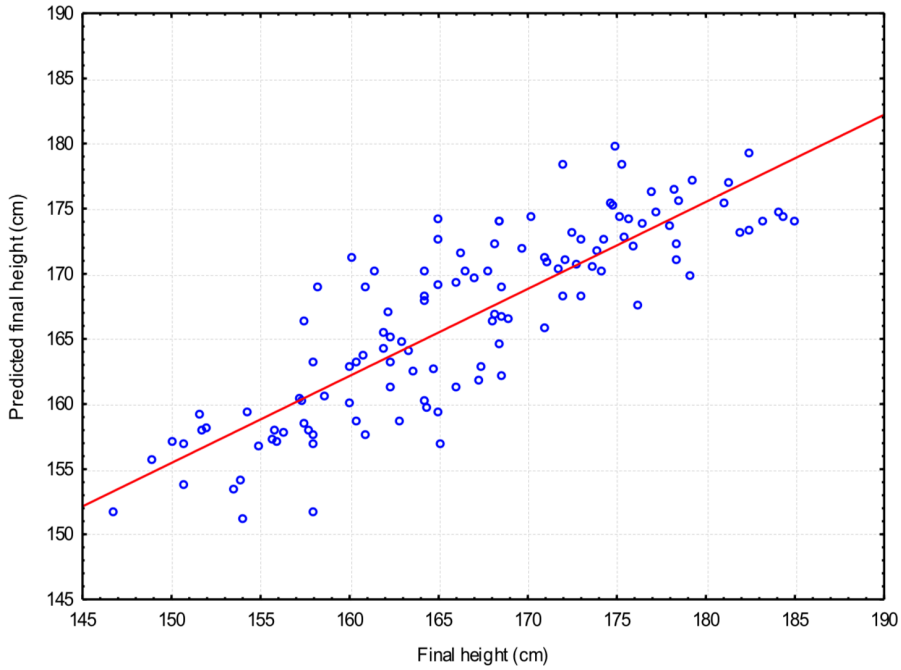

Fig. 1. Scatterplot of target and predicted final height (n=121)

4 Discussion

The quality of our models seems not to be good enough because of small sample we had. Smyczynska et al. [6] developed ANN models based on 245 cases predicted FH with RMSE 3.9 cm, explaining 78.7% of its variability, and FH SDS with RMSE 0.60 SD, explaining 42.0% of variability. Our results are worse (RMSE 4.8 cm and R2 71.3% for FH) most probably because we have twice less cases. Results of predicting FH SDS are also not good - RMSE 0.75 SDS and R2 50%. Similar situation is described by [6]. The predictor sets of our models and [6] greatly differ, both in quantity and quality, some predictors were not available in our dataset, for example we had no data on serum concentration of IGF-I and IGF-I SDS. It seems essential to increase dataset and re-develop our models. However, ANN demonstrated to be the efficient approach to mathematical modeling for clinical purposes.

The ability to predict the individual effectiveness of growth hormone replacement therapy is of great importance. Based on patient's features the endocrinologists are able to manage regime and drug doses. The models provide personalized approach to treatment of patients with GH-deficiency. ANN allows making dose of rhGH and regimen of injection individually adjusted and contribute to improved overall outcomes. ANN can also be useful for evaluating effectiveness of the therapy in patient subgroups and for demonstrating factors determining FH. Prediction models may also reduce the drug costs for GH treatment.

References

1. Mortensen,H.B.,Main,K.,Michaelsen,K.F.etal.Predictingandmonitoringofgrowthin children with short stature during the first year of growth hormone treatment. Acta Paediatr Scand, 80(12), 1150-1157 (1991).
2. Schönau, E., Westermann, F., Rauch, F., et al. A new and accurate prediction model for growth response to growth hormone treatment in children with growth hormone deficiency. Eur J Endocrinol, 144(1), 13-20 (2001).
3. Ranke, M.B., Martin, D.D., Lindberg, A. Prediction model of total pubertal growth in idiopathic growth hormone deficiency: analysis of data from KIGS. Horm Res, 60, 58-59 (2003). DOI: 10.1210/jc.2006-1259
4. Wikland, K.A., Kriström, B., Rosberg, S., et al. Validated multivariate models predicting the growth response to GH treatment in individual short children with a broad range in GH secretion capacities. Pediatr Res, 48(4), 475-84 (2000). DOI: 10.1203/00006450- 200010000-00010
5. de Ridder, M.A., Stijnen, T., Hokken-Koelega, A.C. Prediction of adult height in growth- hormone-treated children with growth hormone deficiency. J Clin Endocrinol Metab, 92(3), 925-931 (2007). DOI: 10.1210/jc.2006-1259
6. Smyczynska, J., Hilczer, M., Smyczynska, U., et al. Neural network models - a novel tool for predicting the efficacy of growth hormone (GH) therapy in children with short stature. Neuro Endocrinol Lett, 36(4), 348-353 (2015).
7. Rebrova, O.Yu. Application of methods of intellectual data analysis to solve the problem of medical diagnostics. News of Artificial Intelligence, (3), 76-80 (2004) (in Russian).