Artificial Neural Network for the Prediction of Chromosomal Abnormalities in Azoospermic Males

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Purpose: To evaluate whether an artifical neural network helps to diagnose any chromosomal abnormalities in azoospermic males.

Materials and Methods: The data of azoospermic males attending to a tertiary academic referral center were evaluated retrospectively. Height, total testicular volume, follicle stimulating hormone, luteinising hormone, total testosterone and ejaculate volume of the patients were used for the analyses. In artificial neural network, the data of 310 azoospermics were used as the education and 115 as the test set. Logistic regression analyses and discriminant analyses were performed for statistical analyses. The tests were re-analysed with a neural network.

Results: Both logistic regression analyses and artificial neural network predicted the presence or absence of chromosomal abnormalities with more than 95% accuracy.

Conclusion: The use of artificial neural network model has yielded satisfactory results in terms of distinguishing patients whether they have any chromosomal abnormality or not.

Keywords: Artificial neural network; azoospermia; chromosomal abnormality; infertility; prediction.

INTRODUCTION

Since to first introduction of artificial neural network (ANN) to andrology by Niederberger in 1993,[1] there are scarce papers in this area. Andrology is a special field with the opportunity for mathematical modelling. Generally, at least in our country-Turkey, somewhat complicated cases are referred to tertiary care clinics without providing sufficient information to the patient/couple. Computer technology is used widely worldwide. Simple diagnostic tools might help the clinician in seconds to find out satisfactory information. Producing diagnostic tools using statistical or ANN models is the duty of academicians.

Azoospermia is still a frustrating condition and needs to be diagnosed adequately and quickly to be able to make an explanation to the couple. The male has to be examined with lots of diagnostic tests. As known, there are some clinical and laboratory parameters showing the cause/s of azoospermia. Whether the males should be genetically evaluated and the required genetical evaluations should be practically decided. It might seem as an easy problem. If the male is azoospermic, with very little testicles and taller than general population, the diagnosis is a kind of hypogonadism most probably before any test is performed. All of the following questions might irritate the clinician: In all azoospermic males, is it necessary to perform genetical tests, what are their costs, are the duration of the tests increase the distress of the couple? The aim of this study is to develop an ANN model which may predict which azoospermic male with cytogenetic evaluation requirements.

MATERIALS AND METHODS

Study Design

A non-interventional, retrospective study was designed in Erciyes University, Department of Urology.

Study Population

The data of pellet negative azoospermic males were evaluated retrospectively. If the evaluated parameters which might help the diagnosis were complete, the data of 425 patients were taken into consideration by the below-mentioned exclusion criteria:

Exclusion Criteria

a) absence of one or two testicles, b) the presence or history of cryptorchidism (with or without surgery), c) the presence of significant testicular atrophy of one or two testicles later on life d) size discrepancy between the testicles more than 50%, e) Prior chemo and/or radiation therapy for any reason/region, f) any hormonal treatment which could have effected the testicular volumes or hormones, g) history of mumps orchitis.

Evaluations

All patients were evaluated in the same clinic and generally by the same physician (OE). The height (cm) and body weight (kg) of the patients were measured and recorded. Testicular volumes were determined by using Prader orchidometer. All semen analyzes were done in the same laboratory. Semen samples were obtained after a 3 to 5 days period of ejaculatory absti-

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Table 1. The distribution of the patients according to the diagnosis and training and test

Diagnosis	Training	Test	Total
	N	N	N
Nonobstructive azospermia	158	60	218
Klinefelter's syndrome	70	25	95
Vasal agenesia	29	11	40
Unidentified	19	7	26
Epididymal obstruction	12	4	16
Hypogonadothropic hypogonadism	11	4	15
Other chromosomal abnormalitiesa	8	3	11
Distal ejaculatory duct obstruction	3	1	4
Total	310	115	425

[a]Significant sex chromosome abnormalities like 46XX, 46XY /45X0.

nence, and semen analyzes were performed according to 2010 World Health Organization (WHO) guidelines.[2] Semen analyzes were performed at least twice and pelleting was performed. Patients with negative pellet test were considered as azoospermic. Some males could not ejaculate (especially hypogonadothropic ones), their ejaculate volumes were taken as zero. All hormonal evaluations were performed in the laboratory of our center. Peripheral blood samples were used for cytogenetical examinations and at least 20 metaphases have been evaluated.

Total testicular volume (right and left), body weight, height, body mass index (BMI), total testosterone (TT), follicle stimulating hormon (FSH), luteinizing hormon (LH), prolactin (PRL), estradiol (E2) and ejaculate volume were the intended to evaluate data. These data were evaluated one by one with binary logistic regression analysis whether they could help the diagnosis. If not, they were not used in artificial neural network (ANN) and other statistical analyses.

There were 425 eligible azoospermic cases. Among them, 310 were chosen as the education set and 115 as test set randomly for the ANN evaluation. All statistical evaluations were made for these sets separately and as whole group.

Multilayer perceptron neural networks

Multilayer perceptron (MLP), called also multilayer feed forward neural network, is one of the most popular ANN architectures. The MLP is very efficient for function approximation in high dimensional spaces. The architecture of the MLP with a three layer topology. An MLP network is composed of neurons connected to each other. The input signal propagates from the input layer to the output layer. The number of neurons in the input and the output layers depend on the number of input and output variables, respectively. The number of hidden layers and the number of neurons in each hidden layer affect the generalisation capability of the network.

The performance of an MLP network depends mainly on the weights of its connections. The training process of an MLP network involves finding values of the connection weights, which minimise an error function between the actual network output and the corresponding target values in the training set. The knowledge is represented and stored by the strength (weights) of the connections between the neurons. After the MLP network is satisfactorily trained and tested, it is able to generalize rules and will be able to respond to unseen input data to predict required output, within the domain covered by the training examples.

Table 2. Variables used both in the ANN and logistic regression analsyes.

	Trainin set[a]	Test set[a]	*p*-value
N	320	115	
Age (years)	31.0 + 5.5	31.4 + 5.7	0.41
Height (cm)	173.0 + 7.6	174.5 + 8.5	0.11
Total testicular volume (mL)	22.9 + 14.8	22.9 + 14.7	0.85
Ejaculate volume (mL)	2.2 + 1.5	2.3 + 1.4	0.51
FSH (mIU/mL)	20.9 + 17.1	19.0 + 15.7	0.30
LH (mIU/mL)	10.8 + 8.6	9.9 + 9.0	0.22
Total testosterone (ng/dL)	377.1 + 229.6	364.6 + 214.1	0.65

[a] Data is presented as mean ± SD

Abbreviations: FSH, Follicle Stimulating Hormone; LH, Luteinizing Hormone.

Application of MLPs to the problem

The MLP neural model used in predicting genetic anomaly is shown in Figure 1. The network employed consists of input layer, hidden layers and output layer. The input layer has six neurons since there are six input variables with height, total testicular volume, ejaculate volume, FSH, LH and total testosterone. Each hidden layer contains eight neurons which were found after many trials, and the output layer has got one neuron which is a measure of probability of genetic anomaly presence. The tangent hyperbolic and sigmoid nonlinear activation functions are used in the neurones of the first and second hidden layers respectively, and the linear activation function is used in the output neuron. The input data tuples were scaled between –2.0 and +2.0 and the output data tuples were also scaled between 0.0 and 1.0 before training. An estimated probability of less than 0.5 indicated no genetic anomaly, whereas an estimated probability of greater than 0.5 suggested the presence of genetic anomaly.

Outcomes

Total 425 data sets were used. 310 of data sets were used for training the network, and the remaining 115 data sets were used for the testing. In this study, Levenberg-Marquardt algorithm that combines the best features of Gauss-Newton and gradient descent methods was used to train the proposed network.[3,4] The learning phase is carried out after the presentation of each set until the calculation accuracy of the network is deemed satisfactory according to a maximum allowable number of training cycles. The number of training cycles was taken to be 1000 epoches. After proper training, the network was tested with 115 data sets.

Ethics

The study was approved by the ethics committee.

RESULTS

The distribution of the patients according to the diagnosis and training and test sets were shown in **Table 1**. Following logistic regression analyses, height, total testicular volume, FSH, LH, TT and ejaculate volume produced significant differences to discriminate whether the patients had sex chromosome abnormalities. Afterwards, only these six variables were used for ANN evaluations(**Table 2**). The evaluated parameters revealed non-significant differences between the training and test sets.

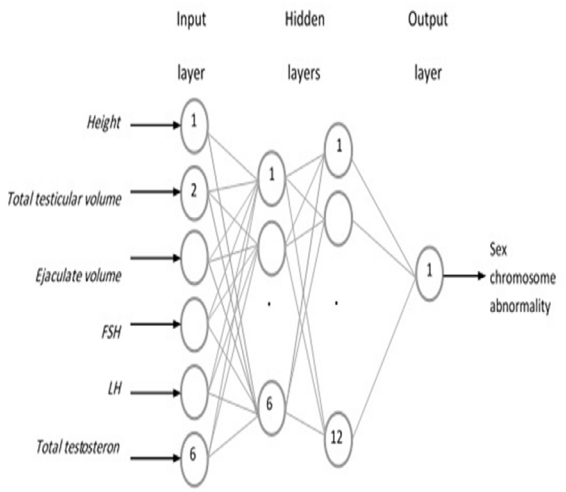

Figure 1. The MLP neural model used to predict genetic anomaly.

In logistic regression analyses, total testicular volume with LH had the highest power to find out who requires sex chromosome evaluation with the expressiveness ratio of 96.5% and 95.2% in the test and the training sets, respectively. In ANN with all parameters in training set the accuracy was 100%. In test set, the ratio was 97%.

DISCUSSION

Azoospermia is diagnosed in approximately 1% of all men and up to 15% of infertile men, depending upon the demographic nature of the infertile cohort.[5] Men with azoospermia should be evaluated in an effort to discover the underlying etiology of their condition, which will guide the formulation of a therapeutic plan.[6] In about 15% of male and infertile subjects, genetic abnormalities may exist, including chromosome aberrations and single gene mutations.[7] The frequency of karyotypic abnormalities in 1790 males with infertility was detected to be high as 12.67% in azoospermia and 4.6% in oligozoospermia, respectively.(8) Genetic risks for couples undergoing in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) are related to transmission of constitutional genetic abnormalities, genetic alterations present only in sperm, or de-novo generated genetic disorders. Therefore, the identification of genetic factors has become a good practice for appropriate management of the infertile couple.[7] Azoospermia is still a frustrating condition and needs to be diagnosed adequately and rapidly to be able to provide an explanation to the couple. The prediction of a genetical abnormality with physical examination and some simple tests are important for the physician. A simple and cheap predictive tool will provide convenience for both patients and physicians. Thus, we attempted to create a diagnostic tool by using artificial neural network. Neural networks have become popular tools in urological research. These systems are now being investigated as predictive methods in many areas, such as bladder cancer research, detection of prostate cancer, spontaneous stone passage in stone disease and bladder outlet obstruction in men with lower urinary tract symptoms.[9-12] Andrology and infertility are special areas with the opportunity for mathematical modelling. In this field, scarce studies (not more than 20) are present and the studies generally focused on assisted reproductive techniques. This is the first study to determine the cytogenetical abnormalities with the help of ANN, in azoospermic males.

Neural computation is a nonlinear modelling technique that adopts features of the physiological function of the biological neuron to inspire its mathematical models.[13] The most common ANN model used in clinical medicine is a special class of ANN, namely the MLP. This model is well suited for solving clinical diagnostic classification problems.[14] ANN and classical statistical methods were used together and compared with each other in several previous studies. We used logistic regression analysis for classical method and it worked as a guide for ANN. We determined the parameters that we used for input layers by logistic regression analysis. Following logistic regression analyses, height, total testicular volume, FSH, LH, TT and ejaculate volume produced significant differences to discriminate whether the patients had sex chromosome abnormalities. Then only these six variables were used for ANN evaluations. Both logistic regression analyses and ANN predicted the presence or absence of chromosomal abnormalities more than 95%.

Total testicular volume and LH had the highest power to find out who requires sex chromosome evaluation in the current study. Contrary to the expectations, the power of the FSH was not so high. This situation may be associated with different subgroups included in our study population.

Artificial neural network and the logistic regression analyses worked well in the problem presented here. This problem seems easy to resolve practically. However, we need practical predictor programmes in phones, computers and etc. This study is also a beginning of the other studies. With the same parameters, we will try to perform multicenter studies whether the predictor works in a same way. In this way, the physcians who work at primary centers will be able to evaluate their patients easier and more accurately.

In previous studies, the researchers produced some ANN models to predict outcomes of some procedures at infertility management such as presence of spermatazoa in testes and IVF/ICSI outcomes. Designed ANN models demonstrated high accurate prediction rates.[15-17] Moreover, some other biomarkers associated with spermatogenesis (inhibin b, leptin) had been combined with ANN models to prediction of sperm retrieval.[18] Combination of ANN models for the management of each step of azoospermic males would be very beneficial for both patients and physicians. To design such a system will not be too difficult with recent technologies. Infertility management is still a challenging process due to its cost, time consuming and uncertainty of results. ANN models may save time and reduce costs by avoiding from unnecessary tests. In addition, predicting outcomes accurately and further informing the couple may make their expectations of treatment more realistic and abstain from unnecessary frustrations.

Although azoospermia may be due to genital tract obstruction, defective spermatogenesis, ejaculatory duct dysfunction or hypogonadotrophism, it is currently classified as obstructive and non-obstructive. This is because, hypogonadotrophic azoospermia and ejaculatory duct dysfunction are rare causes of azoosperm-

ia, accounting for about only 2% of azoospermia.[19] Defective spermatogenesis in 60% and genital tract obstruction in 40% of 102 patients with azoospermia evaluated with testicular biopsy and distal vasography were reported.[20] None of the patients in this series had ejaculatory dysfunction or hypogonadotrophic hypogonadisim. In our study population, some disorders are very rare (**Table 1**). The other intended study is to predict the exact reason of azoospermia. If we may be able to reach a higher number of patients, we might stratify them more easily. If an ANN model that may predict the cause of azoospermia is produced, some patients may not require cytogenetical evaluation.

There is some limitations of our study. All eligible patients were included in the study. If power analysis was performed and the sample size was determined, our results could be more reliable statistically. Some sub-analyzes may be performed by increasing the number of patients. In this way, a possible relationship between LH and testicular volume may be evaluated and even a cut-off value for LH may be detected to predict the patients with the requirement of chromosomal evaluation.

CONCLUSIONS

The use of ANN model has given satisfactory results, in terms of distinguishing patients whether they have any chromosomal abnormality. As more specific input variables become available and number of cases increase, it might be possible to predict the exact diagnosis. Artificial intelligence based models are difficult to train, however easy to use. Possible combinations of ANN models might reduce the treatment cost and predict treatment outcomes.

CONFLICT OF INTEREST

The authors report no conflict of interest.

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