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Predictions of ocular changes caused by diabetes in glaucoma patients

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ABSTRACT

Background and objective: This paper builds different neural network models with simple topologies, having one or two hidden layers which were subsequently employed in the prediction of ocular changes progression in patients with diabetes associated with primer open-angle glaucoma.
Material and Methods: For attempting to indicate whether there is a relationship between glaucoma and diabetes, a simulation method, based on artificial neural networks (ANN), Jordan Elman networks **(**JEN**)** type, in particular, was applied in conjunction with clinical observation. The study was conducted on a sample of 101 eyes with open angle glaucoma included and, in each case, the patients had associated diabetes mellitus. A high degree of accuracy was exhibited by the models, demonstrating the potential effectiveness of this artificial intelligence technique for predicting ocular changes associated with diabetes. The parameters considered in this study for modelling purpose were: glaucoma age, diabetes age, C/D ratio (cup/disk size), glycated haemoglobin level (HbA1c), intraocular pressure (IOP), patient age, mean deviation (MD) and LENS appearance.
Results: Relatively simple models, feed-forward neural networks with one or two intermediate layers, provided clinically meaningful data in direct modelling, the probability of correct answers being of 95%. Inverse modelling was also performed, in which MD depreciation was the output parameter. High accuracy was exhibited, in this case, with Jordan Elman networks, with the confidence interval of ±15%.
Conclusions: The neural models have demonstrated the possibility of their use in successfully predicting the relationship between glaucoma and diabetes in a real clinical environment.

1. Introduction

Diabetes and glaucoma are two chronic diseases that significantly affect the population aged over 40; the opinion on the physiopathology of these diseases when occurring in unison is not consistent. Both diseases lead to degeneration of neural structures of the eye. Many literature reports have found a correlation between diabetes mellitus (DM) and primer open angle-glaucoma (POAG). However, a nearly equal number of reports are unable to find evidence of this correlation [1–4].

In order to establish whether there is a relationship between glaucoma and diabetes, a simulation method based on artificial neural networks (ANN) was used in conjunction with clinical observations. A neural network is capable of building its own algorithm for solving a problem if it is trained by providing a set of representative cases, with sufficient data from which it is able to extract the necessary information. The network is trained based on collected data, i.e. process behaviour learning. In the work or reference phase, the network will use the acquired information to process similar cases in the same way as those contained in the training set. Thus ANN can operate and draw conclusions from data not available in the training process ("unseen data") [5–7].

ANN have been widely used for data processing in medical diagnosis. Papik's review shows that over 2000 publications describing applications of neural networks in cardiology, oncology, pulmonology, gastroenterology, radiology, ENT, gynaecology etc. were published between 1990 and1997 [8]. Thanks to the aforementioned ability of ANN to predict outcomes based on limited training sets, they have found increasing utility as a diagnostic tool in clinical practice. Besides their use in other specialties [9], ANNs have been specifically used in ophthalmology, for measuring the retinal structure and visual function. Various tools of artificial intelligence (neural networks and genetic algorithms) have been ap-

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plied to determine visual field progression for patients with glaucoma, to classify modifications in diabetic retinopathy (presence or absence of retinopathy signs) and in the stage of glaucoma [10–17]. Antón et al. [18] used neural networks for interpretation of retinal lesions in early perimetric glaucoma and concluded that both neural networks and statistical analysis can accurately differentiate early changes caused by glaucoma and other diseases, with an accuracy of 97%. Other studies realized by Goldbaum show that the networks differentiate better between normal and altered visual field than the overall visual field index. [19].

In recent studies, Rigla and others used artificial neural networks in the follow-up of patients with diabetes while promoting the involvement of medical personnel in this area [20]. Furthermore, Singh et al. [21] used artificial intelligence tools in assessing the risk of diabetic foot ulcers in patients with diabetes mellitus type by utilizing both multiple regressional analysis and neural models. They concluded that the artificial networks have a better predictive capacity than statistical models and could be used in assessing the risk of foot ulcers in diabetic patients.

Inspired by previous excellent results in implementing ANN in a diagnostic setting, ANN are used here for the first time to emphasize the relationship between diabetes and glaucoma, as well as to predict ocular modifications related to diabetes for patients with glaucoma. By choosing diagnostic elements for the two diseases as input parameters for building a training database (age glaucoma, diabetes, report C/D, glycated haemoglobin, intraocular pressure, LENS appearance, MD-deviation on visual field) and testing the resulting ANN against a pool of patients not included in the training set, a statistically significant correlation between the two disorders was obtained.

2. Material and method

2.1. Study group

To predict the relationship between glaucoma and diabetes, a database was constructed containing information on 52 patients with glaucoma and diabetes, (101 eyes), examined in the Ophthalmology Clinic I of “ Sf. Spiridon” Hospital, in Iasi, between 2011 and 2013. The criteria taken into account in this study were: normal or hypertensive primer open-angle glaucoma, ocular hypertension and associated diabetes. Patients with other types of glaucoma (pseudoexfoliation, pigment, cortisone, neovascular and primer with angle closure) and those without associated diabetes were excluded. Criteria for the diagnosis of normal and hypertensive POAG were: age greater 35, IOP higher than 21 mm Hg without treatment, camerular angle open to gonioscopy, optic nerve damage typical in glaucoma (ratio C/D > 0.5), abnormal visual field (by Humprey Field Analyzer perimetry) and retinal nerve fibre layer with diffuse or localized defects (Optic Coherence Tomography - Cirrus HD OCT Carl Zeiss Meditec) [22]. Assessment of diabetic retinopathy modifications was made using Volk lens and by retinal photographing on Fundus Camera Zeiss, on dilated pupil, following their presence in all quadrants. Criteria for classification of changes of DR (diabetic retinopathy) (ETDRS) were: no changes (absent signs of DR), mild non-proliferative diabetic retinopathy (presence of a single micro-aneurysm), mild form (micro-aneurysms, haemorrhages in 2–3 quadrants, venous dilatation and thornback rays in one quadrant), severe (micro-aneurysms, haemorrhages in all quadrants, venous dilatation in 2–3 quadrants) and proliferative diabetic retinopathy (retinal neovascularization on disk and retina in different quadrants). Any new clinical element that appeared at subsequent controls was considered as a progression of diabetic retinopathy that led to its classification as severe nonproliferative or proliferative diabetic retinopathy [23]. The information that led to the database development included elements of diagnosis for each disease (Table 1).

Table 1
Characteristics of the patients included in the study.

Characteristics	Average value
Ages	64.85 +/− 7.04
Sex	74.13% F, 25.87% M
Old glaucoma (years)	4.17 +/− 3.46
IOP	18.61 +/− 4.77
	−4.63 db (medium)
Old diabetes (years)	8.05 +/− 6.08
Type diabetes	
I	9.81%
II	58.92%
MIXT	31.37%
HgA1c (%)	6.98 +/− 1.24
Glycemic level(mg/dl)	137.42 +/− 23.17
DR changes	Without DR 89.11%
	Mild DR 5.94%
	Moderate/severe DR 4.95%

IOP (intraocular pressure), MD (mean deviation), type diabetes (I - insulin, non insulin, mixt) DR (diabetic retinopathy), HgA1c (glycated haemoglobin, marker of glycemic control, normal < 6,5%); glycemic level (mg/dl) normal (< 110 mg/dl).

2.2. Neural network design

Neural network modelling of the relation between glaucoma and diabetes involves first the determination of the input parameters, as the main factors influencing this relation. Therefore, the following measurements were selected as input parameters for neuronal models: glaucoma age (A), diabetes age (B), C/D ratio (C), glycated haemoglobin (D), intraocular pressure (E), patient age (F), MD-mean deviation (H) and LENS appearance (G), which was coded as 0 for non modifications and 1-for modifications. The considered output parameter was the presence or absence of diabetic retinopathy modifications (DR). Regarding the output parameter (O), “1” was used to mark the presence of modifications of DR and “0” for no modifications.

Generally, in an inverse neural network modelling, the input and output variables change their places. In order to reinforce the idea of a correlation between diabetes and primer open- angle glaucoma, in the last part of this study, reverse modelling was carried out.

For inverse modelling, as output parameter was considered MD (O”) and the following input variables: age glaucoma (A”), diabetes age (B”), C/D ratio (C”), glycated haemoglobin (D”), intraocular pressure (E”), the age of patients (F”), the presence or absence of modifications of diabetic retinopathy - DR (G”) and the LENS appearance (H”).

Both types of neural modelling, direct and inverse, used common diagnosis elements for diabetes and glaucoma, trying to demonstrate the existing relation between them. Mean deviation is an important parameter for the two diseases, and was chosen as the output in inverse modelling and as one of the inputs in direct modelling.

2.2.1. Neural networks types

In order to find which topology is the best for neuronal models, two types of neural networks, with different architectures, were tested: feed forward neural network (MLP–multilayer perceptron) and Jordan Elman Network (JEN) type.

Feed-forward neural networks are a class of networks commonly used in various fields, including medical diagnosis. They are characterized by the presence of a layer of input neurons, a number of hidden layers and output layer neurons (Fig. 1). In Fig. 1,