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Original Article

Prediction of subclinical gouty nephropathy by using neural networks

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Abstract

Gouty nephropathy may have a subclinical course for years, but with what probability may it occur? We used neural networks or "artificial intellect" to solve this problem. This study aims to recognize the risk factors that correlate with significantly high microprotein indices and build a neural network that will predict the development of subclinical course of gouty nephropathy in percentage without additional tests. A one-center cohort prospective study included 117 gouty arthritis patients who were on scheduled in-patient treatment at the rheumatology department during 2018–2021. All patients had no history of ongoing kidney disease. The study aimed to recognize the risk factors that correlate with significantly high microprotein indices and build a neural network that will predict the development of subclinical course of gouty nephropathy in percentage without additional tests. We can distinguish the factors that are most associated with the development of kidney disease and correlate with microalbumin (r1) and α1-microglobulin (r2) in the urine: hyperuricemia (r1=0.85; r2=0.73), hypouricosuria (r1=-0.79; r2=-0.63), hypertriglyceridemia (r1=0.84; r2=0.78), an increase in LDL levels (r1=0.77; r2=0.79). There were also established correlations between renal disease and the fact of arterial hypertension (r=0.81), diabetes mellitus (r=0.59). The neural network was built. That is why, having input data, it is easy to predict the risk of gouty nephropathy development by using the proposed calculator and beginning early target prophylaxis, even if kidney disease may have a subclinical course.

Keywords: gout, nephropathy, microproteins, neural network.

Introduction

Gout is considered the most common inflammatory disease of joints in men, affecting up to 2% of the planet's adult population [1]. Besides, it is a major cause of loss of workability, limitation of professional capacity and early disability, resulting in a significant social and economic burden for the country [2].

This disease becomes even more challenging due to comorbidities. A frequent combination of gouty arthritis with concomitant pathology (mostly kidney disease and obesity) leads to a reduction in the effectiveness of treatment, with rapid progression of complications and an increase in mortality [3, 4]. A prolonged subclinical course characterizes kidney disease in patients with gouty arthritis (gouty nephropathy). Several studies have shown that the only marker of kidney damage can be asymptomatic microproteinuria, with uncontrolled hyperuricemia being a risk factor. Nevertheless, it is still unclear whether hyperuricemia is a risk factor for gouty nephropathy or *vice versa* [5, 6].

Today we use the newest diagnostic criteria to verify the diagnosis of gout and modern therapy to treat this cohort of patients and move into remission phase. However, we cannot predict the development of complications such as gouty nephropathy due to asymptomatic course that may stay for years. We do not know "who will be the first and when it may start". To solve

such kind of problem, we used neural networks or, in other words – artificial intellect.

The term "neural network" appeared in the mid-XX century. In 1943, Walter Pitts and Warren McCulloch made the first computer model of a neural network. It was based on a theory of brain activity and mathematical algorithms. Artificial neuron was similar to the structure of a biological neuron: dendrites, neuron body and axon. Dendrites are branched processes that collect information. In that case, if the input information has activated a neuron – an excitation wave is generated, which propagates through the membrane of the body of the neuron, and then through the axon, through the emission of a neurotransmitter, transmits the signal to other nerve cells or tissues [7]. The researchers called their "artificial neuron" a perceptron and proposed a mathematical algorithm design that can perform virtually any imaginary, logical or numerical operation. Scientists have also suggested that neural network is able to learn, recognize images and generalize information and has all the traits of intellect [8, 9].

An artificial neuron is a computing unit that receives information, performs simple calculations and transmits it further. It is divided into three main types: input, hidden and output. Each of the neurons has two main parameters: input data and output data (Figure 1) [10].

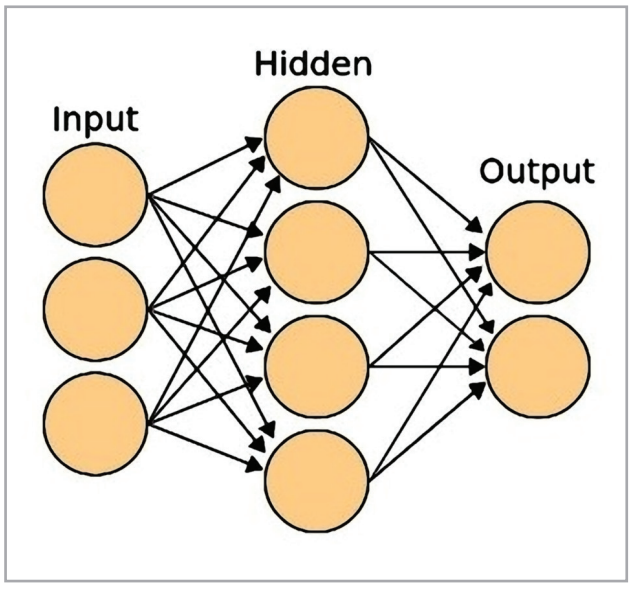

Figure 1: Structure of an artificial neuron.

In the early 1970s, a system for the diagnosis of septic shock (MYCIN) was developed at Stanford. Half of the patients died from this condition within a day, and doctors could detect sepsis only in 50% of the cases. MYCIN seemed to be a real triumph for expert systems technology, as it made it possible to detect sepsis in 100% of cases. However, after a closer acquaintance with this expert system, doctors have significantly improved traditional methods of diagnosis, and MYCIN has lost its importance, becoming a training system [11]. In 1990, William Buxt of the University of California, San Diego, used a neural network to detect myocardial infarction in patients admitted to the hospital with chest pain. Its purpose was to create a tool that could help doctors who were not able to cope with the flow of data characterizing the patient's condition. Another goal was to improve diagnostics. The researcher used only 20 parameters, including age, gender, pain localization, response to nitroglycerin, nausea, vomiting, sweating, fainting, respiratory rate, heart rate, myocardial infarction in history, diabetes, hypertension and ECG changes. The network demonstrated an accuracy of 92% in detecting myocardial infarction [12]. Researchers at Duke University have trained the neural network to recognize mammograms of malignant tissue based on eight features that radiologists usually deal with. It turned out that the network could solve the problem with a sensitivity of about 100% and a specificity of 59%. A similar problem is solved by artificial intellect at the Mayo Clinic, Minnesota when analyzing the results of an ultrasound examination of the breast. A team of researchers from the University of Nottingham has developed an algorithm for assessing patients' risk of cardiovascular disease. Artificial intelligence is trained to determine cardiac disease risk more effectively than real doctors. The algorithm's accuracy was 74–76.4% [13].

The study aimed to recognize the risk factors that correlate with significantly high microprotein indices and build a neural network that will predict the development of subclinical course of gouty nephropathy in percentage without additional tests.

Material and methods

Study design and patients

A one-center cohort prospective study was conducted that included 117 patients with gouty arthritis who were on scheduled in-patient treatment at the Rheumatology Department during 2015–2018. All patients had no history of any ongoing kidney disease (acute/chronic kidney disease, urate nephropathy, kidney stones, other etiology and also any urine sediment changes) or in the past. All procedures performed in the

study were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments. Informed consent was also obtained. The diagnosis of gout was based on the diagnostic criteria of the American College of Rheumatology/European League Against Rheumatism 2015. Statistical analysis was performed with Microsoft Office Excel 2016 (Microsoft Corp., USA) and Statistica 10.0 (StatSoft Inc., USA).

Laboratory, anthropometric and clinical data collection

Given that the patients were on in-patient care – all were scheduled and screened: a general urine analysis, a biochemical blood test (uric acid, glucose, creatinine, urea), uric acid in the urine, lipidogram (total cholesterol, low-density lipoproteins (LDL), high-density lipoproteins, triglycerides), x-ray examination of joints. Also, minute diuresis, glomerular filtration rate, uric acid clearance, and kidney ultrasound were performed. Almost all patients who agreed to participate in the study had obesity of varying degrees. Among 117 patients, 103 had obesity, so it was decided to exclude patients with normal body weight for more reliable statistical data processing.

In addition, all patients were tested for urinary microalbumin and α1-microglobulin. It is a special test that can show the level of microproteins that are not visible in general urine sediment analysis. It is the first direct sign of kidney damage. Unfortunately, the main problem is that this test is not so important in rheumatology; quite expensive and just a few laboratories can perform it. According to the data obtained, the first group (n=58) consisted of patients who showed increased levels of microalbumin and α1-microglobulin in the urine. The second group (n=45) – patients with acceptable indices of microproteinuria, was the control group.

Neural networks are non-linear systems that allow much better data classification than conventional linear methods. They found active use in medicine. The main goal of neural networks is to significantly increase the specificity of diagnostics without reducing its sensitivity. That was the main reason why we chose this one method and built the neural network.

Results

It was found that all subjects were male, with age 50.8 (8.05) years, and the duration of the disease 9.31 (5.02) years. Also, in most of the patients were detected tophi (72.8%) with lost ability to work (57.3%). During the study, patients had 10.51 (2.03) beds in the hospital. Regarding the affected joints, their minimum number was equal to three, and the maximum – was 36 joints with an average value of 12.48 (5.01). In 72.8% of patients were diagnosed one or no episode of exacerbation per year, 23.3% – two episodes of exacerbations per year, and only 3.9% of patients had three or more exacerbations of gouty arthritis per year.

Patients have been of representative age. The majority of the first group had lost the ability to work in comparison with the second group of patients (63.8% and 48.8%) that showed a longer duration (62.1% and 33.3%) and a more severe course of the disease (3.4% and 2.2% accordingly). Comparative analysis of the body mass index allowed us to state that most patients in both groups were detected with first-stage obesity, with predominance in the second group. The rest showed second-stage obesity.

Furthermore, only third-stage obesity was found in patients from the first group. Deeper structural changes that corresponded to the third radiological stage (12.1% and 8.9%), the presence of tophi (77.6% and 66.7%) and the statement of hypouricosuria (94.8% and 57.8%, accordingly) were detected in the first group of patients. In assessing the intensity of VAS pain, the following values were obtained: in the first group – 75.31 (8.20) mm, in the second group – 63.71 (12.39) mm with a prevalence of more than ten affected joints in patients from the first group (81.1% and 73.3%). Comparative characteristics of hyperuricemia showed that all patients from the first group had high abnormal indices of uric acid and only 73.3% of patients in the second group.

The first step in neural network building is to find out the most influential factors on gouty nephropathy formation and they should be selected as input data. As we mentioned that the first direct sign of kidney damaging is microprotein levels elevation – we can distinguish the factors that are most associated with urine microalbumin (r1) and α1-microglobulin (r2): hyperuricemia (r1=0.85; r2=0.73), hypouricosuria (r1=-0.79; r2=-0.63), hypertriglyceridemia (r1=0.84; r2=0.78), an increase in LDL levels (r1=0.77; r2=0.79). There were also established correlations with the fact of arterial hypertension (r=0.81), diabetes mellitus (r=0.59). Age, number of affected joints, cholesterol indices and disease duration had not had such significant correlations but were also included in the author's opinion. The correlation matrix was done.

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	A	B	C	D	E	F	G	H	I	J	K
1	Name	Uab	Uau	Cholesterol	Triglyceride	LDL	AH	DM	Age	Joints	Duration
2	X	0,733	0,92	7,14	4,78	4,86	1	1	62	15	18
3											
4	**Constants**										
5	vector Imin	0,314	0,71	2,49	1	1,41	0	0	0	3	1
6	vector Imax	0,76	4,67	10,94	5,12	5,58	1	1	100	36	30
7	vector W	-1,83	-8,49	-0,63	2,61	-1,57	0,35	0,01	3,51	0,11	-0,12
8											
9											
10	**Input data**										
11	vector I	0,733	0,92	7,14	4,78	4,86	1	1	62	15	18
12											
13	**Calculations**										
14	vector D	0,939	0,053	0,550	0,917	0,827	1,000	1,000	0,620	0,364	0,586
15	number (product of vectors D*W)	1,085									
16	number (-5*D*W)	-5,427									
17	number (e^(-5*d*w))	0,004									
18	number (1/(1+e^(-5*d*w)))	0,996									
19											
20	**Answer**										
21	Probability of development (percentage)	99,6									

Figure 2: Example 1 – Calculator of gouty nephropathy prediction (99.6% probability of development).

Then, the probability of gouty nephropathy development can be determined by the formula:

$$P(I) = \frac{1}{1 + e^{-5\,D*W}}$$

P(I) – probability (Ill), the probability of having gouty nephropathy in a patient. Takes a value from 0 to 1; 0 – absolutely (100%) healthy patient; 1 – absolutely (100%) sick patient. *W* – Weight, vector of weights of synaptic arcs of artificial neuron; *D* – Data, patient data scaled to the interval 0–1 so that the minimum possible value corresponded to 0 and the maximum possible value to 1; *e* – The Euler number.

Discussion

The usage of neural network technologies is uniquely present in modern medicine and may allow the prediction of developing the disease without analyzing additional laboratory parameters [14, 15]. This method will greatly simplify the diagnosis verification and

	A	B	C	D	E	F	G	H	I	J	K
1	Name	Uab	Uau	Cholesterol	Triglyceride	LDL	AH	DM	Age	Joints	Duration
2	X	0,533	1,88	4,14	2,78	2,86	1	0	37	5	1
3											
4	**Constants**										
5	vector Imin	0,314	0,71	2,49	1	1,41	0	0	0	3	1
6	vector Imax	0,76	4,67	10,94	5,12	5,58	1	1	100	36	30
7	vector W	-1,83	-8,49	-0,63	2,61	-1,57	0,35	0,01	3,51	0,11	-0,12
8											
9											
10	**Input data**										
11	vector I	0,533	1,88	4,14	2,78	2,86	1	0	37	5	1
12											
13	**Calculations**										
14	vector D	0,491	0,295	0,195	0,432	0,348	1,000	0,000	0,370	0,061	0,000
15	number (product of vectors D*W)	-1,293									
16	number (-5*D*W)	6,465									
17	number (e^(-5*d*w))	642,102									
18	number (1/(1+e^(-5*d*w)))	0,002									
19											
20	**Answer**										
21	Probability of development (percentage)	0,2									

Figure 3: Example 2 – Calculator of gouty nephropathy prediction (0.2% probability of development).

management of patients, choose the right treatment tactics, and prevent the development of gout complications known as gouty nephropathy and chronic kidney disease. This formula was included in the Microsoft Office Excel spreadsheet application, which is enough to fill only 10 standard patient parameters as input data (blood uric acid indices, urine uric acid indices, total cholesterol indices, triglyceride indices, LDL indices, presence or absence of hypertension and diabetes mellitus, patient's age, number of affected joints, duration of the disease) and automatically receive the probability in percentage of gouty nephropathy development. Examples of the final version of the application are present in Figure 2 and 3.

An example of how the neural network was built as follows:

Formation of the input vector I. Denoted by vector I indicators of the patient from the following measurements: serum uric acid, urine uric acid, total cholesterol, triglycerides, LDL indices, presence or absence of hypertension and diabetes mellitus, age, number of affected joints, duration of the disease. I=(0.481; 1.31; 4.84; 2.42; 3.12; 1; 0; 59; 12; 10).

1. *Calculation of the vector* D. Now we need to "scale" this data to the interval 0–1, that is, to the minimum possible value, 0 and the maximum possible – 1. For this, we need vectors I^{MIN} and I^{MAX}:

I^{MIN}=(0.314; 0.71; 2.49; 1; 1.41; 0; 0; 0; 3; 1) – the minimum possible values from the above measurements;

I^{MAX}=(0.76; 4.67; 10.94; 5.12; 5.58; 1; 1; 100; 36; 30) – the highest possible values from the above measurements.

Vector $D=(d_1, d_2, \dots, d_{11})$ is calculated by the following formula:

$$d_j = \frac{I_j - I_j^{MIN}}{I_j^{MAX} - I_j^{MIN}} \; j = 1.11$$

That is,

$$d_1 = \frac{I_1 - I_1^{MIN}}{I_1^{MAX} - I_1^{MIN}} = \frac{0.481 - 0.314}{0.76 - 0.314} = 0.374;$$

$$d_2 = \frac{I_2 - I_2^{MIN}}{I_2^{MAX} - I_2^{MIN}} = \frac{1.31 - 0.71}{4.67 - 0.71} = 0.152;$$

$$d_3 = \frac{I_3 - I_3^{MIN}}{I_3^{MAX} - I_3^{MIN}} = \frac{4.84 - 2.49}{10.94 - 2.49} = 0.278;$$

$$\dots$$

$$d_{10} = \frac{I_{11} - I_{11}^{MIN}}{I_{11}^{MAX} - I_{11}^{MIN}} = \frac{10 - 1}{30 - 1} = 0.310.$$

So we calculated the vector D:

$D=(d_1, d_2, \dots, d_{11})$=(0.374; 0.152; 0.278; 0.345; 0.410; 1.000; 0.000; 0.590; 0.273; 0.310).

2. *Calculation of the product of vectors* D *and* W.

We have a vector W with constant values:

W=(-1.83; -8.49; -0.63; 2.61; -1.57; 0.35; 0.01; 3.51; 0.11; -0.12)^T.

Now we can calculate their matrix product:

D×W=(0.374; 0.152; 0.278; 0.345; 0.410; 1.000; 0.000; 0.590; 0.273; 0.310)×(-1.83; -8.49; -0.63; 2.61; -1.57; 0.35; 0.01; 3.51; 0.11; -0.12)^T=0.374×(-1.83)+0.152×××(-8.49)+0.278×(-0.63)+⋯+0.310×(-0.12)=0.523.

So, $D \times W$=0.5.

3. *Calculation* $e^{-5\,D \times W}$.

$e^{-5\,D \times W}=e^{-5\times0.5}=e^{-2.5}$=0.073.

4. *Final calculation of the probability of having the disease.*

We get the final answer:

$$P(\mathrm{I}) = \frac{1}{1 + e^{-5\,D*W}} = \frac{1}{1 + e^{-2.5}} =$$

$$= \frac{1}{1 + 0.073} = 0.932 \; or \; 93.2\%$$

Therefore, the presence of gouty nephropathy in this patient is 93.2%.

Testing this method showed that all patients (100%) from the first group (elevated microprotein indices) and 15.6% of patients from the second group (normal microprotein indices) had the probability of gouty nephropathy development within 55.1%–100%. The accuracy of the algorithm is 98%. This means that formula worked greatly and showed significantly correct results without including additional parameters such as microprotein indices.

In modern rheumatology, it is difficult to work without electronic calculators of disease activity (DAS28, SLEDAI, BASDAi, BASFi, ASDAS, DAPSA, ESSDAI, VDI) or make a differential diagnosis without the last diagnostic criteria or calculate cardio-vascular risk without SCORE table. Without prophylaxis, gout patients may live for years with subclinical kidney disease and not know about it. However, when the progression of renal failure begins, prevention will be unsuitable. You will need to receive special treatment, which may lead to complications. That is why the invention of a calculator for predicting kidney disease in patients with gout is extremely important. Therefore, the method is justified, convenient, and relevant for rheumatologists, nephrologists, therapists and family physicians.

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Conclusion

Only having input data (serum uric acid, urine uric acid, cholesterol, triglycerides, low-density lipoproteins indices, the presence or absence of concomitant diseases such as diabetes mellitus and arterial hypertension, the number of affected joints, patient's age and the duration of the symptoms), it is easy to predict the risk of development of gouty nephropathy, even if it may have subclinical course, by using the proposed calculator.

Conflict of interest

The authors declare no conflict of interest.

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