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ORIGINAL ARTICLE

Predicting posterior urethral obstruction in boys with lower urinary tract symptoms using deep artificial neural network

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Abstract

Purpose To assess the prediction model for late-presenting posterior urethral valve (PUV) in boys with lower urinary tract symptoms (LUTS) using artificial neural network (ANN).

Materials and methods 408 boys aged 3–17 years (median 7.2 years) with LUTS were examined and had bladder diary, ultrasound, uroflowmetry, urine, and urine culture. Cystoscopy was recommended when peak flow rate (Q_{max}) was persistently ≤ 5th percentile in patients who were unresponsive to urotherapy and pharmacological treatment (oxybutynin). With four-layered backpropagating deep ANN, the probability of finding PUV was estimated using noninvasive, quantitative parameters (age, Q_{max}, time to Q_{max}, voided volume, flow time, voiding time, average flow rate).

Results There were 97 patients with low Q_{max} and 74 were unresponsive. In 41, cystoscopy was performed and PUV was diagnosed in 37 (9.1%). In multivariate analysis, significant variables in favor of PUV were urgency (OR = 3.96, 95% CI = 1.30–12.03, $p = 0.015$), increased voiding frequency (OR = 3.81, 95% CI = 1.03–14.11, $p = 0.045$), and weak stream/intermittency (OR = 8.30, 95% CI = 2.49–27.63, $p = 0.001$). The ANN dataset included 87 uroflows of children with PUV and 114 uroflows classified as normal. The best performance was with two hidden layers with four neurons each. The best test accuracy was 92.7% and AUROC was 98.0%. With cutoff value of 0.8, sensitivity was 100.0%, specificity 89.7%, positive predictive value 80.0%, and negative predictive value 100.0%.

Conclusions With ANN, we accurately predicted 92.7% of late-presenting PUV using uroflow. Considering the high frequency of PUV in boys with LUTS, especially in cases of urgency, increased voiding frequency, and weak stream or intermittency, accurate prediction could lead to timely treatment.

Keywords Urethral obstruction/congenital · Child · Lower urinary tract symptoms · Urethral obstruction/surgery · Neural networks

Introduction

Lower urinary tract symptoms (LUTS), primarily daytime incontinence and nonmonosymptomatic enuresis, are repeatedly shown as the main complaints of late-presenting congenital obstruction of posterior urethra which can be improved by transurethral incision [1–4]. In these patients, a thorough diagnostic workup is needed, as the maximum success rate of conservative treatment remains under 50% [5]. The most common form of congenital posterior urethral obstruction is the posterior urethral valve (PUV). In addition to Young's classical PUV, the partial valve variations can be found, such as flap valves, which are probably the reason for the late clinical presentation. Clinical data combined with noninvasive and invasive procedures are needed to diagnose the late-presenting PUV, since a true diagnostic reference standard in boys does not exist [6]. Consequently, untimely diagnosis and prolonged course of frustrating symptoms may strongly interfere with the health-related quality of life [7].

Recently, artificial neural networks (ANNs) have been used in various medical fields to deal with the classification problem. ANN is a computing system that mimics the processes found in biological neural networks and can

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recognize patterns and classify observations learning from the previously ascertained data. The goal of deep learning, a method of machine learning, is to find a model which is able to generalize, i.e., able to return good predictions for input values independent of the training data [8]. The purpose of this study was to analyze the accuracy of a deep ANN in predicting late-presenting PUV using quantitative variables produced by non-invasive uroflowmetry report. The primary end point was to build an accurate, reproducible, and online model for everyday use.

Materials and methods

Participants and procedures

This retrospective study included boys aged 3–17 years with LUTS who were examined in the outpatient clinic between January 2014 and December 2017. Patients were referred for initial workup or because of the refractory course of illness. LUTS were defined according to the ICCS [9]. Exclusion criteria were a remarkable neurological examination, malformation of the penis and urethral meatus, psychomotor retardation, and urogenital or rectal surgery. Each patient underwent medical history taking, physical examination, bladder diary, renal ultrasound, urinalysis, urine culture, and uroflowmetry with post-void residual (PVR) volume. None of the patients underwent voiding cystourethrogram (VCUG). A course of antibiotics was prescribed for any acute urinary tract infection (UTI) and the patient was included only if LUTS persisted after the treatment. A history of UTI, with or without fever, was noted. Diagnosed constipation was treated primarily. For uroflow, boys were instructed to void at normal desire in standing position. Thickened bladder wall was classified when > 3 mm was measured for the full bladder. Bladder outlet was not systematically evaluated during the ultrasound examination and was not included in the analysis. Cystoscopy was recommended to all patients who persistently had peak flow rate (Q_{max}) ≤ 5th percentile according to Miskolc nomogram [10] and who were without complete response (< 100% reduction of symptoms) to the conservative treatment (standard urotherapy as defined by the ICCS [9], pharmaceuticals, e.g., oxybutynin). Patients who were diagnosed with PUV underwent transurethral electroincision (TUI).

Cystoscopy and operation protocol

Endoscopy was performed under general anesthesia using an 8.5-F or 11.5-F endoscope. Stephens' description of PUV morphology was followed: type 1 PUV is a valve-like lesion oblique to the urethral axis with posterolateral folds connecting to the verumontanum at the 5 and 7 o'clock positions; and type 3 PUV or Cobb's collar is characterized by a circumferential septum located at the bulbomembranous junction that does not connect with the verumontanum [11]. An earlier agreement was followed that type 2 PUV is over-classified by Young [12]. Transurethral electroincision was performed under the same anesthesia. For obstructive lesions, incisions were made in the 5, 7, and 12 o'clock directions.

Dataset for deep learning

Figure 1 shows the patient flowchart and the selection process used to choose uroflows for the ANN dataset. Uroflow reports from the patients with PUV prior to the TUI were used as the ground truth for posterior urethral obstruction. For the ground truth observations of normal uroflows, retrospective uroflow reports were collected from the patients who underwent uroflowmetry in the same time period and were either without LUTS (e.g., children with hematuria or after non-recurrent UTI) or had treated LUTS with complete response. Uroflows with a bell-shaped curve, a PVR < 20 mL, voided volume > 50 mL, and PVR plus voided volume < 115% of estimated bladder capacity were selected. The total number of normal uroflows was aimed to be equal to the total number of uroflows from patients with PUV. Age (years), Q_{max} (mL/s), time to peak flow (seconds), volume (mL), voiding time (seconds), flow time (seconds), and average flow rate (mL/s) were used as independent input variables. Dependent output variable was labeled 'PUV' and it classified recordings from patients with PUV from normal observations.

Deep learning techniques

We implemented supervised learning and designed back-propagating deep ANN using Keras 2.1.3 (https://keras.io) and TensorFlow 1.4.1 (https://www.tensorflow.org). The development environment was a Mac running OS X 10.12.5 (Apple, Inc., Cupertino, CA, USA), Python language 3.6, and Spyder 3.2.6 distributed by Anaconda 5.1 (https://www.anaconda.com). The ANN was based on the layout illustrated by Kirill Eremenko and Hadelin de Ponteves [13]. The best performance was determined using a different number of the hidden layers (one to four) and neurons (one to ten) in each hidden layer. At each training, the dataset was randomly split into a training and a test set at the ratio 0.2 for the test set. RobustScaler from sklearn library was used for feature scaling of independent variables [14]. For gradient descent optimization algorithm, Adam optimizer was used without any special initialization [15]. We chose binary cross entropy as the loss function [16]. The model was evaluated using K-fold cross-validation for the bias–variance tradeoff [17]. The best-trained model was saved as JSON file.

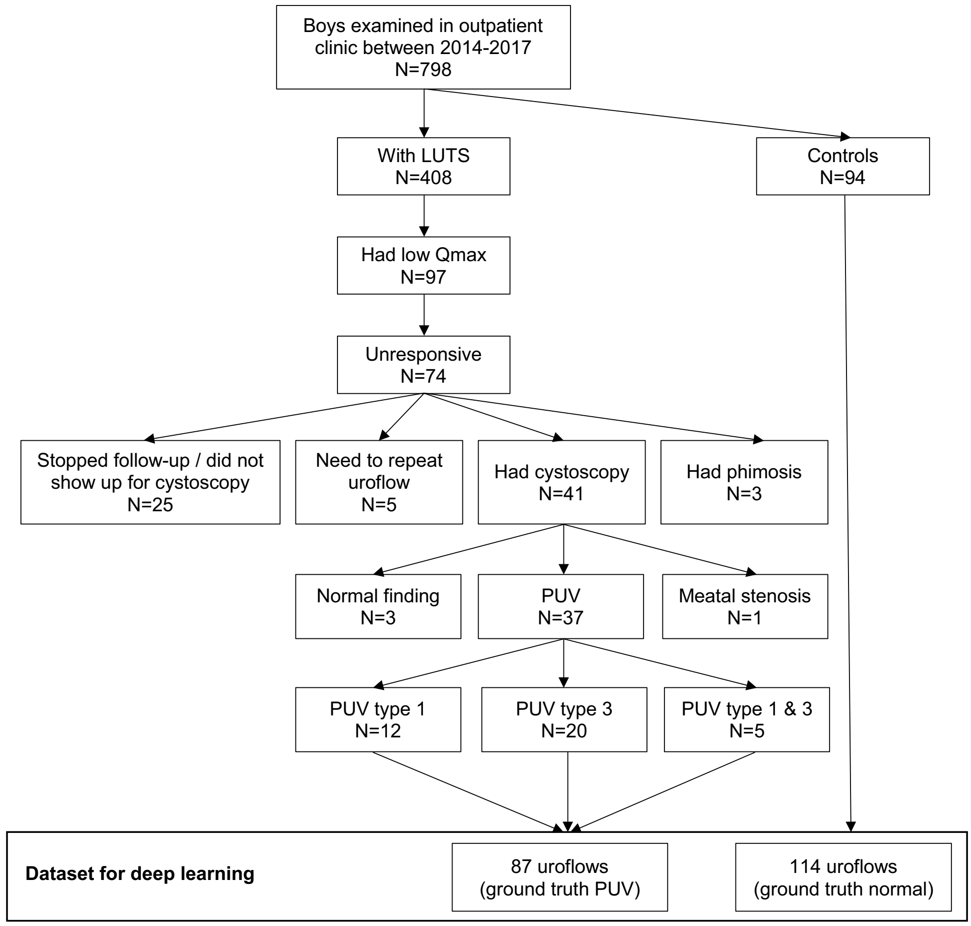

Fig. 1 Patient flowchart and selection process for the artificial neural network dataset. Label 'ground truth' refers to the actual observation we want the model to predict. Controls were selected to equally represent different age groups from 3 to 17 years. Multiple uroflows were collected from the same patient or control when available. *LUTS* lower urinary tract symptoms, Q_{max} peak flow rate, *PUV* posterior urethral valve

Statistical analysis

Mann–Whitney test was used to compare continuous variables and χ^2 test to analyze differences in categorical variables between patients with and without PUV. Fisher exact test was used to analyze differences when the cells contained less than five cases. Binary logistic regression was used to analyze the predictor variables in favor of finding PUV during cystoscopy. Receiver operating characteristic (ROC) metric was used to evaluate the classifier output quality. Accuracy, recall, and precision were used as the ANN test metrics. *p* values less than 0.05 were considered statistically significant. Statistical analysis was performed using SPSS for Windows (version 25; IBM Corporation, Chicago, IL, USA).

Results

Disease and patient characteristics

798 boys were examined in the outpatient clinic during the investigation period. Out of them, 408 had LUTS. $Q_{\max} \leq$ 5th percentile was found in 97 patients (23.8%) and 74 of them (76.3%) were unresponsive to urotherapy. In 41 cases (10.0%), cystoscopy was performed and PUV was diagnosed in 37 boys (9.1%). The most common finding was type 3 PUV (20 cases), followed by type 1 PUV (12 cases), and both type 1 and 3 were found in five patients. None of the patients with PUV had hydronephrosis during the ultrasound examination. A statistically significant difference in median age was not found between patients with PUV (7.3 years; interquartile range 6.4–9.2 years) and without PUV (7.1 years; interquartile range 5.7–9.8 years). Table 1 outlines the differences in clinical characteristics between patients with and without PUV. Statistically significant differences were further investigated by means of binary logistic regression (Table 2).

Deep backpropagating ANN

For the ground truth dataset, there was a total of 87 uroflows of children with PUV and 114 observations which were classified as normal. The best performance was achieved with two hidden layers with four neurons in each layer. Figure 2 outlines the layout of ANN and connections between the

Table 1 Clinical characteristics of patients with and without posterior urethral valve (PUV)

	Without PUV (N=371)	PUV (N=37)	p
Urgency	92 (24.8%)	22 (59.5%)	< 0.001
Increased voiding frequency	94 (25.3%)	20 (54.1%)	< 0.001
Daytime incontinence	107 (28.8%)	14 (37.8%)	0.253
Enuresis	284 (76.5%)	16 (43.2%)	< 0.001
Nocturia	54 (14.6%)	10 (27.0%)	0.057
Hesitancy	10 (2.7%)	8 (21.6%)	< 0.001
Straining	15 (4.0%)	12 (32.4%)	< 0.001
Decreased voiding frequency	12 (3.2%)	1 (2.7%)	1.000
Weak stream/intermittency	24 (6.5%)	18 (48.6%)	< 0.001
Feeling of incomplete emptying	8 (2.2%)	6 (16.2%)	< 0.001
Bladder/urethral pain	10 (2.7%)	3 (8.1%)	0.104
Constipation	72 (19.4%)	4 (10.8%)	0.269
History of urinary tract infection	13 (3.5%)	2 (5.4%)	0.636
Flow rate ≤ 5th centile	62 (16.7%)	35 (94.6%)	< 0.001
Post-void residual	23 (6.2%)	13 (35.1%)	< 0.001
Increased bladder wall thickness	50 (13.5%)	9 (24.3%)	0.086
Small bladder capacity	167 (45.0%)	11 (29.7%)	0.083

units. When fitting the ANN and the training set, a batch size of 5 and 50 epochs was found optimal for this model and dataset. Having more than 60 epochs did not increase the accuracy of the model and increasing the batch size reduced the accuracy. The mean accuracy and variance of the training set were 87.5% and 6.3%, respectively. Increasing the dropout did not improve the variance of the model and was not used. The area under the curve ROC was 98.0%. During the succession of trainings, the best-achieved accuracy for the test set was 92.7%. This model was saved and used for PUV predictions. For the best-saved model, sensitivity was 100.0% (recall), specificity 89.7%, positive predictive value 80.0% (precision), and negative predictive value 100.0%. Prediction threshold for the test was set at 0.80 for maximizing the harmonic mean of precision and recall at the value of 0.88 (F_1 score).

Discussion

Our results demonstrate, for the first time in boys with LUTS, that deep ANN can successfully predict finding late-presenting PUV given quantitative uroflow results. Uroflowmetry is established as a noninvasive and routine investigation in children with LUTS. One of its key parameters is Q_{max}, but studies in adults have shown it has limited sensitivity and specificity for bladder outlet obstruction (BOO) depending on the cutoff used. Lower threshold improves specificity but impairs sensitivity, and vice versa for higher thresholds [18]. A plateau-shaped curve is suggestive of urethral obstruction, but interpreting the flow curve in children had kappa of only 0.65 and 0.66 for inter- and intra-observer reliability, respectively [19]. Voiding pressures of > 55 cm H_2O in combination with a good relaxation of the pelvic floor on EMG are used as the cutoff for obstruction in children [4], yet it is necessary to have good cooperation and it is often avoided or postponed because of discomfort to the child, especially in boys. Of other diagnostic tests, VCUG has been shown as unreliable in patients with late-presenting PUV; up to one-third of the cases would have absent signs of type 1 PUV, while other types of obstructions, such as Cobb's collar, are frequently missed [3, 6, 20]. Hence, a normal urethra at VCUG does not exclude a urethral obstruction as a cause for LUTS in boys [21]. At the moment, cystoscopy is considered to be the reference standard for congenital obstruction of the posterior urethra. However, a precise endoscopic diagnosis is very difficult [2]. When judging cystoscopy results, de Jong et al. [22] found

Table 2 Binary logistic regression with predictor variables in favor of finding posterior urethral valve during cystoscopy

	Univariate				Multivariate			
	OR	95% CI		p	OR	95% CI		p
		Lower	Upper			Lower	Upper	
Urgency	4.45	2.21	8.93	< 0.001	3.96	1.30	12.03	0.015
Increased voiding frequency	3.47	1.74	6.89	< 0.001	3.81	1.03	14.11	0.045
Enuresis	0.23	0.12	0.47	< 0.001	1.15	0.36	3.62	0.812
Hesitancy	9.96	3.65	27.17	< 0.001	0.83	0.11	5.93	0.849
Straining	11.39	4.82	26.94	< 0.001	2.50	0.57	10.87	0.223
Weak stream/intermittency	13.70	6.37	29.46	< 0.001	8.30	2.49	27.63	0.001
Feeling of incomplete emptying	8.78	2.86	26.92	< 0.001	1.98	0.28	14.19	0.496
Post-void residual	8.20	3.70	18.17	< 0.001	3.38	0.89	12.82	0.074
Flow rate ≤ 5th centile	87.22	20.44	372.12	< 0.001	66.07	13.45	324.49	< 0.001

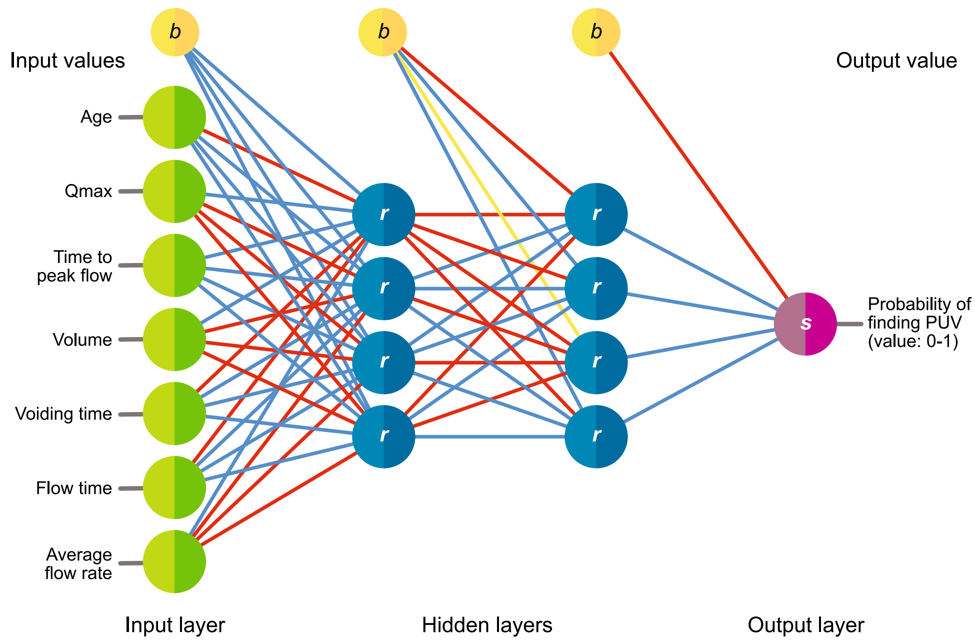

Fig. 2 The layout of the deep backpropagating artificial neural network (ANN) using TensorFlow. Supervised learning ANN for classification problem consists of interconnected nodes called neurons which are positioned in layers (input, hidden, and output). There is one input layer, receiving input signals (e.g., values of diagnostic test results), one or more hidden layers used for computational purposes, and one output layer representing the classification. Neurons in the hidden and output layers receive inputs from the neurons in the antecedent layer (input or hidden). The strength of each separate connection between neurons is represented by weight, a numerical value that multiplies with the input value. Each neuron computes a weighted sum of all received inputs and converts it to activation function. The value of this function is sent through to the next layer if it exceeds a certain threshold. The final is the output layer where, during the training, calculation of the difference between the network output (predicted value) and the expected output (ground truth) is carried out. This is referred to as a loss function and used to adjust all weights to minimize the difference and therefore produce as accurate as possible predicted value, a process called backpropagation. During the training, the process is repeated many times (epochs) to obtain the desired output. During the test, the network is fed with input only, without adjusting once trained weights, and accuracy is calculated as a ratio of correctly predicted cases [23]. Connections between the neurons and the corresponding weight are shown as lines. Blue lines represent weights > 0 (increasing the input increases the output). Negative weights are shown as red lines (increasing the input decreases the output). Weights equal to zero are presented as yellow lines (changing the input will not change the output). Bias is an extra input to the neurons which provides activation even if all the inputs are none. *b* bias (offset) value (always + 1), *r* rectified linear unit (ReLu) activation function, *s* logistic sigmoid activation function

only fair to good agreement on whether a urethral obstruction is present. With the utilization of computer-enhanced visual learning method, endoscopic diagnosis of PUV can be improved; however, such modules need to be introduced into urology training and validated for the late-presenting PUV. These results show that clinical data and combined diagnostic procedures (ultrasound, uroflow, urodynamics, VCUG, cystoscopy) are needed for diagnosis in most cases of late-presenting PUV [6]. The aim of developing an ANN was to find a predicting model for late-presenting PUV based on easily obtainable and noninvasive diagnostic test with adequate accuracy to discern true cases and provide timely treatment in these patients.

Up to now, only two studies using ANN with backpropagation in the prediction of BOO in men with LUTS have been published, and none in children [23, 24]. Both adult studies implemented pressure-flow studies (PFS) as a reference standard in diagnosis of BOO and investigated whether noninvasive parameters could replace invasive, time-consuming and costly PFS. Sonke et al. [23] used eight variables (prostate volume, Q_{max}, voided volume, PVR volume, age, prostate-specific antigen level, International Prostate Symptom Score, and quality-of-life score) and Wadie et al. [24] used four variables (average flow rate, Q_{max}, PVR volume, and total prostate volume) as input. They both found similar and poor accuracy of noninvasive prediction of PFS outcome, 71% and 72%. The reported models did not show additional value over traditional regression analysis in diagnosing BOO in men with LUTS [23]. In comparison, our model achieved 93% test accuracy with none of the false negative classifications, which is shown in the confusion matrix for the test set in Table 3. This could be attributed to not omitting other variables of the uroflow report, which one would consider irrelevant. As outlined above, Q_{max} alone is not enough of a proxy for diagnosing PUV to not need any further analysis. It has been previously shown that

Table 3 Confusion matrix for binary classification for the test set ($N=41$) after loading the best-trained model

True label	ANN		Total
	Normal	PUV	
Normal	26	3	29
PUV	0	12	12
Total	26	15	41

PUV posterior urethral valve, *ANN* artificial neural network

obstructions in the sphincter area and proximal urethra may come with normal or near normal Q_{max} generated by high detrusor pressures [4]. In our sample, Q_{max} alone correctly classified only 81.0% cases and by adding more independent variables we achieved a higher probability of correctly determining the outcome. During training, the ANN model calculated the importance of each input variable by adjusting the weights between interconnected neurons to achieve classification as accurate as possible. Accordingly, each input variable contributes to the classification problem, and opting them out was considered to reduce the generalization. Also, we were thoroughly methodical when selecting uroflows for the dataset. We opted for the precise definition of normal uroflow specified by Franco et al. [25]. By record sampling, we discarded missing, erroneous, and less representative observations and all uroflows used as a ground truth for urethral obstruction were diagnosed by means of cystoscopy. Using cystoscopy as a reference standard had an advantage of differentiating between posterior urethral obstruction subtypes and excluding other types of BOO.

This study has several advantages. First, this model was built on quantitative data from uroflowmetry which is noninvasive, routinely used, and feasible for repeated tests. Second, in contrast to previous adult studies, the ANN is openly accessible online to test new observations (https://isitpuo.herokuapp.com). Third, our model is reproducible—new and bigger models could be built by other teams using their own dataset on our ANN code which is available at Code Ocean [26] and as GitHub repository (https://github.com/slavenabd/isitpuo_ANN). Reproducibility, ability to improve the model with new ground truth observations, less demanding development, and a possibility to create a Web application make machine learning stand out when compared with the statistical approach such as multivariate analysis. In our proposed model, new datasets could be reinforced with additional variables such as signs and symptoms of the lower urinary tract, and only small changes to the original code are necessary to add these new variables to the prediction. In this study, we have not implemented symptoms or history of UTI as input variables, because such an approach would reduce the size of our dataset. With these variables implemented, repeated uroflows of the same patient could not be used since data redundancy would limit the number of PUV observations to a single uroflow per patient—a size too small for reasonable ANN training.

Several limitations need to be addressed. Per protocol, only patients with persistently low Q_{max} were sent for cystoscopy. Therefore, our ANN could be more generalized toward patients with low Q_{max}, meaning it may have false negatives in cases where Q_{max} is > 5th percentile. It would be interesting to test uroflows from published cohorts of late-presenting PUV where none of the plateau-shaped curves were reported [27]. Second, control uroflows were not collected from healthy children, but from patients with hematuria, UTI, or resolved LUTS. In future studies, uroflows from PUV cases with normal Q_{max} and from healthy controls need to be included to improve the ANN model. Furthermore, our study was retrospective in design. A prospective study could have advantages in a larger number of uroflow tests per patient, completed urodynamics for each case of PUV, and filmed cystoscopy which could be reviewed independently. We believe a larger sample of uroflow reports in the training dataset would be of benefit. Increasing only the cases of normal uroflows is amiss, since it will impair generalization and reduce test accuracy. Finally, interpretation of the flow curve shape was not included because of significant intra- and interobserver variation in defining it. Implementing the flow index (actual Q_{max}/estimated Q_{max}) should be investigated in future studies, since it adds a new independent parameter to the network that was shown to be as accurate as visual inspection in defining curve shape [28]. In our model, implementing the flow index did not improve the accuracy of the ANN, and using it alone as a PUV predictor had inferior accuracy (85.6%) and negative predictive value (91.0%).

Conclusion

Deep ANN given routine and noninvasive uroflow variables was found to be accurate in predicting late-presenting PUV in boys. There is a relatively high frequency of PUV in boys with LUTS, especially in cases of urgency, increased voiding frequency, and weak stream or intermittency. While our ANN produced promising results, this is only a step in this line of research. Numerous models have shown that machine learning can find patterns where the human eye cannot. Big data and optimal ground truth observations are key in this process and are dependent on the human effort in producing it. We propose validation of the model on uroflows of children who have urodynamics, measured urethral angle and flexion rate on VCUG, filmed cystoscopy, and were followed up. Finally, other deep learning techniques should be explored, such as convolutional ANN and long short-term memory recurrent ANN using flow curve images and time-series data, respectively. New models could lead to more accurate prediction in patients with normal $Q_{\max}$.

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Author contributions A: protocol development, data collection and management, data analysis, and manuscript writing. C, C, G, F: data collection and management, and manuscript editing. M: data management, statistical analysis, and manuscript writing. B, B: protocol development, data management, and manuscript editing.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Human and animal participants' right All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent For this type of study formal consent is not required.

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