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ORIGINAL ARTICLE

Structural volumetry in NPH diagnostics and treatment—future or dead end?

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Abstract

To assess automated volumetric analysis as a potential presurgical diagnostic tool or as a method to potentially shed light on normal pressure hydrocephalus (NPH) pathophysiology. MRI imaging according to our protocol was performed in 29 NPH patients, 45 non-NPH (but suspected) patients and 15 controls. Twenty patients underwent a second MRI 3 months after ventriculoperitoneal (VP) shunt surgery. All structures relevant to NPH diagnosis were automatically segmented using commercial software. The results were subsequently tested using ANOVA analysis. Significant differences in the volumes of the corpus callosum, left hippocampus, internal globus pallidus, grey and white matter and ventricular volumes were observed between NPH group and healthy controls. However, the differences between NPH and non-NPH groups were non-significant. Three months after, VP shunt insertion decreased ventricular volume was the only clearly significant result (p value 0.0001). Even though a detailed volumetric study shows several significant differences, volumetric analysis as a standalone method does not provide a simple diagnostic biomarker, nor does it shed a light on an unknown NPH aetiology.

Keywords Normal pressure hydrocephalus · MRI · Diagnostic procedures · Structural volumetry · Shunt procedure

Introduction

Normal pressure hydrocephalus (NPH) was first described in 1964 by Hakim [1] as ventriculomegaly with normal cerebrospinal fluid (CSF) pressure during lumbar puncture. Typical presentation is characterized by the triad of gait disturbance, mental deterioration and urinary incontinence. Unlike other types of dementias with similar symptoms and findings, NPH is treatable with CSF diversion, by means of ventriculoperitoneal (VP) or ventriculoatrial shunt placement. It is estimated that there are approximately 2 million people in Europe and 700,000 in the USA that may have the diagnosis of NPH [19]. Only a few percentage of these patients receive a proper diagnosis and treatment. Shunt surgery significantly prolongs life and adds quality-adjusted life years [45]. Unfortunately, the procedure is also burdened with a significant complication rate [13]. Despite the considerable surgical treatment, very little is known about NPH aetiology itself. This is compounded by the ambiguity of available diagnostic tests.

In current practice, functional testing predominates: The spinal tap test, external lumbar drainage or lumbar infusion test [40]. These tests can achieve high predictive accuracy [25], but they are painful and associated with rare, but potentially serious complications [12]. Standard CT and MRI scans are equally good for assessing the basic radiological signs associated with NPH [24], such as Evan's index, callosal angle, tight high convexity, focal sulcal dilation and dilated Sylvian fissures. The listed parameters are definitely predictive of shunt responsiveness [38] but are not sufficiently sensitive and specific. Some clinical symptoms can be explained by the compression of periventricular white matter and the corpus callosum. Diffusion tensor images (DTI) show changes in mean diffusivity and fractional anisotropy in the posterior limb of the internal capsule, the hippocampus and the fornix. Even though the reported specificity and sensitivity of DTI are high, the technical difficulty along with the absence

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of a standardized protocol limits its broad utilization [39]. Frequently observed CSF flow void phenomenon in the aqueductal region has directed research towards CSF dynamics. Aqueductal stroke volume measured on phase-contrast MRI shows promising results, but the examination is technically demanding and hardware dependent [8, 36].

It is likely that the key to understanding NPH lies in the ability to correlate novel neuroimaging tools with clinical biomarkers [22]. In our study, we focused on volumetric changes in the subcortical grey and white matter structures since their altered function may have origins in the respective morphometric changes. Recently introduced voxel-based morphometry enables precise volumetric measurements with the help of automatic segmentation software, such as FSL [20] and SPM [4]. In this study, we used Anatomical Mapping Ver. 1.1, Brainlab AG. Our goal was to evaluate volumetry as a potential presurgical diagnostic tool or as a method potentially shedding light on the NPH pathophysiology.

Patients and methods

Participants

Between September 2016 and October 2019, 92 patients were referred to the Department of Neurosurgery and Neurooncology of the Central Military Hospital with suspicion of NPH. All patients suffered gait disturbance and at least one of the other two typical symptoms: mental deterioration or urinary incontinence. The gait disturbance was evaluated using the Dutch Gait Scale [6, 33]. All patients underwent profound examination by a neuropsychologist: Wechsler Memory Scale III, Mini Mental State Examination, Verbal Fluency test, Trial Making Test, Rey-Osterrieth Complex Figure Drawing Test, Beck Depression Inventory and others [10]. During these tests, six patients were removed from the group because they were diagnosed with another type of dementia (5 cases of Alzheimer's and 1 case of Parkinson's disease). Prior to being referred to our department, all patients had undergone standard MRI imaging and showed ventriculomegaly (Evans' index greater than 0.3). All patients underwent lumbar infusion (modified Katzmann's test, [21]. After finishing the test, lumbar drainage was performed with the same needle and cerebrospinal fluid was drained for 120 h. Shunt insertion was indicated to all patients with positive lumbar infusion test (resistance to outflow above 12 mmHg/ml/min) and showed at least 15% improvement in Dutch Gait Scale after the lumbar drainage. Part of the examination process was a detailed MRI imaging, including a study protocol. Images were reviewed by a radiologist and 9 patients had to be excluded because of coincidental other major pathology: ischemic, tumorous or post-traumatic lesions. Three additional

patients were removed because of major movement artefacts preventing automatic segmentation.

The final study group comprises 74 patients—29 patients from this cohort were diagnosed as NPH after completing all the tests, 45 patients did not meet the criteria (in this article, this group is called non-NPH). Furthermore, 15 healthy controls underwent the MRI imaging protocol to compare with both groups. The age and sex characteristics of all groups are presented in Table 1.

Ventriculoperitoneal shunt was inserted to NPH patients, using OSV II Smart valve (Integra Neurosciences®). Three months after the procedure, the NPH patients underwent same neuropsychological and gait disturbance testing as prior to the surgery and MRI imaging according to the study protocol. We were able to completely examine 20 patients (4 people refused further controls, 1 MRI was not readable due to motion artefactss and 4 patients have not reached 3 months after the surgery). We observed at least 15% improvement in the Dutch Gait Scale in all patients who completed the 3 months control.

MRI imaging protocol

All the MRI images were performed on a 3T GE Signa HDx or GE Discovery 750w MR imaging system (GE Medical Systems, Milwaukee, WI) in the Central Military Hospital, Prague. Standard 8-channel (Signa HDx) or 32-channel (Discovery 750w) head coil was used. Beyond the standard brain MRI protocol, the examination included high-resolution 3D T1 BRAVO and 3D T2 Cube PROMO sequences. Parameters of the 3D T1 BRAVO were the following: TR 10 ms, TE:4 ms, matrix 256×256, FOV 25.6×25.6 cm, flip angle 13°, in-plane resolution 1×1 mm^2 and slice thickness 1 mm, and of the 3D T2 Cube PROMO sequence: TR 3000 ms, TE 125 ms, ETL 130, matrix 288×288, FOV 25.6×25.6 cm, in-plane resolution 0.8×0.8 mm^2 and slice thickness1.2 mm.

Segmentation

Anatomical Mapping Ver. 1.1 as part of Brainlab Elements software was used for automatic segmentation of high-resolution MRI images. All structures were manually checked

Table 1   The age and sex distribution among study groups

Characteristic	NPH patients	Non-NPH patients	Controls
No. of patients	29	45	15
Age	73.6 ± 1.6	74.5 ± 2.2	71.4 ± 6.6
No. of men	19	33	9
No. of women	10	12	6
Pct. of men	65.5%	73.3%	60.0%
Pct. of women	34.5%	26.7%	40.0%

for accuracy with no major adjustments needed. We have successively measured volumes of both white and grey matter, internal and external capsule, corpus callosum, hippocampus, amygdala, caudate nucleus, putamen, internal and external globus pallidus, thalamus, periaqueductal grey and three ventricles. The fourth ventricle was later manually removed from the ventricular system measurement in the level of the cerebral aqueduct because its volume is not related to NPH diagnosis [17]. Pictures from the segmentation process are presented in Fig. 1.

Statistical analysis

Comparisons of continuous variables were made using one-way ANOVA or t tests for repeated measures. Subsequent testing after ANOVA was performed using Fisher LSD test. Comparisons of categorical variables were done using chi-square test. In all cases, a p value of less than 0.05 was considered significant. All computations were performed using STATISTICA 13.5 software. Radar graphs were produced in OriginPro 2015 software.

Results

Our study cohort consisted of 74 patients with suspicion of NPH and 15 age-matched healthy controls. After completing all the tests, 29 patients were diagnosed with NPH and underwent ventriculoperitoneal shunt insertion. Average age

in the NPH group was 73.6 ± 1.6, in the non-NPH group 74.5 ± 2.2 and in the control group it was 71.4 ± 6.6 years. There were 19 men and 10 women in the NPH group, 33 men and 12 women in the non-NPH group and 9 men and 6 women in the control group (Table 1). Measured volumes of the selected structures in these three groups are presented separately for men and women in Tables 2 and 3, respectively.

Diagnostic volumetry

In this part of the study, we compared normalized volumes (counted to the cerebral volume) of selected structures in NPH patients before surgery to non-NPH group of suspected patients without other known neurodegenerative disease and to healthy age-matched controls. The results are presented in Table 4 with highlighted significant differences.

There were statistically significant differences in the volumes of the left hippocampus, the corpus callosum, the left internal globus pallidus, the white and grey matter (Figs. 2 and 3) and in the ventricular volume (Fig. 4) when both groups were compared to healthy volunteers. Relative volumes of subcortical structures are depicted in Fig. 5. The differences between NPH and non-NPH groups were minimal and not significant.

Volumetric changes after shunt insertion

In 20 patients, we managed to get clinical and graphical follow-up 3 months after the shunt surgery. In this group,

Fig. 1 Autosegmentation process: **a** segmentation of basal ganglia, **b** segmentation of all selected structures, **c** 3D ventricular model, **d** 3D cerebrum model
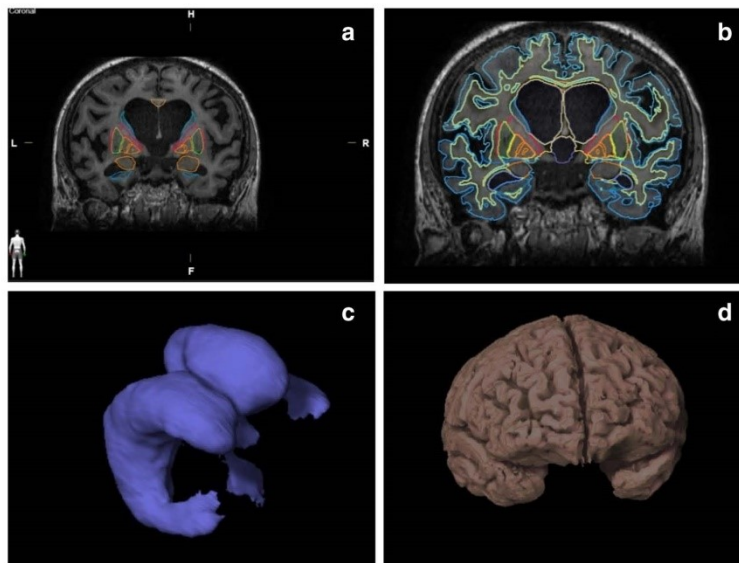
Table 2 The raw structural volumes in ccm measured in men in all groups

Structure	Mean NPH	SD - NPH	Mean non-NPH	SD - non-NPH	Mean controls	SD - controls
Cerebrum	953.65	92.31	926.00	95.21	907.52	58.24
Hippocampus left	3.49	0.43	3.23	0.34	2.96	0.27
Hippocampus right	3.73	0.47	3.61	0.48	3.29	0.35
Internal capsule left	5.55	0.66	5.22	0.61	5.11	0.36
Internal capsule right	5.51	0.51	5.27	0.70	5.14	0.30
Corpus callosum	9.44	1.63	8.55	1.36	7.35	1.07
Temporal lobe left	85.03	9.76	81.59	9.23	78.40	5.45
Temporal lobe right	86.87	8.53	83.85	8.97	83.24	6.03
Amygdala left	1.79	0.15	1.74	0.22	1.55	0.18
Amygdala right	1.87	0.21	1.86	0.26	1.62	0.14
External capsule left	0.82	0.11	0.79	0.12	0.76	0.06
External capsule right	0.83	0.12	0.82	0.10	0.76	0.05
Putamen left	4.58	0.78	4.39	0.65	4.18	0.43
Putamen right	4.59	0.66	4.42	0.59	4.24	0.44
Globus pallidus int left	0.66	0.11	0.65	0.09	0.67	0.09
Globus pallidus int right	0.67	0.09	0.67	0.10	0.66	0.08
Globus pallidus ext. left	1.33	0.17	1.29	0.18	1.23	0.16
Globus pallidus ext. right	1.33	0.16	1.29	0.18	1.27	0.15
Thalamus left	5.86	0.99	5.56	0.67	5.52	0.47
Thalamus right	5.94	1.18	5.68	0.81	5.79	0.47
White matter	454.45	51.62	430.44	54.76	402.89	33.15
Grey matter	464.19	52.12	460.92	57.41	471.88	31.99
Caudate nucleus left	4.36	0.72	4.05	0.75	3.82	0.48
Caudate nucleus right	4.48	0.61	4.25	0.87	3.98	0.46
Periaqueductal grey	0.26	0.06	0.27	0.06	0.26	0.04
3 ventricles	143.94	33.23	125.42	36.70	51.26	22.41

there were 12 men and 8 women. Again both measurements were normalized to cerebral volume. The results are shown in Table 5.

Changes in both ventricular (Fig. 6) and cerebral volume and right putamen were statistically significant. The change in the volume of the corpus callosum was on the verge of significance. Relative volumes of subcortical structures are depicted in Fig. 7.

Discussion

In this study, we present comprehensive volumetric assessment of parenchymal structures in NPH patients both in an attempt to find a new reliable diagnostic biomarker and to enlighten the aetiology of NPH. Recent development of voxel-based morphometry and automatic segmentation software enabled simultaneous measurement of a larger number of key structures. We observed basic intracranial compartments such as ventricular volume and grey and white matter. However, previous studies

proved no or minimal predictive value of volumetric assessment of the listed structures [27, 30]. From the NPH perspective, the most important white matter structures are the internal and external capsules and the corpus callosum. The internal capsule has combined roles both in psychiatric and movement disorders. Bilateral volume reductions of anterior limb were observed in first-episode psychosis subjects [41]. Posterior limb compression affects gait due to corticospinal tract compression. Fractional anisotropy in the posterior limb of the internal capsule compared with healthy controls and other types of dementia is significantly higher [23]. External capsule microstructure correlates with socially desirable behaviour due to connectivity between the prefrontal cortex and the striatum [3]. Another structure that plays an important role in neurodegenerative diseases is the corpus callosum. Previous studies have shown significant corpus callosum atrophy in both Alzheimer's disease and mild cognitive impairment [48]. Previously, a minor but significant left-sided hippocampal volume decrease associated with cognitive decline was observed [37] and

Table 3 The raw structural volumes in ccm measured in women in all groups

Structure	Mean NPH	SD - NPH	Mean non-NPH	SD - non-NPH	Mean controls	SD - controls
Cerebrum	827.80	78.13	818.97	78.05	863.43	84.30
Hippocampus left	2.86	0.19	2.88	0.24	2.86	0.34
Hippocampus right	3.17	3.17	3.09	3.09	3.17	3.17
Internal capsule left	4.52	0.66	4.73	0.61	5.03	0.65
Internal capsule right	4.80	0.71	4.86	0.56	5.15	0.63
Corpus callosum	7.13	0.78	6.97	1.89	6.18	0.55
Temporal lobe left	70.11	6.30	71.03	8.23	74.20	11.14
Temporal lobe right	74.60	5.86	71.84	7.31	79.82	9.73
Amygdala left	1.51	0.21	1.41	0.19	1.67	0.27
Amygdala right	1.63	0.24	1.50	0.19	1.67	0.32
External capsule left	0.69	0.15	0.68	0.09	0.71	0.10
External capsule right	0.69	0.11	0.71	0.11	0.73	0.10
Putamen left	3.71	0.62	3.91	0.71	3.92	0.64
Putamen right	3.78	0.53	4.01	0.84	4.02	0.60
Globus pallidus int left	0.58	0.06	0.58	0.08	0.68	0.08
Globus pallidus int right	0.60	0.08	0.60	0.08	0.07	0.71
Globus pallidus ext. left	1.11	0.14	1.16	0.18	1.24	0.18
Globus pallidus ext. right	1.14	0.15	1.20	0.15	1.27	0.15
Thalamus left	5.14	0.89	4.88	0.56	5.56	0.68
Thalamus right	5.33	0.70	5.19	0.56	5.52	0.54
White matter	386.88	34.32	372.53	47.90	386.07	45.67
Grey matter	411.08	48.24	417.69	41.24	446.13	37.09
Caudate nucleus left	3.60	0.54	3.55	0.65	3.49	0.28
Caudate nucleus right	3.95	0.75	3.81	0.77	3.58	0.31
Periaqueductal grey	0.24	0.06	0.22	0.05	0.23	0.03
3 ventricles	128.43	35.59	93.73	34.52	51.20	28.75

amygdala volume is supposed to be associated with anxiety and irritability in Alzheimer's disease [32]. The basal ganglia are associated with both voluntary motor movements and cognition. The putamen plays a known role in Alzheimer's disease due to amyloid deposits in the early stage of the disease process [7]. Its volume reduction correlates with impaired cognitive function [9]. The caudate nucleus is responsible for adaptable goal-directed behaviour [16] and the right caudate volume is associated with cognitive performance in older adults [5]. The pallidum plays an essential role in walking performance in elderly patients, probably through its involvement in the cortico-striato-pallido-thalamo-cortical circuit [11]. Pallidal volume was identified as the strongest correlate of walking performance in cases of multiple sclerosis [28]. Thalamic lesions were observed in cases of cognitive impairment. Left-sided thalamic lesions were observed in the vascular dementia patients and right-sided lesions in patients who did not meet the criteria for dementia. Left thalamic lesions are supposed to affect both verbal memory and language [42].

Volume of various structures and NPH triad

Gait

NPH gait is characterized by short steps with reduced step height, impaired dynamic equilibrium accented during turning and reduced speed of walking [26]. The gait pattern is sometimes characterized as "glued to the floor" or "magnetic" [14]. Reasons may be due to the impairment of cortico-basal ganglia-thalamo-cortical loops and hippocampi [2]. Our study has shown decreased volume of left internal globus pallidus, left hippocampus and white-matter compared with controls which might contribute to the NPH gait presentation.

Neuropsychology

NPH patients present with alteration of working memory, attention, learning, processing and psychomotor speed, executive, visuospatial and visuoconstructional functions [18]. Memory is presented by delayed recall and recognition [29] and is less severely impaired compared with AD [47]. NPH is

Table 4 The comparison of normalized structural volumes among NPH, non-NPH groups and healthy controls

Structure	Mean NPH	SD - NPH	Mean non-NPH	SD - non-NPH	Mean controls	SD - controls	p value
Hippocampus left	0.0036	0.0004	0.0035	0.0003	0.0033	0.0003	0.0180
Hippocampus right	0.0039	0.0004	0.0039	0.0004	0.0037	0.0004	0.1645
Internal capsule left	0.0057	0.0005	0.0057	0.0004	0.0057	0.0005	0.9461
Internal capsule right	0.0058	0.0005	0.0058	0.0005	0.0058	0.0006	0.9429
Corpus callosum	0.0095	0.0013	0.0091	0.0018	0.0077	0.0009	0.0018
Temporal lobe left	0.0877	0.0064	0.0878	0.0049	0.0861	0.0042	0.5663
Temporal lobe right	0.0909	0.0041	0.0898	0.0041	0.0920	0.0045	0.1907
Amygdala left	0.0019	0.0002	0.0018	0.0002	0.0018	0.0002	0.6078
Amygdala right	0.0020	0.0002	0.0020	0.0002	0.0018	0.0002	0.1142
External capsule left	0.0009	0.0001	0.0009	0.0001	0.0008	0.0001	0.9499
External capsule right	0.0009	0.0001	0.0009	0.0001	0.0008	0.0001	0.2318
Putamen left	0.0047	0.0007	0.0048	0.0007	0.0046	0.0007	0.7631
Putamen right	0.0047	0.0006	0.0048	0.0007	0.0047	0.0007	0.8003
Globus pallidus int left	0.0007	0.0001	0.0007	0.0001	0.0008	0.0001	0.0408
Globus pallidus int right	0.0007	0.0001	0.0007	0.0001	0.0008	0.0001	0.0923
Globus pallidus ext. left	0.0014	0.0001	0.0014	0.0001	0.0014	0.0002	0.7848
Globus pallidus ext. right	0.0014	0.0001	0.0014	0.0001	0.0014	0.0001	0.6473
Thalamus left	0.0062	0.0009	0.0060	0.0005	0.0062	0.0004	0.4306
Thalamus right	0.0063	0.0010	0.0062	0.0006	0.0064	0.0004	0.5781
White matter	0.4736	0.0262	0.4619	0.0319	0.4448	0.0136	0.0066
Grey matter	0.4900	0.0253	0.5011	0.0315	0.5190	0.0130	0.0050
Caudate nucleus left	0.0045	0.0005	0.0044	0.0006	0.0042	0.0006	0.2003
Caudate nucleus right	0.0047	0.0005	0.0046	0.0007	0.0043	0.0006	0.1477
Periaqueductal grey	0.0003	0.0001	0.0003	0.0001	0.0003	0.0000	0.8524
3 ventricles	0.1516	0.0300	0.1299	0.0395	0.0587	0.0308	< 0.0001

a subcortical dementia [46] and decrease in volumes of striatum, hippocampus, thalamus and nucleus accumbens has been previously described [31] compared to healthy controls. We have observed decreased volume of left hippocampus and left internal globus pallidus compared to healthy controls and nucleus accumbens was not segmented in our study. Striatum

Fig. 2 Comparison of relative volumes of white matter among NPH, non-NPH and control groups
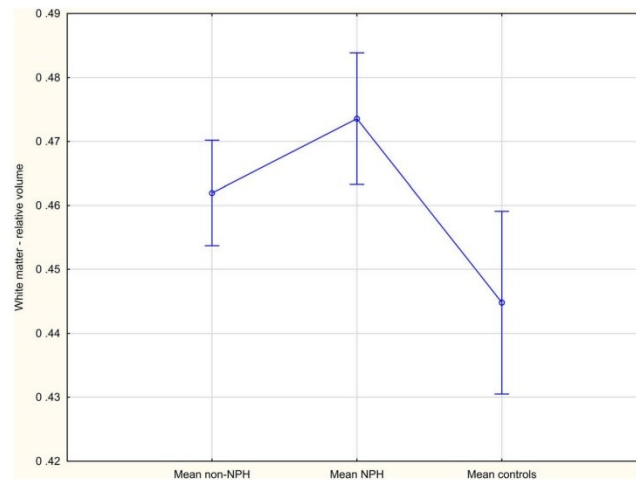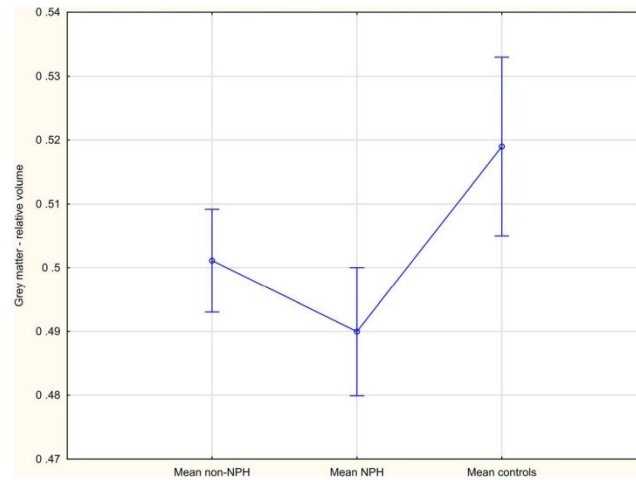
Fig. 3 Comparison of relative volumes of grey matter among NPH, non-NPH and control groups

is linked to the frontal cortex and lesions to the connections can cause executive dysfunction, impaired motivation, apathy and personality changes [43]. Interesting study found decrease in the cerebral blood flow in normal appearing and periventricular white matter, the lentiform nucleus and global parenchyma of NPH shunt responders or non-responders pre-operatively compared to healthy controls with no significant changes between responders and non-responders [51]. These changes may precede atrophy [34], but it is not clear how or whether it is related to volumetric alterations in NPH patients. Lastly, prevalence of another comorbid neurodegenerative disease is high, profound neuropsychologic assessment contributed on the selection of shunt candidates.

Prospective studies with autopsy-proven NPH with absence of other neurodegenerative disease may bring other results [40]; however, this study was dedicated on prediction shunt-responsiveness mainly and we did not found differences between NPH and non-NPH groups.

Urinary incontinence

Lower urinary symptoms are frequent in people older than 60 years. Typically, these symptoms in NPH patients result from the impairment of micturition centers above the pontine level and manifest as detrusor overactivity and later as urge incontinence [35]. An fMRI study on the role of suprapontine

Fig. 4 Comparison of relative volumes of ventricles among NPH, non-NPH and control groups
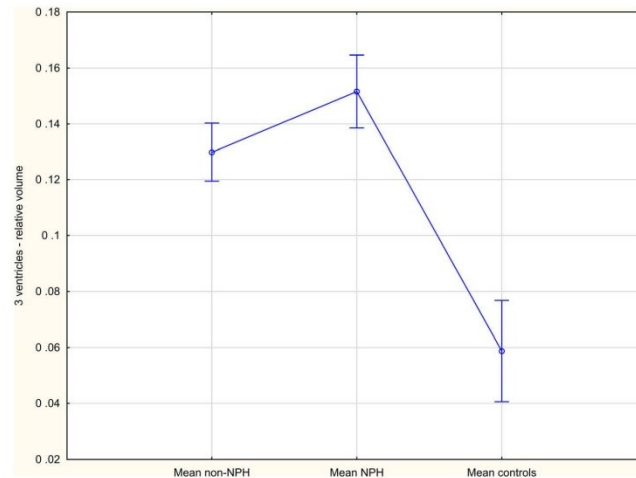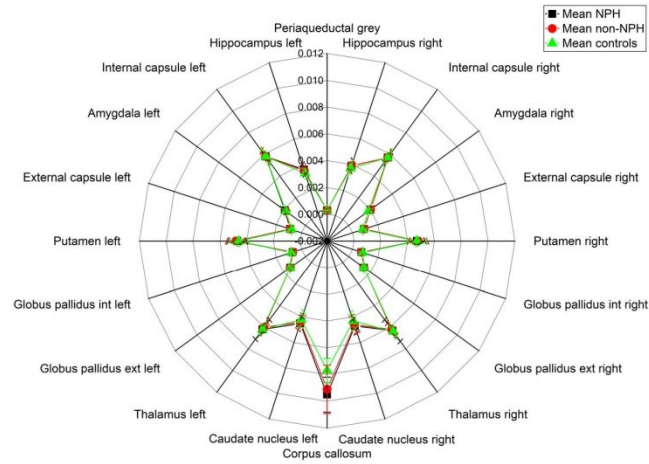
Fig. 5 Comparison of relative volumes of subcortical structures among NPH, non-NPH and control groups


brain structures involved in voiding control has shown that medial prefrontal cortex, basal ganglia and cerebellum are involved in the control of micturition, parietal cortex and limbic system are involved in inhibitory voiding control

Table 5 The comparison of normalized structural volumes of NPH patients before and 3 months after VP shunt surgery

Structure	Mean preop	SD - preop	Mean 3M	SD - 3M	p value
Cerebrum - absoulute volume [ccm]	903.9	103.5	892.6	103.9	0.0469
Hippocampus left	0.0036	0.0004	0.0035	0.0003	0.3756
Hippocampus right	0.0038	0.0003	0.0037	0.0004	0.3359
Internal capsule left	0.0056	0.0005	0.0057	0.0005	0.0609
Internal capsule right	0.0057	0.0005	0.0058	0.0005	0.4139
Corpus callosum	0.0094	0.0014	0.0087	0.0016	0.0591
Temporal lobe left	0.0877	0.0068	0.0878	0.0058	0.8442
Temporal lobe right	0.0897	0.0038	0.0898	0.0046	0.9183
Amygdala left	0.0018	0.0002	0.0018	0.0002	0.8171
Amygdala right	0.0019	0.0002	0.0019	0.0002	0.7535
External capsule left	0.0009	0.0001	0.0009	0.0001	0.7936
External capsule right	0.0008	0.0001	0.0009	0.0001	0.1068
Putamen left	0.0047	0.0008	0.0048	0.0007	0.2842
Putamen right	0.0047	0.0006	0.0049	0.0006	0.0389
Globus pallidus int left	0.0007	0.0001	0.0007	0.0001	0.1749
Globus pallidus int right	0.0007	0.0001	0.0007	0.0001	0.1240
Globus pallidus ext. left	0.0013	0.0001	0.0014	0.0001	0.1510
Globus pallidus ext. right	0.0014	0.0001	0.0014	0.0001	0.7675
Thalamus left	0.0062	0.0011	0.0061	0.0012	0.5709
Thalamus right	0.0063	0.0011	0.0064	0.0015	0.3018
White matter	0.4694	0.0243	0.4672	0.0308	0.7732
Grey matter	0.4940	0.0228	0.4952	0.0294	0.8686
Caudate nucleus left	0.0044	0.0005	0.0044	0.0006	0.9470
Caudate nucleus right	0.0047	0.0005	0.0046	0.0006	0.3743
Periaqueductal grey	0.0003	0.0000	0.0003	0.0001	0.9151
3 ventricles	0.1495	0.0312	0.1276	0.0326	0.0001

Fig. 6 The ventricular volumes of NPH patients before and 3 months after the VP shunt surgery
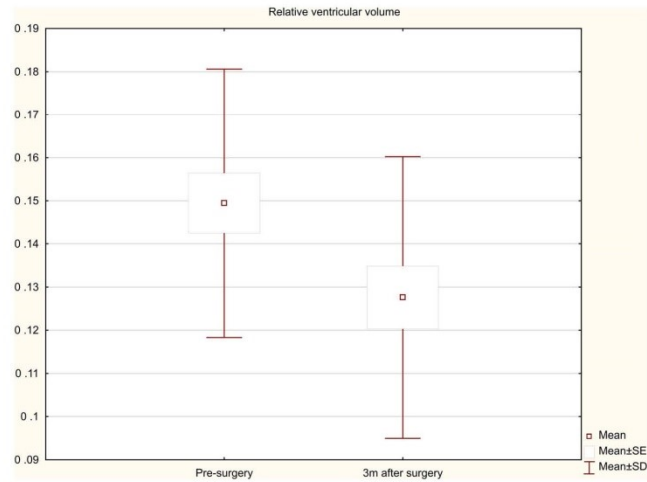

mechanism and right hemisphere seems to be more dominant in these mechanisms [50]. Periaqueductal grey has a paramount role in the control of micturition and its role in NPH symptoms has been suggested for MRI evaluation [49]. Proximity of some of the centers or the connecting pathways to the ventricular system may be the reason of urinary incontinence in NPH [44].

There are few volumetric studies of NPH. In the past, manual segmentation by drawing regions of interest on imaging and subsequent volume calculation was needed. This process was very time-consuming with questionable accuracy. During the past two decades, voxel-based morphometry has changed the accuracy and difficulty of this process. Steadily evolving technology has enabled automated, easy-to-use and time-

efficient segmentation of several structures simultaneously. Nevertheless, the vast majority of published studies are dealing with one or just few of the crucial structures. However, in our study, we are evaluating volumes of all relevant structures in every patient at once, which significantly extends the possibilities of statistical comparison.

Firstly, we have assessed volumetry as a diagnostic tool for NPH suspected patients. All structures mentioned above were measured both in NPH and non-NPH group and compared to healthy control. Statistically significant difference in ventricular volume was confirmed (p value < 0.000001). The difference in white and grey matter was also significant, with p value 0.007 for white matter and 0.005 for grey matter. However, the difference between the NPH and non-NPH group was minimal and

Fig. 7 Comparison of relative volumes of subcortical structures of NPH patients before and 3 months after the VP shunt surgery
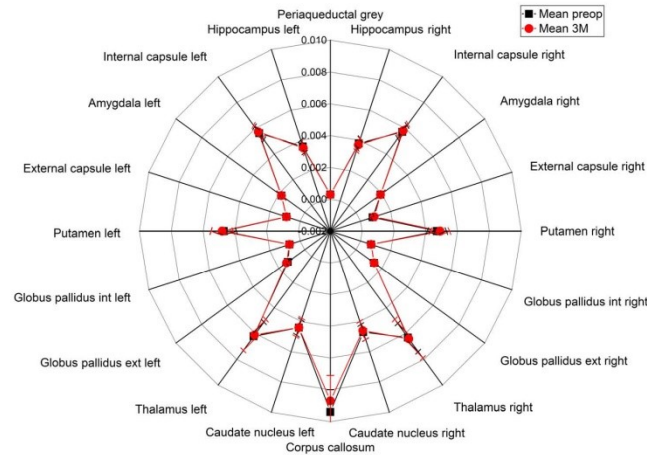
the groups were overlapping. Furthermore, we have observed significant differences in the corpus callosum (p value 0.002), left hippocampus (p value 0.02) and left internal globus pallidus (p value 0.04). Again the difference was mainly compared to control group, whereas compared to non-NPH group it was minimal. Moreover, we have observed larger corpus callosum and hippocampal volume in the NPH group than in the healthy controls, which is in contrast to published data [48]. All observed significant differences were between the NPH suspect group (NPH and non-NPH) and healthy controls. Within the NPH suspect group, where the only difference between NPH and non-NPH was the positivity in functional testing and response to lumbar drainage, the volumetric differences were rather negligible. Our data contradict the routine use of volumetry in NPH diagnostics.

The statistical analysis of changes in structural volumes 3 months after the VP shunt surgery showed expected significant changes in ventricular (p value 0.0001) and cerebral volumes (p value 0.05). The volume of right putamen significantly increased (p value 0.04). This finding could be explained with better drainage of right hemisphere due to the routine placement of ventricular catheter into the right lateral ventricle. This hypothesis is supported by other findings of right-sided structural enlargement, even though these were not statistically significant. All in all, this part of the study does not reveal possible NPH aetiology.

The main limitation of the present study is the limited number of patient controls in 3 months (20/29). It was caused both by a low compliance of some patients and motion artefacts on either preoperative or postoperative images. Only patients with a good quality of both scans were enrolled to the study. Another limitation is the certain inaccuracy of the segmentation process in the case of large ventricles observed by some authors [15].

Conclusion

A detailed volumetric study of NPH patients in both presurgical diagnostics and after VP shunt insertion shows several significant differences. According to our findings, volumetry as a standalone method fails to provide a simple diagnostic biomarker, nor does it shed a light on an unknown NPH aetiology.

Compliance with ethical standards

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

Ethical approval The study was approved by the Military University Hospital Ethical committee.

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REVIEW

Normal pressure hydrocephalus—an overview of pathophysiological mechanisms and diagnostic procedures

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Abstract

Normal pressure hydrocephalus (NPH) is an important differential diagnosis of neurodegenerative diseases. The prevalence of dementia is increasing in line with the worldwide increase in life expectancy. NPH can be divided into idiopathic (iNPH) and secondary (sNPH) which is important in terms of clinical symptoms, future progress, and the outcome of possible treatment. The full clinical triad is not prevalent in all of the cases and the pathophysiology of iNPH remains unclear. Diagnosis is based on the evaluation of clinical symptoms (Hakim's triad) combined with an MRI assessment, evaluation of CSF dynamic parameters by different methods such as a tap test, lumbar infusion test (LIT), and external lumbar drainage (ELD). Despite the development of diagnostic techniques and strategies in management, NPH remains to be a challenge for the specialists despite more than 50 years of research. However, results of this research have brought new opportunities in the diagnosis, therapy, and quality of life as well as survival time of NPH patients with improved symptoms. The aim of this article is to present the pathophysiological hypotheses of NPH and an overview of the diagnostic techniques used for the evaluation of NPH patients.

Keywords Normal pressure hydrocephalus · NPH pathophysiology · Diagnostic procedures · Idiopathic NPH · Hydrocephalus

Introduction

According to a rise of global life expectancy, especially in the last two decades [87], the prevalence of diseases associated with neurodegenerative processes is increasing. In 2010, the estimated number of people living with dementia worldwide was 35.6 million and this number is expected to rise to 65.7 million by 2030 [92].

Normal pressure hydrocephalus (NPH) plays a role in the differential diagnosis of dementia for more than 50 years as Hakim and Adams described three patients in 1965 who had

ventriculomegaly on pneumoencephalography but had no increase in their intracranial pressure (ICP) [38]. They also described a clinical syndrome that consists of a classical triad of symptoms. These are urinary incontinence, dementia, and gait impairment [38]. However, this complete triad is not always seen. In SINPHONI—a Japanese multicenter cohort study looking at the validity of MRI findings in idiopathic NPH (iNPH) [40]—there were only 51% of patients with the complete triad of symptoms. Sexual dysfunction [82], neurological symptoms, psychiatric symptoms, or other infrequently reported signs have circumstantial relation to NPH but may hinder diagnostic processing [99]. Although the prevalence of NPH remains imprecise and is calculated to be 1.30% for those aged $\geq$ 65 years, a severe problem of underdiagnosis seems to exist [75].

NPH can be divided into primary or idiopathic (iNPH) and secondary (sNPH) [80]. The most commonly used treatment of NPH is implantation of a ventriculoperitoneal (VP) shunt, a system draining CSF from the lateral ventricles to the peritoneal cavity [97]. Shunting leads to a clinical improvement in 70–90% of treated patients in contrast to other, often poorly treatable neurodegenerative disorders [52]. Even though the initial clinical improvement rate is generally high and in some cases may be sustained for up to 5 or even more years [93], the

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long-term outcome studies are limited by a large proportion of patients lost to follow-up which may overestimate the reported rate of clinical improvement (average of 65% of cases in at least 3 years after surgery in a systematic review by Toma et al. (2013)) [114] [10]. It is difficult to determine the reasons of lost of follow-up and almost impossible in retrospective studies. The evaluation of iNPH is not an easy task. Some of the patients may die or fail to recognize the returning symptoms or to seek attention for them, fail to return because symptoms remain under control, feel that the follow-up is unnecessary [93], or even might be mistakenly diagnosed with iNPH and instead of it suffer from a developed neurodegenerative disease. [26]

In a recent meta-analysis of 33 studies, complication rate of VP shunting ranged 13–38%, 26–38% of cases shunted with a fixed-pressure valve and 9–16% of cases shunted with an adjustable valve required a revision surgery as the only significant difference between both groups [34].

The lack of sustained follow-up, risks of shunt malfunction, and the rate of shunt complications and revisions remain to be drawbacks of the outcome of shunting in NPH. However, it has been reported in a Swedish cost-utility analysis on 30 patients diagnosed with iNPH based on clinical and radiological criteria only that an average patient gains 1.7 quality-adjusted life-years (QALY) after shunting which is significantly higher than that in Alzheimer's disease (AD) patients treated with donepezil (0.11 QALY) or patients suffering from acute stroke treated with endovascular thrombectomy (0.99 QALY) [116].

Diagnosis is based on clinical symptoms combined with diagnostic procedures. In a recent survey [22] of up to 30% of patients who fill the MRI criterion of hydrocephalus, Hakim's triad was not fully expressed while the tap test was negative and CSF outflow resistance was low. This makes NPH diagnosis a difficult task with a possible lack of reliability while there is a speculative subsequent prediction of shunt response in accordance with a poor knowledge of iNPH pathogenesis. Up to 80% of NPH patients remain unrecognized [52] and thus, their medical treatment is inappropriate.

Methods

We searched the MEDLINE, EMBASE, and Cochrane library (Cochrane reviews, Cochrane central register of controlled trials) databases for the literature. We also reviewed the reference lists of the included articles. The last search was run on 2 February 2019. We used the following keywords to search the databases: "normal pressure hydrocephalus," "idiopathic normal pressure hydrocephalus," "hydrocephalus," "cerebrospinal fluid drainage," "CSF," "tap test," "nph diagnosis," "nph pathophysiology," "lumbar infusion test," "external lumbar drainage." We reviewed the titles and abstracts and those related to normal pressure hydrocephalus were included. Irrelevant studies not pertaining to this query, grey literature publications, Commentaries, Letters, and Editorials were excluded (Fig. 1).

Fig. 1 The flow diagram describing literature search process.
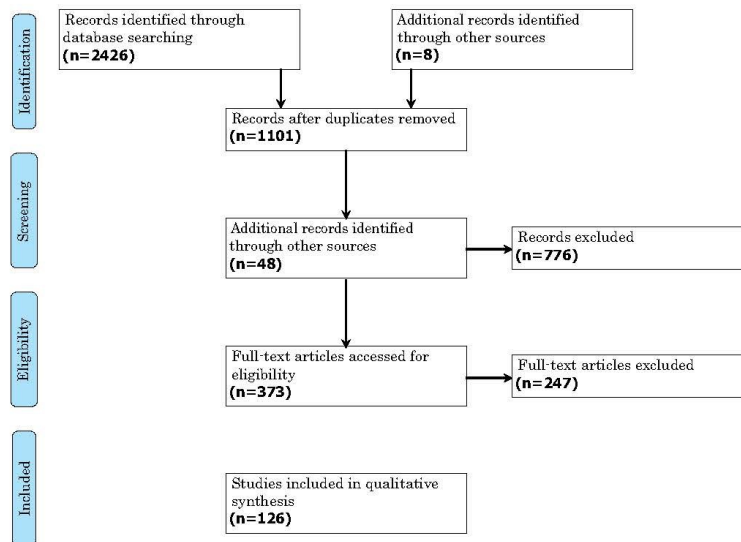
Pathophysiology of NPH

Normal pressure hydrocephalus can be divided into two different entities—idiopathic (iNPH), where the underlying cause is not previously known, and secondary (sNPH), which can be a result of various pathologies such as subarachnoid hemorrhage, trauma, meningitis, malignancy, stroke, and intracerebral hemorrhage [25]. Marmarou et al. (2005) [74] reported that the combination of cases of iNPH and sNPH may lead to considerable controversy in the diagnosis and therapy of such cases.

In the case of sNPH, fibrosis and adhesions in the subarachnoid space and arachnoid granulations can lead to NPH [25]. Products and cellular components of intracranial tumors [89] or proteins and cells from subarachnoid hemorrhage or meningitis may lead to an increase of CSF viscosity and impairment in CSF reabsorption. Both mechanisms lead to an initial increase in the CSF pressure resulting in ventricular enlargement. A new balance between CSF pressure and volume occurs in the CSF space [25]. SNPH may affect every age following the initial incident while iNPH occurs most commonly in the elderly population [25]. The preclinical stage of sNPH is typically much shorter, over weeks or months [72], than the preclinical development of iNPH, which is gradual over years.

In sNPH, the neurological deficits caused by the primary diseases may mask the typical NPH symptoms [18]. However, it was reported that the outcome of shunt surgery was significantly better for sNPH than for iNPH patients while the disease duration of less than 1 year was an important factor [111]. Valve adjustments were found to be more frequent in iNPH than in sNPH cases (49% vs. 32% reported by Zemack and Romner, 2002) [126].

Pathophysiology of iNPH

The first theory defining the pathophysiology of iNPH was published over five decades ago [38]. Over the years, alternative hypotheses to clarify the pathophysiological mechanisms behind this disease have been published (Table 1). Yet, none of them has found a unifying concept to explain these and fundamental questions have still not been answered. INPH may not even be an entity by itself and symptoms and pathogenetic mechanisms resulting from different geneses might be included under the term iNPH [16]. Also, there may be a role of an impairment of the recently discovered glymphatic pathway but further investigations clarifying its function in humans [95] and its implication to neurodegenerative processes are needed [6]. Altered aquaporin 4 expression in astrocytic perivascular endfeet is evident in brain tissue of AD and NPH patients and MRI scans of NPH patients show reduced CSF tracer entry and clearance [28, 39]. On the basis of MRI imaging with intrathecal administration of gadobutrol in 15 iNPH patients and 8 controls, Ringstad et al. [101]

Table 1 List of different iNPH theories (based on Ammar et al. (2017) [5] and Krishnamurthy and Li (2014) [60])

1. Hakim-Adams theory (Hakim and Adams 1965) [38]
2. Transcerebral mantle pressure gradient (Hoff and Barber 1974) [44]
3. Restricted arterial pulsation hydrocephalus (Greitz 1993) [37]
4. Bulk flow theory (Rekate 1988) [98]
5. Unifying theory for definition and classification of hydrocephalus (Raimondi 1994) [94]
6. Hemodynamic theory of venous congestion (Bateman 2004) [7]
7. Evolution theory in cerebrospinal fluid dynamics and minor pathway hydrocephalus (Oi and Di Rocco 2006) [86]
8. Importance of cortical subarachnoid space in understanding hydrocephalus (Rekate 2008) [98]
9. Pulsatile vector theory (Preuss et al. 2013) [91]
10. Reassessing CSF hydrodynamics and novel hypothesis (Chikly B. and Quaghebeur J. 2013) [19]
11. Osmotic gradient theory (Krishnamurthy and Li 2014) [60]
12. Intimate exchange between cerebrospinal fluid and interstitial fluid. (Matsumae et al. 2016) [77]
13. The Comprehensive Idiopathic Normal-Pressure Hydrocephalus Theory (CiNPHT) (Ammar et al. 2017) [5]

hypothesized that the restricted arterial pulsations reduce glymphatic flow leading to the reduction of transport of solutes and CSF through the glymphatic pathway and further reduce intracranial compliance and the obstruction between the paravascular and interstitial spaces may be responsible for retrograde transventricular route of CSF flow. According to the overnight peak of parenchymal gadobutrol enhancement [101] and their reported frequent association of obstructive sleep apnea (OSA) and iNPH (90.3% of iNPH patients had an associated OSA), Román et al. [103] discussed a potential role of sleep-disordered breathing in the iNPH pathophysiology.

Before the advances in the research of glymphatic system, Ammar et al. (2017) [5] reviewed existing theories and created a new concept which summarizes the previously discovered findings into a complex system which connects different pathophysiological mechanisms. This system works as a vicious cycle, where one mechanism determines the other. The goal of current therapeutic options is to disrupt this vicious cycle which, despite all efforts, can only slow down.

Ventricular enlargement is accompanied with a slow CSF flow to subarachnoid space and its impaired absorption which is exceeded by the production. The dilatation increases mechanical stress on the periventricular white matter, causing ischemia and hypoxia in the white matter axons [2]. Chronic healing attempts can lead to decreased brain compliance around the ventricle, which results in "stiff ventricles" [5]. The ependymal layer progressively loses plasticity while pulsatility is concurrently

significantly reduced [37]. This further leads to an impairment of bulk flow through the outlets of the CSF compartments [98]. The expansion of the ventricles will cause pressure on a larger surface area and if the pressure exceeds the elastic tension of the surrounding brain tissue, the ventricles enlarge again and the pressure falls to normal values [38]. Despite the normal pressure in the ventricles, the force on ventricular wall is greater and proportional to the increased surface area [51]. Concurrently impaired blood flow, hypoxia, and ischemia lead to metabolic and biochemical disruptions [59]. Subsequently, demyelination and neural apoptosis occur as a final result. Interstitial fluid accumulates and the transmantle pressure is increased [44] possibly leading to venous congestion, hindrance of intraparenchymal CSF pathways and worsening of transependymal transudation. The increased interstitial fluids and pressure cause damage to the neural and glial cells, alteration of biochemical processes, increased oxidative stress, blockage of oligodendrocyte differentiation, and glial scars [76]. Congested veins lead to a decreased drainage of the brain leading to increased accumulation of the toxic elements [7]. Compression or occlusion of small blood cells causes ischemia, the tissue loses integrity and became stiff, compliance is reduced, and transmission of pulsatile waves is decreased [91]. The CSF is produced at the same rate but the flow through is delayed; the ventricles dilate more which worsens the lesions in surrounding brain tissue which further slows down the flow [5].

In context of the studies clarifying cellular and molecular abnormalities leading to ciliary dysfunction of ependymal cells in congenital hydrocephalus associated with primary ciliary dyskinesia [63], a recent discovery has been made in a Japanese family with multiple individuals with NPH. A loss of product of CFAP43 gene is suggested to be related to morphologic or movement abnormalities of cilia in the ependymal or choroidal cells and is associated with the NPH in these individuals in a heterozygous state. This could be helpful in the elucidation of the pathogenesis of iNPH but more research on cellular dysfunction has to be done [84].

Despite all the currently known characteristics of CSF flow, cerebrovascular system, and brain environment, there is still a lot to be clarified in the pathophysiology of iNPH in correlation with autopsy findings, diagnostic methods, clinical examination, and treatment options to offer an optimal therapy and management of iNPH patients [60, 65].

Natural history of iNPH

The main symptoms of Hakim's triad do not have to be present together and their onset, severity, and progression are variable [99]. The progression can vary but most of the reported cases of iNPH patients without or postponed shunt surgery had deteriorated during the first few months after initial

assessment [113]. INPH is a lifelong disease. Shunt insertion may permanently relieve symptoms but cannot eliminate the chain of the currently poorly known causes of the disease [67]. A systematic review of 30 studies of ventriculoperitoneal shunting showed similar rates of symptomatic improvement after 3 months and 1 year [114] but after the initial improvement, the symptoms relapse despite evidence of a functioning shunt. This is increased in older patients and over the time, the symptoms progress due to the underlying neurodegenerative process [10]. Mirzayan (2010) [81] found no statistically significant difference between outcomes at 18 and 81 months, but many patients were lost to follow-up or died.

Differential diagnosis of NPH

The differential diagnosis (Table 2) includes a high number of diseases that are more or less common in elderly patients. The clinical symptoms of NPH may be subtle and may resemble other neurodegenerative disorders [33], primary urological disorders, vascular dementias, other hydrocephalus conditions, infectious diseases, result of traumatic insult, brain or spinal tumors, metabolic conditions, and organ failures such as dialysis dementia, Wilson's disease, hepatocerebral degeneration and many other diseases [99, 100].

A different condition may be concurrent with NPH—most commonly AD or vascular dementia [9]—and the presence of comorbidity is a statistically significant predictor of shunt therapy outcome in iNPH. This may be evaluated using various tools such as the comorbidity index (CMI) [79]. Characterization of the diseases or wider comparison with clinical symptoms of NPH and its possible diagnostic procedures used to evaluate these diseases (Table 2) is beyond this article. However, a sound knowledge of the etiologies, diagnostic procedures, and possible treatment is needed for an appropriate clinical approach to these disorders. It is important to identify the signs of possible NPH in the evaluation of these diseases and, with further testing, choose the patients who would benefit from shunting. Because the elderly population of NPH patients is prone to the comorbidities mentioned in this article, it is almost impossible to see "pure" NPH [123]. The influence of these diseases on the outcome of shunting could be very large, so a complex testing battery is needed to identify the signs of other disorders and treat the treatable ones—for example resting tremor during clinical exam, hesitance during gait assessment (Parkinson's disease or Lewy body dementia), rapid forgetting of newly acquired information during neuropsychology assessment (Alzheimer's disease), joint pain during gait assessment (arthrosis), and dysuria in the urinary symptoms assessment (urinary tract infection, bladder cancer) [71]. Only with such approach can benefit to these patients be achieved.

Table 2 Differential diagnosis of Normal pressure hydrocephalus including comorbidities and potential causes of sNPH (based on Relkin et al. (2005) [99] and Rigamonti et al. (2014) [100])

Vascular dementias	*Other hydrocephalus conditions*
Cerebrovascular disease	Obstructive hydrocephalus*
Stroke	LOVA
Binswanger's disease	Arrested hydrocephalus
Multi-infarct dementia	Aqueductal stenosis*
Subcortical infarcts	
Leukoencephalopathy	
Cerebral autosomal dominant arteriopathy	
Vertebrobasilar insufficiency	
Infectious diseases	*Urological diseases*
Lyme borreliosis	Bladder or prostate cancer
Human immunodeficiency virus	Benign prostatic hyperplasia
Progressive multifocal leukoencephalopathy (PML)	Stress incontinence or pelvic
Floor laxity syphilis	Urinary tract infection
Neurodegenerative diseases	*Miscellaneous*
Alzheimer's disease	Epilepsy
Parkinson's disease	Depression
Lewy body disease	B_{12} deficiency
Frontotemporal dementia	Collagen vascular disorders
Corticobasal degeneration	Spinal stenosis
Progressive supranuclear palsy	Chronic traumatic brain injury
Amyotrophic lateral sclerosis	Chiari malformation
Huntington's disease	Wernicke's encephalopathy
Spongiform encephalopathy	Carcinomatous meningitis
Multisystem atrophy	Spinal cord tumor
	Brain tumor
	Hypothyroidism
	Organ failures
	Peripheral neuropathy
	Chronic subdural hematoma

LOVA, long-standing overt ventriculomegaly syndrome

*Obstructive hydrocephalus may be due to the obstruction in different parts of the CSF pathway not only in the aqueduct. To point out the differences between these entities, many clinicians use aqueduct stenosis as a separate disease with respect to the pathogenesis; hydraulic mechanisms of compensated states, chronic, subacute, or acute courses; and the degree of the stenosis which in a specific state can be responsible for NPH clinical symptoms [102]

Diagnostic techniques and procedures

Gait assessment

Gait disturbance is typically the first clinical manifestation of NPH and also the most responsive feature to shunting [93]. The NPH gait is characterized by reduced speed, short steps, reduced step height, and impaired dynamic equilibrium with accented expression during turning [74] and is often described as "magnetic" or "glued to the floor" [33]. Enlarged step width, larger foot angles, and no improvement of walking with visual and/or acoustic cues were also described [109]. Patients may also experience difficulty in rising from a chair or walking on stairs [99]. Postural dysfunction is another prevalent finding, which results in a forward leaning posture with provoked or spontaneous backward falling [115]. Blomsterwall et al. (2000) [11] were interested in the correlation between both gait and balance impairment before and after shunt surgery. They found that improvement in balance may partly be responsible for the improved gait (75% of patients improved walking speed and 69% balance).

Gait evaluation often consists of both subjective and objective measurements. The subjective rating scales may include categorical (e.g., bedridden, walk but unstable) [90] or specific ratings (e.g., tandem walking disturbed) [96]. Objective measurements may provide more reproducible and rigorous assessments. Clinicians may observe cadence, step height, step width, stride length, tandem gait, shoulder-hip counter-

rotation, turning, resting sway, posture, start hesitation, and retropulsion in a specific defined manner [115]. The use of a Timed Up and Go test in gait evaluation of NPH patients showed high sensitivity and specificity for the prediction of functional improvement at 1 year after VP shunt surgery and lumboperitoneal (LP) shunt surgery, where VP shunt conveyed better improvements in this gait evaluation method [125]. Other methods include observation and descriptive assessment of gait using videotapes [74] or tests such as 10-m walk test, Berg balance scale, Tinetti scale [31], or GAITRite system [124].

Neuropsychology

The cognitive profile of NPH is comprise of an alteration in working memory, learning, attention, processing speed, psychomotor speed, executive, visuospatial, and visuoconstructional functions [45]. In comparison with AD which is a "cortical dementia," NPH is a "subcortical dementia" [117]. This term refers to a mental decline arising from the impairment of subcortical structures resulting in slowed processing speed and apathy [55]. Frontal functions (such as executive functions) are also disrupted due to damage of fronto-subcortical projections or subcortical structures and are more severely impaired in comparison with AD while memory is presented by delayed recall and delayed recognition [120] and is less affected compared with AD [85]. Iddon et al. (1999) [45] examined a group of NPH patients (MMSE ≥ 24, $n = 6$) using CANTAB (Cambridge neuropsychological test automated battery). These patients were impaired in spatial recognition but unimpaired in pattern recognition compared with healthy controls. This supports the relation of fronto-subcortical changes to the cognitive profile shown in NPH patients [27, 45]. However, as mentioned above, the prevalence of comorbidities is very high. We assume that the "true" cognitive profile of iNPH can only come from prospective studies with autopsy-proven NPH in the absence of other well-developed neurodegenerative diseases.

Neuropsychology assessment is a non-invasive and inexpensive tool for objective measurement of cognitive and behavioral symptoms of NPH [27] and may also be used to predict shunt response if it follows specific patterns [110]. Various neuropsychological batteries for cognitive, behavioral, and emotional evaluation of NPH patients have been developed [43] even combined with gait, balance, and incontinence assessment in iNPH scale [43]. These batteries often consist of well-validated neuropsychological procedures such as Mini Mental State Exam (MMSE), Rey's Auditory Verbal Learning Test (RAVLT), Rey-Osterrieth Complex Figure Test (ROCFT), Controlled Oral Word Association Test (COWAT), Block Design Test (BDT), and Geriatric Depression Scale (GDS), Trail Making Test (TMT; trail A and trail B). Each of these tests targets different aspects of NPH cognitive and behavioral profile.

Assessment of urinary symptoms

The lower urinary tract symptoms (LUTS) are prevalent in a population older than 60 years. The epidemiologic EPIC study [58] reported prevalence of any LUTS in 94% of men and 89% of women and prevalence of overactive bladder (OAB) in 28% of men and 34% of women in population aged ≥ 60 years in the Czech Republic.

According to the International Continence Society, a standardized terminology for urinary symptoms is recommended. Overactive bladder is defined as a urinary urgency with or without urge incontinence and is usually associated with frequency and nocturia [56]. The constellation of all these symptoms is called "storage" or "irritative" symptoms. The constellation of straining, intermittent stream, slowed stream, post-void dribbling, and hesitancy is often termed "voiding" or "obstructive" symptoms [100]. Lesions above the pontine micturition center cause a lack of inhibitory control of the bladder and result in detrusor overactivity with or without incontinence which was described in NPH patients [104]. The proximity of some of the centers that control micturition or their connecting pathways to the ventricular system may result in the urinary symptoms in NPH [115].

Subjective information provided through validated questionnaires developed by the International Consultation on Incontinence Modular Questionnaires (ICIq) has become an accepted mean to standardize the assessment of urinary symptoms and outcome measurement [62]. However, urodynamic testing may be the most important investigative procedure. In this study, the patient is placed on a specialized chair with an infusion of saline through a urinary catheter. An additional catheter is placed in the rectum or the vagina for the simultaneous measurement of intravesical and intraabdominal pressure [100], maximum flow rate, post-void residual, bladder capacity, first sensation, and detrusor activity [61]. The function of the urethral sphincter is measured with an electromyography [56]. The common finding in NPH patients is typically detrusor overactivity, possibly responsible for urinary urgency which is thought to precede urge incontinence in the progression of iNPH [104].

Lumbar infusion test

The consensus of experts combined limited published works to establish the expected range of iNPH opening pressure between 4.4 and 17.6 mmHg [73]. A single measurement of ICP is limited for the diagnosis and outcome; therefore, it is preferable to use CSF dynamic studies to evaluate NPH [73]. One of them is the Lumbar Infusion Test (LIT) with a modification of the technique originally described by Katzman and

Hussey in 1970 [15]. In the LIT, ICP is continuously measured during a constant infusion of artificial CSF or saline into the lumbar subarachnoid space via a lumbar needle (Fig. 2). The flow is applied against the ICP. This flow may determine parameters of CSF dynamics such as the conductance or reciprocal outflow resistance (R_{out}) which is the most important one in most of the LIT protocols [78]. There is a nonlinear correlation between the increase of ICP with increasing R_{out} which is defined as the difference in the final steady-state pressure and the initial pressure divided by the flow rate of infusion [12]. A widely accepted threshold of R_{out} is not established but the value of 12 mmHg/ml/min seems to be the most suitable threshold [54]. Also, research on healthy volunteers has shown that R_{out} does not normally exceed 10 mmHg/ml/min [3].

The sensitivity of LIT between 56 and 100% and specificity between 50 and 90% have been reported in various publications [42]. The positive predictive value of LIT is 80% and the occurrence of false-negatives is up to 16% [50].

Tap test

In the description of NPH by Hakim and Adams in 1965 [38], three patients had 15 ml of CSF removed via a spinal tap with improvement of symptoms in all these patients. Since this reference, many clinicians have used lumbar punctures with the removal of CSF to identify potential shunt responders. However, the borderline of significant improvement has not been formalized [73]. Removing CSF from the subarachnoid space lowers the ICP and CSF resorption for several hours with a possible partial normalization of CSF hydrodynamics [121]. Currently, in a tap test (TT), 30–50 ml of CSF is drained from the patients with a following assessment of symptom improvement [32]. Recent research is focused on clinically used gait, balance, and cognition evaluation methods that can identify improvement from a TT [32].

The positive predictive value of TT between 73 and 100%, sensitivity between 26 and 62%, and specificity between 33 and 100% have been reported in various studies [73]. Therefore, negative results of TT cannot be used to exclude patients from treatment [122].

External lumbar drainage

External lumbar drainage (ELD) is recommended for the evaluation of NPH [120]. The effusion rate varies between 5 and 10 ml/h while the patient is in a horizontal position and the drainage is closed before the patient gets up. The drainage is maintained for 3 to 5 days [73]. The positive effect of ELD can be demonstrated with phase-contrast MRI with CSF flow change in the cerebral aqueduct [107]. The rate of significant complications was reported to be 3% [35].

The positive predictive value of ELD between 80 and 100%, sensitivity between 50 and 100%, and specificity between 60 and 100% have been reported in various studies (Table 3) [73].

In accordance with the statistical values (Table 3), a single predictive for shunting cannot be derived from the invasive procedures to the individual patient. This may be due to the complex pathogenesis of iNPH [70] together with the complexity of intracranial pressure and CSF hydrodynamics [23]. However, ELD seems to have the best and most reasonable prognostic accuracy for the prediction of shunt responsiveness in iNPH patients [20]. According to the reported statistical values (Table 3), we suggest to perform LIT with a subsequent ELD in the evaluation process.

Imaging modalities

Imaging techniques are used in the management of iNPH including CT and MRI for visualization of ventricle expansion and conventional X-rays or radionuclide shunt patency studies
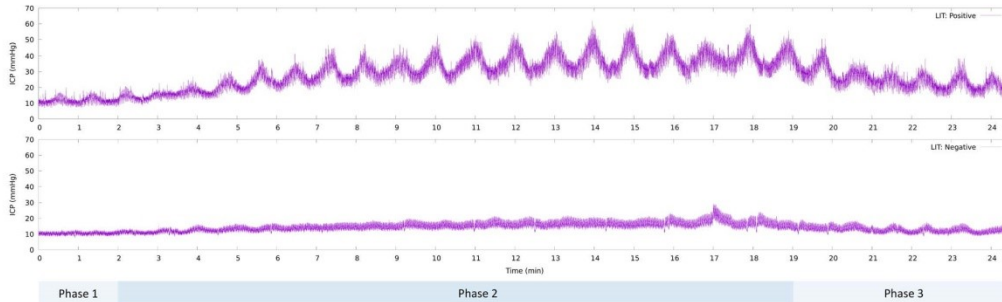

Fig. 2 Comparison of the positive (top) and negative (bottom) lumbar infusion test. The ICP (mmHg) is recorded throughout three subsequent phases. Phase 1: equilibration of the CSF pressure, infusion pump is off (first 2 min); phase 2: infusion of Ringer's solution until a stationary state, ICP plateau is reached, infusion pump is on (approx. 13–20 min); phase 3: recovery of the initial ICP state, infusion pump is off (approx. 4–6 min). Of note are the low-frequency oscillations of the elevated ICP expressed especially in the LIT-positive patient

Table 3 Summary of reported statistic values for LIT, TT, and ELD [42, 50, 73]

	Sensitivity (%)	Specificity (%)	Positive predictive value (%)
Lumbar infusion test	56–100	50–90	80
Tap test	26–62	33–100	73–100
External ventricular drainage	50–100	60–100	80–100

for the evaluation of shunt malfunction [64]. However, it is not possible to diagnose NPH using MRI or CT only. The size of the ventricles does not correlate with flow resistance, resting pressure and pressure-volume index [13].

Various indices (Fig. 3) are used in clinical practice to evaluate ventriculomegaly in NPH patients. Evans index, which was introduced by William A. Evans in 1942 [29], is a standard. It describes the widest distance in the frontal horns divided by the widest transverse distance between the tabulae internae. However, values of the Evans index can significantly vary depending on the level of the brain CT scan image [112] and the volumetric analysis could be more accurate [112]. Other indices such as frontal-occipital horn ratio (FOR), bicaudate ratio (BCR), or bifrontal index (BFI) [8] were introduced, but their use is uncommon. Specific method using CT – CT cisternography is obsolete due to its invasiveness and false-positive results in more than 60% of cases [14].

Postoperative CT scan is important for the description of results and potential complications of shunt surgery. Routine follow-up is often 3, 6, and 12 months and then annually after shunt implantation [66]. However, many authors state that CT scans are not required after 1 year of follow-up period as long as the clinical symptoms are not severely changed [57] as the change in ventricular size does not correlate with the clinical outcome of therapy [80].

However, the images of MRI are more detailed. MRI provides an easier detection of special conditions (aqueduct stenosis), better description accuracy of radiological signs of NPH (Fig. 4). One of these is the presence of "disproportionately enlarged subarachnoid space hydrocephalus" (DESH),

Fig. 3 CT scan of a suspected iNPH patient with equations for calculating various indices

- Evans index

$$\frac{a}{e}$$

- Frontal-occipital horn ratio (FOR)

$$\frac{a+f}{2e}$$

- Bifrontal index (BFI)

$$\frac{a}{b}$$

- Bicaudate ratio (BCR)

$$\frac{c}{d}$$

which was proposed to be a pathognomonic feature of iNPH by the Japanese Guidelines [83]. DESH is composed of three components: ventriculomegaly, high convexity tightness, and enlarged Sylvian fissure [48]. The role of DESH in the identification of shunt responders remains controversial [21, 119] although multiple studies presented results that could indicate this fact [40, 119]. The presence of DESH without clinical symptoms has been termed asymptomatic ventriculomegaly with features of idiopathic normal pressure hydrocephalus on MRI (AVIM) and some authors describe it to actually be a pre-clinical state of iNPH [46]. Another diagnostic feature which could be described on MRI image is a callosal angle (CA). Value of the CA was found to be significantly lower in iNPH patients than that of AD and control groups [47]. The measurement of the CA should be done on a coronal image perpendicular to the AC-PC plane at the level of posterior commissure [118] as well as the description of DESH [83]. The CA may be another non-invasive tool to help predict shunt responsiveness [36, 118]. A cingulate sulcus sign has also been proposed to be a feature of iNPH. It denotes posterior part of cingulate sulcus being narrower than the anterior part with a divider between both parts being a line parallel to the floor of the 4th ventricle [1].

MRI may also provide potential specific protocols such as phase-contrast MRI with the measurement of CSF flow rate in the cerebral aqueduct [76]. CSF flow rate in the cerebral aqueduct has been clinically evaluated by fMRI using the 2D phase-contrast technique with a CSF flow rate of more than 24.5 ml/min with high specificity for NPH (95%) but low sensitivity (46%) and currently is not reliable for prediction of shunt surgery outcome [4]. Aqueductal flow void which is a decrease of signal seen within the aqueduct on T2-weighted images resulting from greater outflow of CSF was found to be correlated with shunt results in the first studies but later studies found that single PC-MRI measurement or CSF flow void alone cannot safely support NPH diagnosis or shunt responsiveness because it has been observed even in healthy individuals [24].

Another interesting area of MRI is diffusion tensor imaging (DTI) with potential future value. Using DTI, specific micro-structural changes in periventricular white matter have been reported [41], changes in the frontal white matter could impair signaling between the frontal cortex and basal ganglia [68], and higher fractional anisotropy in the posterior limb of the internal capsule could possibly explain gait symptoms of iNPH [53]. Magnetic resonance elastography which visualizes
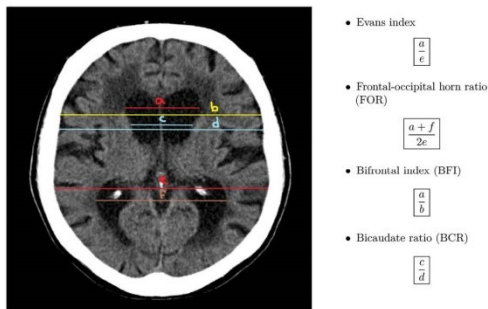
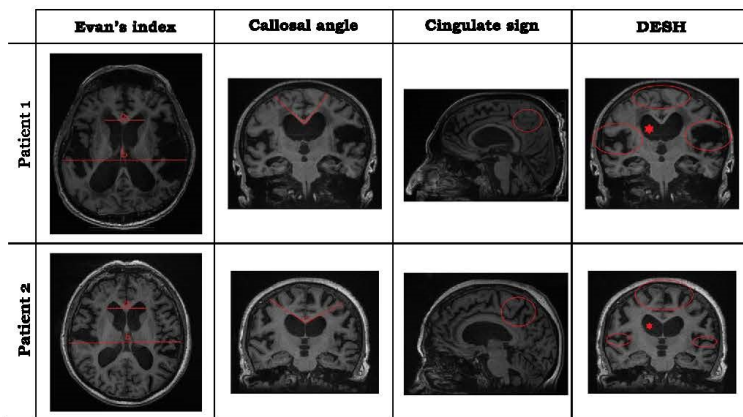|	Evan's index	Callosal angle	Cingulate sign	DESH
Patient 1				
Patient 2				

Fig. 4 MRI findings (T1WI) in two patients positive for Hakim's triad. Both patients had ventriculomegaly (Evan's index = 0.35). Patient 1 (male, 75 years) had an acute callosal angle (= 85°), positive cingulate sign, and disproportionately enlarged subarachnoid space hydrocephalus (DESH). All of these were suggestive of iNPH. Patient 2 (female, 77 years) had an obtuse callosal angle (= 115°), negative cingulate sign, and an absence of DESH. Patient 1 was positive in both LIT and ELD and he was offered implantation of a VP shunt. Patient 2 was negative in both functional tests and VP shunting was not indicated

elasticity of the brain has also a possible future benefit in iNPH evaluation; e.g., significant decrease of viscoelastic properties near the ventricles has been reported [30].

Laboratory findings

Nowadays, there are no disease-specific biomarkers used in clinical practice for evaluation of iNPH. However, recent publications defined potential candidates [49, 69, 105, 106] as well as theories explaining such findings [49]. Li et al. (2006) [69] consider the leucine-rich α-2-glycoprotein (LRG) to be specific for iNPH. Also, other biomarkers of subcortical damage, namely neurofilament light chains (NFL) and myelin basic protein (MPB), are increased in the CSF of iNPH patients but the specificity of all of these three markers was found to be limited [106]. Reduction of amyloid-β-related proteins is associated with reduced or normal p-tau and t-tau in iNPH, while in AD, a reduction of amyloid-β-related proteins is coupled with an increase of p-tau and t-tau [105]. However, interpretation is difficult because of the high concurrence of both diseases [17]. Inflammatory biomarkers (TGF-β1, IL-1β, IL-6, IL-10) are potentially increased, but there is currently no evidence for their validity in evaluation of iNPH [106]. Neurosteroids (pregnenolone, PREG; dehydroepiandrosterone, DHEA; their sulfates and metabolites) appear to be promising analytes in the search for a signature NPH biomarker. In a study by Sosvorova et al. (2015), the proposed OPLS model absolutely discriminates NPH based on CSF steroids and neurosteroids [108]. However, none of the known biomarkers is currently clinically used for predicting shunt responsiveness [88] and further investigations are needed [106].

Conclusion

NPH is an important differential diagnosis of neurodegenerative disorders. It can be divided into iNPH and sNPH. More than 50 years of research did not completely clarify the pathophysiology of iNPH; however, it seems that iNPH is a vicious cycle of different underlying pathophysiological mechanisms. iNPH affects the elderly and many of them have other comorbidities. If these are not sufficient to explain the patients symptoms, iNPH should be considered. The presence of comorbidities does not exclude the iNPH patients from shunting; however, the outcome of shunt surgery is strongly influenced by these disorders; thus, the important part of the iNPH management is to identify any of the treatable conditions.

The diagnostic procedures used in NPH evaluation process include gait, urinary, and neuropsychological assessment which are used to identify characteristic clinical features of the disease. Lumbar infusion test, spinal tap test, and external lumbar drainage explore the CSF hydrodynamics and specific radiological signs are identified during imaging procedures. The laboratory findings are not used in clinical practice and their validity needs to be confirmed by future studies. However, potential candidates such as neurosteroids or identification of different biomarkers in a complex laboratory protocol may possibly provide a valid diagnosis of NPH. Recent research is focused on identification of shunt responders. Callosal angle, DESH, cingulate sulcus sign on the T1W1 of

MRI images, or positive external lumbar drainage seems to be most promising in the evaluation of outcome after shunt implantation. However, the disease itself is a complex entity and it turns out that the successful therapy of NPH requires thorough consideration of the results of different diagnostic procedures to achieve an improvement of survival and quality of life of NPH patients. In spite of putative and supposed pathogenesis of the iNPH that is hindering the care of the patients, its current treatment is more successful than the treatment of other neurodegenerative diseases despite the potential risks of complications, shunt failure rates, or needs for surgical revisions that may reduce its socio-economic benefits.

Compliance with ethical standards

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

Ethical approval For this type of study formal consent is not required.

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Pediatric Ventriculoperitoneal Shunts Revision Rate and Costs in High-Volume sub-Saharan Department

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■ BACKGROUND: Ventriculoperitoneal shunt (VPS) placement is one of the most common neurosurgical procedures. VPSs are associated with high costs, which predominantly arise from relatively high complication and revision rates. It is reasonable to assume that revision rates in developing countries would be higher. In this study we report the single-institution revision rates and costs from a high-volume department in sub-Saharan Africa.

■ METHODS: A pediatric neurosurgical database was studied in the extent of 5 years. The 30-day shunt failure rate, overall revision rate, and costs were calculated, and results were compared with previously published studies from developed countries.

■ RESULTS: In the selected time period 1840 VPS surgeries were performed, of which 592 were shunt revisions (32.14%). The majority of revision surgeries was performed in the first year- 501 (representing 84.63%); second year, 64; third year, 21; fourth year, 6; and fifth year, 2. The overall shunt revision rate was 28.94% with a 30-day revision rate of 14.58%. During the course of the study, costs of VPS surgery, the shunt, and daily ward charges did not change significantly. The average total charge for VPS insertion was 60,000 KES (586 USD), VPS removal 30,000 KES (293 USD), and VPS revision 50,000 KES (489 USD).

■ CONCLUSIONS: This retrospective study proves that VPSs, with their known complication risks, can be performed in a sub-Saharan missionary hospital with acceptable costs and results that are comparable with those achieved in some Western hospitals. Keys to those outcomes include high volume and a highly experienced team.

INTRODUCTION

The first description of hydrocephalus was made by the father of medicine, Hippocrates, in the fifth century B.C. Vesalius in the 16th century determined many of its anatomic and pathologic characteristics, but it was Miculicz in the beginning of the 20th century who made the first attempt to drain cerebrospinal fluid from the lateral ventricle to the subgaleal, subdural, and subarachnoid spaces with the use of gold tubes and cat-gut strands.[1] The ventriculoperitoneal shunt (VPS) was introduced by Kaush in 1908.[2] Since that time VPSs have become the standard treatment for all types of hydrocephalus. This dominance deepened after the development of the first shunt valve in 1952 by Spitz and Holter.[3]

Rapid development followed, resulting in hundreds of thousands of VP shunts placed worldwide yearly. In the United States, approximately 36,000 VPS operations are performed each year, making it one of the most common neurosurgical procedures.[4] The incidence of hydrocephalus in Africa is generally estimated to be higher, even though the exact number of cases has never been determined. Unfortunately, VPSs are associated with high costs, up to $1 billion annually for the United States.[5] The high monetary expenditure is the reason there is an effort in developing countries to treat hydrocephalus endoscopically as often as possible.[6] Endoscopic treatment is preferred in not only patients with an obstructive type of hydrocephalus but also by some authors to regularly treat communicating hydrocephalus in combination with choroid plexus cauterization.[7]

The excessive costs of VPS surgery predominantly arise from relatively high complication and revision rates.[8] It is reasonable to assume that revision rates in developing countries would be even higher.[9] On the other hand, there is an indisputable relationship between surgeon experience and complication rates.[10] In this study we report the single-institution revision rates from a high-volume department in a developing country, directed by an experienced pediatric neurosurgeon.

MATERIALS AND METHODS

A pediatric neurosurgical database was thoroughly studied in the extent of 5 years between 1 January, 2009, and 31 December, 2013 to identify patients with hydrocephalus who were treated by VPSs or endoscopic third ventriculostomies. Each patient underwent cranial ultrasound and a ventricular tap before the operation. By default, the ventricular catheters were inserted in a right parie-tooccipital location and directed to the frontal horn of the lateral ventricle. In case of skin excoriation or gross asymmetry of lateral ventricles, alternative sites were used. With a few exceptions, Chhabra "Slit n Spring" valves were inserted (G. Surgiwear Ltd, Shahjahanpur, Uttar Pradesh, India). Routine follow-up was conducted every 2 months in the first 6 months and then in 1, 1½, and 2 years.

The 30-day shunt failure rate and overall revision rate were studied, and the results were compared with previously published studies from developed countries. The average costs of the VP shunt insertion were estimated and compared with average costs in Western departments.

RESULTS

In the selected time period 1840 VPS surgeries were performed on 1427 patients (both first shunt insertions and revisions), an average of 368 surgeries per year. The sex ratio was 50.3% male and 49.7% female. In the same time interval 261 patients were operated endoscopically. Endoscopic third ventriculostomies were performed in 216 patients, and 45 patients underwent choroid plexus cauterization without endoscopic third ventriculostomy.

Five-hundred and ninety-two shunt revisions (32.14%) were performed (average 118.4 per year). The vast majority of revision surgeries—501 procedures (84.63%)—were performed in the first year with a rapid decrease in subsequent years: 64 procedures in the second year, 21 in the third year, 6 in the fourth, and 2 in the fifth.

From a total number of 1427 patients who underwent surgery in the selected period, 413 needed ≥1 revisions, making the overall shunt revision rate 28.94%. One revision was needed in 287 patients (69.48%), 2 revisions in 91 (22.04%), 3 in 22 (5.33%), 4 in 8 (1.94%), and 5 patients (1.21%) underwent 5 revision surgeries. In the first month after the first shunt insertion, 208 patients needed a revision, for a 30-day revision rate of 14.58%. In total, 265 procedures were needed in the first 30 days, 1.27 revision surgeries per patient. Kaplan-Meier shunt survival curve is presented in Figure 1.
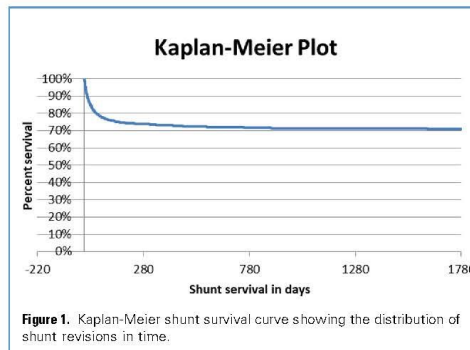

Figure 1. Kaplan-Meier shunt survival curve showing the distribution of shunt revisions in time.

Study Limitation

Building a wide follow-up in a rural sub-Saharan area is extremely difficult. Our study is based on surgical database of Pediatric Neurosurgery Department in Kijabe Hospital. We worked on the assumption that any possible revisions had to be done there. Unfortunately, on the other hand we cannot reliably determine a potential group of patients with serious malfunction resulting in death of a patient before he or she arrived at the hospital.

Costs

During the course of the study, the costs of VPS surgery, the shunt, and daily ward charges did not change significantly. The average total charge for VPS insertion was 60,000 KES (586 USD), VPS removal 30,000 KES (293 USD), and VPS revision 50,000 KES (489 USD). The operations themselves cost 40,000 KES (391 USD), 20,000 KES (195 USD), and 30,000 KES (293 USD), respectively. The valve alone costs 9200 KES (90 USD). In this specific case, all the shunts were donated by the International Foundation for Spina Bifida and Hydrocephalus.

The daily patient charge was 1050 KES (10 USD) on the pediatric neurosurgical unit 2940 KES (29 USD) and on the intensive care unit, 4480 KES (44 USD).

DISCUSSION

Hydrocephalus is the most common neurosurgical condition in children worldwide.[11] The incidence of hydrocephalus in developing countries is higher due to the greater incidence of perinatal and neonatal infections, mother and child malnutrition, and low birth weight, as documented by a recent systematic review and meta-analysis. The pooled incidence of congenital hydrocephalus in Africa is estimated to be 145 per 100,000 births,[12] but the real incidence is probably much higher due to lack of proper diagnostics in this region. Taking into account high crude birth rate, the number of new patients with hydrocephalus in sub-Saharan Africa is estimated to be about 100,000 cases.

VPS placement is the mainstay of hydrocephalus treatment in the world. The mortality of the surgery itself is low, but there are many overall complications related to shunts. Subsequent revisions increase not only risks for the patient but also hospital costs, which are a substantial burden for the patient's family and community. In a large multicenter study, a higher volume of initial shunt placement was associated with a lower revision rate, which was reported to be 37% after initial shunt placement.[13] Most revisions are needed the first month postoperatively and then in the first year subsequently.[14-16] Risk factors associated with shunt malfunction include age, etiology, and multiple previous operations comorbidities.[17] A previous publication from Kijabe Hospital identified head circumference and coincidental spina bifida as the strongest prognostic factors of revisions.[18] Potential infectious complications are much more likely to be caused by gram-negative bacilli in Kenya than they are in developed countries, where *Staphylococcus epidermidis* is by far the most common. Gram-negative bacilli are associated with worse outcome.[19]

The unique role of the pediatric neurosurgical department in Kijabe Hospital, in sub-Saharan Africa, made it one of the busiest pediatric neurosurgical departments in the world during the time interval of this study. It is also the only pediatric neurosurgical department in the region of Kenya. If any revision is needed, it is performed there.

During the studied period, 1840 VPS operations were performed, an average of 368 per year. Almost one third, 32.14%, of these surgeries were revisions. The vast majority of the revision operations (84.63%) were performed in the first year after the initial operation. The 30-day revision rate was 14.58%. These data are comparable with those observed in some Western hospitals. For example, the 30-day shunt failure rate in 1 study from the United Kingdom was 12.9%.[20] Also decreasing necessity of

revision in subsequent years is a frequently presented fact.[21] The incidence of infectious complications is highest in the first several months after the shunt placement.

The 5-year revision rate achieved in Kijabe is better than published data. In our cohort it was 28.94%, whereas in a large multiinstitutional study from the United States it was 37%.[13] This result can partially be explained by the fact that for some families, it is too expensive to repeatedly treat (even to get to the hospital) an ill child.

Hydrocephalus and VP shunt treatment are a big economic burden for the family of the patient and the entire community. In the United States hydrocephalus accounts for only 0.6% of all pediatric hospital admissions but 3.1% of all pediatric hospital charges.[4] Average costs in the United States of initial shunt placement have been reported as $49.317; with an average length of stay of 18.2 ± 28.5 days, this greatly depends on the age of a patient, type of hydrocephalus, complications, and socioeconomic factors.[22] The neurosurgical department in Kijabe Hospital is subsidized by the BethanyKids Christian philanthropic organization, but the majority of the patients participate in paying the costs. Although the average charge for initial VP shunt placement was $586, 84 times less than in the United States, even this price is out of reach for some families.

CONCLUSION

This retrospective study proves that VPSs with their known complication risks can be performed in a sub-Saharan missionary hospital with acceptable costs and results that are comparable with those achieved in some Western hospitals. Keys to those outcomes include high volume and a highly experienced team.

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Boosting Phase Contrast MRI Performance in NPH Diagnostics by Means of Machine Learning Approach
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Abstract:	Background: Phase contrast MRI allows detailed measurement of various parametersof CSF motion. This examination is technically demanding and machine dependent. Machine learning (ML) approaches have already been successfully utilized in medical research, but none was applied to enhance the results of CSF flowmetry yet. Objective: The aim of this study was to evaluate the possible contribution of MLalgorithms in enhancing results of MRI flowmetry in NPH diagnostics. Methods: The study cohort consists of 30 iNPH patients and 15 healthy controls examined on one MRI machine. All major phase contrast parameters were inspected: peak positive and negative velocity, peak amplitude, average velocity, positive, negative and average flow and aqueductal area. We applied ML algorithms on 85 complex features calculated from phase contrast study. Results: The most distinctive parameters with $p<0.005$ were peak negative velocity, peak amplitude and negative flow. From the machine learning algorithms, the Adaptive Boosting classifier showed the highest specificity and best discrimination potential overall, with $80.4 \pm 2.9\%$ accuracy, $72.0 \pm 5.6\%$ sensitivity, $84.7 \pm 3.8\%$ specificity, and 0.812 ± 0.047 AUC. The highest sensitivity was $85.7 \pm 5.6\%$, reached by the Gaussian Naive Bayes model, and the best AUC was 0.854 ± 0.028 by Extra Trees classifier. Conclusions: Machine learning approaches simplify the utilization of phase contrast MRI and significantly increase its predictive value. The highest performing algorithm in our study was Adaptive Boosting, which showed a good calibration and discriminationon the testing data, with 80.4% accuracy, 72.0% sensitivity, 84.7% specificity, and 0.812 AUC.
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Boosting Phase Contrast MRI Performance in NPH Diagnostics by Means of Machine Learning Approach

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Disclosures

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article. The authors declare that they have no conflict of interest.

1 Boosting Phase Contrast MRI Performance in iNPH Diagnostics by Means of Machine Learning
2 Approach

3

4 Abstract

5 Background: Phase contrast MRI allows detailed measurement of various parameters of CSF
6 motion. This examination is technically demanding and machine dependent. Machine learning
7 (ML) approaches have already been successfully utilized in medical research, but none was
8 applied to enhance the results of CSF flowmetry yet.

9 Objective: The aim of this study was to evaluate the possible contribution of ML algorithms in
10 enhancing results of MRI flowmetry in NPH diagnostics.

11 Methods: The study cohort consists of 30 iNPH patients and 15 healthy controls examined on one
12 MRI machine. All major phase contrast parameters were inspected: peak positive and negative
13 velocity, peak amplitude, average velocity, positive, negative and average flow and aqueductal
14 area. We applied ML algorithms on 85 complex features calculated from phase contrast study.

15 Results: The most distinctive parameters with $p<0.005$ were peak negative velocity, peak
16 amplitude and negative flow. From the machine learning algorithms, the Adaptive Boosting
17 classifier showed the highest specificity and best discrimination potential overall, with 80.4 ±
18 2.9% accuracy, 72.0 ± 5.6% sensitivity, 84.7 ± 3.8% specificity, and 0.812 ± 0.047 AUC. The
19 highest sensitivity was 85.7 ± 5.6%, reached by the Gaussian Naive Bayes model, and the best
20 AUC was 0.854 ± 0.028 by Extra Trees classifier.

21 Conclusions: Machine learning approaches simplify the utilization of phase contrast MRI and
22 significantly increase its predictive value. The highest performing algorithm in our study was
23 Adaptive Boosting, which showed a good calibration and discrimination on the testing data, with
24 80.4% accuracy, 72.0% sensitivity, 84.7% specificity, and 0.812 AUC.

25

26 Keywords

27 Normal pressure hydrocephalus; iNPH; Machine Learning; MRI; Phase contrast MRI

28

29 Short Title

30 Phase Contrast MRI Performance in NPH Diagnostics

31

32   INTRODUCTION

33

34   Despite being first described more than 55 years ago [1], normal pressure hydrocephalus (NPH) is

35   still without a sufficiently sensitive and specific diagnostic test. The need for such a test is

36   accentuated by the fact that iNPH is the only curable neurological degenerative disease, with

37   reported improvement of 60-80% after shunt insertion [2]. In current practice the diagnosis consists

38   of clinical examination (typically characterized by the triad of gait disturbance, mental

39   deterioration and urinary incontinence) and functional testing. Functional tests include the spinal

40   tap test, external lumbar drainage, or lumbar infusion test. Although these tests can accurately

41   predict response to treatment [3], they are painful and associated with rare, but potentially serious

42   complications [4]. For these reasons, numerous studies in the past few decades have focused on

43   finding a simple imaging biomarker. Enlarged ventricles are mandatory for iNPH diagnosis, but

44   ventriculomegaly has numerous causes, so the specificity of this sign is naturally very low.

45   Unfortunately, more detailed tests have not resulted in the unambiguous confirmation or

46   exclusion of an iNPH diagnosis. Basic MRI sequences are the source of several significant signs,

47   such as high Evan´s index, dilated Sylvian fissures, tight high convexity, acute callosal angle and

48   focal sulcal dilatation. All these measurements are components of the DESH score, introduced by

49   the Japanese group [5]. Our recent study showed that the DESH score lacks sufficient sensitivity

50   and specificity to be used as a stand-alone diagnostic or prognostic marker for iNPH [6]. Our lab

51   has also tested the hypothesis that structural volume analysis can reveal specific patterns unique

52   to iNPH patients[6]. Despite identifying several interesting differences in structural volumes in

53   iNPH patients, this method did not reveal any signs that differentiate shunt responsive patients.

54   Diffusion tensor imaging repeatedly showed changes in white matter [7,8], but again the sensitivity

55   and specificity was not sufficient for this to be used as a standalone test.

56   The CSF flow void phenomenon observed in the cerebral aqueduct of iNPH patients has led to

57   interest in this region. Phase contrast MRI allows detailed measurement of various parameters of

58   CSF motion [9]. These include aqueductal stroke volume and peak velocity measurements, with

59   several studies showing promising results [10-12]. However, some authors have pointed out that

the

60 examination is technically demanding and machine dependent [13].

61 The aim of this study was to evaluate the possible contribution of machine learning algorithms in
62 enhancing results of MRI flowmetry in NPH diagnostics. In contrast to the previous published
63 studies, we have looked at the method from a wider perspective of all the available features.

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68 METHODS

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70 Patients

71 In the period between September 2016 and March 2020 109 patients were referred to the

72

73   with suspected NPH. Before being referred to our department, all patients had
74 undergone a standard MRI and showed ventriculomegaly (Evans´ index greater than 0.3). All
75 patients suffered gait disturbance and at least one of the other two typical symptoms - mental
76 deterioration or urinary incontinence. The gait was recorded on camera and the disturbance was
77 evaluated using the Dutch Gait Scale [14,15]. All patients underwent thorough neuropsychological
78 examination including Wechsler memory scale III, Montreal Cognitive Assessment, Verbal
79 Fluency tests, Trail Making Test, Rey-Osterrieth Complex Figure Drawing Test and Geriatric
80 Depression Scale [16]. After completing all of the above tests, 86 remaining patients underwent
81 lumbar infusion (modified Katzmann´s) test [17]. All of the patients had normal cerebral spinal
82 fluid (CSF) opening pressure (<20cm H2O), normal CSF composition; biochemistry and cell
83 count. At the end of the test, lumbar drainage was performed using the same needle and CSF was

84 drained for 120 hours. Shunt insertion was indicated to all patients with a positive lumbar

85 infusion test (resistance to outflow above 9mmHg/ml/min) and at least 15% improvement in

86 Dutch Gait Scale after lumbar drainage. After completing all the tests, we identified 40 iNPH

87 patients. All of them were indicated for VP shunt surgery.

88 From this cohort, 30 patients completed the study protocol on the same MRI machine. The same

89 protocol was performed on 15 healthy controls. An algorithm of data acquisition and processing

90 is shown in Figure 1.

91

92 MRI acquisition

93 MRI images were acquired on 3T GE MR 750w, located in The Military University Hospital

94 Prague. A standard 32-channel head coil was used. MRI imaging protocol included a 3D T1

95 BRAVO, 3D T2 Cube, GRE-EPI task-based fMRI, and SE-EPI DTI sequences. In addition a

96 phase contrast CSF flow study was performed with the following parameters: a single oblique

97 axial section perpendicular to the aqueduct with slice thickness 7mm, FOV 16cm, matrix size

98 256x224, TR/TE 33/7.4ms, flip angle 30°. Cardiac gating was applied using an MR-compatible

99 peripheral pulse transducer attached to the subject's finger, producing 32 frames evenly spread

100 throughout the cardiac cycle. Location of the acquisition section was determined by a senior

101 neuroradiologist to the middle of the aqueduct. Default velocity encoding gradient was 20cm/s.

102 102

103   Image interpretation

104   Phase contrast images were reconstructed and reviewed using commercial software

105   (FlowAnalysis, GE). ROI was drawn manually by a senior neuroradiologist and included all

106   voxels with CSF flow signal. Software then extracted velocity and flow-time curves for each

107   subject. Results were transferred to an offline workstation for statistical analysis.

108108

109   Statistical Analysis

110   Comparisons of continuous variables were made using t-tests for independent samples.

111   Comparisons of categorical variables were done using the chi-square test. In all cases, a p-value

112   of less than 0.05 was considered significant. Basic computations were performed using

113   STATISTICA 13.5 software.

114114

115   Feature calculations

116   For each patient seven CSF flowmetry vectors have been obtained directly from MRI: aqueduct

117   area, peak positive velocity, peak negative velocity, average velocity, positive flow rate, negative

118   flow rate, and average flow rate. Each vector is composed of 32 points evenly distributed along

119   one cardiac cycle. To calculate CSF flow features 32 points of each vector were interpolated by a

120   cubic spline. Spline interpolation is often preferred over polynomial interpolation because the

121   interpolation error is minimal even when using low-degree polynomials for the spline. The

122   features of a given vector were calculated using the piecewise smooth interpolating function, and

123   these features characterise the spline behavior. For example: amplitude, maximum/minimum

124   position, area under the curve, first time derivative maximum/minimum, kurtosis, skewness, etc.

125   Altogether 85 features were identified.

126126

127 Machine learning approach

128 A set of selected 87 complex features were calculated for each patient (85+age+sex). The whole

129 patient dataset was divided into training and testing parts by the k-fold (k=5) cross-validation

130 (CV). We improve k-fold CV by using stratified resampling, which ensures that the relative class

131 frequencies (NPH and control) are approximately preserved in each fold according to the original

132 class frequencies in the full dataset. Stratified k-fold CV is useful for small and/or imbalanced

133 datasets (30 NPH and 15 control patients in our case)[18]. Another improvement was the repetition

134 of the k-fold stratified CV process N times (N=10), enabling an estimate of the mean and

135 standard deviation in a performance.

136 The following 8 different state-of-the-art ML models were deployed by using the aforementioned

137 robust CV design: Multilayer perceptron (MLP), Gaussian Naive Bayes (GaussNB), Gradient

138 Boosting Decision Tree (GBDT), Logistic Regression (LogReg), Extra Trees (ExtraTrees),

139 Random Forest (RF), XGBoost (XGB) and Adaptive Boosting (AdaBoost). The listed algorithms

140 are implemented and described in the Scikit-Learn Python library [19] and were run in Python 3.8.

141 Due to better repeatability of the proposed solution, default settings of all algorithms were

142 used. Accuracy, sensitivity, specificity, receiver operating characteristic (ROC) and area under

143 the ROC curve (AUC) were used to compare performance of all ML methods.

144144

145 RESULTS

146146

147 The study cohort consists of 30 iNPH patients consecutively examined on one MRI machine. The

148 average age in the group was 72.8±5.2 years and there were 11 women and 19 men. In the control

149 group there were 9 men and 6 women with an average age of 71.4±6.4 years. The groups were

150 similar in the scope of basic demographic information.

151 Within the scope of phase contrast MRI all major parameters were inspected: peak positive and

152 negative velocity, peak amplitude, average velocity, positive, negative and average flow and

153   aqueductal area. Using the t-test for a direct comparison we found significant differences, with p-

154   values of less than 0.05 in 47 of 85 tested features. Results of the major parameters are listed in

155   Table 1.

156   The most distinctive parameters with p-value less than 0.005 were peak negative velocity, peak

157   amplitude and negative flow. Mean peak negative velocity was -3.0787±1.9189 cm/s in NPH

158   patients and -1.3570±0.5868 cm/s in healthy controls with p-value 0.002. Mean peak amplitude

159   was 6.4252±3.8139 in NPH patients and 3.1535±1.1811 in healthy controls with p-value 0.003.

160   Mean negative flow was -0.1996±0.1561 ml/min in NPH patients and -0.0597±0.0358 ml/min in

161   healthy controls with p-value 0.002. A fourth important feature with a p-value of 0.007 was mean

162   peak positive velocity- 3.3465±2.0426 cm/s in NPH patients and 1.7965±0.7232 in healthy

163   controls. The results of these 4 features are presented in Figure 2.

164   We continued with further computations using 8 different state-of-the-art machine learning

165   models. The results in terms of accuracy classification of respective ML models are presented in

166   Table 2.

167   Table 3 compares accuracies, sensitivities, specificities and AUCs for all ML algorithms

168   developed. From these algorithms, the AdaBoost classifier showed the highest specificity and

169   best discrimination potential overall, with 80.4 ± 2.9% accuracy, 72.0 ± 5.6% sensitivity, 84.7 ±

170   3.8% specificity, and 0.812 ± 0.047 AUC. The highest sensitivity was 85.7 ± 5.6%, reached by

171   GaussNB model, and the best AUC was 0.854 ± 0.028 by ExtraTrees classifier. The final ROCs

172   and calibration curves for all ML models are presented in Figure 3.

173   The importance of a feature by AdaBoost was computed as the normalized total reduction of the

174   criterion brought by that feature (the higher, the more important the feature.). It is also known as

175   the Gini importance [19]. Feature importance differs a lot from the significance counted with the

176   chi-square test. No "major" feature had any importance for the AdaBoost classifier and the most

177   significant parameters regardless of importance played only a minor role in its

178   computations
        Table 3).

179179

180   DISCUSSION

181181

182   According to the most accepted theory, the development of the major symptoms of iNPH is
183   caused by ventricular dilatation leading to mechanical stress on the periventricular white matter.
184   This causes ischemia and hypoxia of axons [20]. The severed ependymal layer progressively loses
185   plasticity, and pulsatility is significantly reduced as a consequence [21]. This process leads to an
186   impairment of bulk flow through the outlets of the CSF compartments [22]. Compressed adjacent
187   white matter loses integrity and becomes stiff, leading to reduced transmission of pulsatile waves
188   [23]. This process causes dilatation of ventricles, which further slows down the CSF flow [24]. The
189   exact pathophysiological mechanism of iNPH remains unclear, but the above theory still remains
190   one of the most widely accepted [25]. Since MRI has become more broadly available, many
191   scientists have had great hopes in phase contrast MRI, which seemed to promise the long
192   anticipated biomarker for selecting shunt responsive iNPH patients [26]. Unfortunately, it has
193   become clear that phase contrast MRI is not easy to interpret as its results vary according to the
194   MRI machine used [13]. Some works even question the most studied parameter of phase contrast
195   MRI: aqueductal stroke volume [27,28]. Conversely, several studies advocate using aqueductal
196   stroke volume in NPH diagnostics as noninvasive complimentary test [10,29] and some find it more
197   accurate than other basic phase contrast MRI parameters [11]. Another widely studied parameter of
198   phase contrast MRI is peak velocity. However the results are again controversial, ranging from
199   favorable [10,11] to no significant difference between the iNPH group and healthy controls [30].

200   The flow curve is defined by seven vectors: aqueduct area, peak positive velocity, peak

negative

201 velocity, average velocity, positive flow rate, negative flow rate, and average flow rate. Direct

202 comparison using t-test identified the three most distinct parameters with a p-value less than

203 0.005 - peak negative velocity, peak amplitude and negative flow. These findings may be related

204 to the increased ICP pulsatility in iNPH patients observed from invasive ICP monitoring [31,32],

205 while the altered negative flow and higher peak amplitude observed on phase contrast MRI in

206 normal conditions could represent increased ICP pulsatility observed in overnight ICP monitoring

207 [33]. The results of ICP monitoring on shunt response prediction in the literature vary [33-35], but the

208 role of altered wave characteristics observed in our study with regards to prediction of shunt

209 response has yet to be clarified.

210 Machine learning approaches have already been successfully utilized in medical research [36].

211 Regarding iNPH, a few models have used this technique, for example in gait [37] or MRI [38]

212 analysis. To our knowledge, no machine learning approach has been applied to enhance the

213 results of CSF flowmetry. We have considered this method beneficial, because some of

214 flowmetry features are difficult to interpret as they lack a clear clinical correlation, and their

215 physiological explanation is rather speculative and under further investigation. Second, the

216 importance of individual features do not necessarily correlate with the p-values. Features that

217 would have been ignored in standard statistical testing as insignificant in iNPH patients

218 discrimination may turn out to be influental in the scope of machine learning and vice versa.

219 Using this method we achieved a sensitivity of up to 85% and specificity of 84%. The best

220 accuracy was 80%. The highest-performing ML algorithm was the Adaptive Boosting. This

221 model showed a good calibration and discrimination on the testing data, with 80.4% accuracy,

222 72.0% sensitivity, 84.7% specificity, and 0.812 AUC.

223 The developed ML models were optimized for highly accurate prediction rather than explanation,

224 and model parameters thus cannot be simply deployed for the purpose of explaining the effect

of

225 individual features on the differentiation of iNPH and healthy patients. Some of the frequently

226 used ML models (especially ensemble-based algorithms) allow the use of the so-called

227 optimization of hyperparameters. This could further improve the performance of the ML models.

228 This approach could be used in the future if the dataset were enlarged. Further external

229 validations on data from multiple neurosurgical centers would be appropriate before using these

230 approaches in clinical practice.

231231

232 Study Limitations

233233

234 We are aware of several limitations of the present study. Firstly, due to a change of MRI

235 machines during the selected study period, 10 out of 40 iNPH patients had to be removed from

236 the study. It has been well documented that phase contrast MRI can vary considerably according

237 to the equipment [13]. The method is also operator dependent. The Region of interest is manually

238 drawn, which emphasizes the importance of an experienced neuroradiologst. Secondly, several

239 patients may be misfiled to or erroneously excluded from the NPH group due to the specificity

240 and sensitivity limitations of the lumbar infusion test and external lumbar drainage test. As these

241 functional tests are current best practice, this problem limits all studies concerning iNPH. Third,

242 despite using an effective 10-times repeated stratified 5-fold CV to validate the ML approaches,

243 the credibility of this methodology could be increased by using a larger dataset with various types

244 of CVs.

245 CONCLUSION

246246

247 Machine learning approaches simplify the utilization of phase contrast MRI and

significantly

248 increase its predictive value. The highest performing algorithm in our study was Adaptive

249 Boosting, which showed a good calibration and discrimination on the testing data, with 80.4%

250 accuracy, 72.0% sensitivity, 84.7% specificity, and 0.812 AUC.

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360   LEGENDS

361 361

362   Figure 1. Diagram summarizing methodology of presenting study.

363 363

364   Figure 2. Boxplots with mean values for the four most significant parameters differentiating the

365   NPH group from the healthy controls: Peak Positive Velocity (A), Peak Negative Velocity (B),

366   Peak Amplitude (C) and Negative Flow (D).

367 367

368   Figure 3. ROC (A) and calibration curves (B) for all individual ML models. The dashed diagonal

369   line represents the performance of an ideal model, where the predicted outcome would
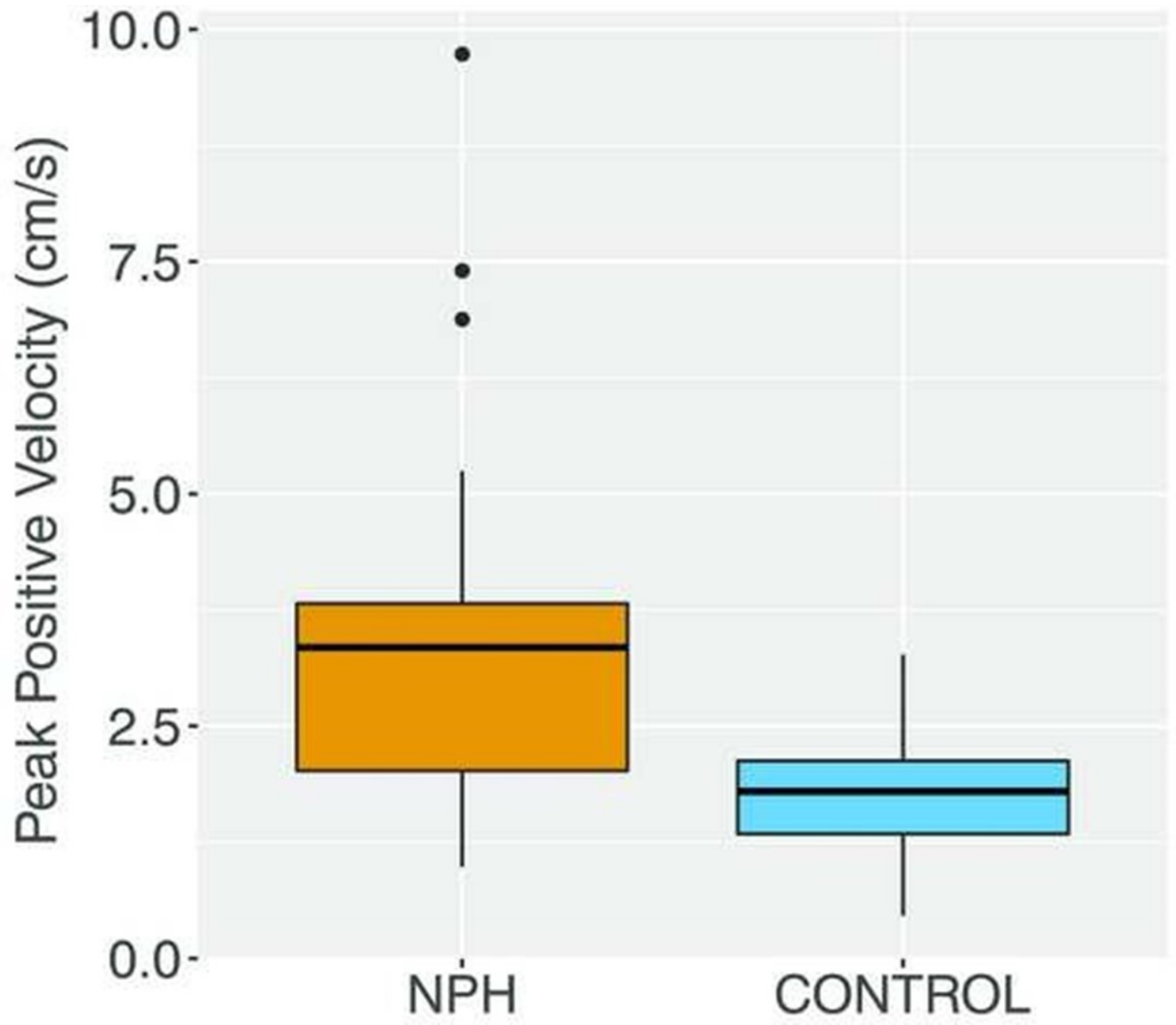
370   correspond perfectly with the actual outcome.
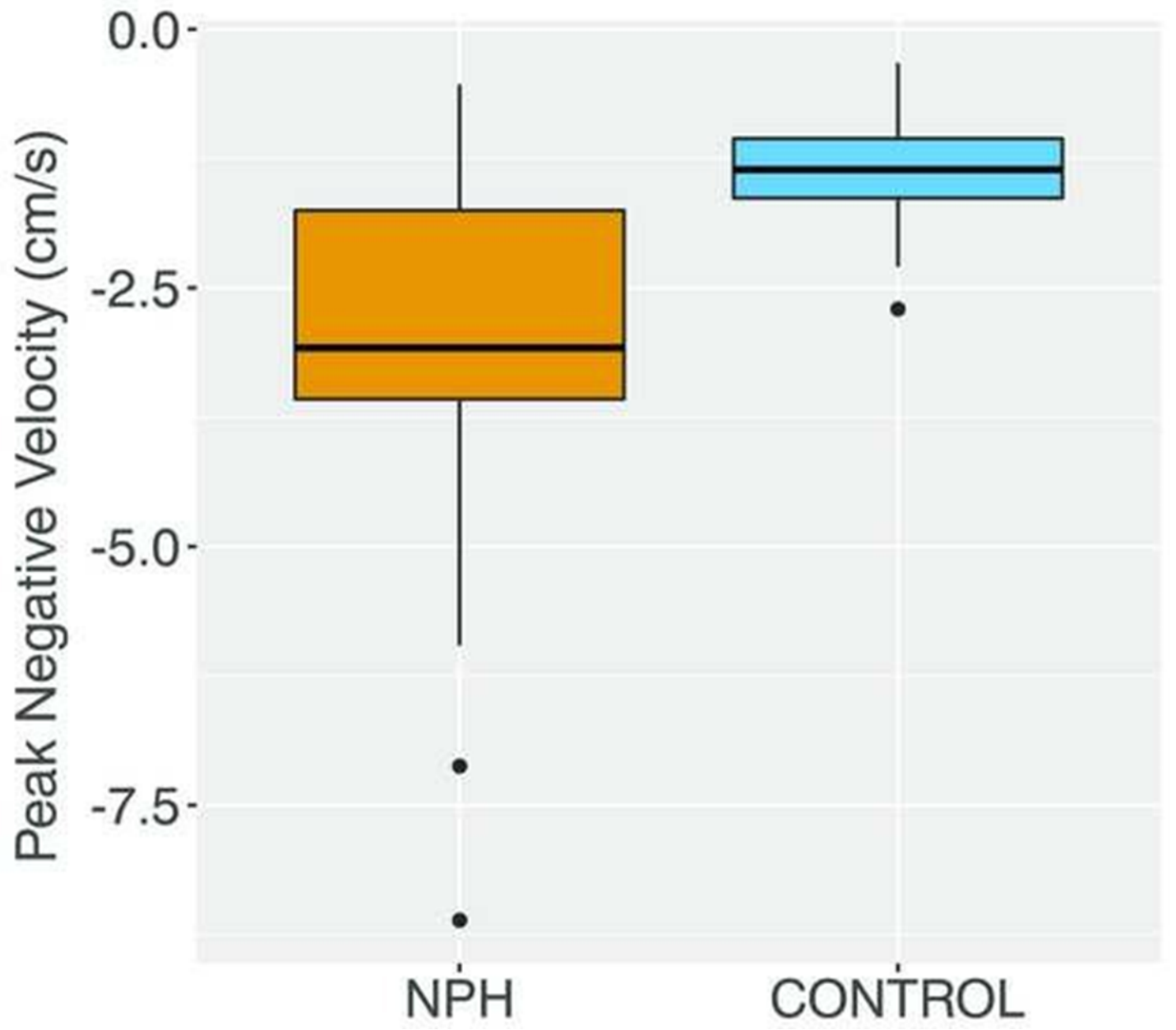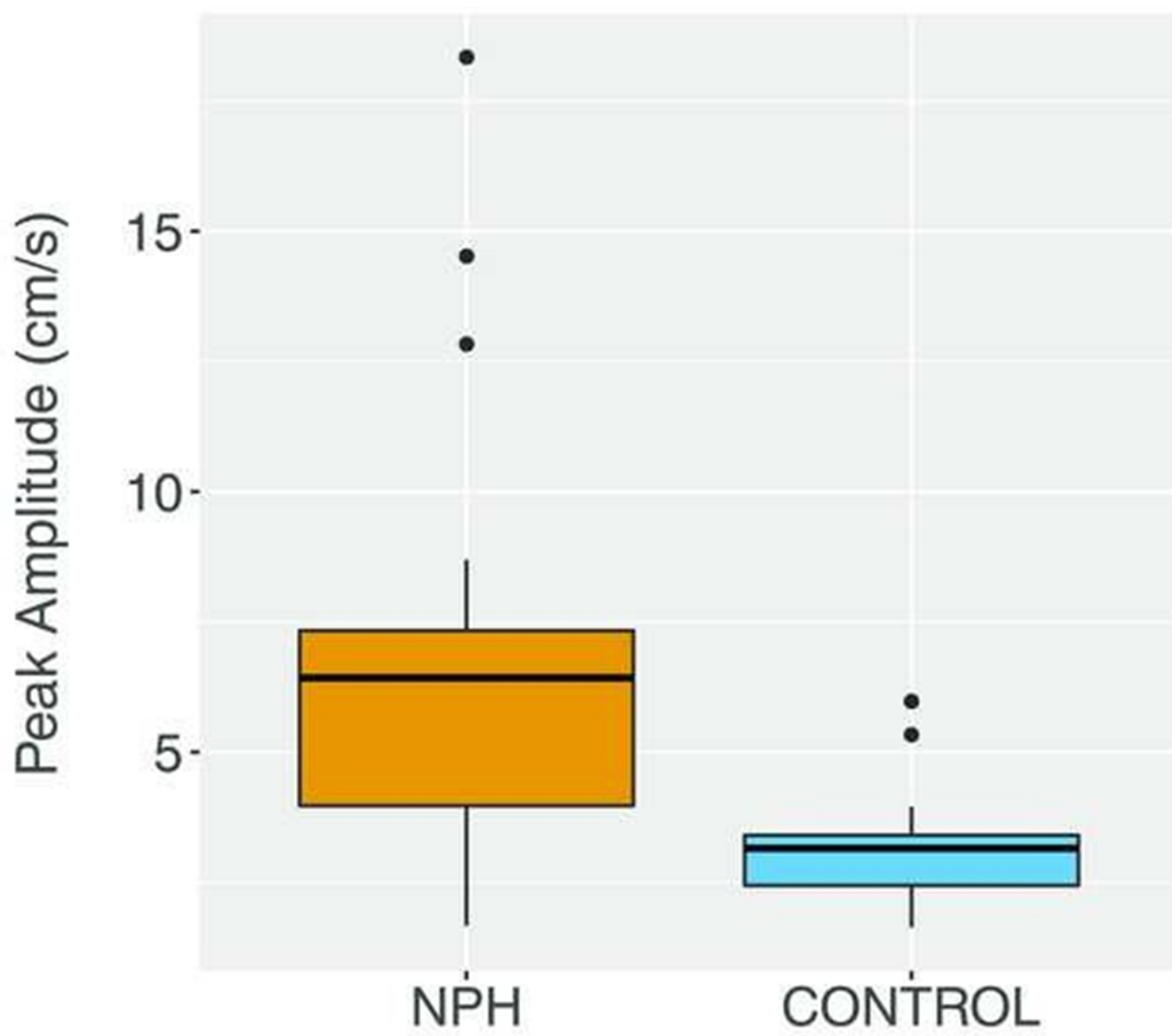
Fig 1
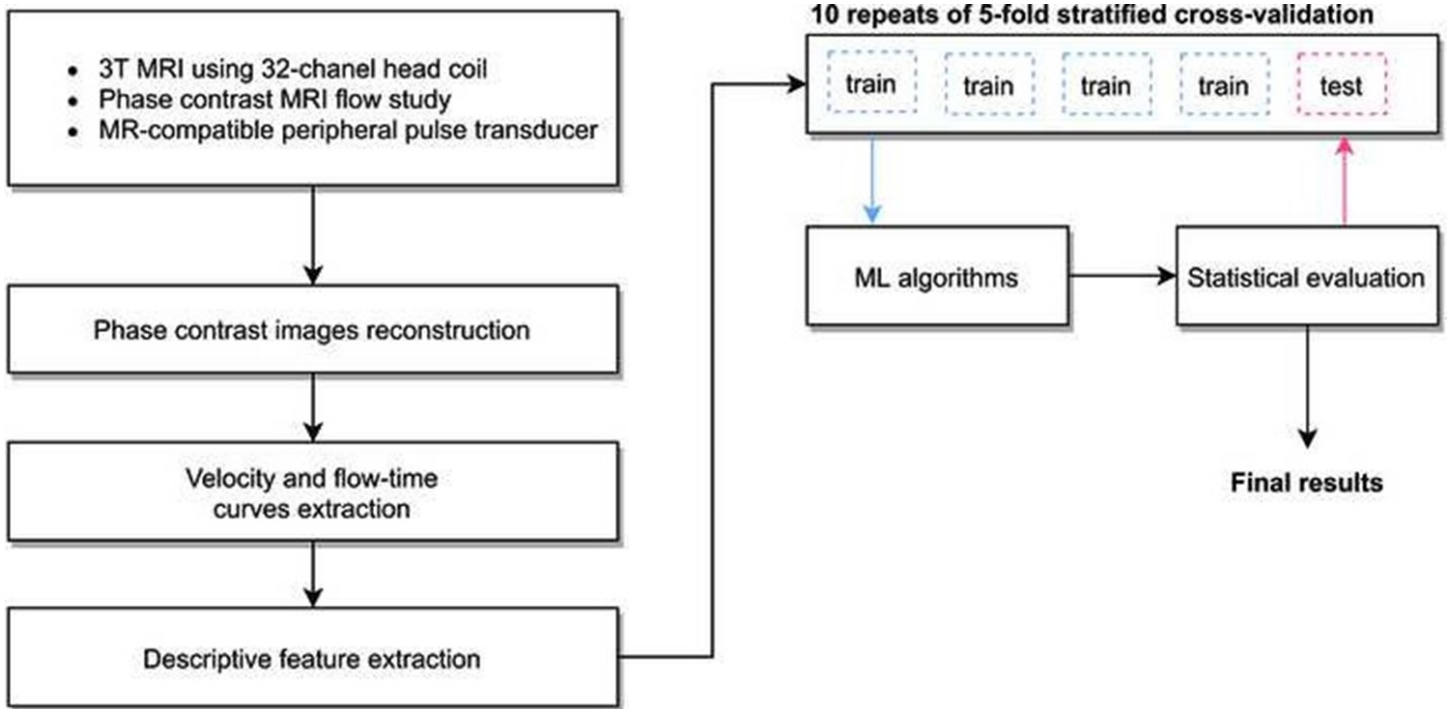
Fig 2A

Fig 2B

Fig 2C

Fig 2D

Fig 3A

ROC

Fig 3B

Calibration curve
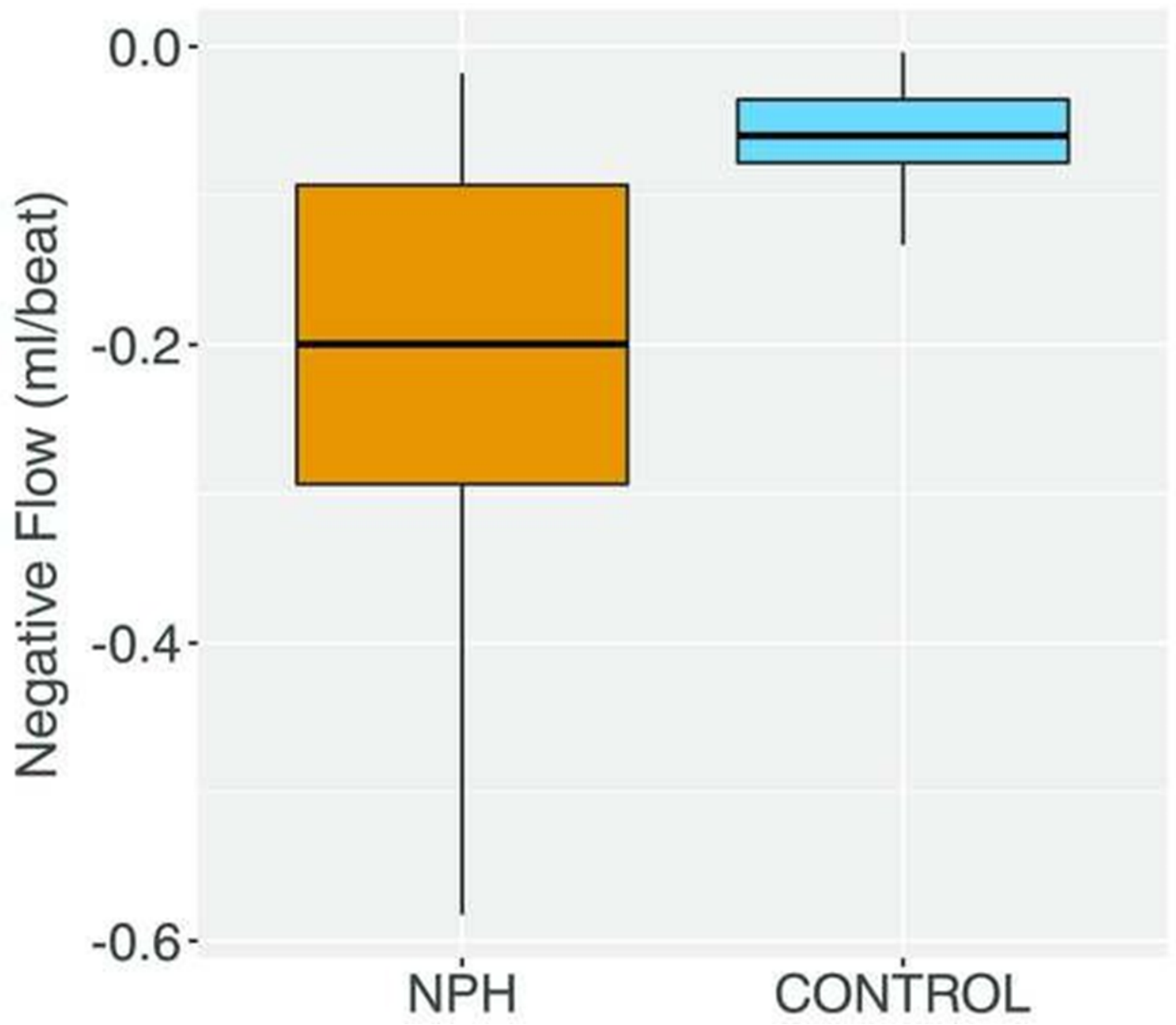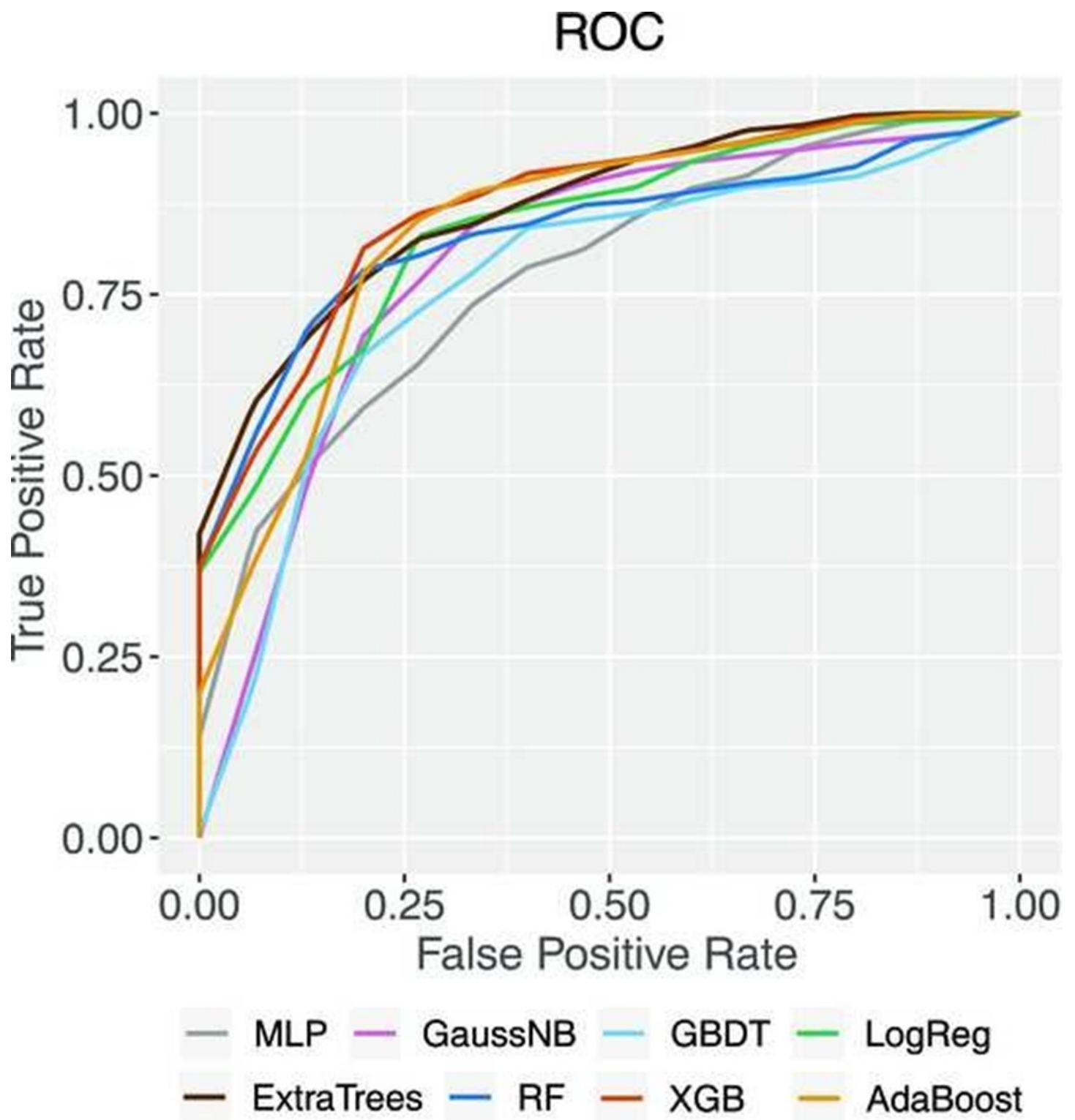
Table 1

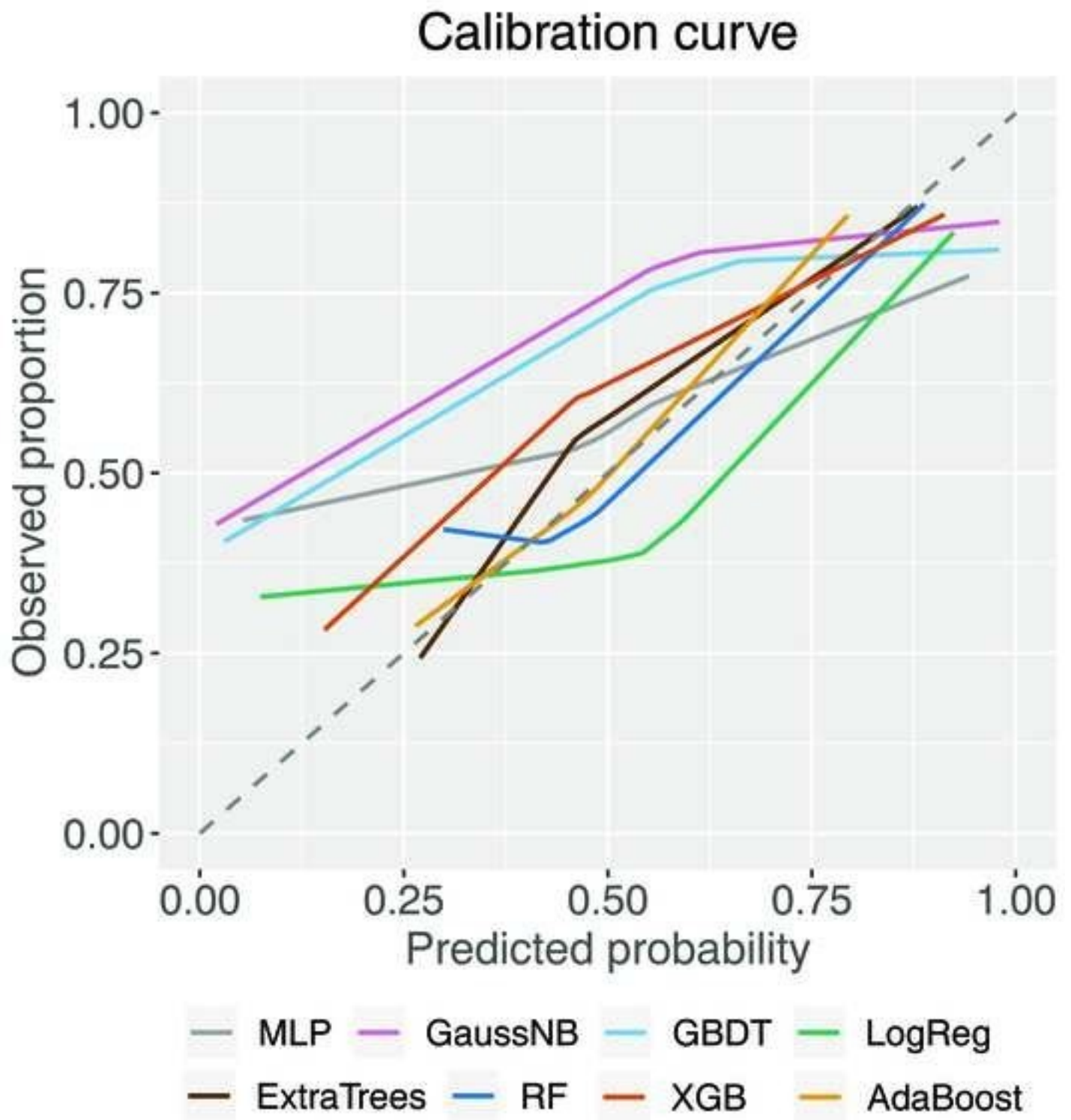|	Group		p-value
	NPH	CONTROL	NPH vs. CONTROL
Aqueductal area → mean	17.2693 ± 9.0799	20.4736 ± 10.0155	0.297
Peak positive velocity → mean (cm/s)	3.3465 ± 2.0426	1.7965 ± 0.7232	0.007
Peak negative velocity → mean (cm/s)	-3.0787 ± 1.9189	-1.3570 ± 0.5868	0.002
Peak amplitude → mean	6.4252 ± 3.8139	3.1535 ± 1.1811	0.003
Average velocity → mean (cm/s)	5.0215 ± 4.2601	5.0106 ± 4.8031	0.994
Average velocity → skewness	2.7707 ± 1.0497	1.8253 ± 1.1654	0.010
Average velocity → kurtosis	11.2075 ± 6.0085	7.1157 ± 5.1639	0.032
Positive flow → mean (ml/min)	0.2561 ± 0.2242	0.1140 ± 0.0707	0.022
Negative flow → mean (ml/min)	-0.1996 ± 0.1561	-0.0597 ± 0.0358	0.002
Average flow → mean (ml/min)	0.0564 ± 0.0944	0.0537 ± 0.0605	0.919
Highest peak positive velocity (cm/s)	8.5090 ± 6.1965	4.4040 ± 2.7988	0.019
Flow (ml/beat)	0.0419 ± 0.0806	0.0403 ± 0.0578	0.947

Table 1. Results of major phase contrast MRI parameters and their significance according to t-test.

Table 2

ML approach	Accuracy	Sensitivity	Specificity	AUC
Multilayer perceptron	72.0 ± 3.4	54.7 ± 5.6	80.7 ± 5.5	0.750 ± 0.048
Gaussian Naive Bayes	73.8 ± 2.4	85.7 ± 5.6	73.3 ± 2.4	0.770 ± 0.009
Gradient Boosting Decision Tree	73.8 ± 4.3	64.0 ±3.7	78.7 ± 6.5	0.747 ± 0.064
Logistic Regression	76.9 ± 4.0	65.3 ± 5.6	82.7 ± 4.9	0.808 ± 0.029
Extra Trees	77.3 ± 1.9	73.3 ± 4.7	79.3 ± 4.9	0.854 ± 0.028
Random Forest	78.2 ± 4.0	74.7 ± 5.6	80.0 ± 4.1	0.813 ± 0.027
XGBoost	79.6 ± 1.9	72.0 ± 5.6	83.3 ± 2.4	0.840 ± 0.037
Adaptive Boosting	80.4 ± 2.9	72.0 ± 5.6	84.7 ± 3.8	0.812 ± 0.047

Table 2. Mean value and standard deviation of the accuracy, sensitivity, specificity and AUC computed over 10 CV repetitions. Individual models are sorted according to the resulting accuracy (from lowest to highest). The best value for each of the parameters is highlighted.

Table 3

	Feature description	p-value	Feature importance by AdaBoost
Best 4 features according to phase contrast MRI	NegFlow → mean	0.002	0
	PeakNegVel → mean	0.002	0
	PeakAmp → mean	0.003	0
	PeakPosVel → mean	0.007	0
Best 4 features according to t-test	PeakNegVel → minimum	0.0001	0
	PeakNegVel → amplitude	0.0002	0.002
	NegFlow → derivation → maximum	0.0002	0.014
	PeakNegVel → standard deviation	0.0002	0.006
Best 4 features according to ML (AdaBoost)	AvgVel → derivation → position of maximum value	0.012	0.016
	NegFlow → derivation → maximum value	0.0002	0.014
	NegFlow → derivation → position of minimum value	0.027	0.013
	NegFlow → maximum value	0.271	0.008

Table 3. Feature importance for the Adaboost classifier. Four most significant parameters according to phase contrast MRI, four most significant parameters from the whole dataset and four most important features for machine learning.