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CSF FLOWMETRY USING PHASE-CONTRAST MRI FOR DIAGNOSIS OF NORMAL PRESSURE HYDROCEPHALUS AND PREDICTION OF SHUNT RESPONSE.

Radiodiagnosis

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ABSTRACT

Background: Differentiating NPH from cerebral atrophy due to other neurodegenerative diseases and normal aging remains a challenge. NPH-related dementia is the only surgically manageable dementia. Response to ventricular shunting in NPH is variable. This study aims to find the CSF flow indices in NPH patients and their prognostic use in selection of shunt candidates. **Methods:** The study group consisted of 36 patients with NPH diagnoses and 10 asymptomatic age-matched controls. Quantitative assessment (peak systolic velocity and stroke volume) of CSF flow through the cerebral aqueduct using Phase-contrast MRI was done. **Results:** Mean value ± SD of peak systolic velocity in controls was 5.5 ± 1.2 cm/s, while in cases was 9.9 ± 3.5 cm/s. It was 10.9 ± 2.9 cm/s in shunt responders and 6.9 ± 2.0 cm/s in non-responders. Mean value ± SD of stroke volume in controls was 29.5 ± 3.2 µl, while in cases was 94.7 ± 60.5 µl. It was 115.2 ± 60.9 µl in shunt responders and 46.7 ± 17.1 µl in non-responders. **Conclusion:** Peak systolic velocity and stroke volume of CSF flow through the cerebral aqueduct are greater in NPH patients as compared to age-matched controls, and also greater in shunt-responsive NPH patients as compared to the non-responders. MRI CSF flowmetry using phase-contrast method can act as a prognostic marker for shunt responsiveness.

KEYWORDS

Normal pressure hydrocephalus, CSF flowmetry, Phase contrast MRI, shunt response

INTRODUCTION

Hakim and Adams, in 1965, were the first to describe Normal Pressure Hydrocephalus (NPH) as a disease defined by: the clinical triad of gait disturbance, urinary incontinence, and memory impairment; the presence of normal CSF pressure on lumbar puncture; the radiologic finding of ventriculomegaly; and improvement after ventricular shunting.[1] The full triad of symptoms initially described by these pioneering researchers are only found in about 60% of patients; however, gait apraxia and enlarged cerebral ventricles are present in 99% of NPH patients.[2] Symptoms typically develop insidiously and typically occur between 50 to 80 years of age.[3-6] NPH can be classified into secondary NPH (sNPH) if it occurs subsequently to other disease processes, including subarachnoid haemorrhage, traumatic brain injury, cerebral infarction, and meningitis,[7,8] and primary/idiopathic NPH (iNPH)with unknown precipitants. Existing research emphasises NPH as a potentially reversible cause of dementia and impaired gait. Though ventricular shunting is considered the standard of care for patients with secondary NPH [7], actual experience with idiopathic NPH has been less successful as multiple researchers describe responses to shunting as variable, short-lived, unpredictable, and with significant risks and complications.[7,9] Several neurodegenerative conditions, such as Alzheimer's or Parkinson's disease, have similar clinical features to NPH which contribute to diagnostic inaccuracies and unpredictable shunt response.

MATERIALS AND METHODS

The study was conducted at a tertiary care institute in North India over a period of two years.

A total of 36 patients and 10 controls were included in the study.

Detailed informed consent was taken from the patients and controls before inclusion in the study.

Study Design: Prospective study

Selection of subjects:
Inclusion Criteria:
1. All patients clinically suspected of NPH i.e., presence of one or more symptoms of the triad
2. Age ≥ 60 years

Exclusion Criteria:
1. Age < 60 years
2. Obstructive hydrocephalus
3. Dementias other than NPH that could cause similar clinical symptoms or radiological findings
4. History or evidence of conditions that might cause secondary NPH
5. Patients with general contraindications to MRI

All Magnetic Resonance Imaging (MRI) studies were performed using a 1.5 Tesla MR system (Magnetom Avanto, Siemens Medical Systems, Erlangen, Germany), with a standard head coil, in neutral supine position.

The following protocol was used:

Table 1: MRI Protocol

Sequence	FOV (mm/%)	Slice thickness (mm)	TR/TE (ms)	NEX	Flip angle (degrees)
flash_through-plane	160/100	4.5	31.75/8.19	1	10
flash_in-plane	240/100	4.5	39.2/11.9	1	10

FOV = field of view, TR = time to repeat, TE = time to echo, NEX = number of excitations, mm = millimetre , ms = millisecond

Phase-contrast MRI was used to calculate CSF flow for comparison with age-matched controls and assess shunt responsiveness in NPH.

In our study, VENC was always selected to avoid velocity aliasing in regions of interest. The VENC value ranged between 12-20 cm/s for cases and 5-7 cm/s for controls.

After the imaging studies were completed, MRI workstation software (Argus, Flow Analysis; Siemens Medical System) processed the data. A circular ROI was drawn on the aqueduct on axial phase images. An additional ROI was drawn on the pons as a reference ROI. Using the software, graphics and values of various CSF flow indices were

obtained. Stroke volume was calculated as the mean value of forward flow volume and backward flow volume.

All patients were assessed pre- and post- shunt surgery using clinical NPH score.

Table 2: Clinical NPH score [10]	
Gait evaluation:	
Patient is bedridden or not able to ambulate	1
Ambulation is possible with help	2
Independent walking is possible but unstable or the patient falls	3
Abnormal but stable gait	4
Normal gait	5
Cognitive function:	
Patient is vegetative	1
Severe dementia	2
Important memory problems with more or less severe behaviour disturbances	3
Memory problems reported by patient or family	4
Cognitive disturbances are only found by specific tests	5
Sphincter disturbance:	
Urinary and faecal incontinence	1
Continuous urinary incontinence	2
Sporadic urinary incontinence	3
Urinary urgency	4
No objective or subjective sphincter dysfunction	5

Total NPH score = gait evaluation score + cognitive function score + sphincter disturbance score.

A patient with ≥ 1 increase in clinical NPH score 3 months after shunt surgery was defined as a shunt responder.

Statistical analysis:

The collected data was entered into Microsoft Excel Spreadsheets. Continuous variables were tabulated as mean and standard deviation and represented as Box plots showing mean (x), 25th percentile, median and 75th percentiles (box) and ±95th percentiles (whiskers). A two-sided p-value was reported and a p-value of < 0.05 was considered statistically significant.

OBSERVATIONS AND RESULTS

The study was conducted on 36 patients and 10 controls. 16 of the 36 patients diagnosed with NPH did not give consent for the shunt operation when the risks and benefits were explained to them. CSF shunt operation was performed on 20 patients. At 3 months follow-up, symptoms of 14 patients lessened (shunt responders), while no change was observed in the symptoms of 6 patients (shunt non-responders).

Table 3: Comparison of peak systolic velocity in controls and cases		
Controls	**Cases**	**P-value**
5.5 ± 1.2 cm/s	9.9 ± 3.5 cm/s	0.00001

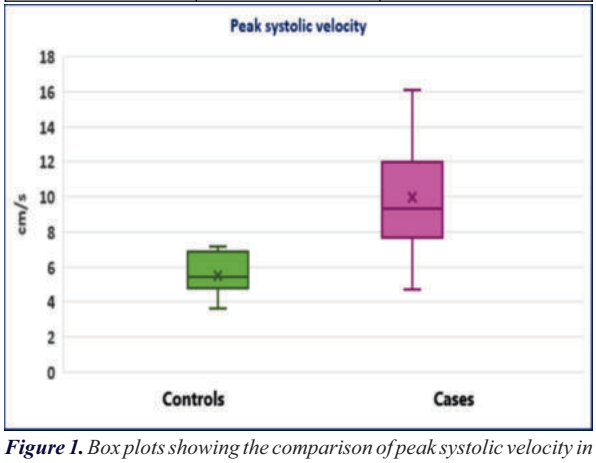

Figure 1. *Box plots showing the comparison of peak systolic velocity in controls and cases*

Table 4: Comparison of peak systolic velocity in NPH responders and non-responders		
NPH responders	**NPH non-responders**	**P-value**
10.9 ± 2.9 cm/s	6.9 ± 2.0 cm/s	0.003

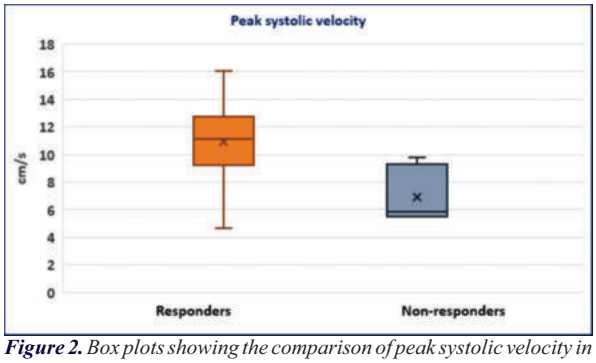

Figure 2. *Box plots showing the comparison of peak systolic velocity in NPH responders and non-responders*

Table 5: Comparison of stroke volume in controls and cases		
Controls	**Cases**	**P-value**
29.5 ± 3.2 µl	94.7 ± 60.5 µl	0.00012

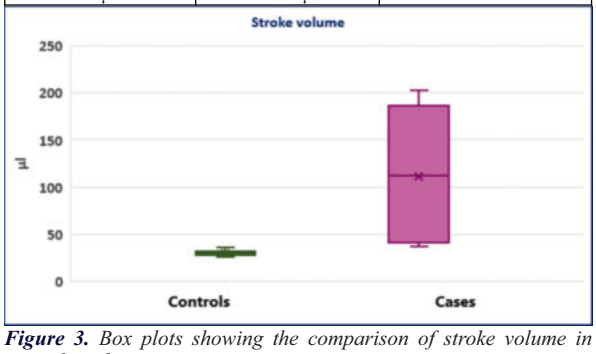

Figure 3. *Box plots showing the comparison of stroke volume in controls and cases*

Table 6: Comparison of stroke volume in NPH responders and non-responders		
NPH responders	**NPH non-responders**	**P-value**
115.2 ± 60.9 µl	46.7 ± 17.1 µl	0.0013

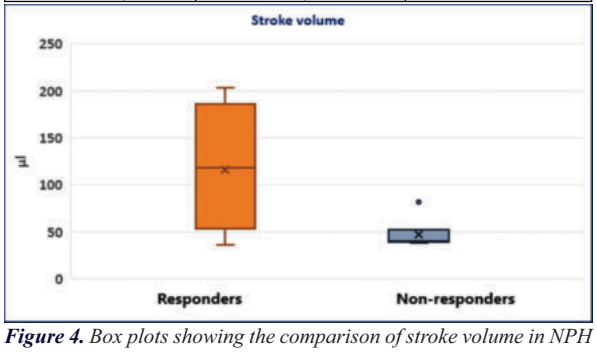

Figure 4. *Box plots showing the comparison of stroke volume in NPH responders and non-responders*

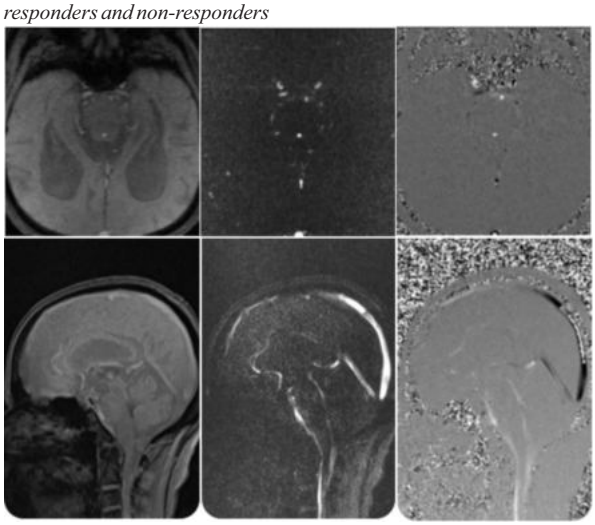

Image 1: *Through-plane & in-plane images of rephased, magnitude & phase series of CSF flowmetry using PC MRI.*

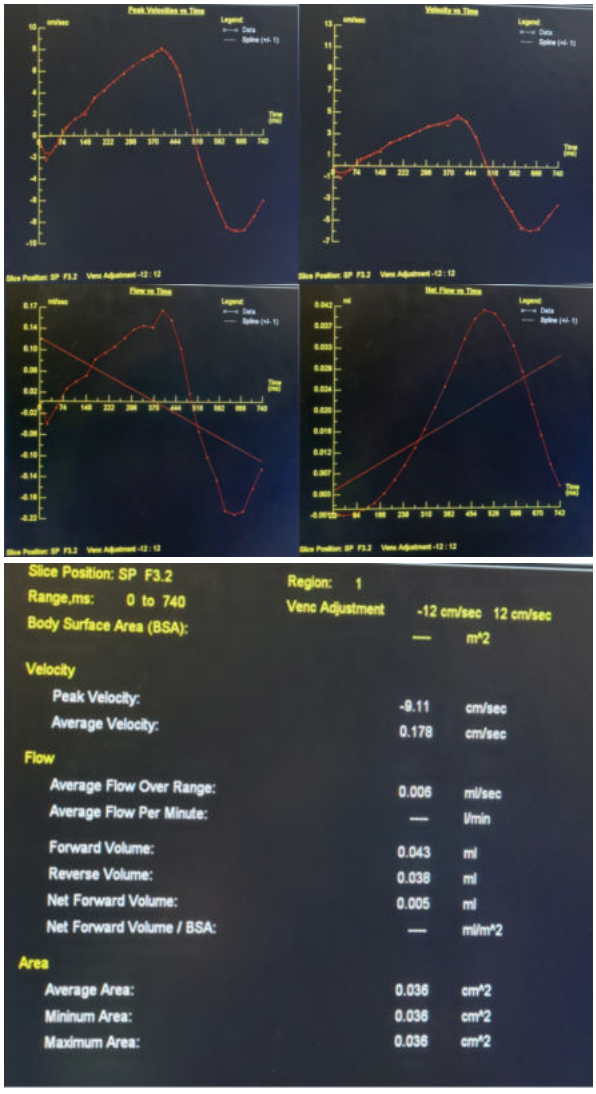

Image 2: Argus flow analysis of CSF flowmetry.

DISCUSSION

The hydrodynamics of CSF in NPH has been investigated using several techniques including imaging methods such as CT, MRI, radionuclide cisternography, and invasive tests such as spinal infusion test, lumbar drainage, and direct intracranial pressure measurement.[11-13] All these methods have a limited contribution to the diagnosis of NPH.[14] Further, invasive tests have serious risks such as meningitis, nerve root irritation, intracranial hypotension, and subdural hematoma.[15,17] Shunt therapy benefits only 30%–70% of cases with NPH diagnosis[11,12,17-19] and is associated with serious complications including infection and haemorrhage. Hebb and Cusimano reported a shunt complication rate of 38%.[7] Besides, post shunt operation, permanent neurologic deficit may occur in 6% of cases.[7] Therefore, the selection of patients who could benefit from shunt therapy is challenging.

MRI sensitivity to molecular movement has been well-known for years.[20] Phase contrast MRI produces contrast in signal between stationary and moving nuclei by sensitising the phase of the transverse magnetisation to the velocity of motion.[21] CSF circulation has two components: bulk flow (circulation) and pulsatile flow (back and forth motion). Pulsatile flow, rather than bulk flow, can be measured and demonstrated by PC MRI as very little CSF water truly circulates through the subarachnoid space. In bulk flow, CSF is produced by choroid plexus and absorbed by arachnoid granulations. In pulsatile flow, blood flowing into the brain parenchyma during systole causes it to expand inward, compressing the ventricles, and outward, compressing the cortical veins and sub-arachnoid space. The inward expansion causes CSF pulsatile outflow (cranio-caudal) via the cerebral aqueduct. During diastole, the decrease in volume of the brain parenchyma causes CSF inflow through the aqueduct (caudo-cranial). This is due to the fixed volume of the skull, according to the Monro-Kellie hypothesis. In NPH patients, the brain is already expanded out against the skull so all systolic expansion is inwardly directed against the enlarged ventricles. This leads to hyperdynamic CSF flow through the aqueduct.[22]

In our study, two parameters were used for the quantitative assessment of CSF flow through the cerebral aqueduct using Phase Contrast MRI: peak systolic velocity (PSV) and stroke volume (SV).

Peak Systolic Velocity:

NPH vs. controls: PSV was higher in cases as compared to controls with a significant statistical difference (p-value < 0.05).

NPH responders vs. non-responders: PSV was higher in shunt-responsive patients than in non-responsive patients with a significant statistical difference (p-value <0.05).

Stroke Volume:

NPH vs. controls: SV was higher in cases as compared to controls with a significant statistical difference (p-value <0.05).

NPH responders vs. non-responders: SV was higher in shunt-responsive patients than in non-responsive patients with a significant statistical difference (p-value <0.05).

Relation between aqueductal stroke volume > 42 µl and shunt responsiveness in NPH patients:

SV > 42:

11 out of 14 patients (78.6%) who responded to shunt had SV above 42.
1 out of 6 patients (16.6%) who did not respond to shunt had SV above 42.

SV < 42:

3 out of 14 patients (21.4%) who responded to shunt had SV below 42.
5 out of 6 patients (83.3%) who did not respond to shunt had SV below 42.

We report obvious elevations of PSV and SV in NPH patients in comparison to the control population, indicating hyper-dynamic CSF circulation in NPH. Our results are compatible with the study performed by Hakim S et al.[1] who reported markedly elevated PSV and SV in NPH compared to normal controls. Similar results were also found in a study by Senger KPS et al.[23]

We also report obvious elevations of PSV and SV in NPH patients who responded to shunt in comparison to those NPH patients who did not. Bradley et al.[24] reported that the relationship between cases with CSF stroke volumes greater than 42 µL and a favourable response to VP shunting was statistically significant. Our results agree with this study. In our study, SV > 42 µl shows a sensitivity of 78.57%, specificity of 83.33%, positive predictive value of 91.67%, negative predictive value of 62.5%, and an accuracy of 80% in predicting shunt responsiveness in NPH patients. Therefore, we endorse the role of CSF stroke volume in the prediction of patients as shunt responders (SV > 42 µl) and less likely possibility of improvement after shunt (SV < 42µl); however, it should not be used as an absolute exclusion criterion for the selection of shunt candidates. Similar results were observed in numerous other studies that shunt response can be predicted by aqueductal peak systolic velocity and stroke volume measurements.[19,25,26] Our results are in contrast to the studies by Algin et al. [27] and Kahlon et al. [11] in which no correlation was found between shunt response and CSF velocity and stroke volume.

CONCLUSION

Peak systolic velocity and stroke volume of CSF flow through the cerebral aqueduct are greater in NPH patients as compared to age-matched controls. In our study, PSV in controls is between 3.60 – 7.16 cm/s while in cases is between 4.65 – 21.34 cm/s but a definite CSF flow velocity cut-off in the local population of our community could not be established.

Peak systolic velocity and stroke volume of CSF flow through the cerebral aqueduct are greater in shunt-responsive NPH patients as compared to the non-responders. MRI CSF flowmetry using phase-contrast method can act as a prognostic marker for shunt responsiveness.

Conflicts of interest: Nil

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