CEREBROSPINAL FLUID MR DYNAMICS AND RISK OF FALLS IN THE ELDERLY


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SUMMARY

Rationale and objectives: To investigate the relationship between CSF dynamics and risk of falls of unknown origin in the elderly.

Population and methods: Phase contrast MR studies allowed CSF aqueductal flow quantification on 23 community-dwelling older people initially explored for mild cognitive impairment. Mobility assessment included report of falls, talking walking test, stance test, one leg standing test, up and go test, and measurement of fast gait speed.

Results: History of falls was associated with larger aqueduct, steeper diastolic slopes higher ratios RDV/SD of diastolic volume/CSF systole duration (p ≤ 0.0006). Amplitude CSF parameters, diastolic slopes and RDV/SD appeared correlated with the aqueduct area (p<0.01).

Conclusions: These preliminary data suggest that disturbances of CSF dynamics could play a role in mobility decline with aging especially in falls of unknown origin.

Key words: MRI, cerebrospinal fluid, flow dynamics, aging, falls.

RÉSUMÉ

Dynamique du liquide cérébrospinal en IRM et risque de chutes chez le sujet âgé

Objectif : Évaluer l’association potentielle entre dynamique du liquide céphalospinal (LCS) et risque de chutes d’origine inconnue chez les sujets âgés.

Population et méthodes : Une quantification du flux du LCS de l’aqueduc de Sylvius par cine IRM en contraste de phase a été réalisée chez 23 sujets âgés ambulatoires avec Déficit Cognitif Léger. Leurs éventuels antécédents de chute ont été notés, leurs vitesses de marche rapide et leur polygone de sustentation mesurés. Différents tests cliniques d’équilibre et de locomotion ont été réalisés : test de “walking when talking”, test d’appui monopodal, test “up and go”.

Résultats : L’antécédent de chutes était associé à un élargissement de l’aqueduc de Sylvius et les modifications suivantes de la courbe de débit à ce niveau; pente diastolique plus raide, ratio R DV/SD de diastolique volume/CSF systole durée (p ≤ 0,0006). Les paramètres d’amplitude des courbes de débit du LCS, la pente diastolique et le ratio R DV/SD apparaissaient corrélés à la largeur de l’aqueduc de Sylvius (p < 0,01).

Conclusions : Ces résultats préliminaires suggèrent que l’alteration de la dynamique du LCS pourrait jouer un rôle dans la survenue de chutes chez le sujet âgé.

Mots-clés : IRM, liquide cérébrospinal, flux, sujet âgé, chutes.

About 25 to 35% of community-dwelling people over the age of 65 years sustain one or more falls each year [1]. Falls in the elderly constitute an important public health problem because of their associated morbidity, mortality and institutionalization [1, 25]. Some of these falls remain of unknown origin [1] and healthy older people are frequently not aware of their risk for falling.

Recently, it has been suggested that dysfunctional CSF dynamics could play a role in the physiopathology of motor decline in the elderly [3]. MRI-CSF flow studies are not invasive and are readily available. They have allowed accurate measurements of CSF oscillatory motions [7, 10] in healthy as well as in patients with normal pressure hydrocephalus [4, 7, 8, 11, 12, 15, 23], a well known cause of gait disturbance in the elderly. However, to our knowledge, there has been no exploration of the relationship between CSF flow MR waveforms and mobility function in healthy older people without mobility complaint or without marked cognitive impairment.

The aim of this study was to investigate the possible relationship between CSF flow dynamics and risk of falls of unknown origin in community-dwelling elderly. For this purpose, CSF dynamics MR patterns were analysed and correlated with the mobility status.

MATERIALS AND METHODS

Population

MRI studies were performed on 23 community-dwelling elderly individuals that were explored for...
mild cognitive impairment [20]. All subjects had given their written informed consent to participate to this study, after the procedure had been explained according to the principles of the Word Medical Association’s Declaration of Helsinki. Subjects were 68–80 years old (74±3 years old, 13 men, 10 women), with no mobility complaint initially. They had Mini Mental State Examination Scores of 26 or more (28±1.2) and did not respond to dementia criteria [20]. Subjects were free of neurologic or musculoskeletal disease, significant podiatric pathology, history of serious visual or somatosensory impairments, clinically obvious vestibular dysfunction, unstable cardiovascular disease or any major acute illness. They were on no medications that could alter mobility (eg phenothiazine, butyrophenone). There was no major obesity (Body Mass Index -BMI- 25±3kg/m²), no clinical depression (Montgomery-Asberg Depression Rating Scale score <20) [17], nor history of severe brain trauma, meningitis or toxic abuse. Some of the subjects had cardiovascular risk factors, arterial hypertension (n=5), angina (n=1), diabetes (n=3), dyslipidemia (n=7), smoking (n=6). None of them had cardiac arrhythmia, urinary incontinence, nor metabolic disorders, hypothyroidism, vitamin deficiency. Brain imaging had documented absence of tumor, infarcts, normal pressure hydrocephalus defined as ventricular enlargement without signs of moderate or marked cortical atrophy [26].

Mobility status evaluation

The assessment of balance and gait was performed by an experienced geriatrician (FO). It included report of falls [1], walking while talking (WWT) test [16], standing balance [24], one-leg standing test [27], timed “up and go” [19, 21] and fast gait speed (Table I). The standing balance and the one-leg standing test evaluated balance performance under static conditions whereas the timed “up and go” evaluated balance performance under locomotor conditions and also reflected gait performance.

CSF flow evaluation

MR explorations were conducted with 1.5T MR system (GE Medical Systems, Milwaukee). MR examination included structural MR sequences and flow quantification sequences. All MR examinations were analyzed by the same experienced radiologist who was blinded to the mobility status of the patients (MCHF).

Quantification of CSF flow

Data acquisition

Quantification of CSF flow used phase contrast MR sequences (TR 23 ms, TE 9.1ms, 2 NEX, flip angle 30°). To characterize the aqueductal jet, a 5mm thick slice was performed perpendicular to the main axis of the aqueduct and passing through its mid portion. The number of pixels per aqueductal area was maximized using a small field of view of 12x12cm², 256x256 acquisition matrix. Direction of velocity encoding was perpendicular to the acquisition plane and velocity encoding gradient set at 15cm/s. Peripheral pulse allowed retrospective cardiac gating. This sequence yielded 16 quantitative flow-encoded images covering the whole cardiac cycle.

CSF parameters analysis

Data processing

Commercially available CV flow software (GE Medical Systems, Milwaukee) was used to extract CSF velocity data. One Region of Interest (ROI) encircled the whole aqueductal area and the surface of this ROI transcribed (figure 1). Background ROI in the adjacent tissues allowed correction of the average throughout the cycle of possible spatially dependent offset velocity.

<table>
<thead>
<tr>
<th>Mobility evaluation</th>
<th>instructions</th>
<th>Higher performance</th>
<th>Lower performance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Report of falls</td>
<td>To report history of falling*</td>
<td>No falls</td>
<td>One fall or more</td>
</tr>
<tr>
<td>Walking while talking test</td>
<td>To start a conversation with a companion while walking</td>
<td>No stop walking</td>
<td>Stop walking</td>
</tr>
<tr>
<td>One-leg standing test (seconds)</td>
<td>To lift up his or her right (left) foot and stand on it as long as possible</td>
<td>&gt;5</td>
<td>&lt;5</td>
</tr>
<tr>
<td>Standing balance</td>
<td>To place their feet together and stand without holding for object or support.</td>
<td>Able to do it</td>
<td>Unsteady</td>
</tr>
<tr>
<td>Timed up and go (seconds)</td>
<td>To stand up from an armchair walk a distance of three meters and sit down again</td>
<td>&lt;16</td>
<td>&gt;16</td>
</tr>
<tr>
<td>Timed fast pace gait</td>
<td>To walk as fast as possible 15 meters</td>
<td>Within the normal range</td>
<td>Below normal values **</td>
</tr>
</tbody>
</table>

* History of falls during the last 6-month period prior to the assessment.
** The normal values were defined by reference to a previously published range of normal data [18].
*Antécédent de chutes durant les six derniers mois.
** les valeurs normales ont été définies selon des normes précédemment publiées [18].
For each of the 16 time frames, the product of the mean velocity and the aqueduct area is an estimate of the volume flow rate (microliter per second) through the aqueduct. The acquisition of 16 values of CSF flow rate over the cardiac cycle then allowed the generation of a CSF flow rate curve as a function of time (seconds) over the cardiac cycle.

**CSF flow structural parameters**

In addition to the aqueduct area assessment, ventricular and sulcal enlargement were assessed on axial images angled to be parallel to the anterior commissure – posterior commissure line [29]. Identification of the presence or absence of marked ventricular and sulcal enlargement (grade 8, [29]) allowed a binary classification of ventricles and sulci.

**CSF flow dynamic parameters**

**Amplitude parameters**

The following parameters of CSF motions through the aqueduct were measured: CSF stroke volume per cardiac cycle [2, 11], systolic and diastolic CSF volumes.

The product of the volume flow rate and the time interval between cine frames (second) is the volume displaced through the aqueduct during this time interval. The sum of the quantity over all frames in which it is positive is an estimate of the volume (microliter) displaced caudally through the aqueduct during one CSF systole or systolic volume (microliter or mm³).

The same sum over negative values is an estimate of the volume displaced in the cranial direction or diastolic volume (microliter or mm³).

The lesser of the two represents the volume that is displaced in a reciprocating fashion over one cardiac cycle or the stroke volume (microliter per cardiac cycle or µl/cycle).

**Temporal and composite indicators of resistance to CSF outflow**

**Systole duration** was defined as the duration of caudal CSF flow through the aqueduct [2, 11].

**Diastolic slope** of CSF flow waveforms was also calculated as an indicator of the compliance of the craniospinal cavity. A polynomial function (rank 2) was used to fit the initial rise of CSF diastolic flow rate. Diastolic upslope was then estimated by calculating the first derivative of this function at the time of beginning of CSF diastole.

The ratio $R_{DV/SD}$ of diastolic volume (microliter) and duration of CSF systole (milliseconds) was used as a composite index of resistance to CSF outflow. Indeed, increased resistance to CSF outflow decreases duration of CSF ventricular outflow i.e. systole duration [11] and amplifies retrograde CSF flow or diastolic volume through the aqueduct [12]. Both changes result in increase of the ratio.

**Statistical analysis**

Comparison of subjects with lower and higher performance on a single mobility assessment test was based on the analysis of nine CSF parameters – including seven aqueduct parameters (Table II), ventricular score and sulcal score –, and eight clinical parameters – including age, gender, BMI, hypertension, diabetes, smoking, dyslipidemia, angina.

Comparison of CSF parameters in subjects with lower and higher performance on a single mobility assessment test was done using the Student t test. Evaluation of potential confounding effect of age and BMI factors was done using the Mann-Whitney test. Evaluation of potential confounding effect of gender, cardiovascular risk factors was done using the Fisher exact test.

To reduce the probability of type I error in multiple comparisons, the statistical significance level ($\alpha=0.05$) was divided by the number of prespecified comparisons ($\kappa=17$). It yielded an adjusted significance level ($\alpha/\kappa$) of $p<0.003$ for a single mobility assessment test.

The 17 univariate analyses were done for each mobility test assessing a risk of falls. Then, they were done three times. Indeed, in our population, risks of falls were detected only in the assessment of the history of falls, WWT test and one-leg standing test (cf. infra). Significance level of $p<0.003$ initially used for a single test was then itself adjusted to correct for this post hoc analysis. Post hoc Bonferroni correction ($k=3$) yielded an adjusted overall significance level of $p<0.001$.

Correlations between the aqueduct area and CSF dynamics parameters were also investigated using the coefficient $r$ of linear regression.

**Fig. 1.** – Axial phase-contrast image perpendicular to the aqueduct shows the ROI for the aqueduct. Background offset of stationary material was also measured with a ROI placed just ventral to the aqueduct.

**Correlations between the aqueduct area and CSF dynamics parameters** were also investigated using the coefficient $r$ of linear regression.
RESULTS

Clinical data

Clinical profile

Fast gait speed ranged from 100 cm/s to 188 cm/s. It could be considered within the normal range of values for the age [18] in all patients except one who showed slightly lower maximum speed. Up and go times ranged 7-20 seconds (mean value 11±3 sec). These values were below the cut off value associated with risk of falls [19] except in one case. There was no abnormal response to the standing balance test.

Risks of falls were then mainly detected in the assessment of the history of falls, WWT test and one-leg standing test. Indeed, seven patients had a history of one or two falls within the previous 6 months. Eleven patients had a positive WWT test. At the one-leg standing test, five patients were unable to stand on one leg at least five seconds.

<table>
<thead>
<tr>
<th>CSF parameters</th>
<th>History of falls</th>
<th>Walking while talking test</th>
<th>One leg standing test</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>aqueduct area (mm²)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Higher performance</td>
<td>8±2</td>
<td>9±2</td>
<td>9±2</td>
</tr>
<tr>
<td>Lower performance</td>
<td>12±2</td>
<td>11±3</td>
<td>12±2</td>
</tr>
<tr>
<td>p value</td>
<td>0.0006*</td>
<td>0.08</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>systolic volume (µl)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Higher performance</td>
<td>57±28</td>
<td>54±28</td>
<td>67±31</td>
</tr>
<tr>
<td>Lower performance</td>
<td>85±25</td>
<td>78±26</td>
<td>60±24</td>
</tr>
<tr>
<td>p value</td>
<td>0.02</td>
<td>0.02</td>
<td>0.3</td>
</tr>
<tr>
<td><strong>diastolic volume (µl)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Higher performance</td>
<td>60±26</td>
<td>55±27</td>
<td>69±32</td>
</tr>
<tr>
<td>Lower performance</td>
<td>96±30</td>
<td>88±28</td>
<td>76±35</td>
</tr>
<tr>
<td>p value</td>
<td>0.004</td>
<td>0.005</td>
<td>0.3</td>
</tr>
<tr>
<td><strong>stroke volume (µl/cycle)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Higher performance</td>
<td>56±26</td>
<td>53±26</td>
<td>66±30</td>
</tr>
<tr>
<td>Lower performance</td>
<td>84±25</td>
<td>78±26</td>
<td>59±25</td>
</tr>
<tr>
<td>p value</td>
<td>0.01</td>
<td>0.02</td>
<td>0.3</td>
</tr>
<tr>
<td><strong>systole duration (ms)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Higher performance</td>
<td>407±62</td>
<td>397±65</td>
<td>398±57</td>
</tr>
<tr>
<td>Lower performance</td>
<td>374±49</td>
<td>397±56</td>
<td>389±76</td>
</tr>
<tr>
<td>p value</td>
<td>0.1</td>
<td>0.5</td>
<td>0.4</td>
</tr>
<tr>
<td><strong>diastolic slope (10⁻³µl/s/s)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Higher performance</td>
<td>1.06±0.46</td>
<td>1.08±0.53</td>
<td>1.4±0.6</td>
</tr>
<tr>
<td>Lower performance</td>
<td>1.89±0.44</td>
<td>1.59±0.58</td>
<td>1.2±0.5</td>
</tr>
<tr>
<td>p value</td>
<td>0.0003*</td>
<td>0.01</td>
<td>0.3</td>
</tr>
<tr>
<td><strong>ratio R_{DVSD} (µl/ms)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Higher performance</td>
<td>0.14±0.06</td>
<td>0.14±0.07</td>
<td>0.17±0.08</td>
</tr>
<tr>
<td>Lower performance</td>
<td>0.25±0.07</td>
<td>0.22±0.07</td>
<td>0.19±0.10</td>
</tr>
<tr>
<td>p value</td>
<td>0.0004*</td>
<td>0.004</td>
<td>0.3</td>
</tr>
</tbody>
</table>

p values are those obtained in the comparison of higher and lower performance groups (i.e. higher and lower risk of falls).

* significant difference between the lower and higher performance groups after Bonferroni correction.

Les valeurs de p sont celles obtenues dans la comparaison des groupes cliniques, l’un constitué de sujets avec bonne performance motrice – et faible risque de chutes –, l’autre constitué de sujets avec mauvaise performance motrice – et risque plus important de chutes –.

* différence significative entre les deux groupes cliniques après correction de Bonferroni.
Age, gender, BMI, cardiovascular factors, and mobility performance

Evaluation of the effect of age, gender, BMI and cardiovascular risk factors showed only a tendency to older patients in the positive WWT test group than in the negative WWT test group (p 0.01 Mann Withney test). This difference was not statistically significant after application of Bonferroni correction.

CSF flow data

Four patients showed marked ventricular enlargement (a) and moderate cortical atrophy (b) in a faller with a high ratio R_{DV/SD} of diastolic volume and duration of CSF systole, and steep diastolic slope (respectively R 0.31 µl/ms, slope 2.3 10^{-3} µl/s/s). Absence of marked ventricular (c) or sulcal enlargement (d) in a faller with a relatively high ratio (0.24 µl/ms) and steep diastolic slope (1.9 10^{-3} µl/s/s). Ventricular (e) and sulcal (f) patterns in a non faller with low ratio and smooth diastolic slope (respectively R 0.06 µl/ms, slope 0.34 10^{-3} µl/s/s).

CSF stroke volume ranged 10-110 µl/cycle. It was below 101 µl/cycle i.e. within 2 standard deviations of the mean value of a previously studied healthy population of younger adults, except for three patients in which CSF stroke volume was only slightly increased above this value.

The average duration of CSF systole of 17 patients with heart rate range 55-80/seconds, was 44±5% of the cardiac cycle. It appeared then shorter than in a previously studied healthy population of younger adults [2, 11]. CSF systole in the whole group averaged 397±59 msec (range 292-497 ms).

The aqueduct area showed significant correlations (p<0.01) with CSF diastolic, systolic and stroke volumes (respectively r=0.75, r=0.75 and r=0.65), the diastolic slope (r=0.58) and the ratio R_{DV/SD} (r=0.77).
CSF flow and clinical data

Evaluation of the effect of ventricular or sulcal enlargement (Fisher test) showed only a weak tendency to larger ventricles in patients with history of falls (p 0.07), positive WWT test (p 0.04) one-leg standing test (p 0.02). After Bonferroni correction, there was no statistically significant difference with respect to marked ventricular or sulcal enlargement.

After Bonferroni correction for multiple comparisons, the only significant changes were observed in the comparison of fallers and non fallers. They included the enlargement of the aqueduct, the increase of diastolic slope and the increase of the ratio R_{DV/SD} in fallers (Table II) (figure 3).

DISCUSSION

This study observed changes of CSF dynamics with risk of falls of unknown origin in the elderly. These differences reached a significant level only in fallers, in good agreement with the history of falls as one of the strongest predictor for future falls [1, 25].

An association of both a slight decrease of systole duration and a slight increase of volume of CSF pulsations could explain the higher ratio of diastolic volume/systole duration and steeper diastolic slopes in fallers. Reduced duration of CSF systole can be considered as an indicator of increased resistance to CSF outflow [11, 23] which seems a frequent finding in the elderly [6]. Age itself is a factor of cerebral microangiopathy [22]. Cerebral microangiopathy results in larger arterial pressure transmission from cerebral vessels to the CSF spaces and increases volume of CSF pulsations [6, 13, 23]. Then changes of CSF dynamics in fallers could result from additive effects of increased resistance to CSF outflow and microangiopathy with aging.

Fallers showed an enlarged aqueduct, even if their mean aqueduct area was smaller than previously observed in hydrocephalus [11]. This is in good agreement with previously reported tendency to larger ventricular spaces or significantly larger ventricular spaces in age-related decline of mobility [5, 28]. In our study, dysfunctional CSF dynamics in fallers, significant correlations between aqueduct size and CSF dynamics parameters suggest that enlargement of the ventricular system could be a compensatory mechanism to prevent pulsatile increase of the intraventricular pressure [9]. Dilatation of the aqueduct is proportionally more important than dilatation of the ventricles in hydrocephalus. This can explain that enlargement of the aqueduct appeared to be a more sensitive indicator of altered CSF dynamics. In the future, voxel-based morphometric comparison of the ventricular system of fallers and non fallers could also help to detect subtle changes of ventricular system.

Then, both dynamics and morphological changes in fallers could be reminiscent of the hydrodynamics changes of hydrocephalus. In these patients, postural decline could result from “CSF water hammer effect” and tissue stress around the frontal horns. Indeed, the neuroanatomic pathways between the leg area of the supplementary motor area and the globus pallidum are closely related to frontal horns [9, 14].

More data are needed to accurately define normal and pathological dynamics states in the elderly. However, our preliminary data suggest that disturbances of CSF dynamics could contribute to falls of unknown origin in the elderly and that MR analysis of CSF waveforms could help to identify these disturbances.

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