Neuroimaging in differential diagnosis of pathologies associated with dementia: Alzheimer's Disease (AD) and Normal Pressure Hydrocephalus (NPH).

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Learning objectives

To describe the experience in the application of structural and functional neuroimaging in early diagnosis, differential diagnosis and follow-up of pathologies associated with dementia in the hospital Fundación Valle del Lili in Cali, Colombia.
Background

According to WHO, people over 60 years is increasing gradually worldwide and it is expected that by 2050 they represent 22% of global population corresponding to about 2.000 million people. Over 20% of this age group are -or will be- diagnosed with a neurological disorder. Dementia is one of the most common neuropsychiatric disease and one of the major causes of disability and dependency among older people.

Dementia is a syndrome characterized by a cognitive impairment usually chronic or progressive that affects memory, thinking, comprehension, learning capacity and ability to develop daily activities. Worldwide, 35.6 million people have dementia and there are 7.7 million new cases per year. The most common cause of dementia is Alzheimer’s disease (AD) which represents between 60% and 70% of the patients. Normal pressure hydrocephalus (NPH) is also an important cause and may contribute to 5% of cases [1]. Diagnosis based in semiology is usually difficult because clinical manifestations may be similar in the different pathologies associated to dementia.

<table>
<thead>
<tr>
<th>Causes of dementia</th>
<th>Proportion of dementia cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alzheimer’s Disease (AD)</td>
<td>60% – 70%</td>
</tr>
<tr>
<td>Vascular Dementia (VaD)</td>
<td>20% – 30%</td>
</tr>
<tr>
<td>Frontotemporal dementia</td>
<td>5% – 10%</td>
</tr>
<tr>
<td>Dementia with Lewy Bodies</td>
<td>&lt; 5%</td>
</tr>
<tr>
<td>Normal Pressure Hydrocephalus</td>
<td>&lt; 5%</td>
</tr>
</tbody>
</table>

Table 1: Causes of dementia.


Dementia also has a significant social and economic implications related to medical costs, direct social costs and the costs of care provided outside institutional environment. In 2010, total cost of dementia was estimated close to US$ 604 billion, which corresponds to 1% of the Gross Domestic Product (GDP).
Although there is no current treatment to cure or reverse the progressive evolution of most causes of dementia, early diagnosis would improve the quality of life of patients by the identification of comorbid physical illness, psychological and behavioral symptoms and training to the family for patient care. Furthermore, differential diagnosis is very important because it allows to establish a opportune and appropriate therapeutic approach in order to achieve the best patient outcomes reducing costs and response times.

Cerebral MRI provides structural information about brain and it has been used for early detection of dementia by identifying progressive atrophy [3, 4]. For many years, imaging studies focused on the evaluation of the structures such as hippocampus and entorhinal cortex [6, 7, 8, 9]. However, in last decade, the research has been more exhaustive allowing to characterize certain patterns of brain atrophy in dementia by describing its beginning in temporal and limbic areas, extending later to parietal association areas and getting finally to the frontal lobe and primary cortices [10, 11, 12].

In addition to brain atrophy, it has been reported greater commitment of white matter in patients diagnosed with dementia associated to AD and NPH compared with those described in normal aging. This has been linked to compression of the brain parenchyma as a result of abnormal ventricular dilation. These lesions are classified qualitatively considering the degree of commitment and type of injury by Age-Related White Matter Changes scale (ARWMC) from some specific MRI sequences where lesions are hyperintense compared to healthy brain tissue [13]. From T1-weighted sequences is possible to perform a more objective analysis by quantifying white matter hypointensities through volumetric assessment.
Evans index is the most common measurement used to establish the ventricular dilation in the diagnosis of NPH, and it is calculated by dividing the width of the frontal horns of the lateral ventricles by the maximum biparietal diameter [14]. Values over 0.30 are abnormal. However, this index is not a reliable measurement to evaluate the patient improvement in the follow-up after lumbar puncture because despite a decrease in the ventricular dilation and clinical improvement are observed, the index value does not change.

In recent years, research studies with functional magnetic resonance imaging (fMRI) and diffusion tensor imaging (DTI) for the characterization of pathologies associated with dementia, mainly in AD, have been growing exponentially. Multiple studies have reported disconnection of the default mode network (DMN) in patients with AD associated with the loss of cognitive functions. Alteration in corpus callosum with disruption of commissural fibers in knee portion and, compression and lateral displacement in some tracts by ventricular dilation have been observed in patients diagnosed with NPH.
Due to advances in neuroimaging techniques in recent decades, these have become into an essential tools in the diagnosis and follow-up of patients with different pathologies associated with the central nervous system by allowing the integration of different structural and functional studies in a multimodal system. Since the clinical criteria for the diagnosis of dementia has not been clearly established, these techniques can play an important role in early identification, differential diagnosis, therapeutic management and follow-up of such diseases.

Fig. 3: functional neuroimaging articles published per year 1996 - 2014.

Findings and procedure details

Procedure details.

Between January and August 2014, 20 male patients between 57 and 91 years old, 10 diagnosed with AD and 10 with NPH, were evaluated by structural and functional neuroimaging in a 1.5 tesla MRI scanner, SIEMENS Avanto, with a 32-channel antenna.

fMRI studies were performed using echo planar sequences (TE: 45 ms; TR: 2000 ms; flip angle: 90º; matrix: 64x64; FOV: 240 mm; slice thickness: 6 mm), at rest. Motion correction with a rigid body transformation, spatial smoothing FWHM= 7 mm, single analysis by decomposition into independent components according to their temporal and spatial properties with a threshold IC= 0.5 were carried out. DMN was identified considering the activation areas, temporal behavior and frequency spectrum. Registration with structural images were performed by global rescale transformation through a double registration process. All image processing were carried out with BET v2.1 (Brain Extraction), MELODIC v3.13 (Multivariate Exploratory Linear Optimized Decomposition into Independent Components) and FLIRT v6.0 (FMRIB's Linear Image Registration Tool) from FSL v5.0.4 (FMRIB Software Library). Fusion between structural and functional images were performed using Mango v3.4 (Multi-image Analysis GUI).

For volumetric analysis, T1-weighted sequences (TR: 1900 ms; TE: 3,37 ms), was processed by FreeSurfer v5.1.0 in a DELL inspiron machine with Intel Core i7 2.10 GHz, 8GB memory and Ubuntu 12.10 as operative system. Results were compared using volume index (VI) and asymmetry index (AI) with an international database taking into account sociodemographic characteristics of patient groups. Cortical thickness were evaluated in milimeters (mm). In addition, volumetric assessment was performed in 8 patients diagnosed with NPH post lumbar puncture.

Echo planar sequences with 20 directions were used for DTI studies. Imaging were processed and analyzed in MR Neuro 3D module of Syngo.Via software. Tractography was performed in the main white matter tracts with angular umbral= 30º, FA umbral= 0.20 and color codification according to the tracts direction. For multimodal imaging evaluation, multiplanar volumes were generated fused with structural T1-weighted images.

Findings.
An abnormal disconnection of the DMN was observed in patients diagnosed with AD mainly in medial prefrontal cortex compared to patients with NPH and normal aging (figure 4).

**Fig. 4**: Default Mode Network. a) normal aging, b) Alzheimer's Disease and c) Normal Pressure Hydrocephalus.

**References**: Fundación Valle del Lili, Fundación Valle del Lili - Cali/CO

In NPH patients, greater white matter compromise compared to AD and normal aging were evidenced. According to the ARWMC scale, 70 % of patients diagnosed with NPH had white matter lesions with diffuse involvement of the entire region, 20 % focal lesions and 10 % no lesions were observed. In AD patients, it was evidenced focal lesions in 60 % of cases and no white matter lesions in 40 %. In basal ganglia, focal lesions in white matter was observed in 20% of NPH cases and none in AD patients. In the quantitative analysis, white matter hypointensities index of patients diagnosed with HCA was 0.935 ± 0.542, in patients with AD was 0.259 ± 0.092 and 0.224 ± 0.263 in normal aging (figure 5).
In AD patients it was observed a decrease in basal ganglia volume index, mainly in thalamus and putamen. However, hippocampus and amygdala were decreased in both pathologies AD and NPH compared to normal aging (table 2).

<table>
<thead>
<tr>
<th>Basal ganglia</th>
<th>NPH</th>
<th>AD</th>
<th>NA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thalamus</td>
<td>0.416 ± 0.079</td>
<td>0.347 ± 0.015</td>
<td>0.450 ± 0.042</td>
</tr>
<tr>
<td>Caudate</td>
<td>0.268 ± 0.073</td>
<td>0.197 ± 0.019</td>
<td>0.218 ± 0.023</td>
</tr>
<tr>
<td>Putamen</td>
<td>0.267 ± 0.067</td>
<td>0.235 ± 0.022</td>
<td>0.308 ± 0.035</td>
</tr>
<tr>
<td>Pallidum</td>
<td>0.082 ± 0.008</td>
<td>0.083 ± 0.003</td>
<td>0.096 ± 0.015</td>
</tr>
<tr>
<td>Hippocampus</td>
<td>0.180 ± 0.027</td>
<td>0.190 ± 0.025</td>
<td>0.265 ± 0.035</td>
</tr>
<tr>
<td>Amygdala</td>
<td>0.079 ± 0.011</td>
<td>0.073 ± 0.001</td>
<td>0.092 ± 0.008</td>
</tr>
</tbody>
</table>

Table 2: Volumetric Index of basal ganglia of patients diagnosed with NPH and AD, compared to normal aging (NA).

References: Fundación Valle del Lili, Fundación Valle del Lili - Cali/CO
Corpus callosum volume was decreased in both conditions (figure 6). However, patients with NPH showed a greater overall commitment while in AD patients the involvement was mainly in central portion. Disruption of commissural fibers in knee portion, compression and lateral displacement of corticospinal, superior and inferior longitudinal and adjacent tracts were also observed in NPH patients.

![Corpus Callosum Volumetric Index vs Age](image)

**Fig. 6:** Corpus Callosum Volumetric Index vs Age. NA: Normal aging, NPH: Normal Pressure Hydrocephalus, AD: Alzheimer’s Disease.

**References:** Fundación Valle del Lili, Fundación Valle del Lili - Cali/CO

Cortical thickness was generally decreased in NPH while in AD the commitment was mostly in fusiform, lateral orbitofrontal and temporal superior gyres (figures 7 and 8).
**Fig. 7:** Cortical Thickness vs Age. NA: Normal aging, NPH: Normal Pressure Hydrocephalus, AD: Alzheimer's Disease.

*References:* Fundación Valle del Lili, Fundación Valle del Lili - Cali/CO

**Fig. 8:** Cortical Thickness. a) normal aging, b) Alzheimer's Disease and c) Normal Pressure Hydrocephalus.

*References:* Fundación Valle del Lili, Fundación Valle del Lili - Cali/CO
Ventricular volumetric index was increased in both diseases, significantly higher in NPH cases (figure 9). Evans index was also greater in this group (0.37 ± 0,05) compared to AD patients (0.28 ± 0,04), where most cases were within normal range.

![Graph showing ventricular system volumetric index vs age](image)

**Fig. 9**: Ventricular System Volumetric Index vs Age. NA: Normal aging, NPH: Normal Pressure Hydrocephalus, AD: Alzheimer’s Disease.

**References**: Fundación Valle del Lili, Fundación Valle del Lili - Cali/CO

After lumbar puncture, ventricular volumetric index was decreased compared to values pre-procedure (figure 10). However, Evans index was equal in both conditions for all patients. Corpus callosum volumetric index and mean cortical thickness were increased but still out of normal ranges (figure 11).
**Fig. 10:** 80 years-old man diagnosed with NPH. Ventricular System Volumetric Index pre and post lumbar puncture.

*References:* Fundación Valle del Lili, Fundación Valle del Lili - Cali/CO

**Fig. 11:** 80 years-old man diagnosed with NPH. Cortical thickness pre and post lumbar puncture.

*References:* Fundación Valle del Lili, Fundación Valle del Lili - Cali/CO
Conclusion

Discussion.

As the clinical diagnostic criteria for dementia has not been clearly determined, structural and functional neuroimaging may play a significant role in the differential diagnosis. The importance of differential diagnosis is the necessity to establish an opportune and appropriate therapeutic approach in cases of dementia in which the symptoms are potentially reversible as in NPH patients where if treatment were performed before loss of cerebral hysteresis and chronic damage in connection and association fibers secondary to prolonged ventricular dilation, patient outcome could be significantly better [15].

Disconnection of the DMN was observed in patients diagnosed with AD probably related to the loss of cognitive functions which is a characteristic of this disease due to the toxic effect of #-amyloid [16]. Although in NPH cases, there was a posterior displacement of Medial Prefrontal Cortex (MPFC) and anterior of Posterior Cingulate Cortex (PCC), no changes were found in signal frequencies of brain regions involved that might suggest a network disconnection, this probably because the loss of functions is due to a mechanical cause and could be reversed by treatment before a structural damage occurs.

Greater involvement of white matter was observed in patients with NPH compared to AD and normal aging, mainly periventricular probably related to the obstruction of venous drainage and reduction of CSF absorption due to the compromise of interstice. Only 20% of NPH cases showed focal involvement in basal ganglia, and there were not any compromise in AD patients.

It was also possible to identify trends and patterns of brain atrophy for each pathology (AD and NPH) and normal aging, which could be useful in the differential diagnosis even at early stages.

Qualitative analysis may be sufficient for identification and diagnosis of NPH, however, in the follow-up after puncture or shunt, brain volumetry is a more sensitive and accurate technique because it allows to evaluate in detail each brain segment and detecting even slight changes in brain volumes and cortical thickness that may have clinical significance.

The same occurs with adjacent tracts to the frontal horns where improvement is observed after puncture due to the decrease of ventricular dilation which has a compressive effect, consistent with clinical improvement reported in these patients.
Conclusion.

Structural and functional imaging have allowed to characterize and differentiate diseases with similar clinical manifestations becoming into a potentially useful tool to the clinician in the early diagnosis, differential diagnosis, therapeutic approach and follow-up of pathologies associated with dementia.


