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Research article

Weekly enhanced T1-weighted MRI with Gadobutrol injections in MS patients: Is there a signal intensity increase in the dentate nucleus and the globus pallidus?

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ABSTRACT

Background and Purpose: Gadolinium-based contrast agents (GBCAs) administration have drastically improved the accuracy of Multiple Sclerosis (MS) diagnosis by highlighting any damage to the brain blood barrier, thereby differentiating between active and non-active lesions. Following multiple administrations of GBCAs, several MS studies have reported a signal intensity (SI) increase on unenhanced T1-weighted images in certain brain regions such as the dentate nucleus (DN) and the globus pallidus (GP). Our aim was therefore to determine the accumulation of macrocyclic GBCAs on enhanced T1-weighted images SI in the DN and the GP of MS patients injected eight times.

Materials and Methods: Five MS patients underwent eight weekly consecutive MRI scans. Enhanced 3D T1-weighted images with Gadobutrol as a macrocyclic GBCA, were acquired. A ROI-based approach was applied for the evaluation of SI in the DN to middle cerebellar peduncle (DN-MCP) and GP to semi-oval white matter (GP-SOWM) ratios. An analysis of variance on repeated measures was used for the statistical analysis of each ratio.

Results: No DN-MCP and GP-SOWM SI ratio differences were observed over the eight-weeks period using the macrocyclic GBCA.

Conclusion: Iterative and weekly injections of macrocyclic GBCAs are not associated with T1 signal increase in the DN and GP of MS patients. These results would suggest a no gadolinium accumulation in the brain using macrocyclic GBCA even after several close injections and promote the use of a macrocylcic GBCA rather than linear agents for MS patients.

1. Introduction

Gadolinium (Gd)-based contrast agents (GBCAs) use in MRI has become an indispensable tool for the detection of various pathological processes, otherwise undetectable with unenhanced MRI, including inflammation, infection, and malignancy [1]. According to their biochemical structure and charge, they can be classified as linear or macrocyclic, and ionic or non-ionic [2]. GBCAs are administered intravenously in the blood and the extravascular-extracellular space. They do not penetrate the intact BBB. Thus, MRI hyperintensities within the brain correspond to areas with a disrupted BBB [3]. GBCAs have drastically improved the accuracy of Multiple Sclerosis (MS) diagnosis by differentiating between active and non-active lesions [4]. MS is an inflammatory disease of the central nervous system. It is characterized

Abbreviations: DMT, disease modifying treatment; DN, dentate nucleus; GBCAs, gadolinium-based contrast agents; Gd, gadolinium; GP, globus pallidus; MCP, middle cerebellar peduncle; MS, multiple sclerosis; RR, relapsing remitting; SI, signal intensity; SOWM, semioval white matter

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by focal diffuse areas of WM demyelination, inflammation, neurodegeneration, and axonal loss [4]. GBCA administration to patients with MS during an MRI exam, highlights any damage to the BBB, reflective of inflammatory active lesions, and helps the neurologist stage the disease evolution. Their significance in the diagnosis of MS has led to the incorporation of MRI outcomes into the McDonald criteria and their successive revisions [4–6]. Moreover, with the emergence of different and often very potent immunosuppressive medications for MS, the combination of GBCAs and MRI has had a crucial role in the assessment of treatment response, and in monitoring potential safety concerns associated with treatments [7].

Following multiple administrations of GBCAs, several retrospective studies on MS and other diseases, have reported a signal intensity (SI) increase on unenhanced T1-weighted images in certain brain regions such as the dentate nucleus (DN) and the globus pallidus (GP) [8–11]. Kanda et al. [9] was the first to link the observed hyperintensities in the DN, and to a lesser extent in the basal ganglia, to the number of enhanced MRI examinations. Most of the following studies examined patients with normal hepatic and kidney function after repeated injections of linear GBCA, such as gadopentetate dimeglumine and gadodiamide [8–15]. Histopathological studies, as well as animal studies, have provided evidence that the reported increased SI in the DN is caused by a certain form of Gd deposition [16,17]. However, following multiple administrations of macrocyclic GBCAs, recent studies reported no SI increases, even after twenty yearly-consecutive injections, thereby highlighting their stability in the patients' system [18–21]. In this study, we evaluate SI in five relapsing remitting (RR) MS patients followed weekly for two months. Eight weekly GBCA doses were administered during the study with each MRI examination. We hypothesize that repeated weekly administrations of macrocyclic GBCAs such as Gadobutrol do not deposit in the brain regions and do not induce hyperintensities in the DN and the Globus Pallidus (GP) of MS patients.

2. Materials and methods

2.1. Subjects

Five patients with RRMS were included in this longitudinal weekly MRI follow-up study of active plaques. Inclusion criteria specified that patients should be diagnosed as RRMS and present at least one new Gd-enhancing lesion during the six months preceding study enrollment. All patients were untreated with disease modifying drugs (DMT) for at least one year before inclusion, and remained untreated along the study period. At screening time, patients who had contraindications to undergo MRI (pace-maker, cardiac vasculopathy, claustrophobia, allergy to contrast agent, and pregnancy) or renal insufficiency with low creatinine clearance were excluded. The number of Gd injections received before the study onset varied between patients. No records of the exact number of injections nor the brand of the administered contrast agent were found in the patients' files. Despite that, we aimed to study the relative changes over the course of eight injections in a short period of time regardless of the previous accumulations. This study was conducted in 2009, before any reports of Gd accumulation in the brain [9]. It was also approved by the local ethics committee, the French national agency for medicines and health products safety (AFSSAPS) that recommended at this period to follow creation clearance every two weeks. Written informed consent was obtained from all patients prior to study initiation.

2.2. Acquisition

Patients underwent a weekly MRI examination during a two-month period (eight scans). A ninth MRI was performed six months after the beginning of the protocol. MRI acquisitions were performed on a 3T Philips Achieva system (Philips Medical Systems, Best, the Netherlands) with a 16-channel head coil. Images were acquired in the axial plane defined by the anterior and posterior commissures on the same day, at the same time (every Tuesday at noon), for all patients between March and December 2009. Conventional MRI protocol included a sagittal 3D FLAIR sequence (TE/TR/TI: 356/8000/2400 ms; slice thickness: 1.2 mm; acquisition matrix: 228*226; reconstruction matrix of 576*576; field-of-view (FOV): 250 mm; yielding a nominal in-plane pixel size of 0.434*0.434 mm), and an axial enhanced 3D T1 turbo field echo sequence (TR/TE: 6.7/3 ms; slice thickness: 0.9 mm; acquisition matrix: 268*211; reconstruction matrix: 512*512; FOV: 240 mm; yielding a nominal in plane pixel size of 0.469*0.469 mm). A standard dose of 0.1 mmol/kg Gadobutrol was administered during each MRI examination with a delay of 60 s between injection and acquisition of the 3D T1 image.

2.3. Image processing

SI measurement of the DN relative to the middle cerebellar peduncle (MCP), and GP relative to semi-oval WM (SOWM) was performed on enhanced T1 images [9]. A T1 hyperintensity was defined as an irregularly folded ribbon-like hyperintensity on enhanced images. Unenhanced 3D T1 sequences were not available for the recruited MS patients because it was not included in the MRI protocol at the time of the study. Therefore, SI was measured on 3D enhanced T1 sequences whereas it was measured on unenhanced T1 images in other retrospectives studies [8–15]. However, visual checking in the studied regions on the first MRI was performed and showed no visible hyperintensities for all five patients.

3D-Slicer (v.4.6.0) was first used to register the baseline 3D FLAIR image to baseline 3D T1 using an affine linear transformation (with twelve DOF). Due to the lack of DN and GP signal on T1 images, ROI delineation was performed by an experienced radiologist on the registered baseline FLAIR image using the Medical Imaging Interaction Toolkit (MITK) workbench software. DN and GP ROI delineation consisted of highlighting the borders of each studied structure. MCP and SOWM were delineated as an oval ROI (eight slices) in the corresponding WM (Fig. 1). Delineated ROIs were checked for the occurrence of lesions and corrected accordingly by excluding them.

Each patient's T1 images were then registered to the baseline T1 using an affine linear transformation (with twelve DOF). Histogram matching algorithm was then applied on all T1 images by taking each patients baseline MRI as a reference. The defined ROIs (on baseline MRI) were finally applied on the other MRIs in order to extract the T1 SI. The dentate nucleus to middle cerebellar peduncle (DN-MCP) and Globus Pallidus to semi-oval white matter (GP-SOWM) SI ratios were calculated by respectively dividing the mean SI of the DN to the MCP and the mean signal intensity of GP to the SOWM.

2.4. Statistical analysis

Statistical analyses were performed using SAS 9.3 software. A sample size calculation on one group of patients with a repeated measures design was performed. An analysis of variance on repeated measurements was used on each ratio to test for significant differences over time. The total variance for each analysis corresponded to the sum of the intra-individual variance (over time difference observed for the same patient) and the residual variance. A model with intercept and random slopes was better suited for the longitudinal data. Additional analysis was performed to correct the results of any influence of the patient's age and disease duration on the SI ratios. A p-value < 0.05 was considered statistically significant.

3. Results

Five patients with RRMS (four women and one man) underwent an MRI follow-up for a period of two months (eight scans), followed by an additional ninth MRI at month six. Patients were not under any DMTs.