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Title: Urinary gadolinium levels; A possible indicator of long term retention after contrast enhanced MRIs.

Background: Gadolinium chelates (GDCA) have been used as contrast agents for MRI imaging since 1982. It is estimated that more than 1 MRI per second is done in the United States. The toxicity of these contrast agents are well established in patients with renal impairment. However, aside from allergic reactions and one case report of pancreatitis, there is no evidence that gadolinium contrast agents cause toxicity in patients with normal renal function. In 2013 Kanda et al describes T-1 hyperintensities in the dentate nucleus in patients with normal renal function and linking it to gadolinium deposition . Although no morbidity was associated with the depositions, there are people with normal kidney function that claim to have symptoms of "gadolinium toxicity", based on the presence of gadolinium in their urine . Pharmacokinetic studies estimate that up to 100% of GDCA doses given IV are excreted in the urine in the first 72 hours. However, there are no peer-reviewed literature published on urinary gadolinium levels in patients with normal renal function beyond 72 hours. Our study will be the first to examine urinary gadolinium excretion over a longer time scale.

Aims:

1. To estimate the variability of urinary gadolinium excretion beyond 72-hours in patients with normal renal function who received gadolinium containing MRI contrast with a comparison to a control group who did not receive any contrast.
2. An exploratory objective is to evaluate the possibility of an association between the persistent presence of gadolinium in the urine with the presence of symptoms.

Methods: STUDY DESIGN: Prospective study, in a tertiary care facility. Enrollment to start on 01/01/2017

Study Population: All patients over the age of 18, who are receiving an MRI are eligible.

Inclusion criteria:

1. Patients receiving MRIs: Contrast (exposed group) and non-contrast MRIs (controls)
2. Able to provide an informed consent

Exclusion criteria:

1. A history of bipolar disorder, personality disorder, schizoaffective disorder or schizophrenia.
2. A history of fibromyalgia, peripheral neuropathy, strokes, transient ischemic attacks, chronic pain, cerebral palsy, or migraines.
3. A history of dermatitis, rheumatoid arthritis, systemic lupus erythematosus, Raynaud's phenomenon, scleroderma, or dermatomyositis.
4. A creatinine level above 1.5 mg/dl or a glomerular filtration rate (GFR) below 59 within a week of the MRI scan.

5. Previous contrast MRI within in the last year. Controls, will be eliminated if they have a history of ever having a contrast MRI.
6. Patients who live outside the courier service pick up area.

Method for selecting the study population:

- Consent to approach the patients will be done by radiology scheduling technicians.
- After patients consent to be approached, they will be screened for eligibility by the primary investigator:
    - A partial waiver of consent for eligibility screening will be requested to review the patients' chart in compliance with HIPPA if needed.
    - After a patient is deemed eligible, they will sign an informed consent prior to enrollment.
    - Controls will be patients who are not receiving GDCA with the current scan, and the exposed group will be patients receiving GDCA with the current scan.
- We are planning to include a 6:1, exposed to control ratio.

Representativeness of the sample:

Since the samples will be from the population of a tertiary care facility, we do not expect this sample to be representative of the general population. As patients within our facility tend to have more co-morbid diseases and suffer from complex medical illnesses. However, this population is representative of patients who obtain MRIs with GDCA.

Definition of Variables:

- Outcome variables:
    - The primary study outcome is the 24-hour urinary gadolinium levels at 3 days, 10 days, and one month.
    - Our exploratory objective outcome variables are measured using a yes/no questionnaire for the presence or absence of symptoms, the frequency of symptoms, and therapies sought out for treatment of these symptoms.

Potential confounding variables:

A. Concentrated or dilute urine: urine gadolinium is corrected for urine creatinine.
B. Dietary changes, such as calcium, zinc or iron supplementation could potentially change gadolinium excretion: we will ask subjects about supplement use and any changes to their supplement use in the questionnaire.
C. Pre-existing medical conditions causing subjects' symptoms; by excluding patients with bipolar disorder, personality disorders, schizophrenia, fibromyalgia, peripheral neuropathy, chronic pain, migraines, dermatitis, rheumatoid arthritis, systemic lupus erythematosus, Raynaud's phenomenon, scleroderma, and dermatomyositis, we are excluding subjects who may present with symptoms that are similar to previous self-reported symptoms.
D. Variable elimination based on body habitus. Body mass index (BMI) will be calculated at the end for all subjects, and an attempt will be made to determine the contribution of BMI to any noted variance in elimination.

Methodology:
Control groups would be patients who were never exposed to GDCAs and have a negative 24-hr gadolinium level at three days. Controls with a positive gadolinium level (defined as greater than 0.4 micrograms per specimen) will be excluded.
Exposed subjects are patients who will be administered a GDCAs as part of their medical work up on the first day of the study.

Method for data collection:

- After enrollment subjects will be assigned an individual ID number and all information collected on each subject will be linked to the unique ID number.
    - 24-hour urinary gadolinium collection:
- Exposure group will be provided with 3 urine collection containers and instructions both written and verbal on how to collect urine.
    - 24-hour urine collections will be obtained at 3 days, 10 days, and one month.
    - The control group will only need one container for a 24-hour urine collection 3 days after the MRI.
- Subjects will also be supplied with packaging, packaging instructions, and shipping labels.
- After collection is complete, a courier service will pick up samples from subjects' homes.
- 2 x 20 mls of the samples will be frozen in our research lab, and kept until batch is ready to be shipped for testing.
- Samples will be sent to the laboratory in batches.
    - A symptomatology questionnaire will be done for both cases and controls in REDCap.
- Response can be either online or by phone depending on the subject's preference.
- If subjects decide to do respond to the questionnaire online, the link will be a REDCap survey link, with a secure password.
- Response window will be 1 week to improve subject compliance.
- Questionnaire attached.
- Mostly yes/no questions for ease of data extraction.
- Free text to assess additional symptoms not included in questionnaire.
    - Data storage and analysis will be using REDCap.

Statistical Procedures for Analysis and Sample Size Determination:
This study is aimed at estimating the variability in gadolinium excretion at 3 days, 10 days, and 1 month post MRI with contrast and the feasibility of having subjects complete and return 24-hour urine collection at several time points.

The study is a pilot study to gain preliminary data for planning a larger study that could more precisely estimate excretion over time. We plan to recruit and enroll n=24 subjects who have an MRI with contrast assuming 50% will follow up with complete information which will provide enough data to roughly estimate the variability of gadolinium excretion at each time point.

We also wish to compare 3-day excretion for subjects having had contrast to those who did not.

For those subjects who did not have contrast, we anticipate levels below that of detection therefore we would have to compare the two groups using Fisher's exact test for presence/absence of gadolinium recognizing this study will not be powered to detect a difference unless the difference is large (>70% with gadolinium present in cases versus 5% in controls).

We will also assess symptomatology using a questionnaire.
The proportion of patients having each symptom will also be assessed with the exact 95% confidence intervals for those who receive GDCA in their scan. SAS Enterprise Guide 6.1 will be used for all the analysis and the significance level will be set at 5%.

Major Limitations/Questions:

- Urinary gadolinium may not be an accurate representation of body burden.
- Our questionnaire is designed based on the validated my medicines and me questionnaire which is used to detect side effects from psychiatric medications. However, since there is no previous disease entity described in peer reviewed literature, and there is no gold standard to assess subjective symptoms, there is no validated questionnaire for this type of study. Our research was extensive, including research in to quality of life questionnaires and NIH questionnaires. We felt that the my medicines and me questionnaire was the most appropriate for this study.
- Our study may not be powered to detect the presence of symptoms, therefore, this aim is an exploratory aim. If a striking presence of symptoms is detected in this small sample size, it will lead to further studies to explore this disease entity.