Should Intravenous Contrast be Administered in MRI Evaluation of Pediatric Outpatients with Chronic Headache?

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**ABSTRACT:** Background: The practice of administering intravenous contrast to children varies by institution depending on their routine. Objectives: To assess the necessity of routine contrast administration in brain magnetic resonance imaging (MRI) of pediatric outpatients referred for chronic headache workups. Methods: We conducted a retrospective review of consecutive pediatric brain MRI examinations performed during January and February 2014 in 30 pediatric outpatients referred for evaluation of chronic headache. Independent review was performed by two board-certified neuroradiologists. The raters reviewed each MRI first as a non-contrast examination (without seeing the post-contrast images) and then with post-contrast images. Results: No abnormalities were found in six patients. One patient had an indeterminate finding of a tubular cerebellar lesion requiring follow-up. In the remaining patients (n=23), the findings were subclinical and included: mucosal thickening in the paranasal sinuses in 9 patients, cystic changes of the pineal gland in 8 (size 2–9 mm), small developmental venous anomalies in 6, non-specific FLAIR hyperintensities in 4, opacification of the mastoids in 2, and telangiectasia in 1 patient. The subclinical cases that were missed on pre-contrast images were: one small developmental venous anomaly, one telangiectasia and one small pineal cyst, none of which hold clinical significance. All kappa inter-rater and intra-rater agreement scores resulted in values above 0.75, excellent agreement according to Fleiss guidelines. Conclusions: There seems to be little reason to medically justify large-scale use of routine IV contrast administration to evaluate a brain MRI of pediatric patients referred for chronic headache.

**KEY WORDS:** pediatrics, magnetic resonance imaging (MRI), chronic headache, intravenous contrast, gadolinium

Headache is a common complaint, even in early childhood. Chronic headache is defined as headache occurring for 15 days or more a month for at least 3 months and not the result of another condition. The prevalence of headache increases with age, ranging from 37% to 51% for children aged 7 years and gradually increases to 57–82% by age 15 [1]. Most children have primary headaches such as a migraine or tension headaches, typically chronic or recurrent. Serious intracranial pathology is rare and includes brain tumors, meningoitis, venous sinus thrombosis, arterial dissection, subarachnoid hemorrhage, and other disorders that may require prompt management [1]. Brain tumors in children < 15 years of age have an annual incidence approximating only 3 per 100,000 (0.003%) [1]. The need to distinguish primary from secondary headaches presents a major challenge, leading to an increase in referrals for brain magnetic resonance imaging (MRI). The question then arises whether or not to administer intravenous (IV) contrast?

The practice of giving IV contrast to children varies by institution depending on their routine. Recent publications by one group discuss the indiscriminate use of gadolinium in neuroimaging [2,3]. The authors concluded that there is no general need for gadolinium administration in MRI of the brain in children younger than 2 years old, with clinical questions regarding seizures and developmental delay; furthermore, gadolinium-based contrast media administration should be reserved for those with suspected or known brain infection and malignancy [2,3].

The use of IV contrast lengthens the study and increases procedure costs, may cause allergic reactions and, rarely, nephrogenic systemic fibrosis. The aim of our study was to evaluate the necessity of routine IV contrast administration in brain MRI of pediatric outpatients referred for chronic headache workups.

**PATIENTS AND METHODS**

This study received institutional review board approval. We conducted a retrospective review of consecutive pediatric brain MRI examinations performed during January and February 2014 in 30 pediatric outpatients referred for evaluation of chronic headache. Excluded were patients who had a concomitant disorder listed in the referral, for example epilepsy.

An independent review of the brain MRI examinations was performed by two board-certified neuroradiologists. The raters reviewed each MRI first as a non-contrast examination.

*The first two authors contributed equally to this study*
RESULTS

After reviewing the medical files of 70 pediatric outpatients who underwent brain MRIs during January and February 2014, 40 were found not to meet the study criteria. Of the 30 subjects who constitute the basis of the evaluation, there was an almost even distribution of males and females; 14 were male (47%). The mean age at the time of examination was 12.3 years (range 7–17). All the MRI examinations were performed without anesthesia. The MRI studies were performed on 1.5T and 3.0T systems (Siemens Aera and Skyra, Erlangen, Germany) in 12 and 18 patients, respectively. All studies were performed with IV contrast administration and included T1, T2, FLAIR, DWI, and post-contrast T1. Additional SWI sequences were done in Twenty-three patients.

In six patients no abnormalities were found. One patient had an indeterminate finding of a tubular cerebellar lesion, suggestive of a thrombosed venous varix and requiring follow-up [Figure 1]. In the remaining patients the findings were subclinical and included mucosal thickening in the paranasal sinuses in 9 patients, cystic changes of the pineal gland in 8 (size 2–9 mm) [Figure 2], small developmental venous anomalies in 6 [Figure 3], non-specific FLAIR hyperintensities in 4, opacification of the mastoids in 2 patients and telangiectasia in 1 patient. Of the 30 patients examined, there were no cases of headache secondary to space-occupying lesion. Twenty-three patients were found to have incidental and subclinical findings [Table 1]. Twenty cases (87%) of incidental findings were revealed on pre-contrast images. When the interpretation differed between the two raters, the final interpretation was reached by consensus. Kappa statistical analysis was used to assess inter-rater and intra-rater agreement.

Kappa inter-rater and intra-rater agreement analysis was performed for subclinical findings resulting in the following (values listed in parentheses):

- radiologist # 1 pre-contrast vs. radiologist # 2 pre-contrast ($\kappa = 0.75$)
- radiologist # 1 post-contrast vs. radiologist # 2 post-contrast ($\kappa = 0.86$)
- radiologist # 1 pre-contrast vs. radiologist # 1 post-contrast ($\kappa = 0.90$)
- radiologist # 2 pre-contrast vs. radiologist # 2 post-contrast ($\kappa = 0.84$).

In two cases (6%), enlargement of glandular tissue was reported by one observer in both pre- and post-contrast studies and omitted by the other observer.

DISCUSSION

The choice whether or not to inject intravenous contrast in pediatric chronic headache sufferers begins with evaluating the appropriateness of referral. Obviously, administration of IV contrast confers added value in diagnosing intracranial lesions and vascular pathology [1]. However, in the patient population of primary headache sufferers, this hypothetical advantage pales in comparison to the low yield of imaging as a screening tool [1]. While the appropriateness of MRI referral for the aforementioned cohort may be in question, we are dealing with a unique situation where the off-site referring physician has been granted approval for the study by the patient’s health management organization and its advisory board which includes an off-site radiologist. In our retrospective study, many of these exams may be considered inappropriate according to the 2012 American College of Radiology appropriateness criteria [1]; however, in the context of off-site referrals and off-site authorization, some institutions may find themselves reluctantly accepting these types of exams. It is in this context that we suggest, according to the Hippocratic Oath primus nos nocerem (first do no harm), not to inject gadolinium when it is not required or essential to provide added value. The choice of whether to inject contrast is also based on practical measures, such as the availability of a neuroradiologist or fellow to supervise the exam. At some institutions, pediatric examinations are supervised by radiologists who decide during the course of the examination whether administration of gadolinium is appropriate, while other institutions opt for predefined routine protocols including automatic and routine gadolinium administration [4]. Supervising pediatric MRI examinations confers the added value of theoretically omitting the unnecessary IV contrast administration according to the findings in each specific case and thus shortening the length of the studies by omitting the unnecessary sequences from the standard protocols. Moreover, supervision may increase the quality of the examinations, where the supervising radiologist may request to repeat suboptimal sequences immediately and perform additional sequences, if necessary. When the MRI examinations are

<table>
<thead>
<tr>
<th>Radiologic finding</th>
<th>No. of patients</th>
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<tbody>
<tr>
<td>Mucosal thickening of paranasal sinuses</td>
<td>9</td>
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<tr>
<td>Benign cystic changes of pineal gland</td>
<td>8</td>
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<tr>
<td>Small developmental venous anomaly</td>
<td>6</td>
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<tr>
<td>Non-specific foci of white matter signal changes</td>
<td>4</td>
</tr>
<tr>
<td>Opacification of mastoids</td>
<td>2</td>
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<tr>
<td>Telangiectasia</td>
<td>1</td>
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<tr>
<td>Tubular cerebellar lesion</td>
<td>1</td>
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Table 1. Brain MRI radiologic findings
Many institutes rely on routine administration of IV contrast when performing brain MRI in pediatric patients. In this study, clinically significant findings were not missed on pre-contrast images. In view of the discomfort caused by placing the IV catheter, the indiscriminate use of gadolinium adds unnecessary cost and time to the MRI examination. In terms of gantry time, additional post-contrast sequences prolong the examination by approximately one-third [4]. Furthermore, contrast media administration may cause contrast-induced nephropathy, the third leading cause of hospital-acquired acute kidney injury accounting for 10% of all cases [6].

One of the major challenges in pediatric neuroimaging is the acquisition of high-quality diagnostic images. Motion artifacts affect the quality of the examination and, as a result, also the ability to correctly interpret the test. In order to overcome this problem infants are sedated or anesthetized for MRI examinations [7]. Much of the reluctance to perform a non-contrast examination is the inconvenience and potential complications of having to put the child through anesthesia a second time. Therefore, anesthesia cases are often routinely performed with contrast administration, unless they are supervised by a neuroradiologist. As children need to be able to verbally communicate that they are suffering from a chronic headache, they tend to be slightly older (> 7 years). This corresponds with our study where the patients’ ages ranged from 7 to 17. Children over age 7 are scanned, where possible, without sedation [8].

This study has several limitations that should be noted. There was a significant difference in the number of years of clinical neuroradiology experience between the two certified neuroradiologists: 15 years for radiologist # 1 (κ = 0.90 intra-rater) and 4 years for radiologist # 2 (κ = 0.8), which may have affected the slight albeit clinically insignificant difference in kappa values of agreement before and after administration of contrast (κ = 0.75, κ = 0.86, respectively). Of note, according to Fleiss guidelines, a kappa value of ≥ 0.75 is considered excellent interpretation, which was observed on intra- and inter-rater agreements. Our results should be interpreted with caution because of the relatively small sample size of this study, only 30 patients. A larger population should be evaluated to further investigate this issue and to further explore the appropriateness of the ACR criteria in the setting of off-site referral and authorization.

There seems to be little reason to justify large-scale use of routine contrast administration to evaluate brain MRI in pediatric patients referred for chronic headache. For children not requiring anesthesia, one should consider performing the
examination without IV contrast administration, and in specific cases where a significant finding is noted the patient can be called back to complete the exam with IV contrast.

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References
1. American College of Radiology (ACR) Appropriateness Criteria headache – references

Capsule

Neutrophils promote Alzheimer’s disease-like pathology and cognitive decline via LFA-1 integrin

Inflammation is a pathological hallmark of Alzheimer’s disease, and innate immune cells have been shown to contribute to disease pathogenesis. In two transgenic models of Alzheimer’s disease (5xFAD and 3xTg-AD mice), neutrophils extravasated and were present in areas with amyloid-β (Aβ) deposits, where they released neutrophil extracellular traps (NETs) and IL-17. Aβ42 peptide triggered the LFA-1 integrin high-affinity state and rapid neutrophil adhesion to integrin ligands. In vivo, LFA-1 integrin controlled neutrophil extravasation into the CNS and intraparenchymal motility. In transgenic Alzheimer’s disease models, neutrophil depletion or inhibition of neutrophil trafficking via LFA-1 blockade reduced Alzheimer’s disease-like neuropathology and improved memory in mice already showing cognitive dysfunction. Temporary depletion of neutrophils for 1 month at early stages of disease led to sustained improvements in memory. Transgenic Alzheimer’s disease model mice lacking LFA-1 were protected from cognitive decline and had reduced gliosis. In humans with Alzheimer’s disease, neutrophils adhered to and spread inside brain venules and were present in the parenchyma, along with NETs. These results demonstrate that neutrophils contribute to the disease’s pathogenesis and cognitive impairment and suggest that the inhibition of neutrophil trafficking may be beneficial in Alzheimer’s disease.

Eitan Israeli

Capsule

The oral and gut microbiomes are perturbed in rheumatoid arthritis and partly normalized after treatment

Zhang et al. carried out metagenomic shotgun sequencing and a metagenome-wide association study (MGWAS) of fecal, dental and salivary samples from a cohort of individuals with rheumatoid arthritis (RA) and from healthy controls. Concordance was observed between the gut and oral microorganisms, suggesting overlap in the abundance and function of species at different body sites. Dysbiosis was detected in the gut and oral microbiomes of RA patients, but it was partially resolved after RA treatment. Alterations in the gut, dental or saliva microbiome distinguished individuals with RA from healthy controls, were correlated with clinical measures, and could be used to stratify individuals on the basis of their response to therapy. In particular, Haemophilus spp. were depleted in individuals with RA at all three sites and negatively correlated with levels of serum autoantibodies, whereas Lactobacillus salivarius was over-represented in individuals with RA at all three sites and was present in increased amounts in cases of very active RA. Functionally, the redox environment, transport and metabolism of iron, sulfur, zinc and arginine were altered in the microbiota of individuals with RA. Molecular mimicry of human antigens related to RA was also detectable. These results establish specific alterations in the gut and oral microbiomes in individuals with RA and suggest potential ways of using microbiome composition for prognosis and diagnosis.

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