Incidental Findings on Brain Magnetic Resonance Imaging From 1000 Asymptomatic Volunteers

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Unexpected abnormalities are occasionally discovered during brain magnetic resonance imaging (MRI), usually in the setting of an investigation for some other reason. The radiologist and referring physician are then placed in a position of determining relevance of the abnormal finding and considering its impact on the patient. To this end, decisions must be made concerning the seriousness of the finding, including whether it is merely within the realm of normal variation.

Studies have been described that attempt to report on the prevalence of such incidental findings. This includes articles pertaining to discussions of sinusitis, white matter lesions, and even pineal cysts. In each case, data are offered addressing prevalence within certain populations, establishing a foundation on which other MRI studies can be compared. All of these prior reports establish statistical occurrence on MRI examinations that had been performed for other reasons, yet not on healthy subjects.

Several investigational protocols throughout the various institutes that make up the National Institutes of Health (NIH) use brain MRI analysis, and many of these also require a healthy brain MRI database for comparison purposes. Each protocol independently admits both patients and healthy volunteers, and a participant history taking and a physical examination are performed by a physician for both populations. Healthy volunteers are actively recruited and are paid for their participation. Subjects with signs or symptoms are excluded. Such MRI studies are widely used, and the topics of investigation vary from measuring specific anatomic structures to complex-functional MRI scans to whole-brain spectroscopy, all of which share a common denominator in generating an initial diagnostic brain evaluation for a clinical review.

We recognized the wealth of information this situation affords in the evaluation of true incidental findings in a population actively selected for healthiness by both the history taking and physical examination. Thus, we retrospectively analyzed brain MRI results from 1000 volunteers who participated as control subjects for various research protocols at the National Institutes of Health. All participants (age range, 3-83 years; 54.6% male) were determined to be healthy and asymptomatic by physician examination and participant history.

Context Previous reports have discussed incidental disease found on brain magnetic resonance imaging (MRI) scans that had been requested for an unrelated clinical concern or symptom, resulting in a selection bias for disease. However, the prevalence of unexpected abnormalities has not been studied in a healthy population.

Objective To evaluate the prevalence of incidental findings on brain MRI scans obtained for a healthy, asymptomatic population without selection bias.

Design, Setting, and Participants Retrospective analysis of brain MRI scans obtained between May 17, 1996, and July 25, 1997, from 1000 volunteers who participated as control subjects for various research protocols at the National Institutes of Health. All participants (age range, 3-83 years; 54.6% male) were determined to be healthy and asymptomatic by physician examination and participant history.

Main Outcome Measure Prevalence of abnormalities on brain MRI by category of finding (no referral necessary, routine referral, urgent referral [within 1 week of study], and immediate referral [within 1 to several days of study]).

Results Eighty-two percent of the MRI results were normal. Of the 18% demonstrating incidental abnormal findings, 15.1% required no referral; 1.8%, routine referral; 1.1%, urgent referral; and 0%, immediate referral. In subjects grouped for urgent referral, 2 confirmed primary brain tumors (and a possible but unconfirmed third) were found, demonstrating a prevalence of at least 0.2%.

Conclusion Asymptomatic subjects present with a variety of abnormalities, providing valuable information on disease prevalence in a presumed healthy population. A small percentage of these findings require urgent medical attention and/or additional studies.

JAMA. 1999;282:36-39 www.jama.com

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results for 1000 healthy volunteers and attempted to categorize them based on the urgency of any findings. We discovered that asymptomatic healthy subjects present with a variety of abnormalities, and a small percentage of these lesions required urgent medical attention and/or additional studies. We also compared a selected few of these abnormalities with epidemiological data.

METHODS
We retrospectively analyzed brain MRI scans for 1000 healthy volunteers performed within a 14-month period from May 17, 1996, to July 25, 1997. Abnormalities were categorized using the method chosen by Bryan et al.8 for the Cardiovascular Health Study. This method classifies all findings into 4 basic categories: (1) no referral necessary; normal or findings common in asymptomatic subjects (eg, sinusitis); (2) routine referral; findings not requiring immediate or urgent medical evaluation, but should be reported to the referring physician (eg, old infarction); (3) urgent referral required within weeks of study for any abnormality that will need further yet nonurgent evaluation (eg, low-grade astrocytoma); and (4) immediate referral required (eg, acute subdural hematoma).

We evaluated brain MRI studies that were often limited but contained at least T1-weighted and T2-weighted imaging sequences. Proton density sequences were available only occasionally and more advanced sequences were rarely available at the time of interpretation. All studies were performed on General Electric Signa scanners (Milwaukee, Wis). All protocols admitted subjects under an intramural project approved by the institutional review board at the NIH (Bethesda, Md). All studies were interpreted by board-certified radiologists who had a certificate for added qualification in neuroradiology.

RESULTS
Of the 1000 patients included within this retrospective analysis, 546 (54.6%) were male and 454 (45.4%) female, with a mean (median) age of 30.6 (29.0) years (range, 3-83 years). Eighty-two percent of the studies were normal.

Abnormal scans accounted for 18% and were classified as follows: 151 (15.1%) without referral, 18 (1.8%) routine, 11 (1.1%) urgent, and 0 (0%) immediate. Abnormalities within the no referral category included old lacune (n = 132), age-related changes (n = 12), solitary nonspecific T2 hyperintensity (unidentified bright objects [UBOs]) (n = 3), and mastoid/petrous fluid (n = 4), of which simple sinus disease constituted a vast majority. Abnormalities within the routine referral category included old lacune (n = 3), possible demyelinating disease (n = 3), choroid cyst (n = 2), pineal cyst (n = 2), t Bombart cyst (n = 2), empty sella (n = 1), nasopharyngeal cyst (n = 1), hypothalamic lipoma (n = 1), prominent temporal horns (n = 1), remote traumatic change (n = 1), and scalp cystic lesion (n = 1). Urgent categories were arachnoid cyst (n = 3), cavernous angioma (n = 2), benign but recommended additional imaging (n = 2), low-grade oligodendroglioma (n = 1), pilocytic astrocytoma (n = 1), low-grade glioma (unconfirmed) (n = 1), and aneurysm (unconfirmed) (n = 1). There were no findings classified as immediate, which was expected for a healthy volunteer population.

Sinus disease was noted in 13.2% of the participants. Overall, sinusitis was more prevalent in the spring months of February, March, and April and maxillary sinuses were more often affected.

Age-related changes occurred in 12 subjects who were older than 55 years: 40% of the women and 60% of the men experienced microvascular disease (mean [median] age, 73 [73] years); 37% of the women and 63% of the men experienced atrophy (mean [median] age, 74 [73] years); and 0% of the women and 100% of the men experienced old lacunar infarctions (mean [median] age, 68 [73] years).

Of great interest is the finding within the urgent category of 2 confirmed and 1 unconfirmed primary central nervous system (CNS) tumors. One of these lesions was subsequently resected at the NIH, and pathologic analysis confirmed low-grade oligodendroglioma. A second lesion was resected at a local institution and histologically graded a pilocytic astrocytoma. A third lesion demonstrated MRI findings suggestive of a low-grade glioma; however, further evaluation at the NIH was not performed, and follow-up care is not known to us.

COMMENT
As expected, a vast majority of healthy volunteers demonstrated a normal MRI scan appearance. It is important to note the young age of our cohort because this dramatically decreased the chance of revealing pathologic findings such as metastases or those related to age, which are found in a much older age group. In fact, there were only 12 patients available who had age-related changes, and we believe it would be inappropriate to draw conclusions for such a small sample size. The young age of the cohort most likely occurred because experimental MRI studies are relatively demanding. The 2 best examples are functional MRI scans and whole-brain spectroscopy; the former requires dedicated intricate instructions as well as volunteer activity, and the latter can take as long as 90 minutes within the scanner bore. Such activity can be demanding and likely appeals to younger individuals more. Additionally, the older population may not feel the need to participate in medical research and/or may not need the small stipend paid to our volunteers. The ratio of male to female volunteers was nearly even.

The NIH is a tertiary care center with strict criteria for inclusion within either an experimental patient protocol or a healthy volunteer study. Thus, any deviation from these strict confines results in removal of the patient/subject. The referring tertiary care center is notified of the abnormal findings for the patients; for healthy volunteers their primary care provider is informed of the abnormality of concern. Nevertheless, in both instances, patients/subjects do not
return to the NIH and thus are lost to follow-up. As the NIH generates nearly 1000 healthy volunteer studies each year, it is untenable to pursue follow-up at the outside institution.

Our findings of paranasal sinusitis are significantly less than the reported literature, which ranges from 41.6% to 49.2%. We believe that our much lower percentage of 13.2% more accurately reflects the true prevalence of sinusitis in healthy populations because our study cohort was specifically chosen for healthiness, whereas prior studies have interpreted sinusitis as incidental findings within a population already undergoing brain MRI for some other reason. One can easily imagine that sinusitis could account for signs or symptoms that might not initially seem localized to the paranasal sinuses, for example, those masquerading simply as a headache as an indication for brain evaluation. Additionally, the largest of these studies had 325 patients, less than one third the number in our study. Our findings that the maxillary sinuses are more commonly involved agree with results previously described.

Age-related findings have been previously described in a fairly large body of literature. Given the young cohort in our study, only 12 subjects fell within this category of findings. A majority of these 12 patients had been enrolled by the National Institute on Aging and likely had been actively recruited.

A large body of literature also exists concerning UBOs within the white matter, which we refer to as solitary non-specific T2 hyperintensity found in 5 subjects (0.5%). We caution against inferring any conclusions from these data for 2 reasons. First, our young cohort puts us at a disadvantage as the classic UBO is found in individuals older than the mean age of our cohort. Second, the images available for interpretation usually contained T1 and T2-weighted techniques, whereas such solitary T2 abnormalities are usually best found on proton density or fluid-attenuated inversion recovery techniques.

We found 3 younger patients (0.3%) with many nonspecific focal T2 white matter hyperintensities. We classified these as possible demyelinating disease (listing additional differential diagnoses within the report) and all were lost to outside follow-up. Thus, we have no idea how many, if any, of these subjects truly had a demyelinating disorder.

Within the urgent referral category, several lesions of interest need to be discussed. We found 3 patients (0.3%) with arachnoid cysts. Robinson states that arachnoid cysts are relatively uncommon and account for approximately 1% of intracranial masses. Unfortunately, the only literature discussion of population prevalence is limited to findings from fetal/neonatal autopsies that describe a 0.17% prevalence. We believe our findings are within an acceptable range.

Cavernous angioma has been reported to occur at a 0.47% prevalence; however, in that report of 66 patients only 9 patients (0.06%) had true incidental lesions, since all others had been referred for imaging investigation of neurologic signs or symptoms. Thus, the acceptable range of prevalence is likely between 0.06% and 0.47%. Our finding of 0.2% falls within this range.

Intracerebral aneurysm prevalence has been described in the literature ranging from 0.2% to 8.9%, with autopsy-based studies yielding the lower and angiography-based studies yielding the higher rate of prevalence. The mechanism of aneurysm formation is unknown and may be secondary to the constant hemodynamic stress placed on arterial branch points over time. Thus, in our young cohort, our 0.1% rate (1 unconfirmed aneurysm) is within an acceptable range.

Most interesting, and potentially worrisome, is our findings in 3 subjects of suspicious primary brain neoplasm. Indeed, 1 of these subjects was allowed to remain at the NIH, and was admitted within an existing brain tumor protocol, and subsequent resection resulted in histological verification of low-grade oligodendroglioma. Meticulous preoperative physical examination of this volunteer by neurosurgeons failed to uncover any signs or symptoms. A lesion in a second subject was resected at a local institution with histological grading of pilocytic astrocytoma. Finally, a third patient demonstrated findings suspicious for low-grade glioma; however, follow-up evaluation is unknown. At a minimum, we can conclude that our population of healthy volunteers included 2 subjects (0.2%) with an asymptomatic and confirmed primary brain neoplasm. A previous report examining brain MRI scans from 3672 patients demonstrated no primary CNS neoplasms, 1 patient with known CNS lymphoma, and 19 meningiomas. However, all of these individuals were older than 65 years and had been enrolled in a longitudinal, population-based study of cardiovascular and cerebrovascular disease. It is interesting to note that this study showed a 1.7% rate in the urgent category, which is close to our rate of 1.1%.

Davis et al have described primary brain tumor incidences from the states of Connecticut, Massachusetts, Missouri, and Utah derived from data that had been entered into the Central Brain Tumor Registry of the United States. This group of states comprises a population of approximately 16 million subjects with 8070 reported primary tumors, for an overall calculated incidence of 9.4/100 000 person-years (0.0094%). They report estimated completeness of reporting to range from 90% to 99% for the 4 states. However, they also address the problem of underascertainment, which they believe may be as high as 30% to 100%, and note that this problem will “. . . require further work.” These data were maintained by the American Association of Central Cancer Registries.

Preston-Martin has also described the epidemiological characteristics of primary CNS neoplasms from Los Angeles County, California. Her study evaluated reporting and showed an overall calculated incidence of 10.4/100 000 person-years (0.0104%). This correlates well with the study by Davis et al. Additionally, this study broke down incidences within age groups, with an overall incidence of 5/100 000.
person-years (0.005%) for ages 25 to 34 years, the range within which our mean ages both fall. Her study also stated that “. . . there is often a significant underascertainment of cases. . .”16

Our observation of 0.2% for primary neoplasm is difficult to interpret. Given the following definitions: prevalence = N/total at time t, incidence = n at risk / period of observation), our data more closely approximate that of a prevalence and do not strictly adhere to either definition. As described earlier, the reported incidence for primary CNS neoplasm is 20- to 30-fold lower than our findings. We are measuring closer to a disease prevalence, which may help explain the large discrepancy with the reported literature. However, we also feel this is still higher than what should be expected, and that the difference likely cannot be explained by underascertainment alone.

Both articles discussed earlier fail to discuss tumor prevalence in their populations. This raises several questions: Is the rate of primary brain neoplasm actually much higher than that reported in the literature? Do patients feign healthiness, perhaps for a free evaluation of symptoms they have or for money? Are the admitting history taking and physical examinations not rigorous enough? We are unsure of the answer, and it may be a combination. We do warn that the true rate of primary brain neoplasm may be higher than that reported, but heavily caution that our findings are based on a much smaller sample population (1000) subjects compared with the millions evaluated in the aforementioned literature and may merely represent a statistical anomaly. However, as the availability of MRI becomes more uniform throughout all geographic regions, we feel the number of abnormal findings relegated into an urgent referral pattern probably will increase. This will likely also result in a corresponding increase in primary CNS neoplasm diagnosis both at the clinical and histological levels. We also caution that the literature discussions of anatomic lesion incidence or prevalence are fraught with selection bias, because a vast majority of imaging is performed for the evaluation of patient signs or symptoms. Thus, it is not always straightforward whether an identified abnormality is the causal agent or a true incidental finding, making it difficult to infer a true population prevalence. In this article, we present data for 1000 subjects who were actively selected for their healthiness, which should free our findings from such bias.

REFERENCES