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Ethical consideration of incidental findings on adult brain MRI in research

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Abstract

Objective: To characterize the frequency and severity of incidental findings in brain MRIs of young and older adult research volunteers, and to provide an evaluation of the ethical challenges posed by the detection of such findings. *Methods:* The authors reviewed 151 research MRI scans obtained retrospectively from subjects recruited to studies as healthy volunteers. Incidental findings were classified into four categories: no referral, routine, urgent, or immediate referral. *p* Values for significance were computed from χ^2 tests of contingency. *Results:* Of 151 studies, the authors found an overall occurrence of incidental findings having required referral of 6.6%. By age, there were more findings in the older cohort (aged >60 years) than in the younger cohort ($p < 0.05$) and in more men than women in the older cohort ($p < 0.001$). Three of four (75%) findings in the younger cohort were classified in the urgent referral category; 100% of the findings in the older cohort were classified as routine ($p < 0.05$). *Conclusion:* The significant presence but different characteristics of incidental findings in young and older subjects presumed to be neurologically healthy suggest that standards of practice are needed to guide investigators in managing and communicating their discovery.

Recent interest in the occurrence of incidental findings in brain imaging studies of adults and children has invigorated discussion and review of research protocol requirements and ethical obligations of clinicians and investigators.[1-3] For the clinical community, studies of incidental findings provide a useful window on base rates in nonclinical samples for the normal

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asymptomatic population. For nonclinical researchers, these studies establish when clinical input is needed to confirm the neurologic status of participants and for experimental design.

However, the relationship of researchers to their participants is also fundamentally different from that of clinicians and their patients. Although research participants may not expect clinical benefit and acknowledge this through the informed consent process, who should assume the burden of disclosing unexpected findings when they occur, and what that process should be are questions that require thoughtful consideration. The specific circumstances that obligate a researcher to consult with specialists, such as radiologists or—in the case of exposure to liability—even lawyers, have yet to be decided. What are the consequences of a missed abnormality of any significance?

We sought to examine the frequency and clinical significance of incidental findings in brain MRI scans of adults with specific attention to age-related factors, and to examine ethical challenges they raise.

Methods

Source material

Structural MRI research scans from 151 normal adult control subjects at Stanford University and SRI International were pooled for review. The scans were requested from investigators who conduct studies involving research MRI, fMRI, or both, and were accepted without bias to type of study. The time between the original imaging studies and the present study ranged from months to years. MRI scan parameters varied because of the time course over which scans were initially acquired but included one or more of the following standard acquisitions: conventional short repetition time (TR), short echo time (TE) spin-echo (T1-weighted) images, T2-weighted spin-echo or fast spin-echo images using long TR and long TE, proton density-weighted spin-echo or fast spin-echo images using long TR and short TE, and high-resolution T1-weighted three-dimensional spoiled gradient recalled echo (SPGR) images.

We reviewed the scans of 151 subjects (age 18 to 90 years; mean age, 47.1 years), 82 were men (54%; mean age, 49.7 years) and 69 were women (46%; mean age, 44.1 years). The scan pool was divided into two clusters for analysis: younger (aged 18 to 59 years) and older (aged ≥60 years) adults. The mean age of the aged <60 years group was 25.5 years (men, 25.8 years; women, 25.3 years) and of the aged ≥60 years group was 75.5 years (men, 79.2 years; women, 71.8 years).

The Institutional Review Boards (IRBs) at the participating institutions approved all original MRI studies. Exclusion criteria at the time the studies were conducted included implanted metal objects and any other condition for which MRI scanning is contraindicated. Based on clinical histories, subjects were also screened by self-report for any neurologic, developmental, or psychiatric condition that could have jeopardized their status as control subjects. Written consent was obtained at the time of imaging, and participants were informed that the images were obtained for research and not for clinical diagnosis. Examination of explicit differences in the language used to consent participants was not a focus of the present study.

Separate IRB approval was obtained to conduct the study.

Classification of incidental findings

All findings and classifications were derived by consensus of two board-certified neuroradiologists (L.H. or R.G. and S.W.A.). Replicating methods used in previous studies by others and our own,[3-5] findings were classified to have required referral into one of four categories.

1. No referral necessary, common normal findings in asymptomatic subjects (e.g., minimal paranasal sinus disease)
2. Routine referral (e.g., acute sinusitis or nonspecific white matter lesion)
3. Urgent referral required within 1 week (e.g., nonacute intraparenchymal or extra-axial lesion other than small white matter focus)
4. Immediate referral required (e.g., acute process with significant mass effect)

Statistical analysis

All p values were computed from χ^2 tests of contingency.

Results

Of the 151 scans examined, we detected incidental findings in 47% (71/151). Of the total, 6.6% (10/151) were classified to have required clinical follow-up evaluation; of the 71 actual findings, these represent 15% (10/71). Of the 71 findings, 9.8% (n = 7) were classified to have required routine referral, and 4% (3/71) were classified to have required urgent referral. Findings classified to have required routine referral were bilateral mastoid disease, mild chronic small vessel ischemic disease, mild pontine, and supratentorial chronic small vessel disease. Findings classified in the urgent referral category were a cavernous angioma and arterio–venous malformations identified in the posterior right temporal lobe and anterior of the right frontal lobe. None was classified to have required immediate follow-up evaluation.

By gender, findings were identified in only marginally more men (54%; 44/82) than women (39%; 27/69; $p = 0.075$), and those requiring referral did not significantly differ by gender (7.3% men and 5.7% women).

By age, findings were identified in more of the older cohort (64%; 41/64) than the younger cohort (34%; 30/87; $p < 0.001$). In the older cohort, there was a difference between men (81%; 30/37) and women (41%; 11/27; $p < 0.001$). There was no effect of gender in the younger cohort.

Three of the four (75%) findings requiring referral in the younger cohort were classified in the urgent category; by contrast, 100% (6/6) of the findings in the older cohort were classified as routine ($p < 0.05$). The fourth finding in the younger cohort was classified to have required routine referral.

Discussion

In this retrospective study of brain MRIs from adult subjects recruited to research studies as healthy volunteers, we found an age-specific effect for incidental findings. We detected few findings considered to have required referral in the younger cohort, but the majority was of high clinical significance. In the older cohort, we detected findings in >50%, although of those classified to require referral, all were classified as routine. Insufficient numbers precluded a discrete analysis of the data by age and decade; therefore, the coarse separation of the cohort into younger and older groups is a limitation of this study. The significant gender difference in the older cohort may be consistent with greater incidence of vascular disease in men than in women but merits specific examination in future research. Nonetheless, the double dissociation between age and severity underscores the imperative to consider the significance of unexpected brain anomalies in healthy control subjects and the means to manage them. This is especially the case as a large majority of adult brain imaging research studies involve either college students easily accessible in the academic environment for studies of normal cognition or older adults in studies of normal aging and those who serve as controls for studies of age-related

diseases. To our knowledge, most findings identified in the present study were not detected or reported to participants at the time that the original imaging studies were conducted.

Informed consent is essential to respect the autonomy of parties participating in any form of medical research, as is understanding of each person's underlying motivation to participate. However, the issue of autonomy becomes complicated when pathology is uncovered in someone who has not asked to be screened for his or her own immediate benefit or when a discovery has downstream impact on another party. Such issues take on even greater importance as the number of studies and procedures further accelerate and as CNS anomalies that are not only of structural but also of functional significance are discovered.

In light of these issues, we propose that informed consent and protocols generated on an institution-by-institution basis are not adequately responsive to the problems of incidental findings, at least for the CNS. With recent attention paid to incidental findings on brain MRI, the no-clinical benefit clause has been updated in consent forms at our own institution (Stanford University) to include a request for primary physician contact information and a statement that any follow-up treatment decision lies solely with the subject and physician. However, some investigators may consider that even this augmented text is insufficient because the risk of anxiety associated with the discovery of an abnormality, financial costs of additional diagnostic testing, and the potential for related medical complications are not addressed.

Beyond explicit recommendations for consent, guidelines also should be considered for other protocol issues. For example, we must balance the benefit of involving medical personnel trained to read scans and interact with participants against the legal risk and financial burden of clinician assessment of all participant MRIs and the workload challenges associated with sheer volume. Further, careful consideration must be given to standards for the lag time between image acquisition and reading given the differing types and severity of abnormalities, and to professional level and training appropriate to primary operation of medical equipment such as MRI scanners so that participant safety and confidentiality are ensured (Illes et al, submitted for publication, 2004).[6] To achieve this goal and an appropriate evenness in the way that guidelines are ultimately adopted by laboratories, journals, and research sponsors, discussion and debate are needed among investigators, physicians, and even participant representatives themselves who can bring valuable information about their expectations to the discussion. These measures will ensure the protection of participants, provide safeguards for clinicians and investigators, and enhance the overall integrity of the research.

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