



ETHICAL RESEARCH INVOLVING CHILDREN

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HARMS AND BENEFITS

Incidental brain findings in neuroimaging research

Background context:

Incidental brain findings (IBFs) are brain abnormalities with no outward symptoms that are detected in healthy children and adults during their participation in research studies which apply neuroimaging techniques such as structural (MRI) and functional (fMRI) magnetic resonance imaging, magnetoencephalography (MEG), electroencephalography (EEG-ERP), and near-infrared spectroscopy (NIRS). IBFs could have clinical significance because of their potential to cause future symptoms or influence eventual treatments. However, the scientific community does not yet have an accurate estimate of their incidence since no systematic reporting exists, and there is no consensus that disclosure of findings that are minor or normal is in the interest of research participants. Furthermore, at present there is a significant procedural variability in research units regarding engaging and protecting participants, and detecting and communicating abnormal findings to them. When IBFs occur in children and adolescents, multiple ethical concerns are raised.

The ethical challenge:

The presence of any significant clinical findings in a non-clinical setting is a matter of bioethical and medical concern. A major challenge is whether to treat research participants with IBFs and how to do it. Consequently, the detection, significance, and the management of the IBFs are keys to the welfare of the research participants as well as to the integrity of the studies. However, the evidence is insufficient on what to do because of the lack of appropriate controlled studies of treatments and the availability of neuroimaging studies – mainly MRI and fMRI – for only two or three decades, which means that there are no data on long-term prognosis. Based on studies from the last decade, IBFs incidence varied between 7% and 36% and can be classified as neoplastic (e.g., benign and malignant tumors) or non-neoplastic (e.g., cysts, structural vascular abnormalities, agenesis of the corpus callosum, inflammatory lesions, hydrocephalus, malformations, white matter hyperintensities, silent brain infarcts, brain microbleeds, early multiple sclerosis). Once IBFs are discovered, researchers have to decide what to do. From the researcher's perspective, the awareness of the presence of an abnormality might lead to interventions aimed at modifying risk factors. In this sense, a primary need is to establish procedures for handling IBFs. For example, possible actions may include providing no referral, neurologic routine referral, urgent referral, immediate referral and/or later follow-ups. However, the urgency of referral is difficult to consider without available evidence on whether and how to treat asymptomatic incidental findings. The absence or lack of appropriate procedures increases the likelihood of a potential imprudence if waiting for a catastrophic event or even for legal actions. From the participant perspective, the

detection of incidental findings can provoke anxiety about a possible abnormality – which in turn might be a false positive reading, a cascade of costs for further studies and eventual complications, and worries about the consequences of no treatments. Thus, a second need is to decide how to communicate the findings to participants especially when they are children or adolescents, and to consider the limits of participant confidentiality, for example in regard to parents and primary care physicians.

Examples and choices made:

In a recent study, Kumra and colleagues (2006) found IBFs in 8 out of 6 (13.3%) healthy children and adolescents who participated in MRI research at their center. All of the identified cases were communicated to the child or adolescent, their parents, and the primary care physician. In three cases, a clinical neuroradiologist suggested referrals: (a) in the first case (i.e., hyperintensity within the left cerebellar hemisphere), a MRI with a contrast agent was recommended. After a follow-up analysis the neuroradiologist and the neurologist thought that the finding was nonspecific; (b) in the second case (i.e., an increased signal in the right parietal white matter), the neuroradiologist considered that the finding could be nonspecific or secondary to migraine headaches, Lyme disease, a reaction to an inflammatory or infectious process, and/or demyelination. After a two-year follow-up study the same unchanged finding was found, which allowed the abnormality to be viewed as not clinically significant; (c) in the third case (i.e., prominent flow voids in the pineal gland potentially associated with a vascular malformation), the participant was re-evaluated with an alternative neuroimage protocol and no signal or anatomic abnormality was reported. The previously described finding was thought to be a technical artifact. In the remaining five cases, the findings did not require additional referrals after interventions of a neuroradiologist and pediatric neurologist, who considered them as normal variants of anatomical events.

Reflexive questions/considerations:

Guidance on ethical issues regarding the participation of healthy children as volunteers in brain imaging research is just emerging. Several researchers in the field of neuroethics have raised questions that deepen the approach to the IBFs during brain research. The following summarizes some of the key points that are necessary to consider:

- Volunteers (children and parents) for research studies that use brain imaging technologies should be provided with accurate information on the chance and consequences of discovering IBFs, as part of the informed of how findings will be handled, and the limitations of each neuroimaging technique. Parents and participants should be asked their disclosure preferences, and given the choice to not be told about the IBFs with the exception of urgent and immediate referrals (follow-up).
- Researchers need to consider the potential IBF findings when designing studies and creating research teams (i.e., building capacity for graduate students and postdoctoral researchers, and access to pediatric neuroradiology and neurology consultation for researchers and participants to eventual referrals and follow-up interventions).

- Research centers and Ethics Committees should collaborate to build ethical approaches for adequate handling and communicating incidental brain findings to participants. Part of this effort should consider archiving IBFs, and the adoption of guidelines for handling variation in neural activation. □

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