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CLINICAL REPORT

Incidental Head and Neck Findings on MRI in Young Healthy Volunteers: Prevalence and Clinical Implications

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SUMMARY: We determined the prevalence and clinical relevance of incidental brain and head and neck findings in young healthy volunteers with MR imaging. We retrospectively analyzed the MR images obtained from 203 healthy young adult volunteers (mean age, 21.9 years; range, 18–35 years). The prevalence of the categories of findings (no referral necessary, routine referral, urgent referral, and immediate referral) was scored by a head and neck radiologist or neuroradiologist. We found a high prevalence of incidental brain and head and neck abnormalities (9.4% and 36.7%, respectively); 4.4% of the brain findings and 5.5% of the head and neck findings were classified as in need of referral. Only 1 incidental finding classified as in need of referral (a skull lesion consistent with fibrous dysplasia) was actually referred at the time of the study (5.2%). These findings suggest that a high prevalence of incidental findings is common in healthy young volunteers, though the clinical implications are negligible.

ABBREVIATION: NeXT = Netherlands XTC Toxicity

For years the number of neuroimaging studies has shown a dramatic increase. A large proportion of this rise is due to the use of new imaging techniques such as fMRI to study human cognition and behavior, often involving healthy young volunteers.[1] In combination with the ability to better detect subtle brain lesions due to higher field strengths and more sensitive MR imaging sequences, these healthy young volunteers may increasingly be confronted with incidental brain findings. Incidental findings have been defined as observations of potential clinical significance unexpectedly discovered in healthy subjects or in patients recruited to brain imaging research studies and unrelated to the purpose or variables of the study.[2]

However, there is a great lack of knowledge regarding the implications and ethics of how these findings should be handled. Issues focus on whether incidental findings in research should be disclosed to subjects at all, and if so, what are the obligations of researchers to communicate these and when and to whom? The discussion is made especially complex by the absence of knowledge on the clinical relevance of the unexpected findings and the lack of professional guidelines. Moreover, imaging studies are often performed by undergraduate and graduate students, fellows, and MD and PhD investigators, and many studies lack a physician competent to read scans (ie, a neuroradiologist). Only 36% of investigators who conduct MR imaging studies report that all their research scans are read by a neuroradiologist.[3] One of the greatest sources of discussion of the recently established Working Group on Incidental Findings in Brain Imaging Research is whether a neuroradiologist should review all research imaging studies.[2] The sensitivity for detection of brain abnormalities is probably much higher when the scans are read by a neuroradiologist.[3]

There have been a few reports on the prevalence of clinically relevant unexpected asymptomatic findings in healthy volunteers participating in research. These involved either elderly subjects (older than 45 years age),[4,5] a heterogeneous age group,[6,7] or very young subjects (younger than 18 years of age).[8] In these studies, the reported prevalence of clinically relevant incidental findings ranged from 1.7% to 10.2% (without white matter lesions). So far, only 1 study was conducted in young healthy volunteers (17–35 years of age), reporting a prevalence of clinically relevant incidental findings of 5.8%.[9] This is striking because it has been shown that characteristics of incidental findings in healthy young adults differ from those in healthy elderly subjects.[10] Another point of concern is that in most of the above-cited studies, including the study in young healthy volunteers,[9] the MR imaging scans were not reviewed by a neuroradiologist.

Here we report, for the first time to our knowledge, on the prevalence of incidental brain and head and neck findings in a group of 203 healthy young adult volunteers by using high-resolution state-of-the-art brain MR imaging. All variations and abnormalities were categorized by an experienced head and neck radiologist/neuroradiologist. This study will provide important data on the prevalence of incidental brain findings in an age group most frequently exposed to brain MR imaging and will shed new light on the clinical implications and potential benefits of these incidental findings.

Case Series

Source Population

Subjects of this study were 203 control participants in studies on the effects of the popular recreational drug ecstasy (3, 4 methylenedioxymethamphetamine), such as the Netherlands XTC Toxicity (NeXT) study at the Academic Medical Center in Amsterdam between April 2002 and July 2009. The objectives and methods of the NeXT study

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are described in detail elsewhere.[11] Subjects were between 18 and 35 years of age.

The institutional review board at the Academic Medical Center in Amsterdam approved the studies, and all participants gave written informed consent. Exclusion criteria were implanted metal objects and any other condition for which MR imaging scanning is contraindicated. Subjects were clinically screened for any neurologic, developmental, or psychiatric condition that could have jeopardized their status as control subjects.

MR Imaging Parameters

Images were acquired by using a 1.5T scanner with a standard quadrature head coil (Signa Horizon; GE Healthcare, Milwaukee, Wisconsin) and in 7 subjects by using 3T with a phased-array sensitivity encoding 6-channel receiver head coil (Intera; Philips Healthcare, Best, the Netherlands). The MR imaging protocol included 3D high-resolution sequences, an axial and coronal proton-attenuation-weighted sequence, and a T2-weighted sequence, followed by a 3D T1-weighted postcontrast sequence (gadobutrol; Gadovist; Schering, Berlin, Germany). The section thickness was 1.5 mm for the proton-attenuation-weighted and T2-weighted sequences and 1.4 mm for the postcontrast series. All sections were contiguous. The 7 subjects scanned at 3T only underwent a 3D T1-weighted sequence with a section thickness of 1.0 mm.

Assessment of Incidental Findings

All scans were read for incidental findings within 3 days of scanning by an experienced head and neck radiologist or neuroradiologist with $>$12 years of experience (C.B.L.M.M. and N.F., respectively). The readings were performed on a digital PACS. The reviewer was unaware of any clinical information on the subjects. MR imaging findings were retrospectively divided into 3 classes: 1) normal; 2) variations of the norm; and 3) abnormal as described previously.[9] Examples of variations of the norm include conditions like cavum septum pellucidum, mega cisterna magna, widened subarachnoid spaces, and sinus hypoplasia. Abnormal findings on scans were defined as incidental findings of potential clinical relevance. Examples included arachnoid and sinonasal retention cysts, Chiari I malformations, aneurysms, and brain and head and neck tumors, as described previously.[9] Abnormal findings on scans were further categorized with a method previously used and described by others[6,8,10,12,13]: 1) no referral necessary, findings common in asymptomatic subjects (eg, occasional white matter lesions); 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 nonemergent evaluation (eg, arachnoid cyst); and 4) immediate referral required (eg, acute subdural hematoma). None of the incidental findings were histologically or surgically confirmed.

Statistical Analysis

We calculated the prevalence of each incidental brain finding in the study population. Multiple similar findings within 1 participant (eg, $>$1 white matter hyperintensity) were counted as a single finding. Because there was $>$1 incidental finding in several participants, we introduced a hierarchical structure in the data. The 3 main categories (1 = strictly normal findings on brain scans, 2 = abnormal brain scan findings, 3 = variants of the norm) were structured as follows: category 1 is the highest in hierarchy and therefore excludes findings in category 2 or 3. Category 2 is higher than 3 but does not exclude findings in category 3. Prevalences were compared with those in the literature, particularly the study by Weber and Knopf[9] containing a detailed description of the prevalence of incidental brain findings in a very similar age group ($n = 2536$; 17–35 years of age).

Results

Brain

Of the 203 participants included in this study, 92 (45.3%) were men and 111 (54.7%) were women, with a mean age of 21.9 ± 3. 2 years (range, 18–35 years). Sixty-three percent of the subjects had normal findings on the brain scan; 30.5% had variations of the norm. Abnormal scan findings accounted for 9.4% and were classified as follows: 10 (5.0%) without referral, 8 (3.9%) routine, 1 (0.5%) urgent, and 0 (0%) immediate referral. Of the 19 subjects with abnormal findings, 9 (47.4%) should have been referred to a physician. The prevalence of clinically relevant incidental findings that needed referral was thus 4.4% (9/203). Of these, only 1 (11.1%) was classified as urgent.

The 3 most common intracranial variations of the norm were the following: a pineal gland cyst (6.1%), widened bifrontal subarachnoid space (6.1%), and Rathke cleft cyst (3.9%). The most common abnormal findings were occasional/not important white matter lesions (4.4%) and Chiari I malformations (1.0%). All abnormal findings were clinically silent.

Findings classified to require routine referral were heterotopic gray matter, Chiari I malformation, and lacunar infarction. Only 1 finding was classified as medically urgent: a skull lesion, probably eosinophilic granuloma or fibrous dysplasia. There were no findings classified as immediate referral, which was expected for a healthy volunteer population. No cases of cerebral aneurysm were found, though no dedicated neurovascular MR images were obtained.

Although 9 subjects were retrospectively classified as in need of routine or urgent referral, at the time of the study, only 1 participant (classified as urgent referral with an osseous skull lesion) was in fact referred to a neurosurgeon. Additional diagnostic evaluations, a CT scan and a follow-up MR imaging scan 1 year later, were conducted. It was concluded that the osseous lesion was a case of fibrous dysplasia, a skeletal developmental anomaly requiring no further follow-up.

Head and Neck

In 180 participants included in this study, we were able to evaluate the upper head and neck region. Sixty-six percent of the subjects had a normal upper head and neck region (119/180); only 3.3% were considered variations of the norm (6/180). Abnormal findings on scans accounted for 36.7% (55/180) and were classified as follows: 45 (25.0%) without referral, 9 (5.0%) routine, 1 (0.5%) urgent, and 0 (0%) immediate referral. The prevalence of clinically relevant incidental findings in the head and neck region that needed a referral was thus 5.6% (10/180). Of these, 1 (10.0%) was classified as urgent.

The most common head and neck variation of the norm was a hyoplastic frontal or maxillary sinus. The most common abnormal findings were the following: a sinonasal retention cyst or polyp (10%), isolated mucosal swelling (6.1%), and pharyngeal or parotid lymphadenopathy (5.0%). Abnormal findings in need of routine referral were the following: cystic lesion in the parotid gland (1.1%), bilateral osteomeatal pathology (1.1%), sialolithiasis, isolated mucosal swelling, orbital vascular malformation, and orbital wall fracture with herniation of orbital fat (all 0.5%). Only 1 finding was classified as medically urgent: extensive bilateral cervical lymphadenopathy. There were no findings classified as immediate referral. Although 10 subjects (5.5%) were retrospectively classified as in need of routine or urgent referral for an abnormal finding in the upper head and neck region, at the time of the study, no participant was referred.

Discussion

We found a high prevalence of incidental brain and head and neck abnormalities (9.4% and 36.7%, respectively) in a population of healthy young adult volunteers (18–35 years of age) when scans were retrospectively read by an experienced head and neck radiologist or neuroradiologist; 4.4% of the brain findings and 5.5% of the head and neck findings were classified as in need of referral (clinically relevant), including 2 findings classified as urgent referral. Of the 19 findings categorized as in need of referral, only 1 (skull lesion consistent with fibrous dysplasia) was actually referred at the time of the study (5.2%).

Our finding of an incidence of 36.7% of MR imaging scans with any incidental finding is quite similar to that recently reported,[14] in which an incidental finding of any kind was found in 42.9% of the brain examinations. However, our prevalence rate of potentially clinically relevant incidental brain abnormalities is higher than that reported previously in a similar age group of healthy volunteers[9]: 5.8% versus 9.4% in this study. The most likely explanation is that in the present study, all scans were read by an experienced neuroradiologist, whereas this was not the case in the study by Weber and Knopf.[9] Both studies used high-resolution contrast-enhanced T1-weighted sequences; therefore, technique-related issues are not a plausible explanation for the observed difference.

In a postmortem study including 4069 consecutive cases, a prevalence of 2.5% of developmental venous anomaly (the most frequent cerebral vascular malformation) was reported. In the present study, we report a prevalence rate of 2.0%, whereas Weber and Knopf[9] reported a prevalence rate of only 0.12%, suggesting that brain abnormalities were underscored in the study by Weber and Knopf. A recent meta-analysis on incidental findings revealed an overall prevalence rate of incidental brain findings on brain MR imaging scans of 2.7%.[15] However, most of the studies included in the meta-analysis did not use high-resolution MR imaging sequences (eg, section thickness of $<$3 mm), a factor that does affect the detection rate, as pointed out in the meta-analysis. In addition, the use of low-field MR imaging scanners (1T) and interpretation by unspecified observers (nonradiologists) make it difficult to compare the 2 datasets and likely explain the discrepancy between this study and the meta-analysis.

There are 2 other studies that included young adult subjects and reported on the incidence of brain abnormalities in which scans were read by a neuroradiologist. However, these included very heterogeneous age groups: in subjects 18–90 years of age, which included a "younger" cohort,[10] and in subjects 9–50 years of age.[7] In the first study,[10] 6.6% needed referral, and in the latter, 10.2%. Similar to our study, the latter study involved high-resolution images, which were, however, obtained at 3T. Their prevalence rate was higher than the 4.4% reported in the current study. Thus, incidental brain abnormalities on MR imaging scans are also common in healthy young adult volunteers when the scans are read by a neuroradiologist, by using high-resolution MR imaging sequences and a homogeneous age group.

To our knowledge, no previous studies looked into incidental head and neck findings. The high occurrence of abnormal findings (36.7%) in the upper head and neck region is mainly explained by simple sinus disease. Excluding simple sinus disease from our analyses would reduce the incidence to 14.4%. The incidence of clinically relevant head and neck findings was similar to clinically relevant brain findings (5.4% versus 4.4%), though none were referred at the time of study.

The most frequent incidental findings classified as routine referral were important white matter lesion and a retention cyst or sinonasal polyp. Although extensive white matter changes have been shown to be associated with increased risks of stroke and cognitive decline, none of our subjects met these criteria (Fazekas 2 or higher). A retention cyst or polyp in the maxillary sinuses is never an indication for surgical treatment. Bilateral cervical lymphadenopathy, however, should be evaluated to differentiate between serious disease (eg, malignant lymphoma, inflammatory or granulomatous disease) and reactive changes.

Other incidental routine referral findings that we found are sporadically associated with complications or may be an explanation for a "subsymptomatic" state of the participant (eg, cognitive impairment due to gray matter heterotopia). The clinical relevance of incidental findings classified as urgent referral is expected to be much more evident because these require an urgent referral within weeks of the study for any abnormality that will need further yet nonemergent evaluation (hence the name).

However, at the time of the study, only 1 of the 19 relevant findings that were later categorized as in need of referral (5.2%) was actually referred, suggesting that the clinical predictive value of an abnormal research MR imaging scan is quite low. This is in line with a previous study in which only 2.2% of the incidental brain findings on MR imaging received further action.[14] This probably relates to the fact that abnormal findings on scans were classified on their potential clinical relevance and that the currently used (and previously frequently used) classification system does not take into account the risks and benefits associated with incidental brain findings.[13]

When applying a recently suggested classification system that takes the potential benefit in disclosing an incidental brain finding to the research participant into account,[13] the results are more in accordance with our observations: Nearly all abnormal findings on scans (94.7%) would be classified as of unlikely benefit to the participant (no serious health condition, only a burden for the participant in receiving this information). Only 2 findings in 203 subjects ($<$1%) would be considered of possible benefit to the participant (a serious condition that cannot be treated but is likely to be important to the participant), namely the findings classified as urgent referral: an osseous skull lesion and extensive bilateral lymphadenopathy. Findings of possible benefit may be disclosed to research participants, unless they elect not to know; findings that are unlikely to be of benefit should not be disclosed to the research participant, as suggested by Wolf et al.[13]

A major strength of our study is that all scans were read by an experienced head and neck radiologist or neuroradiologist (along with the high technical quality of the MR images), leading to a high number of detected abnormalities. As pointed out by Illes et al,[3] the time has come when we must balance the benefit of involving medical personnel trained to read (brain) scans and interact with participants against the legal risk and financial burden of clinical assessment of all MR imaging scans of the participants and the workload that comes with it. Although the findings of the present study suggest that there is a need for specialized medical personnel to review all MR images (a high prevalence of potential clinically relevant incidental findings and a higher number of detected abnormalities than reported in the literature), there is no benefit from a clinical point of view, or from a participant's point of view, in having all brain MR imaging scans evaluated by specialized medical personnel. This is in line with recommendations made by Wolf et al,[13] pointing out that researchers have no duty to search for incidental findings because the goal of research is to seek generalizable knowledge, not to provide health information to individuals. In line with this recommendation, Orme et al[14] recently demonstrated not only that incidental findings are common in MR imaging of the head but that most incidental (brain) findings are of "unclear significance." On the other hand, in several opinion pieces,[16-18] it was stated that research centers should have trained imagers to provide appropriate follow-up imaging or care to research participants and that a protocol for reporting and initiating treatment should be mandated in all neuroimaging research.

Conclusions

We demonstrate that incidental head and neck and brain abnormalities on MR images are common in healthy young adult volunteers. Although the sensitivity for detection of abnormalities is much higher when the scans are read by an experienced radiologist, the clinical implications and benefits to the research participant are very small/negligible. Our observations should advance the discussion on the implications and ethics of how incidental brain findings should be handled.

Disclosures: Jan Booij—*UNRELATED*: *Consultancy:* GE Healthcare, *Comments*: This consultancy work relates to the use of radiotracers (SPECT/PET) and did not influence the submitted work. Gerard den Heeten—*UNRELATED*: *Consultancy*: Philips ICT Research, Eindhoven, Germany, *Comments*: not related to imaging, *Patents (planned, pending, or issued)*: in mammography. Wim van den Brink—*RELATED*: the Netherlands Organisation for Health Research and Development (ZonMW),* *Comments*: ZonMW is similar to the National Institute of Mental Health in the United States. * Money paid to the institution.

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