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Incidental Findings on Brain Magnetic Resonance Imaging of Children with Sickle Cell Disease

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Abstract

Objective—Incidental findings identified by MRI of the brain have been reported in up to18% of healthy adults, with clinically significant neuropathology in 0.5-2%. There are two smaller series of incidental findings on MRI of the brain in children. We describe the prevalence and range of incidental intracranial abnormalities identified by MRI of the brain in a large group of children screened for a clinical trial.

Methods—We included 953 children between 5 and 14 years of age screened with MRI of the brain for the Silent Infarct Transfusion Trial. All have sickle cell anemia or sickle β-null thalassemia. MRIs were interpreted by 3 neuroradiologists. MRIs reported to have any

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For the SIT Trial Investigators (see appendix for full list).

abnormality were re-reviewed by 2 study neuroradiologists. Incidental findings were classified into 4 categories: no referral, routine, urgent, and immediate referral recommended. Cerebral infarcts and vascular lesions were not considered incidental and were excluded.

Results—We identified 63 children (6.6%, 95% CI: 5.1 to 8.4%) with 68 incidental intracranial MRI findings. Findings were classified as urgent in 6 children (0.6%), routine in 25 children (2.6%), and no referral required in 32 children (3.4%). No children required immediate referral. Two children with urgent findings underwent surgery in the next 6 months.

Conclusions—In this large cohort of children, incidental intracranial findings were identified in 6.6%, with potentially serious or urgent findings in 0.6%. These data should assist pediatricians and researchers in planning for and counseling families when unexpected, incidental findings are encountered on MRI of the brain.

Keywords

Incidental Findings; MRI-Magnetic resonance imaging; Brain imaging; Children; Sickle Cell Disease

Introduction

Incidental findings identified by MRI of the brain have been reported in up to 18% of healthy adults[1] with clinically significant neuropathology identified in 0.5-2% of healthy adult volunteers.[1, 2] Population-based studies of older adults have found “urgent” incidental findings on MRI of the brain, primarily aneurysms and benign or low-grade tumors, in 1.7%[3] and 3.4%.[4] A recently published meta-analysis of incidental findings in 16 primarily adult research studies found an overall prevalence of 2.7% for all incidental findings on brain MRI and 4.3% prevalence using high resolution MRI sequences.[5]

The largest series of incidental MRI of the brain findings in pediatric patients included 225 healthy children recruited for multiple neuroimaging studies at a large academic center.[6] Incidental abnormalities were found in 21%, for a total of 47 children. Within this group, acute or chronic sinusitis represented 57% (27 of 47) of the incidental findings. Excluding extracranial findings such as sinusitis, 20 (8.9%) of these healthy children had incidental intracranial abnormalities. Just one child (0.4%) had a lesion deemed potentially serious enough to warrant urgent referral for evaluation. These adult and pediatric studies used a standardized method of classifying the significance of incidental MRI findings. A second pediatric study reported incidental MRI findings in a series of 60 children, but did not use a standardized method to classify incidental findings.[7] The authors reported that 8 (13%) children had incidental findings and only 3 findings (5%) were thought to require “further evaluation.” These findings were a 3-mm focus of increased fluid-attenuated inversion recovery (FLAIR) signal in the parietal white matter, a subcentimeter focus of T2 and FLAIR hyperintensity in the left cerebellar hemisphere, and prominent flow voids in the pineal region suggesting a possible vascular malformation. With detailed follow-up imaging, the first lesion was an artifact, the second remained unchanged over 2 years; in the third participant, cerebral blood vessels were felt to be normal with no vascular malformation present.

In the current study, 953 children with hemoglobin (Hb) SS or sickle β-null thalassemia had an MRI of the brain to screen them for inclusion in the Silent Infarct Transfusion (SIT) Trial. Children with an infarct seen on screening MRI who chose to continue participating in the study were examined by a study neurologist blinded to their MRI findings to confirm that the infarct was clinically silent. The prevalence of incidental MRI findings in sickle cell disease (SCD) is unknown and data regarding incidental findings in all children is limited.

Information from this study will assist neurologists and hematologists in the interpretation of incidental MRI findings in children with SCD and may be applicable to children in general.

We sought to describe the prevalence and range of incidental intracranial abnormalities on MRI of the brain in children with SCD and to classify their significance based on a previously published method.[8]

Patients and Methods

The SIT Trial is a multi-center randomized clinical trial; details of the study design and methods have been reported.[9,10] See also: www.clinicaltrials.gov identifier NCT00072761. In brief, the major hypothesis is that prophylactic blood transfusion therapy in children with SCD with silent cerebral infarcts will result in at least an 86% reduction in the rate of subsequent overt strokes or new or enlarging cerebral infarcts as defined by MRI of the brain. The presence of a silent cerebral infarct-like lesion can only be established with a MRI of the brain; therefore 953 consecutive children, ages 5 to 14 years, have been screened with MRI (without sedation) to date. Children with a history or a finding on neurological exam by a pediatric hematologist concerning for overt stroke were ineligible. Of note, findings related to the primary aims of this study (ischemic stroke or vascular disease) were excluded from this analysis as they will be reported separately.

MRI Protocol

Details of the SIT trial MRI Protocol are available in an on-line supplement and in a paper in press.[9] Briefly, the imaging protocol consists of sagittal T1, axial T2, axial and coronal T2 FLAIR images, and axial diffusion-weighted images. The vast majority of images were obtained on 1.5 Tesla scanners with a few centers switching to 3.0 Tesla scanners in 2008. Forty-six of the 953 MRIs were completed on a 3.0 Tesla scanner; none of these 46 children had an incidental MRI finding. No intravenous gadolinium-based contrast material was administered.

The SIT Trial protocol for handling incidental MRI findings is as follows: All MRI studies are read within 24 hours of being uploaded into the study website to allow detection of any urgent or emergent medical condition that will require follow up at the local site. This initial reading is performed by one assigned study neuroradiologist. This rapid review has been incorporated into the study protocol in order to accommodate several study sites that are using a research MRI facility, without a local clinical interpretation. If an immediate or urgent referral is necessary, the neuroradiologist e-mails and telephones either the study principal investigator, or the chair of the neurology committee. One of these physicians will call and e-mail the local site investigator with the critical medical information. This chain of communication is to keep the neuroradiologists ‘blinded’ to any other clinical conditions that may be discussed during the exchange of pertinent clinical information. Disclosure of other non-urgent incidental findings is made to the site study coordinator and site principal investigator who relay the information to the study participant and their family.

Grading of MRI abnormalities

We used methods designed for the Cardiovascular Health Study,[8] that were utilized in two published studies of incidental MRI findings in adults and children.[6,11]

Four categories were established:

(1) no referral necessary; findings common in asymptomatic subjects (e.g. cavum septum pellucidum)

(2) routine referral; findings not requiring immediate medical attention (Chiari I malformation without tonsillar crowding or spinal cord abnormality)

(3) urgent referral recommended within weeks of the study for abnormality that will require further evaluation (e.g. low-grade glioma, Chiari I malformation with tonsillar crowding or syrinx)

(4) immediate referral recommended (e.g. acute subdural hematoma, lesion with mass effect)

Three study neuroradiologists interpreted brain MRIs in screened children and independently recorded results. MRIs reported to have any non-vascular abnormality were re-reviewed by two study neuroradiologists (MAK and RCM) masked to earlier interpretations, and abnormalities were then classified into one of the four above categories. Disagreements about the proper category were resolved by consensus between the neuroradiologists. Chiari I malformation was defined as cerebellar tonsils more than 5 mm below the foramen magnum.[12,13]

Statistical Analyses

We calculated the Kappa statistic for inter-rater reliability pre-consensus, for the presence or absence of a specific incidental MRI finding. Using exact methods, we determined prevalence and 95% confidence intervals (CI) of all incidental intracranial MRI abnormalities in children with SCD and those requiring urgent or routine referral.

We compared the frequency of incidental intracranial MRI findings in the SIT Trial to the frequency of incidental intracranial MRI findings in the pediatric study of Kim *et al*.[6] and in a German study of young adults[2] via a binomial comparison of proportions.

We conducted analyses using STATA 10.0 (College Station, TX) and considered a p-value of <0.05 significant for all analyses.

The study was approved by the SIT Trial Data and Safety Monitoring Board and the Johns Hopkins Institutional Review Board.

Results

We included 953 children screened with MRI of the brain for the SIT trial between February 2005 and September 2008. These children were 51.5% male, and 96% of African ancestry, 0.5% Caucasian, 0.5% Asian and 3% other race. The median age of the children was 9.1 years, with a range of 5.1 to 14.9 years. We identified 6.6% (63 of 953) (95% CI: 5.1 to 8.4%) with 68 incidental intracranial MRI findings, re-confirmed by two study neuroradiologists. (Tables 1 and 2). Five children had two incidental findings each. Chiari I malformations were the commonest malformation seen, followed by cavum abnormalities. Cortical dysplasia, grey matter heterotopia, and various types of cysts were the other types of abnormalities seen. Incidental MRI findings were of varying urgency. No child had MRI findings that were considered to merit immediate attention, i.e. referral to an emergency room. Urgent MRI findings were identified in six children (0.6%) (Figure 1). Routine findings were identified in 25 children (2.6%), and 32 children (3.4%) had MRI findings that were considered insignificant, such that no further evaluation or testing was required (Figure 2). The Kappa coefficient between neuroradiologists for identifying incidental findings over the entire study population was 0.918 (95% CI: 0.865 to 0.971) with 99.1% agreement. In the 63 children with incidental findings, there was 88.5% agreement for specific findings

amongst the neuroradiologists. Both values supported excellent agreement between the two readers.

The number (chi square 1.1, p=0.29) and type (requiring routine or urgent referral, chi square 1.5, p=0.22) of incidental findings did not differ by gender.

Incidental MRI Findings and Neurologic Signs

All children who met eligibility criteria for the SIT trial with an MRI of the brain showing an infarct and who agreed to further evaluation to determine eligibility randomized portion of the trial had a standardized neurological examination by study pediatric neurologist. Of the 953 screening MRIs performed, 175 children underwent this detailed neurological evaluation. Of these 175 children, only 9 also had an incidental MRI finding to allow assessment of whether the incidental MRI finding actually had a clinical correlate on neurological examination. Of these 9 children, two had an abnormal neurological examination. The first child was felt to have mild, non-impairing cognitive-behavioral problems. The incidental finding on his MRI was a small pineal cyst. The second child had a lesion in the splenium of the corpus callosum and had no focal findings on neurological exam. The neurologist who examined him was concerned about this patient's cognitive performance, including poor naming and figure copying.

Of the 63 children found to have incidental findings on their screening MRI, urgent MRI findings were identified in 6 children (0.6%, 95% CI: 0.2 to 1.4%). Two children had Chiari I malformation with spinal cord syrinx (Figure 1a and b). Four children had lesions suspicious for low grade brain tumor (Figure 1c-f). None of these six children with urgent MRI findings had neurological symptoms that correlated with their lesion. Both children with an incidentally identified Chiari I and cervical spinal cord syrinx were reconfirmed to have a normal neurological examination prior to neurosurgical decompression of the Chiari malformation. Two of the four children with lesions suspicious for low grade brain tumor had follow-up MRI of the brain which did not show any progression of the lesions and have remained asymptomatic. In two children, follow-up MRI is planned but has not yet occurred. One of these children is the child mentioned above with a lesion in the splenium of the corpus callosum and a normal neurological examination except for concerns regarding cognitive performance including poor figure copying. The second child has a possible tectal glioma, and was reconfirmed to have a normal neurological examination; in particular, eye movements were normal. Serial neurological assessments and MRI of the brain are planned for both children. In this small subset of the study population, no child had findings on neurological exam attributable to the incidental finding.

Specific imaging findings

Incidental cortical dysplasia or gray matter heterotopia were identified in two children and five children respectively, or 0.7% (95% CI: 0.3 to1.5%) of the study population. Per the study intake questionnaire, none of these children had a seizure disorder. Twenty-two children (2.3%, 95% CI: 1.4.to 3.4%) were found to have Chiari I malformation.

Comparison to similar studies

Upon evaluating healthy volunteers for research studies in California, Kim *et al.*[6] found urgent MRI findings in 0.4% (1 of 225) of children compared with 0.6% (6 of 953) of children in this current study, a 0.2% difference in proportions that is not significant (95% CI: −0.8% to 1.1%, p=0.75). Incidental MRI findings requiring routine referral for neurological evaluation were seen in 5.3% (12 of 225) of children in the Kim study and 2.6% (25 of 953) of the current study, a 2.7% difference in proportions which was significant (95% CI: 0.3 to 5.8%, p=0.03).

A German study of incidental MRI brain findings in 2,536 young adult male Air Force applicants reported that 6.5% (166 of 2536) of young men (95% CI: 5.6 to 7.6%) had abnormal findings;[2] however, findings that were considered normal variants were classified separately (cavum vergae, pineal cyst, enlarged Virchow Robin spaces, absent septum pellucidum) When this classification system is applied to our data, incidental findings in children screened for the SIT Trial are found in only 4.6%, significantly less than in young German Air Force recruits (risk difference 1.9%, 95% CI: 0.3 to 3.6%, p=0.03).

In this same German study, 1.7% had Chiari I, (95% CI: 1.2 to 2.3%).[2] Confidence intervals overlap with the current study; therefore the prevalence of Chiari I in these two quite different study populations is not significantly different. The pediatric incidental findings study[6] found that only 0.4% of children had tonsillar ectopia, but again this difference was not significant when compared to SIT trial data (risk difference 1.9%, 95% CI 0.6 to 3.1%, p=0.07).

Discussion

This is the largest group of children screened with MRI of the brain to date, with four times as many children imaged as the next largest study. The prevalence of incidental intracranial MRI findings in these school-age children was 6.6%. Overall, when compared to studies of children and healthy young adults, incidental intracranial findings were slightly less common, though potentially urgent or serious abnormalities were equally common and present in 0.6% of children.

We excluded findings such as ischemic or vascular lesions, as these are central to the major aims of the study and therefore not incidental. The prior pediatric incidental finding study, Kim *et al*. did not find any ischemic or vascular lesion in their 225 children,[6] and we do not consider them to be normal findings in school age children. In contrast, Weber and Heinz reported 13 (0.5%) young male Air Force applicants (mean age 20.5 years) with vascular abnormalities, including 5 (0.2%) with brain arteriovenous malformations. Importantly, prior studies of incidental finding in children and young adults found no infarct-like lesions. These lesions in children with SCD are pathological findings likely caused by the occlusion of small vessels[14] and should not be considered incidental.

A unique aspect of this series is that all children who met eligibility criteria for the SIT trial with an MRI of the brain showing an infarct and who agreed to enter the randomized portion of the trial after screening underwent both detailed neuroimaging and careful, standardized neurological examination by a board-certified pediatric neurologist. Of the 953 screening MRIs performed, 175 children underwent this detailed neurological evaluation as a part of the study. Only 9 of the children with these exams also had an incidental MRI finding. Of these 9, no children were reported to have neurologic abnormalities corresponding to their incidental MRI finding. Neurological exams on the 6 children classified as having urgent MRI findings were confirmed as unremarkable or unrelated to the lesion on MRI.

Strengths of this study include the standardized imaging protocol, review of all MRIs of the brain by three neuroradiologists, and the large study population. Limitations to the generalizability of this work include the study population as all have SCD (are not healthy children), and participants are ethnically restricted as 96% are of African descent. The prior relatively large pediatric study of incidental MRI findings also suffered from racial homogeneity, as it included 225 children of primarily European or Asian descent.[6] Nonetheless, despite the dramatically different populations, both studies suggest a prevalence of approximately 0.5% for incidental findings on MRI of the brain requiring urgent referral for medical evaluation.

Overall, incidental intracranial findings were slightly less common than reported in other studies of children and young adults, even when the same inclusion and exclusion criteria were applied, as we excluded vascular and ischemic lesions and extracranial abnormalities such as sinusitis. Our study design does not allow us to determine whether the lower number of incidental MRI findings is related to ethnicity or is perhaps more representative of the true prevalence of incidental intracranial MRI findings in children given the larger study population.

Physicians often ask whether a child should be referred for neurological evaluation for an incidental MRI finding. In this study, the MRI classification of incidental findings is based on a neuroradiologist's assessment of the potential significance of the finding. Many findings, such as gray matter heterotopia and cortical dysplasia may vary in significance based on the appearance of the individual MRI and the patient history. The risk of seizure in a child with a gray matter heterotopia or cortical dysplasia is unknown.

All of the children in this study underwent an MRI for research purposes. The more common clinical situation occurs when a child has an MRI of the brain for a marginal indication, such as uncomplicated headache, and is found to have an MRI abnormality, unrelated to the presenting complaint. Frequently, these children are then subjected to multiple "follow up" studies to confirm that the incidental MRI finding is indeed benign. Hopefully studies such as this one will aid clinicians as they counsel families. For example, arachnoid cysts are typically benign findings and occurred in at least 0.5% of children in this study and 1.7% in young adults.[2]

Ethics

Ethical concerns have been raised over the last several years about the proper disclosure of incidental abnormalities found in healthy volunteers for research studies.[11,15,16] There is currently no consensus, despite an NIH workshop to discuss these issues in January, 2005.[17] A recent paper, based on this workshop, reviews practical approaches to handling incidental findings in brain imaging research in various settings.[18]

A survey of healthy volunteers who had participated in brain imaging studies found that 97% of these volunteers wanted any abnormalities disclosed to them, regardless of clinical significance.[11] There is no consensus in the medical or research community that disclosure of findings that are minor or even "normal variant" such as a cavum septum pellucidum is in the patient's or research participant's best interest. In the SIT Trial, incident finding information is provided rapidly to the local study coordinator and site principal investigator for disclosure to the patient. This system and the fact that every MRI had a prompt clinical reading by an expert neuroradiologist are strengths of the SIT Trial protocol. Incidental findings may lead to additional studies with significant cost to the healthcare system and potentially to the study participant's family. The potential risk of identifying an incidental finding is included in the consent form for the study.

Conclusion

This series of 953 school-age children is the largest reported pediatric study of incidental MRI of the brain findings. Incidental intracranial findings were identified in 6.6% with potentially serious or urgent findings in 0.6%. Incidental findings on MRI of the brain are relatively common in children and most are benign. The clinical implications of many of these findings are unclear, resulting in limited recommendations to parents. Given the existing data, we recommend routine referral to a pediatric neurologist for findings that are currently asymptomatic and are of uncertain significance, (such as a migrational abnormality seen on MRI that may predispose to epilepsy, in a child who has never had a seizure). In

addition to its clinical applications, this work may also be useful for investigators using MRI in children who must plan for incidental findings in their studies based on estimated prevalence.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Abbreviations

MRI	Magnetic Resonance Imaging
SIT	(Silent Infarct Transfusion) Trial
CI	confidence interval

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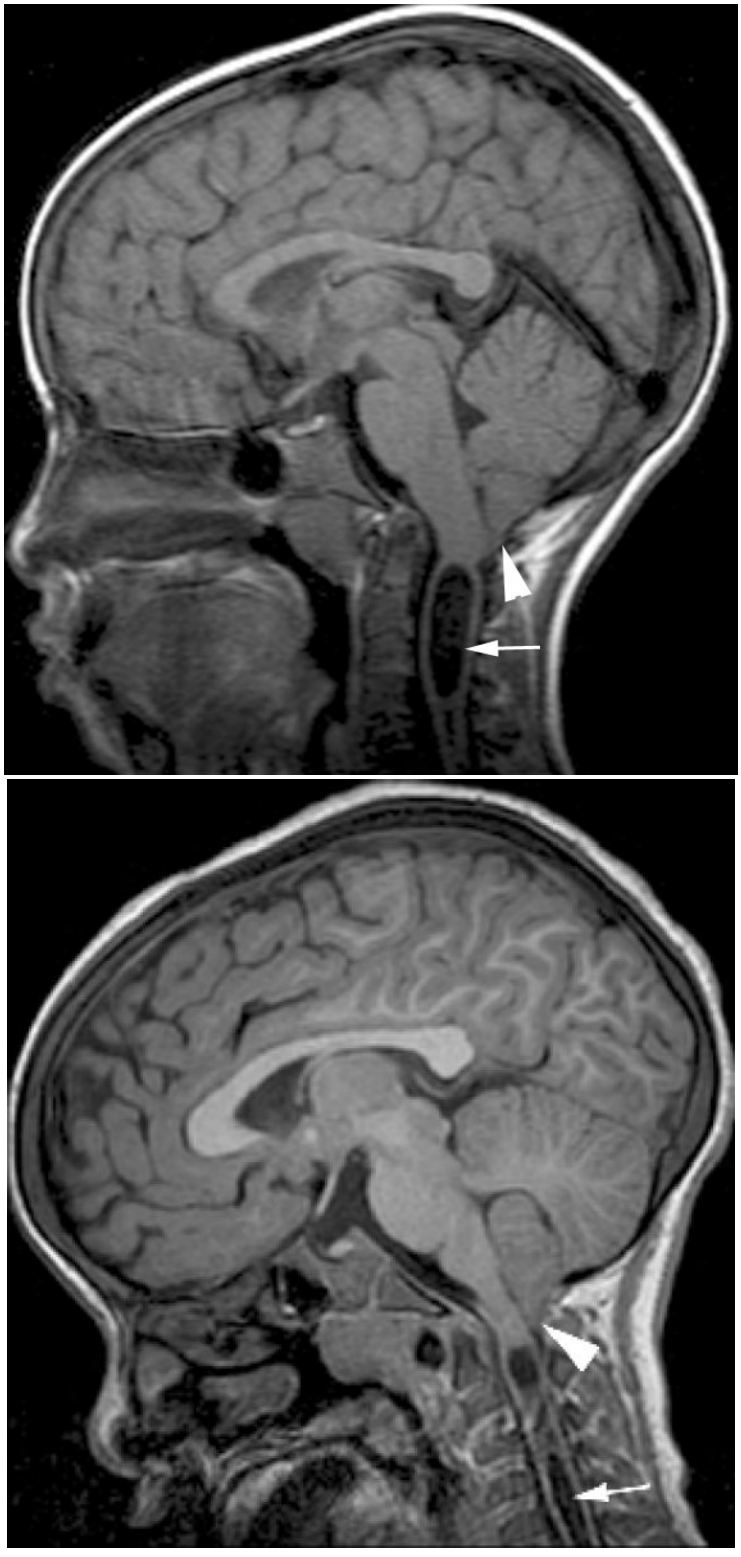

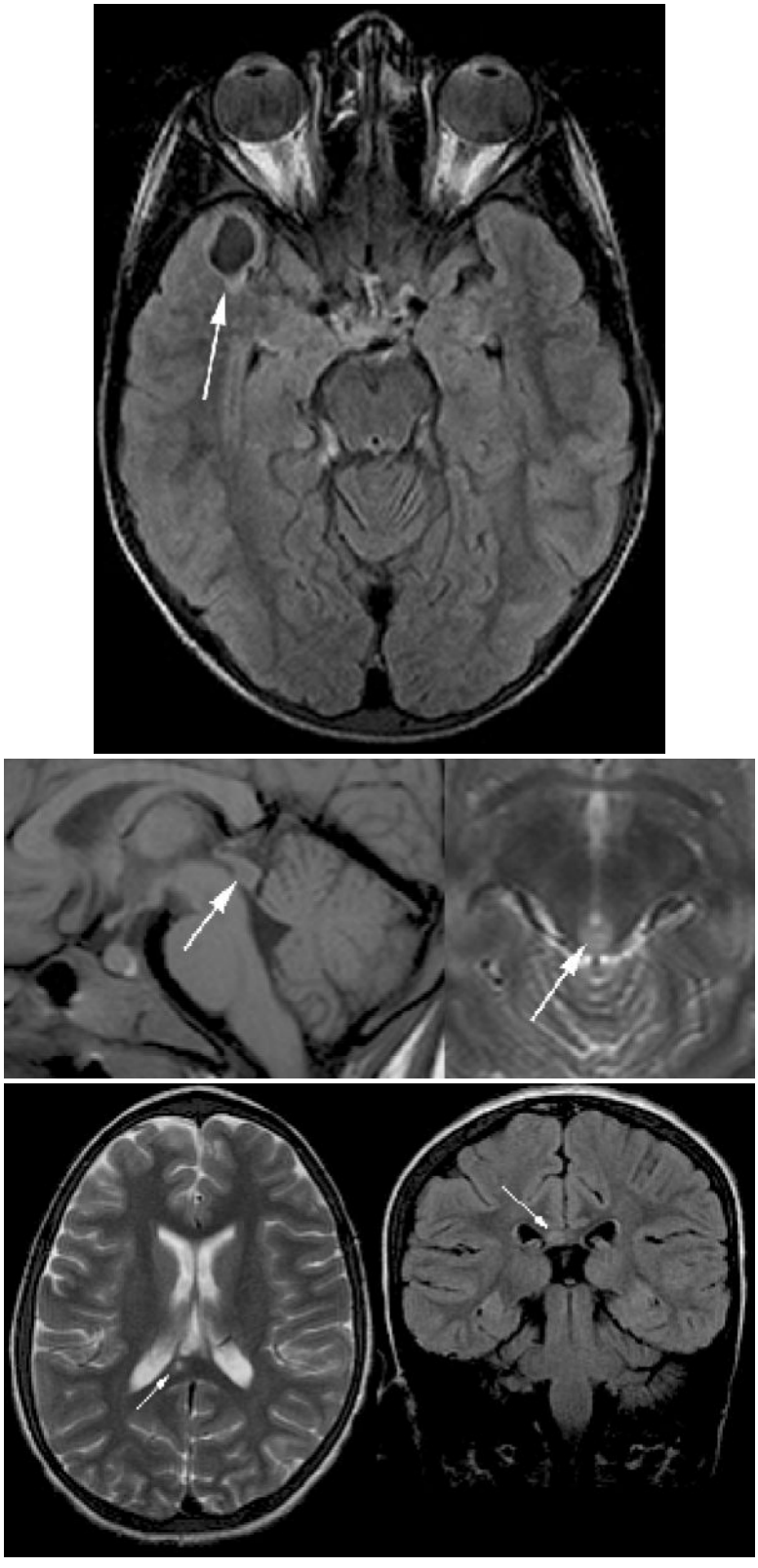

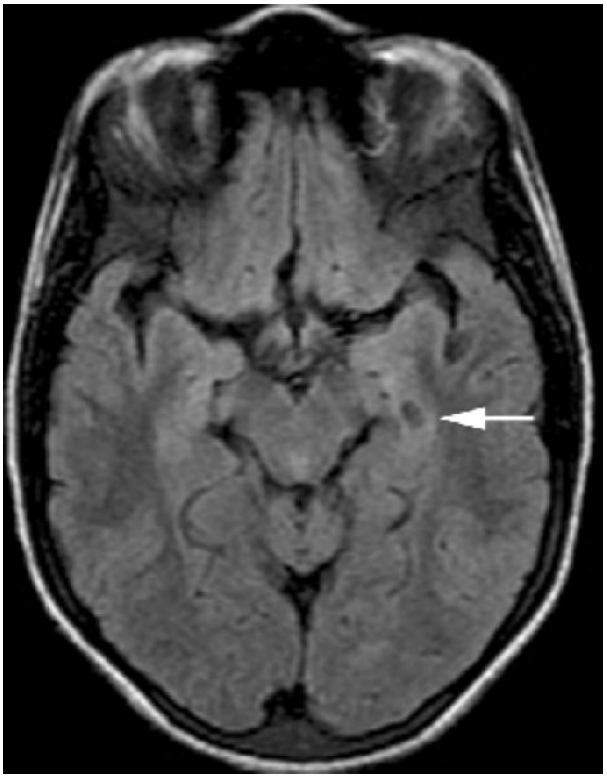

Figure 1(a-f).
Urgent Incidental MRI Findings.
1a) Sagittal T1 view of an incidental Chiari I malformation (arrow head) with cervical spinal cord syrinx (arrow).
1b) Sagittal T1 view of an incidental Chiari I malformation (arrow head) with cervical spinal cord syrinx containing plicae or septations (arrow).
1c) Axial FLAIR image with an incidentally detected cystic lesion in the right temporal lobe that could represent a tumor. Arrows point to the cyst and an area of nodularity within the cyst.
1d) T1 sagittal and T2 axial views of an incidental tectal lesion, possible glioma (arrows).
1e) Axial T2 and coronal FLAIR images of an incidental corpus callosum lesion, potentially representing a tumor or an infarct (arrows).
1f) Axial FLAIR image of a left hippocampal cystic lesion (arrow), possible tumor versus a focus of dysplasia.

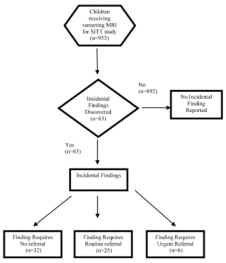

Figure 2.
Flow Chart of Incidental Findings in Children Screened for the SIT Trial.

Table 1

Incidental Intracranial MRI Findings in 953 Children with Sickle Cell Disease Screened for the SIT Trial

Classification and Abnormality	Number
No referral	
Cavum septum pellucidum/vergae/velum interpositum	11
Choroidal fissure cyst	6
Gray matter heterotopia	5
Arachnoid cyst	4
Prominent pervascular (Virchow-Robbin) Spaces	3
Pineal cyst	3
Absent septum pellucidum	2
Arachnoid cyst vs. prominent CSF space	1
Occipital bone cyst, possibly epidermoid	1
Routine Referral	
Chiari I	20
Idiopathic ventriculomegaly	1
Temporal lobe cystic change	1
Cortical dysplasia	2
Arachnoid cyst, large	1
Rathke cleft cyst, purely intrasellar	1
Urgent Referral	
Chiari I with large spinal cord syrinx	2
Possible tumor, tectal glioma	1
Possible tumor vs. dysplasia, temporal lobe cystic lesion	1
Possible tumor, hippocampus	1
Possible tumor, corpus callosum	1
Total	68*

*68 incidental findings in 63 children i.e. 5 children with 2 incidental findings.

Table 2

Referral Classifications for Incidental Intracranial MRI Findings in Children with SCD

Classification*	Number of Children	Percentage of Total Participants (n=953)
No referral	32	3.4%
Routine referral	25	2.6%
Urgent referral	6	0.6%
Emergent referral	0	0%

*Classification of incidental findings is according to the method of the Cardiovascular Health Study[4]