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The Utility of MRI in Children with Autism Spectrum Disorder

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Abstract

Autism spectrum disorders (ASD) are a group of brain based disorders associated with co-occurring medical conditions, such as epilepsy. With highly specialized imaging technology revealing functional and structural abnormalities in the brains of patients with ASD, the role of routine structural conventional Magnetic Resonance Imaging (MRI) is controversial and may not be a useful tool for the purpose of diagnosis and treatment. This study evaluated the utility of conventional routine MRI in ASD with and without co-occurring epilepsy. We reviewed the records of children with ASD ages 8-17 years and performed statistical analysis comparing MRI brain abnormalities and epilepsy. Seventy-seven of 253 subjects underwent brain imaging, 55 had MRI results available and, of these, 8 had brain parenchymal abnormalities. These abnormalities included two subjects with Chiari I malformation, one each with hamartoma, enlarged vascular space, venous angioma, and three with abnormal white matter signals. Brain MRI parenchymal abnormalities were not associated with the presence of epilepsy in children with ASD. In our cohort, conventional routine MRI was not useful as a tool that could lead to immediate diagnosis or treatment. The benefit and risks of conventional brain MRI for children with ASD should be carefully weighed. If an imaging study is highly suggested, some of the clinically available advanced imaging technologies should be considered in place of conventional MRI.

Keywords: Magnetic resonance imaging; Autism spectrum disorders; Parenchymal brain abnormalities; Epilepsy; Neuroimaging

Introduction

Numerous volumetric or highly specialized magnetic resonance imaging (MRI) studies have shown varied abnormalities in research laboratories [1-5]. The use of this newer imaging technology has helped to define specific neuroendophenotypes in autism spectrum disorder (ASD). High resolution volumetric structural MRI (sMRI) has revealed anatomic anomalies in various areas of the brain in ASD including the cortex, cerebellum, basal ganglia, and corpus callosum, as well as indications of specifically abnormal growth trajectories in early childhood [6-8]. Studies of the amygdala and the hippocampus, among other areas, have also shown differences in structural studies but findings have been inconsistent [6]. Task dependent and resting state functional MRI (fMRI) has aided in outlining neural connectivity (or under connectivity as it is often referenced in ASD) [7,9]. Magnetoencephalography (MEG) studies have delineated atypical white matter processes with regards to working memory of the brain in ASD [10]. Finally, the use of clinically accessible single-photon emission computed tomography (SPECT) and positron emission tomography (PET) technologies have shed light on metabolic mechanisms in the brains of children with ASD. A review by Zurcher et al. outlines how these techniques have been used to elucidate the characteristics of neurotransmitters, cerebral blood flow, and glucose metabolism in ASD [11]. High tech imaging has yielded useful information in research laboratories, but it is unclear how this translates to clinical practices. In addition, these specialized MRI services are not widely available in community based hospitals in day to day routine practice.

The Academy of Pediatrics (AAP) and the American Academy of Neurology (AAN) do not recommend routine neuroimaging for clinical diagnosis and screening in ASD [12,13]. However, the role of conventional neuroimaging is still controversial. Theories are emerging regarding the connection between underlying brain abnormalities in children with ASD and associated comorbidities, among which epilepsy is well recognized as a disorder of brain dysfunction. Parents and caregivers, often out of desperation to determine a cause for a child's ASD, frequently request some sort of diagnostic imaging which leaves the clinician to balance patient desire with clinical utility. Although some high tech imaging is becoming more widely available, conventional MRI is the primary tool in the clinician's imaging arsenal for the clinical evaluation of children with ASD. With that in mind, our study investigated the utility of conventional MRI in children with ASD (i.e., is there any point in pursuing conventional MRI in ASD?).

A 2005 study found no parenchymal abnormalities on conventional MRI or CT scan of 70 children with ASD with and without developmental regression, while Steiner et al. documented significant abnormalities in children with ASD due to a specific syndrome diagnosis and concluded these results were more likely related to the underlying syndrome rather than the diagnosis of ASD [3,14]. Additionally, Zeegers et al. found a high prevalence of brain abnormalities including Chiari Malformation and arachnoid cysts in children with developmental disorders including autistic disorder,

pervasive developmental disorder, not otherwise specified (PDD-NOS), mental retardation, and language disorders. These brain abnormalities may represent clinically relevant findings affecting the treatment and prognosis of the underlying disorders of the patients although they are likely not implicated in the diagnosis or treatment of ASD [5]. A study by Boddaert et al. compared the MRI findings of 77 children with Non-Syndromic ASD versus the same number of control subjects which revealed a higher than expected number of abnormalities in the ASD group. These findings included white matter hyperintensities, temporal lobe signal abnormalities, and dilated Virchow-Robin spaces, however, the clinical significance of these findings is unclear [2]. A 2014 study compared sulcal patterns in 59 male children with ASD against 14 age matched peers and found structural and pattern differences between the two groups using sMRI [1].

In addition to attributing the core manifestations of ASD to brain abnormalities, comorbid conditions such as epilepsy could also reflect an underlying brain dysfunction and/or anomaly. The association between epilepsy and ASD is established, with a prevalence of 8-30% of children with ASD suffering from epilepsy according to a 2014 review by Lai et al. [15]. In clinical practice, routine MRI of the brain is frequently performed in individuals with epilepsy especially when there is a focal abnormality detected in electroencephalographic (EEG) studies.

The purpose of this study is to evaluate whether the utility of conventional routine MRI of the brain remains to be unhelpful in children with ASD, and whether the presence of epilepsy warrants imaging in children with ASD. Our study is unique in that only patients with idiopathic ASD were included in the study.

Methods

A research database containing clinical information from 253 children with ASD, ages 8-17, years was utilized for this study. The diagnosis of ASD was based on DSM IV-TR criteria and included children with autistic disorder, PDD-NOS, and Asperger disorder [16]. Children with ASD whose etiology was known were excluded from this study. Known etiologies included children with Down's syndrome, fragile X syndrome, premature birth (children born before 36 weeks gestation), birth asphyxia, cerebral palsy, and children with chromosomal abnormalities or other known well defined genetic disorders. Children with Rett syndrome or disintegrative disorders were also excluded. All subjects were evaluated at the Autism Center of New Jersey Medical School, Rutgers University.

The diagnosis of epilepsy was made or confirmed by the pediatric neurologist (XM) with epilepsy being defined as 2 or more unprovoked seizures. Results of conventional routine brain MRI (using standard radiological technique and methods on a 1.5 Tesla MRI scanner) and epilepsy were analyzed using Chi squared test in SPSS software (version 11, SPSS Inc, Chicago, Illinois). The Institutional Review Board of Rutgers New Jersey Medical School approved this retrospective chart review study and monitored with human subject protection procedures.

Results

Of the 253 children in the research database, 77 underwent brain imaging and 22 MRI findings were not available (MRI studies performed elsewhere and were inaccessible). The remaining 55 subjects with available MRIs were used to evaluate the relationship between parenchymal brain abnormalities and epilepsy in ASD. The median age of the 55 subjects was 10.3 years. 18 subjects were females and 37 subjects were males. Subjects were drawn from throughout New Jersey and represented a diverse racial and ethnic group identifying themselves as Caucasian / White, African American/Black, Asian and Hispanic / Latino American. Diagnosis of the 55 subjects as assigned by DSM IV-TR criteria identified 31 subjects with Autistic disorder, 21 subjects with PDD-NOS, and 3 subjects with Asperger Disorder. Subjects underwent MRI for various reasons, including ASD diagnosis, comorbidities, and/or request by parents or guardians. The MRIs were not performed specifically for the purpose of this study.

Among the 55 subjects whose results were available, 47 were reported as normal brain imaging. 8 subjects were found to have brain parenchymal abnormalities. The abnormalities included two subjects with Chiari I malformations. Another patient had a MRI signal abnormality compatible with hamartomas in the brain in conjunction with 6 café au lait spots on skin, but did not qualify for the diagnosis of neurofibromatosis. One patient showed enlarged Virchow Robins space. One patient's imaging revealed a small venous angioma within the white matter of right frontal lobe. Three subjects showed abnormal white matter signals on MRI, including one with a small focal area of increased signal intensity in the left parietal lobe, one with left parietal and right frontal isolated foci of increased signal intensity, and the third with abnormal frontal lobe signal intensity. All white matter signal abnormalities of the three subjects were interpreted by our neuroradiologists as nonspecific findings. In addition, four subjects showed findings not known to cause developmental disorders, including one each of mucosal thickening in sinuses, adenoidal hypertrophy, sinusitis and paranasal sinus inflammatory disease. Three subjects with these incidental findings were reported with otherwise normal brain MRIs while one subject with paranasal sinus thickening was also noted to have a parenchymal brain abnormality of a small venous angioma.

From the 55 MRI images available, we further assessed the association of epilepsy and brain parenchymal abnormalities. Epilepsy was comorbid in 9 of the 47 subjects with normal MRIs and 3 of the 8 subjects with abnormal MRIs. Chi square analysis showed no significant association between the diagnosis of ASD with abnormal MRIs and the presence of epilepsy (Table 1).

	ASD with no epilepsy	ASD with epilepsy
Normal MRI	38	9
Abnormal MRI	5	3
Pearson Chi-square=1.35, p=0.352		

Table 1: Brain parenchymal abnormalities and epilepsy in patients with ASD.

Discussion

Over the last few decades, imaging technology has advanced rapidly in both the clinical and research settings. While mostly available at the research level, high tech specialized sMRI uses MRI technology to analyze the shape and size of white matter in the brain giving insight as to the integrity and three dimensions of brain structures. Additionally, fMRI maps the brain both spatially and temporally by following blood flow (and thus neuron activation) and is often coupled with the subject performing tasks in order to identify centers in the brain associated

with specific functions. MEG technologies are now becoming available at specialized centers. MEG measures brain function by analyzing electrical currents relating to neuronal activity. This information can be combined with structural imaging to provide insights in activity in specific locations in the brain. Finally, PET and SPECT are non-invasive (but do require an injection of radioactive labelled substance), clinically available technologies which examine the neurotransmitters and their receptors in the brain. This information can reveal functional neuroendophenotypes in addition to their structural images. However, these specialized MRIs either are not readily available or are cumbersome procedures at community hospitals in routine clinical practice.

The results of this study reiterates the notion that routine conventional MRI is not helpful for ASD per se. Parenchymal brain abnormalities found in this group of children may not be unique or specific, and there is little indication for change in treatment plan or expected prognosis based on the findings. Two patients with ASD in this cohort were incidentally diagnosed Chiari 1 malformations that were without symptomatology or evidence of cerebral spinal fluid obstruction or syringomyelia, therefore there was no indication for surgical intervention [17]. Although treatment at this time is unwarranted, discovery of Chiari 1 malformations might be of value in the future as patients may go on to develop symptoms. As individuals affected by ASD may have difficulty expressing or describing symptoms related to Chiari 1 malformation, ongoing imaging in these patients may be indicated when clinical suspicion warrants. While two studies have reported a link between enlarged Virchow Robin spaces in children with ASD, no clinical management strategies have been developed which target this finding [4,5]. Similarly, venous angiomas also known as developmental venous anomalies require no intervention as they are benign and surgical treatment is associated with unnecessary risk of bleeding or infarction [18]. As such, our findings suggest a poor utility for the use of conventional MRI in ASD in general, which is in line with current recommendations.

While routine neuroimaging has not been routinely recommended in ASD, it is not clear whether conventional MRI is indicated when epilepsy and ASD co-occur in the same individuals. Though the association between ASD and epilepsy has been acknowledged, it is not clear whether there is an association between patients with idiopathic ASD and epilepsy and possible parenchymal brain abnormalities. This retrospective chart review study found no significant link between the presence of epilepsy in ASD children and evidence of parenchymal brain abnormality on conventional routine MRI. Epilepsy did not present as a specific risk factor in identifying a structural abnormality by conventional MRI in this cohort of children with ASD.

Although it is difficult to draw conclusions given the small sample size and other limitations of this study, the use of conventional MRI was not helpful in identification of structural abnormalities that are clinically significant. The decision to use conventional MRI should be guided by a strong suspicion of focal deficits including, but not limited to, abnormal neurological exams, progressive increases in head circumference in the first years of life, progressive abnormal neurologic symptoms and abnormal focal EEGs. A careful analysis of risks and benefits should also be performed. In addition to the potential complications of sedation, children with ASD may be vulnerable to further risks including idiosyncratic reactions to the anesthesia as well as psychological trauma associated with the procedure itself. In summary, the decision to use conventional MRI in ASD must be a holistic one that carefully weighs the risks and the benefits to the subject.

In light of our findings regarding conventional MRI in ASD, is it time that we begin to consider the use of higher tech imaging in a clinical setting? Several of these technologies, including PET and SPECT are available at the clinical level at major medical centers. Although generally used in research settings or highly specialized medical facilities, other imaging technology such as functional MRI (fMRI), sMRI and MEG have yielded important information with regards to structural and functional anomalies in the brains of ASD patients. The clinical implications of these results have not been defined but Mahajan and Mostofsky cite the need for further neuroendophenotype imaging as it 'may potentially help with delineating subgroups that may shed light on comorbid disorders in ASD, with monitoring treatment responses or carrying out clinical trials to personalize interventions' [6].

This study has several important limitations, which must be considered when interpreting its findings. The images were interpreted by different radiologists although all the abnormal MRIs were reviewed by a single neuroradiologist. Confirmation of epilepsy diagnosis was based on historical information evaluated by a single pediatric neurology practice; EEG recording was performed and reviewed at our institution and outside institute, which may not be standardized. In addition, all subjects were patients of a neurologic clinic so selection bias may also play a role in the detection of MRI abnormalities in this patient group.

Conclusion

Detection of brain lesions in ASD by conventional MRI is of low yield in general. No obvious association was detected between epilepsy and MRI brain abnormalities in this cohort of children with ASD.

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