Brain Imaging in Adolescents and Young Adults With First-Episode Psychosis: A Retrospective Cohort Study

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ABSTRACT

Objective: Despite the lack of clear guidelines, neuroimaging (computed tomography [CT] or magnetic resonance imaging [MRI]) is frequently performed in subjects presenting with first-episode psychosis (FEP). The objective of this study was to determine if the use of neuroimaging adds diagnostic yield in adolescents and young adults presenting with FEP.

Methods: The sample consisted of 443 subjects aged 15–24 with FEP (*DSM-IV-TR* and *DSM-5*) and no focal neurologic findings. Consecutive charts from January 1, 1998, to June 30, 2016, were reviewed retrospectively. A positive finding was defined as a result leading to urgent follow-up or intervention.

Results: Twenty-five (5.6%) of 443 subjects showed incidental findings unrelated to psychosis. The prevalence of positive findings from neuroimaging was 0%, indicating no diagnostic yield from neuroimaging.

Conclusions: Routine neuroimaging did not provide diagnostic information leading to a change in clinical management and should not be recommended in the investigation of FEP.

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The term *psychosis* refers to abnormalities in 1 or more of the following domains: delusions, hallucinations, disorganized thinking, grossly disorganized or abnormal motor behavior, and negative symptoms.[1] The underlying etiology of psychosis can be broadly divided into either primary (formerly functional; without an identifiable cause) or secondary (formerly organic; indicating some underlying pathology). In *DSM-5*,[1] the latter is referred to as a "psychotic disorder due to another medical condition." The vast majority of psychoses are considered primary, while a small portion of psychoses are secondary.

Clinical symptoms suggestive of a secondary psychosis include acute onset, later age at onset, features of delirium, catatonia, disturbance of memory, and visual hallucinations; however, diagnosis of secondary psychosis based purely on presenting symptoms is rarely possible.[2] An abnormal neurologic examination or history can also be noted but is not always present. Secondary etiologies include structural abnormalities, neurologic illnesses, neurometabolic disorders, and toxic, infectious, or autoimmune etiologies.[2,3]

This distinction between primary and secondary psychosis has important treatment and prognostic implications. Guidelines regarding the appropriate use of investigations during the initial assessment of first-episode psychosis (FEP) are not uniform. One contentious topic is the use of neuroimaging, in the form of either magnetic resonance imaging (MRI) or computed tomography (CT) scans, to rule out a secondary cause of FEP that may be medically or surgically treatable. The recent Canadian Psychiatric Association guidelines[4] do not recommend routine brain imaging during investigation of FEP but state that brain imaging should be considered on a case-by-case basis if history raises suspicion of an intracranial pathology. However, the American Psychiatric Association guidelines[5] recommend the use of brain imaging in FEP and suggest utilizing an MRI over CT. The Australian and New Zealand Guidelines[6] also recommend an MRI scan, but not a CT scan, as part of the workup, while stating that expert opinion on neuroimaging is divided. The United Kingdom National Institute for Health Care Excellence guidelines[7] do not recommend routine neuroimaging for workup of FEP. The Canadian Choosing Wisely Guidelines[8] counsel against the routine use of neuroimaging to investigate FEP unless there is a suspicion of intracranial pathology.

A recent study[9] has estimated the annual incidence of psychosis in the adolescent and young adult population at 86 in 100,000. Brain scans in younger subjects have limited utility due to lower prevalence of pathological findings in this population, both in patients with FEP and in the general population.[10,11] CT scans have the downside of radiation exposure, which is an important

Clinical Points

- There remains a lack of consensus guidelines regarding the use of neuroimaging in the workup of first-episode psychosis.
- For young patients presenting with first-episode psychosis and a normal neurologic examination, neuroimaging does not provide diagnostic benefit leading to a change in clinical management.

consideration in young patients, since early radiation exposure elevates cancer risks in later years.[12,13] MRI scans have no radiation exposure and better gray-white matter differentiation.[14] The rate of abnormalities discovered through MRI in the general population has been reported as high as 18%, with less than 3% requiring any referral for further imaging or medical management.[15] Despite fewer health consequences related to MRI scans, guidelines for other neurologic conditions (eg, concussion) try to limit the number of unnecessary scans.[16]

Early studies have reported some success using neuroimaging for the workup of psychosis. Goodstein[17] reported abnormal findings in 30% of CT scans in psychotic individuals, but these were primarily incidental and unrelated to the presenting psychosis. Gewirtz et al[18] discovered abnormal findings in 6.6% of CT scans and recommended that CT scans be used in FEP workup. However, recent studies[10,19–24] analyzing the utility of neuroimaging for secondary causes of FEP have found their diagnostic value to be minimal, generally recommending them only for patients with an abnormal neurologic examination or clinical picture.

The aim of this study is to determine, through retrospective chart review, whether neuroimaging in young patients presenting with FEP has significant diagnostic value. These patients constitute an important and vulnerable subpopulation that is often amalgamated into general psychoses presentations. The present study attempts to supplement other reports of imaging in this specific population by examining the utility of both CT and MRI scans. We postulate that neuroimaging conducted in the younger population with FEP will not impact clinical management.

METHODS

Sample

The present study is a retrospective chart review of patient referrals to the Early Psychosis Intervention Program (EPIP) at the Foothills Medical Centre in Calgary, Alberta, who underwent brain imaging. The program accepts referrals from clinicians working in the Calgary region.

Charts from January 1, 1998, to June 30, 2016, were retrospectively reviewed to ensure that a neurologic evaluation had taken place by a physician in either the hospital or community setting prior to diagnostic imaging. Inclusion criteria were (1) age range from 15 to 24 years; (2) first-episode psychotic disorder confirmed by a consulting psychiatrist; (3) normal neurologic examination; (4) referral to the EPIP from January 1, 1998, to June 30, 2016; and (5) neuroimaging study (MRI or CT) available. If an abnormal neurologic examination was reported, the patient was excluded from the data set.

Permission to conduct this study was granted by the University of Calgary's Conjoint Health Research Ethics Board. The study was initially approved on October 23, 2013, and was extended to October 23, 2017, to account for a larger accumulated sample size. Due to the retrospective nature of the study and the fact that brain imaging is currently part of routine evaluation of FEP patients in Calgary, no explicit patient consent was needed.

Our data collection period spans a change in terminology from the *DSM-IV-TR* to *DSM-5*. To account for this change, the diagnosis of "Psychosis Not Otherwise Specified" was changed uniformly to "Unspecified Schizophrenia Spectrum and Other Psychotic Disorder." This change affected 153 subjects. A diagnosis of psychosis was made by a psychiatrist using criteria from the aforementioned *DSM* editions.

Measures

Clinical neuroimaging scans were obtained as part of the diagnostic workup of subjects presenting with symptoms of FEP. If neuroimaging had not been ordered by either the emergency physician or community clinician prior to commencing treatment at EPIP, a CT or MRI was requested by the consulting physician. Clinic policy left it to the discretion of the treating physician to decide which imaging modality would be ordered. CT and MRI scans were read by consulting general radiologists and subspecialty neuroradiologists at different hospital and community sites in Calgary and classified into 3 categories: normal study, abnormal study with routine follow-up, and abnormal study necessitating urgent follow-up and intervention. A study was considered positive if the findings caused a change in the clinical management, ie, neurologic or surgical intervention was required. The diagnostic yield for either CT or MRI was determined from the number of positive studies.

Procedures

This study was conducted as a retrospective chart review. The investigators were provided with a list of all admissions to EPIP from January 1, 1998, to June 30, 2016. Only subjects meeting the inclusion criteria were included in further analysis. Immediate data anonymization occurred after each subsequent chart analysis by way of assigning unique codes to patient files. These codes were linked to a master list containing patient date of birth and health care number (in case a patient file must be revisited). Computers and USB drives containing patient information of any kind were password protected and stored in a locked facility.

Data Analysis

Diagnostic yield for the present study was defined as a finding on brain imaging that caused a change in clinical

Table 1. Clinical Characteristics of Patients Presenting With FEP Who Underwent Brain Imaging[a]

Diagnosis	Male	Female	Age, Mean y	% CT Scan Incidental	% MRI Scan Incidental
Bipolar disorder	4	0	20.0	0 of 3 (0%)	0 of 1 (0%)
Brief psychotic episode	6	8	20.1	1 of 13 (7.7%)	1 of 2 (50%)
Delusional disorder	1	0	20.0	0 of 1 (0%)	0 of 0 (0%)
MDD with psychotic features	1	3	18.6	0 of 4 (0%)	0 of 1 (0%)
Schizoaffective disorder	9	10	20.2	0 of 14 (0%)	1 of 6 (16.7%)
Schizophrenia	125	31	20.0	8 of 139 (5.8%)	5 of 29 (17.2%)
Schizophreniform disorder	25	10	20.0	1 of 27 (3.7%)	0 of 10 (0%)
Substance-induced psychosis	17	2	19.3	1 of 15 (6.7%)	0 of 4 (0%)
Unspecified schizophrenia spectrum and other psychotic disorders	146	45	19.7	7 of 164 (4.3%)	6 of 39 (15.4%)

[a]None of the neuroimaging findings resulted in a change in patient management.
Abbreviations: CT = computed tomography, FEP = first-episode psychosis, MDD = major depressive disorder, MRI = magnetic resonance imaging.

Table 2. Summary of Incidental Findings in CT and MRI Scans

Finding	Number
Arachnoid cyst	7
Nonspecific hyperintensity (MRI)	7
Nonspecific hypodensity (CT)	4
Calcification	3
Atrophy	3
Prominent perivascular space	2
Prominent cisterna magna	1
Ventricular asymmetry	1
Cavum septum pellucidum	1
Focal cystic encephalomalacia	1
Pituitary cyst	1
Developmental venous anomaly	1

Abbreviations: CT = computed tomography, MRI = magnetic resonance imaging.

management (ie, urgent follow-up or neurointervention). Incidental findings or routine follow-up did not change management and therefore did not add to the diagnostic yield.

RESULTS

Of the 443 subjects referred to EPIP during the study period, 351 (79.2%) received a CT scan, 63 (14.2%) received an MRI scan, and 29 (6.5%) received both a CT scan and an MRI scan. Of the total 472 scans, 33 had incidental findings, which corresponded to a prevalence of 7.0%. Correcting for multiple neuroradiological assessments, 25 (5.6%) of 443 subjects had incidental findings on neuroimaging.

Table 1 illustrates the clinical characteristics and diagnosis of patients presenting with FEP. Eighteen (4.7%) of the 380 CT scans and 13 (14.1%) of the 92 MRI scans had incidental unrelated findings that did not change clinical management. Of the subjects who had only MRI scans, 7 (11.1%) of 63 had incidental findings (Table 1).

Table 2 displays the incidental findings on neuroimaging. These findings were not deemed related to the psychosis and did not lead to a change in clinical management.

Table 3 presents a detailed breakdown of the imaging findings and radiology reports. In the 18 individuals with abnormal CT scans, 8 (44%) of those scans led to a follow-up MRI and 10 (56%) did not warrant any follow-up. In these 8 individuals who underwent a follow-up MRI study, 6 (75%) of the follow-up scans determined that findings on the CT scans were within normal limits, 1 (12.5%) demonstrated a new incidental finding, and 1 (12.5%) confirmed a finding of intracranial calcification/ossification. In the 15 individuals who underwent MRI scans, 3 (20%) of those scans led to routine follow-up, and 12 (80%) led to no routine follow-up.

None of the neuroimaging findings (0% of subjects) was considered to be causal or contributory to a secondary FEP, and none required urgent follow-up or neurointervention. It was therefore determined that neuroimaging provided no diagnostic yield for workup of FEP.

DISCUSSION

Despite recent advances resulting in a better understanding of etiologic and psychopathologic factors, first-episode psychosis remains a clinical diagnosis. The role of structural neuroimaging in the initial investigation of subjects with FEP remains controversial. We therefore conducted a retrospective chart review of patients admitted to an early psychosis program who underwent a neuroimaging study. To our knowledge, the present study is the largest of its kind. Our study aligns with previous studies[24–26] that investigated neuroimaging in young subjects presenting with FEP and confirms previous recommendations that neuroimaging in FEP provides inadequate diagnostic and clinical efficacy to justify its routine use. It should be again noted that these findings are limited to the well-defined population of young subjects exhibiting FEP in the context of a normal neurologic examination. Our inclusion criteria were restricted to investigate a targeted age range and ensure greater uniformity of imaging results. The rates of abnormalities in young patients in our study do not appear to differ from rates in the healthy general population.[15]

It is well known that schizophrenia is associated with brain abnormalities that are present at disease onset. Ventricular enlargement, loss of temporal lobe matter, and an increase in nucleus accumbens volume are commonly observed in schizophrenia, although these findings are not

Table 3. Neuroimaging Findings With Radiologist Comments

Diagnosis	Scan(s)	Age, y	Sex	CT Scan	MRI Scan
BPE	CT, MRI	19	M	Focal white matter hypodensity	Normal physiological variant
SCZA	MRI	22	M	...	Arachnoid cyst × 2
SCZ	CT, MRI	20	F	Hypodensity within sella	Normal
SCZ	CT	24	M	Mild cerebral atrophy	...
SCZ	CT, MRI	17	M	Calcification within left globus pallidus	Normal physiological variant
SCZ	CT, MRI	19	M	Multiple hypodensities within parietal lobes & left frontal lobe	Normal physiological variant
SCZ	CT, MRI	20	M	Prominent left sylvian fissure	Arachnoid cyst
SCZ	CT, MRI	19	M	Arachnoid cyst	Normal physiological variant + multiple hyperintensities within frontal lobe white matter
SCZ	MRI	20	M	...	Multiple hyperintensities within cerebral white matter
SCZ	CT	22	M	Arachnoid cyst	...
SCZ	CT	21	M	Arachnoid cyst	...
SCZM	CT	17	M	Cavum septum pellucidum	...
SIP	CT	19	M	Arachnoid cyst	...
USCHZ	MRI	16	F	...	Pituitary cyst + multiple white matter hyperintensities, right frontal DVA
USCHZ	MRI	24	F	...	White matter hyperintensity within left frontal lobe
USCHZ	CT	24	M	Hypodensity within left caudate head	...
USCHZ	CT, MRI	23	M	Right frontoparietal inner calvarial ossification/calcification	Confirmed finding
USCHZ	CT	24	M	Mild cerebral atrophy	...
USCHZ	MRI	16	M	...	Multiple hyperintensities within cerebral white matter + focal cystic encephalomalacia in the left frontal cortex
USCHZ	CT	21	M	Arachnoid cyst	...
USCHZ	CT	21	M	Prominent cisterna magna	...
USCHZ	CT, MRI	16	M	Asymmetry of lateral ventricles	Normal
USCHZ	MRI	15	M	...	Multiple white matter hyperintensities within frontal lobes
USCHZ	CT	21	M	Parafalcine calcifications	...
USCHZ	MRI	19	M	...	White matter hyperintensity within parietal lobe

Abbreviations: BPE = brief psychotic episode, CT = computed tomography, DVA = developmental venous anomaly, F = female patient, M = male patient, MRI = magnetic resonance imaging, SCZ = schizophrenia, SCZA = schizoaffective disorder, SCZM = schizophreniform, SIP = substance-induced psychotic disorder, USCHZ = unspecified schizophrenia.
Symbol: ... = scan was not performed.

specific and are also associated with other conditions such as bipolar disorder.[27–29] Many of these changes are thought to be unrelated to the use of antipsychotic medications.[30] In addition, clinical neuroimaging studies do not specifically assess these factors.

Some studies have attempted to use neuroimaging to predict clinical outcome in FEP, and most of these focused on cortical thinning.[31–33] MRI scans obtained at the initial presentation of psychosis may help to distinguish continuous and more severe cases of psychosis from episodic and less severe cases of psychosis based on spatially distributed information in brain tissue.[31,34] In childhood-onset schizophrenia, cortical thickness at the initial presentation is positively correlated with remission rate.[35] Using a computerized algorithm, MRI scans may be able to distinguish schizophrenic patients from healthy controls and patients with mood disorders.[36] That said, a recent meta-analysis[37] in children and adolescents with FEP illustrated limited utility of these predictive models and that clinical outcomes remain better predictors of clinical course than neuroimaging. Sample size has been identified as a persistent confounder in neuroimaging studies in FEP. It has been reported that sample sizes of less than N = 130 are typically considered unreliable.[38]

Despite these current limitations, MRI scans may prove beneficial for the diagnostic workup of FEP. The concept of "machine learning" has recently been applied to psychiatry and could provide valuable diagnostic and prognostic information. Machine learning attempts to create a model that will automatically discover regularities in data and use this information to classify data into different categories, in turn discriminating between different patient groups (eg, subjects with schizophrenia vs healthy controls).[39,40] A number of problems exist in establishing validity using current models. These include technical issues such as differences between scanners at different sites, legal issues regarding data sharing and confidentiality, and computational complexity stemming from large data sets.[41] Large data sets from single-center studies are excellent candidates to be applied to machine learning research. While potentially promising, these approaches are not yet being used in clinical neuroimaging.

There is conflicting evidence regarding the efficacy of CT versus MRI scans to detect brain lesions in FEP. Some studies[10] show no difference between CT and MRI scans to detect brain lesions in FEP, while other studies[14] find that MRI scans result in more incidental findings. The present study found more incidental findings on MRI scans than CT scans, even when excluding the MRI scans that were performed as follow-up to abnormal CT scans. This difference may be due to a better ability of MRI scans to differentiate gray and white matter when compared with CT scans. Eight individuals in our study underwent both CT and MRI scans. Six individuals (75%) had an abnormality detected

on CT scan, but the follow-up MRI scan showed findings were within normal limits. These data may suggest that, when compared with MRIs, CT scans have less diagnostic value and a greater tendency to give false positive results. That said, patients whose clinical presentation suggests an abnormal finding may be referred directly for an MRI rather than a CT; therefore, this finding should be taken cautiously.

In addition to diagnostic benefit, which appears to be similarly low for both types of scans, the cost and risks associated with each investigative modality should be considered. Both cost and anticipated delay are lower for CT scans than for MRI scans. CT scans are often sufficient to detect mass lesions or hemorrhages requiring immediate intervention.[14] CT scans are a source of radiation exposure, which is even more salient in the younger population.[12] The clinical presentation and perceived urgency of investigation should be considered when deciding between the 2 scans. The lack of radiation exposure and the potential applicability of MRI scans to anticipate clinical course may favor their use should neuroimaging be required, although these factors should be weighed against the greater sensitivity of MRI for detection of nonpathologic incidental findings. In our study, neither imaging modality impacted clinical management. Their incorporation as part of a routine workup in this target population is therefore of limited value.

Limitations of the present study include lack of a control group for comparison, unknown interrater reliability between general radiologists and neuroradiologists, and differences in scanning equipment and imaging protocols across sites. There was also a lack of information regarding ethnicity or social demographics, which are known to influence psychosis rates. It is not clear to what degree these factors are substantially related to primary versus secondary psychopathology.[42,43] The main strength of this study is the large sample size for both CT and MRI scans in this target population. An additional strength comes from the broad demographic base, as subjects were recruited from the entire city of Calgary and surrounding areas.

CONCLUSIONS

Our results are consistent with previously published reports that neither CT nor MRI scans play a significant role in the diagnostic workup of FEP. Our recommendation is therefore that brain imaging studies should not be included in the routine diagnostic workup of FEP unless clinically indicated by an atypical clinical presentation or an abnormal neurologic examination. In those cases, MRI scans may be the modality of choice due to better gray-white matter differentiation, lack of radiation exposure, and better prognostication ability. Any physician who decides to order an imaging examination will need to consider whether doing so will inform clinical management. Furthermore, regardless of the imaging modality, there is a chance for an incidental finding, which while not expected to impact clinical outcome, could be distressing to the patient and family if not properly communicated. The outcome of this study could be taken together with the findings of other recently published studies[19–26] to inform physicians on indications for imaging in young patients presenting with FEP.

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