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Clinical correlates of enlarged cavum septum pellucidum in schizophrenia: A revisit through computed tomography

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ABSTRACT

Like prevalence of abnormal cavum septum pellucidum in patients of schizophrenia remains controversial, its role in clinical outcome, duration of illness and effect on treatment remains less understood as well. Our study examined clinical correlates of enlarged cavum septum pellucidum in schizophrenia. A total of 139 patients diagnosed with schizophrenia during the year 2012 and 2013 were taken for the study. We compared them in respect to the presence and absence of enlarged cavum septum pellucidum. We found 16 patients with enlarged cavum septum pellucidum and were compared with those without enlarged cavum septum pellucidum for socio-demographic and clinical variables. We also correlated these clinical variables with dimension of cavum septum pellucidum. We found statistically significant increased current age and duration of illness in patients with enlarged cavum septum pellucidum. The implications of these findings are discussed with possible confounding effect of current age on neuroimaging. No meaningful correlation was found. No difference in clinical variables was found. Retrospective design and use of computed tomography were limitation of our study.
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1. Introduction

Patients with schizophrenia have been found to have significant abnormalities in midline brain regions such as the corpus callosum (Woodruff et al., 1995; Tibbo et al., 1998) septum pellucidum (Nopoulos et al., 1997; Kwon et al., 1998; Nopoulos et al., 1998) and cerebellar vermis (Rossi et al., 1993; Tran et al., 1998; Nopoulos et al., 1999). Among these several researches have been conducted on cavum septum pellucidi (CSP). But both the presence of CSP and its significance in schizophrenia remains unclear. It is suggested that CSP, particularly if it is large, should be considered a developmental anomaly that may contribute to neuropsychiatric abnormalities (Sarwar, 1989; Nopoulos et al., 1997). Several studies have documented that patients with schizophrenia have an increased rate of enlarged cavum septum pellucidum (CSP) compared to healthy control groups (DeGreef et al., 1992a; DeLisi et al., 1993; Jurjus et al., 1993; Scott et al., 1993; Nopoulos et al., 1996; Galarza et al., 2004; Filipovic et al., 2005) while this was not replicated in a recent study (Rajarethinam et al., 2007). Earlier and recent studies have attempted to examine relationships between CSP measures and clinical and demographic variables (Jurjus et al., 1993; Mathew et al., 1985; Shioiri et al., 1996), symptoms (Mathew et al., 1985; Nopoulos et al., 2000), duration of illness (Fukuzako et al., 1996; Mathew et al., 1985), family history of illness (Uematsu and Kaiya, 1989), intellectual functioning (Nopoulos et al., 2000). While some studies have not documented any relationships between these variables and presence of CSP (DeLisi et al., 1993; Galarza et al., 2004; Jurjus et al., 1993; Rajarethinam et al., 2001; Shioiri et al., 1996), few have found intriguing evidence. Uematsu and Kaiya (1989) reported that CSP was significantly related to family history of schizophrenia while Nopoulos et al. (2000) reported a significant inverse relationship between size of CSP and IQ scores. Mathew et al. (1985) reported a significant correlation between age and septal area, and between duration of illness and septal area. Although the overall incidence of CSP between patients and controls was not found to differ, Fukuzako et al. (1996) noted that patients with a history of long-term institutionalization (>3 years) had a significantly higher incidence of CSP. One recent case report has highlighted that abnormally large CSP may indicate worse prognosis in schizophrenia (Liao et al., 2012). Overall the functional implications of CSP in schizophrenia has not been consistently replicated and

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remain unclear. Hence, the present study tried to examine whether patients of schizophrenia with enlarged CSP have different sociodemographic and clinical profile than patients of schizophrenia without enlarged CSP. This study also examined whether a relationship could be identified between CSP measures and clinical symptoms of patients of schizophrenia.

2. Method

2.1. Subjects

This is a retrospective study which was undertaken at Central Institute of Psychiatry, Ranchi, India. Initially all patients diagnosed with schizophrenia, who had undergone computed tomography (CT) of brain since 1st January, 2012 to 31st December, 2013 were included in this study. Diagnosis of schizophrenia was made according to Clinical Description and Diagnostic Guidelines (CDDG), International Classification of Diseases—10th version (ICD-10) by World Health Organization (WHO, 1993). Indications for neuroimaging were clinical suspicions of any organicity by treating psychiatrists or inadequate response to psychotropics. A total of 212 patients with schizophrenia had undergone CT of brain in the said period. Method of chart review was adopted. Any patient with a history of neurological illness, head injury with loss of consciousness, systemic illness with potential cognitive sequelae, or current substance abuse or past history of substance dependence were excluded. Finally total of 139 patients were recruited for this study. Ethical approval was obtained from institutional ethical committee before collecting data.

2.2. CT acquisition

A Siemens 16 slice CT machine was used to obtain images for this study. As per imaging protocol slices were obtained from base of skull through vertex with slice width 4.8 mm in the axial plane. Further the images were reconstructed at thinner sections, up to 0.75 mm thickness in axial and coronal planes for detailed analysis. The slice with best dimensions of CSP had been chosen for measurement. We had taken length and width of cavity and width of septum. During the procedure the radiologist was kept blinded to the case notes of the patients.

2.3. CSP measurement

To determine the presence and dimensions of the CSP, we used the criteria used frequently in previous studies (Kwon et al., 1998; Nopoulos et al., 1998; Choi et al., 2008). We defined any CSP equal to or greater than 6 mm in length, as being abnormally large CSP or enlarged CSP. First we measured the dimensions of all CT scan showing CSP whether normal or abnormal and then selected only those which were abnormally large or enlarged according to criteria to be included in the study group. The control group constituted patients with no CSP and normal CSP.

2.4. Statistical analysis

We used χ^2 (Chi-square) test and Fisher exact test for categorical variables. Student t-test was used for continuous variable (age of the patients at the time of CT of brain) and Mann–Whitney test for other continuous variables (age of onset of illness and duration of illness) after checking for normal distribution. Spearman's correlation was used to assess the correlation between length of abnormal CSP, age of the patients, age of the onset of illness and duration of illness. Two-tailed $p < 0.05$ was considered statistically significant.

3. Results

Our study sample consists of 16 (11.51%) patients with enlarged CSP and 123 (88.49%) patients with either normal CSP ($n = 17$) or no CSP ($n = 106$). The length of CSP in these patients with enlarged CSP was equal to or more than 6 mm. Significant differences were found for mean age of the patient and duration of illness between two groups. The mean age for patients with and without enlarged CSP was 38.88 ± 12.75 and 32.94 ± 9.27 years, respectively (Table 1). Similarly significant difference was also found for duration of illness between these two groups, with mean of 12.06 ± 10.94 and 7.06 ± 6.48 years in patients with and without CSP groups, respectively ($p = 0.009$) (Table 2). Spearman's correlation between length of abnormal CSP, age of the patients, age of the onset of illness and duration of illness did not reveal any significant correlation.

4. Discussion

The literature to date has been inconsistent in identifying functional significance of enlarged CSP in schizophrenia. The current study found 11.51% of patients with schizophrenia had enlarged CSP which was in line with some earlier studies. (Rajarethinam et al., 2001; Flashman et al., 2007; Hagino et al., 2001; Keshavan et al., 2002). In general, these prevalence rates are lower than those reported in other studies of schizophrenia (DeGreef et al., 1992a,b; DeLisi et al., 1993; Nopoulos et al., 1997; Kwon et al., 1998; Takahashi et al., 2008). The reason for the discrepancies among studies with respect to CSP prevalence remains unclear. Different criteria used to ascertain the presence of abnormal CSP, different methods used for CSP measurement and as well as clinical and demographic differences among samples might be the probable reason for this. Regarding significance of CSP, a recent meta-analysis suggest that patients of schizophrenia with enlarged CSP may have more psychopathological impairment due to distinct patterns of altered brain morphology (Trzesniak et al., 2011). Our study doubts this. In our study, no differences were found between any of the clinical symptoms in both the samples. This is in line with some earlier studies (Jurjus et al., 1993; Nopoulos et al., 2000). But in a recent study, Flashman et al. (2007) found positive correlation between negative symptoms and length of CSP. We did not find any significant difference for family history between two groups while it was significantly higher in patients with enlarged CSP in an earlier study (Uematsu and Kaiya, 1989). In line with some earlier studies (Fukuzako et al., 1996; Kwon et al., 1998), our study found significantly longer duration of illness thereby more chronic course of schizophrenia in enlarged CSP group. As two groups did not differ in their age of onset of illness, this findings must be interpreted with caution. The confounding effect of statistically significant mean age difference between two groups on neuroimaging could not be ruled out. Researches have shown age related volumetric differences in brain structures in the vicinity of CSP (Ellison-Wright et al., 2008; Meisenzahl et al., 2008; Trzesniak et al., 2011). Hence, whether enlarged CSP in study group was due to age related or due to neurodevelopmental disease process could not be established. Also, considering the heterogeneity of schizophrenia as a syndrome the possibility of enlarged CSP indicating a chronic course for a subgroup of schizophrenia patients should be kept in mind and be examined in future research. Finally, other earlier and some recent studies did not find significant correlations between duration of illness and measures of CSP (DeGreef et al., 1992a; Galarza et al., 2004; Kasai et al., 2004; Keshavan et al., 2002; Shioiri et al., 1996; Takahashi et al., 2007; Takahashi et al., 2008). Earlier studies did not examine use of antipsychotics (DeLisi et al., 1993; Flashman et al., 2007; Jurjus et al., 1993; Kwon et al., 1998; Nopoulos et al., 1997; Rajarethinam et al., 2001; Shioiri et al., 1996). As these drugs may influence

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