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Cup to Disc Ratio (CDR) in Patients with Schizophrenia A Preliminary Cross-Sectional Study

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Abstract

Background: Routine ophthalmoscopy of patients with schizophrenia revealed an increased cup to disc ratio (CDR). A medline search revealed no literature on schizophrenia and CDR. We attempted to see if there was a difference in the cup disc ratio in patients with schizophrenia compared to the normal population.
Method: In a cross-sectional study, the authors compared the CDR of 100 patients with schizophrenia with that of 100 healthy controls. Schizophrenia was diagnosed using DSM IV criteria. Patients and controls with active medical illness were excluded from the study. A single ophthalmologist recorded the CDR of the patients and controls. The data obtained was analyzed.
Results: Patients with schizophrenia had greater CDR than the control population. Patients who were on an anticholinergic medication had a higher mean CDR than those who were not. There was a positive correlation between the dose of the anticholinergic and the CDR (Spearman's rho =0.75, p<0.001).
Conclusion: The possible explanations for the above finding include the illness itself contributing to the change, or a medication induced change. (German J Psychiatry 2008; 11: 51-55).

Keywords: schizophrenia, cup to disc ratio, antipsychotics, anticholinergics

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Introduction

Although psychopharmacological treatment for schizophrenia has become more sophisticated and effective, antipsychotics continue to form the basis for the treatment and patients continue to be on medications for long periods of time, often lifelong (Lehman et al., 2004a). In addition to the extrapyramidal side effects of antipsychotics, several other systemic side effects have been well documented in patients with schizophrenia, including weight gain, de novo diabetes mellitus and lipid abnormalities (Van Harten et al., 1999; Cohn and Sernyak, 2006). Recent guidelines on monitoring of physical health in patients with schizophrenia recommend regular physical health monitoring so as to facilitate earlier detection of common, serious risk factors that could contribute to impaired health of patients with schizophrenia (Marder et al., 2004).

On routine ophthalmoscopic examination, it was suspected that patients with schizophrenia had high cup to disc ratios (CDR). Whether this was a chance finding, was not known. A MEDLINE search with the key words 'cup to disc ratio' and 'schizophrenia' failed to yield any results.

Table 1: Group characteristics of patients and controls

	Patients (n=100)	Controls (n=100)	Statistic	p
Mean age, (SD)	35.18 (11.2)	33.7 (12.5)	Unpaired t test; t = 0.84	0.40 (CI: -1.900 – 4.720); N.S.
Male, n(%)	57 (53.3%)	50 (46.7%)	Chi square test; χ^2= 0.99	0.32; N.S.
Female, n(%)	43 (46.2%)	50 (53.8%)		
CDR >0.5, n (%)	23 (95.8%)	1 (4.2%)	Chi square test; χ^2= 22.9	<0.001
Mean CDR (SD)	0.36 (0.12)	0.30 (.06)	Mann-Whitney U test; U = 3855	0.002

Cup to disc ratio (CDR)

On fundoscopy, the cup to disc diameter is usually expressed as a ratio – 'the cup to disc ratio'. It is usually around 0.3, in the normal population (Quigley, 1993). It is postulated that in patients with raised intra ocular pressure, as nerve fibers are destroyed, the neural rim of the disc shrinks and the physiological cup within the disc enlarges, to form the pathological cup. This leads to progressive increase in the cup disc ratio. The CDR hence assists in identifying small glaucomatous discs (Garway-Heath et al., 1998). The probability of abnormality increases dramatically with values above 0.5 (Quigley, 1993).

The aim of the present study was to compare the CDR of patients with schizophrenia with that of normal controls and also look for any relationship between CDR and duration of illness, duration of treatment and medication.

Material and Methods

The study protocol was approved by the local ethics committee at B Y L Nair Hospital Mumbai, where the study was conducted. The patient group included 100 consecutive cases, 18 years and older, of either gender, who met the DSM-IV diagnostic criteria for schizophrenia undergoing treatment at the hospital. Patients with a history of substance dependence and those taking medications for any physical illness were excluded from the study. The control group consisted of 100 healthy volunteers without a history of mental illness, who were not undergoing treatment for a physical illness, and did not have a family history of mental illness. We also excluded people with a history of high myopia from the study. Written informed consent was taken from the participants for instillation of a mydriatic in the eyes. Pupils were dilated using tropicamide 1% eye drops and optic nerve head assessment was done by direct ophthalmoscopy (Kirwan et al., 2000). This was done by a single observer – a trained ophthalmologist (R.T.), to reduce the chance of inter-observer variation. The vertical cup to disc ratio was measured. This method has been shown to have a sensitivity of 64% and specificity of 73 - 96% depending on the CDR (Harper and Reeves 2000; Quigley et al., 1992). Both eyes were examined, and the higher CDR value of the two was included in the study. The ophthalmologist was blind to whether the subject was a patient or a control. Patient's case records were reviewed and the following data collected: their age, duration of illness, duration of treatment and the details of the medication.

STATISTICAL ANALYSIS

Using Russell Lenth's java applet for power and sample size calculation, to detect an effect size (difference in mean CDR between the case and control) of 0.05, with 90% power, when the significance level set at *alpha = 0.05*, and the *sigma* in each group at 0.1, we needed a sample size of 88 subjects in each group (Lenth, 2004, Lenth, 2001). The data obtained was subjected to statistical analysis using SPSS version 12 (SPSS, 2003). Categorical variables were compared using chi square test. Distribution of continuous data was tested using the Kolmogorov-Smirnov test. Where the data assumed normal distribution, the difference of means between two groups was tested using unpaired t tests. Where the data did not assume normality as in the case of CDR, we used the Mann-Whitney U test to compare the two groups. The CDR among various medication groups was first compared using the Kruskall-Wallis test. Since there was a significant difference, CDR between groups, was compared using Mann Whitney test. We calculated effect size from the Z scores using the formula $r = Z/\sqrt{N}$, where N is the total number of individuals included in the test. Mean and standard deviation are shown in the tables for meaningful interpretation of data. Association between continuous variables and CDR was tested using Spearman's correlation.

Results

Patients vs. controls (Table 1)

Mean age of the sample was around 35 years. There was no gender difference. Mean CDR was higher in the patients (mean = 0.36; s.d. = 0.1) compared to controls (mean = 0.30; sd = 0.06). This difference was statistically significant (U = 3855.0; p = 0.002). The size of the effect was small (r = -0.22). We divided the study population into those with CDR < 0.5 and those with 0.5 and above, on the basis that the probability of abnormality increased for values above 0.5 (Quigley, 1993). We found that there were more patients than controls in the group with CDR 0.5 and above. This was statistically significant.

Table 2: Demographic, treatment and medication details of patients

	Males (n=57)	Females (n=43)	p	
Mean age (SD)*	36.7(11.6)	33.2 (10.4)	t= 1.5	0.1 (CI: -0.925 – 7.839); N.S.
Mean duration of illness (SD)*	9.4 (7.7)	8.4 (6.2)	t=0.71	0.5 (CI: -1.772 – 3.765); N.S.
Mean duration of treatment (SD)*	7.5 (5.3)	7.2 (5.5)	t= 0.27	0.8 (CI: -1.874-2.485); N.S.
Medication by group				
Typical Antipsychotic (AP)	18	10	χ^2= 6.3	0.2N.S.
Typical AP and Trihexyphenidyl	17	21		
Atypical Antipsychotic	6	6		
Atypical and Trihexyphenidyl	16	6		
Medication			**Mean dose (SD)**	**Mean CPZ equivalent (SD)**
Antipsychotics				
Haloperidol	23	20	9.2 (3.4)	459.3 (171.9)
Trifluperazine	12	11	13.0 (3.3)	260.9 (65.6)
Olanzapine	4	5	10.0 (2.5)	200 (50)
Risperidone	18	7	5.9 (1.2)	285.2 (80.9)
Antiparkinson drug Trihexyphenidyl	33	27	3.8 (1.7)	n.a.

*Unpaired t test
CI, 95% CI of difference.

Patients and Medication

Baseline characteristics of the cases are shown in Table 2. There was no significant correlation between the age, duration of illness and duration of treatment and the CDR. The sample was divided into four groups according to class of medications they were on. Distribution of cases in the groups is shown in table 2. The anticholinergic in this study was trihexyphenidyl. None of the patients were on more than one antipsychotic. The doses of each medication are shown in table 2. There was a highly significant correlation between the dose of trihexyphenidyl and the CDR (spearman's rho =0.75, p<0.001). There was no significant correlation between the chlorpromazine equivalent dose of the antipsychotics and the CDR.

Details of the CDR in different medication groups are shown in Table 3. There was a statistically highly significant difference in CDR among patients on various medications, as shown by the Kruskal-Wallis test. Between group comparison using Mann-Whitney U test showed that patients on trihexyphenidyl (mean = 0.41; s.d. = 0.115) had a higher CDR compared to those not on the medication (mean = 0.273; s.d. = 0.06). This difference was statistically significant (U = 364.0; p<0.001). The effect size was moderate to large (r = -0.6). The mean CDR of patients not on trihexyphenidyl (mean = 0.273; s.d.= 0.06) was lower than the control population (mean = 0.302; s.d. = 0.06). This again reached statistical significance (U = 1497.0; p = 0.007), but the effect size was small (r = -0.2).

Table 3: Comparison of CD ratio among patients in different medication group

Drugs	N	Mean CDR (SD)	CI*
Typical	28	0.261 (0.06)	0.239–0.283
Atypical	12	0.300 (0.07)	0.253–0.347
Atypical + trihexyphenidyl	22	0.382 (0.11)	0.335–0.428
Typ + trihex	38	0.432 (0.12)	0.393–0.471
Controls	100	0.302 (0.06)	0.290–0.314

*Kruskal-Wallis test, df = 4; CI, 95% confidence interval
χ^2=62.674; p<0.001

Discussion

The present study was undertaken because of the incidental observation that patients admitted with schizophrenia into the inpatient unit, had high CDR. The findings of the study confirms the above observation, although the size of the effect was small. The increase in CDR was clinically significant so as to be noticed by a trained ophthalmologist.

The etiopathogenesis and relevance of the finding in the present study is not clear. As an increased CDR may suggest neuronal damage, and considering the optic nerve to be an extension of the central nervous system, the possibility of its relevance to the etiopathogenesis of schizophrenia may be worth looking into (Marenco and Weinberger, 2000; Lieberman, 1999).

In the present study, we found no association between the CDR and the age of the individual, and the duration of illness. Longitudinal studies and studies in first episode drug naïve patients could confirm if the increase in CDR is a state or a trait abnormality and if it is stationary or progressive.

An interesting finding which came up in our study was that people, who were on antipsychotics alone, had a lower CDR compared to normal controls. Although the size of the effect was small. This could be explained on the basis of an ocular hypotensive action of dopaminergic antagonists like haloperidol (Sheppard and Schaid, 1986; Chiou, 1984a; Chiou, 1984b). Typical antipsychotics used in the present study were high potency drugs with low anticholinergic activity.

Even more interesting and significant was the finding that patients on anticholinergic medication, showed significantly higher CDR compared to those who were not. The size of this effect was moderate to large. This supports the hypothesis of a drug induced change. The association found between the dose of trihexyphenidyl and CDR complements the above hypothesis. The association was found to be significant, contributing to more than 50% of the variance.

There is evidence to suggest that drugs with anticholinergic action exacerbate or precipitate narrow angle glaucoma in susceptible individuals (Reid et al.,1976; Tripathi et al., 2003). Trihexyphenidyl (half life = 3.7 hours) is usually administered in divided doses. Repeated transient rise in the intra ocular pressure when the medication is administered, leading to repeated insults on the optic disc, may explain the observation.

It should be noted that 60% of the patients were on an anticholinergic medication for an average of around 7 years, in spite of the recommendations in existing guidelines (Lehman et al., 2004b).

Implications of these findings are not clearly obvious. Are these findings clinically significant or neurological soft signs (Dazzan and Murray, 2002)? Do they provide a clue towards the pathogenesis of schizophrenia? Or are they medication induced? Further longitudinal studies using more reliable techniques of measuring CDR in drug naïve first episode patients and subjects with family history of schizophrenia would be valuable in providing clues to the above questions.

The study reinforces the importance of physical examination in patients with Schizophrenia. This study is a preliminary observational study and needs replication using more stringent methodology.

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