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Refractive errors and schizophrenia

Asaf Caspi [a,*], Tali Vishne [b], Abraham Reichenberg [c,d], Mark Weiser [a,e,f], Ayelet Dishon [a], Gadi Lubin [f], Motti Shmushkevitz [f], Yossi Mandel [g], Shlomo Noy [a,e], Michael Davidson [a,c,e]

[a] Department of Psychiatry, Sheba Medical Center, Tel-Hashomer, Israel
[b] Beer-Yaacov Ness-Ziona Mental Health Center, Ness-Ziona, Israel
[c] Department of Psychiatry, Mount Sinai School of Medicine, New York, USA
[d] Department of Psychological Medicine, Institute of Psychiatry, King's College London, London, UK
[e] Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel
[f] Division of Mental Health, Israel Defense Force, Israel
[g] Department of Ophthalmology, E. Wolfson Medical Center, Holon, Israel

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ABSTRACT

Background: Refractive errors (myopia, hyperopia and amblyopia), like schizophrenia, have a strong genetic cause, and dopamine has been proposed as a potential mediator in their pathophysiology. The present study explored the association between refractive errors in adolescence and schizophrenia, and the potential familiality of this association.
Methods: The Israeli Draft Board carries a mandatory standardized visual accuracy assessment. 678,674 males consecutively assessed by the Draft Board and found to be psychiatrically healthy at age 17 were followed for psychiatric hospitalization with schizophrenia using the Israeli National Psychiatric Hospitalization Case Registry. Sib-ships were also identified within the cohort.
Results: There was a negative association between refractive errors and later hospitalization for schizophrenia. Future male schizophrenia patients were two times *less* likely to have refractive errors compared with never-hospitalized individuals, controlling for intelligence, years of education and socioeconomic status [adjusted Hazard Ratio = .55; 95% confidence interval .35–.85]. The non-schizophrenic male siblings of schizophrenia patients also had lower prevalence of refractive errors compared to never-hospitalized individuals.
Conclusions: Presence of refractive errors in adolescence is related to lower risk for schizophrenia. The familiality of this association suggests that refractive errors may be associated with the genetic liability to schizophrenia.

1. Background

Schizophrenia, which has a lifetime prevalence of about 1% is a familial complex genetic disorder (Sadock and Sadock, 2003; Sullivan et al., 2003). All effective pharmacological treatments for schizophrenia affect dopamine (DA) neurotransmission strongly suggesting, but not proving, that DA might be involved in its pathophysiology (Sadock and Sadock, 2003). Schizophrenia patients show compromised intellectual functioning (Heinrichs and Zakzanis, 1998; Reichenberg and Harvey, 2007), which in some patients is evident already in childhood and adolescence, many years before a clinical diagnosis is assigned (Davidson et al., 1999; Reichenberg et al., 2002; Reichenberg et al., 2005; Woodberry et al., 2008).

Despite the strong genetic contribution to the etiology of schizophrenia, linkage and association studies have yielded only weak and sometime inconsistent findings (Crow, 2007). One approach that may improve power to find genes for complex disorders is to target biological traits found in ill subjects and their unaffected relatives, so-called intermediate

* Corresponding author.
E-mail address: acaspi@netvision.net.il (A. Caspi).

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phenotypes or endophenotypes, in addition to clinical diagnosis in order to reduce heterogeneity. Such traits may be more directly related to the biological effects of susceptibility genes (Gottesman and Gould, 2003). There is an ongoing search for plausible endophenotypes for psychiatric disorders. Cognitive, electrophysiological and neurological endophenotypes have been proposed for schizophrenia (Egan et al., 2001a,c; Gottesman and Gould, 2003). It is also plausible that medical conditions may constitute potential endophenotypes.

Myopia (Nearsightedness), is the most common refractive error (Morgan, 2003). It is a vision condition in which near objects are seen clearly, but distant objects appear blurred. Twin studies have demonstrated that genetic factors have an important contribution to the aetiology of myopia. Estimates of the heritability of myopia range between 60% and 90% (Hammond et al., 2001; Hu, 1981). Qualitative evidence for gene–environment interactions in ocular refraction was obtained in a population study of twins (Hammond et al., 2001). The pathogenesis of myopia is still not known. Humans are born with significant refractive errors, but these refractive errors generally disappear with development (Wildsoet, 2008). This process is termed emmetropization. There are several studies that suggest a role for dopamine in the emmetropization process, and that disruption of this balance will induce the development of refractive errors (Stone et al., 1990; Stone et al., 1989).

Studies have shown that refractive errors, especially myopia, are more frequent among people with higher intelligence score (Cohn et al., 1988; Teasdale et al., 1988).

Taken together, the relationship between refractive errors and intelligence, schizophrenia and intelligence, and the role of DA in the etiology of both disorders, point to a plausible association between refractive errors and risk for schizophrenia. We hypothesized that the frequency of refractive errors will be *lower* in schizophrenia patients compared to normal individuals. We report results from a population-based historical prospective study of the association between refractive errors and schizophrenia and the familiality of refractive errors in siblings discordant for schizophrenia.

2. Methods

2.1. Subjects and assessments

The study builds on the Israeli Draft Board assessment of intellectual, medical, and psychiatric eligibility for service of the *unselected* population of Israeli-born Jewish adolescents at age 17 years and on the availability of the Israeli National Psychiatric Case Registry.

2.1.1. Israeli Draft Board assessment

Israeli law requires that all Jewish male adolescents between the ages of 16–17 undergo pre-induction assessment to determine their intellectual, medical and psychiatric eligibility for military service. It includes individuals who will be eligible for military service, as well as those who will be excused from service based on medical, psychiatric or social reasons. The Draft Board assessment consists of: (a) a physical examination, review of systems, and psychiatric history all conducted by a physician; (b) an assessment of intellectual ability; and (c) an interview assessing behavioral traits conducted by a psychometrician.

The physical assessment includes a mandatory standardized visual accuracy test which is described in detail elsewhere (Bar Dayan et al., 2005). In short, best corrected visual acuity is determined by a qualified optometrist using a standard Snellen chart. The intellectual assessment is comprised of four subtests (*Arithmetic-R, Similarities-R, OTIS-R and RPM-R,* described in details elsewhere (Davidson et al., 1999; Gal, 1986)), and yields a total score, which is a highly valid measure of general intelligence equivalent to a normally distributed IQ score. Information about years of education is also collected.

2.1.2. The National Psychiatric Hospitalization Case Registry

The registry, contains a complete listing of all psychiatric hospitalizations in Israel, and includes the ICD-10 diagnoses assigned at admission and discharge by a board-certified psychiatrist. Diagnoses recorded in earlier ICD codes are routinely upgraded. Reporting is monitored by a special department at the Ministry of Health that verifies compliance with reporting and consistency of the information, ensuring the completeness and correctness of the data in the registry. Registry diagnoses have shown good sensitivity and specificity when measured against research diagnosis (Weiser et al., 2005).

2.1.3. The analytic cohort

After receiving approval from the local ethics committee, the Draft Board data file was linked with the National Psychiatric Hospitalization Case Registry file by the managers of the registry using an algorithm to preserve medical record confidentiality (Rabinowitz, 1998). The linking variable was the unique individual identification number (ID, equivalent to the US Social Security number). Subjects were 678,674 males consecutively assessed by the Draft Board. The linkage with the psychiatric case registry identified 2614 subjects with a last discharge diagnosis of schizophrenia, who were not hospitalized in a psychiatric ward prior to the Draft Board assessment or within one year following the assessment, and who did not receive any psychiatric or neurological diagnosis during the Draft Board screening. 2093 of the schizophrenia patients had at least one sibling in the cohort that was never hospitalized for schizophrenia. The cohort also included 294,985 sib-ships, where none of the siblings had been hospitalized for schizophrenia during the follow-up period.

2.2. Statistical analysis

Cox proportional hazards regression models were used to examine the association between refractive errors and schizophrenia. Hazard ratio (HR) and 95% confidence intervals (CI) were calculated. *p*-values were computed using Wald chi-square, and significance level was set at 0.05 (two-sided). Time intervals were rounded to the nearest year and individuals were censored on the last day of follow-up, which was the date of merging the Draft Board data with the Israeli National Psychiatric Hospitalization Case Registry. First, refractive error status was included as the only predictor in the model. A second model adjusted for potential confounders, including intellectual functioning, and education (Davidson et al., 1999; Reichenberg et al., 2002; Teasdale et al., 1988), and socioeconomic status (SES) (Byrne et al.,

2004). The SES measure was based on Israeli National Bureau of Statistics data linking parental residential address to income (Israel-Ministry-of-the-Interior, 1995).

Analyses were repeated examining the association between refractive errors and schizophrenia for schizophrenia cases from the discordant sibships, and for individuals from sibships with no family history of schizophrenia. First, refractive errors status was included as the only predictor in the model. A second model adjusted for potential confounders. To examine the association between refractive errors and genetic liability for schizophrenia, logistic regression models were applied to the non-schizophrenic siblings from the discordant sibships and individuals from sibships with no family history of schizophrenia. Odds ratio (OR) and 95% confidence intervals (CI) were calculated. *p*-values were computed using Wald chi-square, and significance level was set at 0.05 (two-sided). First, refractive error status was included as the only predictor in the model. A second model adjusted for potential confounders. Only one randomly selected sibling per family was used for these comparisons to avoid violating assumptions of independence of observations.

3. Results

Twenty four of the 2614 future schizophrenia patients had refractive errors (0.92%), compared to 37,587 of 676,060 controls (5.56%). This was reflected by a negative association between presence of refractive errors at ages 16–17 and schizophrenia [HR = .47; 95% CI .32–.71, $\chi2(1) = 13.19$, $p < .0001$]. In the analysis that adjusted intelligence, years of education and socioeconomic status, the adjusted hazard ratio was .55 [95% CI = .35–.85; $\chi2(1) = 7.12$, $p = .008$], indicating that future schizophrenia patients were almost two times less likely to have refractive errors, holding intelligence, years of education and socioeconomic status constant.

In the cohort of discordant siblings, 21 of the 2093 future schizophrenia patients had refractive errors (1.00%), 75 of the 2093 non-schizophrenic siblings of the schizophrenia patients had refractive errors (3.58%), and 14,857 of 292,898 control siblings had refractive errors (5.07%). In the analysis that adjusted for intelligence, years of education and socioeconomic status, the adjusted hazard ratio for the association between refractive error and schizophrenia was .625 [95% CI = .0.41–.96, $\chi2(1) = 4.53$, $p = 0.03$]. Logistic models demonstrated an association between refractive errors and genetic liability for schizophrenia [OR = 0.73; 95% CI: 0.65–0.82; $\chi2(1) = 8.52$, $p = .004$]. The relationship between refractive errors and genetic liability for schizophrenia was maintained after adjustment for intelligence, years of education and socioeconomic status [Adjusted OR = 0.65; 95% CI: 0.40–0.99; $\chi2(1) = 3.73$, $p < .05$].

4. Discussion

In a historical prospective population-based cohort study, we have demonstrated an inverse relationship between refractive errors at age 17 and later hospitalization for schizophrenia in males. Refractive errors were less prevalent among future male schizophrenia patients as compared to the general population. The effects persisted after adjustment for socioeconomic status, education and IQ. We also observed that the prevalence of refractive errors among male siblings of future schizophrenia patients was intermediate between future patients and controls, suggesting that refractive errors may be associated with the genetic liability to schizophrenia.

The role of DA in schizophrenia has long been debated. However, over the past five years genetically determined variations in DA metabolism in the frontal cortex have been linked to schizophrenia. Variation in the Catechol-O-methyltransferase (COMT) gene which is associated with the regulation of the dopaminergic system has been associated with risk of schizophrenia (Akil et al., 2003; Egan et al., 2001b). In myopia DA may act as an inhibitor of growth (Morgan, 2003; Stone et al., 1989). It had been shown that myopia can be attenuated by dopamine agonists (Iuvone et al., 1991), and increased dopamine release can partially block the development of myopia (Rohrer et al., 1993). Thus, it is possible that the relationship between myopia and schizophrenia is the result of a common neurotransmitter developmentally effecting both cortical–subcortical cognition network/s, and vision.

Another possible explanation for the association between schizophrenia and low prevalence of myopia could be related to reduced near work load in premorbid schizophrenic patients. Near work has long been characterized as one of the main environmental risk factors for the development of myopia (Saw, 2003). It is possible that future schizophrenic patients read less, and therefore have a lower risk for the development of myopia. However, our analysis controlled for the potential confounding effects of education and intelligence.

A major strength of the study is the fact that the Draft Board carries a mandatory standardized visual accuracy assessment. Furthermore, all schizophrenia patients were first hospitalized at least one year after Draft Board assessment. The results of the study thus cannot be accounted for by inadequate correction of visual impairment, patient's unawareness of visual deficits, or physicians failure to notice such deficits, which have previously been documented in psychiatric populations, particularly in schizophrenia (Prager and Jeste, 1993).

Limitations of the current study should also be noted. First, the Draft Board applies a wide definition of refractive error (Rosner and Belkin, 1991), that is, myopia, amblyopia and hyperopia are all listed under the heading of refractive error, without the ability to distinguish between them. However, unpublished data from the Draft Board indicates that that vast majority of individuals diagnosed with refractive errors by the Draft Board have myopia. Second, the study was restricted to males. Nevertheless, while over 98% of the Jewish males born in Israel are assessed by the Draft Board, the proportion for females is lower, mostly since orthodox women are exempted from military induction. Finally, individuals who had expressed psychotic symptoms or had developed schizophrenia by age 18 were excluded from the analyses. It is possible that this may have biased the sample away from more severe forms of the disorders. On the other hand, cases with an age of onset after 40 years would also have been missed.

In summary, we found a negative association between refractive errors in male adolescence and risk for later hospitalization for schizophrenia. A similar association was observed for the non-schizophrenic siblings of individuals

destined to develop schizophrenia. Given the familiality of the association between refractive errors and schizophrenia, refractive errors may be viewed as an intermediate phenotype. Knowledge about genes associated with refractive errors may help target plausible candidate regions for linkage and association studies in schizophrenia. The epidemiological research method described in the present study may be utilized in future studies to identify additional medical conditions as potential intermediate phenotypes in schizophrenia and other psychiatric disorders.

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Contributors

Study design: Drs. Caspi, Reichenberg, Weiser and Davidson

Data acquisition: Drs. Reichenberg, Weiser, Davidson, Lubin, Shmushkevitz and Mandel.

Data analysis: Drs. Vishne and Reichenberg.

Drafting of the manuscript: Drs. Caspi and Vishne, and Ms. Dishon.

Critical revisions of the manuscript: Drs. Caspi, Vishne, Reichenberg, Weiser, Mandel and Davidson.

Administrative support: Drs. Lubin, Shmushkevitz, Noy and Weiser.

All authors contributed to and have approved the final manuscript.

Conflict of interest

The authors have no conflicts of interest to disclose in relation to this manuscript.

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