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Toxoplasma gondii and Other Risk Factors for Schizophrenia: An Update

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The failure to find genes of major effect in schizophrenia has refocused attention on nongenetic, including infectious factors. In a previous study, antibodies to *Toxoplasma gondii* were found to be elevated in 23 studies of schizophrenia (OR 2.73; 95% CI 2.10–3.60). The current study replicates this finding with 15 additional studies (OR 2.71; 95% CI 1.93–3.80) and compares this with other identified schizophrenia risk factors. The highest risk factors are having an affected mother (relative risks [RR] 9.31; 95% CI 7.24–11.96), father (RR 7.20; 95% CI 5.10–10.16), or sibling (RR 6.99; 95% CI 5.38–9.08) or being the offspring of immigrants from selected countries (RR 4.5; 95% CI 1.5–13.1). Intermediate risk factors, in addition to infection with *T. gondii*, include being an immigrant from and to selected countries (RR 2.7; 95% CI 2.3–3.2), being born in (RR 2.24; 95% CI 1.92–2.61) or raised in (RR 2.75; 95% CI 2.31–3.28) an urban area, cannabis use (OR 2.10–2.93; 95% CI 1.08–6.13), having minor physical anomalies (OR 2.23; 95% CI 1.42–3.58), or having a father 55 or older (OR 2.21–5.92; 95% CI 1.46-17.02). Low-risk factors include a history of traumatic brain injury (OR 1.65; 95% CI 1.17–2.32), sex abuse in childhood (OR 1.46; 95% CI 0.84–2.52), obstetrical complications (OR 1.29–1.38; 95% CI 1.00–1.84), having a father 45 or older (OR 1.21–1.66; 95% CI 1.09–2.01), specific genetic polymorphisms (OR 1.09–1.24; 95% CI 1.06–1.45), birth seasonality (OR 1.07–1.95; 95% CI 1.05–2.91), maternal exposure to influenza (RR 1.05; 95% CI 0.98–1.12), or prenatal stress (RR 0.98–1.00; 95% CI 0.85–1.16).

Key words: schizophrenia/*Toxoplasma gondii*/risk factors

Introduction

For many years, it was assumed that the "putative antecedents of schizophrenia are largely genetically determined,"[1] and that decoding the human genome would lead to an understanding of schizophrenia's etiology. However, genome-wide association studies (GWAS) of the disease have "revealed a few weak-effect associations, which account for only a small part of the genetic risk" so that "among scientists in the field, there is a sense of disappointment in the air."[2] The failure of the genetic studies, in turn, has led to a renewed interest in nongenetic risk factors and how these might interact with predisposing genes.

One such nongenetic risk factor is *Toxoplasma gondii*, a coccidian protozoa of the apicomplexa family. When it infects pregnant women, it may cause a congenital syndrome that includes deafness, retinal damage, seizures, and mental retardation. In immunocompromised individuals, it may produce severe central nervous system (CNS) symptoms. A 2007 meta-analysis of 23 studies of the prevalence of *T.gondii* antibodies in individuals with schizophrenia reported a combined OR of 2.73 (95% CI 2.10–3.60).[3] Since that time additional studies have been published. This article is an attempt to replicate the *T.gondii* antibody studies and a comparison of *T. gondii* with the other identified risk factors for schizophrenia.

Methods

Data Sources

A keyword search of MEDLINE, Ovid, and Google Scholar was used to identify relevant publications on *T. gondii* and schizophrenia. Studies were translated as needed. Criteria for inclusion in the meta-analysis included (1) a clear diagnosis of schizophrenia using the *Diagnostic and Statistical Manual of Mental Disorders* (United States), *International Classification of Diseases* (Europe), or *Classification of Diagnostic Standards of Mental Disorders in China* (China); (2) inclusion of a defined control group; and (3) use of a standard diagnostic assay.

To identify studies of other possible risk factors for schizophrenia, a MEDLINE search was undertaken. Matheson et al[1] recently published a study of nongenetic risk factors and identified 24 such studies after reviewing 469 publications; the present study included many of the same studies but only those for which the results were given as ORs or relative risks (RR) and thus were roughly comparable. In the present study, we divided risk factors into those associated with conception and the perinatal

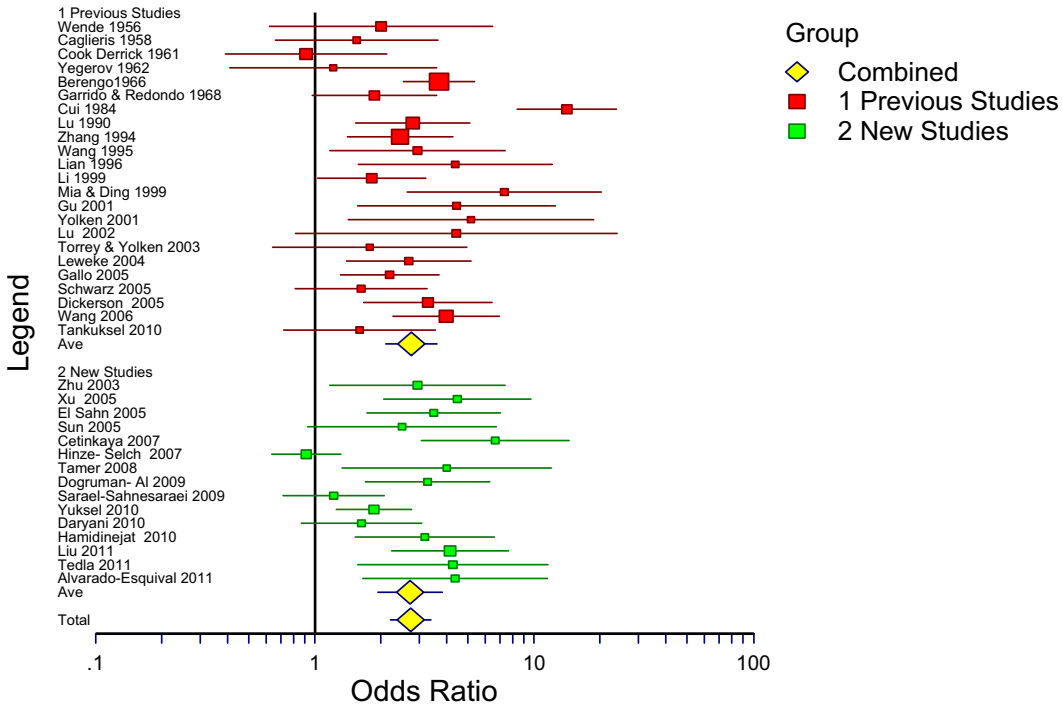

Fig. 1. Forest plot of 23 previous and 15 new studies and their combination.

period (family history, genetic polymorphisms, paternal age, maternal exposure to influenza, prenatal stress, minor physical anomalies, winter/spring birth, urban birth, and obstetrical complications) and risk factors associated with childhood or early adulthood (urban living in childhood, sex abuse in childhood, traumatic brain injury, cannabis use, and immigration). Only studies published since 1999 were used because these appeared to cover all that were relevant.

Statistical Methods

The data summarized by meta-analysis in this report originate from a series of classic 2 group binary-event studies. For our study, we are looking at the exposure rate of positive *T. gondii* antibodies in individuals with a diagnosis of schizophrenia vs a group of controls without that diagnosis. The results of each study are reported in a classic 2-by-2 contingency table. The proportion of infected individuals in each group is denoted by pt and pc, respectively, for the exposed group (t) and the control group (c).

For 2-by-2 binary-event studies, the statistic summarized is the OR, defined as (pt/[1−pt])/(pc[1−pc]). An OR of unity implies no difference between the 2 groups. An OR of 2, for example, implies that the numerator group is at a twice higher risk than the denominator group. The graphics in this report present the OR and the length of the CI for each study as well as the combined results. The software program NCSS (NCSS Statistical System for Windows, Kaysville, UT: Number Cruncher Statistical Systems, 2004) was used to analyze the raw data for the meta-analysis. We used the random effects model, which incorporates a weighted method of analysis; this is not the inverse variance-weighted method that has known limitations. The random model is also more conservative than the fixed model with wider confidence intervals, a decision supported by statistically significant chi-square heterogeneity tests. In addition, the epidemiology of *T. gondii* supports this decision in that we expected the rate of positive test results to vary from site to site as it would on exposure, hence, the use of the random model.

Because opinions vary on the appropriate methods for performing a particular meta-analysis, we examined the robustness of the findings by using a sensitivity analysis. In addition, because statistically significant results are more likely to get published, this can distort the findings in a meta-analysis. Sensitivity was thus assessed by exploring the correlation association of the size of the OR and its CI vs the size of the study because smaller ORs can be statistically significant in larger studies.

Studies of other identified risk factors have been reported both by ORs and RR. According to a textbook on biostatistics, if the disease affects less than 5% of the population, then OR and RR are approximately equal. However, when a higher percentage is affected, then OR and RR are less comparable.[4] Both OR and RR are reported in this article. Studies using measures other than OR or RR were not included. In addition, one study

Table 1. Serological Studies of *Toxoplasma gondii* Antibodies in Individuals With Schizophrenia and Controls

Year	Authors	Country	% Patients Antibody Positive (%)	% Controls Antibody Positive (%)	OR
2003	Zhu et al[6]	China	11/104 (11)	8/210 (4)	2.93
2005	Xu et al[7]	China	64/136 (47)	9/56 (16)	4.45
2005	El-Sahn et al[8]	Egypt	60/75 (80)	45/85 (53)	3.47
2005	Sun et al[9]	China	9/40 (23)	9/87 (12)	2.49
2007	Cetinkaya et al[10]	Turkey	66/100 (66)	11/50 (22)	6.62
2007	Hinze-Selch et al[11]	Germany	109/277 (39)	89/214 (42)	0.91
2008	Tamer et al[12]	Turkey	16/40 (40)	5/37 (14)	3.98
2009	Dogruman-Al et al[13]	Turkey	42/88 (48)	19/88 (22)	3.26
2009	Saraei-Sahnesaraei et al[14]	Iran	58/104 (55)	58/114 (51)	1.22
2010	Yuksel et al[15]	Turkey	182/300 (61)	68/150 (45)	1.85
2010	Daryani et al[16]	Iran	58/80 (73)	61/99 (62)	1.63
2010	Hamidinejat et al[17]	Iran	56/98 (57)	14/48 (29)	3.16
2011	Liu et al[18]	China	98/477 (21)	12/210 (6)	4.12
2011	Tedla et al[19]	Ethiopia	209/216 (97)	62/71 (87)	4.25
2011	Alvarado-Esquival et al[20]	Mexico	10/50 (20)	8/150 (5)	4.35
		Totals	2185 total patients	1669 total controls	

which had been unpublished in our previous study has been published.[5]

Results

The 15 additional *T. gondii* antibody studies in the present study resulted in an OR of 2.71 (1.93–3.80). It thus replicates the results of the previous meta-analysis of 23 antibody studies (OR 2.73; 95% CI 2.10–3.60). For all 38 studies combined the OR was 2.73 (95% CI 2.21–3.38). The new studies are summarized in table 1.[6–20] The 15 studies included 4 studies each from China and Turkey, 3 from Iran, and 1 each from Germany, Egypt, Ethiopia, and Mexico. All except one reported that individuals with schizophrenia were more likely than controls to have antibodies to *T. gondii* with ORs from 1.22 to 6.62. When added to the 23 studies previously reported,[3] the total number of patients is 6058 and controls is 8715, and the cumulative OR is 2.73 (95% CI 2.21–3.38), unchanged from the previous study. This is shown in figure 1 as a forest plot.

The results of other risk factors for schizophrenia are shown in table 2.[21–42] There appear to be 3 levels of risk. The highest risk factors are having a first-degree relative with schizophrenia (RR 6.99–9.31)[21] or being the offspring of an immigrant from selected countries (RR 4.5).[42] Intermediate risk factors include being an immigrant from selected countries (RR 2.7)[42]; being born in (RR 2.24) or raised in (RR 2.75) an urban area[34]; cannabis use (OR 2.10–2.93)[39–41]; having minor physical anomalies (average of 6 anatomical sites) (OR 2.23)[31]; or having had a father age 55 or older at the time of birth (OR 2.21).[27] Regarding the last, the study which reported an OR of 2.21[27] included 3 additional data sets than did the study reporting an OR of 5.92.[26]

The lowest risk factors for the development of schizophrenia are having a history of a traumatic brain injury (OR 1.65)[38]; sex abuse in childhood (OR 1.46)[37]; obstetrical complications (OR 1.29–1.38)[35,36]; a father age 45 or older at the time of birth (OR 1.38–1.66)[27,28]; specific common genetic polymorphisms (OR 1.09–1.24)[22–25]; seasonality of birth (OR 1.07–1.95)[32,33]; maternal exposure to influenza (RR 1.05)[29]; or prenatal stress (RR 1.00).[30]

Discussion

Having antibodies to *Toxoplasma gondii*, presumed evidence of past infection, was found to be an intermediate risk factor for the development of schizophrenia. The risk (OR 2.73) is approximately equal to the risk of being an immigrant from selected countries (RR 2.7), being raised in an urban area (RR 2.75), or being a cannabis user (OR 2.10–2.93). The plausibility of *T. gondii* as a risk factor is strengthened by the findings of infectious and immune-related genes as the strongest finding in GWAS studies,[24] the ability of *T. gondii* to make dopamine,[43] shared metabolic pathways,[44] and various epidemiological findings.[45]

One striking finding from the comparison of risk factors for schizophrenia is the discrepancy between the risk associated with having a first-degree relative with schizophrenia (RR 6.99–9.31) and risk associated with specific genetic polymorphisms (OR 1.09–1.24). A familial disease pattern suggests the involvement of shared genes but also suggests shared nongenetic factors such as diet and exposure to infectious agents. The failure of genetic studies to date to explain the familial pattern of schizophrenia suggests that nongenetic factors, which are likely to interact with predisposing genes, deserve closer examination.

Table 2. Other Risk Factors for Schizophrenia

	OR or Relative Risk
I. Risk factors associated with conception and the perinatal period	
Family history of schizophrenia	
Mortensen et al[21]	Mother RR 9.31 (7.24–11.96)
	Father RR 7.20 (5.10–10.16)
	Sibling RR 6.99 (5.38–9.08)
Genetic polymorphisms	
Allen et al[22]	OR 1.24 (1.06–1.45)
Shi et al[23]	OR 1.14 (1.07–1.12)
Stefansson et al[24]	OR 1.18 (1.12–1.25)
Chen et al[25]	OR 1.09 (1.04–1.15)
Paternal age	
Wohl and Gorwood[26]	35–54 OR 1.16 (1.03–1.31)
	>54 OR 5.92 (2.03–17.02)
Torrey et al[27]	>44 OR 1.38 (0.95–2.01)
	>54 OR 2.21 (1.46–3.37)
Miller et al[28]	45–49 OR 1.21 (1.09–1.34)
	>49 OR 1.66 (1.46–1.89)
Maternal exposure to influenza	
Selten et al[29]	RR 1.05 (0.98–1.12)
Prenatal stress	
Selten et al[30]	Six-Day War RR 0.98 (0.85–1.13)
	Yom Kippur War RR 1.00 (0.86–1.16)
Minor physical anomalies	
Weinberg et al[31]	OR 2.23 (1.42–3.58)
Seasonality of births	
Davies et al[32]	OR 1.07 (1.05–1.08)
Messias et al[33]	OR 1.95 (1.31–2.91)
Urban birth	
Pederson et al[34]	RR 2.24 (1.92–2.61)
Obstetrical complications	
Geddes et al[35]	OR 1.38 (1.05–1.84)
Cannon et al[36]	OR 1.29 (1.00–1.66)
II. Risk factors associated with childhood or early adulthood	
Urban living during childhood	
Pederson et al[34]	RR 2.75 (2.31–3.28)
Sex abuse in childhood	
Chen et al[37]	OR 1.46 (0.84–2.52)
Traumatic brain injury	
Molloy et al[38]	OR 1.65 (1.17–2.32)
Cannabis use	
Semple et al[39]	OR 2.93 (2.36–3.64)
Henquet et al[40]	OR 2.10 (1.70–2.50)
Moore et al[41]	OR 2.58 (1.08–6.13)
Immigration	
Cantor-Graae et al[42]	1st Generation RR 2.7 (2.3–3.2)
	2nd Generation RR 4.5 (1.5–13.1)

It is also of interest that, except for family history, risk factors associated with childhood and early adulthood (eg, immigration, cannabis use, urban living, infection with *T. gondii*) appear to be more important than risk factors associated with conception and the perinatal period (eg, genetic polymorphisms, exposure to influenza, prenatal stress, winter/spring birth, obstetrical complications). This suggests that carefully following children prospectively in long-term studies, doing serial assessments and collecting blood specimens, may be useful to better understand the etiology of schizophrenia. Since some of these risk factors may be interactive, it is best if all studies are done on the same patients. This is one of the objectives of the National Children's Study, just underway (www.nationalchildrensstudy.gov).

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