

Childhood Head Injury and Expression of Schizophrenia in Multiply Affected Families

Philip AbdelMalik, BSc; Janice Husted, PhD; Eva W. C. Chow, MD, JD, FRCPC; Anne S. Bassett, MD, FRCPC

Background: The etiology of schizophrenia is believed to include genetic and nongenetic factors, with the pathogenesis involving abnormal neurodevelopment. We investigated whether mild head injury during brain maturation plays a role in the expression of schizophrenia in multiply affected families.

Methods: We compared the history and severity of head injuries in childhood (age, ≤ 10 years) and through adolescence (age, ≤ 17 years) in 67 subjects with narrowly defined schizophrenia and 102 of their unaffected siblings from 23 multiply affected families. In subjects with schizophrenia, only head injuries preceding the onset of psychosis were considered.

Results: Subjects in the schizophrenia group ($n=16$ [23.9%]) were more likely than the unaffected siblings group ($n=12$ [11.8%]) to have a history of childhood head injury ($P=.04$; odds ratio, 2.35 [95% confidence inter-

val, 1.03-5.36]). Subjects in the schizophrenia group with a history of childhood head injury had a significantly younger median age at onset of psychosis (20 years) compared with those with no such history (25 years; $z=-2.98$; $P=.003$). The severity of head injury ranged from minimal to mild, including concussions, but within this narrow range, severity was correlated with younger age at onset ($r_s=-0.66$; $P=.005$). Head injury occurred a median of 12 years before the onset of psychosis. Results were similar if head injuries during adolescence were included, but did not achieve statistical significance.

Conclusions: Mild childhood head injury may play a role in the expression of schizophrenia in families with a strong genetic predisposition. Prospective studies of mild head injury should consider genetic predisposition for possible long-term neurobehavioral sequelae.

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From the Centre for Addiction and Mental Health (Mr AbdelMalik and Drs Chow and Bassett) and the Department of Psychiatry, University of Toronto (Drs Chow and Bassett), Toronto, Ontario, and the Department of Health Studies and Gerontology, University of Waterloo, Waterloo, Ontario (Dr Husted).

SUSCEPTIBILITY to schizophrenia is believed to be due to multiple genetic and interacting nongenetic factors.¹ In contrast to other multifactorial disorders such as coronary heart disease, however, much less is known about the specific factors involved. The onset of schizophrenia occurs most commonly from late adolescence to midadulthood. Mild congenital physical features, subtle neurobehavioral abnormalities, and structural brain abnormalities may precede onset of major psychotic features, supporting the hypothesis that abnormal neurodevelopment is involved in the pathogenesis of schizophrenia.² The search for nongenetic factors has therefore focused on the period from conception through childhood. Although evidence in later-onset neurobehavioral disorders suggests that head injury may modify risk³⁻⁵ or age at onset,⁴ childhood head injury has been little studied in schizophrenia.^{6,7}

In adults, an association of severe head injury with subsequent onset of psychotic illness has been suggested.^{8,9} However, head injuries are most common during childhood,¹⁰ and most are of minimal to mild severity, including concussions.^{11,12} Short-term sequelae include subtle cognitive and neurobehavioral impairments,¹⁰ but limited information exists on long-term sequelae^{11,13} and whether genetic predisposition for specific outcomes has an effect. Two retrospective studies have reported a greater prevalence of childhood head injury in patients with schizophrenia than in comparison groups,^{6,7} but these studies did not consider genetic predisposition.

The purpose of the current retrospective study was to investigate whether head injury during brain maturation, before onset of psychotic symptoms, may play a role in the expression of schizophrenia in multiply affected families likely to have a strong genetic predisposition to schizophrenia. We hypothesized that a history of child-

hood head injury would be associated with the subsequent development of schizophrenia among genetically predisposed individuals. We therefore predicted that individuals with schizophrenia would have higher rates of childhood head injury than their siblings without schizophrenia. We further hypothesized that the presence of a childhood head injury would modify the expression of schizophrenia, and that this would be evidenced by a younger age at onset of psychosis in individuals with pre-onset childhood head injury.

METHODS

SAMPLE AND DIAGNOSTIC ASSESSMENT

Subjects were adults from Canadian families, ascertained as part of an ongoing study of familial schizophrenia and recently reported to have highly significant evidence of genetic linkage of narrowly defined schizophrenia (schizophrenia or chronic schizoaffective disorder) to a locus on chromosome 1q21-q22.¹⁴ On average, 13 subjects participated per family, including 3 with schizophrenia.¹⁴ Subject ascertainment and assessment methods are detailed elsewhere.^{14,15} Briefly, pedigrees were selected if they had a proband and at least 1 other relative with schizophrenia, and if multiple affected and unaffected family members were willing to participate. All participating subjects were directly interviewed by a psychiatrist using the Structured Clinical Interview for DSM-III-R (SCID-I),¹⁶ modified by the principal investigator (A.S.B.) to obtain information on head injury and other medical issues. Collateral information, including extensive family history and medical records where available, was also collected. After a review of all available information, lifetime DSM-III-R¹⁷ diagnoses were assigned, which enabled determination of narrow and broad definitions of schizophrenia.¹⁴ The latter included schizophrenia spectrum disorders (delusional disorder, psychosis not otherwise specified, brief reactive psychosis, schizophreniform disorder, schizotypal personality disorder, and paranoid personality disorder) in addition to narrowly defined schizophrenia. Ethics approval was granted by the ethics review board of the University of Toronto, Toronto, Ontario, and all subjects provided written, informed consent to participate in the study.

The sample used in the present study consisted of 67 subjects with narrowly defined schizophrenia (schizophrenia, $n=50$; schizoaffective disorder, $n=17$) from 23 families with familial schizophrenia and 102 of their siblings without schizophrenia, who were considered unaffected (unaffected group). Thirteen subjects in the unaffected group had schizophrenia spectrum disorders. On average in this study, 2.9 schizophrenia and 4.4 unaffected group subjects were included per family. We excluded the following subjects: 2 subjects with schizophrenia who had no unaffected siblings, 16 subjects with schizophrenia and 9 unaffected subjects with missing or insufficient information regarding head injury, and 2 subjects with schizophrenia who had onset of psychosis at older than 50 years. Age at onset of psychosis in schizophrenia was determined from SCID-I findings, medical records, and collateral information.

ASCERTAINMENT OF HISTORY OF HEAD INJURY

Data on head injury were obtained primarily from the modified SCID-I, supplemented where available by collateral information from family members and medical records. All subjects were asked whether they had ever had any head injuries

and whether they had ever lost consciousness. Loss of consciousness (LOC) was determined to be momentary (ie, dazed, stunned, or unconsciousness for <2 minutes) or longer. Additional questions and collateral information determined the following information with regard to each head injury: age of occurrence, circumstances of the injury, and any sequelae, including approximate duration of LOC and treatment received. Three investigators (J.H., E.W.C.C., and A.S.B.) independently rated the occurrence and severity of head injury while masked to the diagnostic group, age at onset, and identifying data. The investigators used the following coding scheme developed for a study of head injury in Alzheimer disease⁴: 1 indicates no head injury; 2, minor head injury with no LOC and no history of being stunned or dazed; 3, minor head injury with momentary LOC only, or a history of being stunned or dazed; 4, head injury with LOC more than momentary but less than 1 hour, and/or dizziness, confusion, and/or behavioral changes in the days following; 5, head injury with LOC for more than 1 hour but less than 1 day, and/or headaches, dizziness, and/or confusion in the months following; 6, head injury with coma lasting 1 to 4 days; and 7, head injury with coma lasting 5 days or longer. Consensus ratings were used for each subject included in the study, with ratings of 2 or greater indicating the occurrence of a head injury.⁴ Childhood head injuries were defined as those occurring at or younger than 10 years, consistent with 2 previous studies.^{6,7} Since the most critical period of neurodevelopment related to risk for schizophrenia is unknown, we also examined head injuries occurring through adolescence, ie, up to and including 17 years of age. In the schizophrenia group, only head injuries occurring before onset of psychosis were considered. Three subjects in the unaffected group and no subject in the schizophrenia group had a history of multiple head injuries; for these subjects, the earliest head injury was used in the analyses.

STATISTICAL ANALYSES

We used t -test and χ^2 -test statistics to compare the 2 subject groups on demographic variables and lifetime and childhood head injuries. We computed odds ratios (ORs) to compare the likelihood of childhood head injury in the schizophrenia group with that in the unaffected group. In the schizophrenia group, we used Wilcoxon rank sum tests to compare the age at onset of psychosis in those with and without head injuries and Spearman rank correlations to assess the relationship between age at onset of psychosis and severity of head injury. To adjust for the effect of family membership, we calculated a Mantel-Haenszel OR (OR_{MH}), a weighted average of the family-specific ORs.¹⁸

RESULTS

SOCIODEMOGRAPHIC CHARACTERISTICS

We found no significant difference in the proportion of male subjects between the schizophrenia ($n=34$ [50.7%]) and unaffected ($n=41$ [40.2%]) groups ($\chi^2_1=1.82$; $P=.18$). Mean age at assessment of the schizophrenia (44.6 years [SD, 13.2 years]) and unaffected (43.3 years [SD, 12.7 years]) groups was similar ($t_{166}=0.65$; $P=.51$). In the schizophrenia group, mean age at onset of psychosis was 23.2 years (SD, 7.5 years; range, 8-46 years) and was not significantly different between male (23.6 years [SD, 6.9 years]) and female (22.8 years [SD, 8.2 years]) subjects ($t_{63}=0.42$; $P=.68$).

Table 1. Occurrence of Childhood Head Injury in Familial Schizophrenia and Unaffected Sibling Groups

History of Head Injury	Subject Groups, No. (%)		Analyses	
	Familial Schizophrenia (n = 67)	Unaffected (n = 102)	OR (95% CI)	P Value
Childhood (age at occurrence ≤10 y)				
Yes	16 (23.9)	12 (11.8)	2.35 (1.03-5.36)	.04
No	51 (76.1)	90 (88.2)		
Childhood through adolescence (age at occurrence ≤17 y)				
Yes	23 (34.3)	22 (21.6)	1.90 (0.95-3.79)	.07
No	44 (65.7)	80 (78.4)		

Abbreviations: CI, confidence interval; OR, odds ratio.

GENERAL CHARACTERISTICS OF CHILDHOOD HEAD INJURIES

All childhood head injuries were closed and of relatively mild severity (rating range, 2-4), with the exception of 1 unaffected subject (rating, 7). Hemispheric location of most head injuries was unavailable. We found no instances of posttraumatic seizures or evidence of other severe immediate sequelae such as intracranial hemorrhage. The severity of childhood head injury was not significantly different between the groups ($z = -0.39$; $P = .69$). The median severity rating was 3 for both groups, and the median age of occurrence was 6 years in the schizophrenia group and 7 years in the unaffected group. Most childhood head injuries were attributed to falls ($n = 8$ [50.0%] in the schizophrenia group and $n = 5$ [41.7%] in the unaffected group). The remainder consisted of sports-related injuries (schizophrenia group, $n = 1$ [6.2%]; unaffected group, $n = 3$ [25.0%]), blows to the head (schizophrenia group, $n = 5$ [31.2%]; unaffected group, $n = 3$ [25.0%]), motor vehicle crashes (schizophrenia group, $n = 1$ [6.2%]; unaffected group, $n = 1$ [8.3%]), and other causes (schizophrenia group, $n = 1$ [6.2%]). No injuries were associated with alcohol or other drug use.

We found no sex differences in childhood head injuries in the overall sample (male, $n = 14$ [50.0%]; female, $n = 14$ [50.0%]) or within the schizophrenia (male, $n = 9$; female, $n = 7$; $\chi^2 = 0.25$; $P = .62$) or the unaffected (male, $n = 5$; female, $n = 7$; $\chi^2 = 0.33$; $P = .56$) group. We also found no significant sex differences when the definition was broadened to include head injuries occurring through adolescence (male, $n = 27$ [60.0%]; female, $n = 18$ [40.0%]) ($\chi^2 = 1.80$; $P = .18$).

LIFETIME HEAD INJURY

The proportion of subjects with a lifetime occurrence of head injury was not significantly different between the schizophrenia ($n = 29$ [43.3%]) and unaffected ($n = 32$ [31.4%]) groups ($\chi^2 = 2.49$; $P = .11$). Most head injuries in both groups occurred at age 17 years or younger. Age distributions for head injury in the schizophrenia and unaffected groups were 2 and 0 subjects, respectively, at younger than 3 years; 4 and 3 subjects, respectively, at 3 to 5 years; 10 and 9 subjects, respectively, at 6 to 10 years;

7 and 10 subjects, respectively, at 11 to 17 years; and 6 and 10 subjects, respectively, at older than 17 years.

HISTORY OF CHILDHOOD HEAD INJURY AND THE DIAGNOSIS OF SCHIZOPHRENIA

Consistent with our hypothesis, a significantly greater proportion of subjects with schizophrenia (23.9%) than unaffected siblings (11.8%) reported a history of childhood head injury ($P = .04$). The odds of having experienced a childhood head injury in the schizophrenia group were 2.35 times those in the unaffected group (**Table 1**). This association remained after adjusting for family membership (OR_{MH} , 3.35 [95% CI, 1.22-9.20]). The OR_{MH} is based on only those 15 families with 1 or more subjects with a history of childhood head injury (131 subjects).

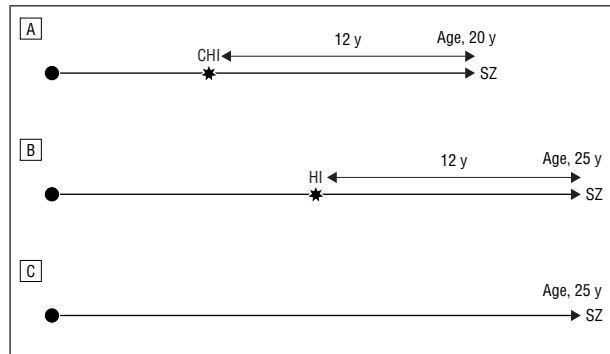
When the definition of childhood head injuries was broadened to include those occurring in adolescence (Table 1), the association between childhood head injury and schizophrenia was weaker and no longer statistically significant (OR , 1.90 [95% CI 0.95-3.79]; OR_{MH} , 2.18 [95% CI, 0.90-5.31]). Since the definition used for childhood head injury was arbitrary, we performed post hoc analyses of head injuries occurring through each age from 11 to 17 years. The results indicated that head injuries occurring at 15 years or younger were significantly associated with schizophrenia (OR , 2.27 [95% CI, 1.08-4.78]; $P = .03$). When the primary analysis was repeated using the broad definition of schizophrenia, which included an additional 13 subjects with schizophrenia spectrum disorders, one of whom had a history of childhood head injury (age of occurrence, ≤10 years), the effect of childhood head injury was reduced (OR , 1.91 [95% CI, 0.84-4.38]).

HEAD INJURY AND AGE AT ONSET OF PSYCHOSIS

As hypothesized, childhood head injury was found to be significantly associated with younger age at onset of psychosis in the schizophrenia group. The median age at onset of psychosis was significantly younger ($P = .003$) in the presence of a history of childhood head injury (**Table 2**). The relationship remained significant when 2 subjects with age at onset of psychosis younger than

Table 2. Childhood Head Injury and Age at Onset of Psychosis in Familial Schizophrenia

History of Head Injury	No. of Subjects (n = 67)	Age at Onset of Psychosis, y			Analyses	
		Mean (SD)	Median	Range	z	P Value
Childhood (age at occurrence ≤10 y)						
Yes	16	18.4 (4.0)	20	8-24	-2.98	.003
No	51	24.7 (7.7)	25	8-46		
Childhood through adolescence (age at occurrence ≤17 y)						
Yes	23	21.3 (7.0)	20	8-42	-1.55	.12
No	44	24.2 (7.6)	25	8-46		



Median age at onset of psychosis in schizophrenia (SZ) in individuals with a genetic predisposition to familial SZ (solid circle) with childhood head injury (CHI) (age at occurrence, ≤10 years; n=16) (A), adolescent and young adulthood head injury (HI) (age at occurrence, 12-22 years; n=9) (B), and no HI (n=42) (C) preceding onset of psychosis. Double-headed arrows indicate the median latency in years from CHI or HI to SZ.

12 years were excluded ($z = -2.87$; $P = .004$) and when male and female subjects underwent separate analysis ($z = -2.12$ [$P = .03$] for male subjects; $z = -2.25$ [$P = .02$] for female subjects). The severity of the childhood head injury was significantly correlated with younger age at onset ($r_s = -0.66$; $P = .005$). Again, results were similar but weaker when the definition of head injury was broadened to include those that occurred in adolescence and failed to reach statistical significance (Table 2). Post hoc analyses of head injuries occurring during each age from 11 to 17 years indicated that head injuries occurring at 15 years or younger were significantly associated with an earlier age at onset ($z = -2.32$; $P = .02$), with similar correlations between severity and age at onset ($r_s = -0.65$; $P = .001$).

We found no correlation between the specific age at which a childhood head injury occurred and the age at onset of psychosis in the schizophrenia group ($r_s = 0.03$; $P = .92$). The median latency between a childhood head injury and the onset of psychosis was 12 years (range, 1-23 years). The median latency was also 12 years (range, 1-25 years) for the 9 subjects with schizophrenia who had a preonset head injury in adolescence (n=7) or in adulthood (n=2). The median age at onset of psychosis (25 years) in this subgroup with later head injuries did not differ from that in the 42 subjects with schizophrenia who had no history of head injury before onset (25 years) ($z = 1.01$; $P = .31$). The **Figure** diagrams these results.

COMMENT

Findings from this study suggest that in familial schizophrenia, mild head injuries occurring during childhood may be associated with the subsequent development of schizophrenia and a younger age at onset of psychosis. Psychosis occurred on average about 5 years earlier in subjects with a childhood head injury. To our knowledge, this is the first report of the possible effects of head injury on age at onset in schizophrenia. Although the head injuries reported herein were of minimal to mild severity consistent with concussions, younger age at onset of psychosis was significantly correlated with greater severity of head injury. The significant effects were found with preonset head injuries occurring at 10 years or younger and were restricted to narrowly defined schizophrenia. We found no apparent effects of sex or family membership on these findings in this sample. These results support the possibility that in individuals from families with an elevated genetic predisposition to schizophrenia, childhood head injury may interact with genetic effects to modify the expression and course of the disorder.

The study findings are consistent with the limited available literature that has suggested a significant association between schizophrenia and childhood head injury.^{6,7} However, the head injuries reported in those studies were of greater average severity than in the present investigation, family history of schizophrenia was unknown, and the relationship to the age at onset of psychosis was not reported.^{6,7} Genetic predisposition to schizophrenia was also unknown in a long-term outcome study of head injuries in more than 3000 Finnish men during wartime,¹⁹ which reported that schizophrenic psychoses were more strongly associated with mild head injuries without LOC and occurring before 20 years of age. Latency from injury to onset of illness in that study was longer than 10 years,¹⁹ similar to that in the present study. The importance of genetic predisposition was emphasized in a recent study of 45 patients ascertained through neuropsychiatric and medicolegal clinics who had a history of moderate to severe head injuries and later development of a schizophrenialike psychosis.⁸ That study reported that the factor most strongly differentiating these subjects from a sample matched on age, sex, and age at injury was a positive family history of psychotic illness; however, the mean latency from injury to onset of psychotic illness was about 4 years, and

only 3 subjects had a childhood head injury (age, ≤ 10 years).⁸ In the only other report regarding head injury in familial schizophrenia, age at onset of psychosis and rates of preonset head injury were not reported,²⁰ making it difficult to compare results with those from the present study.

The precise mechanisms by which head injury could play a role in the expression of schizophrenia are unknown, since limited knowledge is available about the pathogenesis of mild traumatic brain injury or schizophrenia. Indications of perturbed neurodevelopment in schizophrenia exist,^{2,21,22} but the neuropathology of schizophrenia during childhood is entirely unknown. Childhood head injuries may involve microscopic and/or molecular structural brain damage, including tension (tearing apart of tissues), compression, and shearing of brain tissue,²³ and may result in serious sequelae, even in the absence of LOC.^{11,24} Evidence suggests that the primary impact of closed-head injury is of a diffuse, nonspecific nature, which is attributed to diffuse shearing and tearing of axonal fibers.^{23,25} Furthermore, although a child's brain may better absorb injuries and may therefore be more resilient to focal damage,⁹ this quality has the potential to contribute to greater generalized shearing damage.²³ Such effects could contribute to the disconnectivity hypothesized in schizophrenia. The effects of head injury in the developing brain can initially be silent and become evident only later when the compromised brain is challenged, eg, by age-appropriate behavioral demands.^{23,25} This may partially explain why some studies of mild childhood head injury find short-term neurobehavioral sequelae²⁶ and others do not.¹¹

A possible mechanism for associations between disease states and head injury that has long been proposed²⁵ and recently reviewed²⁷ is the cerebral reserve or threshold theory of causation. According to this model, individuals with greater vulnerability (eg, genetic vulnerability) to functional impairment have a lower brain reserve capacity (eg, reduced neuronal redundancy) and thus a lower tolerance for exceeding a neuropathological threshold, with or without acquired conditions such as head injury.²⁷ This mechanism has been proposed for the observed association between head injury and neurodegenerative disorders such as Alzheimer disease and Parkinson disease.³⁻⁵ Although the pathogenesis of schizophrenia is hypothesized to be neurodevelopmental, with less evidence of neurodegeneration,²² a similar threshold mechanism may apply.^{6,20} Results from the present study and others⁸ support the likelihood that a postnatal event during neurodevelopment, such as childhood head injury, could interact with genetic predisposition in a dynamic pathway leading to expression of schizophrenia.^{21,22}

An alternative explanation for our findings is that head injury may be related to an underlying genetic predisposition to schizophrenia. For example, head injuries may occur more frequently in children who are already exhibiting subtle premorbid features of schizophrenia such as motor developmental delays or other soft neurological signs such as incoordination.²¹ Damage resulting from the head injury could then accelerate the development of schizophrenia. The present study can-

not distinguish between the possibility of such an iterative process and genetic endowment and head injury as separate factors in a pathogenetic pathway.

The main advantages of the present study relate to the familial schizophrenia sample used. The recent finding that narrowly defined schizophrenia is significantly linked to chromosome 1q21-q22 in most of the families studied¹⁴ provides evidence of relative genetic homogeneity in this sample. A familial sample, particularly one with enhanced genetic homogeneity, may facilitate the study of nonshared environmental factors in siblings, especially factors that are independent of genetic risk.²⁸ Individual genetic susceptibility to schizophrenia cannot be assessed, however, until disease alleles have been identified and the specific penetrance of these alleles has been elucidated.

There are several limitations to the current study. As with all retrospective studies, the reliability of the information gathered on head injury is uncertain. We attempted to minimize recall and information bias by performing the initial data gathering masked to the specific hypotheses of the study, reviewing all available medical records, and using masked consensus ratings of head injury categorization. However, head injuries in most cases occurred decades before the interview, and mild childhood head injuries may be underreported,¹³ especially those occurring in infancy or those with no immediate sequelae. If one assumes that such errors occurred with equal frequency in the schizophrenia and unaffected groups, these errors would have led to an underestimation of the association between childhood head injury and schizophrenia. Alternatively, if subjects ascribed a causal connection between childhood head injury and schizophrenia, head injuries may be more likely to be reported by affected subjects than unaffected siblings. Such a reporting bias would overestimate the association. However, one would expect this overestimation to involve injuries more proximate to the onset of illness. This is not supported by results from the present study, which became nonsignificant when preonset head injuries through adolescence were included. Another limitation was that the scale used to evaluate head injuries was developed for adults and primarily used LOC as a measure of severity, which may not be appropriate for assessment of childhood head injuries.^{9,11} However, the scale included ratings for minimal head injuries with no LOC and head injuries that would be considered concussions. Two further limitations relate to the sample. Although post hoc analyses indicated that results remained significant for head injuries occurring at 15 years or younger, because of the small sample sizes involved, this study had insufficient power to determine conclusively an upper age limit of childhood head injuries for the observed associations. Also, ascertainment of a form of schizophrenia likely to be genetic meant that subjects with schizophrenia believed to result from a serious head injury would not have been included. Thus, head injuries in this sample were limited to a mild range, and results may not be applicable to more severe head injuries. Findings from the study by Sachdev et al,⁸ for example, suggest that more severe head injuries occurring at any time from childhood through early adulthood may be associated with devel-

opment of a psychotic illness after a relatively short latency period, although genetic predisposition still appeared to be an important factor in this process.

CONCLUSIONS

Our results suggest that mild childhood head injury may accelerate the expression of schizophrenia in families with a strong genetic predisposition to the disorder. Our use of a relatively homogeneous familial schizophrenia sample¹⁴ may have maximized our ability to detect this possible gene-environment relationship. Further studies will be necessary to determine whether these findings are common to other forms of schizophrenia, familial or otherwise, and whether vulnerability of schizophrenia to acquired brain injury varies. We also plan to investigate the relationship of childhood head injury to symptoms and outcomes for familial schizophrenia. Most mild childhood head injuries are insignificant¹¹ and will have no major sequelae. However, head injuries are common in childhood,²³ and the lifetime morbid risk for schizophrenia is about 1% in the general population.²⁹ The observed relationships between head injury and the expression of familial schizophrenia highlight the need for a better understanding of the possible long-term neurobehavioral sequelae of mild childhood head injury and the importance of considering genetic predisposition to specific sequelae.

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Corresponding author and reprints: Anne S. Bassett, MD, FRCPC, Centre for Addiction and Mental Health, 1001 Queen St W, Toronto, Ontario, Canada M6J 1H4 (e-mail: anne.bassett@utoronto.ca).

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