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Schizophrenia-like psychosis following traumatic brain injury: a chart-based descriptive and case–control study

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ABSTRACT

Background. Head injury has been reported to increase the likelihood of the development of schizophrenia-like psychosis (SLP), but its features and risk factors have been insufficiently investigated.

Method. Between 1987 and 1997, we examined 45 referred patients with SLP following brain trauma. These subjects were matched with 45 head-injured subjects without SLP on age (current and at injury) and gender, and their case records reviewed systematically. The groups were compared and logistic regression analyses performed.

Results. The psychoses had a mean age of onset of 26·3 years, a mean latency of 54·7 months after head injury, usually a gradual onset and a subacute or chronic course. Prodromal symptoms were common and depression often present at onset. Paranoid delusions and auditory hallucinations were the predominant features, with formal thought disorder, catatonic features and negative symptoms being uncommon. The SLP group had more widespread brain damage on neuroimaging, especially in the left temporal and right parietal regions, and were more impaired cognitively. Fewer (non-significantly) SLP subjects had epilepsy which was more likely to be well-controlled in this group. On regression analysis, a positive family history of psychosis and duration of loss of consciousness were the best predictors of SLP.

Conclusions. Head injury-related psychosis is usually paranoid-hallucinatory and subacute or chronic in its presentation. A genetic predisposition to schizophrenia and severity of injury with significant brain damage and cognitive impairment may be vulnerability factors.

INTRODUCTION

The relationship between schizophrenia and brain trauma has generated research interest for over a century (Von Krafft-Ebing, 1868). A study by Lishman (1968), that used contemporary diagnostic criteria, identified only five patients with a schizophrenia-like illness in 670 patients with penetrating head injury. Achte *et al*. (1969), in a large Finnish series, reported psychosis in 8·9% of 3552 brain injured men, with 24% of these being schizophrenia-like, occurring more commonly with mild injuries in younger persons. The survey by Davidson & Bagley (1969) suggested a 2–3 fold increase in the risk of schizophrenia in head injured individuals. While anecdotal reports continued to be published (Miller, 1966; Merskey & Woodforde, 1972; O'Callaghan *et al*. 1988; Buckley *et al*. 1993), doubt remained whether this was more than a chance association of relatively common conditions. A retrospective study from Belgium (de Mol *et al*. 1987) further supported an increased prevalence of chronic psychosis in head injured individuals.

The recent interest in the neurodevelopmental origins of schizophrenia has raised the issue of

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the possible role of early brain trauma in the genesis of schizophrenia. Evidence has been presented (Murray & Lewis, 1987; Dalman *et al*. 1999) to implicate pregnancy and delivery complications, some of which result in traumatic brain injury, in an increased risk for the development of schizophrenia. In a large retrospective study, Wilcox & Nasrallah (1987) concluded that childhood head trauma at less than 5 years of age was more likely to have occurred in schizophrenic patients, but there was no relationship to location of injury. Gureje *et al*. (1994), in another retrospective study, also found an association between childhood brain trauma and schizophrenia. These patients had mixed laterality in adulthood, possibly attributable to left hemispheric damage.

If head injury does make a contribution to the development of schizophrenia-like psychosis (SLP), what are the injury and subject characteristics that determine the outcome? The literature suggests the following risk factors: early age of injury (Wilcox & Nasrallah, 1987), left hemispheric lesions (Buckley *et al*. 1993), closed rather than penetrating head injury (Lishman, 1968), and an underlying genetic or other environmental vulnerability (Wilcox & Nasrallah, 1987). We present the results of a relatively large case–control study of SLP in head-injured patients seen in a tertiary neuropsychiatric unit and a medico-legal neuropsychiatric clinic over a 10-year period. We hypothesized that SLP was most likely to be associated with a head injury that involved the left temporal lobe and occurred before the age of 5 years in an individual genetically vulnerable to schizophrenia.

METHOD

Sample

The sample comprised 45 subjects with SLP following head injury seen between 1987 and 1997. Of these, 11 were referred to a tertiary neuropsychiatric unit and the remainder referred for a medico-legal opinion. The following were necessary, as assessed independently by two authors (P.S. and J.S.S.), for entry into the study: (*i*) subject met DSM-IV criteria A to C and E for schizophreniform disorder or schizophrenia; (*ii*) subject did not meet criteria for dementia, mania, major depression or alcohol or drug dependence at any time, and delirium currently; (*iii*) there was a history of brain trauma preceding the onset of psychosis which had led to presentation to an emergency medical service, and at least a loss of consciousness for >5 min and/or anterograde amnesia >1 h documented by an ambulance officer and/or an emergency medical officer; (*iv*) there was no history of psychosis prior to the head injury.

Each SLP case was matched with a patient with history of head injury but no history of psychosis, major depression or drug or alcohol dependence on gender, age at injury (within 1 year), current age (within 2 years), and time of injury (within 2 years). The index (SLP) and matched (non-SLP) subjects were drawn from the same sources (i.e. hospital or medico-legal consultation), in the same proportion, and the selected control was the one closest to the index case for time of assessment that matched on the above variables. The comparison subjects were selected from a pool of over 1200 potential subjects, 64% of whom were male.

The study was approved by the South-Eastern Sydney Area Health Service Ethics Committee.

Assessment

All subjects were assessed thoroughly by one of the authors and detailed case records were maintained on sociodemographic information, details of head injury, psychiatric history, phenomenology of psychosis, family history of schizophrenia or other psychiatric disorder, history of birth or perinatal trauma, developmental history (abnormality in motor, intellectual or behavioural development), drug and alcohol history and physical examination. All subjects had a brain computerized tomographic (CT) scan reported by a radiologist. These detailed reports were reviewed for focal lesion or atrophy, diffuse cortical atrophy and ventricular dilatation. Subjects underwent a detailed neuropsychological assessment by experienced clinical psychologists. As these assessments were performed by different psychologists, a standard test battery was not used. However, assessments were comprehensive enough in the majority to estimate verbal and non-verbal IQ and decide whether there was cognitive dysfunction in a number of domains: verbal and non-verbal memory, frontal-executive functioning, parietal lobe functioning (constructional

ability, agnosia, apraxia) and language. The decision that a particular test related to which cognitive domain was made in consultation with a clinical neuropsychologist based on the suggestions provided by Christensen *et al.* (1997) and Lezak (1997). Definite abnormality was considered to be present in a cognitive domain if performance on a test pertaining to that domain, e.g. Rey Auditory Verbal Learning Test for Verbal Memory, had a performance below the fifth percentile on Australian norms for that age group.

The clinical data were transferred to a data form prepared for this study by a trained research assistant not aware of the main hypotheses. Initially, the reliability of the data forms was investigated by having two research assistants record data from five subjects independently. Reasons for any discrepancy were discussed and resolved. On a further 10 subjects, intra-class correlation coefficients between 0·70 and 0·92 were achieved on key variables. Since the same information was sometimes available from multiple sources, the 'best estimate' information was recorded. The neuroimaging and neuropsychological data were similarly transcribed by the research assistant blind to the diagnostic grouping of the subjects.

Statistical analysis

The two groups were compared using the *t* test for normally distributed continuous variables and χ^2 test for categorical variables. For non-categorical data, the assumption of univariate normality was tested within each group using a two-tailed *z* test of skewness and kurtosis. The assumption of univariate homogeneity of variance was tested using the Levine test. The Bonferroni correction was applied for determining significance at the 0·05 level. The results of these analyses were used to determine the variables to be used to build a logistic regression model for risk factors predicting the development of SLP after head injury. All analyses were performed using the SPSS 9.0.1 for Windows® software (SPSS, 1999).

RESULTS

Sociodemographic characteristics

The mean age of the SLP patients was 34 years (range 18–63 years), and the majority (78%) were male. They were adequately matched with the non-SLP head injured group (see Table 1).

Characteristics of head injury

The mean age at time of head injury for the SLP group was 21·6 (S.D. 10·1) years (range 2–49 years); two (2·4%) subjects had head injury before the age of 5 years, and 10 (22·2%) before the age of 16 years. The majority (80%) had a closed head injury, with motor vehicle accidents being the predominant cause. Intracranial hemorrhage occurred in 12 subjects, which was cerebral in eight, subarachnoid in three and brain stem haemorrhage in one patient. Surgical intracranial intervention for haemorrhage or raised intracranial pressure occurred in seven cases. The severity of the head injury varied considerably, with 38·2% having a post-traumatic amnesia for less than one day, and 47·1% for more than one week. In about 40% cases, the head injury was followed by personality or behavioural change, the main characteristics of which were impulsivity (35%), aggressiveness (38%), loss of social graces (39%), moodiness (33%) and, less commonly, apathy (14%), but these were not different from behavioural changes seen in non-SLP subjects. Three SLP subjects had a period of depression in the immediate post-traumatic period, and three other subjects had psychotic symptoms best explained as features of a period of post-traumatic delirium. Only one had treatment by a psychiatrist for these.

Fewer SLP subjects (9% *v.* 18%) had epilepsy. In three (of four) SLP subjects with post-traumatic epliepsy, seizures were fully controlled, and two had been able to successfully discontinue anticonvulsant medication. One had partial complex epilepsy and the others had generalized convulsions without a clinically defined focal origin. The non-SLP group all had focal seizures with secondary generalization (one motor, one motor-sensory, one frontal, one partial complex, one multi-focal). The epilepsy was poorly controlled in seven (of eight) despite anticonvulsant medication ($\chi^2 = 6{\cdot}31$, df 2, $P = 0{\cdot}04$).

There was evidence for brain damage in the temporal, parietal and frontal lobes, more often unilateral than bilateral (Table 2) on the basis of neuroimaging, clinical and neuropsychological data. Cerebellar damage was present in three

Table 1. *Sociodemographic and developmental characteristics of subjects* (*N and* (%) *unless otherwise stated*) *and the characteristics of their head injuries* (*schizophrenia-like psychosis after head injury* (*SLP*) *and non-psychotic head injured controls* (*non-SLP*))

	SLP		Non-SLP					
	N	(%)	*N*	(%)	*t*	χ^2, df	Matched *N* in each analysis*	*P*
Sociodemographic and developmental characteristics								
Current age, mean (S.D.)	34·0	(10·4)	34·0	(10·2)	0·021		45	0·98
Years of education, mean (S.D.)	10·7	(2·7)	10·8	(1·9)	0·20		43	0·84
Occupational status†, mean (S.D.)	4·95	(2·5)	5·59	(2·6)	1·11		39	0·27
Ethnicity (1/2/3/4/5/6)‡, *N*s	29/2/4/8/2/0		37/1/3/2/0/2			9·05, 5	45	0·11
Currently married (% yes)	4	(10)	19	(49)		13·87, 1	39	< 0·001 +
Gender (% male)	35	(78)	37	(82)		0·278, 1	45	0·60
Birth abnormality	2	(5)	1	(3)		0·347, 1	37	0·56
Developmental abnormality	8	(22)	9	(24)		0·076, 1	37	0·78
1^0 relative with psychosis§	8	(24)	1	(3)		6·28, 1	34	0·01
Drug abuse or dependence	13	(36)	7	(19)		2·49, 1	36	0·11
Characteristics of head injury								
Cause of injury (% MVA)	33	(89)	35	(96)		0·725, 1	37	0·39
Injury closed/open (% closed)	36	(84)	41	(95)		3·10, 1	43	0·08
Intra-cranial intervention (% yes)	7	(19)	8	(22)		0·084, 1	36	0·77
Intracerebral haemorrhage	12	(35)	11	(32)		2·6, 3	34	0·45
Cerebral	8		5					
Subarachnoid	3		6					
Brainstem	1		0					
Age at injury (1/2/3/4/5)¶	1/2/7/13/18		2/4/2/8/25			6·11, 4	41	0·19
Loss of consciousness (1/2/3/4)‖	17/3/8/11		19/6/10/4			4·60, 3	39	0·20
Anterograde amnesia (1/2/3/4)‖	2/11/5/16		2/12/5/15			0·091, 3	34	0·99
Retrograde amnesia (1/2/3/4)‖	2/11/5/16		2/12/5/15			0·091, 3	34	0·99
Epilepsy present (%)	4	(9)	8	(18)		1·54, 1	45	0·18
Good/partial/nil control	3/1/0		1/6/1			6·31, 2	45	0·04

* The actual number of matched subjects in each analysis due to missing data.
† Highest occupation attained on the Australian Standard Classification Occupations (Australian Bureau of Statistics, 1997).
‡ 1, Anglo; 2, Mediterranean; 3, East European; 4, Middle East; 5, Chinese; 6, South-East Asian.
§ Schizophrenia or schizophreniform psychosis.
¶ (< 5 years/6–10/11–15/16–20/> 20).
‖ (< 1 hour/< 1 day/2–7 days/> 7 days).
\+ Significant after Bonferroni correction (alpha = 0·05/12 = 0·004).
MVA, Motor vehicle accident.

(8%) subjects. Neuroimaging evidence of brainstem damage was present in only one subject. None of the inter-group differences was significant after Bonferroni correction for multiple comparisons.

Neuropsychological function

The SLP group had more neurological deficits at the time of assessment, and scored lower on verbal and non-verbal IQ measures (see Table 3). They were more likely to have abnormalities on measures of verbal and non-verbal memory and frontal-executive functioning, differences that were significant after Bonferroni correction. They also tended to have more disturbance in language and parietal lobe functioning, suggesting a diffuse impairment in neuropsychological functioning in comparison with the non-SLP group.

Description of psychosis

The mean age of onset was 26·3 (S.D. 10·2) years. There was a latency of a mean 54·7 (S.D. 55·6) months between the head injury and the onset of psychosis, with the minimum being 2 weeks and the maximum 17 years. Psychotic symptoms that were possibly part of a delirium post-injury were excluded from this analysis. The onset of psychosis was usually gradual, with only two patients presenting within 1 month of onset of their illness (see Table 4). Prodromal features were recognized in the majority, the most common being bizarre behaviour, affective instability, antisocial behaviour, scholastic or work deterioration and social withdrawal. Depression was present at the time of onset in nearly one-half subjects but without meeting criteria for a major depression. In four subjects,

Table 2. *Evidence of lateralized brain damage as assessed by imaging or clinical and neuropsychological tests in head-injured schizophrenia-like psychosis (SLP) and non-SLP subjects*

	Imaging evidence of brain damage						Clinical and neuropsychological evidence of brain damage					
	SLP ($N = 38$)		CNT ($N = 38$)				SLP ($N = 39$)		CNT ($N = 39$)			
Brain area	N	(%)	N	(%)	χ^2	P*	N	(%)	N	(%)	χ^2	P*
Frontal left	8	(21)	9	(24)	0·076	0·783	14	(36)	7	(18)	3·19	0·074
Frontal right	9	(24)	7	(18)	0·317	0·574	12	(31)	3	(8)	6·69	0·010
Temporal left	10	(26)	3	(8)	4·55	0·033	14	(36)	7	(18)	3·19	0·074
Temporal right	8	(21)	4	(11)	1·58	0·208	13	(33)	4	(10)	6·09	0·014
Parietal left	7	(18)	4	(11)	0·957	0·328	5	(13)	2	(5)	1·41	0·235
Parietal right	10	(26)	3	(8)	4·55	0·033	6	(15)	1	(3)	3·92	0·048
Occipital left	1	(3)	0	(0)	1·01	0·314	0	(0)	0	(0)	—	—
Occipital right	2	(5)	0	(0)	2·05	0·152	0	(0)	0	(0)	—	—
Brainstem	1	(3)	1	(3)	0·00	1·00	13	(33)	13	(33)	0·00	1·00
Cerebellum	3	(8)	0	(0)	3·12	0·077	3	(8)	2	(5)	0·214	0·644
Unilateral (left or right) damage												
Frontal	12	(32)	12	(32)	0·00	1·00	15	(38)	7	(18)	4·05	0·044
Temporal	12	(32)	7	(18)	1·75	0·185	17	(44)	9	(23)	3·69	0·055
Parietal	13	(34)	6	(16)	3·44	0·064	8	(21)	3	(8)	2·65	0·104
Occipital	2	(5)	0	(0)	2·50	0·152	0	(0)	0	(0)	—	—
Bilateral damage												
Frontal	5	(13)	4	(11)	0·126	0·723	11	(28)	3	(8)	5·57	0·018
Temporal	6	(16)	0	(0)	6·51	0·011	10	(26)	2	(5)	6·30	0·012
Parietal	4	(11)	1	(3)	1·93	0·165	3	(8)	0	(0)	3·12	0·077
Occipital	1	(3)	0	(0)	1·01	0·314	0	(0)	0	(0)	—	—

* No significant group differences after Bonferroni correction (alpha = 0·05/8 = 0·006).

Table 3. *Neurological abnormality and neuropsychological functioning in head injured schizophrenia-like psychosis (SLP) and head injured non-SLP subjects*

	SLP ($N = 45$)		CNT ($N = 45$)		Test	Matched	
Measure	N	(%)	N	(%)	value	N in each analysis†	P
Physical abnormality (% yes)	21	(57)	21	(57)	0·00‡	37	1·00
Neurological abnormality	26	(70)	17	(46)	4·50‡	37	0·034
Verbal IQ (mean [S.D.])	83·2	[22·6]	94·1	[16·1]	2·0§	27	0·050
Non-verbal IQ (mean [S.D.])	86·7	[24·4]	96·5	[17·8]	1·66§	26	0·102
Verbal memory (% abnormal)	25	(83)	13	(43)	10·34‡	30	0·001*
Non-verbal memory (% abnormal)	22	(73)	9	(30)	11·28‡	30	0·001*
Frontal executive function (% abnormal)	17	(77)	7	(32)	9·17‡	22	0·002*
Parietal function (% abnormal)	6	(67)	1	(11)	5·84‡	9	0·016
Language reception/expression (% abnormal)	7	(54)	2	(15)	4·25‡	13	0·039

* Significant after Bonferroni correction (alpha = 0·05/9 = 0·006).
† The actual number of matched subjects in each analysis due to missing data.
‡ Chi-square test, df = 1.
§ Student's t test.

there was evidence of altered consciousness at the time of onset of psychosis, which cleared with the middle stages of the illness.

The psychosis was characterized by delusions and hallucinations. One or more delusions were present in all subjects, with persecutory (55·5%), referential (22·2%), control (22·2%), grandiose (20%) and religious (15·4%) delusions being the most common. Delusions of thought alienation (thought insertion, withdrawal or broadcast) were present in 6 (13·3%) and somatic passivity in 3 (6·7%). Delusions commonly reported in secondary psychoses (e.g. mis-identification, Capgras, erotomania, people stealing or hiding) were not seen in any of the patients. Hallucinations were predominantly auditory (84·4%),

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Table 4. *Characteristics of psychosis* (*N and* (%) *unless otherwise stated*) *following head injury*

Characteristics of psychosis	*N*	(%)	Total *N*
Age of 1st consultation, mean (S.D.)	27·1	(9·7)	43
Age of onset of psychosis, mean (S.D.)	26·3	(10·2)	45
Latency between head injury and onset of psychosis (months), mean (S.D.)	54·7	(55·6)	45
Presentation			
Depression at presentation (% yes)	18	(46)	38
Mania at presentation (% yes)	0	(0)	39
Symptoms stable/fluctuating (% stable)	16	(62)	39
Confusion (1/2/3/4)[a]	34/4/0/0		26
Nature of onset (1/2/3)[b]	2/5/37		44
Duration of psychosis (1/2/3/4)[c]	2/3/6/18		39
Course of psychosis (1/2/3/4)[d]	18/2/3/3		26
Response to neuroleptics (1/2/3)[e]	5/15/1		21
Prodromal symptoms			
Social withdrawal	11	(31)	36
Bizarre behaviour	18	(50)	36
Anti-social behaviour	13	(36)	36
Affective instability	14	(39)	36
Scholastic or work deterioration	12	(33)	36

[a] (Not present/beginning/middle/throughout).
[b] (< 1 month/1–6 months/> 6 months).
[c] (< 1 month/1–6 months/> 6 months/> 2 years).
[d] (Chronic and persisting/chronic with exacerbations/acute with full remission and no relapse/acute with full remission but relapse).
[e] (Full/partial/none).

with voices commenting on the person (55·5%) being the most common. Visual hallucinations were reported by nine (20%) and tactile by two (4·4%) patients. Formal thought disturbance was not generally a feature at the time of assessment, with only two (4·4%) patients demonstrating tangentiality or derailment. The psychosis was predominantly a positive syndrome with only 10 (22·2%) patients demonstrating flattening of affect, avolition or asociality. Agitated and aggressive behaviour was common (40%).

The psychosis was generally responsive to neuroleptic drugs that all patients were treated with, with only one patient not responding in 6 months of treatment. In only five (11·1%) was the total duration of the psychosis, including the prodromal period, less than 6 months.

Risk factors

Putative risk factors were explored initially by direct comparison of the two groups. While the two groups did not differ on perinatal or developmental abnormalities and drug abuse or dependence, the SLP group had a higher family history of psychosis in first-degree relatives suggesting a genetic vulnerability. The SLP and non-SLP groups did not differ significantly on the following: age at head injury, characteristics of the injury, or the behavioural and personality changes following the trauma. The comparison of the two groups on neuroimaging data suggested greater damage in the SLP group in the left temporal and right parietal regions, these differences were not significant after Bonferroni correction. When neuropsychological and clinical data were considered, deficits in the temporal, frontal and parietal regions tended to be greater in the SLP group, but without unequivocally reaching statistical significance. The presence or absence of neuroimaging evidence of brain damage in the right or left frontal, temporal, parietal or occipital regions, the brainstem and the cerebellum were examined as predictors of group membership (SLP *v.* non-SLP) using a logistic regression model with each variable entered one at a time. Only left temporal damage was significant in this model ($B = -2{\cdot}29$, S.E. $= 1{\cdot}03$, OR $= 0{\cdot}10$, $P = 0{\cdot}027$). When a similar analysis was repeated with the presence or absence of focal brain damage on the basis of clinical and neuropsychological data, no significant predictor emerged.

A final logistic regression model was then examined using the suggested and hypothesized risk variables from clinical, imaging and neuro-

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Table 5. *Predictors of membership in schizophrenia-like psychosis (SLP) or non-SLP groups after head injury using a logistic regression (enter) analysis*

	SLP ($N = 28$)	CNT ($N = 32$)	Total ($N = 60$)	χ^2	P
Correctly classified, *N* (%)	18 (64)	26 (81)	44 (73)	16·00	0·025
Variables in the equation	B	S.E.	OR	P	95·6% CI
Injury open/closed (closed)	−1·79	1·23	0·17	0·15	0·01–1·87
Epilepsy (yes/no)	1·15	1·30	3·16	0·38	0·25–40·71
Loss of consciousness (yes/no)	0·072	0·43	2·05	0·09	0·88–4·76
Anterograde amnesia*	−0·23	0·34	0·80	0·51	0·41–1·56
Drug abuse or dependence	−0·1	0·83	0·90	0·90	0·18–4·63
Relative with psychosis	−3·06	1·36	0·05	0·02	0·003–0·67
Temporal lobe damage (right or left)					
Imaging	−0·66	0·91	0·52	0·46	0·09–3·04
Clinical/neuropsychological	0·84	0·72	2·32	0·24	0·58–9·55
Frontal lobe damage (right or left)					
Imaging	−0·55	1·09	0·58	0·62	0·07–4·92
Clinical/neuropsychological	0·38	0·78	1·47	0·63	0·31–6·8

* Categorized as (< 1 h, 1 h–1 day, 1–7 days, > 7 days).

psychological variables as listed in Table 5. Family history of psychosis again emerged as the most significant variable, with duration of loss of consciousness also being significant. Damage to any particular brain region (temporal, frontal or parietal) did not emerge as being significant on regression analyses.

DISCUSSION

We have reported a large series of patients who developed schizophrenia-like psychosis for the first time following a head injury. The profile of post-traumatic SLP that emerges is that of a predominantly paranoid-hallucinatory psychosis with usually a gradual onset and a subacute or chronic course. In only 11% was the duration of the illness less than 6 months. The psychosis was preceded by prodromal symptoms of bizarre or antisocial behaviour, social withdrawal, affective instability and deterioration in work, often for many months. Depressive symptoms were often present at the time of presentation but confusional symptoms at onset were unusual. A range of delusional symptoms, similar to that seen in schizophrenia, was present, and while this included first rank Schneiderian symptoms, organic themes such as those described by Cutting (1987) were absent. Hallucinations were predominantly auditory in modality. Formal thought disorder and catatonic features were usually absent, and negative symptoms were uncommon. The phenomenology of the psychosis was therefore similar to that seen in primary schizophrenic disorders, especially the paranoid type, and the mean age of onset was consistent with this (Häfner *et al.* 1993). The finding is similar to other studies of secondary schizophrenia which suggest considerable overlap between the phenomenology of primary and secondary schizophrenias (Davidson & Bagley, 1969; Cutting, 1987; Johnstone *et al.* 1987; Feinstein & Ron, 1990). Our study did not include a primary schizophrenia comparison group and therefore we cannot comment on some of the subtle differences in phenomenology that other studies have reported.

Since we studied a clinic population, we cannot conclude from our study that the incidence of SLP after head injury was greater than chance expectation. Others (Davidson & Bagley, 1969; Lishman, 1998) have come to this conclusion after reviewing all the available evidence. The characteristics of the head injury in our sample did not provide substantial evidence for the unequivocal role of trauma in the aetiology of SLP. The head injury was not more likely to be in childhood, contrary to what we had predicted. The interval between the injury and the onset of SLP was very variable. The SLP group was predominantly male, a finding commonly

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reported in secondary schizophrenia (Lewis, 1995). In our sample, this could however reflect the male excess in the overall sample, with males comprising 64% of the total head-injured individuals from which the samples were drawn. The SLP group did have a more severe injury with brain damage in many brain regions, both by neuroimaging and neuropsychology. The SLP groups more often had evidence of damage to the temporal, parietal and frontal brain regions than the non-SLP group on CT scans, lower IQ and memory and frontal-executive dysfunction. The duration of loss of consciousness was a predictor of the development of SLP. The majority of patients had a close-head injury, but an open injury was not necessarily protective against future SLP, as has sometimes been suggested (Achte *et al*. 1969). While the left temporal and right parietal regions did emerge as being particularly affected on our preliminary analysis, this finding was not significant on regression analysis. The SLP group were more likely to have neuropsychological deficits of the frontal lobe type, but did not have neuroimaging evidence of greater frontal lobe damage. Since the neuropsychological assessments followed the development of psychosis, it is difficult to estimate what contribution SLP might have made to the frontal-executive deficits (Frith & Donne, 1988).

What was most significant was a genetic vulnerability to psychosis as reflected in the family history, even though this was present in only a fraction of patients. First-degree relatives were diagnosed as 'psychotic' and not 'schizophrenic' because we were unable to ascertain with confidence whether a DSM-IV diagnosis of schizophrenia or schizophreniform disorder could be sustained. However, we tried to exclude cognitive disorders and primary affective disorder from the diagnosis of psychosis in a family member. We did not establish that this putative genetic vulnerability translated into developmental abnormalities.

The subjects had considerable post-injury but pre-psychosis behavioural and personality problems, but these were no different in the comparison subjects. A surprising finding was that the SLP group had fewer cases, albeit non-significantly, of epilepsy and these had, except in one case, responded to medication. On the other hand, epilepsy was only partially controlled by medication in seven non-SLP cases. This was contrary to our expectation that continuing epilepsy, especially partial complex epilepsy, might play a role in the genesis of SLP. This finding leads us to speculate that continuing epileptic seizures may in some way play a protective role and reduce the likelihood of subsequent SLP. This is not inconsistent with the hypothesis that the development of SLP in epilepsy patients is not a direct consequence of the seizures but rather a result of the underlying brain damage, and the seizures may have a modifying rather than a causative role (Sachdev, 1998).

Our study had many limitations. Being a case–control study that drew upon referred patients, the sample was not truly representative and data gathering was retrospective. The family history data were based on the interview of the subject and often an informant, and a bias toward increased reporting in the SLP group cannot be dismissed. It is also possible that positive family history was under-reported in the control group because the presence of psychosis is likely to lead to an increased effort to elicit a positive family history. The neuroimaging data were qualitative, limited to CT scans and based on reports by different radiologists. The neuroanatomical inferences drawn from the neuropsychological data can be criticized as being simplistic as most neuropsychological functions involve networks of brain regions. However, there is a long history of the type of inferences that we drew (Miller, 1966) despite which our interpretations were cautious. The conclusions about risk factors from our study should therefore be considered tentative, and confirmed by a longitudinal follow-up of a head-injured cohort large enough to have sufficient power to prospectively included a sufficiently large sample of SLP. We acknowledge the practical difficulties a study of this scale will present.

The conclusion we reach is that head injury, affecting many brain regions but in particular the left temporal and right parietal regions, and leading to cognitive deficits in a vulnerable individual, is related to the later development of SLP which then takes the form of primary schizophreniform disorder or schizophrenia. This is in disagreement with Achte *et al*. (1969) who reported that mild injuries were more likely

to lead to schizophrenia than severe injuries. The lack of a strong association with damage to any particular brain region is consistent with the conclusions reached by Achte *et al*. (1969), Davison & Bagley (1969) and Feinstein & Ron (1990). Other authors have reported an association with temporal lobe damage, especially on the left side (Hillbom, 1951; Buckley *et al*. 1993). The Hillbom (1951) study predates the use of standardized diagnostic criteria and neuroimaging, and the Buckley *et al*. (1993) report concerned three cases of schizophrenia only. Our study shows that temporal and/or frontal lobe damage is sufficient but not necessary for the development of SLP. Inferring a cause-and-effect relationship is not possible from our study, although the suggestion is that head injury may be bringing out a vulnerability. This is of significance in the medico-legal setting when third party compensation for head injury has to be decided.

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