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'Pfropfschizophrenie' revisited

Schizophrenia in people with mild learning disability

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Background It is reported that people with mild learning disability have a higher point prevalence of schizophrenia than the normal population, the reasons for which are unclear.

Method Thirty-nine subjects with mild learning disability and schizophrenia, 34 control subjects with schizophrenia and 28 control subjects with mild learning disability were seen. Interviews with relatives and carers were also conducted. Assessments were made of clinical variables, psychopathology, neurological 'soft' signs, IQ, memory and family history. Blood was taken for karyotypic analysis from comorbid subjects.

Results The comorbid group had more negative symptoms, episodic memory deficits, soft neurological signs, epilepsy and receive more community supports than control subjects with schizophrenia. Comorbid subjects had a tendency to belong to multiply affected families and show high rates of chromosomal variants on routine karyotypic testing.

Conclusions Future work on the generality of schizophrenia should include people with premorbid learning disability, as a discrete subtype from whom valuable genetic aetiological clues may be obtained.

In 1919 Kraepelin estimated that around 7% of all cases of dementia praecox arose in individuals with premorbid cognitive impairment. He termed this 'pfropfschizophrenie'. Few studies in the past 25 years have attempted to take a holistic approach to the biological origins of schizophrenia in subjects with learning disability (Reid, 1972; Heaton-Ward, 1977; Hucker *et al*, 1979). However, epidemiological studies consistently demonstrate that people with mild learning disability have higher rates of mental illness than those seen in the normal population (Penrose, 1938; Heaton-Ward, 1977; Corbett, 1979). Turner (1989), following a review of the literature, reports the point prevalence of schizophrenia in people with mild learning disabilities to be three times (approximately 3%) that of the normal population (1%). Given the raised point prevalence of schizophrenia in people with mild learning disability, it may be possible to obtain clues as to the biological basis of the generality of schizophrenia by study of this population.

METHOD

The Information and Statistics Division of the Scottish Health Service has detailed records of all psychiatric admissions in Scotland from 1970 (Kendrick & Clark, 1993). Individuals with at least one in-patient admission in either Lothian or Fife between 1970 and 1993, with discharge diagnoses of mild learning disability and schizophrenia or paranoid state (ICD–8 and 9; World Health Organization, 1967, 1978) were identified from this database (n=248). Subjects aged under 16 years or greater than 65 years at the time of the study were excluded. Research Diagnostic Criteria (RDC; Spitzer *et al*, 1975) for schizophrenia were applied to case records to establish eligibility. Evidence of remedial education was taken as confirmation of the existence of premorbid cognitive impairment and was a prerequisite to inclusion. Subjects with a documented premorbid IQ below 50 or above 70 were excluded. Individuals believed to have Down's syndrome were excluded from the cohort as cognitive testing was to form an integral component of the study protocol and these people are known to be at increased risk of developing Alzheimer's disease (Heston, 1982).

Two control subjects were selected for every index subject completing the protocol. The first control subject with a history of mild learning disability of undetermined aetiology, a documented IQ between 50 and 70 and no known history of psychosis or current antipsychotic usage, was recruited using the Lothian Psychiatric Case Register (LPCR) in conjunction with active community learning disability nursing case lists. The second control subject with a history of schizophrenia conforming to RDC, but no evidence of premorbid cognitive impairment, was also recruited by reference to the LPCR. Both sets of control subjects comprised individuals matched for gender and within five years of age to the index comorbid subject. For all subjects permission to contact the subject was first obtained from their psychiatrist (if applicable) and general practitioner.

Case records were reviewed to provide socio-demographic and clinical information for each subject. The diagnostic validity of the Schizophrenia and Affective Disorders Schedule–Lifetime version (SADS–L; Endicott & Spitzer, 1978) for schizophrenia in people with mild learning disability has been shown to be acceptable for research purposes (Meadows *et al*, 1991). The SADS–L and Positive and Negative Syndrome Scale (PANSS; Kay *et al*, 1987) were administered to all subjects. RDC, DSM–III–R (American Psychiatric Association, 1987) and St Louis Criteria (Feighner *et al*, 1972) for schizophrenia were applied to all comorbid subjects and the control subjects with schizophrenia.

All subjects were asked to complete the Quick IQ Test (Ammons & Ammons, 1962) and the Rivermead Behavioural Memory Test (RBMT; Wilson *et al*, 1985). A National Adult Reading Test (NART; Nelson & O'Connell, 1978) was given to the control subjects with schizophrenia, to confirm a premorbid IQ within the normal range. Each subject was then neurologically assessed using the Neurological Evaluation Scale (NES; Buchanan & Heinrichs, 1989). A family history of learning disability or psychosis was sought

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Table 1 Mean (s.d.) ages of onset of psychoses

Variable	Total	Males	Females
Age at first symptoms			
Comorbid group (n=38)	24.4 (10.2)	23.8 (9.9)	25.1 (10.7)
Schizophrenia group (n=32)	22.8 (5.1)	21.9 (4.0)	23.9 (6.3)
Age at first consultation			
Comorbid group (n=38)	23.7 (10.2)	22.9 (10.3)	24.6 (10.4)
Schizophrenia group (n=32)	22.8 (6.0)	21.4 (5.6)	24.6 (6.3)
Age at first antipsychotic administration			
Comorbid group (n=36)	28.1 (9.4)	27.7 (8.6)	28.4 (10.3)
Schizophrenia group (n=26)	24.8 (5.4)	23.4 (4.3)	27.5 (6.5)
Age at first admission			
Comorbid group (n=39)	25.2 (11.3)	23.5 (10.7)	27.1 (11.9)
Schizophrenia group (n=33)	26.5 (7.5)	24.8 (6.7)	28.7 (8.2)
Age at first diagnosis			
Comorbid group (n=36)	30.0 (9.5)	30.4 (8.1)	29.5 (11.2)
Schizophrenia group (n=32)	27.8 (7.8)	26.2 (7.9)	29.8 (7.3)
Time interval (symptoms to diagnosis)			
Comorbid group (n=36)	4.9 (7.3)	5.9 (8.7)	3.8 (5.4)
Schizophrenia group (n=32)	5.0 (5.6)	4.3 (5.7)	5.9 (5.4)

P=NS between comorbid and schizophrenia groups on all variables, by t-test.

by meeting with a relative (where possible), questioning the subject and reviewing case records. Comorbid subjects were asked to provide a blood sample for karyotypic analysis. Ratings of movement disorders and adaptive behaviour were also made, but are not reported here. Data were analysed using SPSS, release 7.5.1.

RESULTS

Sample acquisition

The total sample comprised 39 subjects with the comorbid state (mild learning disability and schizophrenia), 34 control subjects with schizophrenia and 28 control subjects with mild learning disabilities. Fifty-four per cent of comorbid individuals approached participated in the study, compared with 64% of subjects with schizophrenia and 93% of those with learning disabilities. The nature of the population required up to eight visits per individual to complete the protocol.

Age, IQ and socio-demographic variables

The mean age of the index subjects (48.6 years) was not significantly different from control groups (48.6, schizophrenia only group; 47.2, learning disability only group). There were no significant gender differences between groups, male subjects constituted between 54% and 57% of all groups. The mean Quick IQ score of comorbid subjects was not significantly different to that of control subjects with learning disabilities (60.5 and 64.3, respectively; t-test P=0.560). In the control group with schizophrenia the NART scores (mean=111.1, s.d.=10.8, range=85–128) suggest that no subject had a premorbid IQ within the mild learning disability range (50–70).

It was not possible to ascertain paternal occupation in 8.8% of subjects with schizophrenia and approximately one-third of comorbid and learning disability group subjects. Where paternal occupation was known, most subjects with comorbidity (22/26) and learning disabilities (16/18) were from classes III, IV and V and subjects with schizophrenia (28/31) from classes I, II and III (HMSO, 1980). The majority of all subjects were single and not living in hospital accommodation. Almost half (48.8%) of the comorbid subjects, 28.6% of subjects with learning disabilities and 8.8% of subjects with schizophrenia were living in non-hospital supported accommodation. Many subjects with schizophrenia lived alone (44.1%), contrasting with only 12.8% of comorbid subjects and 17.9% of subjects with learning disabilities. There was a significant difference in the living circumstances of the comorbid subjects compared with the subjects in the schizophrenia control group (χ^2=25.6, d.f.=5, P<0.001), and a trend for the living circumstances of comorbid subjects to be different from those of learning disability control subjects (χ^2=10.8, d.f.=5, P=0.055). None of the comorbid subjects had been in non-supported employment in the preceding five years, relative to 28.6% of subjects with learning disabilities and 8.8% of subjects with schizophrenia.

Age of onset of psychosis

There are no significant differences between groups (t-test) in any of the five ages considered (Table 1). When groups are split by gender the general trend is for all ages of onset of psychosis under study to be slightly earlier in men than women, however, analysis both between groups and within groups shows no significant effect of gender (t-test).

Service utilisation

Current

At the time of study, 28.2% (n=11) of index comorbid subjects and of 17.6% (n=6) of control subjects with schizophrenia were hospital in-patients. Considering only the 58 subjects in these groups living in the community, only one (a control with schizophrenia) was managed under the Mental Health (Scotland) Act 1984. More subjects with comorbidity than schizophrenia alone, received services from community psychiatric nurses (53.6 $v.$ 17.8%; P=0.005) and social workers (32.1 $v.$ 10.7%; P=0.05). There were no differences between these two groups in the number of subjects attending day hospitals, day centres, receiving voluntary agency care or home help.

Lifetime

There was a significant difference in the mean numbers of lifetime hospitalisations between comorbid subjects and control subjects with schizophrenia (6.87, s.d.=4.7; 9.85, s.d.=6.73, respectively; Mann–Whitney U-test P=0.034). However, comorbid subjects had not spent any less time in in-patient care than the control subjects with schizophrenia and therefore had fewer admissions, but for longer periods, than those with schizophrenia.

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Table 2 Past medical history

Condition	Comorbid group (n=39) n (%)	Schizophrenia group (n=34) n (%)	Learning disability group (n=28) n (%)
History of epilepsy	17 (43.6)[1]	1 (2.9)	9 (32.2)
Aetiology of epilepsy			
Idiopathic	11 (28.2)	1 (2.9)	5 (17.9)
Febrile convulsions	2 (5.1)		1 (3.6)
Trauma	2 (5.1)		2 (7.1)
Medication	1 (2.6)		
Unable to ascertain	1 (2.6)		1 (3.6)
Frequency of seizures			
Daily			
>2/week			
Weekly			2 (7.1)
2–4/month	1 (2.6)		1 (3.6)
Monthly	1 (2.6)		1 (3.6)
<12/year	1 (2.6)		2 (7.1)
Yearly			
<yearly	1 (2.6)	1 (2.9)	
None for >5 years	13 (33.3)[2]		2 (7.1)
Unable to ascertain			1 (3.6)
History of meningitis	2 (5.1)	0	3 (10.7)
History of encephalitis	1 (2.6)	0	0
History of head injury	2 (5.1)	0	1 (3.6)

1. $P<0.0001$ v. schizophrenia group, by χ^2 test.
2. $P=0.013$ v. learning disability group, by χ^2 test.

Medication

The mean present chlorpromazine equivalent doses of antipsychotic medication were not significantly different between the comorbid group and the schizophrenia control group (583 mg, s.d.=660; 748 mg, s.d.=735, respectively). There were no differences between these groups in the numbers of subjects receiving depot antipsychotic preparations, antidepressants, lithium or antimuscarinic medication at the time of the study. Similarly, there were no differences between groups in the number of subjects who had ever received the novel antipsychotics clozapine or risperidone.

Past medical history

Comorbid subjects were more likely to have a history of epilepsy than the control subjects with schizophrenia (χ^2=16.2, d.f.=1, $P<0.001$), but not than the control subjects with learning disability (see Table 2). Comorbid subjects were more likely to have been seizure-free in the past five years than control subjects with learning disabilities (χ^2=6.1, d.f.=1, P=0.013). There were no differences in the age of first onset of epilepsy between these two groups.

Focusing on the comorbid subjects, there were no differences between those subjects with and without epilepsy when the number of psychiatric hospital admissions, total time in hospital, or mean ages of onset, consultation, admission, diagnosis of schizophrenia and first antipsychotic administration were considered. No differences were seen in this group between people with a history of epilepsy and people without, in terms of acts of deliberate self-harm or those charged with offences.

Five comorbid subjects and four control subjects with learning disabilities had a history of either meningitis, encephalitis, or head injury associated with loss of consciousness. None of the control subjects with schizophrenia had a history of any of these conditions.

Forensic history

There were no significant between-group differences in the number of offences (alleged or convicted), or the number of subjects ever charged with an offence (comorbid group n=13, learning disability group n=6, schizophrenia group n=13). Nine comorbid subjects, five control subjects with learning disabilities and eight control subjects with schizophrenia had had psychiatric court reports. Two comorbid subjects, two control subjects with learning disabilities and four subjects with schizophrenia had been in prison. These differences between groups do not reach statistical significance.

Substance and alcohol misuse

None of the control subjects with learning disabilities, three comorbid subjects and five control subjects with schizophrenia had a history of drug misuse. Similarly, none of the learning disability group, three comorbidity group subjects and four of the schizophrenia group subjects met RDC for alcohol dependency syndrome. These differences do not reach statistical significance.

Deliberate self-harm

Only one control subject with learning disability (4%) had ever engaged in deliberate self-harm relative to six (18.2%) comorbid subjects and 18 (52.9%) control subjects with schizophrenia (comorbid v. schizophrenia χ^2=11.6, d.f.=1, P=0.001).

Application of RDC, Feighner and DSM–III–R criteria for schizophrenia

All comorbidity and schizophrenia group subjects met at least one of these three criteria for schizophrenia. Thirty-seven of the comorbidity group and all schizophrenia group subjects fulfilled RDC, St Louis Criteria (definite and probable) and DSM–III–R criteria.

PANSS

The results of the PANSS, RBMT and NES are presented in Table 3. Significant differences exist between the three subject groups in all four major categories of the PANSS, that is, negative, positive, general and total symptoms. The comorbid group had significantly more negative symptoms, but showed no differences in positive, general or total symptom profiles compared with the schizophrenia control group. The mild learning disability control group showed significantly fewer symptoms in all four categories relative to the other two groups.

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Rivermead Behavioural Memory Test

A degree of memory impairment was present in all three groups relative to a normal population (17–21 poor memory, 10–16 moderate impairment, 0–9 severe impairment; Wilson *et al*, 1985). Statistically significant differences exist between the three groups. The comorbidity group subjects performed significantly worse than either of the two control groups. The control group with mild learning disability performed worse than the schizophrenia control group. Spearman's two-tailed correlations show significant positive correlations between Quick IQ and Rivermead standardised profile scores in all three groups.

Neurological Evaluation Scale

There were significant differences between the mean overall scores for the three groups. The comorbidity group and the mild learning disability control group both showed more neurological soft signs than the schizophrenia control group. There were no significant correlations between NES overall scores and Quick IQ in any of the three groups.

Family history

Schizophrenia

Twenty (57%) of the 35 subjects in the comorbidity group, where a reliable family history was ascertained, had at least one first- or second-degree relative with a history of schizophrenia (see Fig. 1). This compares with 12 (39%) of 31 subjects in the schizophrenia control group (Fisher's exact test two-tailed; $P<0.15$) and 2 (9%) of 23 subjects in the learning disability control group (Fisher's exact test; $P<0.001$).

Learning disability

Fifteen (43%) of 35 subjects in the comorbidity group had first- or second-degree relatives with learning disabilities (six with learning disability alone and nine from multiply affected families). This compared with two (7%) of 31 subjects in the schizophrenia control group (Fisher's exact test $P=0.001$) and 12 (53%) of 23 subjects in the learning disability control group (Fisher's exact test $P=0.59$).

Learning disability and schizophrenia

In the comorbidity group nine subjects (26% of the total number from whom a family history is available) were from multiply affected families in which first- or second-degree relatives (up to a maximum of 10) were affected by one of three conditions – schizophrenia without learning disability, learning disability without schizophrenia or schizophrenia and learning disability (the comorbid state). This contrasts with only two subjects out of 31 (7%), with such family histories in the schizophrenia control group (Fisher's exact test $P=0.049$), and one subject out of 23 (4.5%) in the learning disability group (Fisher's exact test $P=0.07$).

When the multiply affected families were excluded from the analysis the percentage of subjects with a family history of schizophrenia alone in first- and second-degree relatives was remarkably constant between the comorbidity group and schizophrenia control group (31 and 32%, respectively).

A highly significant difference was seen between subjects with no family history of either learning disabilities or schizophrenia in the comorbid group (9/35) and the schizophrenia control group (19/31; Fisher's exact test $P=0.006$).

Karyotyping

Blood samples for karyotypic analysis were obtained from 29 subjects in the comorbid group. Four of these subjects were found to have a chromosomal heterochromatic variant, three of these had a family history of schizophrenia in first- or second-degree relatives and one of these was from a multiply affected family, as described above. Two other subjects were found to have definite chromosomal abnormalities, one of these had a family history of schizophrenia.

Chromosomal variants

Three G-band variants were found, they comprised additional, presumed satellite, material. One subject had 15ps+, another 21ps+, and a third had 21ps+ and 22ps+. The rates with which these variants occur are population-dependent, however, reasonable estimates of their occurrence in the general population are; on chromosome 15, 3.1%, and on chromosome 21 and 22 around 2.5% for each (Lubs & Ruddle, 1970).

A fourth subject showed C-band variants on both chromosomes 9 (9qh+ and inv9(p11q13)). The estimated frequency of 9qh+ in a Scottish newborn population is 0.5–7%, depending on size, and of total

Table 3 Positive and Negative Syndrome Scale (PANSS), Rivermead Behavioural Memory Test (RBMT) and Neurological Evaluation Scale (NES) results

Variable	Schizophrenia and mild learning disability mean (95% CI)	Schizophrenia mean (95% CI)	Mild learning disability mean (95% CI)
PANSS	*n*=39	*n*=32	*n*=24
Positive symptoms (normal range 7–49)	12.6 (10.8–14.4)	14.0 (12.0–16.0)	7.6** (7.1–8.0)
Negative symptoms (normal range 7–49)	23.3** (20.5–26.2)	18.3** (15.3–21.3)	9.2** (8.0–10.3)
General symptoms (normal range 16–112)	30.8 (27.1–34.4)	27.9 (25.1–30.7)	19.1** (17.6–20.6)
Total symptoms (normal range 30–210)	66.3 (59.0–73.5)	60.2 (53.5–66.8)	35.5** (33.0–37.9)
RBMT	*n*=37	*n*=34	*n*=27
Standardised profile score total (normal range 0–24)	10.2* (8.7–11.8)	18.4** (17.0–19.8)	12.6* (10.5–14.7)
NES	*n*=37	*n*=34	*n*=28
Total score (normal range 0–64)	20.8 (18.2–23.3)	8.4** (6.6–10.3)	18.3 (15.3–21.3)

One-way ANOVA with post-hoc LSD.
*$P<0.05$; **$P<0.01$ relative to both other groups.

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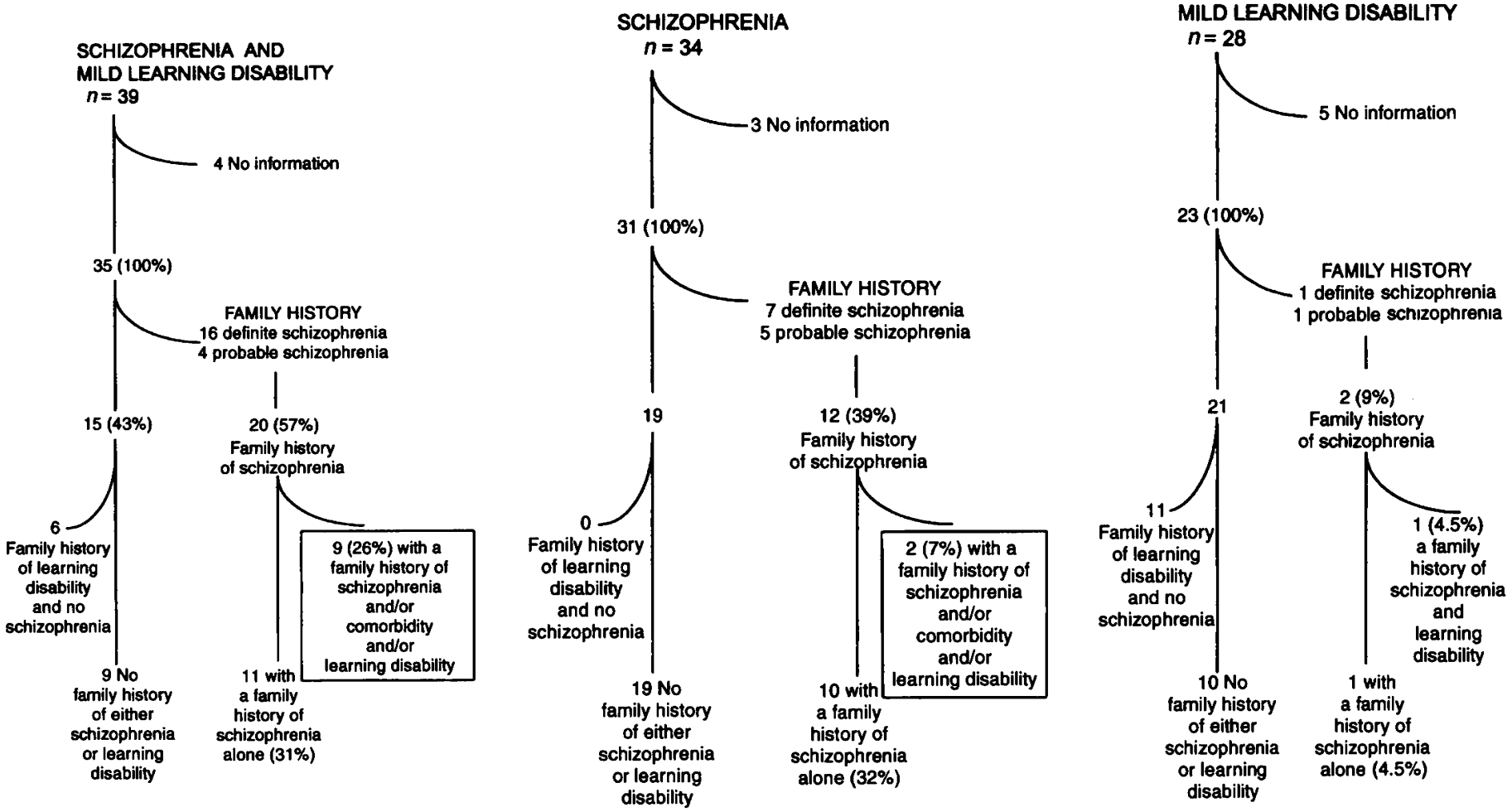


Fig. 1 Family history of learning disability or schizophrenia or comorbidity (first- and second-degree relatives only)

and partial inversions of chromosome 9 heterochromatin, 0.7 and 3.7%, respectively (Buckton *et al*, 1976).

Chromosomal abnormalities

Two subjects had chromosomal abnormalities. The first had a complex re-arrangement involving a chromosome inversion and a balanced reciprocal translocation between chromosomes 2 and 11. Fluorescence *in situ* hybridisation studies are underway to define break points. The patient had a family history of schizophrenia. Reciprocal translocations occur in around 0.1% of the population.

The second subject has a gender chromosome abnormality, 47; XXX (trisomy X syndrome), the expected frequency of this occurring in newborn females is 1/1000. This subject did not have a family history of schizophrenia.

DISCUSSION

The present study was designed to evaluate people with comorbid schizophrenia and mild learning disability, relative to age- and gender-matched control groups. The index population had a high rate of non-participation relative to the learning disability group but not to the schizophrenia control group. Although this raises the possibility of ascertainment bias, there were a diversity of reasons for non-participation (e.g. subject untraceable, seen but refused, medical/carer refusal, deceased) and this suggests relative preservation of heterogeneity in both comorbidity and schizophrenia control groups.

Service utilisation

Many of the comorbid subjects had had contact with both general adult psychiatry and learning disability service providers. This had arisen as the comorbid diagnosis of mild learning disability and schizophrenia fell within the remit of both services at differing chronological points in both the subject's history and the evolution of modern-day service provision.

The increased level of community support provided to the comorbid group does not appear to be a function of more extensive forensic, self-harm, drug and alcohol histories, current detention under the Mental Health Act or additional psychiatric diagnoses, relative to the schizophrenia control group.

The combination of an increased need for community support and the pattern of fewer, yet longer admissions in the comorbid group, may be indicative of a different or more treatment-resistant form of illness, or alternatively be a consequence of poor continuity of care, differing policies between service providers, or simply the need for complex packages of care to be provided for longer periods of time among this group.

Past medical history

A history of epilepsy is present more commonly in both comorbidity group and learning disability group subjects than those with schizophrenia alone. A third of the comorbid group (n=13) had a history of epilepsy, but no seizures in the past five years, relative to 7.1% (n=2) of the learning disability group (P=0.013). This is perhaps surprising given that none of the learning disability group was receiving epileptogenic antipsychotic medication.

As the learning disability group also derives from a population which has been, or is in contact with hospital services, this finding is unlikely to be the result of the comorbid group having greater contact with services, with the consequence that their epilepsy is better controlled. Alternatively, the finding may represent a selection bias, the learning disability control group being in contact with services as a consequence of intractable epilepsy.

The phenomenon of 'forced normalisation' has been described in relation to the schizophreniform psychoses of epilepsy (Trimble, 1996), whereby a reduction in seizure activity following the introduction of anticonvulsant agents is associated with an exacerbation of psychotic symptomatology. It is possible that such a mechanism may be of aetiological significance in the comorbid population, where cerebral dysfunction as evidenced by epilepsy, contributes to the combined conditions of learning disability and schizophrenia.

Family history, chromosomal variance and chromosomal abnormalities

Comorbid subjects were more likely to have a family history of learning disability, or to come from multiply affected families than the control subject, with schizophrenia. There is also a high rate of chromosomal variants detected in people from the comorbid group with a family history of schizophrenia. This suggests that a highly familial form of schizophrenia may be occurring in the comorbid group, the phenotypic appearance of which is variable in affected relatives. It is tentatively suggested that this may be consistent with either an autosomal dominant mode of inheritance with variable gene expression, or a non-Mendelian anticipatory effect.

Two chromosomal abnormalities were detected in comorbid subjects, a reciprocal translocation and a trisomy X syndrome. The latter is reported to be associated with schizophrenia (DeLisi *et al*, 1994).

Mechanisms

Five possible mechanisms addressing the reasons for an increased point prevalence of schizophrenia in people with mild learning disability might be postulated.

Chance co-occurrence

This implies that when schizophrenia and mild learning disability co-occur in the same individual they do so by chance alone. The two conditions are otherwise unrelated to each other.

Kallman *et al* (1941) found no increase in learning disability in the relatives of people with schizophrenia and no increase in schizophrenia in the relatives of people with learning disability. This was considered to be evidence that the comorbid state represented a chance co-occurrence of two distinct entities, as opposed to a separate condition with a hereditary component. However, unlike the present study, probands with the comorbid state were not selected. Our study concurs with the work of Kallman when the family history of subjects with schizophrenia and subjects with mild learning disability are considered. Yet, when comorbid probands are considered both schizophrenia and learning disability, in addition to the comorbid condition, occur commonly in first- and second-degree relatives. This finding and the existence of the multiply affected families described above would seem to indicate that a chance co-occurrence of the two conditions is unlikely to be the sole mechanism operating in these comorbid cases.

Common aetiology

The causes of both schizophrenia and learning disability are uncertain, although it is widely considered that the basis of each

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of these lies in some form of brain pathology, the nature of which is, as yet, obscure in most cases. This mechanism suggests it is possible that this common pathology may be more extensive than has previously been appreciated.

It is favoured by the histories of meningitis, encephalitis and epilepsy obtained from comorbid subjects and by their excess of neurological 'soft' signs. The findings relating to epilepsy may be indicative of an infective, traumatic or genetic link between schizophrenia and mild learning disability.

An epiphenomenon

This mechanism suggests that a deficit in one area of adaptive functioning in an individual with learning disability may result in increased susceptibility to develop impairments associated with schizophrenia. This would essentially be analogous to the situation concerning deafness and paranoid psychosis. It is established that people with deafness are more susceptible to develop paranoid psychoses (Cooper *et al*, 1974) and it is suggested that the underlying mechanism is the overload upon comprehension imparted by partially heard stimuli. If adaptive capacity is compromised (as may be the case in some individuals with learning disability), then such processes may readily become 'overloaded' and themselves become prone to malfunction. In some circumstances, this may result in the evolution of symptoms associated with schizophrenia.

This is perhaps the most difficult mechanism to address from the available data. Neuropsychological assessment of the comorbidity and learning disability group is limited by the necessity of comparison with the schizophrenia group. There are few neuropsychological tests that are thought to be independent of IQ. The results of the RBMT indicate that the comorbid group show memory impairment relative to both control groups. Given that both control groups were also impaired in this task, the results may indicate that the comorbidity group may demonstrate an additive effect consequent upon the impairment produced by each individual condition. This study *per se* provides no direct evidence for the confirmation or rejection of the epiphenomenon mechanism.

A 'severe' schizophrenia

It has long been established that in patients with schizophrenia there is a relationship between pre-psychotic IQ and disease prognosis (Offord & Cross, 1971).

Many studies of schizophrenia exclude people with premorbid learning disability. It is possible that in some of these people, the primary pathology has always been that of schizophrenia, but that this has not been considered in childhood, when learning disability is diagnosed, as psychotic symptoms are not manifest until early adulthood.

It is of interest that the four measures of age of onset of psychosis in this study are comparable in the comorbidity group and the schizophrenia control group. There are no group differences seen between gender and age of onset – although the general trend is for men to become ill at an earlier age, this effect is not significant. It has been suggested that the onset of schizophrenia may be earlier in people with impaired premorbid IQ and that this may be suggestive of a more malignant form of schizophrenia (DeQuardo *et al*, 1994). It does not appear that this is true of the comorbid subjects in this study.

It is possible that the phenomenon of 'diagnostic overshadowing' (Reiss & Szyszko, 1983), may be operating in the comorbid population, that is, there is a delay in the recognition of psychosis in people with pre-existing cognitive impairment as symptoms are initially attributed to behavioural difficulties, rather than illness *per se*. However, it has been shown that the time interval from the onset of initial symptoms to a formal diagnosis of schizophrenia being made is no different in the comorbidity group and the schizophrenia control group.

In terms of some of the main outcome parameters this study addressed, for instance, total time in hospital, offending behaviour, current chlorpromazine equivalent medication, deliberate self-harm attempts, there is no evidence that the comorbid group were more impaired than the schizophrenia control group. However, the comorbid group had more negative symptomatology, memory impairment, neurological soft signs, epilepsy and received greater amounts of community support, relative to the schizophrenia control group.

The finding of multiply affected families among comorbid probands has raised the possibility of an anticipatory mode of inheritance, with the most severe form of illness manifesting as the comorbid condition. If this is the case, then characterising the features of the illness in these individuals may help to characterise the nature of severe schizophrenia, which may be of genetic aetiology.

A 'de novo' condition

None of the last three hypotheses precludes the possibility that schizophrenia, as it occurs in people with premorbid cognitive impairment, may be a *de novo* condition, that is, a disorder separate from the generality of schizophrenia and learning disability which has not yet been described.

The core features of schizophrenia appeared to be the same in both the comorbid group and the schizophrenia control group. There were no major differences in age of onset or subsequent clinical course in terms of admission history, between the two groups. The finding of multiply affected families in the comorbid group was of interest when considering the possibility of a *de novo* disease. However, in view of the constancy of other features of the syndrome there does not appear to be sufficient evidence from this study to suggest a *de novo* disease may be present.

IMPLICATIONS

This study has shown that biological and psychological markers may distinguish, quantitatively, but not qualitatively, people with a premorbid IQ in the mildly learning disabled range who develop schizophrenia, from those people with schizophrenia alone. Comorbid subjects have more negative symptoms, episodic memory deficits and soft neurological signs than people with schizophrenia and a normal premorbid IQ. Comorbid subjects also have a tendency to belong to multiply affected families and show high rates of chromosomal variants on routine karyotypic testing.

In terms of the five mechanisms that this paper has considered to account for an excess of schizophrenia in people with mild learning disability, it is recognised that the mechanisms are not mutually exclusive. However, in some people with mild learning disability, schizophrenia will occur by coincidence. In other people, a severe form of schizophrenia may occur, where schizophrenia and learning disability arise together from a common genetic aetiology.

There is evidence that the comorbid group have a familial loading for schizophrenia that is at least as great as the control group with schizophrenia, and for

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learning disability that is at least as great as the control group with learning disability. Assuming that there is an excess incidence of the comorbid condition, these familial findings in the comorbid group cannot be considered independent.

Further study of people with pfropfschizophrenie might lead to a greater understanding of the nature of the genetic predisposition to psychosis and thus enable the identification of people with learning disability who subsequently develop schizophrenia before the onset of psychotic symptomatology.

Although it remains true that the inclusion of such people in general studies of schizophrenia can produce skewed results, as this study has shown, there is a need for this subtype to be included in comparative studies with separate statistical analyses. These findings suggest that commonly used research methods may have caused the most severe cases of schizophrenia to be positively excluded from many studies. Such a restriction of the concept of schizophrenia may have limited our understanding of the disorder.

CLINICAL IMPLICATIONS

- In some people with schizophrenia and premorbid mild learning disability a severe form of schizophrenia may occur where schizophrenia and learning disability arise together from a common genetic aetiology.
- The comorbid group is more likely to have epilepsy, neurological soft signs and episodic memory deficits than people with schizophrenia and no learning disabilities.
- The comorbid group differs from control subjects with schizophrenia in psychiatric admission profiles (fewer admissions, but longer) and community service utilisation (increased supported accommodation, community nursing and social work resources).

LIMITATIONS

- It was not possible for the clinical rater to be blind to diagnosis in this study.
- Karyotyping was not performed in control groups.
- The ascertainment of family history of schizophrenia and learning disability is difficult when so many probands have little or no family contact or knowledge. Hence, the figures derived may be an underestimate of family history, especially in comorbidity and learning disability groups.

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