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Elevated rates of schizophrenia in a familial sample with mental illness and intellectual disability

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Abstract

Background—It is unknown whether intellectual disability (ID) is more familially related to psychotic mood disorders or schizophrenia. L. S. Penrose's large sample of families with two or more members admitted to psychiatric hospitals provided a unique opportunity to investigate the familial relationship between mild ID, schizophrenia and psychotic affective disorders.

Method—There were 183 affected relative pairs comprising probands with mild ID (95 male, 88 female) and their first or second degree relatives with schizophrenia or psychotic affective disorder.

Results—There were nearly twice as many relatives with a diagnosis of schizophrenia ($n = 121$) as relatives with affective disorders ($n = 62$) among the intellectually impaired probands. This excess of schizophrenia was statistically significant, even after accounting for the increased risk of hospitalization for schizophrenia ($P = 0.005$), and was fairly constant across the different relative types. First-degree relatives with either mental illness were more likely to be parents ($n = 77$) than siblings ($n = 51$) or children ($n = 3$), but there was no excess of mother–son pairs.

Conclusions—These results suggest a stronger familial relationship of ID with schizophrenia than psychotic affective disorder, and lend some support to the neurodevelopmental hypothesis of schizophrenia.

Keywords

genetic; heritability; mental retardation; neurodevelopmental; risk; schizophrenia

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Introduction

Dual diagnosis and family studies suggest that a common genetic pathogenesis may underlie some forms of intellectual disability (ID) and psychotic illness. Individuals with ID are at increased risk for psychotic illness as compared with the general population (Penrose 1938; Heaton-Ward 1977; Turner 1989). Rates of schizophrenia in individuals with ID are about three times higher than general population rates (Reid 1993) and rates of comorbid bipolar affective disorders are also reported to be higher than expected (Ruedrich 1993). However, whether schizophrenia is just as 'familial' as psychotic affective disorders among relatives of intellectually impaired individuals remains unclear. While there may be a considerable overlap in genetic susceptibility to schizophrenia and psychotic affective disorders, it is possible that certain genes and environmental factors have more specific effects that lead to the diagnosis of schizophrenia and associated neurodevelopmental impairments, rather than affective disorders. The few studies that have examined this issue have reported increased rates of both schizophrenia (Penrose 1938; Gustavson *et al.* 1986) and affective disorders, when broadly defined (Penrose 1938) in relatives of probands with ID. Schizophrenia family studies have found increased rates of ID in first-degree relatives of schizophrenic probands (Heston 1966; Modrzewska 1980; Alaghband-Rad *et al.* 1998). Relatives of probands with comorbid ID and schizophrenia have shown elevated rates of ID as well as schizophrenia (Doody *et al.* 1998). However, other studies have not shown an increased rate of ID in relatives of schizophrenic probands (Kallmann *et al.* 1941), and little is known about risk for ID in relatives of individuals with a serious affective disorder like bipolar illness.

We used a large archival sample originally ascertained by L. S. Penrose (reported posthumously by Penrose 1991) to compare the frequency of schizophrenia vs. psychotic affective disorders in relatives of individuals with ID. This representative sample, described in detail elsewhere (Bassett & Husted 1997; Husted *et al.* 1998), comprises 7339 individuals from 3109 families, representing approximately 10% of the total psychiatric population in Ontario. Individuals were eligible to be included if both they and one or more of their relatives had ever been admitted to an Ontario psychiatric hospital for mental illness, or had committed suicide, from the mid- 1800s to 1944. This sample contains no 'control' individuals; only mentally ill relatives are included.

Evidence that genes may underlie disease risk may come from several sources. One convincing argument for genetic risk is based on excess risk to relatives (Risch 1990), relative to the population risk. In this sample, as no unaffected relatives are included, we cannot estimate population risks. However, we can obtain a valid estimate of the ratio of risks for a schizophrenic relative vs. an affective relative (Box 1). We hypothesized that there would be an excess of schizophrenic relatives of intellectually disabled probands, when compared with the number of relatives with psychotic affective disorder.

Box 1

Let ID denote a proband with intellectual disability, and SZ and AF denote, respectively, whether a relative (of a particular type) is diagnosed with schizophrenia or psychotic

affective disorder. Note that Penrose recorded the year of first admission for all individuals.

We would like to estimate the probability of a relative with SZ given a proband with ID: $P(\mathrm{SZ} \mid \mathrm{ID})$, and similarly, $P(\mathrm{AF} \mid \mathrm{ID})$. Without all unaffected relatives, we cannot estimate these quantities. However, assuming that only a small proportion of hospitalized relative pairs were not ascertained, and that the distribution of ascertained relative pairs is similar to the distribution of non-ascertained relative pairs, we can estimate the ratio of these two quantities, as

$$\frac{P(\mathrm{SZ}|\mathrm{ID})}{P(\mathrm{AF}|\mathrm{ID})}=\frac{P(\mathrm{SZ},\mathrm{ID})}{P(\mathrm{AF},\mathrm{ID})}$$

Define $\lambda_{SZ} = P(\mathrm{SZ} \mid \mathrm{ID})/P(\mathrm{SZ})$ to be a measure of excess schizophrenia hospitalizations in relatives of intellectual disability probands, where the denominator is the probability of any Ontarian being hospitalized at least once with schizophrenia during the Penrose study (cumulative incidence), and define λ_{AF} similarly. Therefore,

$$\frac{\lambda_{SZ}}{\lambda_{AF}}=\frac{P(\mathrm{SZ}|\mathrm{ID})P(\mathrm{AF})}{P(\mathrm{AF}|\mathrm{ID})P(\mathrm{SZ})}$$

Penrose reported rates of first admissions for various mental illnesses in 1943 (Penrose 1991); hence $P(\mathrm{AF})/P(\mathrm{SZ})$ can be estimated by 419/546 = 0.767, assuming this ratio stayed constant over the years spanned by his study of relative pairs. Hence, the ratio of excess hospitalizations for the two mental illness categories can be estimated by taking the observed ratio of pair types and multiplying by 0.767.

Materials and methods

Penrose sample

For each individual in the sample, the following data were recorded: diagnostic category, year of birth, year of first admission to a psychiatric hospital, and relationship of the individual to other family member(s) in the sample (e.g. father, daughter, brother, etc.). Penrose used the medical chart diagnoses to form 13 broad categories of mental illness. Approximately equal numbers of subjects had a diagnosis of schizophrenia (30.8%) and affective disorder (manic depression, mania, schizoaffective illness, depression) (29.8%), 6% were categorized as mentally defective (intellectual disability), and 33.4% were diagnosed with other psychiatric illnesses. On the basis of generally conservative diagnostic practices and findings comparable to those of contemporary studies, other studies have justified the use of similar historical clinical diagnoses for severe psychiatric illnesses (Kendler & MacLean 1990; Vogel *et al.* 1990). In the Penrose sample, the relevant proportions of diagnoses (e.g. approximately equal numbers in schizophrenia and affective disorder categories) and demographic characteristics (e.g. later age at onset for affective disorders than for schizophrenia) would support this position.

Only limited information is available about what specific disorders are contained within these diagnostic categories (Penrose 1991; Bassett & Husted 1997; Husted *et al.* 1998). This information suggests that affective disorders in this sample were primarily severe and psychotic in nature: manic depression, mania, schizoaffective illness, and depression. We also know that in the time frame of the study, individuals with moderate to profound ID in Ontario were placed in special institutions rather than psychiatric hospitals (Orillia Census 1879–1913; Hodgins 1919). Individuals with milder forms of ID usually lived in the community and were hospitalized in psychiatric hospitals only when they exhibited significant psychiatric symptoms or behaviour changes (Hodgins 1919). It is therefore likely that subjects in the mentally defective category in this sample had borderline to mild ID and accompanying psychiatric features. The mean age at psychiatric hospitalization for probands with ID in the entire Penrose sample was 20.6 years (SD 13.3 years) providing support for likely comorbidity of psychiatric symptoms with mild ID as opposed to more severe forms of ID which would likely have had an earlier age of institutionalization. All subjects in the Penrose sample were coded as to their relationship to their family members. Almost half of affected relative pairs in the sample were siblings; next most common were parent–offspring pairs comprising approximately 32% of the sample (Penrose 1991). The Review Ethics Board of the University of Toronto approved the use of this sample for the current study.

Samples used in the current study

To derive the data set used for the analysis, all 469 subjects diagnosed with ID, and all their relatives (368 families, total 943 individuals) were selected from the total Penrose sample. We then kept only the 199 families (543 individuals) in which there was at least one relative diagnosed with schizophrenia or affective disorders. Pairs of relatives were formed where one member of the pair had ID, and the other had mental illness (schizophrenia or affective disorder). Sixteen families were excluded where the relationship between the pair members was grandparental or greater, to restrict sampling to one or two generations. Among the remaining 183 families, in 63 families more than one pair could be formed, so we randomly selected one pair per family. Therefore, the final sample consisted of 183 pairs from 83 families. Relative pairs were grouped by type: parent–offspring, avuncular, and siblings.

Although the sample was believed to be primarily comprised of milder forms of ID, we investigated the possible effects of late maternal age (≥39 years) (Trimble & Baird 1978), a known risk factor for Down syndrome and other trisomies (Penrose 1933; Hook 1981), which are the most frequent causes of severe ID (McDonald 1973; Gustavson *et al.* 1977; Dykens *et al.* 2000). Because the Penrose sample is comprised of affected relative pairs, only pairs with affected mothers could be assessed for maternal age. We compared these pairs with two different samples of mother–offspring pairs selected from the Penrose data. We selected relative pairs where both mother and offspring were hospitalized for schizophrenia (n = 97 pairs), and relative pairs where both mother and offspring were hospitalized for affective disorders (n = 95 pairs). When more than one pair per family was possible, we randomly selected one pair per family in each case. Selection for schizophrenia pairs was carried out independently of selection for affective disorders pairs; however, no families were represented in both samples.

Analyses

In families with an intellectually disabled individual, if schizophrenia is just as ‘familial’ as psychotic affective disorders among relatives of cases with ID, then we would expect the proportion of pairs with a schizophrenic relative should be determined by the relative population rates, or cumulative incidences, of hospitalizations of the two mental illnesses (Box 1). Affective disorders are known to be more common than schizophrenia in the general population. However, among hospitalized patients in Ontario during the relevant time period, the best estimates available are those contained in Penrose’s original report (Penrose 1991), based on the entire Penrose sample and based on a representative sample of first admissions from 1943. In the Penrose sample there were 3350 members of relative pairs with schizophrenia and 3345 with affective disorders (proportion with schizophrenia = 0.50); in 1943 there were 546 first hospitalizations for schizophrenia and 419 first hospitalizations for affective disorders (proportion with schizophrenia = 0.5658). One-tailed binomial tests were used to compare the proportion of pairs containing a relative with schizophrenia to (1) 0.50, and (2) 0.5658. Scenario (1) tests whether there are more pairs containing a relative with schizophrenia and scenario, and (2) tests whether there is an excess of pairs containing a relative with schizophrenia, when compared with the first admission rates for 1943. Logistic regressions were used to test whether the distribution of the two pair types varied by sex of the ID case, by sex of the mentally ill relative, or by relative type. We also investigated any effects of randomly selecting one pair when multiple pairs could be formed within a family, by repeating the random selection five times and repeating the analysis.

Chi-squared tests compared pair types between mothers and fathers and by maternal age.

Results

There were 95 male (52%) and 88 female (48%) probands with ID. The mean age of psychiatric hospitalization for these 183 probands was 21.0 years (SD 12.2 years). The mean age of first psychiatric hospitalization for the 121 relatives with schizophrenia was 33.8 years (SD 11.5 years) and 43.1 years (SD 13.2 years) for the 62 relatives with affective disorders, similar to results reported for the total sample (Penrose 1991). Consistent with our hypothesis, there were significantly more pairs containing a relative with schizophrenia than with a psychotic affective disorder, even after using the more conservative comparison based on first hospitalization rates for 1943 (see Table 1). There were nearly twice as many relatives with a diagnosis of schizophrenia than relatives with affective disorders. This proportion was fairly consistent across the different relative types, and was considerably in excess of either comparison rate used, although not statistically significant for some relative types when compared with 1943 hospitalization rates (see Table 1).

The specific relationships between ID and mental illness appeared similar for both types of mental illness. There were more parent–offspring pairs than sibling pairs for both schizophrenia and psychotic affective disorders, in contrast to the predominance of sibling pairs in the Penrose sample as a whole. There were only three parents with ID and fewer aunts/uncles than nieces/nephews with ID (see Table 1).

If X-linked transmission of ID were prevalent in this sample one would have expected an excess of male probands, and more mother–son than mother–daughter pairs. However, the proportion of mother–son pairs was not greater than mother–daughter pairs in either schizophrenia–ID (31% vs. 33%, $P = 0.80$) or affective disorder–ID pairs (29% vs. 25%, $P = 0.70$). There was also no significant difference in the proportion of mothers and fathers with affective disorder (binomial $P = 0.34$). However, there were more mothers than fathers with schizophrenia (binomial $P = 0.00003$), consistent with well-documented reduced reproductive fitness in men with schizophrenia (Bassett *et al.* 1996).

The results of the logistic regression analysis showed that the proportion of pairs with schizophrenia was not affected by the sex of the intellectually disabled proband, the sex of the mentally ill relative, the sex of the transmitting parent, or whether the relative was first or second degree. The results were also consistent with the five different random selections of independent pairs, when multiple pairs could be formed within a family.

Both the mean maternal age and the proportion of mother–offspring pairs with late maternal age were similar between the schizophrenic and affective mothers who were relatives of intellectually disabled cases [31.1 years (SD = 7.7) and 31.7 years (SD = 8.0); $t = 0.25$, df = 53, $P = 0.80$, respectively, and 18.45% (7/38) and 23.5% (4/17); $\chi^2 = 0.19$, df = 1, $P = 0.66$, respectively]. The mean maternal age and proportion of mother–offspring pairs with late maternal age was also similar between 97 pairs with schizophrenia and 95 mother–offspring pairs with affective disorders [28.8 years (SD = 5.7) and 27.9 years (SD = 5.6); $t = 1.06$, df = 190, $P = 0.29$, respectively, and 6.2% (6/97) and 2.1% (2/95); $\chi^2 = 2.00$, df = 1, $P = 0.16$, respectively]. Given the similarity in maternal age between the schizophrenic and affective mothers in the sample of relatives of intellectually disabled cases, and between the schizophrenia mother–offspring pairs and affective disorder mother–offspring pairs, we decided to compare the proportion of pairs with late maternal age in the total sample of mother–offspring pairs of the intellectually disabled probands with that in the total sample of mother–offspring pairs of mentally ill probands. The proportion of pairs with late maternal age was found to be significantly higher in the mother–offspring pairs of the intellectually disabled (20% vs. 4.2%; $\chi^2 = 15.01$, df = 1, $P = 0.0001$).

Discussion

This study found a stronger familial relationship between schizophrenia and ID than between psychotic affective disorders and ID. In the familial sample studied, schizophrenia was almost twice as common as affective disorders in relatives of probands with ID. We can estimate the excess ‘familiality’ for schizophrenic relatives of intellectually disabled probands, relative to affective cases (Box 1). The ratio of the relative risks is approximately (121/62) × 0.767 = 1.48. Hence, from the Penrose data, we can estimate that an intellectually disabled proband is nearly 1.5 times more likely to have a relative hospitalized with schizophrenia than with a psychotic affective disorder. This was observed across all relative types, although the finding was particularly strong for mother–offspring pairs, and was not statistically significant for some small subgroups of relative types after adjusting for a higher estimated risk of hospitalization for schizophrenia. The sample used in this study is likely to comprise subjects with mild to borderline ID and comorbid psychiatric conditions. These

results are therefore consistent with a recent study (Doody *et al.* 1998) which found elevated rates of schizophrenia in first- and second-degree relatives of probands with comorbid mild ID and schizophrenia. The results are also consistent with studies showing an increased prevalence of ID in relatives (Alaghband-Rad *et al.* 1998), particularly offspring (Heston 1966; Modrzewska 1980), of probands with schizophrenia.

Undoubtedly, there is heterogeneous causation of ID in the current study that is likely to include a chance occurrence of ID and mental illness in some families. There are also limitations given the nature of the archival sample used, such as lack of specific information regarding the severity of ID. Given that individuals had to be hospitalized in a psychiatric institution to be included in the sample, generalizability of the findings is likely to be limited to individuals with mild ID and severe behavioural disturbances. Another limitation relates to the possibility that the stronger relationship between ID and schizophrenia than between ID and psychotic affective disorder results from detection bias. For instance, prior hospitalization of a schizophrenic parent or sibling could lead to earlier detection and treatment of a subsequently affected offspring. However, this type of bias, if present, would presumably operate in the psychotic affective disorder relative pairs as well. Furthermore, the stronger relationship between ID and schizophrenia is observed in the second-degree relatives as well, where such detection bias is likely to be reduced. In spite of these limitations, the size of the sample, the magnitude of the results, and their consistency with other studies allow speculation about possible genetic or environmental risk factors that could account for the observed familial cooccurrence of mild ID and psychotic illnesses, especially schizophrenia.

Possible genetic relationships

The results suggest the possibility of genetic anticipation (increasing severity of illness with successive generations). ID co-occurring with psychotic illnesses in offspring probands could represent a severe form of psychosis (Doody *et al.* 1998) that may arise from a common genetic aetiology transmitted by an affected parent with a less severe form of the same condition. Anticipation has previously been observed in the Penrose sample using schizophrenia–schizophrenia affected relative pairs and controlling for selection bias effects (Bassett & Husted 1997). There is also evidence for anticipation in other samples of familial schizophrenia (Bassett & Honer 1994) and manic depression (McInnis *et al.* 1993). However, to our knowledge previous studies of anticipation in psychiatric samples have not included relatives with ID.

There was no support for X-linked transmission of ID for relative pairs with either schizophrenia or psychotic affective disorder, in the current study, despite the fact that X-linked inheritance is the most common known mechanism for inherited causes of ID (Simonoff *et al.* 1996; Muir 2000). There was, however, some suggestion of a parent-of-origin influence, with an excess number of mothers relative to fathers, which was particularly dramatic among schizophrenic parents. The maternal excess was also observed in the avuncular relations where reduced reproductive fitness in men with schizophrenia was not a factor.

Late parental age

Late maternal age appeared to be a risk factor for offspring with ID in a minority of relative pairs in the current study. However, there appears little likelihood that the 11 subjects comprising late maternal age offspring represent mainly individuals with Down syndrome. The risk of Down syndrome approaches only 1% at a maternal age of about 40 years (Cuckle *et al.* 1987) and there is no evidence for elevated rates of psychotic illnesses in Down syndrome (Collacott *et al.* 1992) or in relatives of Down syndrome patients (Andersson 1993; Scott *et al.* 1997). Also, the moderate level of ID seen in Down syndrome would likely have led to institutionalization of these individuals in another type of facility (Hodgins 1919).

An alternative possibility that would be consistent with elevated rates of late maternal age in mothers with either schizophrenia or affective disorders who had offspring with ID is that advanced maternal age is acting as a marker for advanced paternal age, as maternal and paternal ages are highly correlated (Penrose 1955; Vogel & Motulsky 2000). There are reports of older paternal age in offspring with schizophrenia (Johanson 1958; Hare & Moran 1979; Malaspina *et al.* 2001) and affective psychosis (Hare & Moran 1979) compared with the general population, even after controlling for confounding effects of maternal age. The proposed mechanism involves an increased rate of genetic mutation in spermatogenesis with increasing paternal age (Penrose 1955; Vogel & Motulsky 2000). The possibility of interaction between paternal sporadic mutations and transmitted maternal genetic risk factors for mental illness, leading to a more severe phenotype (i.e. ID) in offspring, provides an alternative explanation for the appearance of anticipation (Bassett & Honer 1994). Given limitations on data available from the Penrose sample we were unable to control for the effects of paternal age in our analysis of maternal age. However, a comparison of paternal age between father–offspring pairs of the intellectually disabled probands (n = 21 pairs) and father–offspring pairs in the Penrose sample where both father and offspring were either hospitalized for schizophrenia (n = 36 pairs) or for affective disorders (n = 88 pairs) found no difference in paternal age.

Possible nongenetic factors

Intellectual disability may also be caused by nongenetic factors such as teratogens that may be related to the presence of mental illness in a parent. For example, alcohol use disorders are common comorbid diagnoses, especially in men with schizophrenia, and psychosis may be comorbid to learning disabilities in fetal alcohol syndrome (Famy *et al.* 1998). However, fetal alcohol syndrome accounts for only a small percentage of ID in the general population (Jones 1997) and is therefore unlikely to be a major factor in the current study. Other possibilities include poor maternal nutrition although there is limited evidence for this as a cause of permanent forms of ID (Stein & Susser 1985).

Comparison with Penrose's Colchester survey

Interestingly, the findings from the current study differ from Penrose's landmark 1938 Colchester survey of 1280 individuals institutionalized for ID (Penrose 1938). The Colchester survey found affective disorders were more common than schizophrenia (33% vs. 17%) in 610 first-degree relatives of probands with ID. The difference in results between the

two studies is likely to result from differing ascertainment strategies. Probands in the Colchester study were ascertained from institutions for the intellectually disabled and their relatives were personally assessed by Penrose, whereas in the current study all subjects had been hospitalized in a psychiatric institution. The range of affective illness severity in the Colchester sample was therefore likely to have been broader and the severity of ID greater than in the current study. However, the Colchester survey's high prevalence (17%) of schizophrenia in relatives and the greater frequency of schizophrenia than affective disorder as a comorbid condition in probands with ID are consistent with results from the current study.

Conclusion

Results from the current study support the possibility of a common pathogenesis for some familial forms of ID and psychotic illness, especially schizophrenia, and the likelihood that comorbid mild ID and schizophrenia represent a severe form of schizophrenia (Turner 1989; Doody *et al.* 1998). Determining which genetic and other factors may be involved will require further studies. Recent research indicates that a genetic syndrome, 22q11 Deletion Syndrome, is common in individuals with a dual diagnosis of psychosis and ID and likely represents a genetic subtype of schizophrenia with prevalent learning disabilities (Bassett & Chow 1999; Bassett *et al.* 2000). Inclusion of subjects with borderline to mild ID in studies of schizophrenia could be a valuable tool to help understand both the causes and underlying neurodevelopmental mechanisms of schizophrenia (Simonoff *et al.* 1996; Doody *et al.* 1998; Reiss *et al.* 2000). More family and genetic studies are also needed to further delineate the familial relationship between ID and major psychiatric illnesses, investigate possible parental age effects, and help identify other genetic subtypes of schizophrenia and possibly affective disorders.

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Table 1

Diagnosis of 183 relatives of 183 probands with intellectual disability (ID) by relationship type

Relatives with psychotic illness			Probands with ID			Analyses* *P*-values	
Relative type	**Schizophrenia *n* (%)**	**Affective disorder *n* (%)**	**Relative type**	***n***	**Male**	**Scenario (1)**	**Scenario (2)**
All	121 (66%)	62 (34%)	*All*	183	95 (52%)	<0.00001	0.005
First degree							
Parent	49 (64%)	28 (36%)	Offspring	77	39 (51%)	0.011	0.128
Mother	39	17		56	29 (52%)		
Father	10	11		21	10 (48%)		
Sibling	32 (63%)	19 (37%)	Sibling	51	27 (53%)	0.05	0.229
Sister	18	11		29	18 (46%)		
Brother	14	8		22	9 (41%)		
Offspring	2 (67%)	1 (33%)	Parent	3	2 (67%)	–	–
Second degree							
Aunt/uncle	30 (68%)	14 (32%)	Nephew/niece	44	23 (52%)	0.011	0.079
Maternal	21	9		30	14 (50%)		
Paternal	9	5		14	9 (56%)		
Niece/nephew	8 (100%)	0	Uncle/aunt	8	4 (50%)	0.004	0.011
Maternal	4	0		4	4 (100%)		
Paternal	4	0		4	0		

*One-tailed binomial tests were used to determine whether there was an excess proportion (*P*) of ID proband pairs where the relative had schizophrenia. Two possible scenarios were assessed: (1) assuming cumulative incidences of hospitalization for schizophrenia and affective disorder were equal (*P* = 0.50), and (2) assuming cumulative incidence of hospitalization for schizophrenia was greater than that for affective disorder (*P* = 0.5658), as recorded for first admission rates in 1943 (Penrose 1991).