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The Expression of Schizophrenia, Affective Disorder and Vulnerability to Tardive Dyskinesia in an Extensive Pedigree

JOHN L. WADDINGTON and HANAFY A. YOUSSEF

The demography, psychiatric morbidity, and motor consequences of long-term neuroleptic treatment in the 14 children born to a father with a family history of chronic psychiatric illness and a mother with a late-onset affective disorder resulting in suicide are documented. Twelve siblings lived to adulthood, nine of whom were admitted to a psychiatric hospital in their second or third decade, and required continuous in-patient care; five remaining in hospital, with long-term exposure to neuroleptics, had chronic, deteriorating, schizophrenic illness and emergence of movement disorder. Two siblings showed no evidence of psychosis but developed a late-onset affective disorder. The implications for the issues of homotypia, vulnerability to involuntary movements, and interaction with affective disorder are discussed.

While there is a widely accepted body of evidence for a genetic component in the aetiology of schizophrenia, the underlying mechanisms remain obscure (Gottesman & Shields, 1982; Baron, 1986; Murray *et al*, 1986; McGuffin *et al*, 1987). Analysis of the pattern of expression of psychosis through successive generations of family pedigrees constitutes one of the most powerful approaches to clarifying these issues (Weissman *et al*, 1986). However, there are very few studies that have been able to identify **and** systematically investigate multiple affected siblings within the same generation. In addition to potentially providing further information about mode of transmission, this could help clarify whether such genetic vulnerability includes a common predisposition to particular psychiatric symptoms and course of illness, and perhaps to particular neurological signs associated with the long-term treatment of that illness with neuroleptic drugs. A multiplex family with psychiatric disorder associated with basal-ganglia calcification has been described, several members of which showed an unusual sensitivity to the parkinsonian side-effects of neuroleptics (Francis & Freeman, 1984).

In our studies on the relationship between cognitive dysfunction, negative symptoms, and involuntary movements (tardive dyskinesia) in schizophrenia (Waddington & Youssef, 1986*a*,*b*; Waddington *et al*, 1987), one patient was found to have three brothers, each resident in a different ward in the same hospital (St Davnet's, Monaghan). It was found that their parent's marriage had resulted in a total of 14 children, including two sets of twins, with an unusually large number of these siblings affected by serious psychiatric illness. Our studies on this extensive pedigree are the subject of this report.

Method

Information on the 14 siblings and their parents was obtained from the following sources: all case-notes of those patients currently resident in a psychiatric hospital; all available clinical and other documentation relating to those patients then deceased; personal interviews with one sibling unaffected by psychotic illness; personal interviews with the daughter of a deceased sibling; personal interviews with a contemporary still resident in the village of their birth, who had attended school and grown up with many of the siblings; and documentation from the office of the General Registrar for Ireland, Department of Health, Dublin.

Each sibling then resident in a psychiatric hospital was interviewed and assessed clinically. Movement disorder was evaluated using the Abnormal Involuntary Movement Scale (AIMS; National Institute of Mental Health, 1976). This was followed by neuropsychological assessment, using an abbreviated 10-question mental test of the basic cognitive functions of orientation, awareness, and immediate memory (Waddington & Youssef, 1986*a*).

Results

The parents

The father died from cardiac arrhythmia aged 79, in a state of 'senility'. While there was no formal record of him having suffered from any specific psychiatric illness, a brother had been a psychiatric in-patient in St Davnet's hospital for an otherwise unspecified disorder. The mother committed suicide at home, aged 52. She had become depressed, with weeping and inability to cope. Fig. 1 illustrates the family pedigree.

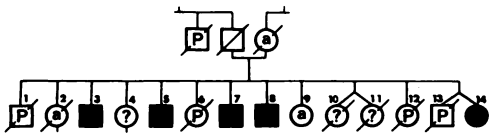

FIG. 1 Pedigree relating to the 14 children born to a father with a family history of chronic psychiatric illness, and a mother with a late-onset affective disorder resulting in suicide. Key for siblings: ■ = schizophrenic illness of early onset; P = chronic psychiatric illness of early onset, patient deceased; a = affective disorder of late onset; ? = unknown, individual reclusive or died at birth; / = deceased at time of study

Their children

All births were at home, in rural Co. Cavan. Deliveries were assisted, as was common in rural Ireland in the era of their birth (1909–1925), by a woman neighbour who acted as local midwife.

1. Their eldest son was admitted to St Davnet's hospital with an unspecified psychiatric disorder. As his immediate younger brother was the first to be admitted to St Davnet's, his own admission was calculated to be at the age of at least 17. In hospital, he subsequently contracted tuberculosis, and died, single, at the age of 29.

2. Their eldest daughter had her first psychiatric admission in Dublin at the age of 58, having become depressed, tearful, and wandering. During a subsequent hospital stay within the same year, following an overdose of barbiturates, she received amitriptyline, diazepam, and chlorpromazine, and a course of ECT. Her final diagnosis was endogenous depression, despite some elation on admission, and she was discharged on the above medications. She died of cancer, aged 69. From her marriage there were three sons and three daughters, aged 32–47 at the time of the study, who were well. One was a most helpful family historian.

3. Their second son was mentally handicapped from birth. He was admitted to St Davnet's hospital at the age of 14 because of severe behavioural problems. On admission, he was violent, with incoherent speech and echolalia. During his subsequent continuous stay in hospital, he remained periodically aggressive and disturbed. On examination in 1986 at the age of 74, he showed irritability, stereotyped and ritualistic types of behaviour and self-mutilating biting; he was then mute, except for occasional screaming. He had been treated with several neuroleptics and anticholinergics for a total of 26 years. On two occasions, once when receiving neuroleptics, and 8 months later when receiving only diazepam, the extent of his stereotyped and ritualistic types of behaviour and biting precluded definitive evaluation with the AIMS. Neuropsychological assessment was not possible.

4. Their second daughter, aged 73 at the time of the study, lived on the west coast of Ireland. Both she and an only son from her first marriage were said not to have received psychiatric treatment, but neither of two members of her family were prepared to reveal her location to us or to initiate contact on our behalf.

5. Their third son was admitted to St Davnet's hospital at the age of 18 with behavioural problems and delusions; he was single, dull, and slow in replying to questions. Over his subsequent continuous hospital stay, he was at various times seclusive, wandering, incoherent, hallucinated, and deluded. He had swings of mood at the age of 66. The possibility of some degree of mental handicap had been entertained. Examination in 1986, when he was aged 71, indicated marked poverty of speech, obsessional rituals of touching people, and blunting of affect. He satisfied the criteria of Feighner *et al* (1972) for a diagnosis of schizophrenia. He had been treated with several neuroleptics and anticholinergics for a total of 20 years. Evaluation with the AIMS, when he was under treatment with neuroleptics, revealed minimal involuntary movements, but an elevated blink rate. His mental test score was 3. Neuroleptics were subsequently discontinued because of a dystonic episode. Six months after neuroleptic withdrawal, under treatment only with diazepam, he showed mild but clearly abnormal involuntary movements of the tongue and jaw. He satisfied the criteria of Schooler & Kane (1982) for a diagnosis of tardive dyskinesia.

6. Their third daughter was admitted to a local county home at the age of 19, and transferred 9 months later to St Davnet's hospital with an unspecified psychiatric disorder; she was single. Two months after her admission, when aged 20, she contracted a virulent infection, which proved fatal.

7. Their fourth son was admitted to St Davnet's hospital at the age of 20 because of threatening behaviour; he was single, dull, and incoherent in speech. Over his subsequent continuous hospital stay, he also showed inane laughter, seclusiveness, poverty of speech, and paranoid ideation. He had swings of mood at the age of 61. Examination in 1986, when he was 69, indicated blunting of affect. He satisfied Feighner criteria for a diagnosis of schizophrenia. Treatment had been with several neuroleptics and anticholinergics, for a total of 18 years, with occasional use of antidepressants. Evaluation with the AIMS revealed mild but clearly abnormal involuntary movements of the lips and jaw, satisfying Schooler & Kane criteria for tardive dyskinesia. His mental test score was 6.

8. Their fifth son was admitted to St Davnet's hospital at the age of 19 because of wandering and attempted suicide; he was single, dull, incoherent, and deluded. Over his subsequent continuous hospital stay, he was at various times withdrawn, hallucinated, and affectively flat. He had swings of mood at the age of 62. Examination in 1986, when he was aged 67, indicated poverty of speech, avolition, blunting of affect, and asociality. He satisfied Feighner criteria for a diagnosis of schizophrenia. Treatment had been with several neuroleptics, for a total of 14 years. Evaluation with the AIMS revealed mild but clearly abnormal involuntary movements of the lips, jaw, and tongue, satisfying Schooler & Kane criteria for tardive dyskinesia. His mental test score was 6.

9. Their fourth daughter became depressed at the age of 55. She presented to her general practitioner in Dublin, who prescribed antidepressants and benzodiazepines. This continued intermittently over the subsequent decade. Interviews in 1986 and 1987, when she was aged 66, revealed a shy but most helpful historian who wept on relating her

family's vicissitudes. She continued to receive treatment with antidepressants. Her cognitive and motor functions were unimpaired. There were no children from her marriage.

10. and 11. Their fifth and sixth daughters were twins who were born 15 min apart. They died 1 h and 4 h afterwards, from otherwise unspecified "debilities on birth".

12. Their seventh daughter was admitted to St Davnet's hospital with an unspecified psychiatric disorder. She soon contracted tuberculosis and died, single, at the age of 17.

13. and 14. Their sixth son was admitted to a school for the mentally handicapped at the age of 12. On admission, he had no violent or dangerous habits or propensities, and a fair capacity for education, training, and work. He left the school at 15, but was subsequently admitted to St Davnet's hospital for an unspecified psychiatric disorder. There he contracted tuberculosis and died, single, at the age of 19.

His co-twin, their parents' eighth daughter, was mentally handicapped from birth. She was admitted to a Dublin psychiatric hospital at the age of 17 because of wandering and rough treatment of children; she was single, deluded, and talking to herself. In the year after admission, she reported auditory hallucinations. Over her continuous hospital stay there was little subsequent evidence of positive psychotic symptoms, and she became dull, apathetic, and slow to answer questions, with interpolated episodes of impulsive agitation. After a decade of essentially asocial and negativistic behaviour, and increasing cognitive impairment, tricyclic antidepressants were given when she was aged 48 as an adjunct to neuroleptics; whereas her case-notes had previously contained (and subsequently reverted to) a diagnosis of schizophrenia with mild mental handicap, a re-diagnosis of mood swings in mental handicap was temporarily made. On examination in 1986 and 1987, when she was aged 61, she had no psychotic symptoms or prominent disorder of affect; her speech was sparse but normal in content. She had been treated with several neuroleptics and anticholinergics for a total of 23 years, with occasional use of antidepressants. Evaluation with the AIMS revealed moderate involuntary movements of the jaw, and mild but clearly abnormal involuntary movements of the lips and tongue. She satisfied the criteria of Schooler & Kane for a diagnosis of tardive dyskinesia. Her mental test score was 3.

Discussion

This study documented the demography, psychiatric symptoms, and motor consequences of long-term neuroleptic treatment in the 14 children of a father with a family history of chronic psychiatric illness, and a mother with a late-onset affective disorder resulting in suicide. Such a highly unusual and extensive sibship presented a rare opportunity to probe the extent to which genetic vulnerability to schizophrenia might carry with it a common predisposition to specific forms of symptoms and course of illness, perhaps to particular movement disorders associated with their treatment, and might interact with other genetic vulnerabilities. The principal characteristics of the 12 children living to adulthood are summarised in Table I.

There were four siblings (numbers 5,7, 8, and 14) who had a first psychotic episode in their late teens or twenties and whose subsequent chronic illness was typical of schizophrenia. For a fifth sibling (number 3), his marked mental handicap complicated considerably such a psychiatric diagnosis by modern operational criteria. However, this could be entertained on the basis of the onset in his teens of sudden changes in an established personality and system of social relationships, with altered affective responses, unusual rituals, and abnormalities in interpersonal behaviour, which became superimposed on his original intellectual deficit (Heaton-Ward, 1977; Parsons *et al*, 1984); there is now some considerable weight of opinion (Reid, 1972; Heaton-Ward, 1977; Parsons *et al*, 1984) that the typical symptoms, natural history, and treatment response of schizophrenia are little modified in patients with milder mental handicap. Additionally, four other siblings (numbers 1, 6, 12, and 13), long deceased, and for whom little additional information was available, had also been admitted to the same psychiatric hospital in their teens or twenties, where they had remained as in-patients until their death; this clinical picture, which was similar to that of their father's brother, was consistent with (but does not prove) a schizophrenic illness such as that diagnosed in several of their siblings who were still alive.

This sibship presented an opportunity to study familial homotypia (the extent to which affected siblings might belong to the same sub-type of schizophrenia and show similar patterns of symptoms and course of illness); the literature on this much-debated topic has been recently reviewed (Gottesman & Shields, 1982; McGuffin *et al*, 1987). In nine siblings, there appeared to be a clear commonality of early onset and poor outcome, as indicated by age at first admission to a psychiatric hospital and no subsequent discharge. In the five cases where detailed information was available, this was characterised by positive symptoms on, and in the period immediately following admission. Thereafter, over several decades, their illnesses had a similar deteriorating course, with such florid psychotic signs becoming less evident. For the male siblings, there was a common progression to a defect state of negative symptoms; even for the brother whose marked mental handicap was a complicating factor, there was clear evidence of deterioration from incoherent speech and echolalia in his teens to subsequent muteness.

TABLE I
Clinical features of the 12 children living to adulthood

	Sibling number											
	1	2	3	4	5	6	7	8	9	12	13	14
Age	Died aged 29	Died aged 69	74	73	71	Died aged 20	69	67	66	Died aged 17	Died aged 19	61
Sex	M	F	M	F	M	F	M	M	F	F	M	F
Diagnosis	P	AFF	SCH	?	SCH	P	SCH	SCH	AFF	P	P	SCH
Age of onset of psychiatric symptoms	⩾17	58	14	?	18	19	20	19	55	⩽17	>15	17
Duration of neuroleptic treatment	—	—	26 years	—	20 years	—	18 years	14 years	—	—	—	23 years
Cognitive dysfunction	—	—	Yes	—	Yes	—	Yes	Yes	No	—	—	Yes
Negative symptoms	—	—	Yes	—	Yes	—	Yes	Yes	No	—	—	No
Orofacial dyskinesia	—	—	?	—	Yes	—	Yes	Yes	No	—	—	Yes

SCH = schizophrenic illness; AFF = affective disorder; P = died in a psychiatric hospital, specific diagnosis unknown. ? = data insufficient to determine entry; — = not applicable or no data available, patient deceased or reclusive

Such commonality of clinical course in this multiplex family would be consistent with the twin-study analyses of Dworkin & Lenzenweger (1984) and McGuffin *et al* (1987), which showed a higher rate of concordance when the proband exhibited a high rate of negative symptoms. Our data indicate substantial homotypia for early onset, poor outcome, and deterioration to the defect state, especially in the male siblings. For one sister (number 14), initial positive symptoms diminished similarly, although over several decades of continuous hospital stay there was less evidence of progression of negative symptoms. This would be consistent with the view that deterioration may be less pernicious in schizophrenic females than in males (Seeman, 1986).

This multiply affected family also allowed investigation of any common vulnerability to the emergence of involuntary movements during the long-term treatment of psychotic illness, with neuroleptic drugs. There is now some weight of evidence that schizophrenic patients with involuntary movements are characterised by greater cognitive dysfunction than otherwise indistinguishable patients without such movements, and that this might indicate an 'organic' component to their vulnerability (Waddington, 1987). In our own studies, we have found the presence of cognitive dysfunction and/or negative symptoms to have a much stronger association with the presence of involuntary movements than any index of treatment with neuroleptics; this was evident not just in schizophrenic in-patients (Waddington & Youssef, 1986*a*,*b*) but also in an out-patient population, where those with late-onset psychosis and poor cognitive function were particularly at risk (Waddington & Youssef, 1986*c*). These associations were most robust in relation to the presence of buccal–lingual–masticatory dyskinesia (Waddington *et al*, 1987).

The five psychotic siblings assessed had all received neuroleptics for periods of 14–26 years. The brother with marked mental handicap showed a wide spectrum of stereotyped and ritualistic motor disorders, including biting; it was not possible to specify whether typical involuntary movements were present or absent with so elevated and complex a baseline. However, his four siblings each showed typical tardive orofacial dyskinesia, and each had a mental test score lower than the mean of two groups of schizophrenic in-patients of similar age who did not show such movements (Waddington & Youssef, 1986*a*,*b*).

There are only two published reports on familial aspects of tardive dyskinesia within individual pedigrees. Yassa & Ananth (1981) reported concordance for the presence of involuntary movements in each of two brother–sister pairs, and concordance for the absence of such movements in each of six other brother–sister, male-twin, sister–sister, or mother–son pairs with various disorders for which neuroleptics had been prescribed. Similarly, Weinhold *et al* (1981) reported involuntary movements in each of two schizophrenic brothers, one of whom showed marked, and the other mild, cognitive impairment.

Using a different strategy, Bartels *et al* (1985) reported an overall reduced likelihood of a family history of psychosis in schizophrenic patients with, compared with those without, tardive dyskinesia; however, they did not investigate concordance for involuntary movements within those families having more than one member with a diagnosis of schizophrenia. The present study suggests that familial predisposition to psychotic illness with cognitive impairment may carry a shared predisposition to the emergence of orofacial dyskinesia. This would support the proposition (Waddington, 1987; Waddington *et al*, 1987) that the pathophysiologies of these two processes may be related.

It should not be overlooked that, although we have considered siblings 1, 3, 5, 6, 7, 8, 12, 13, and 14, others (numbers 2, 4, and 9) experienced no such early psychotic breakdown and subsequent continuous hospital stay. The two females for whom information was available had developed an affective illness relatively late in life, in their sixth decade, as had their mother. The third was considered by her relatives to require protection from the potential distress of our wish to contact her, because of her otherwise unspecified 'disposition'; such circumstances relating to this lady are no basis for any reliable presumption of psychiatric morbidity. Thus, the unusual marriage of a father with a family history of (probable) schizophrenia, and a mother with a late-onset affective disorder, had resulted in 12 of 14 children living to adulthood, 11 showing psychiatric illness as follows: nine (6M, 3F) who appeared to have developed a chronic schizophrenic illness of early onset, and two (2F) who developed a late-onset affective disorder.

The comparative genetics of schizophrenia and of affective disorders, and the extent to which they may breed true, have recently been reviewed from a variety of often-controversial perspectives (Crow, 1986; McGuffin *et al*, 1987; Andreasen *et al*, 1987; Rice *et al*, 1987). Of the six siblings (numbers 2, 5, 7, 8, 9, and 14) who were assessed in detail in the absence of marked mental handicap, sisters 2 and 9 had developed a late-onset depressive illness in their sixth decade, with no evidence of psychosis. While brothers 7, 8, and 9 had developed typical schizophrenia in their second decade, their clinical histories revealed that each had shown swings of mood that became particularly evident in their seventh decade; however, in no instance did these symptoms endure to predominate a lifetime diagnosis of schizophrenia. Similarly, their psychotic sister (number 14) began to show swings of mood at age 48 after a decade of relative quiescence. Thus, there was some evidence to suggest the transient emergence of late-onset affective symptoms even in those siblings with schizophrenia characterised by early onset and a chronic, deteriorating course. However, there remained a clear difference between schizophrenia of early onset and a much-later onset of depression without psychotic symptoms.

Although chance cannot be excluded, there are at least three factors that might contribute to this high incidence of morbidity in these multiple siblings. Firstly, there was mental handicap in some members of the family, and evidence exists that schizophrenia, particularly of early onset, may be more likely to occur if a static neurological disorder is also present (Parsons *et al*, 1984; Weinberger, 1987). Secondly, there was rudimentary pre-/post-natal care and assistance at delivery during the mother's pregnancies; obstetric complications are known to be associated with an increased risk of schizophrenia, although this phenomenon can be incorporated into different theoretical schemes (Murray *et al*, 1985; McGuffin *et al*, 1987). Thirdly, there is the possible presence of two genotypes in an individual; one genotype (e.g. for affective disorder) may increase the likelihood of the other (e.g. for schizophrenia) being expressed (Owen & Nimgaonkar, 1987).

This multiplex family is a highly unusual contribution to the study of schizophrenia, particularly in relation to the controversial issues of homotypia, vulnerability to involuntary movements, and possible interactions with affective disorder. It might be of some considerable potential for genetic-marker and/or genetic-linkage studies.

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*John L. Waddington, MA, MSc, PhD, *Senior Lecturer in Clinical Pharmacology, Royal College of Surgeons in Ireland*; Hanafy A. Youssef, DPM, MRCPsych, *Consultant Psychiatrist, St Davnet's Hospital, Monaghan, Ireland*

*Correspondence: *Royal College of Surgeons in Ireland, St Stephen's Green, Dublin 2, Ireland*