Family history of primary movement disorders as a predictor for neuroleptic-induced extrapyramidal symptoms

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Background A genetic susceptibility to extrapyramidal symptoms caused by treatment with neuroleptic medication has been suggested.

Aims To identify predictor variables for neuroleptic-induced extrapyramidal symptoms, particularly considering family history of primary movement disorders.

Method We investigated 100 in-patients receiving a stable neuroleptic medication with regard to occurrence of extrapyramidal symptoms, drug history and detailed family history of primary movement disorders.

Results Step-wise logistic regression analysis revealed that a positive family history was a significant predictor for lifetime prevalence of extrapyramidal symptoms, including reported and currently observed symptoms. The duration of exposure to neuroleptic medication and age were further predictors.

Conclusions Our findings underline the notion of genetic susceptibility for secondary extrapyramidal symptoms and suggest possible shared genetic factors in primary and secondary movement disorders as well as psychotic disorders.

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Neuroleptic-induced extrapyramidal symptoms often lead to non-compliance and consequently poorer treatment outcome (Gerlach, 2002). Extrapyramidal symptoms may also occur with modern, atypical neuroleptic medication (Tarsy *et al*, 2002). Risk factors include age, psychiatric diagnosis, psychopathology, and dosage and duration of neuroleptic exposure, but no clear-cut predictor has been identified as yet (Ayd, 1961; Swett, 1975; Nasrallah *et al*, 1988; Berardi *et al*, 2000; Srinivasan *et al*, 2001). More recently, genetic factors have been suggested to have a role in the susceptibility to extrapyramidal symptoms (Basile *et al*, 2002; Segman *et al*, 2002). Given that a genetic predisposition may increase the susceptibility to such symptoms, a positive family history of primary movement disorders may be associated with their development. An increasing number of polymorphisms in dystonia and parkinsonism genes have been shown to be associated with primary movement disorders (Klein & Ozelius, 2002; Gasser, 2003). We therefore investigated whether a family history of primary movement disorders might be a predictor of extrapyramidal symptoms in patients receiving typical and atypical neuroleptic medication.

METHOD

Patients and diagnosis

Participants were consecutively recruited from people admitted as in-patients of the Department of Psychiatry and Psychotherapy at the University of Lübeck. Each participant gave written informed consent after having been carefully informed about the study. The study was approved by the local ethics committee. Participants had to meet the following inclusion criteria:

(a) stable neuroleptic medication for at least 1 week;

(b) no neurological disease;

(c) no significant history of head trauma;

(d) no other medication that could potentially induce movement disorder.

Operational psychiatric lifetime diagnoses according to DSM–IV (American Psychiatric Association, 1994) were established using the German version of the Mini-International Neuropsychiatric Interview (MINI; Sheehan *et al*, 1998) and the Structured Clinical Interview for Personality Disorders (SCID–II; Spitzer & Williams, 1987). Diagnoses were divided into four categories: organic psychiatric disorders, including all forms of alcohol and drug dependence; psychotic disorders; affective disorders; and other Axis I or Axis II disorders. Psychopathological symptom severity was rated on the Brief Psychiatric Rating Scale (BPRS; Overall & Gorham, 1962). Each participant underwent a complete neurological examination with particular emphasis on specific signs of acute dystonic reaction, parkinsonism, akathisia and tardive dyskinesia. The following rating scales were used to assess the severity of extrapyramidal symptoms (van Harten *et al*, 1997): the Abnormal Involuntary Movement Scale (AIMS; National Institute of Mental Health, 1975); the Tsui Rating Scale for Cervical Dystonia (Tsui *et al*, 1986) and the Burke Rating Scale for Primary Torsion Dystonias (Burke *et al*, 1985); Part III of the Unified Parkinson's Disease Rating Scale (UPDRS; Movement Disorder Society Task Force on Rating Scales for Parkinson's Disease, 2003); the global score on the Hillside Scale (Fleischhacker *et al*, 1991) and the Barnes Akathisia Scale (Barnes, 1989). History of extrapyramidal symptoms on previous neuroleptic treatment was explored in a structured interview developed by our group, covering the typical symptoms of acute dystonic reaction, parkinsonism, akathisia and tardive dyskinesia. To check the reliability of their answers, participants were asked about the consequences of the development of their movement disorder (for example, change in medication or administration of biperiden). In addition, clinical records covering former treatment phases were reviewed to complete the information. Family history of movement disorders was obtained by means of a structured interview developed in our department, specifically covering symptoms of Parkinson's disease (stiffness of movement, gait problems, tremor, change in facial expression, lateralisation of symptoms), dystonia and psychiatric disorders in first-degree to third-degree relatives. This

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structured interview had previously been shown to provide reliable data in a large epidemiological study (Klein *et al*, 1999). A diagnosis of a primary movement disorder was only made if the criteria for the disorder were clearly fulfilled by the symptom description given by the patient. Relatives were asked to also undergo the structured interview whenever possible.

Statistical procedure

Pearson's chi-squared tests for independence were performed to investigate the relationship between categorical outcome variables (lifetime occurrence of extrapyramidal symptoms, including reported and currently observed symptoms; reported extrapyramidal symptoms during previous treatment phases; currently observed extrapyramidal symptoms; extrapyramidal symptoms on typical neuroleptic medication; extrapyramidal symptoms on atypical neuroleptic medication; lifetime occurrence and currently observed acute dystonic reaction, parkinsonism, akathisia and tardive dyskinesia) and possible categorical predictor variables (gender; age; psychiatric diagnostic category; dosage range; duration of exposure to any neuroleptic medication; duration of exposure to typical neuroleptic medication; duration of exposure to atypical neuroleptic medication; positive family history of primary movement disorder). To achieve the required expected cell frequency of more than 5 in χ^2-tests, we defined three different age groups: 18–40 years, 41–60 years and >60 years. For the same reason, duration of exposure to neuroleptic medication was categorised as <6 months, 6 months to 5 years, and >5 years. For easier comparison, drug dosages were defined as low, medium or high, based on current clinical practice. Chi-squared values are reported with two-tailed probabilities. Relationships between possible predictor and outcome variables with $P<0.5$ revealed by χ^2-tests were entered in a step-wise logistic regression analysis to identify predicted probabilities for extrapyramidal symptoms (probability to enter at 0.05). By use of a logistic regression analysis, all predictor variables are considered within one testing procedure, including intercorrelations, which reduces the probability of type I errors. All statistical procedures were performed using the Statistical Package for the Social Sciences (version 11.0).

RESULTS

Demographic and clinical data are listed in Table 1. Most patients (62%) had been admitted for treatment of a psychotic disorder: schizophrenia or schizophreniform disorder (*n*=50), schizoaffective disorder (*n*=10) or delusional disorder (*n*=2). Fourteen patients were receiving neuroleptic treatment for an organic psychiatric disorder: substance-induced psychotic episodes (*n*=10), delirium (*n*=3) or organic delusional disorder (*n*=1). Eighteen patients were treated for an affective disorder: unipolar depressive disorder with psychotic symptoms (*n*=10), bipolar disorder with psychotic symptoms (*n*=8; five manic and three depressive episodes). Six patients had other psychiatric disorders: borderline or combined personality disorder (*n*=5) or dissociative disorder (*n*=1). Analysis of variance including *post hoc* comparisons revealed that patients with an affective disorder were significantly older than patients from the other groups (*F*=3.89, d.f.=3, *P*=0.01), who did not differ significantly with respect to age. The distribution of men and women differed significantly between the diagnostic groups (χ^2=17.74, d.f.=1, *P*<0.01), whereas symptom severity measured by BPRS scores was similar in all groups. More patients had ever been treated with atypical neuroleptic medication (87%) than with typical neuroleptics (64%).

Lifetime prevalence of extrapyramidal symptoms

Lifetime prevalence of extrapyramidal symptoms, including both reported and currently observed symptoms, was 65% (Table 2). Acute dystonic reactions occurred most commonly (41%), followed by parkinsonism (37%), akathisia (19%) and tardive dyskinesia (4%). It should be noted that several patients suffered from more than one type of extrapyramidal symptom. Of those who had experienced such symptoms, more patients had been exposed to typical than to atypical medication. Details of mean age and distribution of gender are given in Table 2.

Currently observed extrapyramidal symptoms

At the time of examination, most patients were taking an atypical neuroleptic medication (Table 3). Extrapyramidal symptoms were diagnosed in 34% of patients.

The most commonly observed symptom was parkinsonism (19%), followed by acute dystonic reaction (15%), akathisia (5%) and tardive dyskinesia (3%). Again, some patients were diagnosed with more than one type of extrapyramidal symptom. Table 3 gives further clinical characteristics and details concerning dosages of neuroleptic medication.

Reported symptoms and family history of primary movement disorders

Fifty-three patients (29 men and 24 women, mean age 36.3 years, s.d.=13.2) reported that they had experienced extrapyramidal symptoms during previous treatment phases. Information about the family history of primary movement disorders was available for 98 participants and could be assessed for a total of 1316 relatives, 438 of whom were first-degree relatives. Thirty-two of these 98 patients (20 men and 12 women) reported a positive family history, resulting in a total of 47 affected relatives, or a prevalence of a primary movement disorder of 3.5% among all relatives. Specifically, the prevalences were 1.1% (*n*=14) for Parkinson's disease, 1.6% (*n*=21) for tremor and 0.9% (*n*=2) for dystonia. Among relatives of patients with lifetime extrapyramidal symptoms (*n*=848), the prevalences were 1.4% (*n*=12) for Parkinson's disease, 2.4% (*n*=20) for tremor and 1.1% (*n*=9) for dystonia, whereas among the relatives of patients without lifetime extrapyramidal symptoms (*n*=468), the prevalences were 0.4% (*n*=2) for Parkinson's disease, 0.2% (*n*=1) for tremor and 0.6% (*n*=3) for dystonia. A subgroup analysis was performed using data from 27 (2.1%) first-degree relatives of 21 patients who were seen personally by one of the investigators. In all of them, the presence or absence of a primary movement disorder was confirmed as established by the family history interview (25 relatives without a primary movement disorder, 1 with dystonia and 1 with tremor). In order to avoid multiple inclusion of patients with more than one affected relative in further statistical analyses, we considered only the closest relative of those patients. This resulted in 12 patients with a relative with Parkinson's disease (5 first-degree relatives and 7 second-degree relatives), 11 patients with a relative with tremor (6 first-degree relatives and 5 second-degree relatives) and 9 patients with a relative with dystonia

Table I Demographic and clinical characteristics of the sample

	n	Age, years	Gender (male/female)	BPRS score	Duration of exposure		
		Mean (s.d.)	n/n	Mean (s.d.)	< 6 months n	6 months to 5 years n	< 5 years n
Psychiatric disorder							
Organic disorder	14	37.6 (14.9)	12/2	34.2 (12.2)			
Psychotic disorder	62	38.5 (13.8)	32/30	38.5 (10.7)			
Affective disorder	18	49.6 (15.8)	3/15	39.7 (11.1)			
Other Axis I or II	6	31.5 (8.6)	1/5	45.3 (9.1)			
Total sample	100	39.9 (14.7)	48/52	38.5 (11.0)			
Exposure to neuroleptic medication							
Any neuroleptic	100				38	38	24
Typical neuroleptic	64	39.1 (14.0)	34/30	37.6 (10.7)	27	19	18
Atypical neuroleptic	87	39.0 (14.6)	42/45	38.3 (11.1)	39	39	9

BPRS, Brief Psychiatric Rating Scale.

(7 first-degree relatives and 2 second-degree relatives).

Relationship between possible predictor and outcome variables

Family history of primary movement disorder

The family history of primary movement disorders was related to lifetime prevalence of extrapyramidal symptoms (EPS) (χ^2=8.35, d.f.=1, $P<0.01$), currently observed EPS (χ^2=8.05, d.f.=1, $P<0.01$), prevalence of reported EPS (χ^2=6.75, d.f.=1, $P<0.01$) and lifetime prevalence of acute dystonic reaction (χ^2=4.69, d.f.=1, $P=0.03$). Table 4 shows that the prevalence of these four related outcome variables was higher in participants with a positive family history than in patients with a negative history. Furthermore, lifetime prevalence of acute dystonic reaction was related to the subtype of primary movement disorders occurring in relatives (χ^2=8.27, d.f.=3, $P=0.04$). Lifetime acute dystonic reaction occurred in 7 of 9 (78%) patients with a family history of dystonia, but only in 7 of 12 (58%) patients with a family history of Parkinson's disease, 4 of 11 (36%) patients with a family history of tremor and 22 of 44 (50%) patients with a negative family history.

Age

We further observed a strong relation between age and lifetime prevalence of EPS (χ^2=15.13, d.f.=2, $P<0.01$), reported EPS (χ^2=15.70, d.f.=2, $P<0.01$) and lifetime prevalence of acute dystonic reaction (χ^2=9.82, d.f.=2, $P<0.01$). The prevalence of the three related outcome variables was higher in the youngest age group than in either of the other age groups (Table 4).

Duration of exposure to neuroleptic medication

The duration of exposure to any neuroleptic medication was related to the lifetime prevalence of EPS (χ^2=17.86, d.f.=2, $P<0.01$), the prevalence of reported EPS (χ^2=34.96, d.f.=2, $P<0.01$) as well as the lifetime occurrence of parkinsonism (χ^2=6.67, d.f.=2, $P=0.04$) and akathisia (χ^2=8.41, d.f.=2, $P=0.02$). More specifically, the duration of exposure to typical neuroleptics was associated with the lifetime prevalence of EPS (χ^2=18.71, d.f.=3, $P<0.01$), the prevalence of reported EPS (χ^2=27.78, d.f.=3, $P<0.01$), occurrence

Table 2 Clinical characteristics and lifetime prevalences of extrapyramidal symptoms

	n	Age, years	Gender (male/female)	Duration of exposure		
		Mean (s.d.)	n/n	< 6 months n	6 months to 5 years n	< 5 years n
Lifetime prevalence of						
Any EPS	65	37.6 (14.7)	34/31			
Acute dystonic reaction	41	35.6 (13.8)	20/21			
Parkinsonism	37	38.0 (13.5)	20/17			
Akathisia	19	35.8 (13.8)	11/8			
Tardive dyskinesia	4	36.8 (11.0)	3/1			
Symptoms experienced under exposure to						
Any neuroleptic	65			15	30	20
Typical neuroleptic	47	38.7 (15.2)	25/22	15	17	15
Atypical neuroleptic	34	37.3 (15.9)	17/17	13	16	5

EPS, extrapyramidal symptoms.

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Table 3 Clinical characteristics and prevalences of extrapyramidal symptoms at the time of examination

	n	Age, years Mean (s.d.)	Gender (male/female) n/n	Symptom score Mean (s.d.)	Neuroleptic dosage		
					Low n	Medium n	High n
Current exposure to							
Typical neuroleptic	14	44.4 (13.9)	6/8	39.8 (10.9)[1]	4	7	3
Atypical neuroleptic	78	39.2 (14.9)	36/42	38.1 (10.9)[1]	18	41	19
Both	8	39.2 (14.7)	6/2	41.3 (12.5)[1]	0	4	4
Currently observed EPS							
Any EPS	34	41.1 (17.9)	16/18	40.0 (10.2)[1]	6	21	7
Current EPS under exposure to							
Typical neuroleptic	4	56.8 (19.2)	1/3	42.8 (2.6)[1]	2	2	0
Atypical neuroleptic	25	39.5 (17.6)	11/14	38.6 (10.7)[1]	4	17	4
Both	5	36.4 (14.3)	4/1	46.0 (10.6)[1]	0	2	3
Acute dystonic reaction	15	38.0 (20.0)	7/8		2	10	3
Burke scale							
Severity				6.8 (8.3)			
Handicap				3.4 (2.7)			
Tsui scale				3.8 (4.6)			
Parkinsonism	19	43.4 (18.3)	9/10		2	12	5
UPDRS				29.8 (19.1)			
Akathisia	5	33.0 (4.7)	3/2		2	1	2
Hillside scale				3.0 (1.6)			
Barnes scale				10.0 (7.5)			
Tardive dyskinesia	3	31.7 (5.1)	2/1		–	2	1
AIMS				5.0 (2.8)			

AIMS, Abnormal Involuntary Movement Scale; EPS, extrapyramidal symptoms; UPDRS, Unified Parkinson's Disease Rating Scale.
1. Score on the Brief Psychiatric Rating Scale.

of EPS on typical neuroleptics ($\chi^2=7.83$, d.f.$=2$, $P=0.02$), lifetime prevalence of acute dystonia ($\chi^2=10.68$, d.f.$=3$, $P=0.01$), parkinsonism ($\chi^2=12.75$, d.f.$=3$, $P<0.01$) and akathisia ($\chi^2=8.59$, d.f.$=2$, $P=0.04$). The duration of the exposure to atypical neuroleptics was related to the prevalence of reported EPS ($\chi^2=14.91$, d.f.$=3$, $P=0.01$). As summarised in Table 4, we found the prevalence of all statistically related outcome variables to increase with longer duration of neuroleptic medication.

For all other relationships between possible predictor variables (gender, psychiatric diagnostic category or dosage range) and outcome variables considered in χ^2 tests, $P>0.05$. Thus, only the following possible predictor variables were entered in a logistic regression analysis: family history of primary movement disorders; age; duration of exposure to any neuroleptic medication; duration of exposure to typical neuroleptics; and duration of exposure to atypical neuroleptic medication. Occurrence of tardive dyskinesias was excluded

from outcome variables because of the small number of cases identified.

Predictors revealed by logistic regression analysis

We found that lifetime occurrence of EPS (yes or no) could be correctly predicted in 74% of all cases by knowing the duration of treatment with typical neuroleptics, and family history of primary movement disorders. Lifetime occurrence of acute dystonic reaction (yes or no) could be predicted in 65% of cases taking into account the exposure to typical neuroleptic medication and age. Both lifetime occurrence of parkinsonism (yes or no) and of akathisia (yes or no) were predicted correctly in 72% and 82%, respectively, by the duration of typical neuroleptic medication. Reported EPS (yes or no), regardless of the subtype, were correctly predicted in 82% of cases by the duration of exposure to typical neuroleptic medication, age and family history of primary movement disorders. Currently

observed EPS (yes or no) were predicted in 68% of all cases by the family history of primary movement disorders. Extrapyramidal symptoms on typical neuroleptic medication (yes or no) could be predicted in 73% when considering the duration of exposure. As can be seen from the regression coefficients B in Table 5, the probability for the occurrence of symptoms always increased with the duration of exposure to neuroleptic medication, younger age and positive family history.

DISCUSSION

The main purpose of our study was to identify predictor variables for neuroleptic-induced extrapyramidal symptoms, for the first time considering family history of primary movement disorders.

Prevalence rates for extrapyramidal symptoms and primary movement disorders

Based on a sample that represents a typical cohort of in-patients with acute psychotic symptoms, we observed a lifetime prevalence of extrapyramidal symptoms of 65% and a point prevalence of 34%, comparable to rates reported in large epidemiological studies (Ayd, 1961; Swett, 1975; Owens & Johnstone, 1982). Compared with these studies, the mean age of our patients was low, and the rate of patients ever having been treated with atypical neuroleptics was high (87%). The percentage of patients who had been exposed to neuroleptics for less than 6 months was high (38%). The overall prevalence of about 3% for primary movement disorders in all relatives seems plausible. Higher prevalence rates of Parkinson's disease, tremor and dystonia among relatives of patients with lifetime extrapyramidal symptoms than among relatives of patients without such symptoms are comparable with results reported by others, although our study was not designed as a population-based case–control study (Marder *et al*, 1996; Louis *et al*, 2003). The relatives' diagnoses could be confirmed in a small subgroup.

Predictors of extrapyramidal symptoms

In our sample, logistic regression analysis revealed that a positive family history had significant predictive value for the occurrence of extrapyramidal symptoms. The

Table 4 Distributions of outcome and possible predictor variables

Possible predictor	Outcome variable						
	Lifetime EPS (yes/no) n/n	Reported EPS (yes/no) n/n	Currently observed EPS (yes/no) n/n	EPS with typical neuroleptic (yes/no) n/n	Lifetime ADR (yes/no)	Lifetime parkinsonism (yes/no)	Lifetime akathisia (yes/no)
Family history[1,2]				$P > 0.05$		$P > 0.05$	$P > 0.05$
Positive	27/5	23/9	17/15		18/14		
Negative	36/30	29/37	16/50		22/44		
Age				$P > 0.05$		$P > 0.05$	$P > 0.05$
18–40 years	46/11	40/17			31/26		
41–60 years	12/18	9/21	$P > 0.05$		7/23		
>60 years	7/6	4/9			3/10		
Lifetime exposure to any neuroleptic[2]			$P > 0.05$		$P > 0.05$		
<6 months	15/23	6/32				10/28	2/36
6 months to 5 years	30/8	27/11		$P > 0.05$		13/25	9/29
>5 years	20/4	20/4				14/10	8/16
Lifetime exposure to typical neuroleptic[2]			$P > 0.05$				
<6 months	17/10	14/13		15/12	11/16	6/21	5/22
6 months to 5 years	18/1	16/3		17/2	12/7	7/12	6/13
>5 years	15/3	15/3		15/3	10/8	13/5	6/12
No exposure	15/21	8/28			8/28	11/25	2/34
Lifetime exposure to atypical neuroleptic[2]	$P > 0.05$		$P > 0.05$	$P > 0.05$	$P > 0.05$	$P > 0.05$	$P > 0.05$
<6 months		14/25					
6 months to 5 years		28/11					
>5 years		7/2					
No exposure		4/9					

ADR, acute dystonic reaction; EPS, extrapyramidal symptoms.
1. Date available for 98 participants.
2. Numbers in each outcome variable column were compared within one testing procedure.

Table 5 Step-wise logistic regression analysis revealing significant predictor variables for occurrences of extrapyramidal symptoms (d.f.=1 in all tests)

EPS	Predictor	B	s.e.	Wald	P
Lifetime occurrence of EPS	Duration of typical neuroleptic	0.78	0.25	10.65	< 0.01
	Age	−0.85	0.35	5.95	0.02
	Positive family history	1.30	0.60	4.67	0.03
Lifetime occurrence of acute dystonia	Duration of typical neuroleptic	0.54	0.20	7.16	< 0.01
	Age	−0.88	0.36	6.17	0.01
Lifetime occurrence of parkinsonism	Duration of typical neuroleptic	0.53	0.20	7.16	< 0.01
Lifetime occurrence of akathisia	Duration of typical neuroleptic	0.63	0.24	6.81	< 0.01
Reported EPS	Duration of any neuroleptic	1.98	0.41	23.28	< 0.01
	Age	−1.30	0.45	8.54	< 0.01
	Positive family history	1.45	0.62	5.57	0.02
Currently observed EPS	Positive family history	1.27	0.46	7.69	< 0.01
EPS under typical neuroleptics	Duration of typical neuroleptic	0.90	0.40	4.97	0.03

B, regression coefficient; EPS, extrapyramidal symptoms; s.e., standard error.

probability of observed symptoms at the time of examination, for which it was the only predictor, as well as of lifetime prevalence of symptoms and reported symptoms, was increased in patients who had a relative with a primary movement disorder. The strongest predictive value was found for the duration of treatment with typical neuroleptics (lifetime occurrence of EPS, acute dystonic reaction, parkinsonism, akathisia, and EPS on typical neuroleptics) as well as with any neuroleptic medication (reported EPS). The probability of extrapyramidal symptoms increased with longer duration of exposure. Furthermore, younger age was also a significant predictor for the occurrence of symptoms, especially for acute dystonic reaction.

Positive family history of primary movement disorders

The finding that a positive family history of primary movement disorders had a significant impact on the occurrence of extrapyramidal symptoms has two main implications. First, our results suggest that primary and secondary movement disorders may share common genetic factors. Second, the association with primary movement disorders observed in patients suffering from psychotic symptoms and developing extrapyramidal symptoms may represent a dysfunction within a common pathway of the dopaminergic system. This system is involved not only in primary and secondary movement disorders but also in psychotic disorders. Earlier hypotheses suggest that such symptoms might represent exacerbated involuntary movements that are directly related to cerebral dysfunctions underlying psychotic diseases – i.e. a dysfunction within the dopaminergic system (Ayd, 1961; Owen & Johnstone, 1982). Indeed, both Kraepelin (1971) and Bleuler (1950) described 'spasmodic phenomena in the musculature' and 'extraordinary movements of the tongue and lips' in patients with psychosis long before the introduction of neuroleptic drugs. Other studies have confirmed this observation by the finding that prevalence and distribution of extrapyramidal symptoms were the same in treated and never-treated patients and depended only on the age at onset of the psychotic illness (Owen & Johnstone, 1982; Srinivasan et al, 2001). Further studies should address the question whether the occurrence of such

symptoms represents an endophenotype for schizophrenia, as has been shown for other neurological dysfunctions in neuroleptic-naïve patients with psychosis (Gottesman & Gould, 2003). Genetic association studies of candidate genes, such as dopamine receptor genes, will be the natural extension of our study to elucidate the hypothesised common underlying mechanism at the molecular level.

Duration of neuroleptic medication

We observed a strong effect of duration of exposure to neuroleptic medication, especially of typical neuroleptics, on the occurrence of extrapyramidal symptoms, including the subtypes acute dystonic reaction, parkinsonism and akathisia. Although many authors have proposed such an effect, retrospective studies rarely confirmed this notion (Marsalek, 2000). From our results, however, it can be assumed that the longer the exposure to neuroleptic drugs, the higher the prevalence of these symptoms. This finding may support the hypothesis of an accumulating toxic effect of neuroleptic drugs that is suggested to be higher in the typical drugs than in the atypicals, with the exception of clozapine (Gil-ad et al, 2001). An effect of dosage on occurrence of extrapyramidal symptoms at the time of examination could not be confirmed.

None of the predictor variables entered in the logistic regression analysis was found to predict the occurrence of extrapyramidal symptoms in patients taking atypical neuroleptics. The significant relation observed in the χ^2 test between reported symptoms and the duration of medication with atypical neuroleptics may be interpreted as a trend. However, the long-term effect of atypical neuroleptics on extrapyramidal symptoms may yet not have been verified, since only a small proportion of patients had been exposed to these drugs for more than 5 years (10%), and this aspect remains a matter of debate (Tarsy et al, 2002).

Other possible predictors: age, gender and psychiatric diagnosis

We were able to validate young age as a predictor for the occurrence of extrapyramidal symptoms, especially of acute dystonia (Ayd, 1961; Swett, 1975). This finding gives further support to the genetic influence on occurrence of these symptoms. In contrast, there is no evidence from our data

for either diagnostic specificity or gender as a predictor for the occurrence of symptoms.

Methodological limitations

Our study design must be regarded as somewhat explorative, since for most of the relatives the diagnosis of a primary movement disorder could only be established through the family history interview. This procedure might have reduced the validity and reliability of the data, although special efforts were made to rate a family history as positive only if the criteria were unambiguously fulfilled. In a clinical setting, this is also the most practical way to gather information and decide whether a patient is at risk of developing extrapyramidal symptoms because of a positive family history.

We are aware that the way in which we categorised neuroleptic dosages may appear arbitrary. By definition, atypical neuroleptic dosages cannot be converted to chlorpromazine equivalents. We therefore decided to use a categorisation based on clinical experience. The distribution of dosage ranges in our sample appears reasonable (22% on low, 52% on medium and 26% on high medication dosages). Exact dosages could only be assessed for the time of examination.

Genetic considerations

Our data imply two hypotheses. First, our findings underline the notion of genetic susceptibility for secondary extrapyramidal symptoms, and second, they suggest possible shared genetic factors in primary and secondary movement as well as in psychotic disorders.

REFERENCES

American Psychiatric Association (1994) *Diagnostic and Statistical Manual of Mental Disorders* (4th edn) (DSM–IV). Washington, DC: APA.

Ayd, F. J. (1961) A survey of drug-induced extrapyramidal reactions. *JAMA*, **175**, 1054–1060.

Barnes, T. R. E. (1989) A rating scale for drug-induced akathisia. *British Journal of Psychiatry*, **154**, 672–676.

Basile, V. S., Masellis, M., Potkin, S. G., et al (2002) Pharmacogenomics in schizophrenia: the quest for

individualized therapy. *Human Molecular Genetics*, **11**, 2517–2530.

Berardi, D., Giannelli, A., Biscione, R., et al (2000) Extrapyramidal symptoms and residual psychopathology with low-dose neuroleptics. *Human Psychopharmacology – Clinical and Experimental*, **15**, 79–85.

Bleuler, E. (1950) *Dementia Praecox or the Group of Schizophrenias* (trans. J. Zinkin). New York: International Universities Press.

Burke, R. E., Fahn, S., Marsden, C. D., et al (1985) Validity and reliability of a rating scale for primary torsion dystonias. *Neurology*, **35**, 73–77.

Fleischhacker, W. W., Miller, C. H., Schett, P., et al (1991) The Hillside Akathisia Scale: a reliability comparison of the English and German versions. *Psychopharmacology*, **105**, 141–144.

Gasser, T. (2003) Overview of the genetics of parkinsonism. *Advances in Neurology*, **91**, 143–152.

Gerlach, J. (2002) Improving outcome in schizophrenia: the potential importance of EPS and neuroleptic dysphoria. *Annals of Clinical Psychiatry*, **14**, 47–57.

Gil-ad, L., Shtaif, B., Shiloh, R., et al (2001) Evaluation of the neurotoxic activity of typical and atypical neuroleptics: relevance to iatrogenic extrapyramidal symptoms. *Cellular and Molecular Neurobiology*, **6**, 705–716.

Gottesman, I. I. & Gould, T. D. (2003) The endophenotype concept in psychiatry: etymology and strategic intentions. *Journal of American Psychiatry*, **160**, 636–645.

Klein, C. & Ozelius, L. J. (2002) Dystonia: clinical features, genetics, and treatment. *Current Opinion in Neurology*, **15**, 491–497.

Klein, C., Vieregge, P., Hagenah, J., et al (1999) Search for the PARK3 founder haplotype in a large cohort of patients with Parkinson's disease from northern Germany. *Annals of Human Genetics*, **63**, 285–291.

Kraepelin, E. (1971) *Dementia Praecox and Paraphrenia* (trans. R. M. Barclay & G. M. Robertson). New York: Krieger.

Louis, E. D., Levy, G., Mejia-Santana, H., et al (2003) Risk of action tremor in relatives of tremor-dominant and postural instability gait disorder PD. *Neurology*, **61**, 931–936.

Marder, K., Tang, M. X., Mejia, H., et al (1996) Risk of Parkinson's disease among first-degree relatives: a community-based study. *Neurology*, **47**, 155–160.

Marsalek, M. (2000) Tardive drug-induced extrapyramidal syndromes. *Pharmacopsychiatry*, **33** (suppl.), 14–33.

Movement Disorder Society Task Force on Rating Scales for Parkinson's Disease (2003) The unified Parkinson's Disease Scale (UPDRS): status and recommendations. *Movement Disorders*, **18**, 738–750.

Nasrallah, H. A., Churchill, C. M. & Hamdan-Allen, G. A. (1988) Higher frequency of neuroleptic-induced dystonia in mania than in schizophrenia. *American Journal of Psychiatry*, **145**, 1455–1456.

National Institute of Mental Health (1975) Abnormal Involuntary Movement Scale (AIMS). *Early Clinical Drug Evaluation Unit Intercom*, **4**, 3–6.

Overall, J. E. & Gorham, D. R. (1962) The Brief Psychiatric Rating Scale. *Psychological Report*, **10**, 799–812.

Owens, D. G. C. & Johnstone, E. C. (1982) Spontaneous involuntary disorders of movement. *Archives of General Psychiatry*, **39**, 452–461.

Segman, R. H., Heresco-Levy, U., Yakir, A., et al (2002) Interactive effect of cytochrome P450 17α-hydroxylase and dopamine D3 receptor gene polymorphisms on abnormal involuntary movements in schizophrenia. *Biological Psychiatry*, **51**, 261–263.

Sheehan, D. V., Lecrubier, Y., Sheehan, K. H., et al (1998) The Mini-International Neuropsychiatric Interview (MINI): the development and validation of a structured diagnostic psychiatric interview for DSM–IV and ICD–10. *Journal of Clinical Psychiatry*, **59** (suppl. 20), 22–57.

Spitzer, R. L. & Williams, J. (1987) *Structured Clinical Interview for DSM–III–R (SCID)*. New York: New York State Psychiatric Institute, Biometrics Research Department.

Srinivasan, T. N., Thara, R., Padmavathi, R., et al (2001) Relationship of extrapyramidal symptoms to age at onset and drug treatment in middle-aged and elderly schizophrenic patients. *Schizophrenia Research*, **47**, 69–75.

Swett, C. (1975) Drug-induced dystonia. *American Journal of Psychiatry*, **132**, 532–534.

Tarsy, D., Baldessarini, R. J. & Tarazi, F. I. (2002) Effects of newer antipsychotics on extrapyramidal function. *CNS Drugs*, **16**, 23–45.

Tsui, J. K., Eisen, A., Stoessl, A. J., et al (1986) Double-blind study of botulinum toxin in spasmodic torticollis. *Lancet*, **ii**, 245–247.

van Harten, P. N., Hoek, H. W., Matroos, G. E., et al (1997) The inter-relationship of tardive dyskinesia, parkinsonism, akathisia and tardive dystonia: the Curaçao extrapyramidal syndromes study II. *Schizophrenia Research*, **26**, 235–242.

CLINICAL IMPLICATIONS

■ Neuroleptic medication with a known low risk of extrapyramidal symptoms (i.e. an atypical neuroleptic) is preferable for patients with a family history of primary movement disorders, especially dystonia.

■ Atypical neuroleptics are also preferable in patients under 40 years old, particularly to reduce the occurrence of painful acute dystonic reaction.

■ Patients who have been exposed to long-term typical neuroleptic medication should be switched to an atypical agent even though extrapyramidal symptoms might not have been observed as yet.

LIMITATIONS

■ Our study design must be regarded as somewhat explorative owing to the family history approach.

■ Our data-set might have been too small to confirm any dosage effect.

■ The small sample size might also have been the reason why we did not observe the gender effect described elsewhere of a higher prevalence of acute dystonia in men and of parkinsonism, akathisia and tardive dyskinesia in women.

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