Eur Arch Psychiatry Clin Neurosci (2006) 256:407–413 DOI 10.1007/s00406-006-0653-7

ORIGINAL PAPER

Victor Peralta · Manuel J. Cuesta · Jose F. Serrano

Obstetric complications and neurological abnormalities in neuroleptic-naive psychotic patients

Received: 15 March 2005 / Accepted: 19 January 2006 / Published online: 20 June 2006

Abstract Studies addressing the relationship between a history of obstetric complications (OCs) and neurological abnormalities in schizophrenia have produced contradictory findings. Using a pre-post-treatment design in a neuroleptic-naive sample of psychotic patients, we examined the relationship of a history of OC to primary and drug-induced neurological signs. Fifty neuroleptic-naive non-affective psychotic inpatients were assessed for a history of OC by using the McNeil-Sjöström scale, and for neurological signs including parkinsonism, dyskinesia, akathisia and catatonia, which were rated before and after inception of neuroleptic treatment. A subsample of 28 patients were also examined for neurological soft-signs. Ratings of OCs were related to admission levels of parkinsonism, dyskinesia, akathisia and neurological soft-signs, but not to levels of catatonia. By obstetric period, pregnancy complications were related to levels of parkinsonism, dyskinesia, and neurological soft-signs, and neonatal complications were related to levels of akathisia. Drug-induced neurological signs were not associated with a history of OCs. We argue that the association pattern between a history of OCs and primary neurological signs from several domains suggests a causal link among these variables. Having a history of OCs does not convey a vulnerability for developing drug-induced neurological signs in the short term.

Key words schizophrenia · extrapyramidal symptoms · basal ganglia · drug-naive state · antipsychotic drugs

V. Peralta (✉) · M.J. Cuesta · J.F. Serrano
Psychiatric Unit
Virgen del Camino Hospital
Irunlarrea 4
31008 Pamplona, Spain
Tel.: +34-948/422-488
Fax: +34-948/429-924
E-Mail: victor.peralta.martin@cfnavarra.es

Introduction

Obstetric complications constitute an early environmental factor that is a well known source of neurological and behavioral abnormalities in non-psychotic populations [1, 2] and has received considerable attention as a risk factor for the subsequent development of schizophrenia [3, 4]. There exists some evidence for an association of obstetric complications with brain structure anomalies in schizophrenia [3, 5, 6], but the association with neurological signs such as neurological hard and soft signs, dyskinesia or parkinsonism is rather controversial [7, 8 and 9–11]. In addition, data on such an association with catatonic signs and akathisia are lacking. Moreover, it has been hypothesized that a history of OCs represents a vulnerability factor for developing more and more severe drug-induced neurological signs [12], the existing data, however, are scarce and contradictory. The sole study examining the relationship between OCs and drug-induced parkinsonism reported a positive association [7], and the various studies examining the relationship between OCs and tardive dyskinesia (reviewed by 11] have produced contradictory results.

In examining the relationship between antecedents of OCs and the neurological manifestations of psychotic disorders it is essential to differentiate between primary (i.e. disease-based) and secondary (i.e. drug-induced) neurological signs. This issue is further complicated by the fact that antipsychotic drugs may both cause [13–15] and ameliorate [10, 16–18] neurological signs. Given that previous studies examining this issue have been conducted in medicated patients, the actual relationship between a history of OCs and primary or drug-induced neurological signs remains uncertain. Furthermore, conflicting results may also result from using different OCs rating scales, since they vary in their discriminant ability for detecting OCs and relationships with other pathological processes involved in schizophrenia. In this respect, the

McNeil-Sjöström scale has been shown to be more sensitive for detecting OCs in schizophrenia than other frequently used OCs scales [19], and for detecting significant associations with other etiological factors such as a family history of psychosis and month of birth [20].

Taking into account the above mentioned issues, we reasoned that examining OCs by means of a standardized and validated OCs scale, and neurological signs in neuroleptic-naive psychotic patients before and after starting neuroleptic treatment may provide cues about the actual relationship between a history of OCs and neurological signs. Using such a design, this study was aimed at examining the association of OCs with neurological signs at the drug-naive status and after inception of neuroleptic treatment. We hypothesized that OCs are associated with (a) neurological signs at the neuroleptic-naive status (i.e. primary neurological signs), and (b) neurological side-effects of antipsychotic medication. We also examined the relationship of type and timing of OCs to neurological ratings without a priori unidirectional hypotheses.

Methods

Subjects

The study sample consisted of 50 psychotic inpatients recruited from consecutive admissions to the Psychiatric Unit of the Virgen del Camino Hospital in Pamplona, Spain. To be included in this study, subjects had to be neuroleptic-naive, have her/his mother alive and able to be interviewed, and met *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV) criteria for a functional psychotic disorder that was not primarily affective. The exclusion criteria were a history of drug abuse, evidence of organic brain disorder including mental retardation and head injury, meaningful somatic disease, or premature discharge before inpatient treatment was completed. After the procedure had been fully explained, all the subjects gave written informed consent to participate in the study.

Socio-demographic variables, symptoms and diagnosis were assessed by VP using the Comprehensive Assessment of Symptoms and History [21]. Information for rating symptoms and diagnosis was derived from all available sources of information, including interviews with the subject and close relatives, a comprehensive review of medical records, and direct observation of the patient over the hospitalization period. Based on information from these sources, DSM-IV diagnoses were generated. The family data for psychiatric disorder in first-degree relatives were collected by means of the FH-RDC [22] using the family history method.

The DSM-IV diagnoses of the patients were schizophrenia (N = 22), schizophreniform disorder (N = 11), schizoaffective disorder (N = 4), brief psychotic disorder (N = 7), delusional disorder (N = 4) and atypical psychotic disorder (N = 2). The mean age of the subjects was 26.2 years (sd = 7.5), and they had a mean educational level of 11 years (sd = 3.5). Thirty-four patients were male, 44 were single, and 7 had a first-degree relative with a FH-RDC non-affective psychotic disorder. The mean length of illness, determined from the time the patients first exhibited illness-related behavioral symptoms was 42.5 months (sd = 54.3), that determined from the time the patients first exhibited psychotic symptoms was 35.3 months (sd = 52.5), and that determined from the time the patients first exhibited continuous psychotic symptoms was 25.1 months (sd = 51.2).

Treatment variables

To determine the neuroleptic-naive status, the history of previous psychopharmacological treatment was carefully assessed by means of a comprehensive review of medical records, interviews with each patient and his/her relatives, and, if appropriate the patient's primary physician. At admission 4 patients were taking benzodiazepines, and over the illness course a total of 6 patients had been exposed to benzodiazepines, 4 patients to antidepressants, and 1 patient to mood stabilizers.

After baseline assessment at admission, all patients were treated under open conditions by using monotherapy with antipsychotic medication chosen by the patient's treating psychiatrist, which was administered on an individual dose regime. Thirteen patients were treated with olanzapine, 25 with risperidone and 12 with haloperidol. The average daily dose of chlorpromazine equivalents administered over the index admission was 899.3 (SD = 649.3). Other medications were allowed if needed, and over the index episode they included biperiden (N = 16), benzodiazepines (N = 15), antidepressants (N = 7) and mood stabilizers (N = 7).

OCs assessment

History of obstetric complications for each patient was obtained through a detailed and structured interview with the patient's mother using the McNeil-Sjöström scale [23]. The scale was rated by JFS who was blind to the neurological status of the patients. The McNeil-Sjöström scale provides a systematic evaluation and weighting of several hundred specific factors occurring during pregnancy, labor-delivery and neonatal periods scored according to a 6–point scale reflecting the potential somatic damage in the offspring. The severity of each complication is scored as follows: 1 not harmful or relevant, 2 = not likely harmful or relevant, 3 = potentially but not clearly harmful or relevant, 4 = potentially clearly harmful or relevant, 5 = potentially clearly greatly harmful or relevant, and 6 = very great harm or deviation in the offspring.

While this severity classification can be used in a number of different ways, on the basis of the study's hypotheses, the OC global scores chosen for analyses were the total number of OCs at severity level 4 "clearly harmful or relevant" or higher (type A score), and the highest severity level of any existing OC (type C score). Thus, these two global scores respectively represent the amount of clearly harmful or relevant OCs, and the highest severity of any existing OC during the entire reproductive sequence. Type A scores were also generated for each reproductive period: pregnancy, labor-delivery and neonatal. Lastly, and for the purpose of case definition, we dichotomized the sample on the basis of the type A score for the entire reproductive period into patients with a history of OCs (score at level 4 or above) and without a history of OCs (score at level 3 or less).

Neurological assessment

The assessment of the neurological status was carried out by VP who was blind to the OCs history. It was undertaken within a few hours after admission before the patient started neuroleptic treatment, and on the day of discharge an average 3.1 weeks (SD = 1.3) after admission. Neurological assessment at the two points included ratings of parkinsonism as assessed by means of the Simpson-Angus Rating Scale [24], dyskinesia as assessed by means of the Abnormal Involuntary Movements Scale [25], akathisia as assessed by means of the Barnes scale [26], and catatonia as assessed by means of the modified Rogers scale for the assessment of motor disorders [27]. Neurological ratings at admission were considered to reflect primary neurological abnormalities.

A neurological worsening score was calculated for each neurological rating scale by subtracting the admission score from discharge score and setting the negative values to 0 (no worsening). These worsening scores control for the neurological signs present at the neuroleptic-naive status and are intended to reflect the actual

neurological deterioration due to antipsychotic drugs. In addition, we assessed the occurrence of neuroleptic-induced acute dystonia over the hospitalization period.

A subsample of 28 patients were also examined for neurological soft-signs using the Neurological Evaluation Scale (NES) [28]. Whenever possible the NES was administered prior to the introduction of neuroleptic medication, however, for most patients the examination was deferred until they were capable of cooperate, generally a few days after starting antipsychotic medication. Given that for these patients it was not longer possible to maintain the pre-post-treatment design, the discharge assessment was not conducted. For the sake of simplicity, the NES ratings were included under the admission ratings and were intended to reflect primary manifestations.

For each neurological rating scale the total score was used, excepting for the akathisia scale in which the global rating was employed.

Statistical analyses

The data for the outcome variables (neurological and obstetric ratings) were first screened for distributional properties. All these scores were non-normal distributed. After log-transformations the distributions remained non-normal, particularly for the neurological scores. Accordingly, and unless that otherwise specified, we decided to use non-parametric statistical procedures. For hypothesis testing we examined the relationship of OC ordinal ratings to primary and drug-induced neurological signs by using Kendall's tau-b correlation coefficients [29]. Mean comparisons were made with Mann-Whitney-Wilkoxon rank sum tests. One-tailed tests were employed for all analyses testing the study hypotheses. For all other statistical analyses two-tailed tests were used. The level of statistical significance was set to $p < 0.05$. All analyses were performed using the Statistical Package for the Social Sciences (SPSS, version 10.0; SPSS Inc, Chicago, Ill).

To analyze the relationship between a history of OCs and neurological scores, the obstetric ratings were examined in a hierarchical way. We first examined global ratings of obstetric variables, including that for case definition. Second, we examined the timing of OCs (i.e. pregnancy, labor-delivery and neonatal). And third, we examined the relationship between the more frequent individual OCs (those having a prevalence rate greater than 10%) and neurological scores.

Results

OCs ratings

The mean number of OCs at severity level 4 or higher was 2.82 (sd = 3.61, range 0–15), and the mean rating for the most potentially harmful OC was 3.88 (sd = 1.12, range 0–6). The mean number of OCs for each reproductive period was as follows: pregnancy = 0.70 (sd = 1.27, range = 0–4), labor-delivery = 1.14 (sd = 1.73, range = 0–6), and neonatal = 0.98 (sd = 1.81, range = 0–8). Thirty-three patients (66%) had at least one "clearly harmful or relevant" OC along the entire reproductive period.

The number (type A) and the highest severity (type C) scores for the entire reproductive sequence were highly correlated ($tau_b = 0.825$, $p < 0.001$, 2-tailed). Pregnancy complications were correlated with neonatal (tau-b = 0.328, p = 0.01, 2-tailed) but not with labor-delivery complications (tau-b = 0.081, p = 0.51, 2-tailed). Neonatal and labor-delivery complications were significantly correlated (tau-b = 0.309, p = 0.014, 2-tailed).

Neither Type A and C scores (Mann-Whitney-Wilkoxon rank sum tests) nor OCs rates (χ^2 tests) significantly differed in terms of gender, diagnosis (schizophrenic vs non-schizophrenic psychosis), presence of a non-affective psychotic disorder in the first-degree relatives or type of neuroleptic administered (typical vs atypical).

Neurological ratings

At admission, the mean (sd) ratings for Parkinsonism, dyskinesia, akathisia, catatonia and neurological soft-signs were 2.12 (3.21), 0.46 (0.89), 0.22 (0.74), 3.02 (5.28) and 11.6 (10.7), respectively. Worsening ratings for Parkinsonism, dyskinesia, akathisia and catatonia were 2.64 (3.48), 0.04 (0.28), 0.34 (0.72) and 0.10 (0.58), respectively. Neither primary nor drug-induced neurological ratings significantly differed in terms of diagnosis (schizophrenia vs other psychotic disorders).

Correlations among primary neurological ratings and among drug-induced neurological ratings were examined to test whether they tend to co-vary or not, and thus representing respectively interdependent or independent neurological domains. The only significant correlation coefficients involved the catatonia scores: at admission catatonia and dyskinesia ratings were correlated ($thau_b=0.370$, p = .003, 2-tailed), as were drug-induced catatonia and drug-induced parkinsonism ($thau_b=0.288$, p = .02, 2-tailed). Ten patients developed acute dystonia over the hospitalization period, and patients who did and who did not develop acute dystonia did not differ in levels of worsening ratings. Taken together, these results indicate that, at the two assessment points, the different neurological abnormalities represent relatively independent domains.

Given the potential effect of medication other than antipsychotics on the neurological worsening scores, we examined these scores in patients with and without concomitant medication. The only significant association of worsening scores with non-neuroleptic drugs was for drug-induced parkinsonism with biperiden (patients on biperiden, n = 16, 4.18 ± 3.86; patients without biperiden, n = 34, 1.91 ± 3.07, Mann-Whitney-Wilkoxon rank sum test $z = -2.25$, p = .02, 2-tailed). Likewise, for acute dystonia the only significant association with non-neuroleptic drugs was with biperiden treatment (on biperiden and acute dystonia n = 11, without biperiden and acute dystonia n = 2, $\chi^2 = 29.70$, df = 1, $p < .0001$, 2-tailed).

Relationship between global ratings of OCs and neurological ratings

Table 1 shows the relationship between the alternative OCs global ratings and neurological scores. Admis-

Table 1 Relationship between obstetric complications (OCs) and neurological signs in 50 non-affective psychotic patients

	McNeil–Sjöstrom scale				
	Scores		Case definition		
	Type A tau-b	Type C tau-b	OCs present (N = 33) Mean ± SD	OCs absent (N = 17) Mean ± SD	z
Neuroleptic-naive status					
Parkinsonism	0.196*	0.216*	2.81 ± 3.68	0.76 ± 1.25	−2.31**
Dyskinesia	0.261*	0.338**	0.63 ± 0.99	0.12 ± 0.48	−2.10*
Akathisia	0.211*	0.143	0.30 ± 0.67	0.20 ± 0.75	−1.67*
Catatonia	0.051	0.128	2.60 ± 5.90	1.88 ± 3.40	−1.30
Soft-signs[a]	0.259*	0.380**	14.66 ± 11.99	6.30 ± 5.01	−2.13*
Worsening ratings					
Parkinsonism	0.124	0.176	3.12 ± 3.07	1.70 ± 2.86	−1.49
Dyskinesia	−0.147	−0.215	0.00 ± 0.00	0.11 ± 0.48	−1.39
Akathisia	−0.154	−0.133	0.21 ± 0.48	0.58 ± 1.00	−1.17
Catatonia	0.006	0.118	0.15 ± 0.71	0.00 ± 0.00	−1.02

[a]N = 28, only assessed at admission
* p < 0.05, ** p < 0.01, one-tailed

sion ratings for neurological signs showed a consistent association pattern with OCs ratings in that levels of parkinsonism, dyskinesia, akathisia, and neurological soft signs, but not that of catatonia, were significantly related to the three alternative global ratings of OCs. The exception to this rule was represented by akathisia that was significantly associated with number of OCs and presence of any OC, but not with the highest severity level of any existing OC.

OCs scores were unrelated to neurological worsening scores. Likewise, patients who did and who did not develop acute dystonic reactions did not differ in mean number of OCs (3.60 ± 3.78 vs 2.62 ± 3.60, Mann-Whitney-Wilkoxon rank sum test z = −0.82, p = .20, 1-tailed), mean severity of OCs (4.00 ± 1.41 vs 3.85 ± 1.05, Mann-Whitney-Wilkoxon rank sum test z = −0.56, p = .29, 1-tailed) and rate of OCs (70% vs 30%, $\chi^2 = 0.08$, Fisher exact test p = .53, 1-tailed).

Reproductive period

Analyses examining the relationship of number of OCs (type A score) and highest severity of any existing OC (type C score) by reproductive period with neurological scores produced virtually the same pattern of results, hence only the type A score correlation pattern is shown (Table 2). Admission scores of parkinsonism, dyskinesia and soft-signs were significantly related to pregnancy complications, and akathisia was significantly related to neonatal complications. Labor-delivery complications were unrelated to neurological scores.

Neurological worsening scores were unrelated to any OC. Likewise, patients who did and who did not develop acute dystonia did not differ in mean number of pregnancy complications (0.70 ± 1.49 vs 0.70 ± 1.22, Mann-Whitney-Wilkoxon rank sum test z = −0.51, p = .30, 1-tailed), mean number of labor-delivery complications (1.40 ± 2.21 vs 1.07 ± 1.60, Mann-Whitney-Wilkoxon rank sum test z = −0.39, p = .35, 1-tailed), and mean number of neonatal complications (1.50 ± 2.55 vs 0.85 ± 1.59, Mann-Whitney-Wilkoxon rank sum test z = −0.51, p = .30, 1-tailed).

Individual obstetric complications

Given that there was no evidence for an association of global ratings and timing of OCs with drug-induced neurological ratings, we examined only the relationship between individual OCs and primary neurological signs. No specific association pattern was found between individual OCs and neurological scores at admission (Table 3). Only two OCs (neonatal jaundice and operative delivery or intervention) were significantly associated with more than one neurological domain. The neurological domain that was associated with more types of OCs was dyskinesia, since it was related to bleeding from vagina during

Table 2 Kendall's tau-b correlations between the number of obstetric complications assessed with the McNeil-Sjöström scale and neurological signs in 50 non-affective psychotic patients by reproductive period

	Reproductive period		
	Pregnancy	Labor-delivery	Neonatal
Neuroleptic-naive status			
Parkinsonism	0.222*	0.095	0.117
Dyskinesia	0.236*	0.105	0.153
Akathisia	−0.067	0.206	0.270*
Catatonia	0.072	-0.019	0.127
Neurological soft-signs[a]	0.364**	0.117	0.150
Worsening ratings			
Parkinsonism	0.110	0.141	-0.036
Dyskinesia	−0.087	−0.107	−0.105
Akathisia	−0.111	−0.171	−0.027
Catatonia	0.041	0.021	-0.149

[a]N = 28, only assessed at admission
* p < 0.05, ** p < 0.01, one-tailed

Table 3 Relationship between the presence of the most frequent (>10%) OCs according to the McNeil–Sjöström scale and neurological signs assessed at admission

		N¶	Parkinsonism		Dyskinesia		Akathisia		Catatonia		Neurological soft-signs	
			Mean ± sd	z	Mean ± sd	z	Mean ± sd	z	Mean ± sd	z	Mean ± sd	z
Congenital structural malformations	Present	9 (4)	1.11 ± 1.76	-0.96	0.77 ± 0.97	−1.45	0.44 ± 0.88	−1.33	2.22 ± 2.43	−0.44	18.50 ± 14.84	−1.28
	Absent	41 (24)	2.34 ± 3.42		0.39 ± 0.86		0.17 ± 0.70		3.19 ± 5.72		10.54 ± 9.87	
Bleeding from vagina during pregnancy	Present	9 (4)	3.66 ± 4.58	−1.16	1.11 ± 1.16	−2.46**	0.00 ± 0.00	−1.09	3.55 ± 6.65	−0.66	11.00 ± 5.59	−0.55
	Absent	41 (24)	1.78 ± 2.78		0.31 ± 0.75		0.26 ± 0.80		2.90 ± 5.02		11.79 ± 11.47	
Prolonged labor	Present	9 (7)	1.55 ± 1.30	−0.59	0.33 ± 1.00	−0.81	0.00 ± 0.00	−1.09	3.77 ± 6.64	−0.58	7.71 ± 3.72	−0.77
	Absent	41 (21)	2.24 ± 3.50		0.48 ± 0.87		0.26 ± 0.80		2.85 ± 5.01		13.00 ± 12.02	
Stimulation and induction of labor	Present	9 (7)	1.33 ± 2.29	−0.05	0.44 ± 1.01	−0.11	0.22 ± 0.66	−0.12	3.33 ± 6.91	−0.84	7.00 ± 5.09	−1.16
	Absent	41 (21)	2.29 ± 3.49		0.46 ± 0.86		0,21 ± 0.75		2.95 ± 4.96		13.20 ± 11.78	
Gastrointestinal disorders in newborn	Present	8 (5)	1.75 ± 1.66	−0.56	1.00 ± 1.19	−1.89*	0.50 ± 0.92	−1.52	6.87 ± 10.1	−0.89	11.20 ± 5.71	−0.63
	Absent	42 (23)	2.19 ± 3.43		0.35 ± 0.79		0.16 ± 0.69		2.28 ± 3.50		11.78 ± 11.65	
General anesthesia during delivery	Present	7 (5)	2.28 ± 2.75	−0.36	0.42 ± 1.13	−0.44	0.14 ± 0.37	−0.29	2.42 ± 5.56	−1.03	22.60 ± 14.46	−2.19*
	Absent	43 (23)	2.09 ± 3.30		0.46 ± 0.85		0.23 ± 0.78		3.11 ± 5.29		9.30 ± 8.41	
Neonatal jaundice	Present	6 (3)	1.66 ± 3.61	−1.06	1.33 ± 1.03	−2.63**	0.66 ± 1.03	−2.01*	2.33 ± 1.63	−1.07	7.66 ± 4.72	−0.48
	Absent	44 (25)	2.18 ± 3.19		0.34 ± 0.80		0.15 ± 0.68		3.11 ± 5.60		12.16 ± 11.22	
Preterm or lowbirthweight	Present	9 (5)	3.22 ± 3.27	−1.35	0.88 ± 1.67	−1.60	0.77 ± 1.39	−2.54**	2.44 ± 4.85	−0.67	15.40 ± 12.79	−0.90
	Absent	41 (23)	1.87 ± 3.18		0.36 ± 0.79		0.10 ± 0.43		3.14 ± 5.42		10.86 ±10.40	
Timing of rupture of membranes	Present	6 (4)	1.33 ± 1.21	−0.03	0.00 ± 0.00	−1.43	0.33 ± 0.81	−0.57	1.50 ± 1.87	0.14	15.00 ± 16.55	−0.16
	Absent	44 (24)	2.22 ± 3.28		0.52 ± 0.92		0.20 ± 0.73		3.22 ± 5.56		11.12 ± 9.88	
Operative delivery or intervention	Present	7 (5)	3.14 ± 2.11	−2.22**	0.57 ± 1.13	−0.31	0.42 ± 0.78	−1.63	4.00 ± 5.23	−0.71	22.00 ± 15.49	−1.80*
	Absent	43 (23)	1.95 ± 3.34		0.44 ± 0.85		0.18 ± 0.73		2.86 ± 5.32		9.43 ± 8.29	

¶ the number in parenthesis indicate the presence or absence of the particular OC in those patients who underwent the neurological soft signs evaluation (N = 28)

pregnancy, gastrointestinal disorders in newborn, and neonatal jaundice.

Discussion

This is the first study describing the relationship between a history of OCs and neurologic signs in a sample of neuroleptic-naive psychotic patients before and after inception of neuroleptic treatment. This study design allowed us to differentiate primary from drug-induced neurological signs and to examine their putative association with a history of OCs. The hypothesis that OCs are associated with primary neurological signs, could be mostly confirmed. Using ordinal and dichotomic ratings of OCs, we found a relationship of a history of OCs to parkinsonism, dyskinesia, akathisia and neurological soft signs. Catatonia was the only primary neurological domain unrelated to OCs. This negative finding may reflect either the lack of a true association between catatonia and OCs, or alternatively heterogeneity of the catatonia construct as assessed by the modified Rogers scale [30].

By reproductive period, pregnancy complications were related to parkinsonism, dyskinesia and neurological soft signs, neonatal complications were related to akathisia, and labor-delivery complications were unrelated to neurological abnormalities. While a specific association pattern between the most frequent OCs and admission neurological ratings was not observed, dyskinesia was associated with more individual OCs than any other neurological domain. We did not further explore the relationship between pregnancy complications by trimester and neurological signs because there were too few subjects with a history of clearly harmful or relevant OCs in each trimester. Meaningful analyses of this type are beyond the scope of this article, which should be addressed in larger samples of patients.

The prediction that patients with a history of OCs were more likely to present drug-induced neurological signs could not be confirmed. It should be noted that this negative finding only apply to neurological side-effects observed during the hospitalization period and may not extend beyond this period. Therefore, our data do not inform about the relationship between OCs and late neurological effects of antipychotic drugs such as tardive dyskinesia or tardive akathisia.

Our study design allows for no direct comparison with previous studies examining this issue since they were conducted in chronic and medicated samples of patients in which it was not possible to reliably differentiate between primary and drug-induced neurological signs. Indeed, contradictory findings across previous studies underscores the need for examining

reliable definitions for primary and drug-induced neurological signs. OCs in addition of being a risk factor for developing schizophrenia spectrum disorders seem also to contribute to the expression of neurological manifestations in this population. It must be acknowledged, however, that although we found significant associations between OCs and primary neurological signs across some domains, the degree of association in terms of explained variance was rather modest. Obstetric factors must thus act additively or interactively with other factors (i.e. genetic) in producing the neurological manifestations observed in psychotic patients.

The link between OCs and neurological signs need to be understood in the context of the relatively well-established associations of OCs both with brain damage [3, 5, 6] and premorbid neuromotor dysfunction in psychotic patients [3, 31]. These links, however, do not seem to be specific for the psychotic illness as they have been also demonstrated in non-psychotic populations [1, 2, 5]. To date, there are no studies examining the causal links among OCs, brain abnormalities and neurological signs in psychotic patients, although the evidence mentioned above together with that provided by a recent study [32] examining these three variables conjointly in an adolescent population makes such causal links rather plausible in psychotic patients.

While the neural sequelae of OCs are numerous and dependent on the severity and timing of the insult, the precise mechanisms whereby OCs leads to neurological manifestations are unclear. Our findings are compatible with a neurodevelopmental view of schizophrenic signs and symptoms [33] and support the view that the earlier the putative brain damage takes place, the greater the neurological manifestations. Some OCs (bleeding during pregnancy, low birth weight and operative delivery) may cause CNS abnormalities through hypoxia in the foetus, whereas other (anesthesia during delivery and neonatal jaundice) may directly cause CNS damage. We also can only speculate as to the neural mechanism(s) responsible for the neurological manifestations due to OCs. Extrapyramidal signs such as parkinsonism, dyskinesia and akathisia clearly reflect basal ganglia dysfunction. Furthermore, neurological soft signs suggest compromise of systems that are involved in motor speed, coordination and sequencing, functions in which basal ganglia also play a major role [34–36]. Therefore, previous studies converge to indicate that OCs may cause neurological dysfunction that is, at least in part, mediated by the basal ganglia. This notion is consistent with findings from neuroimaging studies of neuroleptic-naive psychotic subjects indicating caudate or lentiform nucleus pathology [37, 38, 39]. Interestingly, we found that dyskinesia and akathisia were related to neonatal jaundice that is a well-known cause of basal ganglia dysfunction [40].

Some potential limitations of our study should be considered. First, generalization to other samples of psychotic disorders may be limited because selection bias: inpatient status, available mother as informant and absence of drug abuse. Second, we relied on maternal recall to retrospectively ascertain a history of OCs, however, this method has proved to be reliable [4, 41] and more likely to produce false negative results that false positive ones [41]. Third, it must be recognized that OCs represent risk for, but not necessarily the presence of, an early brain insult, accordingly our results need to be interpreted in terms of risk for brain damage instead of actual brain damage. Fourth, for most patients undergoing the neurological soft-signs examination it was not possible to assess them at the neuroleptic-naive status and they were assessed a few days after starting antipsychotic treatment. It has been shown, however, that NES scores rated in neuroleptic-naive and minimally treated patients do not differ [42], which reinforces our consideration of NES ratings as representing a primary neurological dysfunction. Lastly, we decided not to correct for multiple testing for two reasons: this may give rise to false negative results [43], and mostly because, to examine obstetric ratings, we proceeded in a hierarchical way in that three sets of nested analyses were done, namely, global ratings, ratings by reproductive period and individual OCs. Furthermore, we used three alternative global ratings of OCs (number, severity and rates), all of which produced consistent and converging results. With such a procedure, the results reinforce each other rather than detracting from each other as required by the correcting methods (Bachetti 44], thus protecting against the finding of spurious results.

References

1. Breslau N, Chilcoat HD, Johnson EO, Andreski P, Lucia VC (2000) Neurologic soft signs and low birthweight: their association and neuropsychiatric implications. Biol Psychiatry 47:71–79
2. Hediger ML, Overpeck MD, Ruan WJ, Troendle JF (2002) Birthweight and gestational age effects on motor and social development. Pediatr Perinatol Epidemiol 16:33–46
3. Lewis SW, Murray RM (1987) Obstetric complications, neurodevelopmental deviance and risk of schizophrenia. J Psychiatric Res 21:413–421
4. McNeil TF (1995) Perinatal risk factors and schizophrenia: selective review and methodological concerns. Epidemiol Rev 17:107–112
5. McNeil TF, Cantor-Graae E, Weinberger DR (2000) Relationship of obstetric complications and differences of brain structures in monozygotic twin pairs discordant for schizophrenia. Am J Psychiatry 157:203–202
6. Falkai P, Schneider-Axmann T, Honer WG, Vogeley K, Schönell H, Pfeiffer P, Scherk H, Block W, Träber F, Schild HH, Maier W, Tepest R (2003) Influence of genetic loading, obstetric complications and premorbid adjustment on brain morphology in schizophrenia: A MRI study. Eur Arch Psychiatry Clin Neurosci 253:92–99

7. McCreadie RG, Hall DJ, Berry IJ, Robertson LJ, Ewing JI (1992) The Nithsdale Schizophrenia Surveys X: Obstetric complications, family history and abnormal movements. Br J Psychiatry 162:799–805
8. Cantor-Graae E, McNeil T, Rickler KC, Sjöström K, Rawlings R, Higgins ES, Hyde TM (1994) Are neurological abnormalities in well discordant monozygotic co-twins of schizophrenic subjects the result of perinatal trauma? Am J Psychiatry 151:1194–1199
9. Cantor-Graae E, Ismail B, McNeil TF (2000) Are neurological abnormalities in schizophrenic patients and their siblings the result of perinatal trauma? Acta Psychiat Scand 101:142–147
10. Lane A, Colgan K, Moynihan F, Burke T, Waddington JL, Larkin C, O'Callaghan E (1996) Schizophrenia and neurological soft signs: gender differences in clinical correlates and antecedent factors. Psychiatry Res 64:105–114
11. Ismail B, Cantor-Graae E, McNeil TF (2001) Neurodevelopmental origins of tardivelike dyskinesia in schizophrenic patients and their siblings. Schizophr Bull 27:29–642
12. Waddington JL, Youssef HA (1987) Is schizophrenia a neurodevelopmental disorder? Br Med J 295:997–998
13. Rifkin A, Quitkin F, Klein DF (1975) Akinesia: a poorly recognized drug-induced extrapyramidal disorder. Arch Gen Psychiatry 32:672–675
14. Gelenberg AJ, Mandel MR (1977) Catatonic reactions to high-potency neuroleptic drugs. Arch Gen Psychiatry 34:947–950
15. Delgalarrondo P, Gattaz WF (1994) Basal ganglia abnormalities in tardive dyskinesia. Possible relationship with duration of neuroleptic treatment. Eur Arch Psychiatry Clin Neurosci 244:272–277
16. Fernandez HH, Krupp B, Friedman JH (2001) The course of tardive dyskinesia and parkinsonism in psychiatric inpatients: 14 year follow-up. Neurology 56:805–807
17. Martényi F, Metcalfe S, Schausberger B, Dossenbach MRK (2001) An efficacy analysis of olanzapine treatment data in schizophrenia patients with catatonic signs and symptoms. J Clin Psychiatry 62:25–27
18. Peralta V, Cuesta MJ (1999) Negative, parkinsonian, depressive and catatonic symptoms in schizophrenia: a conflict of paradigms revisited. Schizophr Res 40:245–253
19. McNeil TF, Cantor-Graae E, Sjöström K (1994) Obstetric complications as antecedents of schizophrenia: empirical effects of using different obstetric complication scales. J Psychiat Res 28:519–530
20. McNeil TF, Cantor-Graae E, Nordström LG, Roselund T (1997) Does choice of scale for scoring obstetric complications influence their relationship to other etiological risks factors in schizophrenia? J Nerv Mental Dis 185:27–31
21. Andreasen NC, Flaum M, Arndt S (1992) The Comprehensive Assessment of Symptoms and History (CASH): an instrument for assessing diagnosis and psychopathology. Arch Gen Psychiatry 49:615–623
22. Andreasen NC, Endicott J, Spitzer RL, Winokur G (1977) The family history method using diagnostic criteria: reliability and validity. Arch Gen Psychiatry 34:1229–1235
23. McNeil TF, Sjöström K (1995) McNeil-Sjöstrom Scale for Obstetric Complications. Lund University Department of Psychiatry, Malmö University Hospital, Malmö, Sweden
24. Simpson GM, Angus JWS (1970) A rating scale for extrapyramidal side effects. Acta Psychiat Scand 212:11–19
25. Guy W (1976) ECDEU Assessment Manual for Psychopharmacology: Publication ADM 76–338. Washington DC, US Department of Health, Education, and Welfare, pp 534–537
26. Barnes TRE (1989) A rating scale for drug-induced akathisia. Br J Psychiatry 154:672–676
27. McKenna PJ, Lund CE, Mortimer AM, Biggins CA (1991) Motor, volitional and behavioural disorders in schizophrenia 2: The 'conflict of paradigms' hypothesis. Br J Psychiatry 158:328–336
28. Buchanan RW, Heinrichs DW (1989) The Neurological Evaluation Scale: a structured instrument for the assessment of neurological signs in schizophrenia. Psychiatry Res 27:335–350
29. Arndt S, Turvey C, Andreasen NC (1999) Correlating and predicting psychiatric symptom ratings: Spearman's r versus Kendall's tau correlation. J Psychiatr Res 33:97–104
30. Peralta V, Cuesta MJ (2001) Motor features in psychotic disorders. I. Factor structure and clinical correlates. Schizophr Res 47:107–116
31. Rosso IM, Bearden CE, Hollister JM, Gasperoni TL, Sanchez L, Hadley T, Cannon TD (2000) Childhood neuromotor dysfunction in schizophrenia patients and their unaffected siblings: a prospective cohort study. Schizophr Bull 26:367–378
32. Stewart AL, Rifkin L, Amess PN, Kirkbride V, Towsed JP, Miller DH, Lewis SW, Kingsley DPE, Moseley IF, Foster O, Murray RM (1999) Brain structure and neurocognitive and behavioural function in adolescents who were born very preterm. Lancet 353:1653–1657
33. Henn FA, Braus DF (1999) Structural neuroimaging in schizophrenia. An integrative view from the neuromorphology. Eur Arch Psychiatry Clin Neurosci 249(Suppl. 4):48–56
34. Flashman LA, Flaum M, Gupta S, Andreasen NC (1996) Soft signs and neuropsychological performance in schizophrenia. Am J Psychiatry 153:526–532
35. Keshavan MS, Sanders RD, Sweeney JA, Diwadkar VA, Goldstein G, Pettegrew JW, Schooler NR (2003) Diagnostic specificity and neuroanatomical validity of neurological abnormalities in first-episode psychoses. Am J Psychiatry 160:1298–1304
36. Dazzan P, Morgan KD, Orr KG, Hutchinson G, Chitnis X, Suckling J, Fearon P, Salvo J, McGuire PK, Mallet RM, Jones PB, Leff J, Murray RM (2004) The structural brain correlates of neurological soft signs in AESOP first-episode schizophrenia study. Brain 127:143–53
37. Buchsbaum MS, Haier RJ, Potkin SG, Nuechterlein K, Bracha HS, Katz M, Lohr J, Wu J, Lottenberg S, Jerabek PA, Trenary M, Tafalla R, Reinolds C, Bunney WE Jr (1992) Frontoestriatal disorder of cerebral metabolism in never-medicated schizophrenics. Arch Gen Psychiatry 49:935–942
38. Keshavan MS, Rosenberg D, Sweeney JA, Pettegrew JW (1998) Decreased caudate volume in neuroleptic-naive psychotic patients. Am J Psychiatry 155:774–778
39. Schmitt GJ, Frold T, Dresel S, la Fougere C, Bottlender R, Koutsouleris N, Hahn K, Möller HJ, Meisenzahl EM (2006) Striatal dopamine transporter availability is associated with the productive psychotic state in first episode, drug-naive schizophrenic patients. Eur Arch Psychiatry Clin Neurosci 256:115–121
40. Hansen TW (2001) Bilirubin brain toxicity. J Perinatology 21(suppl. 1):48–51
41. Cantor-Graae E, Cardenal S, Ismail B, McNeil TF (1998) Recall of obstetric events by mothers of schizophrenic patients. Psychol Med 28:1239–1243
42. Browne S, Clarke M, Gervin M, Lane A, Waddington JL, Larkin C, O'Callaghan E (2000) Determinants of neurological dysfunction in first episode schizophrenia. Psychol Med 30:1433–1441
43. Rothman KJ, Greenland S (1998) Modern Epidemiology. Lippincott Williams & Wilkins, Philadelphia, PA, pp 225–229
44. Bacchetti P (2002) Peer review of statistic in medical research: the other problem. Br Med J 324:1271–1273