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The Clinical Correlates of Neurological Soft Signs in Chronic Schizophrenia

D. J. KING, A. WILSON, S. J. COOPER and J. L. WADDINGTON

Among 16 chronic schizophrenic in-patients, all had at least one neurological soft sign (NSS), and 6 (40%) had definite neurodysfunction. NSS and TD scores were highly intercorrelated, and NSS were significantly correlated with neuroleptic drug exposure. NSS correlated positively with both positive and negative symptoms and cognitive impairment but not with cerebral ventricular size on CT. Patients with neurodysfunction had more positive and negative psychopathology, cognitive impairment and TD than those without. Cerebral ventricular sizes and family histories of schizophrenia were similar in both NSS groups. The presence of NSS may be a simple but important way of identifying a subgroup of schizophrenics with neurodevelopmental predisposing abnormalities, and vulnerability to TD.

Neurological soft signs (NSS) have been reliably documented in schizophrenia and occur with a reported prevalence of 50–60% (Heinrichs & Buchanan, 1988). Their significance, however, is unclear, and the correlation with other clinical abnormalities or outcome is variable (Kolakowska *et al*, 1985; Wegner *et al*, 1985). Nevertheless, NSS were the best single predictor of abnormalities in three modalities: neurological examination, electroencephalograph (EEG) and computerised tomography (CT) scan, in one study of 39 patients who underwent these three tests (Woods & Short, 1985). There has, however, been a surprising paucity of studies relating the occurrence of these signs to CT scan findings and two studies have been contradictory: Weinberg & Wyatt (1982) found an association with enlarged cerebral ventricles while Kolakowska *et al* (1985) did not. Furthermore, the presence of tardive dyskinesia (TD), which is increasingly suspected of indicating underlying predisposing organic factors (Waddington, 1987), has not always been taken into account in surveys of NSS. Finally, the role of neuroleptic medication continues to be debated. While the consensus view appears to be that these signs are not an artefact of medication (Mosher *et al*, 1971; Cox & Ludwig, 1979; Torrey, 1980; Woods *et al*, 1986; Liddle, 1987; Kolakowska *et al*, 1985) this has been challenged by Quitkin *et al* (1976) who, although finding no association with medication in the group of schizophrenics with most signs (those with pre-morbid asociality), did find such an association in the remaining mixed group of schizophrenics and continue to argue that this factor has not yet been adequately excluded (Quitkin *et al*, 1985).

Accordingly, we decided to study the extent and severity of NSS in a group of chronic schizophrenic in-patients who had had CT scans and also to relate these findings to the degree of psychopathology, cognitive impairment, TD, previous neuroleptic drug histories and family history of schizophrenia.

Method

A group of 16 chronic schizophrenic (DSM–III; American Psychiatric Association, 1980) in-patients (10 men, 6 women) who had had CT scans carried out as part of a previous study (King *et al*, 1985) were selected for study. Mean age of the group was 44.4 years (s.d. 12.2, range 30–68) and mean duration of illness 21.41 years (s.d. 10.64, range 5.3–41.2). The interval between the CT scan and this study ranged from two and a half to three years. The patients were examined for TD (by JLW & AW) on two occasions six months apart and on the second occasion they were also examined for the presence of NSS. TD was assessed using the Abnormal Involuntary Movement Scale (AIMS; National Institute of Mental Health, 1976) and 10 NSS: mirror movements, speech, right/left confusion, finger-to-thumb opposition, finger-to-thumb mirror movements, pronation–supination, foot tapping (right/left), face–hand (sensory inattention), graphaesthesia and hopping (right/left), were derived from those used by Quitkin *et al* (1976), Torrey (1980) and Kolakowska *et al* (1985). They were rated on a three-point scale (0 absent; 1 present; 2 marked), so that the total possible range was 0–20. 'Adventitious overflow' was excluded from the Quitkin *et al* (1976) signs since it was indistinguishable from TD. At the time of the examination for NSS the patients were also assessed for psychopathology using the Krawiecka Rating Scale (KRS; Krawiecka *et al*, 1977) as modified by Johnstone *et al* (1978), which gives four positive symptoms (hallucinations, delusions, incoherence and emotional incongruity), two negative symptoms (poverty of speech and affective flattening) and three non-specific symptoms (depression, anxiety and psychomotor retardation), and cognitive function using the Withers & Hinton Test (1971). All available information on the current and lifetime

Table 1
Raw data

Parameter	*n*	Range	Mean	s.d.
Krawiecka (positive)	16	2–16	9.3	4.66
Krawiecka (negative)	16	2–8	4.9	1.69
Krawiecka (total)	16	5–29	17.4	7.00
Withers and Hinton	14	25–104	57.3	23.52
AIMS	16	0–22	6.4	6.76
NSS	15	1–14	6.87	4.19
VBR[1] × 100	16	5.0–19.7	9.76	3.541
Neuroleptic drug treatment: current daily dose:				
mg/CPZ	16	200–10000	3223	3236.1
duration: years	16	3.2–26.5	14.4	8.25
Total: g CPZ	16	1069–11470	4301	2846.0

1. Ventricle : brain ratio.

neuroleptic drug treatment was gathered from the case notes and prescription cards. This was then converted to chlorpromazine (CPZ) equivalents using the tables provided by Davis (1976) and Suy *et al* (1982).

The patients' data were divided in three ways:

(a) presence or absence of family history
(b) presence or absence of TD according to Schooler & Kane (1982) criteria
(c) presence or absence of prominent 'neurodysfunction', i.e. two or more individual signs being rated two (marked).

Thus all six patients with neurodysfunction had a NSS total score of four or more; of the nine without neurodysfunction, five showed several NSS but none was present to a marked degree. The data were analysed using non-parametric statistics (Mann–Whitney *U* and Spearman's correlation coefficients) unless otherwise stated.

Results

Two patients were virtually mute and could not be rated on the Withers & Hinton test and one of these would not co-operate with the examination of NSS. One patient had a missing hand, limiting the number of NSS that could be assessed. The means, ranges and standard deviations of all the data obtained are given in Table 1 and the inter-correlation coefficients in Table 2. The comparisons of patients with and without neurodysfunction and TD are shown in Tables 3 and 4 respectively.

These patients were severely ill and cognitively impaired, on average 44 years of age, ill for 21 years and treated with high doses of neuroleptics for 14 years (Table 1). NSS scores correlated positively with both positive and negative schizophrenic symptoms and TD, and negatively with the Withers & Hinton score (Table 2). There was a positive correlation with duration of neuroleptic treatment and current neuroleptic dose but not with total lifetime exposure. However, when the six patients with the most marked neurodysfunction were compared with the rest (Table 3) it was clear that they were the most severely ill and cognitively impaired, but there was no difference in their mean cerebral ventricular size or neuroleptic drug exposure.

The presence or absence of family history of schizophrenia did not distinguish between the patients on any of the measured variables. TD and NSS were highly intercorrelated (Spearman's rho 0.96, $P<0.01$) (Table 2). TD (Schooler & Kane criteria) was found to be present on both occasions in four patients (persistent TD group) and in four additional patients on the second occasion (transient TD group). In two of the latter patients, anticholinergic drugs had been added in the interval between examinations, in a third the dose of neuroleptics had been reduced and in the fourth the involuntary movements were confined to the trunk and extremities and no oral-facial movements were detected on either occasion. There were progressively more positive, negative and total symptoms, cognitive impairment, NSS, current medication and total exposure to neuroleptics from the no TD group to the transient and persistent TD groups (Table 4). Both TD groups showed highly significant differences in NSS and cognitive impairment from those who never had TD. The increase in psychopathology was statistically significant for negative symptoms in the persistent TD group. None of the differences between the measures of neuroleptic drug exposure were statistically significant in any of the three groups.

Table 2
Spearman correlation coefficients

	Krawiecka score Negative	Krawiecka score Total	Winters and Hinton	AIMS	NSS	VBR	Treatment (duration)	Treatment (total)	Treatment (current)
Krawiecka (positive)	0.512*	0.912**	−0.602*	0.651**	0.765**	−0.001	0.581*	0.460*	0.429*
Krawiecka (negative)		0.704**	−0.643*	0.476*	0.602*	0.138	0.292	0.340	0.291
Krawiecka (total)			−0.724**	0.555*	0.862**	0.021	0.518*	0.388	0.422
Withers and Hinton				−0.803**	−0.818**	−0.207	−0.223	−0.074	−0.204
AIMS					0.964**	0.041	0.288	0.298	0.358
NSS						0.057	0.934**	0.228	0.435*
VBR							0.270	−0.117	−0.175
Treatment (duration)								0.324	−0.193
Treatment (total)									0.660**

*$P<0.05$.
**$P<0.01$.

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Table 3
Comparisons between patients with neurodysfunction (2 or more neurological soft signs of marked degree) and those without

	Neurodysfunction Present ($n=6$) mean (s.d.)	Neurodysfunction Absent ($n=9$) mean (s.d.)	P*
Krawiecka (positive)	11.83 (4.75)	7.33 (4.06)	0.05
Krawiecka (negative)	6.17 (1.47)	3.89 (1.05)	0.01
Krawiecka (total)	21.33 (4.97)	13.44 (5.53)	0.02
Withers and Hinton	33.20 (5.67)	70.67 (17.85)	0.001
AIMS	12.83 (6.79)	2.78 (2.44)	0.002
VBR × 100	10.97 (5.32)	9.00 (2.02)	NS
Medication			
current: mg CPZ	4894.50 (4306.21)	2362.33 (2113.06)	NS
duration: years	14.08 (9.47)	13.82 (8.11)	NS
total: g CPZ	4722.50 (3221.56)	4179.44 (2879.96)	NS

*Mann–Whitney U test.

Table 4
Comparisons between patients with persistent tardive dyskinesia, transient tardive dyskinesia and with no tardive dyskinesia (Schooler & Kane criteria)

	Tardive dyskinesia None ($n=8$) mean (s.d.)	Transient ($n=4$) mean (s.d.)	Persistent ($n=4$) mean (s.d.)
Krawiecka (positive)	7.0 (4.11)	11.0 (2.94)	12.25 (5.56)
Krawiecka (negative)	4.0 (1.51)	5.25 (1.26)	6.5[1] (1.29)
Krawiecka (total)	13.75 (7.48)	19.5 (1.91)	22.5 (5.92)
Withers and Hinton	77.0 (13.8)	43.25[4] (9.25)	30.0[2] (5.0)
NSS	3.29 (1.60)	9.5[4] (3.42)	10.5[3] (2.89)
VBR × 100	9.3 (2.03)	7.38 (1.70)	13.05[5] (5.25)
Medication:			
current: mg CPZ	2149.88 (2294.40)	3710.75 (4121.03)	4881.00 (4005.40)
duration: years	12.48 (7.32)	17.73 (10.15)	14.80 (9.37)
total: g CPZ	3103.50 (899.19)	5100.00 (4377.80)	5897.50 (3372.53)

1. Different from both 'No TD' and combined (No TD and transient TD) groups, $P<0.03$.
2. Different from 'No TD' ($P<0.02$) and combined ($P<0.006$) groups.
3. Different from 'No TD' ($P<0.006$) and combined ($P<0.04$) groups.
4. Different from 'No TD' group, $P<0.006$.
5. Different from combined group, $P<0.02$ (Student's t).

Cerebral ventricular size (VBR) did not correlate with any of the measured variables (Table 2). A significant difference was, however, found between the four patients with persistent TD and the rest ($P<0.02$) (Table 4), as previously reported elsewhere (Waddington *et al*, 1985).

Discussion

There are a number of inevitable limitations to a study of this size which means our conclusion must be tentative. Our numbers are small and therefore, although we can be confident in the positive findings of our non-parametric statistical analysis (such as the correlations between NSS, TD and cognitive impairment), a type II error may have reduced our chances of detecting other associations. There was also a delay between the CT scans of the 1985 study and the assessment of neurological status for the present study. There are very few serial CT scan studies in schizophrenia but what information is available suggests that our findings after up to a three-year interval are valid (Nasrallah *et al*, 1986; Weinberger, 1988). The information on neuroleptic drug exposure was collected from the patient's case notes and while this suffers from inaccuracies due to incomplete records and patient compliance, we assume that these apply equally to all patients with similar diagnoses and lengths and numbers of admissions, and that there has therefore been no systematic bias.

Our patients were chronically and severely ill and all had at least one NSS. If criteria similar to Kolakowska *et al*'s (1985) had been applied (i.e. two signs 'present' or one sign 'marked') 13 of our 15 patients (86.7%) would have had some degree of neurodysfunction. Using our more stringent criteria we found six (40%) of our patients had definite clinical signs of neurodysfunction. The reported prevalence of NSS varies widely, from 29% to 80% (Cadet *et al*, 1986), but our findings are similar to those reported by Torrey (1980; 49%), Kolakowska *et al*, (1985; 46%) and Woods & Short (1985; 58%). The latter authors found a much lower incidence (19%) if signs putatively attributable to age, medication or cognitive impairment were excluded.

We have confirmed a strong association with cognitive deficit in agreement with several previous reports (Mosher *et al*, 1971; Quitkin *et al*, 1976; Kolakowska *et al*, 1985; Liddle, 1987). We have also found a high degree of correlation between NSS and TD, unlike Kolakowska *et al* (1985), but in agreement with Wegner *et al* (1985) and Marsalek *et al* (1988), and Youssef & Waddington (1988) who found a higher incidence of primitive reflexes in patients with TD. While both TD and NSS were correlated with both positive and negative schizophrenic

symptoms (Table 2) and patients with neurodysfunction had significantly more positive and negative symptoms than those who did not (Table 3), patients with persistent TD had significantly more negative but not positive symptoms than those who did not (Table 4). The close association between NSS and severity of psychopathology is in agreement with Mosher *et al* (1971) and Keshavan & Yeragani (1987). The latter further noted that in longitudinal studies a fluctuation in the appearance of primitive reflexes occurred with episodes of psychosis.

Those with a family history of schizophrenia could not be distinguished from those without such a history on any of the measured variables, which does not support a familial/sporadic distinction (Murray *et al*, 1985), but our numbers may have been too small to detect this. Although the VBR in our total group of patients was significantly greater than their age-matched controls ($P<0.001$) (King *et al*, 1985), there was only one significant within-group difference in VBR with respect to the other variables measured in the present study: the presence or absence of persistent TD (Table 4). The general lack of correlation between VBR and other clinical variables, apart from TD, is consistent with several other recent reports (Williams *et al*, 1985; Owens *et al*, 1985; Romani *et al*, 1987; Smeraldi *et al*, 1987).

There was a trend for an association between NSS and neuroleptic medication (Table 2). It is possible, however, that the association with duration of treatment could be because NSS were commoner and more marked in early-onset cases (Torrey, 1980; Woods *et al*, 1986), and that the association with current medication was due to increased treatment in patients with more severe psychopathology (with which NSS were also correlated). Furthermore, there was no significant difference in the neuroleptic exposure between those patients with and those without neurodysfunction (Table 3). Unfortunately, there were inadequate numbers in this study for a multivariate analysis which is required to control for the intercorrelations between these factors. Accordingly, in agreement with Quitkin *et al* (1985), we are unable to exclude some influence of medication in the appearance of these signs.

The significance of NSS in schizophrenia is unclear. Some of the motor disturbances involved have been attributed to bradykinesia. Although this was not formally quantified in the present study, none of the patients had any clinically significant extrapyramidal signs, nor did the retardation score on the KRS differ between the patients with neurodysfunction and those without. NSS have been reported to reflect fronto-parietal (Cox & Ludwig, 1979) and fronto-temporal (Taylor & Abrams, 1984) abnormalities. Liddle (1987) thought that three separate schizophrenic syndromes could be distinguished by different symptom clusters and were associated with different patterns of cognitive deficit. He found that the two frontal lobe syndromes, the disorganisation syndrome (inappropriate affect, poverty of content of speech and thought disorder) and the psychomotor poverty syndrome (poverty of speech, decreased spontaneous movement and affective blunting) were associated with NSS, but that the temporal lobe syndrome – reality distortion (delusions and hallucinations) – was not. A high prevalence of 'harder', localising signs has also been found in both schizophrenics (Woods *et al*, 1986) and their relatives (Kinney *et al*, 1986). In spite of one report to the contrary (Cox & Ludwig, 1979), however, they do not appear to be specific for schizophrenia (Walker, 1981; Nasrallah *et al*, 1982; Woods *et al*, 1986; Gureje, 1988) and probably reflect diffuse cerebral dysfunction (Keshavan & Yeragani, 1987; Youssef & Waddington, 1988). Although there appears to be some fluctuation with severity of symptoms (Keshavan & Yeragani, 1987), there is increasing evidence from longitudinal studies of children at high risk for schizophrenia that early neuro-integrative deficits antedate and predispose to subsequent psychosis (Erlenmeyer-Kimling *et al*, 1982). A neurodevelopmental hypothesis of schizophrenia has recently been elaborated by Murray & Lewis (1987) and Murray *et al* (1988).

Our demonstration of a strong association between NSS and both TD and cognitive impairment in chronic schizophrenic patients emphasises the importance of a full neurological examination in psychotic patients (Woods & Short, 1985). Although unlikely to be of value in predicting outcome or response to treatment (Kolakowska *et al*, 1985), our findings suggest that NSS may be an important clinical means of identifying a sub-group of patients with neurodevelopmental predisposing factors which may have both genetic (Kinney *et al*, 1986) and environmental (Murray & Lewis, 1987; Cooper & King, 1987) origins, and the strong association with TD suggests that their presence might be of value in predicting vulnerability to TD.

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