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Late Onset Involuntary Movements in Chronic Schizophrenia: Relationship of 'Tardive' Dyskinesia to Intellectual Impairment and Negative Symptoms

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Intellectual impairment, negative symptoms, and medication history were assessed in chronic schizophrenic patients with and without abnormal involuntary movements (tardive dyskinesia). Patients with involuntary movements had received neither longer nor more intensive treatment with neuroleptics or anticholinergics. However, the presence or absence of involuntary movements was prominently associated with the presence or absence of intellectual impairment/negative symptoms; these features are characteristic of the defect state/type II syndrome of schizophrenia, in which structural abnormalities of the brain may be over-represented. The role of subtle organic changes in conferring vulnerability to the emergence of such involuntary movements should be re-evaluated.

More than 20 years of research has failed to identify the essential factors which determine whether late-onset involuntary movements (tardive dyskinesia) occur in individuals receiving long-term treatment with neuroleptic drugs. The extensive literature on this topic (Jeste & Wyatt, 1981; Kane & Smith, 1982; Waddington, 1984; Waddington *et al*, 1986) indicates that affected individuals have had neither longer nor more intensive treatment with neuroleptics, but suggests that older age increases the likelihood of developing involuntary movements. Vulnerability to their emergence resides more within the central nervous system of the individual patient, usually diagnosed as schizophrenic, than with the treatment.

It has been proposed that patients with pre-existing forms of organic brain dysfunction may be more likely to develop involuntary movements. However, previous studies on heterogeneous patient groups with varying indices of organicity are inconclusive on this issue (Kane & Smith, 1982). Increasing attention is now being paid to chronic schizophrenic patients who show intellectual impairment and whose clinical picture includes prominent negative symptoms—the 'defect state' or type II syndrome (Crow, 1980). These characteristics are over-represented in the subgroup of schizophrenic patients who show structural abnormalities of the brain on computerised tomography (CT) scan, particularly ventricular dilatation (see Crow, 1982; Andreasen & Olsen, 1982; Seidman, 1983; Waddington *et al*, 1986). The present study specifically investigated associations between the presence of involuntary movements and of intellectual impairment and negative symptoms in chronic schizophrenia, in relation to exposure to neuroleptic and anticholinergic medication.

Method

Our study population comprised 68 long-stay in-patients, aged 30–90 years, who satisfied the criteria of Feighner *et al* (1972) for a diagnosis of schizophrenia and who consented to assessment.

Movement disorder was evaluated using the Abnormal Involuntary Movement Scale (NIMH, 1976); this was followed by neuropsychological assessment of intellectual/cognitive function using an abbreviated form of the Roth-Hopkins test, similar to that described by Qureshi & Hodkinson (1974). The investigator was blind to clinical and medication histories until after this index evaluation.

There is the possibility that objective evaluation of negative symptoms (e.g. poverty of speech and blunting of affect) in relation to involuntary movements will be compromised by the essentially self-revealing nature of such movements. Therefore, they were indexed as follows: muteness was taken as an extreme of poverty of speech, and considered present when verbal production was absent during motor assessment and during attempts at neuropsychological evaluation; in the presence of muteness, no estimate of intellectual function was made. Blunted affect was considered present when review of those periodic case-note reports made prior to the index evaluation, by the consultant in charge of each patient, made specific reference to the presence of this symptom. While these reports appeared thorough, practice in recording blunted affect would undoubtedly vary between the several consultants involved. Thus, both of these estimates of the presence or absence of negative symptoms were conservative, by virtue of their

sensitivity only to the more prominent signs, but had the clear advantage of objectivity.

During the subsequent case-note review, demographic details and history of drug treatment were obtained. Doses of neuroleptics were converted to chlorpromazine equivalents according to standard tables (Davis, 1976) and length, average, and current daily dose and total lifetime intake of neuroleptics were determined. Data were expressed as means ± SEM or as percentage prevalences, and were analysed using Student's *t*-test or the chi-squared test.

Results

As noted in the majority of reports in patients with long-term exposure to neuroleptics (e.g. Owens *et al*, 1982; McCreadie *et al*, 1982; Karson *et al*, 1983), involuntary movements of the limbs and trunk were rare in comparison with those of the orofacial region. Since several recent studies additionally suggest that limb and trunk movements may constitute a pathophysiologically distinct syndrome (Kidger *et al*, 1980; Karson *et al*, 1983), all further references to abnormal involuntary movements (AIM) relate to these hallmark characteristics of the tongue, jaw, lips, and muscles of facial expression.

Out of our population of 68 chronic schizophrenic patients, 28 exhibited at least mild but definite AIM of one or more orofacial areas; in the remaining 40 patients, either no or minimal movements were present. As recommended by Schooler & Kane (1982), movement examination was repeated within one week of the index evaluation in a random group of 12 patients with AIM, particularly to estimate the reliability of assessments made at the 'mild' level of abnormality. Of these 12 reassessed patients, abnormality was confirmed in 11; the remaining individual showed minimal movements on that occasion, and was included in the group of 40 patients without abnormality. There were no significant sex differences in the prevalence of AIM, which were present in 8 of 22 males (36%) and in 20 of 46 females (43%).

Medication

Patients with AIM were significantly older than those without AIM (Table I). There was a non-significant trend for AIM patients to have a longer duration of illness and to have been older when first given neuroleptics. The two groups had received neuroleptic drugs for indistinguishable periods of time. However, those with AIM had received significantly smaller average daily doses of neuroleptics, and had significantly smaller total lifetime intakes of neuroleptics. The two groups were not distinguished by the presence or absence of current neuroleptic treatment at the index evaluation.

For those individuals not currently receiving treatment, the period that had elapsed since drug withdrawal did not differ between the two groups (without AIM: 4.9 ± 1.3 years; with AIM, 4.5 ± 1.1 years). Patients with AIM were somewhat more likely to have been drug-free for at least one month (72% were drug-free, compared with 46% of those without AIM) and tended to have spent a longer total time drug-free (3.5 ± 0.8 years drug-free, compared with 2.4 ± 0.6 years for those without AIM) since initiation of neuroleptic treatment; these trends approached, but did not attain statistical significance.

TABLE I

General characteristics and medication histories of schizophrenic patients with and without AIM (mean ± SEM, unless otherwise indicated)

	Without AIM (n=40)	*With AIM (n=28)*
General		
Age: years	61.6 ± 2.1	68.5 ± 2.7*
Duration of illness: years	33.4 ± 1.8	38.5 ± 2.5
Neuroleptic treatment		
Age at start: years	44.4 ± 2.2	50.6 ± 2.6
Duration: years	13.8 ± 1.0	13.0 ± 1.3
Daily dose: mg chlorpromazine	449 ± 69	259 ± 49*
Lifetime intake: g chlorpromazine	2233 ± 386	1180 ± 231*
Current dosage: *n*		
0	9 (23%)	10 (35%)
25–1000 mg chlorpromazine/day	19 (47%)	17 (61%)
> 1000 mg chlorpromazine/day	12 (30%)	1 (4%)
Anticholinergic treatment		
Duration: years	5.9 ± 0.8	4.9 ± 0.9
Currently receiving treatment: *n*	10 (25%)	6 (21%)

*$P < 0.05$, Student's *t*-test

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TABLE II
Intellectual impairment and negative symptoms in schizophrenic patients with and without AIM

	Without AIM (n=40)	*With AIM (n=28)*
Intellectual impairment[1]		
Mean score (±SEM)	6.7±0.3	5.3±0.6*
Score <50%: *n*	2 (6%)	6 (38%)**
Negative symptoms		
Muteness: *n*	6 (15%)	11 (39%)**
Blunted affect: *n*	7 (17%)	11 (39%)
Defect state/type II signs		
One or more of muteness, blunted affect, or intellectual impairment	14 (35%)	25 (89%)***

1. $n=32$ (without AIM), $n=16$ (with AIM)
*$P<0.05$, Student's t-test
**$P<0.05$, chi-squared
***$P<0.001$, chi-squared

The two groups were not distinguished by any measure of the anticholinergic treatment which almost all patients had received at some stage during neuroleptic therapy, i.e. current dosage and total duration of treatment with anticholinergics (Table I). Comparisons of anticholinergic doses did not help to distinguish the two groups, because of the consistent use of only a small number of drugs over equivalent daily dose ranges (usually benztropine, 2–4 mg).

Intellectual impairment and negative symptoms

Intellectual impairment was assessed in 48 of the patients; of the remainder, 17 were mute and three refused to co-operate with neuropsychological evaluation. Mean scores were significantly lower in the group with AIM, indicating greater intellectual impairment in comparison with those patients without AIM (Table II). Prominent intellectual impairment was defined by a score of less than 50% on neuropsychological assessment, and occurred with significantly greater frequency in patients with AIM. Negative symptoms, defined as above, also occurred more frequently in patients with AIM; for muteness, this excess was statistically significant, while for blunted affect it just fell short ($P<0.1$) of significance. Table II also shows the number of patients in each group who showed at least one of these three features; while only 35% of patients without AIM showed one or more of these signs, 89% of those with AIM were characterised by these features ($P<0.001$). This difference could not be accounted for by the slightly but significantly greater average age of the group with AIM. In two age-matched groups, derived by elimination of data from individuals at the extremes of age, this clinical difference was essentially unaltered; 40% of those without AIM (age = 64.2±1.8 years, $n=35$), compared with 87% of those with AIM (age = 65.6±2.8 years, $n=24$), showed one or more of the characteristics of prominent intellectual impairment, muteness, or blunted affect ($P<0.001$).

Discussion

The prevalence of AIM (41%) in this group of schizophrenic patients was typical. Patients with AIM had a slightly but significantly higher mean age, consistent with the majority of studies. The phenomenon appears to reflect an increased vulnerability with ageing and chronicity, rather than increased exposure to neuroleptics with increasing age (Kane & Smith, 1982; Waddington & Youssef, 1985). In further agreement with the majority of studies (Kane & Smith, 1982), our schizophrenic patients with AIM had received neither longer nor more intensive therapy with neuroleptics. Rather, patients with AIM had received significantly smaller average daily doses and total lifetime intakes of neuroleptics over their period of exposure. This finding is consistent with the report by Smith *et al* (1978) of a similar inverse relationship between involuntary movements and total neuroleptic intake during hospital treatment. It might suggest that patients with AIM were less severely ill than their counterparts, or that the form of their illness was different in some way.

Over the past few years, there have been a number of reports suggesting that a greater extent of drug-free periods during long-term neuroleptic treatment

may in fact be associated with an increased risk of AIM (Kane & Smith, 1982; Branchey & Branchey, 1984). Our patients with AIM tended to have had more discontinuous treatment, but the data were inconclusive. We also found patients with AIM not to be distinguished by greater exposure to anticholinergic medication. The literature as a whole (Kane & Smith, 1982) supports this finding in relation to vulnerability to AIM.

Although we had greater difficulty in distinguishing our two groups of patients in terms of medication history, the presence or absence of certain symptoms was a powerful discriminator of the presence or absence of AIM: intellectual impairment, poverty of speech, and blunted affect. These are prominent features of the defect state or type II syndrome of schizophrenia (Crow, 1980). Even using the present conservative indices, almost 90% of our patients with AIM had one or more of these symptoms, while only about one-third of those without AIM were characterised in this way. The strength of this discrimination ($P<0.001$) suggests an intimate relationship between features of the defect state and AIM in schizophrenia.

Other studies support this notion. Regarding intellectual impairment, Famuyiwa *et al* (1979) found schizophrenic patients with AIM to be more impaired on a paired-associate learning test; they did not show greater impairment on the Withers & Hinton test of the sensorium, but were some 15 years younger than our own patients. More recently, Wolf *et al* (1983) found no difference in cognitive function between schizophrenic patients with and without AIM respectively, using the indices of Wechsler and of Rey, in patients a decade younger than our own. However, in younger patients, Struve & Wilner (1983) found those with AIM to be more impaired on the Conceptual Level Analogy Test. Regarding negative symptoms, McCreadie *et al* (1982) noted that older schizophrenic patients with AIM more commonly showed flattening of affect, and older schizophrenic patients with these features of intellectual impairment and negative symptoms may show AIM even in the absence of a history of exposure to neuroleptics (Owens & Johnstone, 1980; Owens *et al*, 1982). Thus, neuroleptics might not cause such movements, but rather, might enhance a usually covert, but sometimes overt predisposition towards AIM (Waddington *et al*, 1983, 1986).

This over-representation of intellectual impairment and negative symptoms in our AIM group might be the basis of their reduced exposure to neuroleptics in the present study. A clinical picture in which these features predominate would require less intense treatment with neuroleptics. The case-notes revealed that the psychiatrists caring for our patients had attempted to reduce neuroleptic dosage to match the extent of positive symptoms, and also to minimise medication of patients with the defect state, where least benefit is likely to be derived (Crow, 1982). This interpretation is supported by the study of Opler *et al* (1984), who found that schizophrenic in-patients with negative symptoms had been less heavily medicated than patients with positive symptoms. Similarly, the trend towards more discontinuous medication in our patients with AIM may be explicable in these terms: case notes indicate that drug-free periods were not a result of non-compliance, but rather a clinical decision that in the absence of positive symptoms, neuroleptic treatment was not warranted. However, patients with AIM were slightly older, and tended to have had a greater duration of illness when neuroleptics were first introduced; this may in itself have contributed to a less enthusiastic approach to neuroleptic treatment.

Involuntary movements and intellectual impairment/negative symptoms may be two separate manifestations of a common pathophysiological process that both underlays deterioration to the defect state and confers vulnerability to the emergence of AIM during long-term neuroleptic treatment. Our point-prevalence study cannot indicate whether AIM and these features of type II schizophrenia tend to arise together, or whether either one might precede the other. This would only become clear from prospective studies in schizophrenia.

Our data indicate that signs of type II schizophrenia are a much better predictor of the presence or absence of AIM than any variable related to medication. Such features of the type II syndrome have been associated with a variable excess of structural abnormalities of the brain by CT scan, particularly ventricular dilatation (Crow, 1982; Andreasen & Olsen, 1982; Seidman, 1983). While CT scan studies in relation to the presence or absence of AIM are not consistent, this may reflect heterogeneous groups which include non-schizophrenic patients with other potential structural or organic changes (Waddington *et al*, 1986). In the light of the present evidence, we suggest that a role for various subtle organic factors in rendering a patient vulnerable to the emergence of AIM should be reconsidered, not just in schizophrenia but also in patients with other diagnoses who are given neuroleptics and in whom AIM are demonstrable.

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