CHAPTER 3
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THE 2-YEAR STABILITY OF NEUROLOGICAL
SOFT SIGNS AFTER A FIRST EPISODE OF
NON-AFFECTIVE PSYCHOSIS.

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ABSTRACT

We examine the 2-year stability of neurological soft signs (NSS) in 29 patients after a first episode of psychosis. The numbers of NSS at inclusion and at 2 years follow-up were similar but there was a significant increase in the numbers of NSS in the sub-group of patients whose dosage of antipsychotic medication had increased over time.

INTRODUCTION

The increased prevalence of neurological soft signs (NSS) in first episode psychosis (Dazzan and Murray 2002) and schizophrenia (Boks et al. 2000; Leask et al. 2002) is well established. An increase in NSS has also been established in the siblings of schizophrenia patients (Ismail et al. 1998; Cantor-Graae E. et al. 2000) and in schizophrenia patients with a family history of psychosis (Woods et al. 1991), leading to the hypothesis that NSS represent a genetic vulnerability to schizophrenia. There has been an ongoing debate about the influence of medication on NSS, with the majority of studies arguing against such an influence. However, to date only four longitudinal studies have been published; Chen et al (2000) followed 43 patients during 5 years, Smith et al (2000) 37 patients with 5 years interval, Torrey (1980) 31 patients with 1 years interval and finally Madsen et al (1999) 18 patients with 5 years interval. All studies but one (Madsen et al. 1999) were conducted in chronically hospitalised schizophrenia patients. Two studies found no major changes in the neurological soft signs at follow up (Torrey 1980; Smith et al. 1999) and one study found an increase of NSS at follow up (Chen et al. 2000). The fourth study also failed to find a significant increase in the number of NSS in the group of schizophrenia patients as a whole at follow up but did find an increase in the number of NSS in the males and in those with high genetic loading, obstetric complications or persistent psychosis (Madsen et al. 1999). We investigated whether the number of NSS increased or remained stable over the two years following a first episode of psychosis. We examined the possible influences of changes in antipsychotic dose and severity of psychopathology on the total number of NSS.

METHOD

All patients admitted at the university hospital Groningen with a first episode of psychosis were asked to participate. After complete description of the study to the patients, written informed consent was obtained. At six weeks NSS were assessed by means of the Cambridge Neurological Inventory (CNI) (Chen et al. 1995), a standardised comprehensive neurological examination. This inventory includes most neurological signs from the Neurological Evaluation Scale (NES) (Buchanan and Heinrichs 1989) along with other neurological signs. DSM IV diagnoses were made using the Schedules for Clinical Assessment in Neuropsychiatry (Wing et al. 1990). Symptoms were assessed by means of the Positive and Negative Symptom Scale (PANSS) (Kay et al. 1987) on the same day as the NSS. After 2 years consecutive patients with a diagnosis in the schizophrenia spectrum were asked for follow up. 29 patients completed the follow up and were included in this study. Previously we reported on the interrater reliab-
lity (which was satisfactory, ICC=0.83) and on a significant increase in the number of NSS in patients versus healthy controls at inclusion (Boks et al. 2004).

We examined whether there were significant differences in the numbers of NSS between the first and second assessment using a paired t-test. We calculated the Intra Class Correlation (ICC) as measures of agreement between the first and second rating. We then divided the patients into three groups: PANSS scores increased, unchanged or diminished, and tested any changes in the number of NSS with the Wilcoxon signed rank test. We also divided patients into three groups: medication dosage increased, unchanged and decreased, and again tested any differences in the number of NSS with the Wilcoxon signed rank test. Tests were two-sided, and p-values of 0.05 were considered significant.

**RESULTS**

Mean age at inclusion was 26.9 years (sd 6.3), 18 patients (62.1%) were male. DSM IV diagnosis at inclusion were; schizophrenia (N=15, schizophreniform disorder (N=7), schizoaffective disorder (N=2), delusional disorder (N=1), psychosis Not Otherwise Specified (N=4). At inclusion 15 patients used atypical antipsychotic drugs and 11 patients classical antipsychotic drugs, 3 patients were medication naive. There were no patients at inclusion or on follow-up who used more than one antipsychotic drug. Chi-square tests showed no significant differences in the ratio of classical and atypical antipsychotic drug, or in the ratio of patients with and without other medication, at inclusion and follow up. Mean dosage in haloperidol equivalents at inclusion was 4.0 (SD 3.0), at follow up 3.8 (SD 3.2).

The total numbers of NSS at inclusion (7.5, SD=7.1) and follow up (8.9, SD=5.5) did not differ significantly (paired t-test, two-sided, t=1.5 p=0.15), and the measures of agreement were substantial (ICC 0.66). There were also no significant changes in the numbers of NSS in the groups based on change in PANSS scores. However we found a significant increase in the number of NSS in the group in which the dosage of antipsychotic medication had increased since inclusion (5.9 (SD 7.1) vs 9.0 (SD 5.2), Wilcoxon signed rank test (Z=2.09, p= 0.036). To investigate the possibility that this was a medication effect we repeated the analysis excluding those signs that may have been influenced by medication ie. all signs from the EPS and TD categories of the CNI (Chen et al. 1995). The results were similar (Wilcoxon signed rank test, Z=2.15, p= 0.032), suggesting that the increase of NSS in this group was not just the side effects of medication.

**DISCUSSION**

We found no significant changes in the numbers of NSS 2-years after a first episode of psychosis, and the level of agreement between the two assessments was substantial. The number of NSS was increased in patients with an increase of medication, although a decrease in medication had no effect. This group may represent patients with more severe illness who failed to adequately respond to the initial dose. However, since the mean number of NSS at inclusion is slightly lower in this group, this finding could instead represent regression to the mean.
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Strengths of this study include a longitudinal design, inclusion of first episode patients and the relatively low doses of medication. The statistical power is however limited by the sample size. Our results support earlier reports that overall NSS appear to be stable over time, although perhaps not in specific groups.

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