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Research article

Motor sequencing abnormalities are the trait marking neurological soft signs of schizophrenia

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HIGHLIGHTS

- 84 Black Africans with first-episode schizophrenia were studied.
- We investigated the one year profile of neurological soft signs (NSS).
- We examined whether NSS are stable despite changes in psychopathology.
- Motor sequencing exhibited trait marking features.
- Other NSS marked the psychopathology state.

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ABSTRACT

We describe the profile of NSS across the one-year course of schizophrenia in 84 Nigerian first-episode patients. They were assessed at baseline and 3 monthly for 12 months using the Neurological Evaluation Scale and the Positive and Negative Syndrome Scale (PANSS), and treated with flupenthixol decanoate. The pattern of NSS total and sub-category scores obtained from repeated measurements were investigated for responders (≥50% reduction of baseline PANSS scores) and non-responders using the method of repeated measures analysis of variance. Trait-like features of NSS categories were quantified using intraclass correlation coefficients (ICCs). NSS were present in 96.4% of the patients at baseline (mean 21.5 ± 11.1). The motor-sequencing sub-category was found unrelated to changes in schizophrenia psychopathology with treatment (positive, $r = 0.19$, $p = 0.136$., negative, $r = 0.12$, $p = 0.350$; disorganization, $r = 0.16$, $p = 0.245$; overall, $r = 0.20$, $p = 0.112$). Regardless of decrements in psychopathology, motor-sequencing scores remained relatively unchanged across the course of the disease (main effects: 'responders' $F = 2.44$, $p = 0.930$, 'poor responders' $F = 0.27$, $p = 0.764$, entire sample $F = 1.87$, $p = 0.160$). ICC was "substantial" at 0.8 (95% C.I = 0.6–0.9). Only the motor-sequencing NSS appear to be trait marker of schizophrenia in this sample. Other NSS seem to reflect symptomatic states of the disorder.

1. Introduction

Neurological soft signs (NSS) are subtle but clinically measurable abnormalities that are now recognized as part of the expression of schizophrenia [1,2]. They have been theoretically grouped into three major categories derived from the neurological evaluation scale (NES) [3]: sensory integration, motor co-ordination and motor sequencing. These signs are attractive as potential trait markers for the disorder because the pattern of their occurrence suggests they have been present before the onset of the schizophrenia phenotype [4].

An ideal trait marker would be expected to exhibit a degree of stability across the course of the relevant disease. This characteristic of NSS has been demonstrated in Caucasian and mixed samples of patients with schizophrenia [5,6]. These studies have often examined stability without exploring the pattern of change in NSS according to the different levels of response to treatment. Yet, investigation of the temporal stability of NSS in relation to longitudinal changes in psychopathology among first episode schizophrenia patients may clarify the groups of NSS that are

Abbreviations: SIN, sensory integration; MCN, motor co-ordination; MSN, motor sequencing.

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markers of vulnerability to the disease, and those that reflect the different expressions of the overt phenotype. In the absence of specific genes for schizophrenia, such information may be of value for the understanding of gene functions in the disorder. In particular, the study of a homogenous racial group may improve the contextual validity of such information.

There are presently no studies of the longitudinal profile of NSS in a homogeneous group of indigenous Africans with first episode schizophrenia. The present report aimed at describing the profile of both the total and the sub-categories of NSS in mostly medication naïve Black African patients showing good or poor response to biomedical treatment across the one-year course of schizophrenia. We hypothesized that regardless of changes in psychopathology, the scores for groups of NSS will remain relatively unchanged across the one year course of the disease.

2. Materials and methods

Ethical approval for the study was obtained from the University of Ibadan ethics committee. Participants provided written consent before interviews were conducted.

The study was conducted among patients presenting for treatment for the first time as in- or out-patients at the two general hospitals with psychiatric units in Ibadan, Nigeria.

2.1. Subjects

The sample comprised mostly anti-psychotic naive patients with first episode schizophrenia (5 participants had less than 12 weeks lifetime oral antipsychotic exposure). For inclusion, they had to meet criteria in the fourth revision of the diagnostic and statistical manual of mental disorders (DSM-IV) [7] following a semi-structured interview conducted by a psychiatrist. Patients also had to be aged between 16 and 45 years. We excluded patients with previous depot antipsychotics treatments, current substance abuse [7], significant physical illnesses (e.g., open tuberculosis), and clinical history suggestive of intellectual disability. On the bases of these criteria we recruited 84 patients consecutively between April 2009 and June 2011. They were evaluated as far as possible before antipsychotic medication was prescribed.

2.2. Measures

Diagnostic assessment was conducted with the structured clinical interview for DSM-IV- patients' edition (SCID-P) [8].

2.3. Neurological assessment

NSS were evaluated using the NES [3]. The scale includes subscales which reflect signs of motor co-ordination (tandem walk, rapid alternation, finger-to-thumb opposition, and finger-to-nose test), sensory integration (audiovisual integration, stereognosis, graphesthesia, extinction, and right-to-left confusion tests), and motor sequencing (first-ring, the first-edge-palm, Ozeretski, and rhythmic tapping tests). The items are scored with reference to the descriptive anchors provided on a three-point scale (no abnormality = 0; mild, impairment = 1; marked impairment = 2). Similar to criteria in previous studies [9], a neurological abnormality was defined as a rating of 2 on any item on the NES. The tests were administered by a psychiatrist who had been trained in the use of the NES. The assessments conducted at baseline, 6 and 12 months are the focus of this report.

2.4. Psychiatric assessment

The severity of the baseline psychopathology was evaluated with the Positive and Negative Syndrome Scale (PANSS) [10]. The PANSS five factor solution [11] was adopted for this study based on its stability and superior validity when compared to the older three factor model [10]. It includes factors for positive (delusions, hallucinations, unusual thought content, suspiciousness, and grandiosity), negative (lack of spontaneity, blunted affect, emotional withdrawals, social withdrawals, motor retardation, poor rapport, and social avoidance), disorganization (stereotyped thinking, poor attention, disorientation, disorganization, and poor abstraction), excitement/hostility (impulsivity, excitement, hostility, and uncooperativeness), and emotional distress (anxiety, depression, guilt, and tension).

The overall clinical status was assessed using Clinical Global Impression (CGI-severity) [12], while pre-morbid adjustments, depression, and extrapyramidal symptoms (EPSE) were explored using the pre-morbid adjustment scale (PAS) [13], Calgary depression scale for schizophrenia (CDSS) [14], and extrapyramidal symptom rating scale (ESRS) [15], respectively. These measures have been used for the assessments of African patients with schizophrenia in previous studies [16].

2.5. Treatment

A wash-out period of one week was allowed for the 5 participants who had lifetime oral anti-psychotic exposures. After ruling out hypersensitivity, flexible doses of deep intramuscular flupenthixol injections starting from 5 mg or 10 mg in two or four weekly intervals were administered, with increases of up to a maximum of 30 mg depending on age, tolerability or response. Concomitant medications such as lorazepam, benzhexol, and propranolol, for sedation, EPSE and akathisia, respectively, were allowed at the discretion of the investigators. Depot antipsychotic was chosen for this study to rule out covert non-adherence, a common phenomenon in first episode schizophrenia [17]. Additional measure to improve adherence included the incorporation of a multi-disciplinary assertive monitoring team in the design of this study.

Duration of untreated psychosis (D.U.P) was defined as the period in months from the onset of psychotic phenomena to first presentation for biomedical treatment. Onset of psychosis was defined as the presence for one week or more of psychotic symptoms with marked deterioration of functioning.

In all cases, pre-morbid functioning was the retrospective rating of patients' functioning up to six months before the defined onset of psychosis.

2.6. Outcome

Outcome was assessed in terms of symptom reduction between baseline and month 12. Response was defined as 50% or more reduction in the PANSS scores from baseline to month 12.

2.7. Statistical analysis

Descriptive statistics such as means and standard deviations were used to summarize quantitative variables. Characteristics of the study sample who met criteria for response (good responders) were compared with those not meeting such criteria (poor responders) using the chi-square test or *t*-test, for categorical or continuous variables, respectively. Reduction in PANSS score was calculated by subtracting the total PANSS scores for each participant at months 12 from the scores at baseline. The correlations