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Motor Neurological Soft Signs Among Patients with Schizophrenia: A Clinical Significance

(Petanda Neurologi Motor Tidak Ketara dalam Kalangan Pesakit Skizofrenia: Satu Kepentingan Klinikal)

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ABSTRACT

Neurological soft signs (NSS) are subtle indicators of brain dysfunction which are present in excess among patients with Schizophrenia. Its clinical significance remains unclear despite extensive researches in this area. The objective of this work was to determine the proportion of schizophrenia patients who have motor NSS and then to compare the clinical features between these two groups; with and without motor NSS. This cross-sectional study which utilized the brief motor scale (BMS) was used to investigate the presence of motor NSS in 80 schizophrenia patients who attended Universiti Kebangsaan Malaysia Medical Centre (UKMCC) Psychiatric clinic. The diagnosis of schizophrenia was confirmed by mini international neuropsychiatic interview (MINI). Symptomatology and abnormal motor movement were assessed using the brief psychiatric rating scale (BPRS) and abnormal involuntary movement scale (AIMS), respectively. A brief battery of cognitive tests covering aspects of attention, working memory and executive function was administered. The bivariate analyses were applied to look for any relationship between the study factors. Majority of schizophrenia patients (68.8%) in this study have motor NSS. The motor NSS were associated with ethnic group, level of education, age of onset, duration of illness and performance in cognitive assessment; verbal fluency, digit span forward, digit span backward and trail making B ($p<0.05$*) but not with trail making A. The assessment of motor NSS represents a brief, inexpensive and meaningful tool in assessing the cognitive functions in schizophrenia. It has the potential as an illness marker and a link between neurobiological research and clinical practice.*

Keywords: Cognitive function; neurological soft signs (NSS); schizophrenia

ABSTRAK

Tanda-tanda neurologi yang tidak ketara (NSS) merupakan petunjuk samar-samar disfungsi otak yang agak sukar dikesan tetapi dialami oleh ramai pesakit skizofrenia. Walaupun telah banyak kajian dijalankan, kepentingan klinikal tanda-tanda ini masih tidak jelas. Objektif kajian adalah untuk menentukan kadar pesakit Skizofrenia yang mengalami NSS motor yang tidak ketara dan kemudian membandingkan tahap sosio-demografi, ciri-ciri klinikal dan fungsi kognitif antara dua kumpulan; kumpulan yang mempunyai NSS yang tidak ketara dan kumpulan yang tidak mengalaminya. Ini adalah kajian keratan-lintang yang menggunakan skala motor ringkas (BMS) untuk menentukan kehadiran NSS motor yang tidak ketara ke atas 80 pesakit skizofrenia yang hadir ke klinik pesakit luar psikiatri, PPUKM. Diagnosis pesakit telah disahkan dengan menggunakan temuduga neuropsikiatri antarabangsa mini (MINI). Gejala penyakit telah diperiksa dengan skala kedudukan psikiatri ringkas (BPRS) dan pergerakan motor yang tidak normal telah diuji dengan skala gerakan luar kawal tak normal (AIMS). Pesakit juga mengambil ujian kognitif ringkas yang meliputi aspek perhatian, ingatan pintas dan fungsi eksekutif. Keputusan yang diperoleh telah dibandingkan antara dua kumpulan ini. Analisis bivariat telah dijalankan untuk mencari sekiranya ada hubungan antara skor BMS, sosio demografi, ciri-ciri klinikal dan fungsi kognitif. Kadar pesakit skizofrenia yang mempunyai NSS motor yang tidak ketara ini adalah tinggi (68.8%). NSS motor yang tidak ketara berhubung kait dengan kumpulan etnik, tahap pendidikan, umur diagnosis, tempoh penyakit dialami dan juga prestasi ujian kognitif ($p<0.05$*). Pemeriksaan NSS motor yang tidak ketara adalah teknik yang ringkas, murah dan berkesan untuk memeriksa fungsi kognitif pesakit skizofrenia. Ia berpotensi digunakan sebagai penanda penyakit dan menjadi penghubung antara kajian neurobiologi dan klinikal.*

Kata kunci: Fungsi kognitif; skizofrenia; tanda-tanda neurologi motor (NSS)

INTRODUCTION

Neurological soft signs (NSS) are motor, sensory or integrative deviations detected by clinical neurological examination and are not part of a well-defined neurological syndrome (Buchanan et al. 1990). The term 'soft' sign in contrast to 'hard' reflects the absence obvious localised pathological lesion underlying these signs. However, it is no longer valid to assume that there is a lack of localisation

but rather the inability to define the brain-behaviour relationship that underlies the presence of NSS (Heinrichs & Buchanan 1988).

Most of the previous studies agreed that the prevalence of NSS was higher among patients with schizophrenia but the meaning of its presence remains obscure (Buchanan et al. 1990). The reported prevalence rates ranged from 50% to 80% in patients with schizophrenia, compared with only 5% in normal controls (Chan & Gottesman 2008). NSS is categorised into three main neurological domains: integrative sensory function; motor co-ordination and motor sequencing. Sander et al. (2000) claimed that motor performance; particularly motor sequencing tasks appear to be the most promising category of NSS for genetic studies of schizophrenia as it is the most significant heritable item. NSS are considered as a trait feature of schizophrenia and probably genetically transmitted factor contributing to the vulnerability to the disease (Meehl 1990).

Cognitive impairment presents reliably in majority of the patients with schizophrenia (Chan & Chen 2004) and seems to be an intrinsic part of the disorder. Previous studies have offered mixed results on the association between NSS and cognitive deficits among schizophrenia patients, with fewer negative than positive results (Arango et al. 1999). Specific neurological sign categories are selectively correlated with specific domains of cognitive impairment (Mohr et al. 2003). Motor co-ordination signs were significantly related to both verbal performance and executive function components (Chan & Gottesman 2008). Sensory integration signs were generally related to a wider range of neurocognitive in addition to executive functions (Chen et al. 2001).

The detection of NSS through routine physical examination would give us the general impression on the patient's cognitive ability which could be a surrogate measure for patients' functionality. This information would be valuable for clinicians in preparing the long term treatment plan for the patients especially regarding the rehabilitation program that is best suited to their baseline deficit. This study was conducted to determine the proportion of motor neurological soft signs among patients with schizophrenia who attended psychiatric outpatient clinic at UKMMC and to examine their relationship with patients' clinical characteristic including their cognitive function.

Material and Methods

Subjects

The sample was recruited from the patients attending the outpatient psychiatric clinic at Universiti Kebangsaan Malaysia Medical Center (UKMMC) - a tertiary care referral centre located in Cheras, suburb of Kuala Lumpur, Malaysia.

Eighty subjects aged between 18 and 60 years old who were able to read and understand Malay or English were recruited by systematic random sampling method. The subjects were diagnosed as schizophrenia based on the DSM-IV criteria, (American Psychiatric Association 2000) by the psychiatrist or the psychiatric postgraduate trainees working in the department of psychiatry, UKKMC. Mini international neuropsychiatric interview (MINI) (Sheehan et al. 1998) was conducted to generate DSM IV diagnosis and to exclude other diagnoses. Mini mental state examination (Folstein et al. 1975) was performed to exclude any evidence of severe cognitive impairment. Subjects with concomitant mental retardation, organic brain disease, history of illicit substance abuse in the past one month (except tobacco), had electroconvulsive therapy treatment within the last 6 months, hearing impairment, major physical illness and movement disorders and under the care of the investigator were excluded from the study. All subjects and their main carers provided written informed consent. The study was approved by the UKMMC Ethical Committee.

This cross-sectional study was conducted over a period of 3 months (August to October 2008). Using the formula for cross-sectional study (Naing et al. 2006), for a power of 0.8% and 60% was taken as the prevalence rate of NSS with 10% differences from either side of the value, the minimum number of subjects required was 68, to obtain the significant result, if it was present.

Variables Measured and Instruments Used

The subjects were examined for motor NSS using the Brief Motor Scale (BMS) (Jahn et al. 2006) in a standardised manner, as specified for each items and according to the fixed sequence. The BMS was chosen for this study in view of its brevity, clear description on the assessment procedure, good psychometric properties and its' practicality. BMS is easy to use and suitable as a screening tool in daily clinical practice as well as a research instrument. The individual items are chosen based on the factor analysis study done on all the individual tasks included in the neurological evaluation scale (NES) and the Heidelberg NSS scale. The validation of the scale was done in Germany and showed good psychometric properties (Jahn et al. 2006). The permission to use the instrument was attained from the original author, Prof Thomas Jahn.

There are 10 items in this scale which consist entirely of motor tasks. It is sub-categorised into two 2 subscales; motor co-ordination (MOCO) and motor sequencing (MOSE). Each subcategory consists of 5 individual items. MOCO subscales consist of dysdiadochokinesia, foot tapping, bilateral rhythm tapping, oseretzki and gaze impersistence. MOSE subscale comprises of pronation-supination, finger-thumb-oppostion, fist-edge-palm, fist ring and rhythm production. For each of the NSS, a detailed description of the assessment procedure and scoring criteria are described precisely. The three point scale ranging from 0 to 2 (0= normal and 2= maximum) are used. Since each of the subscale consists of five items, the maximal score for each subscale is 10 and the maximum score for total BMS score

is 20. For items which are assessed bilaterally, the average score is used. To define the positive motor NSS, a total score of greater than 1.5 on BMS scale is used. This cut-off value allows the most clear cut separation between patients and controls with a specificity of 84.1% and a specificity of 87.9% (Jahn et al. 2006).

The assessment of psychopathology was conducted using BPRS (Kay et al. 1988). The subjects were assessed for tardive dyskinesia and other abnormal movements using abnormal involuntary movement scale (AIMS) (National Institute of Mental Health 1976). These were done after the assessment of motor NSS and cognitive tests to minimize bias. The data on socio demographic and clinical characteristics were gathered last using a questionnaire that was prepared and conducted via face to face interview by the researcher.

The cognitive tests performed were trail making A (TMA), trail making B (TMB), verbal fluency (VF), digit span forward (DF) and digit span backward (DB). The trail making tests are a short and convenient estimate of executive function. The time taken to complete task A and B were recorded as final score. In general, performance is considered to be impaired if scores exceed 40 s for part A and 91 s for part B. (Lezak et al. 2004).

Digit span tests are comprised of digit span forward (DF) and digit span backward (DB). For the DF items, the subject is required to simply repeat, in order, a series of numbers read aloud by the examiner at the rate of one digit per second. For the DB items, the subjects must repeat the series of numbers in reverse order. The DF and DB tasks become more difficult as the number of digits to be repeated grows longer. In this study, the span of 5 and above is considered normal in DF. For DB, the normal score is taken as span of 4 and above based on previous study (Normala 2005).

Semantic verbal fluency was assessed by requesting patients to name as many items as possible from three categories (food, animal and supermarket items), each category in 1 min. The scores taken are the summation across the three categories and a total of 30 or below was considered abnormal in the present study that suggests impairment in executive function. As there is no normative data, the cut-off point of 30 was chosen as one of the local study (Normala 2005) also used the same value.

The case notes were reviewed to substantiate the findings. The whole assessment and data gathering procedure took about 100-120 min per subject. 10-15 min break was allowed in between interviews.

DATA ANALYSIS

The data collected was analysed using the Statistical Program for Social Science (SPSS version 12.0). The test of normality by Q-Q plot and Kolmogorov had shown significant result which indicated the non–normal distribution for BMS score. Mann-Whitney test was applied to observe any difference in means of BMS score with the independents variables. For the categorical data, the Chi-squared test was conducted. For bivariate analysis, the Spearman's Rho correlations were performed to elicit the relationship between the BMS score and the continuous independent variables. The Pearson's correlation was used to determine any relationship between mean scores of each cognitive scale as they were normally distributed.

RESULTS

One hundred and twenty patients were approached and invited to participate in the study. Thirteen subjects did not consent, nine were excluded and 18 did not complete the study. Eighty subjects were available for the data analysis. The response rate was 89.2%.

Nine subjects were excluded; had other diagnoses (3 subjects), MMSE score less than 24 (2 subjects), taking cannabis within the last one month (2 subjects), history of unconsciousness following motor vehicle accident (1 subject) and learning disabilities during childhood (1 subject).

The socio demographic and clinical characteristic of the subjects are shown in Table 1 and 2. Only ethnic group and educational level showed a significant difference between group with and without NSS.

Bivariate analysis found that age of onset of psychosis and the duration of illness were the only two clinical variables that were positively correlated with BMS score (p value<0.05). The correlation coefficient for both of the variables, 0.266 and 0.269, respectively, was considered to be small indicating a weak relationship between these variables.

MOTOR NSS

The proportion of subjects who were positive for motor NSS was 68.8% (based on a cut-off point of 1.5) which means that motor NSS present in approximately 2 out of 3 subjects.

For MOCO subscale, Oseretzki was the most frequent item that was found to be positive; 58.8% of the subjects. The second highest was disdiadokinesia; 46.3% and foot tapping was the least frequent; 11.3% of the subjects. For MOSE subscale, 70% of the subjects were positive for fist-edge-palm item and it was the most frequent item found to be positive among the subjects. Only two items; fist-edge-palm and fist-ring were positive in more than 50% of the subjects. The least frequent item was finger-thumb-opposition, which was positive in 21.3% of the subjects.

COGNITIVE FUNCTIONS

In terms of percentage of impaired subjects, TMA had the most numbers of impaired subjects, followed by TMB, DB, VF and DF.

The association between cognitive function test scores and socio demographic data and illness characteristics were explored. There were no significant associations between any of the cognitive function tests with gender,

TABLE 1. Summary of socio demographic variables across the two sub-groups of subjects; with motor NSS and without motor NSS

Socio demographic	Categories	Total subjects (*n*=80)	Subjects with motor NSS (*n*= 55)	Subjects without motor NSS (*n*=25)	Chi Square	*p* value
Age = 28.5(13)						
Gender	Male	55	36	19	.89	0.35
	Female	25	19	6		
Marital status	Single	55	41	14	5.82	0.06
	Married	22	11	11		
	Divorced	3	3	0		
Ethnic group	Malay	39	26	13	6.82	0.03*
	Chinese	29	24	5		
	Indian	12	5	7		
Educational level	Primary	1	0	1	8.40	0.02*
	Secondary	55	43	12		
	Tertiary	24	12	12		
Employment status	Unemployed	20	17	3	3.28	0.07
	Employed	60	38	22		

* Spearman correlation with significant level at $p< 0.05$ # Median in years (IQR) IQR= inter-quartile range

TABLE 2. Summary of clinical variables across the two sub-groups of subject; with motor NSS and without motor NSS

Clinical profile	Motor NSS						Mann-Whitney U	*p*-value
	Present			Not present				
	N	Mean rank	Median IQR	N	Mean rank	Median IQR		
Age of onset of psychosis	55	38.0	20+/- 5	25	46.0	21+/-11	550.0	0.15
Duration of illness	55	43.8	10+/- 9	25	33.3	7+/-7.5	508.5	0.06
Duration of untreated psychosis	55	39.7	8+/- 12	25	42.3	12+/-12	643.5	0.64
Number of hospitalisation	55	39.7	2+/- 2	25	42.3	3+/- 3	643.0	0.64
Number of relapse	52	35.1	3+/- 3	18	36.6	3.5+/-7	448.0	0.78
MMSE score	55	39.7	30+/- 1	25	42.2	30+/- 1	644.0	0.61

*significant level at $p< 0.05$ IQR= inter-quartile range MMSE= mini mental state examination

marital status, age of onset of psychosis, type of anti-psychotic used and BPRS score (p value>0.05). In terms of the age of subjects, none of the cognitive tests score were associated with age except DB. Both DF and DB were associated with ethnic group and they were statistically significant, F(78)=6.58, p valued (2-tailed)=0.02 and F(78)=7.00, p value(2-tailed)=0.002, respectively and also with employment status, DB (p=0.006) and DF (p=0.041). For duration of illness factor, again only DF and DB were statistically significant (r=-375, p=0.001) and (r=-.355, p=0.01), respectively. Level of education was associated significantly with all of the cognitive tests except verbal fluency (p>0.05); for DF (p=0.04) DB (p=0.025), TMA (p=0.014) and B (p=0.025). It was very interesting to note that only verbal fluency score was not statistically associated with any of the demographic or illness characteristic.

There were differences in the performance of cognitive function tests between these two groups of subjects; with motor NSS and without NSS. As shown in Table 3, BMS scores were significantly correlated with all the cognitive tests except TMA. DF, DB and VF. Only verbal fluency had a moderate r value which was more than 0.5. The score for TMB was positively correlated with the BMS score. The relationship was rather weak but highly significant.

From the correlation matrix shown in Table 4, VF was the only test that was significantly correlated with all the other four tests. The correlation was highly significant with all but TMA.

DISCUSSION

Replicating previous studies which consistently documented a higher prevalence of neurological signs among patients

TABLE 3. Bivariate analysis between cognitive function tests and the score of brief motor scale (BMS)

	Cognitive functions	Spearman rho R	*p*-value
BMS score	Digit span (F)	-.37	0.001*
	Digit span (B)	-.34	0.002*
	Verbal fluency	-.58	0.001*
	Trail making A	.13	0.25
	Trail making B	.31	0.005*

*level of significance at $p< 0.05$

TABLE 4. The correlation matrix of the 5 cognitive function tests used in the study

Cognitive function tests	Digit span (F)	Digit span (B)	Verbal fluency	Trail making A	Trail making B
	R *p*-value	R *p*-value	R *p*-value	R *p*-value	R *p*-value
Digit span (F)		**.71** .001*	**.32** .004*	-.13 .237	-.15 .182
Digit span (B)			**.25** .001*	-.14 .219	**-.33** .003*
Verbal fluency				**-.23** .042*	**-.36** .001*
Trail making A					**.58** .001*

*level of significance at $p< 0.05$

with schizophrenia (Chan & Gottesman 2008; Dazzan et al. 2008), this study found that the frequency of patients with schizophrenia who attended the outpatient clinic who had NSS was 68.8%. This is the first local study on NSS and the first study in which the subjects were from different ethnic groups. Only a few studies have examined the role of ethnicity: Buchanan and Heinrichs (1989) have found that both African American controls and patients showed more neurological impairment than Caucasians. In another study, non-Caucasians (including African American and other races) had more neurological abnormalities. No clear explanations were given for the differences and it was postulated as being due to the different social classes that the races were in. Among non-western population, NSS in schizophrenia has been studied in Chinese (Chen et al. 2001) and African populations (Gureje 1988).

In this study, there is an association between BMS score and ethnic groups; Chinese and Indians but not with Malays. Indians had a lower BMS score in comparison with non-Indian subjects whereas the Chinese subjects demonstrated higher BMS score when compared with the non-Chinese group. When comparing the racial distribution in the group with NSS, Chinese had a higher ratio of subjects with motor NSS than Malays and Indians. For Indians, the number of subject without motor NSS exceeded the ones with motor NSS. It is very interesting to suggest that the difference exists because Indians could be considered Caucasian, whilst Chinese and Malays are considered as Mongoloid (Tan 1972). Most of the Malaysian Indians are originally from the southern part of India and could be identified as Dravidian. Biologically both the north (Aryan) and south Indians (Dravidian) are of the same Caucasian race but separated by culture, languages and certain physical traits. Caucasian healthy individuals have been reported previously as showing lower NSS rates than other races; Mongoloid and Negroid (Buchanan & Heinrichs 1989). However, in this finding, the relationship between motor NSS and ethnic groups could be a confounding interaction. The three ethnic groups were comparable except the age of onset of psychosis and the performance in digit span forward and backward. The social class of the patients and their family could be a confounding factor for the positive association between ethnic groups and motor NSS and it was not measured in this study.

There is a significant difference between the median score of BMS in the subjects with lower education as compared with the ones who completed higher education. The impairment of cognitive functions could be the actual explanation as most of the domains of cognitive function assessed in this study were correlated well with motor NSS. Low social economic class, which was not measured in this study, could also explain both the presence of motor NSS and the lower achievement in education.

There was a lower degree of motor NSS with increasing age of onset. However, if we compare the group with motor NSS and the group without motor NSS, the age of

onset did not differ. The findings from previous studies are conflicting as well. In the recent study comparing the neurological soft signs among schizophrenia patient with onset in childhood, adolescence and adulthood (Biwas et al. 2007), NSS were seen in all subjects with childhood onset, 90% in adolescence onset and 55% in adult onset schizophrenia. The authors suggested that the high prevalence of NSS in the paediatric onset schizophrenia was due to early cerebral insult that led to diffuse cerebral damage, which manifested as NSS. In this study, 3 out of 80 subjects had the illness at the age of 14 or below and all of them were identified as having motor NSS. However, the status on the early cerebral insult cannot be confirmed.

The score of BMS increase proportionately as the duration of illness increases. When the subjects in this study were grouped into positive motor NSS and negative motor NSS and were compared with respect to duration of illness, no significant difference emerged. Chen at al. (1996) who studied Chinese subjects in Hong Kong found that there was a significant tendency for groups with longer duration of illness to have higher NSS score. However, the result of their study became insignificant when age and education were taken into account. In their review, Bombin et. al. (2005) found that the majority of studies have failed to find correlations between neurological impairment and illness duration.

Comprehensive neuropsychological testing of all relevant cognitive domains requires several hours to be completed. It was not feasible in this study due to limited time and resources. Furthermore, the comprehensive batteries were not practical to be done as a bedside test or to be used during clinic follow up. The 5 tests chosen (trail making A and B, verbal fluency and digit span forward and backward) to assess working memory and executive function were quick and simple tests.

The motor NSS was correlated with all cognitive tests except TMA. However, the effect size for each of the correlation except verbal fluency is rather weak. Evidence from longitudinal studies showed that cognitive impairment and NSS share similar course as both present much earlier than the onset of illness, both are persistently present throughout the illness and become more noticeable during old age (Dazzan et al. 2008). This similar pattern of progression suggests that both cognitive deficit and NSS may share the same underlying pathophysiology. Cognitive impairment and NSS are partially independent phenomenon which may be indirectly related.

In normal individuals, recall of a particular word is dependent on both its associative strength and the number of associative links within its associative network (Lezak et al. 2004). Organization of words at recall reflects the strategies used by the person during the encoding process. Patients with schizophrenia fail to spontaneously use semantic categorization strategies during the encoding process. 25% of subjects have impaired verbal fluency who failed to generate more than 30 words for the 3 categories within 1 min duration for each of the categories. This finding replicates many of the previous studies (Chan & Chen 2004). It could easily be observed that the subjects did not use any form of association in helping them come out with more words. Most of the reviewed studies suggest that there is no loss of semantic information storage but rather poor storing process or loss of access to verbal information, which may account for impairment in verbal fluency in schizophrenia (Chan & Chen 2005).

Studies have reported that if the material is pre-organized or if patients were given enough time to organize material during encoding, patients do eventually produce the same total number of words as controls (Thanker & Carpenter 2007). This suggests that the deficit is not due to a reduction in knowledge but rather the idea that the deficit is due to impairment in accessing or retrieving information from the semantic system. Even though the patients had an inability to associate the words they had said earlier to generate more answers; majority of them rarely mentioned the same word twice. The subjects clearly remembered the words which had have been mentioned, but were unable to use that particular word as a cue to generate more words. Whether these patterns reflect a disorganization of the storage of items or specific deficits in the retrieval process of items in semantic memory require further investigation. The observation indicates that the subjects' recent memory is functioning relatively well, as they remember the words that they had just mentioned and their MMSE scores were within normal range.

The interesting finding from this study is that in comparison with other cognitive tests used, only verbal fluency was not statistically associated with any socio demographic or illness variables. One explanation is that some of the non-significant differences which have been reported may be type II (false negative) errors. On the other hand, it could also indicate the true relationship between motor NSS and verbal fluency. It is possible that both motor NSS and verbal fluency involve complex systems (rather than single brain sites) and that the correlation reflects a partial overlap between the neural mechanisms of motor NSS and verbal fluency.

The association between verbal fluency and motor NSS might reflect the fact that patients with cognitive problems could have difficulties understanding and follow instructions during the examination of NSS. However, it was unlikely that this alone could explain much of the common variance (about 50%). The conduct of the items was shown by the same researcher and for each task; an explanation was given together with a number of trials to ensure that the patient's understanding was optimum.

The finding from this study further substantiate the evidences indicating that neurological abnormalities are prevalent amongst patients with schizophrenia and that it occurs across cultures and could represent a valid and reliable indicator of brain damage or dysfunction as suggested by Bombin et al. (2005). Both cognitive impairment and NSS represent subtle brain damage in patients with schizophrenia, which is in keeping with the model of schizotaxia described by Meehl (1990) much earlier. The combination of both motor NSS and

verbal fluency could serve as a genetic vulnerability to schizophrenia and fit nicely into the schizotaxia model.

There are several limitations in this study. The cross-sectional study was design without a normal comparison group; with possibility of assessor bias and measurement bias and the fact that the sample is hospital based, requires the findings to be interpreted cautiously and may limit the extent to which these result can be generalised. A prospective study is highly recommended in view of the need to determine the causal relationship between soft signs and verbal fluency and other clinical factors that are not measured yet. The stability of the neurological soft signs could also be assessed by adopting a longitudinal design. The comparison with control groups such as other psychiatric diagnosis, patients' relatives (who are free from schizophrenia) and normal control group would be the ideal study design to assess NSS's heritability and their potential as a genetic marker.

The inclusion of more comprehensive and validated instrument such as PANSS, Neurological Rating Scale for EPSE and more comprehensive cognitive batteries are recommended for future study. The assessment of cognitive function should be done by another person who is blinded to the status of BMS score and the clinical factors. The balance between comprehensiveness and the practicality of the tests chosen should be look into. At the end of the day, as a clinician, we need a simple test which we could do at the bed side and more importantly the tests are not very long until the patient unable to proceed.

The next step is to further clarify the association between motor NSS and verbal fluency and its' significance. The prospective longitudinal cohort study of first episode psychosis patients would give us some answer regarding the stability of these two variables. If the combination of motor NSS and impaired verbal fluency is shown to be a viable marker for functional outcome in the future studies, it is very important for the treating team to identify such individuals early. Knowing the status of their neurological soft signs could help us in planning rehabilitation programmes to compensate for the deficits and to have a more realistic expectation for them.

To conclude, there is a high frequency (68.8%) of patients with schizophrenia, attending outpatient clinic at UKMMC who have motor neurological soft signs. There were associations between motor NSS with ethnic groups, education level, age of onset of psychosis and duration of illness, digit span backward, trail making A and B and verbal fluency were all significantly correlated with motor NSS.

The assessment of motor NSS represents a brief, inexpensive and meaningful tool in clinical psychiatry and together with verbal fluency; the two have the potential to be a genetic marker for schizophrenia. The knowledge on NSS, especially motor NSS could become a link between neurobiological research and clinical practice. There are so many unanswered questions regarding neurological soft sign and the uncertainties remain. The one thing that is certain about these signs is that it is a misnomer as these signs are not as 'soft' as what we label them to be.

REFERENCES

American Psychiatric Association. 2000. *Diagnostic and Statistical Manual of Mental Disorders-Text Revision (DSM-IV-TR)*. 4th ed. Washington DC: American Psychiatric Association.

Arango, C., Bartko, J.J., Gold, J.M. & Buchanan, R.W. 1999. Prediction of neuropsychological performance by neurological signs in schizophrenia. *Am. J. Psychiatry* 156: 1349-1357.

Biwas, P., Malhotra, S., Malhotra, A. & Gupta, N. 2007. Comparitive study of neurological soft signs in schizophrenia with onset in childhood, adolescence and adulthood. *Acta Psychiatr. Scand*. 115: 295-303.

Bombin, I., Arango, C. & Buchanan, R.W. 2005. Significance and meaning of neurological signs in schizophrenia: Two decades later. *Schizophr. Bull*. 31: 962-977.

Buchanan, R.W. & Heinrichs, D.W. 1989. The neurological evaluation scale (NES): A structured instrument for the assessment of neurological signs in schizophrenia. *Psychiatry, Res*. 27 : 335-350.

Buchanan, R.W., Kirkpatrick, B., Heinrichs, D.W. & Carpenter, W.T. Jr. 1990. Clinical correlates of the deficit syndrome of schizophrenia. *Am. J. Psychiat*. 147: 290-294.

Chan, R.C.K. & Chen, E.Y.H. 2004. Executive dysfunctions and neurological manifestations in Schizophrenia. *Hong Kong J. Psychiatry* 14(3): 2-6.

Chan, R.C.K. & Chen, E.Y.H. 2004. Development of a Chinese verbal fluency test for the Hong Kong psychiatric setting. *Hong Kong J. Psychiatry* 14(2): 8-11.

Chan, R.C.K. & Chen, E.Y.H. 2005. Assessment of executive function for schizophrenia in Hong Kong. *Hong Kong J. Psychiatry* 15: 23-28.

Chan, R.C.K. & Gottesman, I.I. 2008. Neurological soft signs as candidate endophenotypes for schizophrenia: A shooting star or a Northern star? *Neuroscience and Biobehavioral Reviews* 32: 957-971.

Chen, E.Y.H., Lam, L.C.W., Chen, R.Y.L. & Nguyen, D.G.H. 1996. Neurological Signs, Age, and Illness Duration in Schizophrenia. *J. Nerv. Ment. Dis*. 184: 339-345.

Chen, E.Y.H., Lam, L.C.W., Chen, R.Y.L., Nguyen, D.G.H., Kwok, C.L. & Au, J.W.Y. 2001. Neurological signs and sustained attention impairment in schizopherenia. *Eur. Arch. Psychiatry. ClinNeurosci*. 251: 1-5.

Dazzan, P., Lloyd, T., Morgan, K.D., Zanelli, J., Morgan, C., Orr, K., Hutchinson, G., Fearon, P., Allin, M., Rifkin, L., McGuire, P.K., Doody, G.A., Holloway, J., Leff, J., Harrison, G., Jones, P.B. & Murray, R.M. 2008. Neurological abnormalities and cognitive ability in first episode psychosis. *The British Journal of Psychiatry* 193: 197-220.

Folstein, M.F., Folstein, S. & Mc Hugh, P.R. 1975. Mini-mental state: A practical method for grading the cognitive state of patients for the clinician. *J. Psychiatry Res*.12: 189-192.

Gureje, O. 1998. Neurological soft signs in Nigerian schizophrenics: A controlled study. *Acta Psychiat. Scand*. 78: 505-509.

Heinrichs, D.W. & Buchanan, R.W. 1988. Significance and meaning of neurological signs in schizophrenia. *Am. J. Psychiat*. 145: 11-18.

Jahn, T., Hubmann, W., Karr, M., Schlenker, R., Heidenreich, T., Cohen, R. & Schröder, J. 2006. Motoric neurological soft signs and psychopathological symptoms in schizophrenic psychoses. *Psychiatry Research* 142(2-3): 191-199.

Jahn, T., Cohen, R., Hubmann, W., Mohr, F., Köhler, I., Schlenker, R., Niethammer, R. & Schröder, J. 2006. The brief motor scale (BMS) for the assessment of motor soft signs in schizophrenic psychoses and other psychiatric disorders. *Psychiatry Research* 142(2-3): 177-189.

Kay, S.R., Opler, L.A. & Lindenmeyer, J. 1988. Reliability and validity of positive and negative symptom scale for schizophrenics. *Psychiatry Res*. 23: 99-110.

Lezak, M.D., Howieson, D.B. & Loving, D.W. 2004. *Neuropsychological Assessment*. 4th ed. New York: Oxford University Press.

Meehl, P.E. 1990. Towards an intergrated theory of schizotaxia, schizotypy and schizophrenia. *Journal of Personality Disorder* 4: 1-99.

Mohr, F., Hubmann, W., Albus, M., Franz, U., Hecht, S., Scherer, J., Binder, J. & Sobizack, N. 2003. Neurological soft signs and neuropsychological performance in patients with first episode schizophrenia. *Psychiat Res*. 121: 21-30.

Naing, L., Winn, T. & Rusli, B.N. 2006. Practical issues in calculating the sample size for prevalence studies. *Archives of Orofacial Science* 1: 9-14.

National Institute of Mental Health. 1976. Abnormal involuntary movement scale (AIMS). In: Guy, W. (ed.). *ECDEU: Assessment Manual for Psychopharmacology Department of Health, Education and Welfare*. pp. 534-7.

Normala, I. 2005. Factors associated with neurocognitive impairment in Bipolar Disorder Patients: A case control study in psychiatric clinic of Hospital Universiti Kebangsaan Malaysia (HUKM). Master in Psychiatry, Universiti Kebangsaan Malaysia (unpublished).

Sanders, R.D., Keshavan, M.S., Forman, S.D., Pieri, J.N., McLaughlin, N., Allen, D.N., van Kammen, D.P. & Goldstein, G. 2000. Factor structure of neurologic examination abnormalities in unmedicated schizophrenia. *Psychiat. Res*. 95: 37-243.

Sheehan, D., Lecrubier, Y. & Sheehan, K. 1998. The mini international neuropsychiatric interview (MINI): The development and validation of a structured diagnostic psychiatric interview for DSM IV and ICD 10. *Journal Clinical Psychiatry* 59: 22-23.

Tan, E.S. 1972. Prospects of psychiatric research in a multiracial developing community: West Malaysia. In: *Transcultural Research in Mental Health: Vol. II of Mental Health Research in Asia and the Pacific*. Honolulu: The University Press of Hawai.

Thanker, G.K. & Carpenter, W.T. 2007. *The Year in Schizophrenia*. United Kingdom: Atlas Medical Publishing.

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