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Neurological soft signs in schizophrenia: gender differences and promising suggestions

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Summary

Objective
Neurological soft signs in schizophrenia have been widely discussed, and have been of great interest to many psychiatrists and neuroscientists. Clinical gender differences have been widely detected in schizophrenia, and soft sign studies might help us relate these clinical differences to neurological abnormalities. Our aim was to look for gender differences in "developmental reflexes" soft signs in schizophrenia.

Methods
Fifty patients with schizophrenia and 50 healthy individuals were enrolled in this study. The Neurological Evaluation Scale was used in order to assess for all soft signs in normal subjects and in schizophrenia patients.

Results
Schizophrenia subjects scored significantly higher than normal subjects in terms of the total NSS score. Male schizophrenia subjects scored significantly higher than female schizophrenia subjects in terms of the glabellar reflex score, and total NSS score of all soft signs.

Conclusions
Gender differences in the glabellar reflex might suggest differences in the etiology of the illness between the genders. We think that these differences might involve the basal ganglia. Future studies involving larger samples might confirm these differences.

Key words
Schizophrenia • Glabellar reflex • Neurological evaluation scale • Neurological soft sign • Basal ganglia

Introduction
Defined as "non-localizing abnormalities without diagnostic specificity" [1], neurological soft signs (NSS) represent a tool that is independent of the disorder's core signs and symptoms. However, they reflect significant notions regarding the disorder's developmental etiology.

Many studies have focused on comparing three sets of NSS scores: those of patients, those of their normal first degree relatives, and those of normal non relative subjects. In fact, most of these studies showed that patients had the highest NSS scores among the three sets, and the first degree relatives, although normal, showed scores that were lower in number than those of patients but higher than those of the normal non-related subjects [2]. This has suggested a genetic, developmental etiology governing schizophrenia.

A wide variety of other studies has shown the abundance of gender differences in schizophrenia. These studies showed males having the disorder more commonly than females, with a slight difference in prevalence [3].

Males showed a peak at early adulthood, while females presented two peaks: the first slightly later than that of males, and the second around

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menopause. Another study conducted by Lane et al. showed that males, whose mothers suffered from obstetric complications, had higher NSS scores, while females showing high NSS scores had a family history of schizophrenia. However the study didn't discuss any differences in NSS subscores between the sexes [4]. Furthermore, differences in function and severity were also assessed, with males showing a lower functioning ability prior to their first psychotic break, suggesting the earlier appearance of abnormalities in males than in females [5]. Finally, women with schizophrenia tended to continue to have better outcomes than males regarding their social functioning [5-7]. In fact these clinical differences need to be explained neurologically, and we think that NSS studies might help us define the targets and the aims of future neurological studies.

From a metabolic perspective, the metabolic activity of the caudate nucleus has been studied in schizophrenia, with the results showing an abnormal metabolism within the basal ganglia in schizophrenia, with the most severe abnormality being reported in patients with developmental reflexes. These patients showed an earlier age of psychosis' onset [8].

Our study aims at assessing whether gender differences in "Developmental Reflexes" soft signs do exist in schizophrenia.

Methods

Study design and sample

The study was performed between January 2014 and May 2014, on patients diagnosed with schizophrenia at the Psychiatric Hospital of the Cross (HPC)-Lebanon, the oldest and largest psychiatric institution in Lebanon and the Middle East, and on normal subjects. Normal subjects were chosen randomly from the general population. A total of 100 participants, 50 patients and 50 controls, were enrolled in the study. In addition, patients' demographic and clinical data were collected from patient reports saved at HPC. Patients were diagnosed with schizophrenia according to DSM-IV by psychiatrists of the hospital. Patients with mental retardation, any acute or chronic medical disease, schizoaffective disorder, substance abuse, or patients who have undergone electro-convulsive therapy (ECT) in the previous 6 months, were excluded from the study. Normal subjects with any mental retardation, medical condition, or substance abuse were also excluded. Both samples were matched for sex and age. Males and females were also matched for age, duration of illness and neuroleptic dose. Written informed consent was obtained from all participants before the study was initiated. The study received the approval from the institutional review board of the hospital.

Tools

Patients' demographic characteristics and medical history were collected from the patient files. All subjects' neurological soft signs were examined by a senior psychiatrist at the hospital. The neurological evaluation scale (NES) [9] was used for this purpose. NES is a structured scale which includes 26 items in four subscales (motor coordination, sensory integration, sequencing of complex motor acts and others). Each item is rated on a scale of 0-2 (0 = relatively normal, 1 = some disruption, 2 = major disruption). The motor coordination subscale includes information about tandem walk, rapid alternating movements, finger-thumb opposition and the finger-to-nose test. The sensory integration subscale includes information about audiovisual integration, stereognosis, graphesthesia, extinction and right/left confusion. Sequencing of motor acts investigates the fist-ring test, the fist-edge-palm test, the Ozeretski test and rhythm-tapping test B. Others include adventitious overflow, the Romberg test, tremor, memory, mirror movements, rhythm tapping test A, synkinesis, convergence, gaze impersistence, glabellar reflex, snout reflex, grasp reflex and sucking reflex (Buchanan & Heinrichs, 1989).

We created a total of all soft signs by adding all the score of all the signs (walk, Romberg, overflow, tremor, audiovisual, stereogenesis, graphestesia, FR, FEP, Ozeretski, memory, rhythm A, rhythm B, RAM, FT opposition, mirror, extinction, RL confusion, synkinesis, convergence, gaze, finger, glabellar, snout, grasp, suck).

Chlorpromazine equivalents of the neuroleptic medication that the patients were taking at the time of the study were calculated based on the method of Andreasen et al. [10].

Statistical analysis

Data analysis was performed on SPSS software, version 22. Two sided statistical tests were used; Chi-2 and the Fischer's exact tests for dichotomous or multinomial qualitative variables and student's t test for quantitative variables of normal distribution and homogeneous variances. A p-value of less than 0.05 was considered as statistically significant.

Results

Socio-demographic characteristics

Fifty-two percent of the normal subjects were females versus 58% in the schizophrenia group. Half of the non-schizophrenia patients were aged between 41-50 years, compared to 40% aged between 41-50 years in the schizophrenia group (Table I). All patients were clinically stable.

Table II displays the gender differences in the duration of illness and the total daily dose of chlorpromazine equivalent in patients with schizophrenia. The results

TABLE I. *Sociodemographic characteristics of the participants.*

Factor	Non schizophrenia	Schizophrenia	p-value
Gender			0.546
Male	24 (48%)	24 (48%)	
Female	26 (52%)	26 (52%)	
Age in years			0.528
20-30	5 (10%)	3 (6%)	
31-40	15 (30%)	19 (38%)	
41-50	25 (50%)	20 (40%)	
51-60	(10%)	8 (16%)	

showed that there were no significant gender difference in the duration of illness (p = 0.27) or in the total daily dose of medication doses (1041 ± 544 *vs* 1450 ± 1175; df = 35.85; p = 0.118).

Regarding the glabellar reflex, a significantly higher percentage of males having four or five blinks or more than six partial blinks and those with 6 or more full blinks (87.5% and 88.9%) as compared to females (12.5% and 11.1%) in the schizophrenia group (p = 0.001). In addition, there was a significant difference for the glabellar reflex and the snout sign between persons with schizophrenia versus those without schizophrenia in favor of those with schizophrenia (p = 0.006 and p = 0.025). As for the suck sign, a significant difference was found between patients with schizophrenia compared to those without schizophrenia (32% *vs* 10%) (Table III).

Discussion

In the present study our male schizophrenia patients scored higher than females in terms of the glabellar reflex soft sign.

We used the Neurological Evaluation Scale [9] for the NSS calculation, which has been used in many previous studies. Our results were in line with those of other studies. Any possible involvement of neuroleptic medication effects can be excluded since to many studies succeeded in proving the absence of any effect on soft signs the medication might have [11 12]. One previous study has succeeded in associating the increase in male schizophrenia soft sign scores with obstetric complications, and the increase in female schizophrenia score with genetic history [4]. However, the study didn't discuss any gender difference in the soft sign scores themselves.

The caudate nucleus was shown to play roles in emotion control and decision control [9 13], which are both known to be abnormal in schizophrenia [14]. Another study has suggested that striatal-cortical dysconnectivity may underlie the effects of dopamine dysregulation on the pathophysiologic mechanism of psychotic symptoms [15]. Therefore we think that the glabellar reflex soft sign, which is at least in part controlled by the caudate [16] might suggest a difference in brain pathology between the genders, that might involve the caudate. This needs to be confirmed by future studies. We think that focusing on the caudate and other basal ganglia must be the first step towards understanding the possible gender differences characterizing schizophrenia. However other brain structures might govern those gender differences, like the prefrontal cortex, brainstem or the limbic system. In schizophrenia, higher NSS were associated with reduced cortical thickness and LGI in fronto-temporo-parietal brain areas [17]. We presume that detecting those brain differences can explain the clinical gender differences governing schizophrenia, and can go further towards a new gender based classification. Any classification that is based on solid scientific facts will ultimately enhance the diagnosis and the treatment of schizophre-

TABLE II. *Gender differences for the duration of illness and the daily dose of chlorpromazine equivalent in patients with schizophrenia.*

		Gender		
		Female	Male	
		Frequency (%)	Frequency (%)	p-value
Duration of illness in years	< 10	10 (41.7%)	5 (19.2%)	0.270
	10-20	7 (29.2%)	14 (53.8%)	
	20-30	6 (25.0%)	6 (23.1%)	
	30-40	1 (4.2%)	1 (3.8%)	
		Mean ± SD	**Mean ± SD**	
Daily dose of chlorpromazine equivalent		1041 ± 544	1450 ± 1175	0.118

TABLE III. *Differences in developmental reflex scores between the genders.*

	Subjects without schizophrenia			Patients with schizophrenia			P-value		
	Female	Male	Total	Female	Male	Total	Males *vs* females in the non schizophrenia group	Males *vs* females in the schizophrenia group	Non-schizophrenia *vs* schizophrenia group
Glabellar									
Three or fewer blinks	23 (52.3%)	21 (47.7%)	44 (88.0%)	22 (66.7%)	11 (33.3%)	33 (66.0%)	0.221	0.001	0.025
Four or five full blinks or more than six partial blinks	3 (75.0%)	1 (25.0%)	4 (8.0%)	1 (12.5%)	7 (87.5%)	8 (16.0%)			
Six or more full blinks	0 (0.0%)	2 (100.0%)	2 (4.0%)	1 (11.1%)	8 (88.9%)	9 (18.0%)			
Snout									
No contraction	26 (52.0%)	24 (48.0%)	50 (100.0%)	21 (48.8%)	22 (51.2%)	43 (86.0%)	N/A	0.769	0.006
Any contraction	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (42.9%)	4 (57.1%)	7 (14.0%)			
Grasp									
No flexion of fingers	25 (51.0%)	24 (49.0%)	49 (98.0%)	23 (52.3%)	21 (47.7%)	44 (88.0%)	0.332	0.134	0.131
Mild flexion	1 (100.0%)	0 (0.0%)	1 (2.0%)	0 (0.0%)	4 (100.0%)	4 (8.0%)			
Marked flexion	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (50.0%)	1 (50.0%)	2 (4.0%)			
Suck									
No movement	23 (51.1%)	22 (48.9%)	45 (90.0%)	14 (41.2%)	20 (58.8%)	34 (68.0%)	0.706	0.159	0.007
Any sucking or pursing	3 (60.0%)	2 (40.0%)	5 (10.0%)	10 (62.5%)	6 (37.5%)	16 (32.0%)			
Total score	1.80 ± 3.46	1.00 ± 2.22	1.42 ± 2.93	16.29 ± 6.70	15.84 ± 7.85	16.06 ± 7.25	0.329	0.830	< 0.001

nia. For example, if male schizophrenia was shown to be basal ganglia related, medications that target the basal ganglia must be the mere focus when treating a male schizophrenia patient.

Although it has been shown by many studies that NSSs are not affected by antipsychotic medication [12 18], we thought that when comparing a single soft sign between two groups, it would be mandatory to show that the two samples match for medication doses. Nevertheless neuroleptic medication might affect the severity of a neurological soft sign. In fact, no significant difference in chlorpromazine equivalent doses was found between genders. Although we couldn't compute the year-dose equivalents of patients, we think that the glabellar reflex gender difference is independent of how long each patient has been on a certain dose, because all the patients of our study were chronic schizophrenia patients who have been on constant doses of neuroleptics for a relatively long period of time. In addition to medication doses, both males and females were matched for age and duration of illness for there were no significant statistical differences in these parameters between the two samples.

Limitations

Being a hospital-based observational study, there are some possible limitations, mainly the influence of the environment on the mood of the patients and consequently on their performance. A selection bias is possible since the patients were recruited from one psychiatric hospital. In addition, our inability to compare daily Chlorpromazine doses between the genders would be another limitation.

Conclusions

Until recently, many clinical gender differences characterizing schizophrenia remain neurologically unexplained. The difference in glabellar reflex that we detected might be valuable, and its etiology might be confirmed through accurate imaging methods, like Magnetic Resonance Imaging or Functional Magnetic Resonance Imaging, which we think is valuable. We believe that gender differences might improve our understanding of schizophrenia, and might translate into a clinical classification of "male schizophrenia" versus "female schizophrenia" in the future.

Competing interests

The authors declare that they have no conflicts of interest to disclose.

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