Review Article

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Neurological Soft Signs in Schizophrenia

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Abstract

Neurological Soft Signs (NSS) are postulated to reflect functional disorders in selective areas of the brain. Studies have reported that during the first schizophrenia episode higher total rates of NSS and motor problems are already present. Schizophrenia patients and first degree relatives have more NSS compared to patients with other psychiatric disorders and healthy controls. Whether NSS have a developmental origin or result from some early acquired lesion remains to be decided. Genetic cause of NSS is suggested by studies that indicate that NSS is increased in patients with a positive family history as well as in unaffected first degree relatives of schizophrenia patients. A relationship between NSS and different subtypes of schizophrenia has been observed. Studies indicate that NSS are associated with a more serious clinical course, escalated cognitive dysfunction and unsatisfactory psychosocial outcome has been reported.

Keywords: Neurological Soft Signs; Schizophrenia; Brain Disorder; Genes.

Introduction

"Neurological Soft Signs (NSS)" or "Soft Neurological Signs (SNS)" in schizophrenia have been reported since the 19th century [1]. NSS probably indicate the presence of functional disorders in some brain areas and not diffuse brain dysfunction [2]. The term "Soft Neurological Signs"(SNS) was introduced by Bender who conceptualized it as a "developmental lag", akin to organic signs found in psychiatric disorder in the aged, and defined SNS as follows: SNS is not due to any postnatal neurological insult that may leave residual neurological signs e.g. severe head injury, intoxication, infection or tumor. Grouping of SNS found in an individual should not have a pathognomonic pattern of a kind that would indicate one or more clearly localized structural lesions, generalized encephalopathy or CNS involvement [3]. Subsequent studies supported the idea that NSS may be related to a specific deficit in the function or anatomical regions of the brain[4,5]. NSS are mild, non-localizing, neurological signs that are identified from deficits in performance in domains such as sensory integration, motor coordination, and motor sequencing. At the beginning of the initial episode of schizophrenia both medicated and treatment-naïve patients exhibit elevated rates of NSS and motor abnormalities [6,7]. In addition individuals at high risk for schizophrenia have elevated rates of NSS as compared to controls. [8] NSS have also been detected in other psychiatric disorders like OCD, though rates of NSS are significantly higher in patients with schizophrenia [9].

Neurological abnormalities are traditionally classified as "hard signs" (impairments in basic sensory, motor and reflex behaviors not seen in schizophrenia)and "soft signs". (complex phenomena of aberrations in motor activity,

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integrative sensory functions, sensorimotor integration, and cerebral laterality) [10,11]. Soft signs are traditionally organized into seven categories including: 1) Integrative sensory dysfunction; 2) Motor incoordination; 3) Impaired sequencing of complex motor tasks; 4) Frontal release signs; 5) Abnormal eye movements; 6) Memory impairments; and 7) Cerebral dominance [12].

Over the last five decades numerous studies have reported that patients with schizophrenia and their first degree relatives have significantly more NSS than healthy controls and patients with other psychiatric disorders[13-16]. Prevalence of NSS in schizophrenia range from 50% to 73%, compared with 5% in controls. Positive symptoms tend not to be related to NSS, whereas negative symptoms have been related to soft signs that reflect frontal (motor function) and parietal (sensory integration) functions [13]. Cognitive performance is partially linked with NSS, but is also influenced in a way that soft signs are not by sociodemographic variables such as age, education, sex, and socioeconomic status [13]. NSS have been associated with multiple clinical features of schizophrenia, have been conceptualized as a vulnerability marker for schizophrenia, and may represent a phenotype useful in genetic studies. Although NSS are held to have little localizing value, this is not entirely true; for example, motor perseveration is associated with damage to the dorsolateral prefrontal cortex [17,18] grasp reflex localizes to the frontal lobes, and soft signs have identifiable functional neuroimaging correlates [16,19-20]. However, their value lies more in that their presence indicates dysfunction within the distributed neural networks that underlie complex behaviors [11]. Thus, while most of the primitive reflexes (e.g. palmomental, snout, and glabellar reflexes) are not localizable, they do indicate cortical deterioration or diffuse cerebral dysfunction in patients diagnosed with schizophrenia [21]. NSS may provide valuable prognostic information, as they may be associated with greater psychopathology, [22] more severe cognitive dysfunction, [23] poorer treatment response [24] and a high risk for the occurrence of tardive dyskinesia [21].

Developmental Aspects

Pediatric neurologists widely consider NSS as having a developmental origin. It is supported by the evidence that a higher prevalence of Neurological Abnormalities (NAs) in younger than older children)[25]. These signs follow a maturational curve, which reaches adult level at approximately 8 years in normal individuals [26]. The increase in NAs with age up to 8 years was thought to be the consequence of the maturation of the CNS, as dysfunction can be assessed reliably only when the structure involved has become functionally active. The maturation complete by 9 years [27]. Persistence of these neurological signs after 9 years of age indicates that there has been a "developmental lag" in the process of developing complex integrative function. Testing this hypothesis showed that when children were divided into 2 groups above and below 8 years, proportionately greater number of signs was found in the younger age group [26]. But all children previously shown to be having neurological signs still had neurological signs of one sort or other at follow up[28]. Further, the rate of neurological signs still increased beyond the age of 9 yrs mainly in boys [27].

Another possibility for the origin of NAs is that it results from some early acquired lesion i.e. it represents a feature of brain damage [29]. One study observed a significant excess of low birth weight for gestation among males with NAs at the age of 7 [30]. Another study reported that schizophrenia patients but not their siblings showed significantly more obstetric complications compared to their respective neonatal controls. However there was a lack of significant relationship between NAs and obstetric complications in the patient group, indicating that besides perinatal events there are other determinants of NAs in schizophrenia [31].

A third possibility is that NAs may be a heritable individual difference based on reports of significantly more NAs in the siblings [32] and first degree relatives [15] of schizophrenia patients. These studies indicate a higher rate of NAs characterizing a portion of the offspring's and relatives of schizophrenia patients who are at a higher genetic risk of developing schizophrenia. This is compatible with the view that NSS reflect a familial transmitted alteration in neurological process that constitutes a vulnerability or diathesis to subsequent schizophrenia.

A number of neurological signs have been described as occurring more frequently in children with psychiatric disorders than in normal controls [33-36]. Almost all studies have shown a relationship between presence of these signs and age and I.Q., and for a given age and I.Q. occur more frequently in boys. Many of these signs fail to discriminate between problem and non problem children when such factors are taken into account. However, even after taking account of age, sex, and I.Q, both dysdiadochokinesis and dysgraphaesthesia are more frequently observed in disturbed children [33].

Prevalence of NSS in Psychiatric Illnesses

Hertzig and Birch found that a high population of psychotic patients had abnormal "soft signs". These studies were uncontrolled and did not take account of current drug intake, raters were not blinded, included patients with frank neurological disease, and also listed hyperkinetic behavior as a soft sign [22].

An excess of soft signs was found among patients with schizophrenia and personality disorder, but not in patients with affective disorders in a study of 65 random admissions to 3 adult psychiatric units, with drug free period of 48 hours with 20 staff controls [37]. Another study involved 298 consecutive admissions under age 50, none of whom had organic neurological disease or had been treated previously with ECT, and were drug free for at least 10 days prior to examination.

It was found both the schizophrenia groups, viz. with Premorbid Asociality (adult schizophrenia who had experienced marked personality difficulty in childhood, characteristically being friendless, having academic difficulties and narrow interests) and Emotionally Unstable Character Disorder (characteristically antisocially impulsive, who had frequent but brief non-reactive mood swings), differed from other diagnostic categories in having more of dysdiadochokinesia, agraphaesthesia, mirror movements, finger apraxia, disturbances of speech and gait [38].

Primitive neurological soft signs like grasp, snout and palmomental reflexes are present in a considerable number of older people and in organic and functional psychosis [39]. Higher frequency of neurological signs have been reported in studies in schizophrenic subjects as compared to other psychiatric and non-psychiatric subjects [40,41]. A review reported an average prevalence of 50-60 % neurological abnormalities in schizophrenia patients [13].

Genetic Basis of NSS

An early study showed that schizophrenics with a positive family history manifested significantly more neurological abnormalities than normal controls, and the schizophrenics with no family history were not significantly different from normal or psychiatric controls on any of the measures. The authors hypothesize that schizophrenics with a positive family history constitute a distinct subgroup with genetic contribution greater than the patients without a family history [42].

Schizophrenia patients without positive family history had an excess of primary signs (dysfunction identified by a standard neurological examination, lateralizing limb pyramidal signs and frontal release signs) compared to normal controls. Both the schizophrenic group with positive family history and their first degree relatives showed an increase in integrative signs (depends on integration within the motor and sensory systems or between the motor and sensory systems). These findings indicate that different mechanisms produce the brain dysfunction in familial and sporadic schizophrenia [43].

In 24 schizophrenia patients, 21 of their non-schizophrenic first degree relatives and 29 normal controls, the prevalence of neurologic abnormalities in relatives was congruous to that among schizophrenia subjects but significantly greater than in controls. Based on signs of localizing motor system abnormalities a marked difference was noted between relatives and controls. On the basis of these results the authors suggest that overt schizophrenia may result from the combined operation of two independent familial factors, firstly "psychopathologic" and secondly "neurologic" [32].

NSS was assessed in 58 DSM III schizophrenia patients, their 31 healthy first degree relatives and 38 normal controls by two assessors blind to the diagnoses using a standardized neurological assessment procedure . Schizophrenia patients and their first degree relatives showed more severe NSS than the normal controls indicating that these signs may be the result of a family related pathophysiological process [44]. The lack of family history data for other first degree relatives makes the control of information variance due to illness heterogeneity in terms of genetic loading difficult and the possible influence of medication on NSS cannot be completely ruled out.

Neuroanatomical and Neurotransmitter Abnormalities and NSS

The "cognitive dysmetria" theory explained the diversity of symptoms in schizophrenia by scattered disturbance in the cortico-cerebellar-thalamic-cortical circuit, [45] which may also be related to NSS abnormalities[46]. Though the exact anatomical localization of NSS is yet to be determined, the "network inhibition hypothesis" posits a central role to the interconnections among basal ganglia, cerebellum, cerebral cortex and dopamine neurotransmission which inhibit voluntary movements [47]. 22q11 Deletion syndrome (22q11DS) occurs due to hemizygous microdeletion

on the long arm of chromosome 22. The increased prevalence of NSS in this syndrome is believed to be due to catechol-O-methyltransferase COMT haploinsufficiency, dopamine dysfunction, and white matter abnormalities [48].

Demographic Variables and NSS

Age: Contradictory results have been reported by studies of NSS and age varying from no correlation[49], a negative correlation[50], while one study reported a positive correlation with age [51]. However, most studies fail to give the age range of their patient populations, and it may be the case that the range is too narrow to adequately evaluate or detect an age effect [12].

Sex: Conflicting results are reported by studies of the relationship of sex with NSS. Few studies observed no differences related to gender [49,51] while others reported slightly more [12,22,52] or significantly more [37] neurological impairment in males.

Education: A significant correlation between educational level and soft neurological signs in schizophrenia was demonstrated [44]even after controlling for age and sex [53]. A possible explanation for this relation may be that NSS may be evidence of an early cerebral insult as the resultant CNS dysfunction may lead to poor educational attainment even before the illness. Another argument is that lower education is an index of poor socio-economic status which is more likely to expose these patients to infections and deficiencies in early childhood [53].

Race and Ethnicity: Caucasian patients and controls have lower prevalence of neurological impairment [12,23, 54], and cognitive/perceptual neurological abnormalities [55] compared to African-American patients and controls.

Temporal Stability of NSS

There has been very little attempt to assess the temporal stability of NA across time, with few exceptions, especially in child psychiatry literature. Examination of a group of children for NSS after a few years revealed a reduction in the frequency of NSS in older children, which was attributed to neuronal maturation. However, the number of children with two or more NSS did not differ significantly at the two time points. Stability of positive findings was highest for speech, followed by coordination and double simultaneous stimulation [56]. Since the consistency of signs was directly related to chronological age and maturity, the instability in neurological signs over short term was more likely to occur in the most immature and psychiatrically impaired children [26]. In sub-chronic and chronic schizophrenia patients retested after 2-10 months, 4 out of 6 patients initially equivocal for the presence of neurological signs had demonstrable signs, while 20 out of 24 patients initially positive for presence of neurological signs remained so. However, in acute group, 3 out of 4 patients who had had equivocal signs had no signs of neurological impairment at retesting [57]. Similar findings have been reported by others [21].

No difference in NSS was found in inpatients and outpatients with schizophrenia, groups that would presumably differ in clinical states [52]. A five year follow up study of schizophrenia patients [58] observed a number of neurological abnormalities in patients with a non-remitting course of disease and in patients with genetic predisposition (with obstetric complications). In another study moderate stability of neurological signs from childhood to adolescence has been demonstrated in the offspring of schizophrenic patients [59]. A prospective study comprising of first-episode schizophrenia patients revealed that improvement in motor-related and cortical neurological soft signs at six months, was associated with improvement in psychopathology. However, harder T signs tended to deteriorate [60].

Relation of NSS to Psychiatric Symptoms in Schizophrenia

Till date, several lines of research indicate a relationship between NSS and the pathophysiology of schizophrenia. The base rate of NSS in schizophrenia patients is approximately 60% [12]. As compared to controls higher rates of NSS have been observed in first-episode, [6] as well as both treatment-naive and medicated schizophrenia patients [7] as well as individuals at high risk for schizophrenia (e.g., schizotypal personality disorder)[61]. Furthermore, there is evidence for a genetic component to NSS, as family members of schizophrenia subjects exhibit elevated levels of NSS than matched control subjects [62].

Numerous studies have investigated the relationship between NSS and schizophrenia symptoms with ambiguous results. A relationship of NSS with positive symptoms was reported by one study [63] but not by others [49,64]. Similarly, an association of negative symptoms and NSS was observed in some studies [15,65], but not others. [66-67].

Relationship between NSS and Scores on Rating Scales

Partial correlations, controlling for duration of illness, were used to test the relationships between Baseline NSS ratings and Baseline BPRS subscale scores, and subscale scores after treatment. At Baseline, there were significant positive correlations between levels of NSS and BPRS Positive and BPRS Negative ratings, and a significant negative correlation between NSS and the BPRS Psychological Discomfort subscale scores. The pattern of results after treatment was similar to that at Baseline: there was a significant positive correlation between NSS and BPRS Positive ratings and a significant negative correlation between NSS scores and scores on the BPRS Psychological Discomfort subscale but BPRS Negative Symptoms were not significantly related to NSS [8].

Relation of NSS and Clinical Variables at Different Stages of the Illness

At initial presentation, no significant correlation was found between the levels of neurological soft signs and the levels of positive and negative symptoms, affective symptoms and obsessive compulsive symptoms, or measures of extra-pyramidal signs. The picture is similar upon clinical stabilization following medication .At the end of the first year, a moderate correlation with negative symptoms emerged. A significant correlation of motor coordination NSS with a wider range of negative symptoms was evident by the end of the second year. There were also modest correlations with the global HEN (The High Royd Evaluation of Negativity Scale) [68] score and the negative symptoms subscale scores of the PANSS. By year three, HEN subscales of thought and affect showed significant correlations [69].

Relationship between NSS and the Psychopathology and Course of Schizophrenia

Earlier studies observed a relationship between NSS and different subtypes of schizophrenia, such as chronic v. acute schizophrenia [57]and disorganised v. nondisorganised schizophrenia [70]. NSS were also associated with total number of psychiatric symptoms, [71] thought disorder, [51] negative symptoms [15] and emotional stability [38]. In contrast some studies found no association between NSS and positive symptoms, [49] or paranoid/non-paranoid schizophrenia [52]. Other studies have also characterized similar conflicting results on relationship between NSS and psychopathology in first episode psychosis. Few studies reported an association between NSS and total symptom severity and positive symptoms [63] whereas others found no association with global measures of psychopathology [72] or with positive and negative dimensions of schizophrenia [64]. The discrepant findings could be due to use of different scales for detecting NSS. It has been suggested that the correlation between total NSS and positive symptoms may reflect attentional deficits secondary to untreated symptoms[63].

The association between NSS and a more severe and chronic form of schizophrenia has also been investigated by examining patients at different stages of the illness. This has been supported by the association of NSS with young age at onset, a more chronic course[57], longer index hospitalization [37]and impaired premorbid functioning[38,49]. However, some studies failed to demonstrate an association of NSS with age at onset, poor premorbid functioning, number of hospitalizations in a 3-year follow-up, and lifetime hospitalizations [49,57,71]. A majority of first episode studies have reported no correlation between NSS and age at onset, [58] duration of untre6ted psychosis [58,63], global assessment of functioning [72], and occupational outcome [73]. It is possible that factors such as global assessment of functioning and occupational outcome are worse in more advanced phases of the illness, and are therefore not associated with neurological dysfunction in the early stages. On the other hand, few studies have demonstrated an association between NSS and both poorer premorbid social adjustment [63] and duration of hospitalization [73]. The above mentioned associations may probably be related to the fact that higher rates of NSS are part of a more severe clinical picture, which probably could explain the longer period of hospitalization; it is also possible that this is reflected in longer pharmacological therapy which may give rise to more NSS.

In conclusion, the studies reviewed confirm that an excess of NSS is already evident in patients suffering their first episode of schizophrenia and in high-risk subjects without psychosis. Neurological performance is worse in sensory integration, motor coordination and sequencing, and in developmental reflexes. These NSS are associated with male gender, lower education, and a more severe clinical picture. The NSS are not a consequence of antipsychotic drug use, although first-episode schizophrenia patients on antipsychotic treatment obtain higher NSS scores.

Neurological Soft Signs in Non-Psychotic First-Degree Relatives

In schizophrenia patients, NA are frequently noted but their pathophysiological importance remains

elusive [4,55]. Family studies have consistently demonstrated that nonschizophrenic relatives of probands including parents [44,64], siblings [40], and offspring [59] exhibit increased rates of NAs. A high degree of correlation is seen within families and it has been claimed that the degree of genetic loading for schizophrenia within the family may be a determining factor [40,43,74].

Previous studies of MZ twins discordant for schizophrenia [75-77] indicate that the non-schizophrenic co-twins lie midway between probands and healthy controls in the extent of NAs detected. An association between obstetric complications and NAs in both the probands and their well co-twins [75], and non twin relatives [31] has been reported. Based on the above it was postulated that NAs in schizophrenia reflect the impact of environmental agents in genetically sensitized individuals, and that patients from MZ discordant pairs are subject to greater environmental effect than MZ twins from pairs concordant for schizophrenia [31].

NAs have been divided into primary and integrative subscales. Primary NAs include cranial nerve signs, eye movement abnormalities, lateralizing limb pyramidal neurology and frontal release signs, which are caused by dysfunction that can be detected at routine neurological examination. Integrative NAs reflected dysfunction in the integration of activity within and between the sensory and motor systems, and include dysdiadokokinesia, and the sequencing of complex motor acts, such as the fist-edge-palm test. Primary NAs were elevated in nonfamilial cases of schizophrenia, but not in their well relatives.

In contrast to this, integrative NAs were elevated both in probands and unaffected relatives in families in which multiple members suffered from schizophrenia. In view of the above findings it is believed that environmentally induced neurological damage results in primary NAs, while genetic loading for schizophrenia is the cause of integrative NAs [43].

In accord, most studies have demonstrated that biological relatives of schizophrenia patients have elevated NSS than individuals without an immediate family history [77-79] but some studies reported opposite findings [80]. Additionally NSS severity appears to be graded, with patients showing the most, unaffected controls showing the least, and first degree relatives falling in between[44]. The above findings indicate that the origin of NSS is partly genetic, and that such abnormalities may be intermediate phenotypes, or endophenotypes [81].

Assessment of NSS

The clinical utility of direct examinations is a function of useful information yielded per time spent on the examination. There have been efforts made towards optimizing clinical utility by improving reliability and validity. Undoubtedly, the use of reliable and valid neurologic test items will ensure that the results of a specific test would inform individual cases. Since individual tests have insufficient power, aggregations of items have to be used [82]. However, selecting item aggregations has proved difficult. Few studies treat the neurologic examination as unidimensional, working only if a single summary score documenting the presence or absence of soft signs[83-84]. Others problematically divide items into "hard" and soft) categories [67]. Still others group items based on the effects of lesions acquired after normal brain development. None of these approaches are entirely satisfactory or well supported. Different instruments devised for assessment of NSS are as under:

1. Woods scale [85],
2. Condensed Neurological Examination (CNE) [44],
3. Modified Quantified Neurological Scale (MQNS) [86],
4. Heidelberg Scale [71],
5. Cambridge Neurological Inventory (CNI) [87],
6. Neurological Soft Sign Scale [38],
7. Brief Motor Scale [88],
8. Neurological Evaluation Scale (NES) [4],
9. Extended Standard Neurological Assessment Instrument [40],
10. Short NeurologicalEvaluation Scale (S-NES) [89].

A number of studies have used the NES in samples of patients of schizophrenia. Scores obtained by patients with schizophrenia and their siblings was higher than those of normal controls on the Soft Signs Total, as well as the Sensory Integration and Motor Functioning subscales [40]. Additionally, schizophrenia patients reported higher scores compared to at risk patients, who in turn scored higher than controls on the Soft Signs Total, Sensory Integration, and Other Soft Signs[90]. The Other Soft Signs subscale of the NES correctly classified the maximum number of patients and controls to their true group [23] indicating that the Other Soft Signs subscale is particularly sensitive in identifying individuals with schizophrenia or a proneness to it. The S-NES comprise of 12 empirically determined items of the

NES that showed high agreement with the 26 items in the original NES (sensitivity=96.3%, specificity=100%) [89].

Conclusion

Much debate has centered on the relative contribution of genetic and environmental factors to the etiology of schizophrenia. Review of the literature suggests that NSS are not a consequence of antipsychotic treatment but may imply cerebral dysfunction that needs further investigation, mainly to understand the effect of genetic-environmental contribution to neuro dysfunction in schizophrenia. The base rate of NSS in schizophrenia patients is approximately 60%[12]. NSS in relatives of schizophrenia patients increases with the potential genetic loading [43]. Further, the Total Soft Signs score could be used to distinguish relatives with a genetic vulnerability to schizophrenia from those who were not[63]. The above suggests that the NSS may identify a subject of being a ''gene-carrier'' for psychosis. In contrast, the results of another study suggests that NSS are not an indicator of genetic risk specifically for psychosis[90]. Other causes of NSS may be low birth weight [91] and obstetric complications[31].

NSS have been associated with a worse clinical course of psychosis, poor psychosocial performance, and cognitive dysfunction [38,49,72,92], suggesting a subgroup of patients characterized by a more dire pathophysiological process. Comparison of the prevalence of NSS in patients with psychosis across various studies is confounded by the fact that different scales (some of which may not be published or validated) have been used for assessment of NSS.

Studies conducted till date have several limitations. The presence of significant effect variability in few studies indicate that the average effect sizes may not represent adequately the underlying populations, which may include important subsets of patients. The relationships between NSS and potential moderators like age and duration of illness will need further detailed analysis. NSS are detected in a majority of patients with schizophrenia and are similar to or may even exceed the cognitive, psychophysiological and neuro- anatomic findings as indicators of schizophrenia. Additionally important queries about the illness remain regarding prevalence of specific soft signs, the sources of heterogeneity and effect variability.

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