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Original Research Paper

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NEUROLOGICAL SOFT SIGNS AS CANDIDATE ENDOPHENOTYPES FOR SCHIZOPHRENIA: A MINI-REVIEW

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ABSTRACT Neurological soft signs are non-localizing neurological abnormalities that cannot be related to the impairment of a specific brain region or are not believed to be part of a well-defined neurological syndrome. They were observed in schizophrenia and other psychiatric disorders. Neurological soft signs are here reviewed regarding cannabis use, obstetrics complications, antipsychotic treatments and the potential use of neurological soft signs as candidate endophenotypes for schizophrenia. Neurological soft signs emerge as a potential endophenotype for several disorders rather than a specific endophenotype for schizophrenia. There are no important correlations between neurological soft signs and obstetric correlations and neuroleptic treatment. Cannabis abuse could be associated with the development of neurological soft signs.

KEYWORDS : Neurological Soft Signs, Schizophrenia, Endophenotypes

INTRODUCTION

Neurological soft signs (NSS) are non-localizing neurological abnormalities that cannot be related to impairment of a specific brain region or are not believed to be part of a well-defined neurological syndrome [1,2]. During the past decades, researchers suggested the crucial role of NSS in schizophrenia [3,4,5]. However, NSS is also observed in other psychiatric disorders, including personality and mood disorders [6,7,8].

Recent discussions are suggesting NSS as one of the candidate endophenotypes in schizophrenia [9,10,11,12]. Endophenotypes are defined as trait markers that are present independent of the manifestation of a disease [13]. Researchers have proposed five criteria for candidate endophenotypes. They are an intermediate between genes and signs and symptoms of the disorder. The criteria for defining an endophenotype are a) association with illness in the population; b) heritability; c) state independence; d) familial association; e) co-segregation within families [10,14,15,16].

Several studies have found a positive relationship between NSS and schizophrenic symptoms. In general, the association between NSS and negative symptoms is particularly robust. The relationship between NSS and schizophrenic positive symptoms reported contrary findings [17,18,19,20,21,22, 23,24,25]. Despite a few negative reports [19,26] a substantial body of research has identified lower intelligence to be related to an excess of NSS in schizophrenic patients [27,28,29,30,31].

It remains inconclusive whether NSS could be a trait or a state marker, or both, for the disorder. Initial evidence for NSS as a trait marker is drawn from findings that show an excess of NSS in schizophrenia independent of medication effects. These came from studies of NSS in first-episode medication-naïve patients [32,33,34,35] and studies that have controlled conventional antipsychotic medications [18,36].

Bombin et al. [37] concluded that there is strong evidence to suggest NSS as a trait feature of schizophrenia. Nevertheless, there is also evidence to suggest that NSS varies across time as the illness evolves [38,39,40,41,42,43]. These findings all point to the sensitivity of NSS to changes in disease processes throughout the course of illness, suggesting their possible role as state markers for schizophrenia.

This article aims to review the existing literature discussing the relationship between NSS and obstetric complications, cannabis use, drug therapy, and as a candidate endophenotype for schizophrenia.

MATERIALS AND METHODS

A literature search was conducted on major databases to find useful studies for the purposes of this paper.

DISCUSSION

Mrad et al. [44] found no significant correlation in NSS between patients with and without obstetric complications (OC), there were negative correlations between OC total score and motor coordination and integration sub-scores. These negative correlations suggest that OC could enhance the effects of genetic risk factors for schizophrenia. Boks et al. [45] found significantly more NSS in the group of patients with first-episode psychosis without a history of OC. Peralta et al. [46] obtained that patients having a history of OC do not convey a vulnerability to developing drug-induced neurological signs.

Psychomotor performance has consistently been found to be altered in chronic cannabis users. Cannabis dependence is associated with more NSS and especially motor coordination and sensory integration signs. These results suggest that cannabinoids interact with the brain networks underlying NSS, known to be altered in schizophrenia [47]. Ruiz-Veguilla et al. [48] supported the hypothesis that cannabis abuse could be associated with NSS in first-episode psychosis. Løberg and Hugdahl [49] suggested that cannabis causes a transient cognitive breakdown enabling the development of psychosis, imitating the typical cognitive vulnerability seen in schizophrenia. This is further supported by an earlier age of onset and fewer neurological soft signs in the cannabis-related schizophrenia group, suggesting an alternative pathway to psychosis. Bersani [50] found cannabis is a possible risk factor for the onset of schizophrenia and can induce neurocognitive, behavioral and motor coordination alterations. These findings suggest that NSS are relatively independent from cannabis, but not from clinical features.

Most studies have shown that NSS cannot be simply considered a medication effect. Gupta et al. [33] reported that the rates of NSS did not differ significantly in neuroleptic-naive or neuroleptic-treated patients. Indirect evidence that NSS is not related to neuroleptic treatment also comes from the study of Lawrie et al. [51] assuming that NSS represents a neurodevelopmental risk factor for schizophrenia rather than an exposure to neuroleptic treatment. The substantial independence of NSS from neurologic implications of neuroleptic treatment is also confirmed by Bersani et al. [36].

Other studies have examined whether the severity of NSS determines the efficacy of atypical antipsychotics in schizophrenia pointing out that the presence of high NSS in schizophrenia patients impedes the improvement in cognitive function with atypical antipsychotics treatment [52], while Sevincok et al. [53] found no improvement in NSS with olanzapine treatment. The results of various studies show therefore substantially that the neurological dysfunction observed could not be interpreted as the consequence of neuroleptic medication, and no study suggests that antipsychotics may, directly or indirectly, improve the baseline neurological dysfunction.

NSS have been associated with the neuropsychopathology of schizophrenia, and have been proposed as candidate endophenotypes [54,55]. Although NSS are intrinsic to schizophrenia, their level varies with the clinical course. Thus, NSS may correspond to both genetic liability and the activity of the disease process and may be considered potential predictors of outcome [56]. There is much evidence that NSS is highly prevalent in both adults and children with schizophrenia. In addition, they have been detected as early precursors of a schizophrenic outcome in at-risk subjects. The NSS may be considered as a neurointegrative marker in schizophrenia which has been hypothesized to be a neurodevelopmental disease [57]. Also, their progress over time is an important issue in addressing the course of the illness, suggesting that NSS represent a marker sensitive to a possible late deterioration process in the course of a schizophrenic illness [42,58]. Scheffer found that NSS are positively correlated with clinical symptom changes, and can be modified by treatment [18]. Some studies say that the NSS in schizophrenia is confounded by handedness, inconsistent methodology, and prior treatment with neuroleptics. Other studies of NSS in first-episode medication-naïve patients show an excess of NSS in schizophrenia independent of medication effects [32,33,34]. Venkatasubramanian showed that higher neurological signs in never-treated patients and their lack of association with illness duration suggest neurodevelopmental etiopathogenesis of schizophrenia [35].

Another observation is that there is a higher prevalence of NSS in first-episode patients compared with healthy controls. In particular, significantly higher total rates of NSS in patients with first-episode schizophrenia or schizophreniform disorder have been reported [33]. NSS may likely emerge as a general endophenotype for many disorders rather than a specific endophenotype for schizophrenia [59].

CONCLUSIONS

Neurological soft signs emerged as a potential endophenotype for several disorders rather than a specific endophenotype for schizophrenia. There are no important correlations between neurological soft signs and obstetric correlations. It had been observed substantial independence of NSS from the neurologic implications of neuroleptic treatment. Cannabis use is a possible risk factor for the onset of schizophrenia and can induce neurocognitive, behavioral and motor coordination alterations. Future studies will shed light on the potential role of NSS as a state or trait variable.

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