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Neurological soft signs in psychoses. I: a comparative study of prevalence amongst drug naive first episode patients

Abstract

Background: The aims and objective of the study was to find out the prevalence of neurological soft signs (NSS) amongst the three groups of psychiatric disorder which were brief psychotic disorder, schizophreniform psychosis, and schizophrenia. **Materials and methods**: The study was conducted over a period of seven months starting from 1st of May, 2010 to 30th November, 2010. NSS were assessed by the Heidelberg Manual. **Results**: We found that all the patients from each of the three groups have shown at least one or more neurological abnormalities. The present study found a significant association between types of NSS namely in group of motor coordination, motor sequencing, and sensory integration, and the different category of disorders under study whereas the severity of neurological impairment was not found to be significantly associated within the three groups. **Conclusion**: We hope that in future larger studies observing for long period of time will shed definite lights in the present study findings.

Keywords: Psychiatric Disorder. Neurological Abnormalities. Motor coordination.

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Introduction

Definition

Neurological soft signs (NSS) are minor neurological abnormalities in sensory and motor performance that can be identified by clinical examination. The designation 'soft' is usually taken to indicate that the person with the sign shows no other features of a fixed or transient neurological lesion or disorder. Some described them as non-localising neurological abnormalities that cannot be related to impairment of specific brain region or are not believed to be a part of well-defined neurological syndrome. Hard signs on the other hand refer to impairment in basic motor, sensory, and reflex behaviour.[1]

NSS are defined as those signs that do not in themselves signify to a definite manifest specific neurological response, but taken together may indicate organicity. There is still a lack of consensus on the neurodysfunctional area underlying NSS; some suggest it to reflect a failure in the integration within or between sensory and motor system,[2] while others view it as deficit in neuronal circuits involving subcortical structures (e.g. basal ganglia, brain stem, limbic system).

Historical background and origin of NSS

Lauretta Bender in 1956 was first to introduce the term 'Soft Neurological Signs' (SNS) in print, gave the concept of "developmental lag", parallel to organic signs found in psychiatric disorder in the aged. She defined SNS as follows:[3]

1. The origin of SNS cannot be related to any postnatal neurological insult of the sort that might be expected to leave residual neurological signs, e.g. severe head injury, intoxication, infection, or tumour.
2. Grouping of soft signs found in an individual should not have a pathognomonic pattern of a kind that would indicate one or more clearly localised structural lesions, generalised encephalopathy, or central nervous system (CNS) involvement.

Paediatric neurologists widely consider NSS as having a developmental origin. It is supported by the evidence that a higher prevalence of neurological abnormalities in younger than older children.[4] Shapiro *et al.*[5] proposed that these signs follow a maturational curve, which reaches adult level at approximately eight years in normal's. The increase in neurological abnormalities with age up to eight 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. At nine years, all subsystems tested during the neurological examination can be considered to have completed their development.[6] Therefore, the presence of such signs is significant only after that age and is indicative of developmental lag in the acquisition of complex integrative function.

Another possibility is that neurological abnormalities may be a heritable individual difference which is supported by the findings of more concordance rates in monozygotic twins.[7]

Also, such neurological abnormalities are more prevalent in first degree relatives and siblings of schizophrenia patients,[8,9] compared to a control group or in normal population.

Types of NSS

It is believed that NSS are reflection of functional disorders in selective parts of the brain and the previous belief that these signs only indicate diffuse brain dysfunction does not seem to be correct.[10] With the growing evidence of neurodeficits in some subtypes of schizophrenia, these NSS can serve as a marker for the disease. Earlier studies have shown some types of signs to be more frequent than others like abnormality of integrative sensory functions,[11-13] difficulties in the area of motor coordination,[14,15] and motor sequencing.[12,16] On the other hand, the release reflexes in adults were reported to suggest diffuse cerebral dysfunction,[17-19] with some of these reflexes, e.g. grasp, tonic foot response, palmomental, sucking, snout, also occurring in frontal lobe pathology[20] and basal ganglia lesions. Primitive release reflexes have also been reported to be present more in schizophrenia patients having tardive dyskinesia (TD).[21]

Significance of NSS

More than half a century after NSS' first definition, at this time the role of NSS is more important in elucidating the aetiology,[22] prognosis,[23] differential diagnosis,[12,22] and even prediction to response to treatment in different psychiatric disorder.[4,24]

NSS in general medical conditions

Silent cerebral infarction which is defined as an abnormal magnetic resonance imaging of the brain without history of physical findings of a focal neurological deficit lasting more than 24 hours is the most common form of brain injuries in children with sickle cell disease (SCD) and posits an increased risk for further stroke in later life. The NSS scores are found to be significantly higher in SCD patients with infarction than SCD without infarction and therefore, NSS are important clinical signs that facilitate early identification of patients at maximum risk of developing stroke.[25]

There is increasing evidence in the literature to suggest that human immunodeficiency virus-1 (HIV-1) infection involves the CNS as a result of its direct neurotropic properties and NSS have been found to correlate with the stages of infection which may be considered as a predictor of CNS involvement.[26]

NSS in psychiatric conditions

Nichols and Chen[7] had found a small excess of over-activity and inattention among children who had NSS. Greater prevalence of NSS has been reported in obsessive-compulsive disorder patients.[27,28] Nasarallah *et al.*[16] and Mukherjee *et al.*[29] reported that soft signs are as common in mania and bipolar disorder as in schizophrenia.

NSS in first episode psychosis

Having established that an excess of NSS are present in early phase of psychosis, it is important to know whether or not these excesses pre-dates the onset of psychosis and thus could be a vulnerability marker for psychosis. Impairment of motor development and fine motor coordination has been observed in children from cohort studies who later go on to develop schizophrenia.[30,31] The presence of this abnormality suggests that neurological dysfunction could reflect a neurodevelopmental abnormality that puts the individual at a risk of later schizophrenia.

NSS in drug naïve psychosis

Antipsychotic treatment often causes the emergence of extra pyramidal symptoms (EPS) and/or TD. These motor symptoms may be erroneously rated as neurological signs. Therefore, demonstration that NSS are independent of antipsychotic treatment or side effects would support the hypothesis that neurological signs are related to disease aetiopathophysiology and an overt manifestation of the brain impairment resulting in schizophrenia. Assessments for EPS/TD frequently include items common to NSS scales, such as tremor, adventitious overflow, rigidity, and poor balance. This overlapping increases the likelihood of finding positive correlations.

Keshavan *et al.*[32] in their study with neuroleptic naïve first episode patients have demonstrated that NSS are present before exposure to medications; thus, they are thought to be an intrinsic feature of schizophrenia rather than a side effect of medication. Gupta *et al.*[33] found that NSS and developmental reflexes were present in antipsychotic naïve patients in a significantly higher proportion than normal. The antipsychotic naïve subgroup showed lower prevalence of NSS than the group on antipsychotic and opposite for developmental reflexes.

In the light of the vast majority of studies that lack an association between antipsychotic treatment and NSS prevalence, and along with studies that have demonstrated presence of NSS in antipsychotic naïve patients, the hypothesis of NSS being secondary to antipsychotic treatment should be ruled out.

NSS as trait and state marker

A higher frequency of NSS has consistently been found in studies of patients with schizophrenia.[34] Many follow-up studies have shown that there is an increase in the NSS level during acute psychotic exacerbation and then a return to a genetically determined baseline thereafter. These results are consistent with the Meehl's model of schizotaxia in which dysdiadochokinesia, i.e. a sign of dysfunction in motor coordination, is conceptualised as a marker of baseline defect (hypokrisia).[35] Thus, NSS in schizophrenia seems to adopt characteristics of both state-like and trait-like features. During the early course of acute psychosis when symptoms fluctuate, the state-like features of active disease process may be predominant; on the other hand, the trait-like features that represent the genetically determined baseline may prevail after remission of acute illness.[36]

Importance of the present study

A study on presence of NSS in drug naive psychosis has not been performed in this part of the state and as these markers

are of great importance in determining the course and prognosis of various psychiatric disorders, the present study tried to evaluate these factors at an early part of the illness which in turn may help for early intervention and better outcome.

Aims and objectives

1. To find out the socio-demographic variables of the patients.
2. To find the prevalence of NSS amongst drug naive first episode patients of brief psychotic disorder, schizophreniform psychosis, and schizophrenia.

Materials and methods

Place of the study: The study was conducted in the Department of Psychiatry, Silchar Medical College and Hospital (SMCH), Silchar, Cachar, Assam.

Period of study: The study was conducted over a period of seven months starting from 1st of May, 2010 to 30th November, 2010.

Sample of the study

Definition of case: Cases were defined as subjects who were diagnosed of having any of the following three mental illnesses, namely brief psychotic disorder, schizophreniform psychosis, and schizophrenia, according to the diagnostic criteria of the text revision of the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR),[37] but had never been treated or had received any form of psychotropic medications either as outdoor or indoor treatment prior to the present visit. Subjects who were found to have neurological disorders, alcoholism and other drug abuse, and mental retardation were excluded.

Sample subjects were taken from indoor, outdoor, and emergency patients. Maximum numbers of cases were taken for the study period.

Selection criteria

Inclusion criteria

1. Both the sexes were included in the study.
2. Only drug naive subjects were included in the study.
3. Subjects age ranged from 15 to 50 years.

Exclusion criteria

1. Patients with neurological disorders, alcoholism and drug abuse were excluded from the study.
2. Patients previously treated with psychotropic medications were excluded.
3. Patients with mental retardation.
4. Uncooperative patients.

Psychiatric diagnosis: Psychiatric morbidity was diagnosed according to DSM-IV-TR.

Materials used

1. Socio-demographic proforma standardised in the Department of Psychiatry, SMCH was used for the study.
2. NSS were assessed with the Heidelberg Manual developed by J Schröder, Ch Reitz, and M Binkert, and translated by D Barber.[38]

The Heidelberg Manual is one of the leading standardised systems for assessment of NSS used in various national and international studies. The scale consists of 16 items which evaluates motor coordination, motor sequencing, and sensory integration tasks.

The examination procedure was so chosen that the initial tests were carried out with the patient in standing position. The patient's ability to perform a given exercise was scored:

1=Patient had no, or inconspicuous difficulty with the exercise.
2=Slight, just perceivable, or shortly intermittent problems.
3=Recognisable difficulty with the test exercise.
4=Marked difficulty, continually present problems, or completely defective performance.

In an otherwise normal performance (score=0), clear body side differences are quantified by score=1.

Operational procedure: Subjects who matched the inclusion criteria were recruited from both the outdoor and indoor ward of the Department of Psychiatry during the study period. Before commencement of the interview, informed consent was taken from each subject along with that of their close attendants. The entire interview was held in the Department of Psychiatry, SMCH. The tools administered were in the following order for the subjects:

1. Socio-demographic proforma.
2. The Heidelberg Manual for NSS.

The study was approved by the Institutional Ethical Committee.

Statistical analysis

Data were analysed by descriptive statistics, chi-square test, and analysis of variance (ANOVA).

Results and observations

Socio-demographic variables

The highest percentage (50%) of cases was in the age group of 25-35 years followed by 33.33% in the age group of 15-24 years and 16.66% in 35-50 years. Out of 30 cases, 19 (63%) were male and 11 (37%) were female. Only Hindu and Muslim patients were found, of which Hindus constituted 63.33% and Muslims 36.67%. Most of the patients were educated up to the high school level (46.67%), with illiterate and primary education in 20% each, and only 13.33% were matriculate and above. Most of the patients were farmer and daily wage earner (23.33%) followed by businessman, self-employed, and housewife (20%), then unemployed (16.67%), and lastly by students and government employee or professionals (ten per cent). The study had a married population of 56.67% and single population of 43.33% with no patients who were widow, widower, separated, or divorced. Most of the patients (80%) were from a rural locality. Most (76.67%) patients were from a nuclear family and only 23.33% came from joint family,

whereas no patients were found from extended family. Most of the patients were from the lower economic status (70%) and no patients were found to be from the upper-middle and upper class (Table 1).

Table 1: Socio-demographic variables

Variable	Number of cases	Percentage
Age group (in years)		
15-24	10	33.33
25-34	15	50
35-50	5	16.67
Sex		
Male	19	63.33
Female	11	36.67
Religion		
Hindu	19	63.33
Muslim	11	36.67
Education level		
Illiterate	6	20
Primary (1^{st}-4^{th})	6	20
High school (5^{th}-10^{th})	14	46.67
Matriculate and above	4	13.33
Occupation		
Student	3	10
Unemployed	5	16.67
Housewife	6	20
Farmer and daily wage earner	7	23.33
Businessman and self-employed	6	20
Government workers and professionals	3	10
Marital status		
Single	13	43.33
Married	17	56.67
Widow/widower	0	0
Separated/divorced	0	0
Locality		
Rural	24	80
Urban	6	20
Family type		
Nuclear	23	76.67
Joint	7	23.33
Extended	0	0
Socioeconomic status		
Lower	21	70
Lower middle	4	13.33
Middle	5	16.67
Upper middle	0	0
Upper	0	0

Prevalence of NSS amongst the three groups

Our study comprised of 30 patients who had their first episode of psychosis and were drug naïve. Out of which, brief psychotic disorderconsisted of 14 numbers of patients (46.67%), schizophreniform psychosis consisted of four numbers of patients (13.33%), and schizophrenia consisted of 12 numbers of patients (40.00%).

We had applied the Heidelberg Manual for assessment of NSS in all the cases of the three groups to see the prevalence of the NSS. The cases where there is at least one NSS was found are considered to be positive and where no NSS sign was found are considered to be negative.

In our study, all the patients with brief psychotic disorder, schizophreniform psychosis, and schizophrenia had shown at least one or more neurological impairment assessed by the Heidelberg Manual (Table 2).

One-way ANOVA shows P value <0.0004; comparison between brief psychotic disorder and schizophreniform psychosis (mean difference of 5.188 and P value <0.001), between brief psychotic disorder and schizophrenia (mean difference of 0.3750 and P value >0.05), and between schizophreniform psychosis and schizophrenia shows a mean value of -4.813 and a P value <0.01 with 95% confidence interval (CI).

Table 3 shows the detail distribution of the cases in relation to the 16 Heidelberg Manual items among the three groups of disorders under study. In our study, from the brief psychotic disorder group, 14/14 patients showed impairment in diadochokinesia and right/left orientation, followed by 13/14 patients showing impairment in Ozeretzki's test, fist-edge-palm test, and speech-articulation, while no patients in this group showed impairment in tandem walking and face-hand test. In the schizophreniform group, 4/4 patients showed impairment in diadochokinesia, finger-nose test, finger-thumb opposition, graphaesthesia, stereognosis, right/left orientation, Ozeretzki's test, fist-edge-palm test, arm holding test, pronation-supination, speech and articulation, while no impairment was found in two-point discrimination in this group. And in the schizophrenia group, 11/12 patients showed impairment in diadochokinesia, right/left orientation, fist-edge-palm test, pronation-supination, speech and articulation, followed by 10/12 patients showing impairment in finger-nose test, finger-thumb opposition, graphaesthesia, stereognosis, while no patient from this group showed impairment in tandem walking. The statistical analysis shows that the above mentioned association is highly significant.

Figure 1 shows the distribution of cases of the three groups of disorders under study in relation to the 16 items of the Heidelberg Manual (types of NSS).

Table 2: The NSS positive cases

NSS	BPD (n=14)	SP (n=4)	SC (n=12)	Total
Positive	14	4	12	30
Negative	0	0	0	0

NSS=Neurological soft signs, BPD=Brief psychotic disorder, SP=Schizophreniform psychosis, SC=Schizophrenia

Table 3: Types of NSS in the three case groups

Heidelberg Manual items	Brief psychotic disorder (n=14)		Schizophreniform psychosis (n=4)		Schizophrenia (n=12)	
	n (%)	Mean score	n (%)	Mean score	n (%)	Mean score
Gait	8 (57.14)	1.00	3 (75)	1.00	5 (41.67)	1.00
Tandem walking	0 (0)	0.00	1 (25)	1.00	0 (0)	0.00
Finger-nose test	10 (71.42)	1.10	4 (100)	1.00	10 (83.33)	1.00
Diadochokinesia	14 (100)	1.29	4 (100)	1.50	11 (91.67)	1.45
Finger-thumb opposition	10 (71.42)	1.10	4 (100)	1.00	10 (83.33)	1.30
Mirror movements	3 (21.42)	1.00	2 (50)	1.00	6 (50)	1.00
Graphaesthesia	7 (50)	1.43	4 (100)	2.00	10 (83.33)	1.30
Stereognosis	10 (71.42)	1.10	4 (100)	2.00	10 (83.33)	1.20
Right/left orientation	14 (100)	1.64	4 (100)	2.50	11 (91.67)	1.54
Two-point discrimination	1 (3.57)	1.00	0 (0)	0.00	2 (16.67)	1.00
Ozeretzki's test	13 (92.85)	1.77	4 (100)	2.25	11 (91.67)	2.27
Fist-palm-edge test	13 (92/85)	1.69	4 (100)	2.25	11 (91.67)	1.64
Arm holding test	6 (42.85)	1.00	4 (100)	1.00	8 (66.67)	1.00
Pronation-supination	12 (85.71)	1.33	4 (100)	1.25	11 (91.67)	1.27
Face-hand test	0 (0)	0.00	1 (25)	1.00	1 (8.33)	1.00
Speech and articulation	13 (92.85)	1.54	4 (100)	2.00	11 (91.67)	1.64

Table 4 shows the distribution of the cases and the total NSS score as per the severity of neurological impairment among the three case groups. From the brief psychotic disorder group, 11/14 and from the schizophrenia group, 7/12 cases showed mild impairment, whereas 3/4 cases from the schizophreniform group had moderate impairment. However, no patients from all the three groups showed severe impairment. Statistical analysis was done with the total NSS score using the chi-square test and the findings are found to be extremely significant.

Figure 2 shows the distribution of cases and the mean NSS score as per severity of neurological impairment among the three case groups.

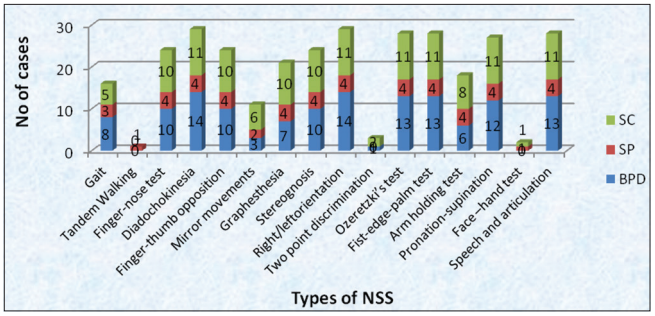

Figure 1: Types of NSS in the three case groups.

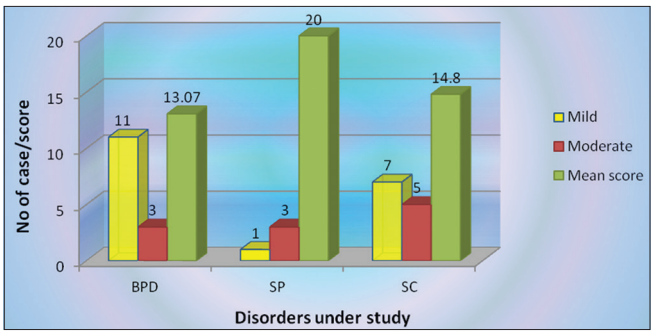

Figure 2: Severity of NSS among the three patient groups.

Discussion

Socio-demographic variables

We found most of the cases (50%) in the age group of 25-34 years, predominantly from the male gender (63%), who were Hindu by religion (63.33%) with an education between fifth to tenth standard (46.67%), who were farmer and daily wage earner by occupation (23.33%). Most of them were married (56.67%), living in a rural area (80%), in a nuclear family (76.67%), with a lower economic status (70%). All these data probably showed the predominant social trend and accessibility of tertiary healthcare centre for them.

The age range in our study seems to be matching with two other studies, one by Dazzan *et al.*[39] who reported a mean age of 27.4 years among the 77 patients of first episode psychosis, and another by Keshavan *et al.*[32] who found a mean age range from 23-25 years among schizophrenia and non-schizophrenia psychosis.

However, the findings of our study was contrasted by the findings of the study by Janssen *et al.*[40] who found a mean age of 16.3 years among three different groups of psychosis included in the study.

Probably the socioeconomic status, level of education, health awareness, and accessibility of medical healthcare system are different in the two countries, and may explain the

Table 4: Severity of NSS among the three patient groups

Severity of NSS	BPD (n=14)		SP (n=4)		SC (n=12)	
	No. of cases	Total score	No. of cases	Total score	No. of cases	Total score
Mild (0-16)	11 (78.57)	127	1 (25)	16	7 (58.33)	81
Moderate (17-32)	3 (21.42)	56	3 (75)	64	5 (41.67)	97
Severe (33-48)	0 (0)	0	0 (0)	0	0 (0)	0
Total	14	183	4	80	12	178
Mean score	13.07		20		14.8	

χ^2=57.688, df=2, and P<0.0001, NSS=Neurological soft signs, BPD=Brief psychotic disorder, SP=Schizophreniform psychosis, SC=Schizophrenia, df=Degree of freedom

difference of mean age of first episode psychosis in the two different studies.

Prevalence of NSS among the three case groups

In our study sample of 14 brief psychotic disorders, four schizophreniform psychosis, and 12 schizophrenia, all the patients from each group (100%) had shown at least one or more neurological disturbances.

This finding is consistent with the findings of Manschreck and Ames,[41] which assessed neurological impairment in 53 schizophrenia, 21 affective psychoses, and 20 normal subjects, and reported an impairment of 92% in schizophrenia patients, 52% of affective disorders, and just five per cent of normal controls. Similar findings were also reported by Browne *et al*.,[42] who studied patients with drug naïve first episode psychosis using two standard scales, the Neurological Evaluation Scale (NES) and the Condensed Neurological Examination (CNE), and reported that 97.1% of patients displayed at least one NSS (defined as one NES item rated two) and 63% showed at least two NSS (defined as two or more NES item rated two).

However, Heinrichs and Buchanan[1] have reported a much lower prevalence (50-60%) in the schizophrenia subjects, which may be due to different instruments that were used to detect NSS in this study.

On the other hand, there are various studies which have consistently shown higher frequency of neurological signs in schizophrenia patients then in other psychiatric and non-psychiatric comparison subjects.[2,12,23,43-47]

In our study, the prevalence of neurological abnormality was found to be almost equal in all the three case groups, which may be due to less number of patients in the schizophrenia group.

Types of NSS in the three case groups

We had found mostly the three groups of NSS, namely motor coordination, motor sequencing, and sensory integration to be predominantly impaired. Wherein motor coordination includes mainly diadochokinesia and finger-nose test, motor sequencing includes fist-palm-edge test and Ozeretzki's test, and sensory integration includes graphaesthesia, stereognosis, and right/left orientation.

The prevalence of these above mentioned groups of NSS in our study ranged from 90-100% in all the three categories of patients.

The findings of our study is in keeping with the study by Tucker *et al*.,[11] who reported an excess of NSS, particularly for motor coordination, in a range of 59-92% in schizophrenia patients.

Our findings on statistical analysis showed that the association between the NSS group and patient category is extremely significant.

Another study by Ismail,[48] who compared 60 schizophrenia patients with 21 non-psychotic siblings and 75 normal controls, and found a significant impairment in the subsets of motor sequencing and motor coordination in the patent group compared to the non-psychotic siblings and normal controls. However, in their study, impairment in NSS in the sensory integration group was not found to be significantly associated between patient group and non-psychotic siblings.

Moreover, The Scottish Schizophrenia Research Group[49] reported only 20% impairment in motor coordination in schizophrenia patients, which is not in keeping with our study.

Severity of NSS among the three case groups

Though we have searched various studies, we have not come across any studies which have evaluated severity of NSS in the different categories like that of us, using the same measurement scale that we have used.

So, we cannot compare directly our findings on the severity of NSS with any other study. However, in our study, we had found around 55-76% of the cases from brief psychotic disorder and schizophrenia groups to show mild impairment, whereas surprisingly in the schizophreniform group, the findings were almost reversed, where (75%) were having moderate impairment and 25% having mild impairment. This is probably due to the very small no of cases (four) in this group rather than any discrete psychopathology. It needs further long-term and larger study to corroborate the findings.

Limitations

1. Period of study was too short.
2. No control group was taken for the study.

Conclusion

Our study found that all the patients from each of the three groups had shown at least one or more neurological abnormalities. The present study found a significant

association between types of NSS, namely in the groups of motor coordination, motor sequencing, and sensory integration and the different category of disorders under study, whereas the severity of neurological impairment was not found to be significantly associated within the three groups. We hope that in future larger studies observing for long period of time will shed definite lights in the present study findings.

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