Original Article

Neurological soft signs in juvenile patients with Asperger syndrome, early-onset psychosis, and healthy controls

María Mayoral, Jessica Merchán-Naranjo, Marta Rapado, Marta Leiva, Carmen Moreno, Marisa Giráldez, Celso Arango and Mara Parellada

Abstract

Aim: The study of neurological soft signs (NSS) in patients with Asperger syndrome may help us to elucidate the neurological basis of this disorder and to clarify its relationship with other neurodevelopmental disorders. The goal of this study was to compare the prevalence of NSS in a sample of patients with Asperger syndrome, early-onset psychosis and healthy controls.

Method: NSS were assessed by means of the Neurological Evaluation Scale in a sample of 29 patients with Asperger syndrome (mean age = 12.86 ± 2.58 years), 30 patients with first-episode early-onset psychoses (mean age 14.17 ± 1.02 years) and 30 healthy controls (mean age 12.33 ± 2.69 years).

Results: Significant group differences were found between Asperger syndrome patients and healthy controls both in all the Neurological Evaluation Scale subscales and in the Neurological Evaluation Scale total score. There were no significant differences between both groups of patients in any of the Neurological Evaluation Scale scores.

Conclusions: NSS are more prevalent in Asperger syndrome than in healthy controls. The NSS profile was not disorder-specific in our samples of patients with Asperger syndrome and early-onset psychoses.

Key words: adolescent, Asperger syndrome, development disorders, neurological examinations, psychosis.

INTRODUCTION

Neurological soft signs (NSS) are minor non-localizable neurological abnormalities that are not believed to be part of a well-defined neurological syndrome. NSS include poor motor coordination, difficulties with sequencing of motor tasks, presence of primitive reflexes and subtly impaired sensory integration. Some researchers believe that NSS represent a developmental lag rather than a fixed neurological abnormality.

NSS have been shown to be abnormal in psychosis, where they have been proposed as an endophenotypic marker. Although autism and psychotic disorders were classified together before the 1970s, they were treated as independent diagnostic categories in the Diagnostic and Statistical Manual of Mental Disorders (DSM)-III, based on clinical, familial and follow-up studies. This distinction has many clinical and practical advantages. However, some data still suggest a possible association between the two entities. In this sense, a recent review about autism spectrum disorders and childhood-onset schizophrenia suggests a common neurobiological process in both disorders and highlights the following findings: high co-morbidity, epidemiological and family studies that show an association between the disorders, risk genes and chromosomal variants shared and similar accelerated trajectories of anatomic brain development. A comparison of the profile of NSS between patients with Asperger syndrome (AS) and psychotic patients might shed some light on the controversial relationship between these neurodevelopmental disorders.
Defective automatization of movements and motor clumsiness in patients with AS have been analysed, and the study of dyspraxia in autistic disorders, its neural basis and its relationship with social and communication deficits is under close scrutiny. However, the specificity of these signs has been compared with other neurodevelopmental disorders only in patients with attention-deficit/hyperactivity disorder. An evaluation of these signs might be useful to elucidate the neurological and genetic basis of AS in an easy, non-invasive and inexpensive assessment.

The aim of the present study is to evaluate and compare NSS in three groups: children and adolescents with AS, children and adolescents with first-episode early-onset psychosis (EOP) and healthy controls (HC). Based on previous studies (hypothesis 1) and on our clinical observations (hypothesis 2), we hypothesize the following: patients with AS will show significantly higher scores than HC both in the total Neurological Evaluation Scale (NES) and in all the NES subscales and in the comparison between AS and EOP patients, there will be significant differences in the total NES score and in all the NES subscales (motor coordination, sequencing of complex motor acts, sensory integration and other) suggesting, respectively, the presence of defective automatization of movements, a greater number of sensory abnormalities and more severe developmental impairment in the AS population than in EOP patients.

METHODS

Sample

A sample of 29 patients with AS (27 males, mean age 12.86 ± 2.58 years) were examined and compared with a group of 30 HC (27 males, mean age 12.33 ± 2.69 years) and 30 patients with first-episode EOP (22 males, mean age 14.17 ± 1.0 years). The HC and AS patients (but not EOP) were matched by age and gender. The groups were not matched by intelligence quotient (IQ).

In the two groups of patients (AS and EOP), the inclusion criteria for participation in the study were as follows: age between seven and 17 years, fulfilling criteria for AS or psychotic disorder and Spanish as a first language. The exclusion criteria were as follows: co-morbidity with other Axis I disorders (including use of drugs – except for sporadic use), presence of known neurological diseases, history of head injury with loss of consciousness, mental retardation and pregnancy or breastfeeding. The disorders included in the EOP group were schizophrenia (n = 10), bipolar disorder (n = 6) and other psychoses (schizophaseniform disorder, n = 7; brief psychotic episode, n = 1; and psychosis not otherwise specified, n = 6).

In the HC group, the inclusion and exclusion criteria were the same except for a diagnosis of AS/psychosis.

After receiving a comprehensive explanation of the study procedures, the participants and a parent or legal guardian gave their written informed consent prior to enrolment.

The study was approved by the Ethics and Clinical Research Boards of Hospital General Universitario Gregorio Marañón.

Assessment

Socio-demographic and clinical scales

We collected socio-demographic data from both patients and controls. The participants from the three groups also underwent a physical examination (weight, height and laboratory tests) and a clinical examination (Table 1).

All diagnoses of AS were made at baseline using DSM-IV or the Gillberg criteria. The Autistic Diagnostic Observation Schedule (ADOS) interview was conducted when needed (11 patients). In the EOP group, all diagnoses were made at baseline using the Kiddie-Schedule for Affective Disorders and Schizophrenia-Present and Lifetime Version.

<table>
<thead>
<tr>
<th>TABLE 1. Clinical examination</th>
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<tbody>
<tr>
<td>Diagnostic assessment</td>
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<tr>
<td>K-SADS-PL Interview</td>
</tr>
<tr>
<td>Lewis Obstetric Complication Scale</td>
</tr>
<tr>
<td>Gillberg Criteria</td>
</tr>
<tr>
<td>The prognostic scale by Strauss and Carpenter</td>
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<tr>
<td>The Premorbid Adjustment Scale by Cannon–Spoor</td>
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</tbody>
</table>

K-SADS-PL, Kiddie-Schedule for Affective Disorders and Schizophrenia-Present and Lifetime.
which was also used to rule out psychiatric conditions in HC. A psychotic episode was defined as the presence of positive psychotic symptoms (within a psychotic episode) such as delusions or hallucinations of less than six months’ duration. This short duration of positive psychotic symptoms was established in order to obtain a more homogeneous sample and to avoid the influence of variables such as years of psychopharmacological treatment or institutionalization. Diagnosis was made by certified psychiatrists with experience in child and adolescent psychiatry and with formal training in the aforesaid semi-structured interview.

The estimated IQ was obtained by means of the Vocabulary and Block Design sub-scores from the Wechsler Adult Intelligence Scale-III or Wechsler Intelligence Scale for Children-Revised (depending on the age of the participant).

NSS

The NSS were assessed using the NES. This scale is composed of 26 items (14 of which are tested and scored separately for the right and left side of the body) clustered into four subscales: ‘Sensory Integration’, ‘Motor Coordination’, ‘Sequencing of Complex Motor Acts’ and ‘Other’ (Table 2). The ‘Other’ subscale includes frontal release signs, primitive reflexes, short-term memory and eye movement abnormalities. Each item is scored on a three-point scale: 0 = no abnormality, 1 = mild impairment and 2 = marked impairment. Therefore, the higher the number in the total score, the more severe the neurological deviation. The scale offers a total score as well as independent scores for each subscale. NSS evaluations were carried out by experienced neuropsychologists. Prior to recruitment, inter-rater reliability for the NES was determined in an independent sample of 10 psychotic patients using the interclass correlation coefficient (ICC), which ranged from 0.86 to 0.96 for the total NES score. The ICC for the four subscales ranged from 0.80 to 0.99.

To limit the potential confounding effect of acute symptoms on NES performance, NSS were assessed when patients were clinically stable (on the fourth to eighth week after recruitment in EOP and at baseline in AS).

Data analysis

Demographic variables in the three groups were compared using a chi-square test for categorical variables (gender) and Student’s t-test for independent samples to assess continuous variables (age).

To evaluate the differences between the patient groups (AS and EOP) and HC in NES performance, the general linear model analysis of covariance (ANCOVA) was used, with groups (AS/EOP/HC) as fixed factors, raw scores of NES as dependent variables, and gender, age and IQ as covariates when needed. Kolmogorov–Smirnov tests were performed and confirmed that all NES scores were normally distributed.

All statistical tests were two-tailed, with the level of significance set at <0.05.

Data were analysed using SPSS for Windows version 13.0 (Chicago, IL, USA).

RESULTS

Socio-demographic data

The comparison of the AS patients and the HC groups revealed no significant group differences in age ($P = 0.446$) or gender ($P = 0.669$) distribution. The comparison between the EOP and the HC group showed differences in age ($P = 0.001$) – the EOP patients were older than the HC and the AS patients ($P = 0.013$) – and there were more males in

<table>
<thead>
<tr>
<th>Sensory integration</th>
<th>Motor coordination</th>
<th>Sequencing of complex motor acts</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Audiovisual integration</td>
<td>Tandem walk</td>
<td>Fist-ring test</td>
<td>Adventitious overflow test</td>
</tr>
<tr>
<td>Stereognosis</td>
<td>Diadochokinesis</td>
<td>Fist-edge-palm test</td>
<td>Romberg test</td>
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<tr>
<td>Graphesthesia</td>
<td>Finger-thumb opposition</td>
<td>Ozeretski test</td>
<td>Resting tremor</td>
</tr>
<tr>
<td>Extinction</td>
<td>Finger-nose test</td>
<td>Rhythm tapping test, version B</td>
<td>Memory</td>
</tr>
<tr>
<td>Right/left confusion</td>
<td></td>
<td>Rhythm tapping test, version A</td>
<td>Memory</td>
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</tbody>
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Neurological signs in Asperger syndrome

TABLE 3. Demographic information

<table>
<thead>
<tr>
<th></th>
<th>Asperger syndrome (n = 29)</th>
<th>Early-onset psychosis (n = 30)</th>
<th>Healthy controls (n = 30)</th>
<th>Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>12.86 ± 2.58</td>
<td>14.17 ± 1.02</td>
<td>12.33 ± 2.69</td>
<td>t(57) = −0.76, P = 0.446†</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>t(36.25) = 2.56, P = 0.013‡</td>
</tr>
<tr>
<td>IQ</td>
<td>88.44 ± 25.47</td>
<td>73.23 ± 21.60</td>
<td>112.90 ± 15.70</td>
<td>t(57) = 4.45, P &lt; 0.001‡</td>
</tr>
<tr>
<td>Gender n (%)</td>
<td></td>
<td></td>
<td></td>
<td>t(53) = −2.37, P = 0.021‡</td>
</tr>
<tr>
<td>Male</td>
<td>27 (93)</td>
<td>22 (73)</td>
<td>27 (90)</td>
<td>t(54) = 7.92, P &lt; 0.001§</td>
</tr>
<tr>
<td>Female</td>
<td>2 (7)</td>
<td>8 (27)</td>
<td>3 (10)</td>
<td></td>
</tr>
</tbody>
</table>

Inter-group comparison.
Statistically significant results are in bold.
†Asperger syndrome versus healthy controls.
‡Asperger syndrome versus early-onset psychosis.
§Early-onset psychosis versus healthy controls.

TABLE 4. Neurological Evaluation Scale (NES)

<table>
<thead>
<tr>
<th></th>
<th>Asperger syndrome (n = 29)</th>
<th>Early-onset psychosis (n = 30)</th>
<th>Healthy controls (n = 30)</th>
<th>Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurological soft signs (total)</td>
<td>34.48 ± 16.79</td>
<td>27.38 ± 8.33</td>
<td>18.90 ± 7.30</td>
<td>F(1) = 21.60, P ≤ 0.001†</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>F(1) = 0.65, P = 0.422‡</td>
</tr>
<tr>
<td>Sensory integration</td>
<td>7.31 ± 3.91</td>
<td>5.23 ± 2.44</td>
<td>4.76 ± 2.04</td>
<td>F(1) = 27.85, P ≤ 0.001§</td>
</tr>
<tr>
<td>Others</td>
<td>16.75 ± 11.68</td>
<td>12.30 ± 3.66</td>
<td>8 ± 3.81</td>
<td>F(1) = 15.19, P = 0.001†</td>
</tr>
<tr>
<td>Sequencing of complex motor acts</td>
<td>5.55 ± 2.47</td>
<td>5.55 ± 3.16</td>
<td>3.20 ± 2.38</td>
<td>F(1) = 13.83, P = 0.001†</td>
</tr>
<tr>
<td>Motor coordination</td>
<td>4.86 ± 2.96</td>
<td>4.46 ± 2.28</td>
<td>2.93 ± 1.81</td>
<td>F(1) = 20.67, P ≤ 0.001§</td>
</tr>
</tbody>
</table>

Inter-group comparison.
Statistically significant results are in bold.
†Asperger syndrome versus healthy controls.
‡Asperger syndrome versus early-onset psychosis.
§Early-onset psychosis versus healthy controls.

the AS group (P = 0.043). Statistical analyses revealed significant differences in average IQs between the three groups (AS vs. HC, P < 0.001; EOP vs. HC, P ≤ 0.001; AS vs. EOP, P = 0.021) (Table 3).

NSS

When the AS patients and the HC were compared, significant group differences were found both in the total score (P < 0.001) and in all the NES subscales (P ≤ 0.004), with the AS patients being more impaired. When the EOP patients and the HC were compared, significant group differences were obtained in the total score of the NES (P < 0.001) and in three of the four subscales (P < 0.001) (all except ‘Sensory Integration’), with the EOP patients being more impaired. Finally, when the AS and the EOP patients were compared, although the AS patients scored quantitatively higher in the total NES and in three subscales, there were no significant differences between the two patient groups in any of the measurements (see Table 4 and Figs 1,2).
Confounding variables

ANCOVA was repeated to control for the potential effect of IQ on NSS levels. The results of the comparison using the IQ as a co-variable were the same as we had previously found (total NES score: AS vs. HC ($P = 0.001$); EOP vs. HC ($P = 0.012$); AS vs. EOP ($P = 0.213$)).

All of the patients in the EOP group were receiving antipsychotic treatment at the time of the evaluation: 40% risperidone ($n = 12$), 37% olanzapine ($n = 11$), 27% quetiapine ($n = 5$), 3% aripiprazole ($n = 1$) and 3% haloperidol ($n = 1$). The mean dose of chlorpromazine equivalent (CPE) was 296, 54 ± 248, 31. The correlation between mean dose of CPE and total NSS was not statistically significant: ($r = -0.292$, $P = 0.125$).

Seven patients (24.13%) in the AS group were receiving antipsychotic treatment at the time of assessment; the most commonly used antipsychotic agent was risperidone 17% ($n = 5$), 7% ($n = 2$) was taking aripiprazole and 3% ($n = 1$) was treated with two antipsychotic drugs (risperidone and levomepromazine). The mean dose of CPE was 182, 85 ± 152, 93. The correlation between mean dose of CPE and total NSS was not statistically significant: ($r = -0.299$, $P = 0.515$).

DISCUSSION

This is the first study to compare the severity of NSS between patients with AS and patients with EOP. In our sample, the patients with AS showed significantly higher scores than HC in ‘Sensory integration’, ‘Motor coordination’, ‘Sequencing of complex motor acts’ and ‘Other’, suggesting more neurological impairment in AS. In the comparison between the two clinical groups, the AS patients had higher – though not statistically significant – raw mean scores, both in the total and in three of the four sub-tests of the NES. As for the qualitative profile of the NES sub-scales, the two clinical groups showed a similar profile in the four sub-scales.

In comparison with HC, the patients with AS showed abnormalities in neurological signs across domains. They presented deviance in motor
coordination, sequencing of complex acts, sensory integration and a variety of other subtle neurological signs. In this regard, our results are consistent with those of previous studies that have shown neurological deficits in motor integration\(^6,8\) and sensory integration\(^12\) in AS and autistic patients. With regard to motor signs, some studies have shown significant deficits in basic motor skills on praxis performance in a group of patients with autism spectrum disorder and a correlation between praxis performance and social, communicative and behavioural symptoms measured by the ADOS-G.\(^10\) In this study, basic motor skill abnormalities do not entirely explain the dyspraxia in this group of patients. In addition, dyspraxia is correlated with social/communication deficits, and it is suggested that other neural systems that are critical for acquisition of the movement patterns necessary for development of skilled tool use and social/communicative gestures are involved as core deficits of autism. In relation to other neurological signs, such as sensory integration deficits, many studies have shown that persons with autism have abnormal auditory, visual, tactile and oral sensory processing when compared with HC. These neurological deficits have been proposed to explain some pathological autistic behaviours, such as unusual responses to sensory stimuli\(^16\) and self-stimulating and self-injurious behaviour.\(^17\) They have also been associated with secondary phenomena, such as affective disorders, presumably as a consequence of worse performance in adaptive behaviours in community and social skills.\(^18\)

The lack of statistical differences between AS and EOP patients could have several explanations. First, NSS are not a valid measure to distinguish between neurodevelopmental disorders, although they can be observed in different psychiatric disorders\(^1\) and merely reflect global damage in the brain or a general vulnerability to mental illness. Whereas some studies suggest this lack of specificity\(^,19,20\) others find differential profiles of NSS between disorders with high co-morbidity and overlap.\(^21\) Therefore, the question of the specificity of NSS remains unclear. This is especially important given current interest in the conceptualization of NSS as an endophenotype for schizophrenia.\(^3\)

Second, an alternative and thought-provoking view is that AS and psychoses have a similar neurological impairment. In fact, both disorders have formed part of the same diagnostic category for a long time. Furthermore, they are often difficult to distinguish in clinical practice (for example schizotypal personality) and share many cognitive features, such as deficits in executive functioning or attention,\(^22,23\) autobiographic memory\(^24,25\) and theory of mind.\(^26,27\) In fact, some authors propose that the current definition of psychiatric illness is not biologically valid and that there is sufficient evidence that biological risk markers do not fit with the DSM classification.\(^3,5\) The consideration of mental disorder as a continuum or a symptom-based approach (vs. disorder-based approach) in the study of clinical disorders may be useful since some neural substrates may be deficit-specific rather than disorder-specific.\(^28\) Our results seem to support this deficit specificity as two different disorders show very similar neurological deficits that may suggest a common neural origin.

A third possible explanation is the small sample size, although other studies find a differential profile of NSS between different psychiatric disorders in groups with sample sizes similar to or smaller than ours.\(^21,29\)

Finally, and with respect to the qualitative profile, our data show that the two clinical groups and the HC present a similar profile. Therefore, it is possible that the poor performance in some of the subscales is more a consequence of the difficulty of the items per se and does not reflect a more marked impairment in some areas. The presence of very high scores in the AS patients in the subscales ‘Other’ and ‘Sensory Integration’ fit with the problems seen in daily clinical practice with autistic patients. The lack of differences in the motor subscales between the two clinical groups could suggest that NES items do not capture motor impairments in autistic patients, which seem to be related with alterations in complex procedural learning.

Our study is limited mainly by its small sample size and the heterogeneity of the EOP group. The differences in IQ and socio-demographic variables are potential confounding variables, and although we controlled their effects in the statistical analysis, we can not conclude that NSS are not mediated by the global intellectual function.\(^30\)

**CONCLUSIONS**

To our knowledge, this is the first study to assess NSS in a sample of AS patients (as a specific subgroup within the autism spectrum disorders) and compare them with a group of psychotic patients. We found that the profile of neurological impairment is similar in both disorders, thus arguing against the specificity of subtle neurological signs for any of the disorders studied. One strength of our study is the fact that all our EOP patients were first-episode and therefore, different from the chronic population
in which there is a bias towards the more severe cases. The fact that NSS appear both in first-episode psychoses and in AS patients with a longer history of illness suggests that NSS are an indicator of the severity of the brain disorder more than an indicator of when the brain disorder takes place. This view is also supported by the fact that NSS are present in non-psychotic siblings and family members of patients with schizophrenia.1

We consider these results exploratory and believe that they can help us to design future research lines. In this sense, further studies are necessary to clarify the role of NSS in symptoms, the potential improvement of these neurological impairments with age, their relationship with cognitive performance and brain imaging in this population, and their specificity as a marker of vulnerability.

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