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The Incidence of Neurological Soft Signs in Children with Isolated Cleft of the Lip and/or Palate

Amy L. Conrad, Ph.D., **John Canady, M.D.**, **Lynn Richman, Ph.D.**, and **Peg Nopoulos, M.D.**
The University of Iowa Hospital and Clinics, College of Medicine

Summary. -

The purpose of this study was to assess neurological soft signs (NSS) in children and adolescents with isolated cleft of the lip and/or palate (iCL/P) compared to healthy controls. Children with iCL/P were recruited through our cleft clinic. Control subjects were recruited through advertisements. Of the 166 subjects who participated (age range 7 – 17 years, $M = 12.49$, $SD = 3.20$), 77 had iCL/P (48 male) and 89 were healthy controls (44 male). All participants took the Physical and Neurological Examination of Subtle Signs (PANESS) and selected tests of motor coordination. A MANOVA assessed differences between subjects with and without iCL/P. Also, a Pearson's Correlation determined the relationship between NSS and age. Subjects with iCL/P had significantly higher levels of all NSS variables. Higher levels of NSS were associated with younger age. Findings lend support to the hypothesis of aberrant brain development in children with iCL/P.

Oral clefts are a common birth defect that are due, in part, to abnormal migration of neural crest cells (Burdi, 2006). *Types of oral clefts differ by location (i.e., lip, palate, or both; unilateral or bilateral) and extent (i.e., complete or incomplete; soft palate only or soft and hard palate; Berkowitz, 2006). About 30% are associated with a known genetic syndrome, but the remaining 70% of clefts occur in isolation or without a known syndrome identified (Jones, 1988).* Over the past few years, there has been mounting evidence to support the notion that in addition to the facial abnormality, there is accompanying abnormal brain development in children with nonsyndromic, or isolated clefts of the lip and/or palate (iCL/P; Nopoulos, Berg, VanDemark, Richman, Canady & Andreasen, 2001; Nopoulos, Berg, Canady, Richman, Van Demark & Andreasen, 2002; Nopoulos, Berg, VanDemark, Richman, Canady & Andreasen, 2002; Nopoulos, Choe, Berg, Van Demark, Canady & Richman, 2005; Goldsberry, O'Leary, Hichwa & Nopoulos, 2006).

It has long been known that the development of the face is intimately entwined with development of the brain. (Sperber, 1992; Kjaer, 1995). Some studies have investigated brain structure and brain function in subjects with iCL/P, reporting abnormal brain structure and an increased incidence of developmental brain anomalies in adult males with iCL/P (Nopoulos, Berg, Canady, Richman, Van Demark & Andreasen, 2000; Nopoulos, et al., 2001; Ward, Magnotta, Andreasen, Ooteman, Nopoulos & Pierson, 2001;, Berg, Canady, et

Corresponding Author: Amy L. Conrad, Department of Psychiatry Research, University of Iowa Hospitals and Clinics, W 278 GH, 200 Hawkins Drive, Iowa City, IA 52242, email (Amy-L-Conrad@uiowa.edu).

al., 2002; Nopoulos, Berg, VanDemark, et al., 2002; Nopoulos, et al., 2005). *Other studies have also recently reported that subjects with iCL/P have phenotypic (visual characteristics resulting from genetics and environment) differences compared to healthy controls including increased incidence of non right-handedness, altered fingerprint patterns, and minor physical anomalies such as atypical hair whorls (Scott, Weinberg, Neiswanger, Brandon, Daack-Hirsch, Murray, Liu & Marazita, 2005; Scott, Weinberg, Neiswanger, Brandon & Marazita, 2005; Scott, Weinberg, Neiswanger, Daack-Hirsch, O'Brien, Murray & Marazita, 2005).* These phenotypic differences have long been thought of as markers of abnormal brain development (Paulsen & O'Donnell, 1980).

Research in brain abnormalities, both developmental and acquired, has included work in the area of neurological soft signs (NSS), also known as subtle signs or equivocal signs. NSS can be defined as "mildly slow or clumsy fine (and sometimes gross) motor performances observed during neurological examination" (Deuel, 2002). Authors have theorized that these abnormal motor performances may be due to failure of interactions within the motor system (Deuel, 2002) or problems in developmental processes (Deuel & Robinson, 1987). NSS are another marker of abnormal brain development and have been associated with various neurologic, psychiatric, and emotional disorders including Autism and Asberger's Syndrome (Jansiewicz, Goldberg, Newschaffer, Denckla, Landa & Mostofsky, 2006), Mania (Basu, Ram & Gupta, 2002), Schizophrenia (Heinrichs & Buchanan, 1988), learning disabilities (Rie, 1987; Gaddes, 1994), and Attention Deficit-Hyperactivity Disorder (Barkley, 1998; Mostofsky, Newschaffer & Denckla, 2003).

Despite recent work suggesting abnormal brain development accompanying iCL/P, no research has examined NSS in a population with iCL/P. A thorough search of the literature shows studies limited to young children and performance on the Bayley motor scale (Bayley, 1969) or other fine motor tasks. For example, Swanenburg de Veye, Beemer, Mellenbergh, Wolters, and Heineman-de Boer (2003) found motor and mental skills of 18-month-old toddlers with CL/P (inclusive of syndromic and nonsyndromic) to be within the average range. The more malformations a child had, the more abnormal their scores. Two studies identified fine motor and perceptual motor deficits in children with cleft palate (Smith & McWilliams, 1968; Fox, Lynch & Brookshire, 1978). There was one study on the incidence of Sensory Integration Dysfunction (SID; inability to organize and interpret sensory information) in children with iCL/P (Brown, 1980). The tests done by occupational therapists were similar to some tests of NSS. Results indicated significantly higher rates of SID in children with iCL/P (Brown, 1980). However, there has been no work to date specifically evaluating NSS within a school-aged population of children with iCL/P.

The purpose of this study was to examine differences in scores on a standardized test of NSS in a sample of children and adolescents with iCL/P and a control group of children without iCL/P. Because NSS have shown a developmental pattern in the past, performance on NSS should be correlated to age. It was hypothesized that subjects with iCL/P would show higher rates of NSS than the control group. Also, younger subjects would have higher rates of NSS than older participants, across both groups, demonstrating the "normal developmental pattern" of NSS.

Method

Participants

Subjects were identified from the University of Iowa Hospital & Clinics' Cleft Clinic database and parents were sent mailings notifying them of the study and inviting them to participate. A total of 166 subjects, ages 7 to 17 years (M = 12.5, SD = 3.20), were recruited and tested. *Of these children, 77 (48 male and 29 female) had a diagnosis of isolated cleft of the lip and/or palate (iCL/P). Of the children with iCL/P, 14 had Cleft Lip Only (iCL), 27 had Cleft Palate Only (iCP), and 35 had Cleft Lip and Palate (iCLP). The remaining 89 participants (44 male and 45 female) were healthy youth without any clefts who were screened for learning, attention and health problems*. The average age of the participants with iCL/P (M = 12.4 years, SD = 3.4) and the Control group (M = 12.6 years, SD = 3.1) were not significantly different ($t_{164} = -0.393$, $p = .695$). The overwhelming majority of both groups *(80.3 % of the group with iCL/P and 95.5% of the Control group)* were of Euro-American ethnicity, consistent with demographics in the region. Socioeconomic Status was not significantly higher for the Control group (2.50 versus 2.44), based on ratings made by parents (Hollingshead & Redlich, 1958), where a lower number indicated higher Socioeconomic Status ($t_{155} = -0.652$, $p = .515$).

Procedure

This study was approved by the hospital's Institutional Review Board, and all parents provided informed consent and participants signed assent documents to participate. Following scheduling, the participants came with their parents to the hospital research clinic where they spent the morning completing the tests. Parents were not present for the child's testing, but completed a demographic questionnaire on their own.

The tests were administered and scored by a research assistant trained in neuropsychological testing. Due to scheduling conflicts, tests were given in the same order for each subject. Short breaks (5–10 minutes) were allowed if the participant needed it. The test battery was completed in about 1 hour.

Measures

The Physical and Neurological Evaluation of Subtle Signs (PANESS; Denckla, 1985). This is a test of neurological subtle signs. In the unpublished 2003 version (Loftis, Personal Communication), used in this study, subjects are required to perform various balance, coordination, and dexterity tasks. Scores are given in task performance, motor overflow, dysrythmia, choreiform movement, clumsiness, and total. Previous versions have shown moderate reliability for the total score (Holden, Tarnowski & Prinz, 1982), *adequate inter-rater reliability (ICC ≥ .70 for all continuous items) and test-retest reliability (ICC ranged from .25 to .87 for continuous items)*, as well as good internal consistency (Cronbach's alpha = .74; Vitiello, Ricciuti, Stoff, Behar & Denckla, 1989).

NEPSY (Korkman, Kirk & Kemp, 1998). This test was designed to assess neuropsychological development of children ages 3 to 12 years on five domains. *Its name is an acronym for* ne*urology and* psy*chology*. Subjects were administered the Fingertip

Tapping subtest from the Sensorimotor Functions domain. *This subtest has shown adequate test-retest (r = .71) and inter-rater (r = .71) reliability. This subtest measures eye-hand coordination and finger movements which become more precise and dexterous with age and have been associated with learning disorders (Levine, 1987)*.

Statistical Analysis

A difficulty in analyzing NSS is that there are no set guidelines on which motor dysfunctions should be categorized as NSS or how tests of motor dysfunction should be conducted, and there is a lack of normative developmental data on many measures (Deuel & Robinson, 1987; Rie, 1987). The PANESS was chosen because it has been used frequently with clinical populations *such as Autism and Asberger's Syndrome (Jansiewicz, et al., 2006), Mania (Basu, et al., 2002), and Attention Deficit-Hyperactivity Disorder (Barkley, 1998; Mostofsky, et al., 2003)*, and has some normative data.

Most NSS can be categorized as: Clumsiness, the inability to manipulate objects well or manipulating them slowly; Dyspraxia, the inability to learn a motor sequence, despite the physical capability and volition; Choreiform Movement, involuntary and irregular movements of whole muscle groups; and Synkinesis, involuntary movements of muscle groups not needed for an intended action (Deuel & Robinson, 1987; Deuel, 2002). Scores from the PANESS and other motor and verbal tasks that fit into the above categories were used as variables of interest. The variables of interest for each category are presented and described in Table 1 *and the distribution of raw scores for each subtest is presented in Table 2*.

In order to standardize subtests without age-appropriate norms, raw scores from the control group were used to create a mean and standard deviation for each subtest. These values were applied to the raw score of every child on each test, resulting in z-scores for all measures listed in Table 1. For PANESS timed tasks, the z-scores for repetition movements (right and left: foot tap, hand pat, finger tap, and tongue wiggling) were summed and averaged separately from the sequence movements (right and left: heel-toe tap, hand pronate-supine, and finger sequences) to create two separate PANESS timed movement measures. *Because the control group was used to create the z-scores, all measures for this group have M = 0 and SD = 1. All z-scores were calculated so that scores below −1 were indicative of more errors (or longer time) than average and scores over +1 were indicative of fewer errors (or shorter time) than average. Because only two children, both with iCL/P, had Choreiform movement, this measure was removed from the analyses due to low power*.

To compare levels of NSS between subjects with iCL/P and controls, a MANOVA was run with subject type, iCL/P versus Control, as the independent variable and each of the z-score NSS measures as the dependent variables. *Age, sex, and SES were controlled for and a Bonferroni correction was applied to control for the number of tests run. Then, a Pearson Correlation was run on each z-score NSS variable and age to assess the relationship between NSS and age for both children with and without clefts*.

Results

NSS in Subjects with iCL/P and Controls

Table 3 displays results of the MANOVA that indicated a significant main effect for Subject Type ($F_{9, 142} = 3.75$, $p < .001$). Post-hoc analysis indicated significant differences for every NSS variable: Dysrythmia ($F_{1, 150} = 13.06$, $p < .001$), PANESS Repetitions ($F_{1, 150} = 8.94$, $p = .003$), PANESS Sequences ($F_{1, 150} = 15.06$, $p < .001$), NEPSY Repetitions ($F_{1, 150} = 14.68$, $p < .001$), NEPSY Sequences ($F_{1, 150} = 17.51$, $p < .001$), NEPSY Preferred Hand ($F_{1, 150} = 19.71$, $p < .001$), NESPY Nonpreferred Hand ($F_{1, 150} = 20.77$, $p < .001$), Total Axial ($F_{1, 150} = 4.75$, $p = .031$), and Total Overflow ($F_{1, 150} = 4.85$, $p = .029$). For each of these variables, subjects with iCL/P had significantly lower z-scores, indicating worse performance than the control subjects (See Table 2).

Age and NSS Variables

Results of the Pearson Correlation for children, both with and without iCL/P, showed significant correlation between NSS and age on most variables. For both participant groups, younger children had higher rates of Total Axial and Total Dysrythmia errors, and took longer to complete PANESS Repetitions and Sequences, and NEPSY Repetitions, Sequences, Preferred Hand, and Nonpreferred Hand (See Table 4).

Discussion

An emerging theory of brain development in children with isolated clefts suggests that abnormal brain development occurs in tandem with abnormal facial development. Research finding increased markers of abnormal development in children with cleft (i.e., atypical hair whorls and fingerprints, and non-right-handedness) lend support to this theory (Scott, Weinberg, Neiswanger, Brandon, Daack-Hirsch, 2005; Scott, Weinberg, Neiswanger, Brandon, Marazita, 2005; Scott, Weinberg, Neiswanger, Daack-Hirsch, 2005). In the current study, subjects with iCL/P had significantly higher levels of NSS across all variables of interest, including measures of Clumsiness, Dyspraxia, and Synkinesis. This finding of increased incidence of NSS adds to the pattern of high levels of markers of abnormal development and strengthens the theory of abnormal brain development.

It is difficult to interpret the presence of NSS among individual children with cleft, because findings in the NSS literature have been mixed. Not all persons with a disorder show NSS and not all persons with NSS have a known disorder (Deuel & Robinson, 1987; Rie, 1987; Heinrichs & Buchanan, 1988). Caution must be taken in interpreting the connection between elevated levels of NSS and brain or CNS abnormalities. *A single marker of abnormal development (i.e., elevated NSS or non-right-handedness) alone may not mean anything. It is when there is a pattern of several markers found within a population that concerns of development arise*.

A further complication in interpreting elevated NSS is that they may be caused by a host of variables. These signs are often associated with neurological or nervous system dysfunction or other psychiatric and emotional disorders (Yule & Taylor, 1987), but it is not known if they are caused by the disorders or occur concurrently with them. *Research has shown that*

adult males with iCL/P have abnormal brain structures, with enlarged anterior regions of the cerebrum and decreased volumes of the posterior cerebrum and cerebellum (Nopoulos, et al., 2002). Previous work has correlated these brain region abnormalities to cognitive functioning (Nopoulos, et al., 2002), social functioning (Nopoulos, et al., 2005), and reading (Shriver, Canady, Richman, Andreasen & Nopoulos, 2006). Work needs to be done to see if NSS findings correlate to these abnormal brain regions, such as decreased white matter or abnormal cerebellum volumes.

While there may be difficulty in interpreting why NSS are found in children and adolescents with iCL/P, their presence can not be ignored. Although most children may not exhibit any consequences from NSS in their daily routine, some children may experience significant disabilities that may affect school or home functioning. In other populations high levels of NSS have been associated with Dysgraphia, Dysnomia, and other motor abnormalities (Deuel & Robinson, 1987). These disorders require accommodation and remediation and can be distressing for children if left ignored. *It is beneficial for clinicians working with children with iCL/P to understand the increased risk for these disorders and recommend accommodations or provide remediation when needed*.

As found in previous literature (Deuel & Robinson, 1987; Rie, 1987), the majority of NSS variables were correlated with age. Younger children had more difficulty with all of the tasks. This relationship was significant for most of the variables. These relationships make sense, as the tasks require fine and gross motor dexterity, which improves with age.

This study was limited by a disproportionate ratio of male and female participants in the group with iCL/P. This ratio is concurrent with the higher proportion of males with iCL/P in the general population, but it creates difficulties in conducting statistical analyses. Further, measures of NSS remain low to moderate in reliability, especially non-continuous measures based on the subjective judgment of the rater. Dual-raters were not utilized, so there was no measure of the reliability of scores obtained. Finally, with a majority of Euro-American subjects, generalizations to other ethnic groups should be made with caution.

This was the first known study to examine the presence of NSS in children and adolescents with iCL/P. It is hoped that future research in this area will continue so that NSS functioning can be better understood within a population of children with iCL/P, and in connection with brain and CNS abnormalities. Future research should incorporate larger samples with greater variability of ethnic groups, utilize similar measures of NSS to promote comparison between samples, and include more extensive measures of cognitive functioning as well as neurological imaging to assess potential relationships.

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Table 1

NSS Categories, Corresponding Variables of Interest, and Descriptions of Each Variable

NSS Category	Variable of Interest	Variable Description
Clumsiness	PANESS Dysrythmia Total Score	Inability to maintain rhythm of actions
	PANESS Total Timed Movements: Repetitions and Sequences	Time to complete dexterity tasks
	NEPSY Finger Tip Tapping: Repetitions, Sequences, Dominant, and Nondominant Hand	Time to complete dexterity tasks
Dyspraxia	PANESS Axial Total Score	Inability to perform a gross motor action without error
Choreiform	PANESS Choreiform Movement	Wriggling of fingers during
Movement	(sum of fingers and tongue)	Rhomberg stance or of tongue during stationary stance
Synkinesis	PANESS Overflow Total Score	Movement of nonessential muscle groups during timed dexterity tasks

Neurological Soft Signs (NSS). *Physical and Neurological Evaluation of Subtle Signs* (PANESS).

Table 2

NSS Raw Score Distributions for Children with and without Cleft

Domain	Variable	Group			
		Control		iCL/P	
		M	SD	*M*	SD
Clumsiness	Dysrythmia	2.9	1.9	4.1	2.5
	PANESS Repetitions	5.2	1.1	5.6	1.3
	PANESS Sequences	6.6	1.5	7.3	1.8
	NEPSY Repetitions	14.4	3.6	16.2	4.0
	NEPSY Sequences	24.4	8.9	29.2	11.2
	NEPSY Dom-Hand	19.2	6.2	22.4	7.3
	NEPSY Nondom-Hand	19.6	5.9	23.1	7.3
Dyspraxia	Axial	1.8	2.1	2.5	2.2
Synkinesis	Overflow	0.6	0.9	1.0	1.6

Neurological Soft Signs (NSS). *Physical and Neurological Evaluation of Subtle Signs* (PANESS). Dysrythmia, Axial, and Overflow are number of errors, where higher values indicates worse performance. PANESS and NEPSY Repetitions, Sequences, Dom-Hand, and Nondom-Hand are timed tasks, where longer time indicates worse performance.

Table 3

MANOVA of Z-scores on NSS Variables for Children with iCL/P

Domain	Variable	iCL/P				
		M	SD	F	p-value	Power
Clumsiness	Dysrythmia	−0.59	1.28	13.60	.001**	.956
	PANESS Repetitions	−0.29	0.92	8.48	.004**	.825
	PANESS Sequences	−0.41	1.01	14.82	.001**	.969
	NEPSY Repetitions	−0.48	1.09	13.64	.001**	.956
	NEPSY Sequences	−0.54	1.25	17.59	.001**	.986
	NEPSY Dom-Hand	−0.52	1.17	19.38	.001**	.992
	NEPSY Nondom-Hand	−0.59	1.24	20.86	.001**	.995
Dyspraxia	Axial	−0.33	1.03	4.88	.029*	.593
Synkinesis	Overflow	−0.43	1.68	5.90	.031*	.594

Neurological Soft Signs (NSS). *Physical and Neurological Evaluation of Subtle Signs* (PANESS).

*Significantly different from the Control group at $p < .05$

**Significantly different from the Control group at $p < .01$

Table 4

Pearson Correlations of Age and NSS Z-score Variable, Controlling for Subject Type

Domain	Variable	Age			
		Control		iCL/P	
		r	p	*r*	p
Clumsiness	Dysrythmia	.321	.003**	.595	.001**
	PANESS Repetitions	.752	.001**	.682	.001**
	PANESS Sequences	.780	.001**	.731	.001**
	NEPSY Repetitions	.728	.001**	.580	.001**
	NEPSY Sequences	.779	.001**	.755	.001**
	NEPSY Dom-Hand	.793	.001**	.726	.001**
	NEPSY Nondom-Hand	.785	.001**	.722	.001**
Dyspraxia	Axial	.355	.001**	.267	.027*
Synkinesis	Overflow	.246	.025*	.089	.468

Neurological Soft Signs (NSS). *Physical and Neurological Evaluation of Subtle Signs* (PANESS).

*Significantly different from the Control group at $p < .05$

**Significantly different from the Control group at $p < .01$