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Newly Identified Developmental Delays in a Large Population of Children With Nonsyndromic Cleft Lip and Palate

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Background: Nonsyndromic cleft lip and/or palate (NSCLP) is the most common congenital craniofacial anomaly. Early recognition of developmental delays associated with NSCLP is critical for counseling and management. This study investigates developmental delays in a large population of children with NSCLP.

Methods: This is an institutional review board–approved, retrospective analysis of children 5–21 years of age with a diagnosis of NSCLP. Demographic and clinical variables were collected for patients and a control group without NSCLP from the 2018 National Survey of Children's Health (NSCH) database.

Results: A total of 617 patients with NSCLP subjects and 29,147 NSCH participants were included. Among orofacial clefts, 45.2% were unilateral cleft lip and palate, followed by isolated cleft palate (30%), bilateral cleft lip and palate (16.4%), and isolated cleft lip (8.4%). NSCLP children with isolated cleft lip (odds ratio [OR]: 3.97), unilateral cleft lip and palate (OR: 2.17) and bilateral cleft lip and palate (OR: 2.91) had significantly higher odds of being diagnosed with attention-deficit hyperactivity disorder than the NSCH cohort. Rates of autism/pervasive developmental disorder were higher in children with isolated cleft lip than cleft lip and palate (11.5% versus 4.7%, $P = 0.06$), but this association was not significant. Children with isolated cleft palate had higher rates of intellectual disability, speech delay, global developmental delay, cerebral palsy, and hearing loss compared with the NSCH cohort ($P < 0.05$).

Conclusions: Higher rates of attention disorders and developmental delays in children with NSCLP highlight the importance of proper risk assessment and multidisciplinary management for this population. *(Plast Reconstr Surg Glob Open 2025;13:e6655; doi: 10.1097/GOX.0000000000006655; Published online 2 April 2025.)*

INTRODUCTION

Orofacial clefts are among the most common congenital malformations worldwide and affect approximately 1 in 700 infants.[1] Clefts occur during neonatal development at 5–8 weeks gestation when there is a disruption in the differentiation and/or proliferation of neural crest cells migrating from the neural tube to the face, resulting in failure of fusion between the medial nasal and maxillary prominences.[2] About 30% of clefts are associated with a known genetic syndrome and/or other congenital anomalies, whereas 70% occur in isolation and are termed nonsyndromic cleft of the lip and/or palate (NSCLP).[3] Children with NSCLP require monitoring and treatment for their physical cleft, speech development, feeding, and hearing.[3] However, even after surgical repair, children with NSCLP are still at risk for a variety of other cognitive and psychosocial deficits.[4] As such, early recognition of any associated developmental delay is important for improving multidisciplinary management and patient outcomes in children with NSCLP.[5]

Large-scale population-based studies that have examined associations between developmental deficits and NSCLP have conflicting reports.[4–16] The majority of studies report that young children with NSCLP score significantly

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lower on measures of speech and language compared with children without NSCLP.[5–10] Young et al[6] demonstrated that children with NSCLP score lower than children with unaffected facial development on receptive vocabulary and memory. Lee et al[7] found that children with NSCLP underachieve in phonological awareness and spelling. However, Lancaster et al[8] demonstrated that often these mild differences in speech and language constructs disappear or decrease with age. Additionally, Holder et al[9] found no significant differences in core, receptive, and expressive language index scores between cleft and noncleft groups, and Boyce et al[10] concluded that children with NSCLP often have language skills that fall in the average range and that health professionals should evaluate each child as they present rather than assuming a child with NSCLP will have language difficulties.

Multiple studies have found that children with NSCLP have weaker skills across all domains of academic achievement, including reading and mathematics, when compared with their noncleft peers.[11–14] However, Bell et al[15] found that these differences in academic achievement are typically mild and insignificant, and Wehby et al[16] found that children with orofacial clefts are, on average, less than one-half of the grade level behind their classmates. Additional research is required to examine the prevalence of a multitude of developmental delays among patients with NSCLP when compared with a cohort of nonaffected controls. The purpose of this study was to determine the rate of developmental delays—cognitive, speech, global, motor, behavioral, and sensory—in a population of patients with NSCLP and to compare these findings to a large, nationally representative control cohort of individuals without orofacial clefting.

METHODS

This is a retrospective study of all children with a cleft lip and/or palate treated by the American Cleft Palate-craniofacial Association–certified, multidisciplinary cleft/craniofacial team at a dedicated children's hospital between 1998 and 2014. All patients with a diagnosis of a genetic syndrome determined via genetic testing or a noncleft congenital anomaly were excluded from this study. Following institutional review board approval, the following patient data were collected: age, sex, body mass index, ethnicity, Zip code, cleft diagnosis, family history, birth history (including birth weight, neonatal intensive care unit stay, maternal history), surgical history, date of last craniofacial clinic follow-up, and other medical history. Within the NSCLP cohort, 4 subgroups were created by diagnosis for (1) isolated cleft palate, (2) isolated cleft lip, (3) unilateral cleft lip and palate, and (4) bilateral cleft lip and palate.

The primary outcome was a diagnosis of any developmental delay, which was subclassified as speech, motor, sensory, behavioral, cognitive, and/or global by our American Cleft Palate-craniofacial Association team leader and geneticist (T.Z.). Our multidisciplinary cleft/craniofacial team's geneticist (T.Z.), registered nurse, social worker, and speech and language pathologist met every patient annually specifically to review developmental milestones and diagnose developmental delays. These delays are explicitly noted in the electronic medical record at each visit and were collected for our study.

Takeaways

Question: What is the rate of developmental delays in children with nonsyndromic cleft lip and/or palate (NSCLP)?

Findings: In a retrospective study comparing children with NSCLP to a control group without NSCLP, higher rates of attention disorders and developmental delays were observed.

Meaning: Children with NSCLP should undergo proper risk assessment for attention disorders and developmental delays and receive multidisciplinary team management to ensure success throughout adolescence.

A control cohort was established using data from the 2018 National Survey of Children's Health (NSCH), a comprehensive survey conducted by the US Census Bureau on behalf of the Health Resources and Services Administration. This survey gathers information on the health and well-being of children across the United States. Demographic and clinical variables were collected from this database. Children with a syndromic diagnosis or any orofacial clefting present were excluded from the analysis.

Statistical analysis for the total incidence of developmental delays was completed using SPSS, version 28 (SPSS, Chicago, IL). The Fisher exact test was used to test for differences in categorical variables between the NSCLP cohort (and subgroups) and the NSCH control cohorts. A *P* value of less than 0.05 was deemed statistically significant.

RESULTS

In total, 617 patients in the NSCLP group and 29,147 patients in the NSCH cohort were included for analysis. A total of 155 patients in the NSCLP group were excluded for associated syndrome or other congenital anomaly, whereas 1363 in the NSCH cohort were excluded for syndromic diagnosis or any orofacial clefting. Among the NSCLP study cohort, 185 patients (30%) had isolated cleft palate, 52 (8.4%) had isolated cleft lip, 279 (45.2%) had unilateral cleft lip and palate, and 101 (16.4%) had bilateral cleft lip and palate, with an age range of 5–21 years (Fig. 1).

Study subjects with isolated nonsyndromic cleft palate (n = 185) had significantly higher rates of intellectual disability (3.2% versus 0.51%, $P < 0.001$), global developmental delay (15.7% versus 5.8%, $P < 0.001$), cerebral palsy (2.2% versus 0.27%, $P = 0.002$), speech delay (70.8% versus 7.1%, $P < 0.001$), and hearing loss (25.9% versus 1.0%, $P < 0.001$) than children in the NSCH cohort (Table 1). Study subjects with isolated nonsyndromic cleft lip (n = 52) had significantly higher rates of speech delay (26.9% versus 7.1%, $P < 0.001$), and hearing loss (5.8% versus 1.0%, $P = 0.02$) than children in the NSCH cohort (Table 2). Children with cleft

lip and palate (unilateral + bilateral) had significantly higher rates of speech delay (68.2% versus 7.1%, $P < 0.001$), cerebral palsy (1.1% versus 0.27%, $P = 0.02$), and hearing loss (17.4% versus 1.0%, $P < 0.001$) than children in the NSCH cohort (Table 3). The rate of learning disability was significantly higher in the NSCH cohort than in children with cleft lip and palate (5.9% versus 2.1%, $P < 0.001$).

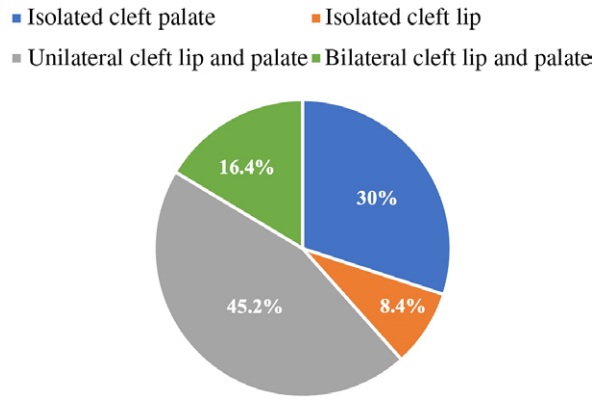

Fig. 1. Distribution of cleft diagnoses in patients with NSCLP.

A comparison between subgroups of our NSCLP study cohort and the NSCH control cohort demonstrated significantly increased rates of attention-deficit hyperactivity disorder (ADHD) among children with isolated cleft lip (7.7% versus 2.3%, $P = 0.03$), unilateral cleft lip and palate (4.6% versus 2.3%, $P = 0.01$), and bilateral cleft lip and palate (5.9% versus 2.3%, $P = 0.03$) (Table 4). However, children with isolated nonsyndromic cleft palate did not demonstrate increased ADHD compared with our control cohort (2.7% versus 2.3%, $P = 0.62$). The odds of being diagnosed with ADHD were higher given the presence of an isolated cleft lip (odds ratio [OR]: 3.97, 95% confidence interval [CI]: 1.51–10.46), unilateral cleft lip and palate (OR: 2.17, 95% CI: 1.25–3.77), bilateral cleft lip and palate

Table 1. Control Cohort vs. Isolated Nonsyndromic Cleft Palate

	Control Cohort (n = 29,147)	Isolated Nonsyndromic Cleft Palate (n = 185)	*P*
Cognitive delay, n (%)			
Intellectual disability (any)	150 (0.51)	6 (3.2)	<0.001*
Learning disability	1728 (5.9)	13 (7.0)	0.53
Speech delay, n (%)			
Speech delay (any)	2056 (7.1)	131 (70.8)	<0.001*
Global delay, n (%)			
Global developmental delay	1683 (5.8)	29 (15.7)	<0.001*
Motor delay, n (%)			
Cerebral palsy	80 (0.27)	4 (2.2)	0.002*
Behavioral delay, n (%)			
Behavioral delay (any)	3315 (11.4)	14 (7.6)	0.13
Autism/PDD	1589 (5.5)	8 (4.3)	0.63
ADHD	665 (2.3)	5 (2.7)	0.62
Sensory delay, n (%)			
Hearing loss	298 (1.0)	48 (25.9)	<0.001*
Vision loss	343 (1.2)	3 (1.6)	0.48

*$P \leq 0.05$.

Table 2. Control Cohort Versus Isolated Cleft Lip

	Control Cohort (n = 29,147)	Isolated Cleft Lip Cohort (n = 52)	*P*
Cognitive delay, n (%)			
Intellectual disability (any)	150 (0.51)	1 (1.9)	0.24
Learning disability	1728 (5.9)	2 (3.9)	0.77
Speech delay, n (%)			
Speech delay (any)	2056 (7.1)	14 (26.9)	<0.001*
Global delay, n (%)			
Global developmental delay	1683 (5.8)	4 (7.8)	0.54
Motor delay, n (%)			
Cerebral palsy	80 (0.27)	0 (0)	>0.999
Behavioral delay, n (%)			
Behavioral delay (any)	3315 (11.4)	8 (15.4)	0.38
Autism/PDD	1589 (5.5)	6 (11.5)	0.06
ADHD	665 (2.3)	4 (7.7)	0.03*
Sensory delay, n (%)			
Hearing loss	298 (1.0)	3 (5.8)	0.02*
Vision loss	343 (1.2)	0 (0)	>0.999

*$P \leq 0.05$.

Table 3. Control Cohort Versus Cleft Lip and Palate

	Control Cohort (n = 29,147)	Cleft Lip and Palate: Unilateral + Bilateral (n = 380)	*P*
Cognitive delay, n (%)			
Intellectual disability (any)	150 (0.51)	2 (0.53)	0.72
Learning disability	1728 (5.9)	8 (2.1)	<0.001*
Speech delay, n (%)			
Speech delay (any)	2056 (7.1)	259 (68.2)	<0.001*
Global delay, n (%)			
Global developmental delay	1683 (5.8)	22 (5.8)	>0.99
Motor delay, n (%)			
Cerebral palsy	80 (0.27)	4 (1.1)	0.02*
Behavioral delay, n (%)			
Behavioral delay (any)	3315 (11.4)	35 (9.2)	0.22
Autism/PDD	1589 (5.5)	18 (4.7)	0.65
ADHD	665 (2.3)	19 (5.0)	0.002*
Sensory delay, n (%)			
Hearing loss	298 (1.0)	66 (17.4)	<0.001*
Vision loss	343 (1.2)	2 (0.53)	0.34

*$P \leq 0.05$.

Table 4. ADHD Rates Compared With Control Cohort

Diagnosis	ADHD Rates, n (%)	*P*	Odds Ratio
Control cohort	665 (2.3)	—	—
Isolated cleft palate	5 (2.7)	0.62	1.30 (0.56–3.06)
Isolated cleft lip	4 (7.7)	0.03*	3.97 (1.51–10.46)
Cleft lip and palate total	19 (5.0)	0.002*	2.25 (1.43–3.58)
Unilateral cleft lip and palate	13 (4.6)	0.01*	2.17 (1.25–3.77)
Bilateral cleft lip and palate	6 (5.9)	0.03*	2.91 (1.31–6.47)

*$P \leq 0.05$.

Table 5. Autism Rates Compared With Control Cohort

Diagnosis	Autism Rates, n (%)	*P*
Control cohort	1589 (5.5)	—
Isolated cleft palate	8 (4.3)	0.63
Isolated cleft lip	6 (11.5)	0.06
Cleft lip and palate total	18 (4.7)	0.65
Unilateral cleft lip and palate	9 (3.2)	0.11
Bilateral cleft lip and palate	9 (8.9)	0.12

(OR: 2.91, 95% CI: 1.31–6.47) compared with not having an orofacial cleft.

However, when examining the cohorts for rates of autism/pervasive developmental disorder (PDD), rates were not significantly different comparing the NSCLP cohort to the NSCH cohort (cleft palate: $P = 0.63$; cleft lip: $P = 0.06$) ‖ unilateral cleft lip and palate: $P = 0.11$; bilateral cleft lip and palate: $P = 0.12$) (Table 5).

Further subgroup analysis examined differences between children with isolated cleft lip to children with cleft lip and palate. Study subjects with isolated nonsyndromic cleft lip had significantly lower rates of speech delay (26.9% versus 68.2%, $P < 0.001$) and hearing loss (5.8% versus 17.4%, $P = 0.04$). Rates of autism/PDD were higher in children with isolated cleft lip than in children with cleft lip and palate (11.5% versus 4.7%, $P = 0.06$), but this association was not significant (Table 6).

Additional subgroup analysis examined differences between children with isolated cleft palate to children with cleft lip and palate. Study subjects with isolated nonsyndromic cleft palate (n = 185) had significantly higher rates of learning disabilities (3.2% versus 0.53%, $P = 0.02$), learning disability (7.0% versus 2.1%, $P = 0.01$), global developmental delay (15.7% versus 5.8%, $P < 0.001$), and hearing loss (25.9% versus 17.4%, $P = 0.02$) than children with cleft lip and palate (Table 7). There were no significant differences in rates of autism/PDD ($P > 0.99$) and ADHD ($P = 0.27$).

DISCUSSION

All facets of childhood development—cognitive, speech, global, motor, behavioral, and sensory—are influenced by a multitude of biological and environmental factors. This study demonstrates that even when a child has no genetic syndrome or additional congenital anomaly, cleft lip and/or palate represent significant morbidity with a clear impact on a child's natural development. This study sought to better determine and characterize the prevalence of various developmental delays in children with nonsyndromic cleft lip and/or palate to better guide individualized care with earlier detection and multidisciplinary intervention.

The makeup of our nonsyndromic study cohort is consistent with the epidemiological data on orofacial clefts reported in the literature;[17,18] unilateral cleft lip and palate constituted the majority of orofacial clefts (45.2%) followed by isolated cleft palate (30%), bilateral cleft lip and palate (16.4%), and isolated cleft lip (8.4%). Because of this

Table 6. Isolated Cleft Lip Versus Cleft Lip and Palate

	Isolated Cleft Lip Cohort (n = 52)	Cleft Lip and Palate: Unilateral + Bilateral (n = 380)	*P*
Cognitive delay, n (%)			
Intellectual disability (any)	1 (1.9)	2 (0.53)	0.32
Learning disability	2 (3.9)	8 (2.1)	0.34
Speech delay, n (%)			
Speech delay (any)	14 (26.9)	259 (68.2)	<0.001*
Global delay, n (%)			
Global developmental delay	4 (7.8)	22 (5.8)	0.54
Motor delay, n (%)			
Cerebral palsy	0 (0)	4 (1.1)	>0.99
Behavioral delay, n (%)			
Behavioral delay (any)	8 (15.4)	35 (9.2)	0.21
Autism/PDD	6 (11.5)	18 (4.7)	0.06
ADHD	4 (7.7)	19 (5.0)	0.5
Sensory delay, n (%)			
Hearing loss	3 (5.8)	66 (17.4)	0.04*
Vision loss	0 (0)	2 (0.53)	>0.99

*$P \leq 0.05$.

Table 7. Isolated Cleft Palate Versus Cleft Lip and Palate

	Isolated Nonsyndromic Cleft Palate (n = 185)	Cleft Lip and Palate: Unilateral + Bilateral (n = 380)	*P*
Cognitive delay, n (%)			
Intellectual disability (any)	6 (3.2)	2 (0.53)	0.02*
Learning disability	13 (7.0)	8 (2.1)	0.01*
Speech delay, n (%)			
Speech delay (any)	131 (70.8)	259 (68.2)	0.56
Global delay, n (%)			
Global developmental delay	29 (15.7)	22 (5.8)	<0.001*
Motor delay, n (%)			
Cerebral palsy	4 (2.2)	4 (1.1)	0.45
Behavioral delay, n (%)			
Behavioral delay (any)	14 (7.6)	35 (9.2)	0.63
Autism/PDD	8 (4.3)	18 (4.7)	>0.99
ADHD	5 (2.7)	19 (5.0)	0.27
Sensory delay, n (%)			
Hearing loss	48 (25.9)	66 (17.4)	0.02*
Vision loss	3 (1.6)	2 (0.53)	0.34

*$P \leq 0.05$.

representative distribution, we can generalize our findings to broader populations. Previous research has indicated that developmental delays are more common in children with NSCLP compared with the general population with variations across subgroups of orofacial clefts.[11] Our study builds upon such previous reports with important new findings.

We report, for the first time, a statistically significant increased rate of ADHD in children with cleft lip (with or without cleft palate) compared with children without any orofacial cleft. Interestingly, this increased rate of ADHD was not observed in children with isolated cleft palate. Although not statistically significant, we also identified a potentially increased risk for autism in children with isolated cleft lip compared with children without any orofacial cleft. Again, this increased rate of autism was not observed in children with isolated cleft palate. Furthermore, in subgroup analysis of our NSCLP study cohort, children with isolated cleft lip had higher rates of autism than those with cleft lip and palate, although this did not reach statistical significance. Overall, the presence of a cleft lip was associated with an increased rate of ADHD and autism. In contrast, cleft palate did not exhibit the same association with these developmental delays and attention disorders.

Our findings are particularly intriguing considering previous research by Tillman et al,[19] which demonstrated an increased risk of autism spectrum disorder in individuals with cleft lip and palate and cleft palate only, regardless of sex. However, women with isolated cleft lip had an increased risk of autism spectrum disorder.[19] The accumulating evidence suggesting underlying neurodevelopmental mechanisms leading to autism has led to the hypothesis that the pathogenesis of NSCLP might also involve morphological, molecular, and cellular brain abnormalities.[20,21] For instance, a study using a mouse model for orofacial clefting found that, by inducing cleft pathogenesis, it would result in an abnormal development of GABAergic neurons, along with disruptions in central nervous system neuronal proliferation and migration.[21] Furthermore, in humans, all craniofacial anomalies,

including cleft lip and palate, are associated with a higher risk of autism.[19,22] These results are further supported by the fact that the normal, full siblings of children with orofacial anomalies do not exhibit a disproportionately increased risk of intellectual disability or autism, suggesting that familial influences are unlikely to be the sole cause of these conditions.[19] These preliminary findings suggest that early identification of autism in cleft patients could lead to improved patient outcomes and also point to the potential involvement of unique neurobiological development in the pathogenesis of developmental delays in patients with NSCLP.

This study also found that patients with isolated cleft palate had significantly higher rates of intellectual disability and global developmental delay compared with the national normative. This finding aligns with existing literature, which suggests that isolated cleft palate is closely linked to poorer academic performance.[12] In a Danish study, Clausen et al[12] observed that children with isolated cleft lip or cleft lip and palate showed no significant difference in ninth grade examination scores compared with healthy controls, whereas those with isolated cleft palate scored significantly lower. In a similar population study of American children, Wehby et al[16] revealed that children with isolated cleft lip, isolated cleft palate, and both cleft lip and palate performed below their classmates in reading, language, and math from Kindergarten through the eighth grade. On average, children with clefts were approximately half a grade level behind their peers without clefts.[16] Notably, the differences were most prominent for those with an isolated cleft palate.[16] Children with isolated cleft palates were also most likely to use special education services; however, there were no statistically significant differences by cleft type.[16] Furthermore, we would expect that orofacial anomalies will contribute to delays in speech and language development, a finding supported by our study and consistent with existing literature.[8] These findings provide further evidence that developmental delays are more prevalent in NSCLP and can be associated with specific cleft pathology.

Despite the prevalence of cognitive delay among cleft patients, the exact causes of cognitive delay in NSCLP is not well defined, and further investigation is needed to understand its underlying mechanisms. One study focusing on genetic factors in Chinese children with NSCLP discovered a significant association between a specific genetic variation known as a single-nucleotide polymorphism and developmental dyslexia, shedding light on the potential genetic influences contributing to cognitive challenges in NSCLP.[23] Another avenue of research has delved into the examination of brain morphology in children with NSCLP. In this context, researchers have revealed that children with NSCLP exhibited an abnormally large cerebral cortex gray matter volume while displaying decreased volume in subcortical gray matter and cerebral white matter structures.[24] These observations suggest that the brains of children with NSCLP may be less mature compared with age-matched controls, hinting at possible neurodevelopmental disparities that could contribute to cognitive delays. Despite these valuable discoveries, the etiology of NSCLP remains a complex puzzle with many facets yet to be explored, but we can gain a more comprehensive understanding of NSCLP by continuing to investigate genetic, neurodevelopmental, and other potential influences.

Given the retrospective nature of this study, our findings are subject to limitations. Although our institutional database was updated and managed by a multidisciplinary cleft/craniofacial team, missing information and coding errors are inherent in all databases. This is also applicable to the control group we constructed using a national database. Moreover, diagnosing developmental delays can be influenced by individual providers and may involve a degree of subjectivity. Although our institution's team leader and geneticist made specific developmental delay diagnoses with uniformity, the same level of consistency may not have been present in the national database. Differences in follow-up time may also impact the rates at which developmental delays are diagnosed. However, the NSCH cohort utilized oversampling for children with special needs (ie, ADHD, autism), resulting in a higher prevalence and likely increasing the sensitivity for identifying developmental delays within this group. Despite this enhancement in the NSCH cohort, significant differences in developmental outcomes were still observed in the NSCLP cohort. Overall, our study effectively outlines the prevalence of multiple developmental delays in a substantial NSCLP cohort, comparing it to an equally large and diverse group of American children and adolescents from the control database.

By carefully analyzing the association between specific developmental delays and various patterns of orofacial clefts, our research aims to inform future management strategies and explore the potential causes of developmental delays.

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DISCLOSURE

The authors have no financial interest to declare in relation to the content of this article.

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