

## Research Article

### Higher Frequency of Food Selectivity and Feeding Disorders in Children with Cornelia De Lange Syndrome vs. Autistic Spectrum Disorder

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#### Abstract

**Review:** Feeding disorders affect either children with Autism Spectrum Disorder (ASD) and Cornelia De Lange Syndrome (CdLS), which is a cohesionopathy characterized, among others, by autism-like disorders. Food Selectivity Disorder (FSD) and Feeding Disorders (FD) can have major deleterious impact on cognitive and behavioral outcomes in ASD and CdLS children. However, if there is a different level of severity for one or both those disorders between these two conditions is not known.

**Goal:** To evaluate if children with CdLS were more severely affected by FSD and/or FD than ASD children.

**Methods:** Griffiths Mental Development Scales, Autism Diagnostic Observation Schedule, and Brief Autism Mealtime Behavior Inventory were administered to CdLS (n=16; 10 male/6 female), ASD (n=35; 20 male/15 female) and typical developing children (TDC) (n=77; 41 male/36 female).

**Results:** Statistical analyses showed that children affected by CdLS had lower total quote of mealtime behavior disorder ( $p<0.001$ ), food selectivity ( $p<0.001$ ), disruptive mealtime behaviors ( $p<0.001$ ) and mealtime rigidity ( $p<0.001$ ) scores in comparison to ASD and TDC.

**Conclusions:** These findings suggest higher frequency of FSD in CdLS vs. ASD and TDC. These findings describe new behavioral aspects in a complex cohesionopathy disorder whose treatment could represent a useful tool for improving quality of life of CdLS children and their parents.

## Abbreviations

CdLS	:	Cornelia De Lange Syndrome
ASD	:	Autism Spectrum Disorder
TDC	:	Typical Developing Children
ADOS	:	Autism Diagnostic Observation Schedule
BAMBI	:	Brief Autism Mealtime Behavior Inventory

**Keywords:** Autism; Cohesinopathies; Feeding Disorders; Food Intake-Caloric Needs

## Introduction

Cornelia De Lange Syndrome (CdLS) is a multisystem congenital syndrome with peculiar facial phenotype, prenatal and postnatal growth delay, upper extremities abnormalities, cardiac defects, gastrointestinal anomalies, hearing loss, myopia, palatal malformations, genitourinary abnormalities and congenital diaphragmatic hernias [1]. CdLS has been associated with mutations of the following genes: NIPBL, SMC1A, HDAC8, RAD21, and SMC3 [2]. These mutations determine complex phenotypic features that belong to a group of genetic disorder known as cohesinopathies [3]. Cohesinopathies are disorders associated with gene regulation abnormalities that occur during critical stages of early development and manifest in different organs and systems [4,5]. Clinically, CdLS presents variable phenotypes that include classic, mild and probable phenotypes [6]. However, each phenotype tends to evolve and differently express during growth [7]. Moreover, various studies reported similar clinical features among patients categorized as a classic and mild type [8-12]. These data, in general, indicate that due to the absence of clear-cut clinical differences among classic, mild and probable appearance, the phenotypic distinction of CdLS children is essentially based on the Gestalt approach [7]. In the context of CdLS though, a Gestalt approach for phenotyping the affected children, should be always followed by more accurate clinical evaluations due to the complexity of this genetic disorder [13].

CdLS subjects present indeed a variegated and complex series of behavioural problems including, among others, psychomotor delay, autism-like phenomena, self-injury aggressive comportment, and self-restraining behavior [13-17]. Among the autistic-like phenomena, children with CdLS can exhibit avoidance of social interaction and physical contact [18,19], repetitive and self-stimulatory behaviour, and ritualistic conducts [20]. Furthermore, CdLS show lack of intentional communicative behavior [21] and reduced emotional expressivity [22]. Curiously, though, although autistic-like features are common in individuals with a diagnosis of CdLS, their specific impact on specific behavioral aspects have not been fully described. In particular, among the typical autistic-like features quite often observed in children with CdLS, food

selectivity disorder (FSD) and feeding disorders (FD) has been poorly studied [23]. FSD is a peculiar and complex behavioural aspect of FD in general, which is frequently associated with inadequate dietary intake and consequential nutritional deficits [24,25].

FD are present in both CdLS and Autism Spectrum Disorder (ASD) children and include, among others, food aversion, eating slowness and food pickiness, which determine a marked limitation in terms of food variety (nutritional completeness) and amounts of food intake (adequate caloric intake). In some severe cases, CdLS children can even express a total rejection for eating and so determining a worsening of multiple nutritional deficits with potentially devastating consequences and global clinical worsening of all other developmental aspects, especially the neurodevelopmental ones. The aim of this investigation was to systematically assess the FSD in children diagnosed with CdLS in comparison to ASD and Typical Developing Children (TDC).

## Materials and Methods

### Population Study

Study patient populations consisted of consecutively 16 subjects diagnosed with CdLS (10 males, 6 females; mean age  $5.12 \pm 1.98$  years) and 35 children diagnosed with ASD (20 males, 15 females; mean age  $4.94 \pm 1.72$  years) from two catchment geographical areas: Campania and Sicily, Italy. All subjects were enrolled consecutively referred to outpatient clinics of Clinic of Child and Adolescent Neuro-Psychiatry Division, Department of Mental Health, Physical and Preventive Medicine, Università degli Studi della Campania “Luigi Vanvitelli”, Caserta, Italy (former Second University of Naples [SUN]), and the Department of Psychological, Pedagogical and Educational Sciences, University of Palermo, Palermo, Italy. In addition, a group of 77 typical developing children (41 males, 36 females; mean age  $4.78 \pm 2.06$  years) were enrolled through Campania and Sicily Regions (Italy) public school’s system and used as Typical Developing Children control subjects group (Controls). The inclusion criteria were: a) any children of both sexes between age 3-17 diagnosed with CdLS or ASD; b) parental consent to participate to the study. The exclusion criteria consisted in the exclusion of all children affected by ascertained genetic syndromes as documented in their medical records or based on clinical evaluations. The data collection for this investigation was performed across a period of 8 years.

### Neurodevelopmental Assessment

Each child enrolled in the study was evaluated using following assessment tools: Griffiths Mental Developmental Scales (GMDS) [26] to assess developmental levels; Autism Diagnostic Observation Schedule (ADOS) [27] for the assessment of autistic spectrum disorders; and the Brief Autism Mealtime Behavior

Inventory (BAMBI) [28] for the assessment of eating/food disorders. Griffiths Mental Development Scales (GMDS). GMDS is a tool to measure rate of infant development between 0 to 8 years of age [29]. Briefly, GMDS scales were designed to measure children from birth to two years and extended to cover from birth to eight years, consisting of 5 sub-scales assessing different aspects of neurodevelopment. A sixth scale (Practical Reasoning) has been added to the five scales comprising the measure for the early years. GMDS consists of the following sub-scales:

- Sub-scale A. Locomotor. Gross motor skills including the ability to balance and to co-ordinate and control movements.
- Sub-scale B. Personal-Social. Proficiency in the activities of daily living, level of independence and interaction with other children.
- Sub-scale C. Language. Receptive and expressive language.
- Sub-scale D. Eye and Hand Co-ordination. Fine motor skills, manual dexterity and visual monitoring skills.
- Sub-scale E. Performance. Visuospatial skills including speed of working and precision.
- Sub-scale F. Practical Reasoning. Ability to solve practical problems, understanding of basic mathematical concepts and understanding of moral issues.

Scores on individual items are written into a record book. The items in the record book are colour coded to draw attention to items of a similar kind. Raw scores are computed for each individual sub-scale and can be converted to four types of standard score:

- Percentiles (using look-up tables in the Analysis Manual or the graphs provided in the record (books).
- Z-Scores (using look-up tables in the Analysis Manual).
- Age Equivalents or Mental Age (using look-up tables in the Analysis Manual).

- General Quotient or GQ (using look-up tables in the Analysis Manual).

In this study, we used: the General Quotient (GQ) in order to define the rate of developmental delay of children [29]; the Autism Diagnostic Observation Schedule (ADOS) [27] to confirm clinical diagnosis and provide a severity score. (ADOS is an investigator-based assessment conducted in naturalistic social situations demanding specific social, communication and restricted/repetitive responses. Although the protocol follows standard administration, the situations themselves were unstructured or semi-structured. Behaviors were scored in the areas of social communication, social relatedness, play and imagination, and repetitive behaviors); the Brief Autism Mealtime Behavior Inventory (BAMBI) to capture mealtime behaviors specific to children with ASD [28]. The BAMBI is scored on a 1–5 Likert scale with a score of 1 indicating the behavior “never” occurs and a score of 5 indicating the behavior “always” occurs at mealtime. Reversed scoring is used for four of the items rating positive mealtime behaviors. A total frequency score is calculated from a sum of all 15 items with higher scores reflecting more mealtime behavior problems.

### Statistical Analyses

In order to compare the three study groups ANOVAs for continuous variables and Chi-square test for non-parametrics analysis were computed. All data were coded and analyzed using the commercially available STATISTICA 6.0 package for Windows (StatSoft, Inc, Tulsa, OK, USA).

### Results

Three study groups were comparable for age ( $p=0.793$ ) and sex ( $p=0.774$ ) distribution. No significant differences were found between CdLS and ASD group in GQ ( $p=0.636$ ) and ADOS total scores ( $p=0.426$ ). See (Table 1).

Table 1	CdLS (N=16)	ASD (N=35)	TDC (Controls) (N=77)	p-value
Age	5.12±1.98	4.94±1.72	4.78±2.06	0.793
Gender (M/F)	10/6	20/15	41/36	0.774
GQ (GMDS)	52.36±11.78	50.42±13.96	-	0.636
ADOS	17.39±3.64	18.35±4.02	-	0.426

**Table 1:** The table shows the main demographic and clinical assessment scale data for all groups of children considered in the study. M=male; F=female; GQ; General Quotient; ADOS: Autism Diagnostic Observation Schedule; CdLS: Cornelia de Lange Syndrome; ASD: Autism Spectrum Disorder; TDC: typically developing children.

<b>Table 2</b>	CdLS (N=16)	ASD (N=35)	TDC (Controls) (N=77)	p-value
Food Selectivity	8.2±3.3	12.0±3.0	6.1±2.8	<0.001
Disruptive Mealtime Behaviors	6.0±2.4	8.4±2.5	4.4±1.0	<0.001
Food Refusal	4.2±1.6	4.7±1.9	4.9±1.0	0.118
Mealtime Rigidity	5.6±2.4	7.8±3.4	5.4±2.3	<0.001
Total Mealtime Behavior Disorders	26.1±8.6	33.0±8.4	24.9±7.7	<0.001

**Table 2:** The table shows the mean scores and standard deviations obtained for each specific type of food disorders across all groups of children. CdLS: Cornelia de Lange Syndrome; ASD: Autism Spectrum Disorder; TDC: typically developing children

BAMBI evaluation scores showed a significantly lower total quote of mealtime behavior disorders ( $p<0.001$ ), food selectivity ( $p<0.001$ ), disruptive mealtime behaviors ( $p<0.001$ ), and mealtime rigidity ( $p<0.001$ ) in CdLS vs. ASD children and Controls (Table 2). No significant differences for food refusal ( $p=0.118$ ) among the three groups were found (Table 2).

## Discussion

While feeding and mealtime problematic disorders seem to be a common behavior problem exhibited in children with ASD and causing additional parental stress than ASD nuclear symptoms [30], much less is known about FD in children diagnosed with CdLS and their consequences on more global neurodevelopmental deficits in these children as well as increased parental stress. In this study, children with a diagnosis of CdLS showed higher frequency and severity of both FSD disorders in association, however, with a surprisingly higher prevalence of ASD symptoms [25]. These ASD-like symptoms though, have probably different outcomes and trajectories since based on pathomechanisms that are only partially overlapping with “pure” ASD disorder. In fact, previous studies, have showed that the profile and developmental trajectories of ASD characteristics in CdLS children are different to those observed in individuals with idiopathic ASD [31].

## Conclusions

Our findings suggest that FD, and FSD in particular, are not only present in CdLS children as part of ASD-like features characterizing this syndrome, but that they are actually more frequent in CdLS than ASD children. This set of data seem to suggest the hypothesis that FSD in CdLS have peculiar features and possible specific trajectories different from those found in ASD children. In general, parents of ASD children reported higher prevalence of food refusals based on the texture of food, mixtures, brand, shape, and taste/smell than did typical developing children [23]. It looks like that mealtime troubles in ASD, differently from CdLS children, are based on the characteristics of food, which may be related to sensory impairments processing, oral or tactile

sensitivity rather than behavioral rigidity as probably in CdLS children. Impairments in sensory processing impact an estimated 40–88% of children with disabilities [32-35] and have been found to be as high as 95% in small samples of children with ASD [36]. Foods possess many sensory characteristics, and children who have difficulties with sensory processing may exhibit higher degree of food refusal based on the characteristics of food. However, while probably also present in CdLS children, sensory impairments have not been well characterized in these patients. In this context though, we may speculate about the causes generating mealtime problems in ASD and ASD-like children, including children with CdLS.

We have to take into account limitations of the present study:

1. Small size of children evaluated, although CdLS is a rare disease.
2. No specific intervention program has been proposed in order to verify the possible change in mealtime behavior.
3. Not available follow-up data.

Despite these limitations, we retain that the present study has identified an important area of clinical research in the contest of a complex genetic syndrome. Our findings seem to represent a possible initial cluster of data that need to be confirmed by future multi-collaborative large studies due to the rarity of CdLS.

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## Availability of Data and Materials

The datasets that were analyzed in the current study are available from the first author, upon reasonable request.

## Authors' Contributions

DI and ME processed, analyzed, and interpreted the data and drafted the manuscript. ME, MC conceived the study; designed the experiment; oversaw data collection, processing, and analysis. FP, LP assisted with the interpretation of the findings and provided critical feedback on the manuscript. MR, ME assisted with the collection of the data. MS, AM, GT, RM, BG contributed to the interpretation of the findings and provided critical feedback on the manuscript. GM provided critical feedback on the manuscript.

## Competing Interests

The authors declare that they have no competing interests.

## Consent for Publication

Not applicable.

## Ethics Approval and Consent to Participate

Written informed consent from parents for all children included in the study was obtained. The Departmental Ethics Committee approved the study (Protocol number# 13891; EuDRACT number 2015-001159-66). The study was conducted according to the criteria of the Declaration of Helsinki.

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