Behavioral phenotype and autism spectrum disorders in Cornelia de Lange syndrome

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Abstract

Cornelia de Lange syndrome (CdLS) is a congenital disorder characterized by distinctive facial features, growth retardation, limb abnormalities, intellectual disability, and behavioral problems. Cornelia de Lange syndrome is associated with abnormalities on chromosomes 5, 10 and X. Heterozygous point mutations in three genes (*NIPBL*, *SMC3* and *SMC1A*), are responsible for approximately 50-60% of CdLS cases. CdLS is characterized by autistic features, notably excessive repetitive behaviors and expressive language deficits. The prevalence of autism spectrum disorder (ASD) symptomatology is comparatively high in CdLS. However, the profile and developmental trajectories of these ASD characteristics are potentially different to those observed in individuals with idiopathic ASD. A significantly higher prevalence of self-injury are evident in CdLS. Self-injury was associated with repetitive and impulsive behavior. This study describes the behavioral phenotype of four children with Cornelia de Lange syndrome and ASDs and rehabilitative intervention that must be implemented.

Introduction

Cornelia de Lange syndrome (CdLS) is a multiple congenital anomaly syndrome characterized by a distinctive facial appearance, prenatal and postnatal growth deficiency, psychomotor delay, behavioral problems, and malformations of the upper extremities.[1-9] The exact incidence of the syndrome is unclear as the data published in the literature are not in agreement: it is in fact reported incidence rates is 1/10,000 births in older works, and 1/20,000 to 1/40,000 births, in more recent papers. CdLS is characterized by autistic features, notably excessive repetitive behaviors and expressive language deficits.[2] The prevalence of autism spectrum disorders (ASDs) symptomatology is comparatively high in CdLS. However, the profile and developmental trajectories of these ASDs characteristics are potentially different to those observed in individuals with idiopathic ASD.[3] A significantly higher prevalence of self-injury are evident in CdLS. Self-injury was associated with repetitive and impulsive behavior.[4] This study describes the behavioral phenotype of four children with Cornelia de Lange syndrome and autism spectrum disorders.

In these subjects an evaluation of symptoms of autistic disorder has been made. This assessment should be carried out through the tools CARS (Childhood Autism Rating Scale), ADOS (Autism Diagnostic Observation Schedule), ADI-R (Autistim Diagnostic Interview, Revised). The CARS is compiled on the basis of the observation of the behavior within the unstructured context. The behavior is compared to that of a peer without difficulty. The ADOS is a semi-structured and standardized assessment of communication, social interaction, play and imaginative use of materials for individuals with ASD. The ADOS consists of standardized activities that allow the examiner to observe those behaviors that are important for the diagnosis of autism spectrum disorder in different chronological age and for different levels of development. Through this tool it can be assessed the child's behaviors in response to situations and stimulus activities predetermined by the test in order to obtain information on the characteristics of interpersonal and communication. The test is based on an evaluation framework designed to generate interactive situations that provide stimuli at the social level, through play and verbal exchanges. ADOS includes four different modules depending on the age and level of expressive language of the subject. The ADI-R is compiled together with their parents and is a semi-structured interview. It allows to compile two different algorithms. Diagnostic algorithm examines the entire history of the development of the subject and the current behavior of the algorithm, which is based on the behavior of the subject over recent months.

Case Report #1

This case concerns a female patient (age 5 years and 2 months) by psychomotor development retardation and postnatal growth retardation. She was the first-born of healthy and non-consanguineous parents with a negative history of genetic diseases. Natural delivery was at the end of the ninth month. The birth weight was 2780 g, the length was 44 cm, and the cranial circumference was 33 cm. The neonatal period was uneventful. Since the first months of life she presented retardation of psychomotor development, feeding difficulties and repeated episodes of airway infection. On physical examination, the stature was 95 cm, the weight was 12 kg, the cranial circumference was 46 cm. Examination showed characteristic facial features: eversion of the lower lateral eyelid, arched eyebrows with the lateral one-third dispersed or sparse, depressed nasal tip, and prominent ears, cleft palate, anomalies of the teeth, blue sclera, skeletal anomalies (clinodactyly of the fifth finger), dermatoglyphic abnormalities (ulnar loops on the fingertips). Neurologic examination showed esotropia (convergent strabismus), generalized hypotonia, joint laxity of the ligaments. On psychological examination, evaluation according to the WPPSI, showed a verbal IQ equal to 45 and a performance IQ of 51. Atypical behaviors included preference to be alone, selective interest in privileged objects used in a stereotyped manner, motor fretting and attention instability. To evaluate and identify the presence and intensity of autistic symptoms have been used the CARS, the ADOS and ADI-R tools. By the administration of these scales was confirmed the presence of an autism spectrum disorder. CARS has achieved an overall score of 24/60. It was used the first module of the ADOS. In language and communication the child gets a score of 4 (cut-off for autism = 4; cut-off for the autistic spectrum = 2), has occasionally echolalia and limited use of gestures restrictive. Reciprocal social interaction gets a score of 6 (cut-off for autism = 7; cut-off for the autistic spectrum = 4), makes little use of eye contact to start and end the social interaction, shows an adequate integration to request certain objects. In the game gets a score of 2, has a beginning game with functional objects, but does not use the objects as symbolic substitutes. Regarding stereotyped

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behaviors and restricted interests get a score 2, the subject has a particular interest in some materials, no mannerisms of the hands and fingers, or aggressive behaviors car. In the subject there was not revealed other abnormal behavior, but only moderate signs of anxiety. The ADI-R has detected anomalies both in the diagnostic and the current behavior in the algorithm is compatible with an autism spectrum disorder. A mutation of the gene MLL2 was identified. The results of neurologic imaging (CT and brain MRI) were normal, as were ECG, EMG, and brain stem auditory evoked potential and visual evoked potential tests.

Case Report #2

This case concerns a male patient (age 5 years and 7 months) affected by generalized epilepsy and intellectual disability. He was born after second pregnancy; the parents were non-consanguineous and their history was positive for neurologic and psychological disorders. Natural delivery was at the end of the ninth months. He has a good neonatal adaptation. The birth weight was 2970 g. the length was 48 cm, and cranial circumference was 35 cm. Psychomotor and language development were delayed. On physical examination, the height was 97 cm, the weight was 17 kg, the cranial circumference was 48 cm. Examination showed characteristic facial features: eversion of the lower lateral eyelid, arched eyebrows with the lateral one-third dispersed or sparse, depressed nasal tip, and prominent ears, cleft palate, hypodontia, bilateral cryptorchidism, brachydactyly, clinodactyly, dermatoglyphic abnormalities (ulnar loops on the fingertips). Neurologic examination showed generalized hypotonia and lax joints. On psychological examination, evaluation according to the WPPSI, showed a verbal IQ equal to 54 and a performance IQ of 66. Motor stereotypes and attitude to isolation were present. To evaluate and identify the presence and intensity of autistic symptoms have been used the CARS, the ADOS and ADI-R. By the administration of these scales was confirmed the presence of an autism spectrum disorder. To evaluate and identify the presence and intensity of autistic symptoms have been used the CARS, the ADOS and ADI-R. CARS has achieved an overall score of 28/60. It was used the first module of the ADOS. In language and communication the child gets a score of 3 (cut-off for autism = 6; cut-off for the autistic spectrum = 2), and echolalia has limited use of gestures restrictive. Reciprocal social interaction gets a score of 7 (cut-off for autism = 7; cut-off for the autistic spectrum = 5), makes little use of eye contact, does not show proper integration to request certain objects. In the game gets a score of 2, does not use the objects as symbolic substitutes. Regarding stereotyped behaviors and restricted interests get a score of 3, the subject has a particular interest in some materials, presents some stereo hands, no self aggressive behaviors. In the subject there was not revealed other abnormal behavior. The ADI-R has detected anomalies both in the diagnostic and the current behavior in the algorithm is compatible with an autism spectrum disorder. A mutation of the gene MLL2 was identified. The brain MRI scan showed cerebellar vermis atrophy. The EEG showed atypical pit waves on the bilateral center-front derivations.

Case Report #3

This case concerns a male patient (age 4 years and 7 months) affected by ASDs. He was born after second pregnancy; the parents were non-consanguineous and their history was positive for neurologic and psychological disorders. The neonatal period was uneventful. The birth weight was 3050 g. the length was 49 cm, and cranial circumference was 36 cm. Psychomotor and language development were delayed. On physical examination, the stature was 101 cm, the weight was 13 kg, the cranial circumference was 46 cm. Examination showed characteristic facial features: eversion of the lower lateral eyelid, arched eyebrows with the lateral one-third dispersed or sparse, depressed nasal tip, and prominent ears, cleft palate, anomalies of the teeth, skeletal anomalies (clinodactyly of the fifth finger), dermatoglyphic abnormalities (ulnar loops on the fingertips). Neurologic examination showed visual-motor coordination difficulty. On psychological examination, evaluation according to the WPPSI, showed a verbal IQ equal to 58 and a performance IQ of 62. Atypical behaviors included inclination to isolation, selective interest in privileged objects used in a stereotyped manner, motor fretting and attention instability. To evaluate and identify the presence and intensity of autistic symptoms have been used the CARS, the ADOS and ADI-R. To evaluate and identify the presence and intensity of autistic symptoms have been used the CARS, the ADOS and ADI-R. CARS has achieved an overall score of 26/60. It was used the first module of the ADOS. In language and communication the child gets a score of 3 (cut-off for autism = 4; cut-off for the autistic spectrum = 2), and echolalia has limited use of gestures restrictive. Reciprocal social interaction gets a score of 7 (cut-off for autism = 7; cut-off for the autistic spectrum = 4), makes little use of eye contact, does not show proper integration to request certain objects. In the game gets a score of 2, does not use the objects as symbolic substitutes. Regarding stereotyped behaviors and restricted interests scores a 3, the subject has a particular interest in some materials, presents some stereo hands, no self aggressive behaviors. In the subject there was not revealed other abnormal behavior. The ADI-R has detected anomalies both in the diagnostic and the current behavior in the algorithm is compatible with an autism spectrum disorder. By the administration of these scales was confirmed the presence of an autism spectrum disorder. A mutation of the gene MLL2 was identified. The results of neurologic imaging (CT and brain MRI) were normal, as were ECG, EMG, and brain stem auditory evoked potential and visual evoked potential tests.

Case Report #4

This case concerns a male patient (age 5 years and 7 months) affected by generalized epilepsy and intellectual disability. He was born after second pregnancy; the parents were non-consanguineous and their history was positive for neurologic and psychological disorders. Natural delivery was at the end of the ninth months. The neonatal period was uneventful. The birth weight was 2970 g. the length was 48 cm, and cranial circumference was 35 cm. Psychomotor and language development were delayed. On physical examination, the height was 97 cm, the weight was 17 kg, the cranial circumference was 48 cm. Examination showed characteristic facial features: eversion of the lower lateral eyelid, arched eyebrows with the lateral one-third dispersed or sparse, depressed nasal tip, and prominent ears, cleft palate, hypodontia, bilateral cryptorchidism, brachydactyly, clinodactyly, dermatoglyphic abnormalities (ulnar loops on the fingertips). Neurologic examination showed generalized hypotonia and lax joints. On psychological examination, evaluation according to the WPPSI, showed a verbal IQ equal to 54 and a performance IQ of 66. Motor stereotypes and attitude to isolation were present. To evaluate and identify the presence and intensity of autistic symptoms have been used the CARS, the ADOS and ADI-R. By the administration of these scales was confirmed the presence of an autism spectrum disorder. CARS has achieved an overall score of 32/60. It was used the first module of the ADOS. In language and communication the child gets a score of 2 (cut-off for autism = 4; cut-off for the autistic spectrum = 2), presents echolalia and gesture to indicate accompanied by verbal language. Reciprocal social interaction gets a score of 5 (cut-off for autism = 7; cut-off for the autistic spectrum = 4), makes little use of eye contact and shows a limited range of facial expressions. In the game gets a score of 3, but does not use the objects as symbolic substi-

tutes. Regarding stereotyped behaviors and restricted interests get a score 2, the subject has a particular interest in some materials, no self aggressive behaviors. There is no clinical signs of hyperactivity and aggression, only moderate signs of anxiety. The ADI-R has detected anomalies both in the diagnostic and the current behavior in the algorithm is compatible with an autism spectrum disorder. By the administration of these scales was confirmed the presence of an autism spectrum disorder. A mutation of the gene MLL2 was identified. The brain MRI scan showed cerebellar vermis atrophy and cerebral cortex atrophy. The EEG did not show atypical pit waves.

Discussion and Conclusions

Cornelia de Lange syndrome is associated with abnormalities on chromosomes 5, 10 and X.[6] The syndrome is characterized by a demonstrated heterogeneity genetics. Currently the confirmation of the clinical diagnosis in laboratory can be obtained in 55-60% of cases. In fact, 45-50% of patients have a mutation in the *NIPBL* gene (located on short arm of chromosome 5), while a further 5% have mutations in the gene *SMC1L1* (localized instead on the short arm of the X chromosome). A third gene (*SMC3*) has been described as related to the syndrome in only one patient. All of these genes encode for proteins belonging to the group of coesine/aderine chromosome.[6-9] The diagnosis is therefore primarily clinical. Given the high variability of expression of the syndrome in some patients, the diagnosis can be made from birth, while in others the suspected diagnosis can be made in childhood or even in adulthood. Prenatal diagnosis is quite complex.[9] It is possible carries out a search of the mutation specification of fetal DNA present in the family obtained by chorionic villus sampling oramniocentesis. In a pregnancy is not at risk, however, can be present some nonspecific sonographic indicators (delay growth restriction) or more specific (defect in limb reduction especially for the segments of derivation ulnar somatic anomalies, diaphragmatic hernia), which may possibly give rise to the clinical suspicion.[7-21] Psychomotor development and intellectual are constantly slowed.

Partial epilepsy is the most common type of epilepsy in CdLS patients. In the majority of cases the prognosis of this epilepsy is favorable and therapy can be withdrawn after few years of complete seizure control.[20]

They were also shown a series of behavioral characteristics associated with CdLS, including aggressive behavior, hyperactivity and autistic traits, such as difficulties in socialization.[6] Self-injurious behavior is one of the most clinically relevant characteristics. Certain forms of self-injurious behavior in some individuals with CdLS are associated with environmental events.[3-6] Prevalence of autism spectrum disorder characteristics is heightened in CdLS. The profile of characteristics is atypical to that of idiopathic autism.[2-3,7,22] Autism has been reported to occur frequently in CdLS, but the frequency of autism in individuals with the milder CdLS phenotype is not well studied.[1] Autistic symptom severity was not significantly different by gender, age groups, and genotypes. There was a significant correlation between higher levels of adaptive functioning and lower scores of autistic symptoms.[1] The comparison between CdLS and idiopathic ASDs indicates subtle group differences in the profile of ASDs symptomatology that are not accounted for by degree of intellectual disability or receptive language skills. These differences may not be evident when relying solely upon clinical and domain level scores, but may be distinguishing features of the ASDs presentations in the two disorders. The findings have implications for the conceptualization and assessment of ASDs in individuals with genetic syndromes.[3] In addition, the syndrome also evidenced significantly higher levels of compulsive behavior. These data suggest that autistic-spectrum disorder is part of the behavioral phenotype of CdLS syndrome and that compulsive behaviors are evident.[6] The area of communication and language is a particularly critical in children with CdLS.[23,24] The expressive language is not reached by a significant number of subjects, and also those who acquire verbal language, they do late.[23] There is a discrepancy in terms of expressive vocabulary and possess the skills of grammar and syntax.[24] In the early years of life, there are less intentional communicative behaviors than is the case in other genetic syndromes, and this seems to be an important early indicator of subsequent development of language and behavior problems.[23] Morpho-syntactic skills are fundamental to the understanding of the phrase, seem selectively compromised and would seem to be one of the factors that most influence the prognosis of development and the occurrence of problem behaviors.[7,16-22] The knowledge of the behavioral phenotype of CdLS led to believe that an early and timely intervention of Augmentative and Alternative Communication (AAC) can be an important support for the development of communication and language, and for the prevention of disorders of behavior in all children with CdLS.[23,24] The intervention of AAC in CdLS must include the early transmission of information to families on the importance of the communicative aspects and linguistic development of their children.[23-24] Specific attention should then be devoted to social anxiety in adolescence, with the introduction of strips of activities, agendas and routines that may not be strictly necessary in previous years, but that in adolescence are essential to decrease anxiety and enable the achievement of greater autonomy and control. Individuals with CdLS demonstrate a heightened probability of anxiety related behavior during social interaction but only at the point at which social demand is high.[25] Behavioral issues and specific psychiatric diagnoses, including self-injury, anxiety, attention-deficit disorder, autistic features, depression, and obsessive-compulsive behavior, often worsen with age.[8] Behavioral problems were highly correlated with the level of adaptive functioning, and also included autism. No correlation of behavior with the type of mutation was found.[9] Clinicians who take care of individuals with CdLS should have a high index of suspicion for autistic features, and refer for further evaluation when these features are present in order to expedite appropriate intervention.[1] This study describes the behavioral phenotype of four children with Cornelia de Lange syndrome and autism spectrum disorders. In these subjects an evaluation of symptoms of autistic disorder has been made by means of CARS, ADOS and ADI-R tools (Table 1). In the cases described here psycho-educational and cognitive-behavioral interventions with several times a week have been recommended. To further increase the capacity of understanding (receptive communication) we suggested to provide a structure and a clarification of the physical environment: each place has to be dedicated to a single activity. Different places have been organized offering visual information of the task. To facilitate the understanding of environmental stimuli, has been suggested as a permanent constant use of visual, verbal

Table 1. Scores of Autism Diagnostic Observation Schedule (ADOS) and Childhood Autism Rating Scale (CARS) tools.

Tools	Case 1	Case 2	Case 3	Case 4
ADOS, language and communication	4	3	3	2
ADOS, reciprocal social interaction	6	7	7	5
ADOS, game	2	2	2	3
ADOS, stereotyped behaviors and restricted interests	2	3	3	2
CARS	24	28	26	32

communications riots that accompanied the subject. It has been improved intentionality in spontaneous communication with strangers (expressive communication). Besides, other appropriate treatments to improve the quality of life of patients are represented by the direct contact with nature and enjoyment of the rural landscape.[26-29] Future research should investigate this behavioral phenotype using contemporary diagnostic algorithms for autism with detailed examination of the phenomenology of compulsive behaviors.[6] The variability of the behavioral profile in CdLS reflected the wide variability in cognitive and adaptive functioning across individuals and led us to conclude that there may be multiple behavioral phenotypes associated with the syndrome. Further comparative studies between CdLS and individuals with intellectual disability or other genetic syndromes may help to provide further understanding of the behavioral phenotype of CdLS.[7]

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