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Research Article

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Progression of Autism in a Young Woman with CHARGE Syndrome: A Longitudinal Follow-up from Birth

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Abstract

CHARGE syndrome (CS) is a rare genetic disease involving somatic malformations and multisensory impairments. The association of CS with autism spectrum disorders remains a controversial issue because it remains challenging to clinically assess symptoms of autism in young children with potential severe somatic conditions, deaf blindness and mental delay and the behavior troubles often encountered in individuals with CS can be considered the consequence of their multisensory deficits and medical history. We report the complex developmental trajectory of a 25-year-old girl with typical CS, with emotional disorders and problematic behaviors that led to a diagnosis of autism. Addressed by a multidimensional and integrative perspective, this situation reveals the coexistence of factors and impairments not causally connected but whose constant interactions during her development must be evaluated. In this way, clinicians can achieve a functional diagnosis enabling the elaboration of a tailored therapeutic proposal.

Keywords

CHARGE syndrome; Deaf blindness; Behavior troubles; Autism

Introduction

CHARGE syndrome (CS) (OMIM 214800) is a rare genetic disease that involves somatic malformations (cardiac, ear, renal, digestive, brain, skeletal etc.) and sensory deficits (hearing, visual, smell and balance impairments) that result in various final phenotypes. The term "CHARGE" is an acronym that describes the features initially considered major: Coloboma, Heart defects, Atresia of the choanae, Retardation of growth and/or development, Genitourinary anomalies, and Ear abnormalities [1-3]. The psychomotor development of children with CS is very often delayed, but their adult mental capacity ranges from profound intellectual disability to normal intelligence [4]. Whatever the phenotype, children with CS often show peculiar behaviors, many of them paralleling autistic-like characteristics, including sensory integration dysfunction [5]. Autistic-like traits have been reported in patients with CS [6-9] and seem to increase with the degree of somatic involvement, and the severity of intellectual disability and sensory impairment, but this development of autism over time has not been described.

We present the longitudinal follow-up, over 25 years, of the behaviour anomalies of a girl with CHARGE syndrome, with initial mental level in the normal range, who exhibited severe autism.

Case Study

C was born at term with weight, length and head circumference within the normal ranges. She is the only child of healthy parents who both have a high level of education. CHARGE syndrome was diagnosed soon after birth with the presence of a cardiac malformation (atrioventricular septal defect), typical external ear anomalies, unilateral facial palsy, and sucking and swallowing deficits. The first years of life were particularly traumatizing and exhausting for the child and her parents because she had chronic cardiorespiratory distress requiring nasal oxygenation and choking episodes. She spent most of her time in hospital until the second cardiac surgery at age 2 that was successful. C needed gastric-tube feeding from birth and then underwent gastrostomy at age 6 months. During the third year, the parents insisted on feeding by mouth and the gastrointestinal tube could be removed at age 3 years. The complete assessment of the malformative syndrome showed, as is usual in typical CHARGE syndrome, bilateral aplasia of semicircular canals, microphthalmia and coloboma of the macula resulting in very low vision in the left eye but good vision and no coloboma in the right eye, cophosis in the left ear and mild hearing loss (30 dB) in the right ear, and brain abnormalities on MRI (thin corpus callosum, cerebellar vermis hypoplasia). She had no other malformations. We confirmed the diagnosis with the identification of a *de novo* mutation in the CHD7 gene (c1480 C>T).

As an infant, C had major hypotonia and acquired the sitting position without support only at 15 months, but she improved rapidly after age 30 months, when she returned home from the hospital. She could walk at age 31 months and had good communication skills. She went to a kindergarten from age 3 years, with good adaptation and no behavioral disorders. The attainment of oral language was nearly normal. At age 3.5 years, C had trans tympanic tubes inserted for seromucous otitis (50-dB deficit). However, at age 4, the hearing from her right (and good) ear worsened without explanation and she needed a hearing aid. Her behavior started to change, with more anxiety and restlessness. Nevertheless, C started school at a normal school, but after 2 years, along with her hearing loss, she presented behavioral difficulties: she was hyperactive, had difficulties complying with rules, and displayed aggressiveness with her peers, with impulsive reactions. At age 6, these difficulties required the prescription of antipsychotic treatment with an anxiolytic aim (thioridazine) and led to a school change. At age 6, C attended a specialized school for deaf children. At this time, she was in a reassuring environment and showed improved school achievements and behavior. The diagnosis of autism was ruled out considering that the early behavioral manifestations were transient and secondary to the developmental issue due to her sensory deficit and personality.

At age 10, C exhibited a homogeneous intellectual profile within the normal range, as shown by IQ measurement with the Wechsler Intelligence Scale for Children-revised [10] (Table 1); she spoke fluently and had a good understanding of oral language via excellent lip-reading associated with cued speech. Concerning motor skills, she could hop on one leg but displayed visuo-spatial difficulties.

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Between age 10 and 12, C's hearing loss progressed to profound deafness between type II and III in the right ear and reduced her oral language. Finally, at age 12, she benefited from the placement of a right cochlear implant with good prosthetic gain because the hearing deficit was 30 dB with the implant. During all these years, her cardiac, respiratory, digestive, and global health was good. Her visual state was stable.

Attending normal secondary school (age 12 years) even with adaptations was a failure (too demanding and stressful). C's behavioral issues worsened when she tried to cope with requirements from her environment. She exhibited self-aggressive behaviors (wrist biting, clawing, hitting her head) and hetero-aggressive behaviors with intolerance to frustration toward her peers, teachers and family. She showed a restrictive interest in dolls and subways. She set rituals in her everyday life that had to be respected or she resisted and became aggressive. She exhibited hand flapping and prancing movements when she was happy. At age 13/14 years, her school learning progress stagnated. At age 16/17, C began to exhibit self-induced violence to her face, glasses and hearing aids when feeling frustration and began to experience panic attacks. A complete pediatric assessment did not show any organic disease explaining the exacerbation, throughout development, of her behavioral difficulties. Neurological examination and electroencephalography findings were normal.

To organize a care project addressing the complexity of the pathology, at age 17, a thorough multidisciplinary evaluation in a psychiatric day unit was decided. The diagnosis was autism spectrum disorder (ASD) comorbid with an anxio-depressive syndrome. ASD was diagnosed according to the DSM-IV criteria, [11] with serious social interaction difficulties, a lack of friendly relations and a tendency to isolation, poor relationships with her parents and very close adults, and major difficulties sharing emotions and lack of understanding of most social rules. In terms of communication, despite her ability to be understood, C showed little reciprocity in exchanges with peers or adults apart from those centered on her own interests. Finally, she presented repetitive and stereotypic behaviors (biting her wrists, rubbing her face, and twisting her nose and turning around when happy), which interfered with her daily routines.

The Autism Diagnostic Interview–Revised (ADI–R) [12] confirmed difficulties in the three domains "reciprocal social interaction", "communication", and "stereotyped and repetitive pattern of behaviors" (scores 18, 8 and 5, respectively), all above the cut-offs for a diagnosis of childhood autism in verbal subjects (cut-off for reciprocal social interaction = 10, max = 30; cut-off for communication = 8, max = 26; and cut-off for repetitive behaviors = 3, max = 12). Moreover, the use of the "current" and "at the age of 5" algorithms of the ADI that her parents completed a posteriori showed that her behavior was already abnormal at age 5 (14, 11 and 5 for the

Table 1: Cognitive and developmental assessments at ages 10, 17 and 23 in a female with CHARGE syndrome.

Assessments	10 y	17 y	23 y	Comments
General cognition Wechsler scales		**WAIS-III**	**WNV**	
Verbal IQ		69		Decreased intellectual level between ages 10 and 17, from a normal level to a mild intellectual disability. However, at 17, intercalary results show a heterogeneous profile. Verbal comprehension and perceptual organization index, contrary to the 2 other sub scores are at the limit intellectual level. At 23, the intellectual level declined even more, reaching a moderate level. However, the patient had significant abilities in perceptive reasoning and in working visual memory as compared to substantial difficulties in visual processing.
Performance IQ	**WISC-R**	63		
Verbal comprehension index	91	79		
Perceptual organization index	98	75		
Working memory index		67		
Processing speed index		50		
Total score		**64**	**46**	
Matrix reasoning			38	
Digit symbol coding	**93**		10	
Spatial memory			24	
Pictures arrangement			17	
VABS: raw score (equivalent age) Communication domain		115 (8.9)	122 (10.3)	At age 17 and 23, scores are comparable to those of people with mild intellectual disability. Results are heterogeneous, with the highest scores in the field of communication as compared with the socialization domain, which is the most disabled.
Daily living skills domain		130 (8.2)	140 (9.6)	
Socialization domain		58 (3.1)	83 (5.7)	
Oral language assessment*				Results reveal impairments in all domains of language, in comprehension and expression, which are underlined by the dual sensory loss. However, these results are heterogeneous: in comprehension as well as in production C has low average level on lexicon and marked difficulties in morphosyntax and pragmatics and highly developed language.
Comprehension				
Lexicon EVIP		27 percentile		
Morphosyntax ECOSSE		5 years		
Picture designation KIKOU		8-9 years		
Morphosyntax vs withholding KIKOU		6-7 years		
Pragmatics PELEA		-3.8 SD		
Highly developed language PELEA				
Incongruities		-3 SD		
Metaphors		-8.7 SD		
Production				
Phonology				
Repetition without lip-reading		82% success rate		
Repetition with lip-reading		96% success rate		
Lexicon DEN 48 – ECLA 16+		-1.1 to 6.5 SD		
Morphosyntax L2MA2		-1.4 to 0.5 SD		
Pragmatics PELEA		-3 SD		
Highly developed language PELEA		-5.5 SD		

VABS: Vineland Adaptive Behavioral Scale. VIQ: Verbal Intelligence Quotient. PIQ: Performance Intelligence Quotient. TIQ: Total Intelligence Quotient. WISC-R: Wechsler Intelligence Scale for Children–Revised. WAIS-III, Wechsler Adult Intelligence Scale, third version. WNV, Wechsler Nonverbal Scale of Ability. ECOSSE: Epreuve de compréhension morphosyntaxique [Test of morphosyntactic comprehension] (Lecocq, 1996). Protocole d'Évaluation du Langage Élaboré de l'Adolescent de 11 à 18 ans. [Assessment Protocol for the Elaborated Language of the Adolescent from 11 to 18 years] Boutard et al. (2010).* scores are given in equivalent age, percentile from age class, distance to mean expressed in standard deviation (SD) from a comparison validation sample.

3 scores, respectively). Then, C had articulation difficulties, spoke too loudly and used neologisms. At that time, the signs were explained by the increase in hearing loss. At age 5, she showed good imitation skills and could use conventional gestures, nod and shake her head; she showed good use of non-verbal behaviors to regulate social interactions, such as direct gaze, social smiling and a variety of facial expressions. The evolution of responses to the ADI from "at the age of 5" to "current" behavior showed an aggravation in social interaction, with increasing difficulties in sharing pleasure and interests with her parents.

Her scores were low on the Vineland Adaptive Behavioral Scale [13], which measures socio-adaptative behavior in communication, daily living skills, and socialization, especially the socialization sub-score, which showed both the intellectual regression and specific problems in socialization (Table 1). At ages 17 and 23, measurement by the Childhood Autism Rating Scale [14], which scores autism severity (from 1=normal, to 4=very severe signs of autism), confirmed the presence of severe impairments in body use, emotional responses, substantial aloofness and difficulties in coping with change. Most of the sub-scores were between 3 and 4. The re-test at 23 showed a slight improvement because of pharmacological and psychological treatments but the same profile (Figure 1).

From age 22, C regularly injured her right (and only good) eye, which led to retinal hemorrhagic detachment and near total blindness. Her intellectual level decreased, and her intelligence profile tested by the Wechsler Adult Intelligence Scale, third version [15], became heterogeneous: results revealed an intellectual level in the boundary zone for verbal comprehension and perceptive organization and in the zone of mild intellectual disability for working memory capacities and IQ processing speed including visual-processing. The oral language examination revealed global and severe impairment, with low scores for comprehension and expression, especially concerning morphosyntax, pragmatics and elaborated language tests (Table 1). At age 23, the sensory profile assessed by the Dunn questionnaire [16] confirmed the striking emotional reactivity, anxiety and difficulty coping with changes in the environment and regulating emotions (tantrums, difficulties in resisting frustration, crying easily) (32/80; significant difference with score<36) and revealed pronounced fatigability, with low muscle tone (26/45; significant difference with score<31).

C is now a young adult, with intellectual disability, blindness, low audition, major anxiety, difficulties regulating her emotions, repetitive actions, and continual questioning. She has lost autonomy and probably her ability to learn. Because of her behavior troubles and visual and audition deficits, finding an adapted care center is difficult. She stays part time at home with her parents and part time in a day center for autistic patients, receiving an anxiolytic and mood stabilizer drug treatment (i.e., diazepam and lithium carbonate), psychological support and relaxing physiotherapy.

Discussion

This case report raises several questions about the links between CHARGE syndrome and autism. The first question is the definition of ASD in light of behavioral troubles in children with complex congenital disorders, with good reasons for their development: precocious and severe somatic lesions; negative effects of the separation from parents during the first months of life; multiple sensory deficits, especially those implicated in relations with others — hearing and vision. Similarly autistic-like features are common in children with deaf blindness in terms of 1) lack of social interaction [17] 2) communication impairments including difficulties in pragmatics [18] and 3) atypical or stereotyped behaviors with their bodies and objects [19]. Hence, during all of C's childhood, we considered that her behavior difficulties were the consequence of her experiences and sensory deficits only. However, on assessment at age 17, the diagnosis of autism was clear, by the clinical definition in the DSM-IV and by specific scales for autism (Childhood Autism Rating Scale and ADI).

The second question is what are the causative factors of this autism? Could we consider autistic symptoms that occurred as soon

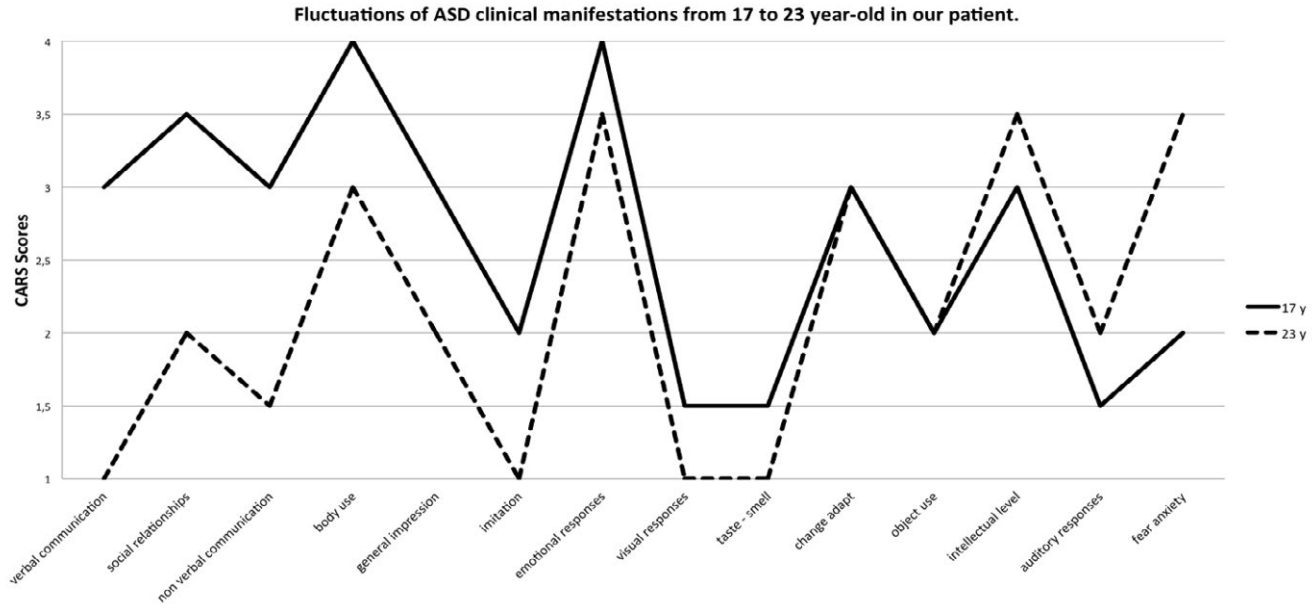

Figure 1: Sub-scores of Childhood Autism Rating Scale (CARS) at ages 17 and 23 in a female with CHARGE syndrome. ASD, autism spectrum disorder.

as C entered nursery school as the unique consequence of both her sensory deficits and her severe medical conditions during her first 3 years? If so, how can we explain, at age 17 and 23 years, the gap between her communication abilities, which were relatively well-preserved, and her social interaction skills, which were severely impaired? Furthermore, how can we explain her abnormal behaviors continuing to worsen during a period of improvement of her hearing abilities (as a result of her cochlear implant at age 12) and her visual acuity (with better visual correction at 17)?

Third, how can we explain the worsening of her autism despite good therapeutic and reeducation intake? This progression is unusual for children with ASDs, especially those with normal IQ [20,21]. Perhaps we underestimated her anxiety. C likely experienced repeated stress from her surrounding that was underestimated. She did not obviously react during her painful first years of life. Because her parents and therapists were both demanding and supportive at this time, she succeeded in walking, speaking, and beginning normal school. However, progressively, her anxiety, the contrast between her capacities and what was asked of her and the first decrease in hearing led to a vicious cycle, until the last step of her sensorial worsening, when she definitively damaged her good eye. Finally, we retrospectively found that autistic-like symptoms were subtle but present when she was 5 years old. No one — neither her family nor medical and re-education teams - mentioned these symptoms because the condition was not yet well known by teams dealing with CS in the beginning of the 1990s.

According to the complexity of the CHARGE developmental disorder, a multidimensional approach with a developmental and integrative perspective could be useful [22]. Integration considers child development as formed by the interaction between different dimensions and puts into perspective various complementary influences. Any factor that affects interactions can increase the severity of autistic symptoms or problematic behaviors because of this population's need to control events and social ties. In this way, the dual sensory loss, according to Johansson (9), as well as the vestibular dysfunction with balance impairments in CS [23] could contribute to aggravating those symptoms. The regular worsening, during childhood, of the challenging behaviors and related emotional disorders (anxiety and depressive disorders) must be understood as the consequence of an interplay between several factors: 1) the fact that C spent her first 3 years of life in the hospital, 2) multisensory impairments and aggravation, 3) autistic symptoms with social interaction impairments and 4) a decrease in intellectual level. Indeed, according to Johansson (9), the severity of autistic behaviors in CS is linked to the severity of intellectual impairment. Moreover, C's experience of this decrease in her intellectual abilities as well as her intellectual disability per se could be the source of difficulties that include oppositionality, anxiety, and poor peer-related social competencies [24].

Conclusion

This case report emphasizes the importance of recognizing precocious behavioral disorders in children with CS and the importance of a multidimensional assessment of patients with complex developmental disorders such as CS. The presence and importance of autistic-like traits in children with CS must be investigated in depth to try to understand the emergence of the symptoms, find their causes and prevent their aggravation in adapting their educational and therapeutical surrounding to promote the child's development.

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