Drug resistant epilepsy in a young male with Cat Eye Syndrome: a case study

Annapia Verri1
Michele Terzaghi2
Marina Maffoni3
Rossella Caselli4
Ilaria Catusi4
Maria Paola Recalcati4
Elisa Rognone1

1 Istituto Neurologico Nazionale C. Mondino - IRCCS, Pavia, Italy
2 Unit of Sleep Medicine and Epilepsy, Istituto Neurologico Nazionale C. Mondino - IRCCS, Pavia, Italy
3 Department of Brain and Behavioral Sciences - Psychology, University of Pavia, Italy
4 Laboratorio Citogenetica Medica e Genetica Molecolare, Istituto Auxologico Italiano, IRCCS, Milano, Italy

Corresponding author:
Annapia Verri
Consulente
IRCCS Fondazione Istituto Neurologico Nazionale, C. Mondino Via Mondino 2
27100 Pavia, Italia
E-mail: annapia.verri@mondino.it

Abstract

The Cat Eye Syndrome (CES) is a rare syndrome associated with gains of the pericentromeric region of chromosome 22. It is usually characterized by multiorgan and physical malformation, skeletal problems, short stature, anal atresia and moderate to severe intellectual disability. We present a case study of a 31-year-old male affected by tetrasomy in the q11.1q11.21 region of the chromosome 22. We also carried out clinical, neurophysiological and neuroradiological evaluations, and psychometric assessment. Moreover, the patient underwent Array-CGH, conventional cytogenetic and FISH analysis. Clinically, we observed a pulmonary venous malformation which had been surgically treated, and several physical malformations. From a neurological point of view, we observed the following characterizing elements: intellectual disability, adaptive impairment and focal epilepsy. Seizures were characterized by loss of contact, staring, face pallor, motor stereotypes such as nose scratching, bimanual automatisms, chewing and severe asthenia. As the child grew seizures became more and more frequent (up to one/two episodes a day) and were drug resistant. Prolonged EEG recordings captured focal seizures originating on the left temporal leads. Magnetic resonance imaging (MRI) documented thinning of the corpus callosum, hypomyelination of the semi-oval centers, extensive and multifocal subcortical malacic areas and gliosis in the brain. Although seizure characterization is lacking in CES, in the present case, paralleling anatomic defects and intellectual disability, epilepsy emerged as a main disturbance in the clinical picture of CES.

KEY WORDS: Cat Eye Syndrome, tetrasomy chromosome 22q11, drug resistant epilepsy, EEG, intellectual disability.

Introduction

The region 22q11 is susceptible to chromosomal rearrangements, leading to various types of congenital malformation and intellectual disability. Several genomic well-described disorders include Cat Eye Syndrome (CES) and DiGeorge/Velocardiofacial syndrome (DGS/VCFS). CES was clinically described for the first time by Haab et al. in the 1879 (1). The name of the syndrome derived by the particular shape of vertical colobomas in the eyes of patients. However, later the eye coloboma was no more required for the diagnosis (2) because numerous CES patients do not show this sign. To date, it is also known as Schmid-Fraccaro Syndrome (2), the two Authors who coined first the peculiar name of CES. However, CES is also called chromosome 22 partial tetrasomy or inverted duplicated 22q11. The more characteristic clinical features of this syndrome are renal and cardiac malformations, cleft palate, micrognathia, preauricular pits/tags, dysmorphic features (downward-slanting palpebral fissures, hypertelorism), unilateral or bilateral eye coloboma, hernias, scoliosis or skeletal problems, short stature and anal atresia, moderate to severe intellectual disability (3). This syndrome is quite rare and it occurs with a fre-
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Frequency of about 1:150,000 liveborn (4). Nevertheless several cases of CES are reported in the literature (3, 5).

Furthermore, epilepsy is reported being one possible comorbidity in CES (3) as well as in other chromosome 22q11 aberrations. Literature reports few CES patients with different kinds of seizures in their history (6-8) and more cases of epilepsy in chromosome 22q11 anomalies (9-18).

In the present paper, we report on a young adult with tetrasomy of the region 22q11.1q11.21 associated with drug resistant epilepsy, severe intellectual disability and cranial and facial dysmorphic features.

Methods

Clinical and instrumental evaluations
Routine clinical, neurophysiological, neuroradiological and psychometric evaluation were carried out during the annual clinical check-ups of the patient. Genetic evaluation was performed using Cytogenetic and Fluorescence In Situ Hybridisation (FISH) Analysis and Array based Comparative Genomic Hybridization (array-CGH) Analysis.

Case presentation

The patient, a 31-years-old male, was the second-born from healthy non consanguineous parents. The pregnancy was regular and the childbirth was natural. The newborn’s weight was 3350 g and his height was 54 cm. He was breastfed the 1st weeks, thereafter he received a formula. Weaning was at the age of 6 months, without any food intolerance.

At birth, a cardiac total anomalous pulmonary venous return was diagnosed and surgical correction was immediately performed. Actually, the patient is regularly checked-up by the cardiologist and his cardiovascular status is quite positive. At the age of two years, the patient presented sporadic episodes of loss of contact and incontinence, followed by severe asthenia. No other signs or symptoms were reported.

When he was six-year-old, a nasal fistula was surgically corrected. The same surgical procedure was repeated when he was 20 years old.

Developmental milestones were severely delayed: independent walking was attained after 3 years. Moreover, no language development is observed to date. Indeed, although on speech/language therapy since the first years of life, the patient now articulates only very few words (“mum”, “dad” and his brother’s nickname). Bowel and bladder control is regular, except during the seizure episodes. However, no neurodevelopmental regression has been detected during the lifetime, differently from what previously reported in literature (17).

From a relational and emotional point of view, the mother reported affection and sociability since the first childhood. Nevertheless, the patient has ever been able to cry.

The patient’s school career was characterized by support teachers from kindergarten to middle school. Currently, he is able to write his name and to recognize the alphabetic letters.

The seizures severity worsened with the patient growth. At the age of 2 years, the patient presented episodes which lasted 15 to 30 seconds, featured by loss of contact, staring, face pallor, motor stereotypes such as nose scratching, bimanual automatisms and chewing, followed by severe asthenia. No aura was reported. The seizures occurred several times a week, only rare intervals of few days without seizures were observed. During the time, seizures became more frequent (up to one/two episodes a day) and epilepsy more and more challenging the patient’s and his caregivers’ routine. Multiple antiepileptic regimen at maximum tolerated doses failed to control seizures; actually he is treated with a daily dose of Levetiracetam 2500 mg/day, with a daily dose of Oxtcarbazepine 900 mg/day. Blood levels are the following: Levetiracetam 21.68 µg/mL, Oxtcarbazepine 25.67 µg/mL. The basal electroencephalohiography (EEG) at the age of 30 years showed slow background activity with theta and delta activity on temporal leads. During NREM sleep spikes and waves were detectable on the same derivations. Prolonged EEG recordings captured focal seizures originating on the left temporal leads (Fig. 1).

At neurological examination, he presents spastic tetraparesis more marked on the right side, turricephaly, ocular hypertelorism, transparent cornea, round and centered pupil, epiphora, blepharitis, obstructed nasolacrimal ducts and nasal fistula. The upper limbs show a bilaterally reduced tone and asymmetric osteo-tendon reflexes. The right leg is ~ 2 cm shorter than the left and severe kyphosis is present in the thoracic and cervical spine.

The magnetic resonance imaging (MRI) of the brain, with particular focus on temporal lobes, documented thinning of the corpus callosum, hypomyelination of the semi-oval centers, extensive, multifocal, subcortical malacic areas and gliosis (Fig. 2 A, B).

The cognitive phenotype is characterized by severe intellectual disability like attested by the performance on Raven’s Colored Progressive Matrices (19) (corrected score: 7/36; <5th percentile). Learning disabilities and specific language impairment are also present.

Furthermore, a behavioral evaluation was also carried out. Compared to a population with intellectual disability, according to the Adaptive Behavior Inventory - ABI (20), Self-Care Skills (2nd percentile), Communication Skills (1st percentile) and Occupational Skills (9th percentile) emerged being significantly deficient. Academic Skills were borderline (25th percentile), whereas Social Skills were in the range (50th percentile).

At the Vineland Adaptive Behavior Scales (21), Communication (raw score: 73) and Daily Living Skills (raw score: 109) are significantly deficient compared
to the target population with severe intellectual disability. Matched to the same clinical population, Motor Skills were in the normal range (raw score: 76) and Socialization subscale was above the mean (raw score: 137).

Generally, behavioral phenotype is characterized by reduced adaptive capacities. Only social skills seem better preserved, although are not adequate to efficaciously living in the environment. Furthermore, hypersensitivity to noise is also reported. He also shows fearfulness of painful situations and the presence of ritualistic behaviors.

From a genetically point of view, at the age of two years, the cytogenetics analysis revealed the presence of a bisatellited small dicentric supernumerary marker chromosome (karyotype 47,XY,+mar, Fig. 3 A). Subsequently, at the age of 24 yrs, the array based comparative genomic hybridization technique (Array-CGH) detected the tetrasomy of about 1.55 Mb region on chromosome 22q11.1q11.21 [arr(hg19) 22q11.1q11.21(17,096,855-18,641,468)x4, Fig. 3 B]. Fluorescence in situ hybridization (FISH) analysis confirmed that the marker contains two copies of the 22q11.1q11.21 region (Fig. 3 C).

Discussion

In the present paper we describe the case of a 31-years-old male with CES resulting from a tetrasomy in the 22q11.1q11.21 region, associated with severe intellectual disabilities and drug resistant epilepsy. CES is rare and is associated with a very heterogeneous phenotype. Indeed, only less than 10% of these patients show the full triad of symptoms, i.e. unilateral or bilateral eye coloboma, anal atresia and preauricular pits/tags (3). Nevertheless, some clinical feature like congenital heart defects and physical malformations are frequently reported (3, 5). This patient presented total anomalous pulmonary

Figure 1 - 24-hour EEG captured focal seizure originating and evolving over the left leads.

Figure 2 - (A) MRI FLAIR; (B) MRI T1SE.
venous return surgically treated like elsewhere reported (8) associated with some CES dysmorphic features. Furthermore, the patient presents also some classical physical malformations like ocular hypertelorism (6, 7, 22), long and asymmetric face (8). From a cognitive and behavioural point of view, the patient presents a severe cognitive disability (7) and a significant impairment in adaptive behaviour and autonomy. In addition, severe speech/language impairment is present and our patient can pronounce very few words. Intellectual disability, speech delay and autistic spectrum disorder are already shown as possible comorbidity with 22q11 anomaly (23).

The main comorbidity of our patient is drug resistant focal epilepsy. Epilepsy is more common in mentally handicapped people than in general population, as well as it increases with the severity of the impairment (24). This difficult comorbidity condition challenges the patient’s and his caregivers’ daily living, as well as it compounds the care system (25). Moreover, epilepsy may be under-diagnosed in mentally retarded or syndromic patients because of the misleading symptoms of other comorbidity condition (26, 27). Indeed, stereotypical pathological or drug induced behavioral, communication and interaction problems, as well as other neurological/psychiatric symptoms may be misinterpreted by caregivers and clinicians. Despite neurological abnormalities are frequent in CES, epilepsy is included in the minor features of the syndrome being reported only in about 6% of the cases (3). Recently, Addis et al. (28), has shown that 22q11.2 duplication could be one of the gene pathway involved in the epileptogenesis of absence seizures. However, seizure characterization is lacking in CES. Valvo et al. (17) reviewed the clinical characteristics of individuals affected by 22q11 microduplication with seizures or abnormal EEG and described three cases of focal epilepsy, two of spasms and one of myoclonic seizures. In our case report, we describe seizures occurring early in life and persisting as drug resistant focal epilepsy. EEG characterization allowed us to define the seizures as originating from the left temporal lobe in a picture of probably symptomatic epilepsy, despite MRI study failed to find specific alteration in the temporal lobes. This seizures pattern differs from that previously described (17) in a case of 22q11.2 microduplication in a young girl affected by epilepsy with continuous spike and waves during sleep. Moreover, no myoclonic jerks (16) has been reported in our patient.

In our case, paralleling anatomic defects and intellectual disability, epilepsy emerged as a main disturbance in the clinical picture of CES.

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Conflict of interest

The Authors declare that they have no conflict of interest.

Ethical Standards

The requirement of a formal endorsement was waived for this descriptive communication that has been reported in accordance with the Declaration of Helsinki ethical standards. Written informed consent was obtained from the patient’s tutor (mother) for scientific purpose.

The present case was partially presented in a poster at the following meeting


References