

4q- Deletion Syndrome: Psychiatric Symptoms in a Rare Chromosomal Disorder

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Abstract

We present the case of an 18-year-old man with the karyotype 46, XY, del (4) (q21.1q21.3), and describe in detail the clinical findings, with emphasis on the psychiatric symptoms and their management. 4q- syndrome comprises all deletions of the long arm of chromosome 4. It consists of facial and digital dysmorphisms, skeletal and cardiac defects, growth retardation and learning difficulties. Our report contributes to the understanding of the natural history and management of this rare chromosomal disorder.

Keywords: Developmental disorders; Challenging behavior; Mental illness; Intellectual disabilities; 4q- syndrome; Rare chromosome disorders

Introduction

Developmental disorders comprise a heterogeneous group of conditions characterized by an interruption in normal development during childhood with many etiologies. These include individuals with genetic syndromes, autism spectrum disorders and individuals who have suffered medical or environmental insults in the prenatal period or during childhood [1,2]. The prevalence of depression, anxiety and psychosis is high in this population, with 30-64% of patients developing comorbid psychiatric conditions [2].

We report the case of an 18 years old man with karyotype 46, XY, del (4) (q21.1q21.3), and describe his psychiatric symptoms and respective management. The term 4q- syndrome was used for the first time by Townes and colleagues referring to chromosome deletions at the breakpoint 4q31 [3], and was later extended to include terminal deletions. The following Table 1 summarizes the 4q syndrome features, organized by system.

The main features of this syndrome are mild facial and digital dysmorphism, developmental delay, growth retardation and skeletal and cardiac abnormalities [3-6]. Autistic spectrum disorder has a significant incidence of 33% in 4q deletion syndrome [7]. The available research supports the existence of a common phenotype in children with deletions of the long arm of chromosome 4, which is partly explained by epigenetics [4]. A hypothetical partial phenotype-genotype map was made for chromosome 4q, which includes BMP3, SEC31A, MAPK10, SPARCL1, DMP1, IBSP, PKD2, GRID2, PITX2, NEUROG2, ANK2, FGF2, HAND2, and DUX4 genes [8]. The evidence in the available articles supports that the molecular characterization of breakpoints is essential for the management of these patients [6].

Facial dysmorphism	Frontal bossing; upwards slanting eyes; hypertelorism; low set ears; wide nasal bridge; receding chin; short neck; enamel defects
Digital dysmorphism	Short fingers and toes; clinodactyly
Musculoskeletal	Scoliosis; Neonatal hypotonia
Vision and hearing	Deafness; impaired vision
Neuro-developmental problems	Severe speech delay; behavioural difficulties; intellectual disability

Table 1: Syndrome features del (4) (q21.1q21.3), organized by system.

Clinical Case

A Caucasian non-consanguineous couple in their late twenty's, with no relevant family history, got pregnant naturally. Three ultrasound screening scans were performed during pregnancy at 12, 21 and 32 weeks. The pregnancy progressed well apart from the late period when oligoamnios occurred. This resulted in fetal distress and a caesarean section was performed. The patient was born with 3100g, hypotonic and with facial dysmorphism, including up-slanting palpebral fissures. Furthermore, he also had small hands, clinodactyly in fingers and syndactyly in toes. (Figure 1 and 2) He developed scoliosis, during childhood (Figure 3).

Since birth, he was followed by a pediatrician due to severe psychomotor developmental delay, characterised by an absence of gait and speech development by the ages of 3 and 5 years old respectively. The summary of cytogenetic and clinical findings is described in Table 2.

His diagnoses included a development disorder with intellectual disability (IQ < 50) and genetic changes. His karyotype test revealed chromosomal problems involving the *long (q) arm of chromosome 4*, an inverted insertion in chromosome 16 of the long arm of chromosome 9 and a reciprocal translocation between the long arm of chromosome 2 and the long arm of chromosome 9.

When the patient was hospitalized in our service, he was an 18-year-old man, single, unemployed, who lived with his mother. He had pedopsychiatric consults at Hospital since the age of eleven due to several episodes of aggression directed to his family. For several years he was treated for aggression and anxiety with risperidone and lorazepam. He was clinically stable until October 2013, when, at the age of sixteen,

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Figure 1: Clinodactyly.



Figure 2: Syndactyly.



Figure 3: Scoliosis.

he developed an aggressive behavior at school directed to his teachers and to other kids. His mother explained that he also had anticipatory anxiety before going to school, which was manifested by psychomotor agitation, refusal to go to school and aggressive behavior. In February

Karyotype	46, XY; t(2;9); ins. (16;9); del (4) (q21.1q21.3)
Musculoskeletal	Flat foot deformity, valgus deformity of the knee and scoliosis
Urological	Phimosis
Endocrine	Obesity and fatty liver grade II
Renal	Left renal cyst
Hearing	Hypoacusis
Psychiatric	Verbal hallucinations; Persecutory delusions

Table 2: Summary of cytogenetic and clinical findings.

2014, he left school and was integrated in a therapeutic center. He only attended there for one month due the persistence of symptoms. His mother decided to stop working, in order to stay at home with him.

In the following month, he started his pedopsychiatric follow-up in another center, with a new doctor, who changed the medication to carbamazepine, olanzapine and escitalopram. After this change in medication an improvement of aggression was observed. However he maintained a refusal to go to school. Between March and November 2014 he presents anguish, fear, soliloquies suggesting verbal hallucinations (the patient seemed to have a conversation with non-existing people or with the television), persecutory delusions (he thought that the neighbors and the colleagues at school want to harm him), initial insomnia and social isolation (he remained confined to his house), not allowing his mother to leave their house. At this point, the therapeutic plan was changed: olanzapine and escitalopram were suspended and clozapine and topiramate were introduced. Carbamazepine was maintained.

Due to the persistence of symptoms, associated with burnout of the family, he was taken to the psychiatry emergency room in a Hospital. The clinical observation concluded that hospital admission was necessary for symptom stabilization and medication adjustment.

During hospitalization he was treated with valproic acid, risperidone and sertraline. A clinical improvement in verbal hallucinations and persecutory delusions was occurred. The behavior became progressively more organized and he was able to perform daily life activities under supervision. During his hospital stay he also did several exams (MRI, EEG, ECG and analytical evaluation), all normal. At discharge, the patient was clinically stable with no alterations in the mental state examination. The serum valproate levels were therapeutic. The recommendations to his mother were to maintain medical follow up and do the following therapeutic: valproic acid, risperidone and sertraline. He was readmitted at the therapeutic center without any evidence of aggressive behavior.

Discussion

This paper describes an adult patient with a rare chromosomal deletion and psychiatric illness.

The cases published in the literature, suggest that aggression is a part of the behavioral phenotype in children with 4q-syndrome. General practitioners and psychiatrists, tend to under diagnose mental health disorders in people with ID mainly due to speech disorders resulting in communication difficulties [2]. When presenting with mental illness, patients are at risk of being included in a special needs education programme with a consequent downgrade in their psychosocial, cognitive and motor skills [1,9-11]. This report, describes the case of an 18-year-old man with ID and an eventual comorbid psychiatric condition. Despite the obstetric complications that may have contributed to the clinical picture, the chromosomal deletion determined several abnormalities: psychomotor development delay,

ID and multiple medical conditions. At seventeen, he presented anguish, fear, soliloquies, verbal hallucinations, persecutory delusions and social isolation. In this patient the therapy with an antipsychotic, mood stabilizer and SSRI was successful in the control of the aggressive behavior and the psychotic symptoms. The association with mood stabilizers and SSRIs is supported by literature. This association is more effective than antipsychotic polimedication. Review studies support that multi component intervention strategies are more efficient than single component ones for the treatment of challenging behavior [9,10]. Behavior interventions can reduce 80-90% of behavior changes [1].

The prognosis in children with 4q-syndrome, depends on the exact chromosomal breakpoint(s) [4,12]. In 4q future research, gene-phenotype correlations are a central focus for global improvement [7]. This publication is relevant to these rare chromosomal disorders, because it increases awareness to the natural history, management and treatment of these group of diseases.

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