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Velo-Cardio-Facial syndrome at the psychiatry consulting-liaison service in a general hospital

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Psychotic syndromes secondary to genomic disorders have low prevalence and may easily go unnoticed in the daily clinical practice. The velo-cardio-facial syndrome or DiGeorge syndrome (VCFS/DGS) is the genomic disorder most frequently associated to an interstitial deletion of the 22q11 region, with an incidence of one per every 4,000 newborns. Clinical manifestations constitute a constellation of cardiac, facial, urogenital and psychiatric disorders, among which schizophrenia or schizophreniform disorder stand out with an incidence of about 30% over the lifetime. In the following, we present the case of a 21 year old female patient who was admitted to the hematology service of our hospital due to pancytopenia secondary to metimazole, who had non-specified psychiatric background and who received antipsychotic treatment.

Key words:

Velo-cardio-facial syndrome. Chromosomes. Congenital malformations.

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El síndrome velocardiofacial en la interconsulta psiquiátrica en un hospital general

Los síndromes psicóticos secundarios a alteraciones genómicas tienen una baja prevalencia y pueden pasar fácilmente inadvertidos en la práctica clínica diaria. El síndrome velocardiofacial o síndrome de DiGeorge (SVCF/SDG) es el trastorno genómico más frecuentemente asociado a una delección intersticial de la región 22q11, con una incidencia de 1 por cada 4.000 recién nacidos. Las manifestaciones clínicas constituyen una pléyade de alteraciones cardíacas, faciales, urogenitales y psiquiátricas, entre las que destaca la esquizofrenia o el trastorno esquizofreniforme con una incidencia de cerca del 30% a lo largo de la vida. A continuación presentamos el caso de una paciente de 21 años de edad que

ingresó en el servicio de hematología de nuestro hospital por una pancitopenia secundaria a metimazol y que presentaba antecedentes psiquiátricos no bien filiados y realizaba tratamiento antipsicótico.

Palabras clave:

Síndrome velocardiofacial. Cromosomas. Malformaciones congénitas.

Genetic syndromes caused by chromosomal rearrangements that lead to altered gene dose are characterized by mental retardation and/or congenital malformations. The 22q11 region is especially susceptible to chromosomal rearrangements¹, the velo-cardio-facial/DiGeorge syndrome (VCFS/DGS) being the most frequently associated to an interstitial deletion, with an incidence of 1 per every 4,000 newborns². Clinical manifestations include mental retardation, learning disorders, conotruncal cardiac defects, urogenital and facial malformations, cleft palate, velopharyngeal insufficiency and nasal language. They may also have agenesis or thymic hypoplasia, hypoparathyroidism, hypocalcemia, neurosensorial deafness or conductive deafness and skeletal disorders. The incidence of psychiatric disorders in these patients is elevated, schizophrenia being frequent (25%-30%)³. In the following, we present the case of a patient with schizophreniform disorder diagnosed 5 years before she was admitted to the hematology service of our hospital for study and treatment of severe pancytopenia. She had different malformations and complications during her admission, finally leading to the syndromic diagnosis.

She is a 21 year old patient with background of: *a)* tetralogy of Fallot surgically intervened in 1985 (closure of interventricular communication (CIV) and right ventricle outflow tract enlargement) and reoperated in 1995 (placement of pulmonary biological prosthesis and closures of residual CIV); *b)* high arched palate; *c)* bilateral hypoacusis since childhood, treated by stapedectomy at 15 years of age; *d)* bilateral strabismus operated on three occasions; *e)* lumbar idiopathic scoliosis operated on in 1993 (metallic fixation and bone graft placement); *f)* dysnomia; *g)* learning retardation detected during childhood; *h)* atrial

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flutter diagnosed in 1995 unsuccessfully treated with ablation of ectopic auricular focus and then with amiodarone; *i*) schizophreniform disorder diagnosed at 16 years of age, characterized by elevated suspicion, delusional and self-referential ideation lasting one year, treated with olanzapine 5 mg/day and without subsequent relapses, and *j*) hyperthyroidism secondary to treatment with amiodarone diagnosed in October 2002, under treatment with metimazole.

The patient was admitted in January 2003 in the hematology service to study severe pancytopenia (leukocytes, $0.9 \times 10^9/l$; neutrophils, $0.3 \times 10^9/l$; Hb, 81 g/l, hematocrit, 25%; reticulocytes, $3.5 \times 10^9/l$, and platelets, $7 \times 10^9/l$) detected due to a febrile syndrome having an abdominal focus. The myelogram showed hypocellular marrow, with decrease of the three hematopoietic series and absence of blast cells. Marrow biopsy showed a very decreased cellularity/fat ratio with persistence of erythroblastic foci and isolated elements of the granulocytic and megakariocytic series. With the diagnosis of bone marrow aplasia probably secondary to metimazole, this drug was withdrawn and wide spectrum empiric antibiotic treatment, G-CSF and transfusional support were begun. During hospitalization, the patient had severe hypocalcemia (calcemia, 6 mg/dl) with tetany, that resolved with calcium. Measurement of PTH and vitamin D₃ as well as urinary elimination of calcium were normal. The patient had intolerance to oral intake that hindered the antipsychotic treatment and alteration of mood state in form of sadness, so that psychiatric assessment was requested.

The psychopathological examination did not show depressive symptoms or alterations suggestive of a psychotic picture, establishing the diagnosis of non-pathological demoralization reaction and treatment was initiated with orodispersable olanzapine and support psychotherapy. Given the context of the patient, a genetic study was requested to rule out DGS, that showed the existence of 22q11 deletion (fig. 1). The patient was discharged at one month of admission with good general condition, euthymic mood, and with normal hemoperipheral values except for the persistence of mild low platelet values ($80 \times 10^9/l$). The successive measurements of thyroid hormones conducted in this period were normal, so that patient did not receive specific treatment.

Study of alterations association to 22q11 deletion was conducted from different scopes. A recent study⁴ suggests that all patients with tetralogy of Fallot associated to other malformations should undergo a specific analysis of this region. Regarding the VCFS relationship with schizophrenia, different studies done in schizophrenic patients have manifested elevated prevalence of 22q11 deletion (superior to 2%)⁵. In this sense, different studies suggest ruling out the existence of 22q11 alterations in those patients with psychotic disorders who have some of the phenotypic or metabolic traits characteristic of VCFS^{6,7}. Recent studies

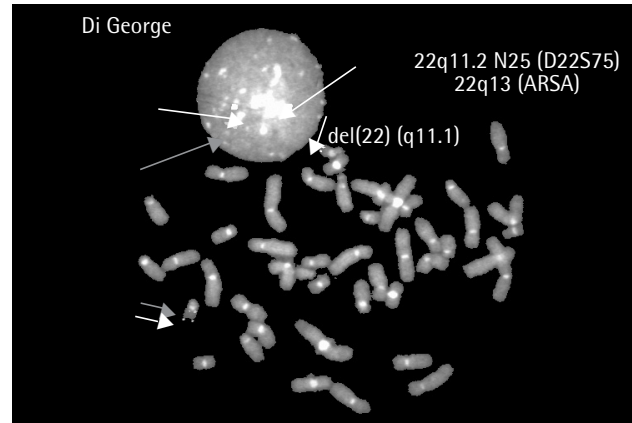


Figure 1 Deletion of 22q11.2 in the DGS/VCFS (CATCH 22 region) through the FISH technique (fluorescence in-situ hybridization), N25 probe (D22S75) SpectrumOrange/ARSA (22q13.3) SpectrumGreen Control Probe. Absence of oral signal in chromosome 22 indicates deletion of 22q11.2 locus.

suggest the importance of the catechol-*O*-methyltransferase (COMT) gene polymorphism (Val158/Met158)⁸. This enzyme, whose gene is located in the 22q11 region, is responsible for the metabolism of dopamine and its dysfunction could be related with the onset of psychosis through the increase of dopamine serum levels.

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