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Clinical report

Cardiofaciocutaneous syndrome, a Noonan syndrome related disorder: Clinical and molecular findings in 11 patients☆

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ABSTRACT

Objectives: To describe 11 patients with cardiofaciocutaneous syndrome (CFC) and compare them with 130 patients with other RAS-MAPK syndromes (111 Noonan syndrome patients [NS] and 19 patients with LEOPARD syndrome).
Patients and methods: Clinical data from patients submitted for genetic analysis were collected. Bidirectional sequencing analysis of *PTPN11*, *SOS1*, *RAF1*, *BRAF*, and *MAP2K1* focused on exons carrying recurrent mutations, and of all *KRAS* exons were performed.
Results: Six different mutations in *BRAF* were identified in 9 patients, as well as 2 *MAP2K1* mutations. Short stature, developmental delay, language difficulties and ectodermal anomalies were more frequent in CFC patients when compared with other neuro-cardio-faciocutaneous syndromes ($p < .05$). In at least 2 cases molecular testing helped reconsider the diagnosis.
Discussion: CFC patients showed a rather severe phenotype but at least one patient with *BRAF* mutation showed no developmental delay, which illustrates the variability of the phenotypic spectrum caused by *BRAF* mutations. Molecular genetic testing is a valuable tool for differential diagnosis of CFC and NS related disorders.

Síndrome cardiofaciocutáneo, un trastorno relacionado con el síndrome de Noonan: hallazgos clínicos y moleculares en 11 pacientes

Palabras clave:
Síndrome de Noonan
Síndrome cardiofaciocutáneo
Síndrome LEOPARD
Estenosis pulmonar valvular
Miocardiopatía hipertrófica
Vía RAS-MAPK

RESUMEN

Objetivos: Describir los hallazgos clínicos y moleculares de 11 pacientes españoles con síndrome cardiofaciocutáneo (CFC), y compararlos con una serie de 130 pacientes con otros trastornos neurocardiofaciocutáneos (111 pacientes con síndrome de Noonan [SN] y 19 con síndrome LEOPARD).
Pacientes y métodos: Se obtuvieron datos clínicos de los pacientes remitidos para estudio genético. Se estudiaron los genes *PTPN11*, *SOS1*, *RAF1*, *BRAF* y *MAP2K1* mediante secuenciación bidireccional de los exones donde se localizan las mutaciones más recurrentes, y todos los exones del gen *KRAS*.

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Rasopatía
PTPN11
BRAF
MAP2K1
Correlación genotipo-fenotipo

Resultados: Se identificaron 6 mutaciones en *BRAF* en 9 pacientes, y 2 mutaciones en *MAP2K1*. La talla baja, el retraso psicomotor, los trastornos del lenguaje y las anomalías ectodérmicas fueron más frecuentes en el CFC que en el resto de los síndromes ($p < 0.05$). En al menos 2 casos el estudio genético contribuyó a reorientar el diagnóstico.
Discusión: Los pacientes con CFC muestran un fenotipo más grave, si bien se describe un paciente sin retraso psicomotor, lo que ilustra la variabilidad del espectro fenotípico asociado a las mutaciones en *BRAF*. El estudio genético es una herramienta útil en el diagnóstico diferencial del CFC y de los trastornos relacionados con el SN.

Introduction

Cardiofaciocutaneous Syndrome (CFC, OMIM 115150) is a disorder characterized by characteristic craniofacial malformations, ectodermal abnormalities, congenital cardiopathies, gastrointestinal disorders, growth retardation, intellectual disability and neurological disorders, among other symptoms.[1] The incidence of this syndrome is unknown, and almost 60 cases have been documented in medical literature, although there are more than 100 instances recorded by international support organizations.[2]

Many of its clinical manifestations are considerably overlapped with those of other entities, such as Noonan syndrome (NS, OMIM 163950) or Costello Syndrome (CS, OMIM 218040). These and other associated disorders, such as LEOPARD syndrome (LS, OMIM 151100) or neurofibromatosis type I (OMIM 162200) stem from germline disorders in terms of RAS-MAPK (Fig. 1) intracellular signalling cascade regulation, and they have been jointly called "Neurocardiofaciocutaneous syndromes",[3] RAS-MAPK disorders[4] or RASopathies.[5] Molecular studies in CFC patients have made it possible to identify mutations in *BRAF*,[6–10] *MAP2K1*, *MAP2K2*,[11,12] and an isolated case in *KRAS*.[13]

We hereby present the phenotypic description of a series of patients with CFC diagnosis, characterized by a genetic mutational study of genes *BRAF* and *MAP2K1*, and the statistical comparison with a wide series of patients carrying other neurocardiofaciocutaneous syndromes with confirmed mutation of genes *PTPN11*, *SOS1*, *BRAF* and *RAF1*.

Patients and method

Clinical data was collected and mutation analysis was conducted subject to the statements of Carcavilla et al.[14] and Ezquieta et al.[15] The stature was assessed in standard deviations regarding the reference population,[16] and it was considered to be small when it was below −2 standard deviations for a certain age and gender. We included study results for genes *BRAF* and *MAP2K1* collected from studies on patients with a CFC clinical diagnosis, conducted by 2 other research centres. These patients were diagnosed with NS (n = 111), LS (n = 19) and CFC, according to clinical criteria. Among CFC patients, there was a case who was referred under clinical suspicion of having another neurocardiofaciocutaneous syndrome, and in 5 other patients it was difficult to establish the type of RASopathy they had, from a clinical point of view.

Results

The study included 11 patients, 5 of whom were females, with ages ranging from 7 months to 7 years of age at the time of clinical assessment. These cases were referred by 6 hospitals from 4 different Spanish communities. Table 1 summarizes clinical characteristics and identified mutations. The most frequent manifestations were congenital cardiopathy, short stature and psychomotor retardation, all of which were present in 10 out of the 11 patients. Referring physicians regarded psychomotor retardation as severe in one case, moderate in 2 cases, and mild in the remaining ones. There was the case of a female patient whose psychomotor development was considered to be normal, except for a speech retardation which was diagnosed at her assessment when she was 6 years old, and there were other 2 cases whose retardation in psychomotor milestones acquisition was mainly attributed to motor retardation and hypotonia. Speech retardation was observed in all patients older than 3 years of age at the time of assessment. Central nervous system (CNS) malformations were identified in 4 patients (malformative encephalopathy with pachygyria and retardation in myelination pattern, subependymal nodular heterotopia, myelination disorder with diffuse corticosubcortical atrophy, and Chiari malformation I).

In 6 out of 9 patients, we obtained a description of ectodermal alterations showing typical disorders (scarce, friable and curly hair, absence of eyebrows).

In 3 patients, deep palmoplantar furrows were described, and another patient had articular hypermobility with redundant skin. Among the documented cases, there were 3 patients with polyhydramnios and one with gestational nuchal fold, and anthropometric perinatal data were within normal ranges, as described in Table 1.

Table 2 describes the characteristics of genetic findings in patients from our series, and Fig. 2 illustrates the mutational distribution identified in gene *BRAF*. Those with mutations previously associated with cancer in the somatic line were 7 months, 2, 3 and 5 years of age at the time the study was conducted, and they have not developed any cancer to date. The referring clinician regarded all cases as sporadic. In 2 cases (7 and 8), DNA samples from both parents were obtained to prove it was a *de novo* mutation. In 2 other cases (2 and 8), a prenatal test was performed on both siblings, obtaining a negative result.

Results from the statistical comparison with the 130 patients suffering from other neurocardiofaciocutaneous syndromes are summarized in Table 3. Clinical characteristics of these patients are described in detail in other publications (Carcavilla et al.,[14] Ezquieta et al.,[15] Carcavilla et al., *underway*). As far as the molecular characterization of these patients, mutation of *PTPN11* was identified in 81 patients with NS and in 16 patients with LS, mutation of *RAF1* was detected in 8 patients with NS and in 2 patients with LS, and mutation of *SOS1* was found in 22 patients with NS. The *BRAF* study also identified a p.Gln257Arg mutation in a patient with an SL clinical diagnosis that had been previously described.[14] *KRAS* gene has been studied in 27 patients with severe neurocardiofaciocutaneous syndrome and significant psychomotor retardation, not having found mutations in any patient. Every identified alteration had been previously described in association with the mentioned symptoms.

Discussion

CFC was originally described in 1986,[17,18] arising considerable controversy as to whether it really was a differentiated syndromic entity or just an NS variant.[19,20] Its clinical peculiarity resides in