CASE REPORT

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Cardiofaciocutaneous syndrome – a longitudinal study of a case over 33 years: case report and review of the literature

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Abstract

Cardiofaciocutaneous (CFC) syndrome [Online Mendelian Inheritance in Man (OMIM) #115150] is characterized by craniofacial dysmorphism, heart malformation, ectodermal abnormalities, neuromotor delay and intellectual disability. It is not a frequent disease, about 300 cases have been reported in the medical literature. We describe the case of a 34-year-old patient presenting with CFC syndrome phenotype, monitored since the age of 1 1/2 years. Clinical findings included craniofacial dysmorphism, development delay, heart malformation and severe intellectual disability. The evolution was with progressive intellectual disability, hypogonadism, hypertrophic cardiomyopathy, wrinkled palms and soles. Molecular analysis showed a heterozygous variant in the B-Raf proto-oncogene, serine/threonine kinase (*BRAF*) gene (7q34): *NM_001354609.2:c.1502A>G*, with pathogenic significance. We report this case, observed along a period of 33 years, for illustration of clinical evolutive particularities, and for difficulties in establishing the positive diagnosis.

Keywords: cardiofaciocutaneous syndrome, craniofacial dysmorphism, intellectual disability, hypertrophic cardiomyopathy.

Introduction

Cardiofaciocutaneous (CFC) syndrome is a very rare syndrome characterized by craniofacial dysmorphism, heart and skin anomalies, developmental delay, and intellectual disability. The syndrome was described by Reynolds *et al.*, in 1986 [1, 2]. It is an autosomal dominant trait but most of the cases are due to *de novo* mutations. CFC is included in the large group of RASopathies. The latter term comprises a group of diseases caused by the appearance of germline mutations in genes encoding rat sarcoma (RAS)/ mitogen-activated protein kinase (MAPK) signaling pathway [3]. This group includes the following syndromes: von Recklinghausen's disease, male Turner syndrome [Noonan syndrome (NS)], LEOPARD syndrome, Costello syndrome (CS), capillary malformation–arteriovenous malformation syndrome, CFC syndrome, neurofibromatosis 1 (NF1)-like syndrome [4]. All these syndromes present few features in common: facial dysmorphism, heart malformations, mental retardation, teaching problems, skin conditions, undescended testicle, high risk for malignant tumors. Thus, from this point of view, it is difficult to make the differential diagnosis only based on the clinical aspect, the molecular being mandatory.

Aim

The purpose of this article was to better understand the genotype–phenotype correlation of this very rare genetic disorder.

Case presentation

The probandus, O.A. male, was in evidence at Regional Center of Medical Genetics, Bihor County, Romania, from the age of 18 months, for development and language delay, neuromotor retardation with delayed stands and walk. The pregnancy was normal. The boy was born at term, spontaneous vaginal delivery, with the birth weight of 3800 g, and a good adaptation at extrauterine life. His parents were young, healthy, non-consanguineous marriage.

Clinical examination

Clinical examination revealed:

- Delayed physical, cognitive, emotional and linguistic development;
- Craniofacial dysmorphism: macrocephaly, high forehead, bitemporal narrowing, thin, brittle, sparse hair, hypoplastic supraorbital ridges, large and depressed nasal bridge,

hypertelorism, very sparse eyebrows and eyelashes, large and posterior rotated ears, thickened helices, short nose, long philtrum, microretrognathia, high arched palate, anomalies of dental eruption, short neck, bilateral cryptorchidism (Figure 1);

▪ Clinical signs newly highlighted throughout our observation: short stature, prominent forehead, ptosis, strabismus, webbed neck, curly hair, dystrophic nails, palmar and plantar hyperkeratosis, hypertrophic cardiomyopathy, compulsive, hetero-aggressive behavior (Figures 2–4).

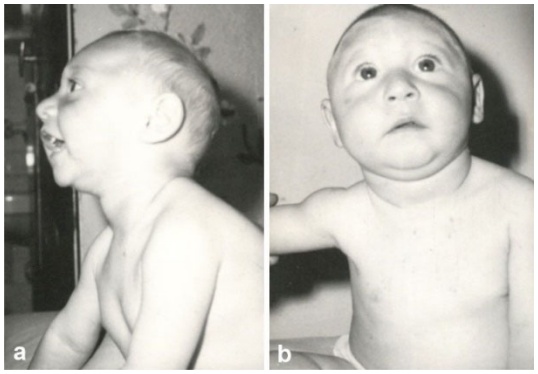

Figure 1 – ***(a and b) The patient at first presentation (age 18 months).***

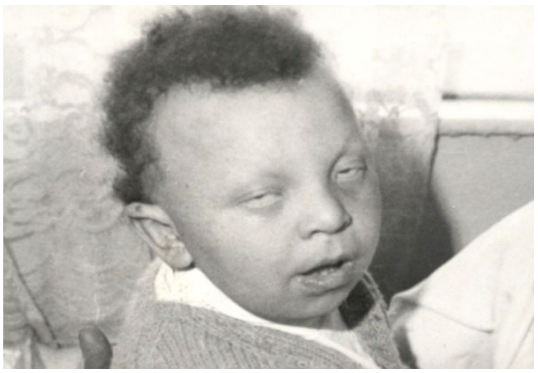

Figure 2 – ***The patient at the age of seven years.***

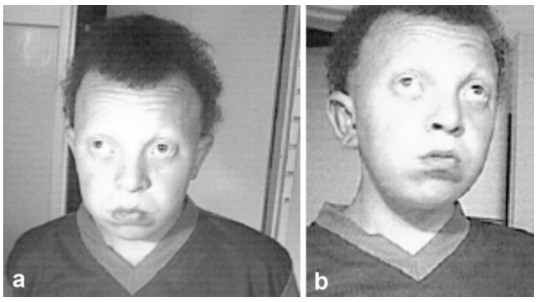

Figure 3 – ***(a and b) The patient at the age of 21 years.***

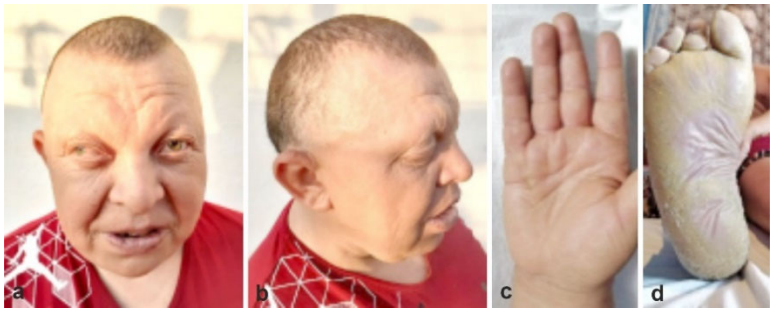

Figure 4 – ***The patient at the age of 34 years: (a and b) Craniofacial dysmorphism; (c and d) Palmoplantar hyperkeratosis.***

Genetic analysis

Molecular diagnosis

Next Generation Sequencing analysis was performed, at the age of 32 years. Genomic deoxyribonucleic acid (DNA) isolation was performed according to the protocol provided by the manufacturer, by using the MagCore® Automated Nucleic Acid Extractor and the MagCore® Genomic DNA Whole Blood Kit (RBC Bioscience). DNA concentrations and DNA purity were evaluated by using Qubit® double-stranded DNA (dsDNA) high sensitivity (HS) Assay Kit (Invitrogen) according to the instructions provided by the manufacturer. Amplicon sequencing libraries were prepared from 50 ng of DNA per sample according to the TruSight® Cardio protocol (Illumina Inc., San Diego, CA, USA). The genomic DNA was fragmented, then the coding sequencing were amplified, and libraries were generated using Illumina TruSight® Cardio Sequencing panel (174 genes). The pooled libraries were sequenced on a microflow cell with V3 chemistry on a MiSeq instrument (Illumina Inc., San Diego, CA, USA). Variants were interpreted according to *American College of Medical Genetics and Genomics* (ACMG) Guide. A heterozygous variant of B-Raf proto-oncogene, serine/threonine kinase (*BRAF*) gene [*NM_001354609.2):c.1502A>G,p.Glu501Gly*, *rs180177039* (chromosome 7q34)] was identified and classified as pathogenic. The variant is not present in population databases and was reported in other patients with CFC syndrome.

Laboratory investigations

Hematological, biochemical and endocrinology work-up were normal.

Lysosomal enzymes at the age of 30 years were normal (alpha-L-iduronidase, iduronate-2-sulfatase, arylsulfatase B and beta-galactosidase).

Imagistic investigations: *X-ray*: the bone age (wrist radiography) at the age of 16 years was delayed with two years, bilateral brachymetacarpia of the first metacarpal. Abdominal ultrasound showed mild hepatomegaly, ptosis of the right kidney and the right renal cyst.

Interdisciplinary checkups

Ophthalmological exam revealed alternate strabismus. Cardiological exam showed moderate mitral, aortic and tricuspid insufficiency and hypertrophic cardiomyopathy. Gynecological exam showed ectopic testis. Neurological exam revealed neuromotor retardation. Psychological exam revealed a severe intellectual disability, intelligence quotient (IQ) <25, behavioral problems, aggression.

Discussions

CFC syndrome is an autosomal dominant syndrome, with complete penetrance [5]. Most affected individuals reported to date have had a *de novo* pathogenic variant. It was first described in 1986 by Reynolds *et al.* [1] and Baraitser & Patton [2]. It is a very rare syndrome; around 300 cases are reported in literature. The real incidence is still unknown, in Japan the prevalence is estimated at 1:810 000 [6, 7]. The clinical diagnosis is not enough, the molecular genetic testing is mandatory. Four genes are involved in CFC syndrome: *BRAF* gene (7q34) present in majority (75%) of the cases, mitogen-activated protein kinase kinase 1 (*MAP2K1* or *MEK*) gene (15q22.1-q22.33) and mitogen-activated protein kinase kinase 2 (*MAP2K2*) gene (19p13.3), both are present in 25% of the cases, and the last, Kirsten rat sarcoma viral oncogene homolog (*KRAS*) gene (12p12.1) present in less than 2% of the cases. All these genes are codifying for proteins of the RAS/MAPK signaling pathway. The RAS/MAPK pathway plays an important role in cell differentiation, proliferation, migration, and apoptosis. Our case presented a heterozygous variant *NM_001354609.2:1502A>G* of the *BRAF* gene [8]. The *BRAF* gene codify a serine/threonine-protein kinase, B-Raf protein, important in the transduction of chemical signals from the cell membrane (outside) to the cell nucleus (inside) and it is important in the postsynaptic responses of hippocampal neurons [9].

Diagnosis

The diagnosis is made based on clinical aspects: cranio-facial dysmorphism, developmental delay, neuromotor delay, intellectual disability, ectodermal abnormalities, heart malformation and hypertrophic cardiomyopathy, cryptorchidism. Our patient presented all these features (Table 1) characteristics of RASopathies and, as particular signs and symptoms, present elongated filter, microretro-gnathism, absence of heart malformation and an important aggressive behavior (he manifests, periodically, physical and emotional abuse on the family and other known and unknown persons, from verbal abuse to physical abuse). What is very particular to our case is the change, over time, of the phenotype. From Table 1, it can be seen that some features are present from infancy, others appear in childhood or adolescence, while others manifest only in adulthood. At the same time, it can be observed that some features change over time either by their accentuation (short stature, mental retardation, cranial dysmorphism, skin changes, and aggressive behavior) or by their regression (bitemporal narrowing, depressed nasal bridge, sparse hair, ectopia testis). These phenotypic changes that occur during evolution create diagnostic difficulties. The case presented by us, evaluated periodically over more than 30 years, was evaluated for multiple differential diagnoses, such as mucopolysaccharidosis, Legius syndrome [Online Mendelian Inheritance in Man (OMIM) #611431], CS (OMIM #218040), NS (OMIM #163950), CFC1 syndrome, the final diagnosis being defined by the molecular test.

Differential diagnosis

The differential diagnosis was made with the other syndromes which are included in RASopaties pathway, in special with NS and CS. Table 2 shows the common signs and symptoms of the three syndromes.

Table 1 – ***The evolution of phenotype over 34 years of life***

Signs and symptoms	18 months	7 years	21 years	34 years
Short stature	-	+	++	++
Developmental delay	+	++	++	++
Intellectual disability	+	++	+++	+++
Macrocephaly	+	+++	+++	+++
Height forehead	+	+++	+++	+++
Prominent forehead	-	+++	+++	+++
Bitemporal narrowing	++	+	+	+
Hypoplastic supraorbital ridges	+	+	+	+
Large and posteriorly rotated ears	+	+	+	+
Thickened helices	+	++	++	++
Sparse eyebrows and eyelashes	+	++	++	++
Hypertelorism	+	++	++	++
Ptosis	-	+	+	+
Strabismus	-	+	+	+
Large and depressed nasal bridge	++	+	+	+
Short nose	+	+	+	+
Long philtrum	+	+	+	+
Microretrognathia	+	++	++	++
High arched palate	+	+	+	+
Webbed neck	-	+	++	++
Short neck	+	+	++	++
Palmar and plantar hyperkeratosis	-	-	+	++
Dystrophic nails	-	+	+	+
Curly hair	-	+	++	++
Sparse hair	++	+	+	+
Hypertrophic cardiomyopathy	-	-	-	+
Bilateral cryptorchidism	+	+	-	-
Compulsive, hetero-aggressive behavior	-	+	++	+

Characteristic features in NS are short stature, short, wide, neck, low posterior hairline, *café-au-lait* spots, aortic or pulmonary stenosis, coagulation disorders. In approximately 50% of patients there have been identified mutations in protein tyrosine phosphatase non-receptor type 11 (*PTPN11*) gene [10–12]. Characteristic features in CS are short stature, failure to thrive, coarse facies, cardiac malformations, mental retardation, deep creases on the palms and soles, elbow joint limitation and predisposition to solid tumors (neuroblastoma) [13, 14]. In 2005, Aoki *et al.* identified a pathogenic variant in Harvey rat sarcoma viral oncogene homolog (*HRAS*) gene in most patients with CS [15].

There are currently not many studies regarding the *genotype–phenotype correlation*. Pierpont *et al.* [4] developed in 2014 a Guideline for genetic testing strategy for CFC syndrome. An important observation is the presence of pulmonic stenosis in 50% of persons with CFC which have mutation in *BRAF* gene; only 36% of persons have *MEK* gene mutation. It was found that *BRAF* mutations are frequently correlated with heart damage (hypertrophic cardiomyopathy, interatrial communication), intellectual disability, eating problems [16–18]. In our report, the patient developed hypertrophic cardiomyopathy after the age of 20 years. He also presented severe intellectual disability. Although dermatological and renal changes are more common in patients with mutations in *MEK* gene, our patient presents palmoplantar hyperkeratosis and right renal cyst [19–21].

Table 2 – ***Clinical signs and symptoms in CFC1 syndrome, Noonan syndrome, Costello syndrome, Legius syndrome and in our case***

Clinical signs and symptoms	CFC1 syndrome	Noonan syndrome	Costello syndrome	Legius syndrome	Our case
Onset 1–2 years	+	+	+		√
Failure to thrive	+		+		
Short stature	+		+		√
Craniofacial dysmorphism					
Macrocephaly	+		+	+	√
Prominent forehead	+				√
Bitemporal narrowing	+				√
Triangular face		+		+	
Coarse facies			+		√
Hypoplastic supraorbital ridges	+				√
Posteriorly rotated ears	+	+	+		√
Thickened helices	+		+		√
Preauricular pits	+				
Hearing loss		+			
Hypertelorism	+	+	+	+	√
Downslanting palpebral fissures	+	+	+	+	
Epicanthal folds	+	+	+	+	
Ptosis	+	+	+	+	√
Nystagmus	+				
Strabismus	+		+		√
Myopia		+			
Depressed nasal bridge	+		+		√
Anteverted nares	+		+		
Deeply, long, philtrum		+		+	√
Thick lips			+		√
High arched palate	+	+	+	+	√
Dental anomalies		+	+		√
Microretrognathia		+	+	+	√
Neck and thorax					
Webbed, short neck	+	+	+		√
Deformed chest		+	+		
Pectus carinatum / *pectus excavatum*		+	+		
Heart problems					
Congenital heart malformation	+	+	+		
Hypertrophic cardiomyopathy	+	+	+		√
Cutaneous					
Deep palmar and plantar creases	+		+		√
Café-au-lait spots				+	
Ichthyosis, hyperkeratosis	+		+		√
Cutis laxa, dark skin, acanthosis, papillomas			+		
Sparse, curly hair, sparse eyebrows	+		+		√
Low posterior hairline		+		+	
Skeletal					
Scoliosis / other vertebral anomalies	+				√
Limbs' abnormalities	+		+		
Neurological					
Developmental delay	+		+		√
Intellectual disability	+	+	+	+/-	√
Hypotonia	+				
Another anomalies					
Cryptorchidism		+			√
Lymphedema		+			
Tracheobronchomalacia			+		
Lung disorders, respiratory failure			+		

CFC1: Cardiofaciocutaneous syndrome 1.

Management of CFC syndrome

There is not specific treatment in CFC syndrome. A multidisciplinary team must be gathered for managing the main issues that are presents in this pathology: cardiac, digestive, dermatological, renal problems; also, the neurological problem and psychomotor development must be monitored periodically.

Genetic counselling

CFC is an autosomal dominant trait with full penetrance. The recurrence risk for the child of an affected person is 50%. Majority of cases presents *de novo* pathogenic variants. The prenatal diagnosis will be possible in situation in which the pathogenic variants (*BRAF*, *MAP2K1*, *MAP2K2*, or *KRAS* genes) have been identified in an affected person from the family.

Conclusions

The clinical appearance of CFC patients partially overlaps with that of patients with other syndromes of RAS/MAPK pathway, therefore, a right diagnosis is crucial for good monitoring and for a good and correct genetic counseling. The identification of the mutation is recommended for each patient with suggestive clinical signs, to establish the most accurate genotype–phenotype correlation. A multidisciplinary team is necessary both to the children and adults with CFC syndrome. As particularities of our case can be mentioned particular phenotypic traits that are not part of the usual picture of the disease; phenotypic changes that occur during multiannual clinical observation and that may induce changes in diagnostic interpretations.

Conflict of interests

The authors declare that they have no conflict of interests.

Consent

Written informed consent was obtained from the patient's parents for publication of this Case Report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this Journal.

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