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CARDIOFACIOCUTANEOUS SYNDROME: CASE REPORT AND LITERATURE REVIEW

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ABSTRACT

Report the case of an ambulatory patient diagnosed with syndrome Cardiofaciocutanea and alerts to your underdiagnosis since it's phenotypic similar to other syndromes socially known and also highlights the need for a multidisciplinary team. Case description: Female patient, brown, 6 years and 11 months, term birth, no birth complications, with maternal hypertension and urinary tract infection on the first and third trimester of pregnancy. At birth weight and length appropriate for gestational age with PCA, CIV + CIA without hemodynamic repercussion. During the breastfeeding, the phase had a delay in psychomotor development with malnutrition secondary to a swallowing disorder, JUP stricture with hydronephrosis, and lacrimal sac cyst. At 6 years the diagnosis was made with genomic DNA analysis by PCR amplification and subsequent direct sequencing that confirmed a pathogenic mutation for her disease. Currently, weight is 14,9kg and height 101 cm, with delayed psychomotor development of about four years. Comments: The Cardiofaciocutânea syndrome is a rare autosomal dominant genetic disease with few cases described worldwide, it results from a mutation of genes in the RAS/ mitogen-activated protein kinase pathway. It is being considered as a RASopathies with Noonan and Costello with similar phenotypic characteristics. The syndrome is characterized by heart diseases, mental retardation and a delay in growth.

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INTRODUCTION

Cardiofaciocutaneous syndrome (CFCS) was first described by Reynolds in 1986 and more than 125 cases were subsequently described. It is characterized by mental retardation, heart disease, growth deficiency, macrocephaly, convex facial profile, bitemporal narrowing, shallow orbital ridges, sparse and curly hair, and skin anomalies.[1] The incidence of CFCS in Japan is estimated at 1 in 810,000 individuals, however, the worldwide prevalence is unknown. In addition to this, there is an increase in the number of cases described annually, leading to a suggestion that the identification of this disease is still underdiagnosed.[2] Its etiology has not yet been fully established because it presents sporadically, but it is believed in an association with advancing paternal age assuming an autosomal dominant inheritance.[3]Figure 2 shows the relationship Weight/age evaluation chart in the z-score parameter according to WHO standards. This disease is found in the group of RASopathies, which include Costello's syndrome and Noonan syndrome so that a mutation in the RAS / MAPK signaling pathways results mainly from mutations in the BRAF gene followed by MAP2K1, MAP2K2, and KRAS.[2,3] The phenotypic similarity is emphasized mainly between the CFCS and Noonan syndrome and can use a CFCS index both for the diagnosis of this anomaly and for the differentiation of these pathologies.[4] Thus, we described the case of a patient who had difficulties in establishing the diagnosis and therapy, seeking to prevent situations of possible underdiagnosis, and emphasizing the need for monitoring by a multidisciplinary medical team.

CASE REPORT

Data sources and search strategy: A total of 92 articles were found involving the MeSH Terms "Cardiofaciocutaneous syndrome, RASopathies, RAS/MAPK, Noonan Syndrome, Costello Syndrome". Initially, it was held the existing exclusion title and duplications following the interest described in this work. After this process, 23 articles were included and discussed in this study (Figure 1). PUBMED, EMBASE, OVID AND COCHRANE LIBRARY databases were searched. Initially, the descriptors were determined by searching the DeCS tool and later verified and validated by the MeSH Terms System (US National Library of Medicine).The present study was elaborated according to the rules of CARE case report (https://www.care-statement.org/).[11]

Patient Information and Clinical Findings: ACS patient, female, brown, 6 years and 11 months, born in Santa Cruz do Rio Pardo. Mother, 36 years old, 165 cm, with type 2 diabetes mellitus. Maternal obstetric history: G3P2A1, first healthy daughter of another father and second daughter the patient in question. Father 36 years old, 160 cm, hypertensive, family history of relatives with short stature and facies characteristic of achondroplasia deny consanguinity. Full-term birth, spontaneous vaginal delivery without complications, with maternal arterial hypertension, and urinary tract infection in the first and third trimester of pregnancy. At birth, the patient had Apgar scores 8 and 9, weight 3.300gr, height 45.5cm, and head circumference 34cm. The clinical examination revealed atypical facies, GIBA, and cleft palate that closed spontaneously. Complementary tests: PCA and CIV + IAC without hemodynamic repercussions. During the infant phase, the child presented delayed neuropsychomotor development and malnutrition secondary to swallowing disorder, being necessary to be fed by a nasogastric tube from the second to the tenth month of life. DNPM: sat without support at 12 months, started to crawl at 2 years old, and walked without support at 4 years old, even at an age that started using monosyllables.

Timeline

From birth to 6 years and 11 months.

Diagnostic Assessment: At 8 months, JUP stenosis was diagnosed on the left with hydronephrosis. In the complementary investigation found in magnetic resonance imaging of the skull, oval lesion of the right orbit with future confirmation of lacrimal sac cyst. At 3 years and 11 months, when he presented sufficient weight for the surgical procedure, left pyeloplastywas performed. Genetics was forwarded to investigate the syndrome at the age of 4, with a 46, XX karyotype. At the age of 6, she was referred to continue genetic research. After formulating the diagnostic hypothesis by the specialist, the genomic DNA was analyzed by PCR amplification and subsequent direct sequencing that confirmed pathogenic mutation for the disease.

Therapeutic Intervention and Follow-up: At 6 years and 11 months, the patient was 14.900 kg in weight, 101 cm in height, height/age below the 2.5th percentile with score-z -3, weight/age below the 3rd percentile and score-z -3, age bone age of 5 years and 10 months according to the Greulich Pyle table, ICD + CIA and PCA resolved, neuropsychomotor development delay of approximately 4 years, cyst in the right eye and hydronephrosis due to JUP stenosis. She is currently being monitored by a multidisciplinary team: endocrinology, cardiology, dentistry, geneticist, urology. It is believed that with the interaction of the multidisciplinary medical team, it will favor the resolution of illnesses and the progression to a stable condition of this patient.

Informed Consent: Those responsible for the patient signed the consent form.

DISCUSSION

The data on dermatological manifestations of cardiofaciocutaneous syndrome (CFCS) remain heterogeneous and almost without specialized dermatological classification. Thus, a study with 45 patients described the dermatological manifestations of CFCS and differentiated CFCS from other RASopathies, including Noonan syndrome (NS) and Costello syndrome (CS); and to test dermatological phenotype-genotype correlations.[1] For this, a four-year, broad, prospective, multicenter, collaborative dermatological and genetic study was carried out. Capillary abnormalities were ubiquitous, including scarcity or absence of eyebrows and wavy or curly hair in 73% and 69% of patients, respectively. Pilar keratosis (KP), ulerythemaophryogenes (OU), palmoplantar hyperkeratosis (PPHK) and multiple melanocytes (MMN; more than 50 naevi) were observed in 82%, 44%, 27% and 29% of patients, respectively. Scarcity or absence of eyebrows, association of OA and PPHK, diffuse KP and MMN better differentiated the CFCS from SN and SC. Oral acitretin can be highly beneficial for the therapeutic treatment of PPHK, while the treatment of OU by 1% topical sirolimus has failed. No significant phenotype-genotype dermatological correlation was determined. Therefore, an in-depth knowledge of the cutaneous manifestations of the CFCS is needed would help in the positive diagnosis and differentiation of the CFCS from SC and NS.[1] In this context, CFCS is one of the developmental disorders caused by a deregulation of the Ras/mitogen activated protein kinase (MAPK) pathway. RASopathies share overlapping clinical characteristics, making diagnosis challenging, especially in the neonatal period.[2]Most cases of CFCS occur due to a mutation in the BRAF, MAP2K1, MAP2K2 or (rarely) KRAS genes. Germline KRAS mutations are identified in a minority of CFCS and Noonan syndrome cases.[3] Cardiofaciocutaneous syndrome is a pathology that affects both sexes in an equivalent way and is characterized by multiple congenital anomalies with a variability of clinical findings, these being craniofacial abnormalities, heart disease, neurological, ocular, gastrointestinal disorders, and growth retardation.[10] From a molecular point of view, Noonan, Costello and Cardiofaciocutaneous syndromes are considered RASopathies, which partly explains the phenotypic overlap between them.[12] In view of the analysis of facial deformities in Cardiofasciocutaneous Syndrome, a bitemporal constriction, shallow orbital ridges, relative macrocephaly with a broad and prominent forehead, low implantation of the ears accompanied by posterior rotation, winged neck, and warped palate are emphasized.[12,13] A Joint assessment of these characteristics presents a broader and longer face when compared to Noonan syndrome, but it does not prevent confusion between these syndromes since there is a phenotypic overlap between them mainly in childhood, attenuating the differences over time. On the other hand, when comparing other RASopathy, like Costello's syndrome, the face is not as coarse.

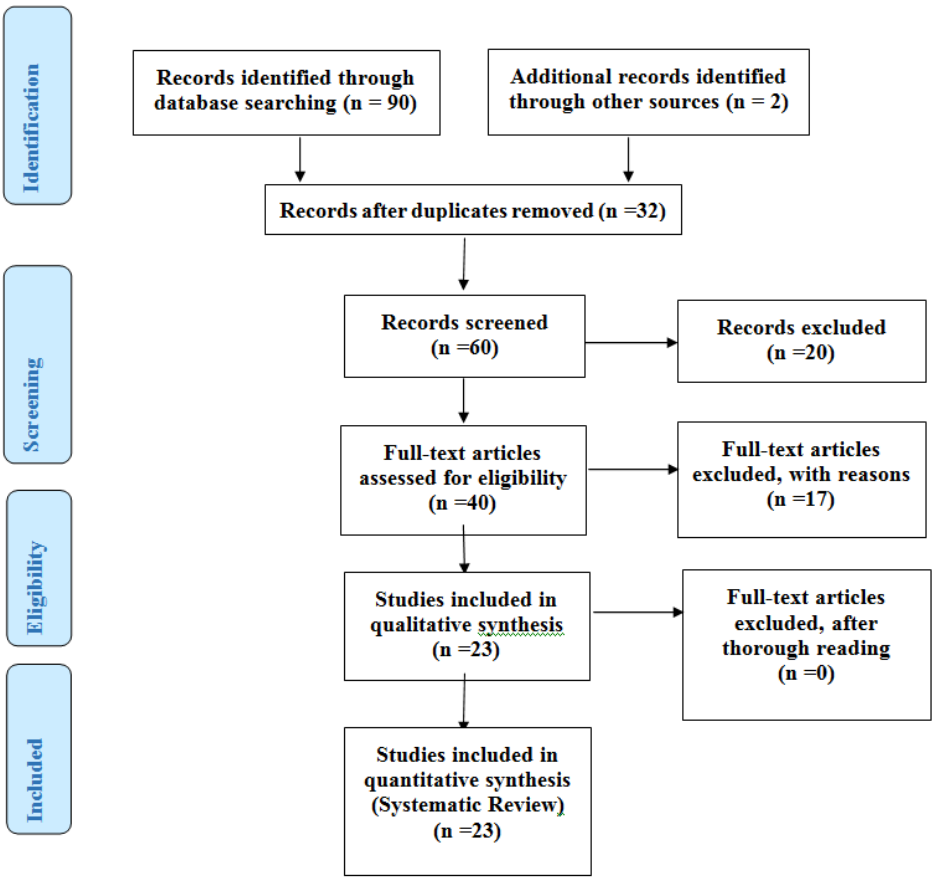

Figure 1. Flow Chart of the article selection process

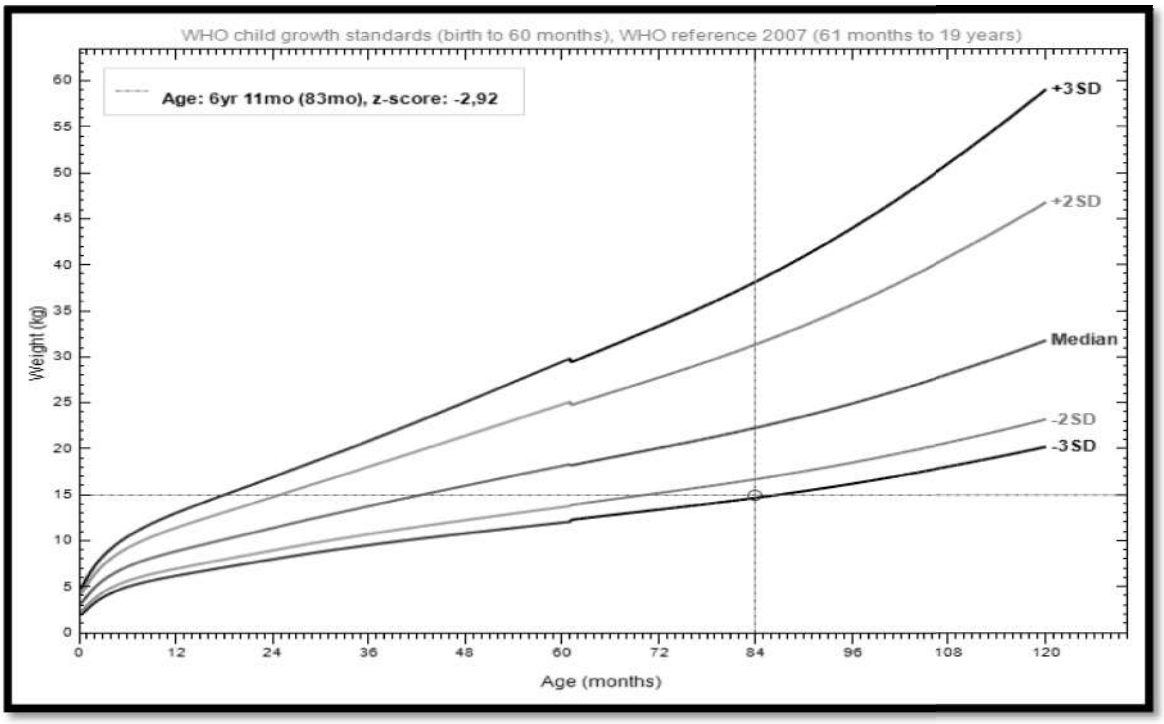

Figure 2. Weight/age evaluation chart in the z-score parameter according to WHO standards

The most frequently described ectodermal anomalies are sparse, slow-growing curly hair, absence of eyebrows and eyelashes, hyperkeratosis of the arms, legs, and face, in addition to ichthyosis. On the nails, opalescence and thinning are identified, being broad, flat and fast-growing.[12,14,15] In ophthalmological evaluation, hypertelorism, hypoplasia of the optic nerve, strabismus, telecanto, and even myopia are noted.

It is noteworthy that despite the majority of CFCS cases having eye problems, there are those who have an ophthalmological examination within normal standards.[12,15] In the clinical evaluation of newborns, the presence of distinctive craniofacial alterations has already been demonstrated, along with that cardiac problems, so that when present are mostly defects in the atrial and ventricular septum, the persistence of

the ductusarteriosus, pulmonary stenosis and anomalies in valves as dysplasia.[16] In addition, it is possible to notice hypertrophic cardiomyopathy and rhythmic disorders throughout life. Few CFCS genotype-phenotype studies have been carried out to date, however, a statistically significant change in the incidence of pulmonary stenosis, which is present in 50% of individuals with CFCS with a BRAF gene mutation, a change that the patient does not demonstrate.[16] The delay in child growth is not demonstrated, in all cases, at birth, especially when accompanied by a birth in due weight and height, however, in childhood, a decline may occur below the percentile.[12] Short stature is a finding common among RASopathies, since the RAS/MAPK pathway plays an important role in the intracellular control of insulin-like growth factor (IGF - 1) signaling, mediating postnatal growth hormone (GH) effects. In addition, the activation of the MAPK pathway is extremely important for the regulation of the proliferation of somatotrophs in the pituitary, releasing and synthesizing GH, therefore, a failure in this pathway can result in several factors that converge to failure in growth and a short stature phenotype.[18,19] It is estimated that approximately two-thirds of individuals with CFCS syndrome are short, so the cause can vary between deficiency in GH production or even resistance to the hormone GH. This pathology is strongly associated with severe malnutrition resulting from gastrointestinal dysfunction. A variety of problems in feeding the individual are common in the infant stage, namely: gastroesophageal reflux, vomiting, oral aversion, intestinal dysmotility, and constipation.[12,18-20] Due to these pathologies, a more invasive approach is often necessary using gastric tubes, which in this case were used for the child in the study. One of the complications that denote a lack and importance both for the diagnosis and for the correct clinical follow-up would be the neurological findings that are, in most individuals, expressed with abnormalities. There is a variation in mental retardation between mild and severe that reverts to a neuropsychomotor delay, resulting, for example, in procrastination of actions such as speech and motor development. There is also hypotonia, abnormalities in the electroencephalogram, hydrocephalus, seizures, and atrophy of the brain stem.[12,21,22]

The phenotypic overlap between Costello, Noonan and Cardiofaciocutaneous syndromes elucidates an analogous mechanism for the development of these pathologies, RASopathies, being this a mutation in the genes in the pathogen protein kinase activated by RAS/MAPK, a pathway that plays a fundamental role in cell differentiation, proliferation, survival, and death. Mutations in this same pathway also contribute to oncogenesis and tumor progression.[5] Currently, the CFCSis related to four main genes, BRAF, MAP2K1, MAP2K2, and KRAS. Heterozygous mutations in BRAF located in 7q34 have been shown to be the most frequent in studied cases, being found in approximately 75% of individuals with the syndrome, with the majority of BRAF mutations in exons 6 (41%), 12 (21%) and 11, so that the most common mutation that occurs in exon 6 is a missense substitution Q257R (29% occurrence), in exons 12 and 11, E501G (12%) and G469E (6%). For the patient under study, PCR and subsequent direct sequencing of all exons coding for the BRAF gene were performed, revealing the presence of the missense pathogenic mutation in heterozygosis: c.77A□G (pQ257R) in exon 6, confirming the diagnosis of CFCS, showing agreement with previous research.[23] The mother was also tested for this mutation and is not a carrier of this pathogenic variant, which points to the occurrence of a new mutation, being very rare for individuals with CFCS to reproduce. It is believed that Cardiofaciocutaneous syndrome is still underdiagnosed in a large spectrum of cases due to its phenotypic presentation similar to other socially better-known syndromes. The initial approach should remain in a referral to a geneticist and genetic tests that will induce more specific tests such as exon sequencing.[23] Therefore, the interaction of a multidisciplinary medical team will favor the resolution of illnesses and the progression to a stable framework for the individual. Among the medical interactions are dermatological and ophthalmological evaluations, use of tests to identify renal and urogenital abnormalities, neurological and cardiological monitoring, assessment of psychomotor development, using methods such as MRI to identify structural changes and electroencephalograms in cases of seizures. A thorough physical examination and an in-depth assessment of growth patterns are required, and it may be necessary to follow up with an endocrinologist in cases of suspected growth retardation. It should be noted that among the methods of metabolic correction, the benefit-risk must be considered in cases of GH use, since there is an association of neoplasms with the described pathology, and the risk must be assessed according to the evolution clinic.

Patient Perspective: Those responsible for the patient in the present study have the perspective that the interaction of a multidisciplinary medical team will favor the resolution of illnesses and the progression to a stable condition of the patient.

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