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CARDIOFACIOCUTANEOUS SYNDROME (CFCS) IN THE LIGHT OF CONTEMPORARY RESEARCH - A REVIEW OF THE LITERATURE

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ABSTRACT

The term RASopathies was introduced to describe a group of genetic syndromes that share similar phenotypic features and a common molecular basis. RASopathies are among the most numerous groups of recognized congenital developmental disorders. These syndromes have variable clinical courses, and the phenotypic features observed in newborns may differ from those seen in later stages of life - childhood, adolescence, or adulthood - which significantly complicates accurate clinical diagnosis. The underlying cause of these disorders involves mutations in genes encoding proteins associated with the Ras/MAPK (mitogen-activated protein kinase) signaling pathway. Cardiofaciocutaneous syndrome (CFCS) is a representative RASopathy, clinically defined by distinctive craniofacial dysmorphism, congenital heart defects, dermatological anomalies, postnatal growth retardation, and varying degrees of intellectual disability. Recent advances in molecular genetics have facilitated, at least to some extent, the differential diagnosis of CFCS, thereby improving diagnostic accuracy. Lifelong, multidisciplinary medical management is essential for both pediatric and adult patients, necessitating coordinated care involving specialists from various medical fields. This article focuses on the molecular pathogensis, clinical features, prenatal findings and recommended evaluations following initial diagnosis.
Materials: We conducted a review and analysis of the literature available in the PubMed database, using keywords.

KEYWORDS

Cardiofaciocutaneous Syndrome, Ras/MAPK, RASopathies, CFC, BRAF Mutation

CITATION

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Introduction

Cardiofaciocutaneous syndrome (CFC) is a rare genetic disorder belonging to the group of RASopathies, caused by germline mutations in genes encoding components of the RAS/MAPK signaling pathway [6, 7, 12]. Despite growing understanding of the molecular mechanisms underlying CFC, many aspects such as genotype–phenotype correlations, long-term outcomes, and cancer risk- remain poorly defined and require further investigation [1, 2]. Treatment involves a multidisciplinary approach including non-pharmacological and pharmacological interventions [2, 4, 6].

Epidemiology

Cardiofaciocutaneous syndrome was first described in 1986 by a group of American physicians, who reported eight initial cases [2]. Since then, hundreds of cases have been documented in the scientific literature, reflecting increased recognition and advances in genetic diagnostics. The precise incidence of CFC syndrome remains unknown. However, in the Japanese population a prevalence of approximately 1 in 810,000 live births [1,2].

Mode of Inheritance

Cardiofaciocutaneous syndrome is a monogenic disorder inherited in an autosomal dominant manner. An affected individual has a 50% chance of transmitting the pathogenic variant to each offspring. Genes implicated in the pathogenesis of CFC syndrome include BRAF (locus: 7q34), accounting for approximately 75% of cases; MAP2K1 (15q22.31) and MAP2K2 (19p13.3), each responsible for about 12% of cases; and KRAS (12p12.1), found in fewer than 2% of patients. Additionally, de novo point mutations in the YWHAZ gene (8q22.3) have been reported in isolated cases presenting with a CFC-like phenotype [1,2,6].

Molecular Pathogenesis

Four genes currently associated with CFC syndrome - BRAF, MAP2K1, MAP2K2 and less frequently, KRAS - encode proteins that function within the Ras/MAPK signaling pathway [1]. This pathway is one of the most extensively studied intracellular signaling cascades and plays a critical role in oncogenesis and tumor progression [1,2,21]. It is essential for the regulation of fundamental cellular processes, including growth, proliferation, differentiation, survival, metabolism, and migration [6]. The Ras/MAPK signaling cascade involves a sequential activation of Ras, Raf, MEK, and ERK proteins. It is typically triggered by extracellular signals such as growth factors. Ras proteins function as molecular switches, cycling between an active GTP-bound and an inactive GDP-bound state [15]. Upon activation, GTP-bound Ras recruits Raf kinases (ARAF, BRAF, and/or CRAF) to the plasma membrane, enabling the phosphorylation and subsequent activation of MEK1 and MEK2 kinases. These, in turn, phosphorylate ERK1 and ERK2, which translocate to the nucleus to regulate the expression of genes involved in the aforementioned cellular processes [1,6,15]. RASopathies, including CFC syndrome, are caused by mutations in single genes encoding components of this pathway [7]. BRAF, a serine-threonine protein kinase and a direct effector of Ras, is the most frequently mutated gene in CFC. MEK1 and MEK2 (encoded by MAP2K1 and MAP2K2, respectively) are dual-specificity threonine/tyrosine kinases that phosphorylate and activate ERK1/2. Mutations in these genes result in constitutive pathway activation, a hallmark of the molecular pathogenesis of CFC syndrome [1,15].

Craniofacial Features

Cardiofaciocutaneous (CFC) syndrome is associated with a distinctive pattern of craniofacial dysmorphology. Relative macrocephaly is commonly observed. The face typically exhibits a triangular shape with coarse facial features and a small chin. Additional findings include low-set ears, a high forehead with bitemporal narrowing, ptosis, hypertelorism, downward-slanting palpebral fissures, and epicanthal folds. The nose is often short with a broad nasal base, bulbous tip and anteverted nares. The mouth is characteristically wide, with a deeply grooved philtrum and a well-defined Cupid's bow of the upper vermilion border. The palate is frequently high-arched and narrow [2,6].

Cardiac Features

Approximately 75% of patients with CFC syndrome exhibit various abnormalities within the cardiovascular system [2]. The most commonly diagnosed defect is pulmonary valve stenosis (PVS), which is observed in approximately 45% of patients [2]. Hypertrophic cardiomyopathy, diagnosed in around 40% of individuals with CFC syndrome, may present as early as infancy [1,2,6]. Clinical course is highly variable. In some cases it progresses rapidly, potentially necessitating heart transplantation or resulting in death, in others it is limited to mild myocardial thickening that does not progress and may even improve over time [1,2,6]. It has been noted that patients with mutations in the *MAP2K1* gene are less likely to develop cardiac conditions [6].

Cutaneous Features

Cutaneous manifestations represent a key component of the clinical presentation of CFCS. Dermatologic abnormalities are observed in nearly all individuals [2]. Common findings include dry skin, brittle, sparse, curly or woolly hair, dystrophic nails and lymphedema [1]. Characteristic features also include sparse or completely absent eyebrows, often associated with ulerythema ophryogenes - erythematous changes in the eyebrow area leading to the loss of hair follicles [2,16]. Patients frequently develop numerous pigmented nevi, which can number over 100 and are not confined to light-exposed areas [16]. Palmoplantar hyperkeratosis typically affects over pressure zones [2]. It is also noteworthy that infantile hemangiomas appear in approximately 25% of CFC patients, a higher prevalence than seen in other RASopathies; however, their clinical course is usually similar to that observed in the general population [2]. Although additional studies are necessary to establish a potential elevated melanoma risk in individuals, sun protection and regular dermatologic evaluations are recommended.[16].

Neurological/Neurodevelopmental Complications

The RAS/MAPK signaling pathway plays a pivotal role in the development of the nervous system by regulating the cell cycle and supporting the maintenance of neuronal progenitor cell populations. These progenitor cells give rise to mature neurons responsible for synapse formation and the establishment of neuronal connections, which are crucial for normal cognitive function. Disruptions in this signaling pathway during cortical development can result in abnormal proliferation and heightened excitability of progenitor cells, negatively affecting both the structure and function of the brain [18]. Recent studies suggest that children with CFC syndrome exhibit the lowest levels of communication skills and social competencies when compared to other RASopathies [14]. Children with CFC syndrome exhibited significantly greater delays in the attainment of motor and language development milestones [18]. Children carrying pathogenic variants of the MAP2K1

gene required more support and experienced greater difficulties with independent locomotion compared to those with variants in the BRAF and MAP2K2 genes [6]. Neuropathy may be present but is often underrecognized. Musculoskeletal pain, which can be both acute and chronic, is not uncommon. Neurobehavioral problems are prevalent and may encompass irritability, reduced attention span, stubbornness, and obsessive and/or aggressive behaviors. Anxiety is frequently reported as well [1]. Children with CFC syndrome typically begin speaking their first words around the age of two, although 9% to 31% remain nonverbal. Sleep disturbances are common and may include sleep disorders, night sweats, episodes of sleep apnea, and night terrors [2].

Hypotonia

Global hypotonia is typically evident in the neonatal period. Characteristic features include muscle weakness and decreased muscle mass. As children grow older, muscle weakness generally improves, although many continue to experience delays in gross motor development [1]. Muscle biopsies have been performed in only a small group of patients with CFCS. These studies revealed the presence of muscle fibers with abnormal size and considerable variability, which may represent one of the potential mechanisms underlying the development of hypotonia. Due to the limited number of available samples, the authors suggest that, although the overall muscle structure remains largely intact, further research is necessary to gain a more detailed understanding of the nature of this myopathy [10].

Seizures

More than half of individuals with CFC syndrome experience seizure disorders. The observed types of seizures include complex partial seizures, generalized tonic-clonic seizures, absence seizures and childhood epilepsy. Seizures often emerge in infancy - interestingly, this type of seizure, which is rare in the general population, occurs much more frequently in patients with CFC. However, in some patients, the first symptoms may not manifest until later [1,2]. Seizures can be challenging to control and may require treatment with multiple anticonvulsant medications, sometimes with limited efficacy [1,2,6]. Treatment-resistant seizures are associated with significant encephalopathic burden [8].

Growth, Bone Metabolism, and Skeletal Deformities

Short stature is a common feature across all RASopathies. The Ras/MAPK signaling pathway plays a pivotal role in intracellular signal transduction associated with insulin-like growth factor 1 (IGF-1), which mediates the postnatal action of growth hormone (GH) [2, 11]. In individuals with cardiofaciocutaneous (CFC) syndrome, growth retardation during infancy is frequently observed and represents one of the characteristic phenotypic features of the disorder [1]. In addition to hormonal factors, the pathogenesis of short stature is influenced by musculoskeletal dysfunction, gastrointestinal disturbances and elevated resting energy expenditure [11]. Available data on the prevalence of osteopenia and osteoporosis in patients with cardiofaciocutaneous syndrome remain limited [11]. The risk of fractures is currently difficult to estimate with certainty; however, long-term monitoring of bone mineral density (BMD) is recommended. In addition to genetic determinants, disturbances in bone homeostasis are also influenced by secondary factors, including reduced mobility, a sedentary lifestyle, and the use of certain medications, such as antiepileptic drugs and proton pump inhibitors [11]. Scoliosis and kyphosis are observed in approximately 20–35% of cases and constitute additional clinically relevant musculoskeletal manifestations. A more severe course of osteoarticular involvement, including a higher prevalence of multiple joint contractures and scoliosis, has been associated with pathogenic variants in the MAP2K1 or MAP2K2 genes [11].

Feeding and Gastrointestinal Issues

Feeding difficulties and inadequate weight gain are among the earliest clinical signs and present significant caregiving challenges during infancy. A high prevalence of neonatal sucking disorders has been reported across nearly all published cohorts [17]. Enteral nutrition, administered via nasogastric tube or gastrostomy, is frequently required, affecting approximately 40–50% of cases. In many instances, nutritional support remains necessary well into late childhood and adolescence. Respiratory complications secondary to swallowing dysfunction may include aspiration pneumonia and choking episodes [2]. The high incidence of gastroesophageal reflux disease (GERD) in early life can lead to an association between feeding and pain, contributing to the development of food aversion and secondary growth disturbances [17].

Ophthalmological Manifestations

Ocular abnormalities are frequently observed and include strabismus, refractive errors, nystagmus, ptosis and optic nerve hypoplasia. These manifestations encompass both functional impairments and structural anomalies of the visual apparatus [1, 2].

Orofacial Features

Within the stomatognathic system, commonly observed anomalies include anterior open bite, posterior crossbite, high attachment of the lower labial frenulum and a high-arched palate. Functionally, frequent findings involve habitual tongue thrusting, bruxism, and persistent mouth breathing. Despite the presence of these abnormalities, the timing of tooth eruption is generally consistent with norms observed in the general population [2].

Urogenital Abnormalities

Urogenital system anomalies are reported in approximately 17–33% of individuals. In males, cryptorchidism is a common finding. Additional reported abnormalities include renal cysts and calculi, hydronephrosis, and ureteral dilatation (ureterocele) [1, 2].

Prenatal Findings

Recent reports suggest that some features of cardiofaciocutaneous (CFC) syndrome may be detectable during the prenatal period. Ultrasonographic findings in fetuses include increased nuchal translucency, the presence of cystic structures, macrosomia, macrocephaly, cardiac anomalies, renal abnormalities, and polyhydramnios, which may indicate the presence of a RASopathy [2, 19]. In the third trimester, the most common indications for performing ultrasound were reduced fetal movement and the presence of polyhydramnios [5]. Unfortunately, none of these ultrasonographic findings are specific to CFC syndrome [5, 13]. As a result, research is ongoing to identify prenatal phenotypic features that could indicate early suspicion of a RASopathy, thereby guiding further genetic diagnostic workup [5]. Preterm birth, defined as delivery before 37 weeks of gestation, is frequently observed and has been reported in numerous clinical cases [1, 3]. Pregnant women suspected of having a fetus with CFC syndrome should be monitored by a specialist due to the increased risk of pregnancy complications. The most commonly reported issues include polyhydramnios, cardiovascular diseases, and maternal hypertension. Additionally, complications such as hyperemesis, gestational diabetes, pregnancy-induced hypertension and preeclampsia may occur [1]. Cesarean delivery is not uncommon in these cases [1, 2].

Genotype–Phenotype Correlations

No definitive genotype–phenotype correlations have been established for specific pathogenic variants in BRAF, KRAS, MAP2K1 or MAP2K2 [1]. In one recent study evaluating neurological and neurodevelopmental features, it was found that the prevalence of seizures in patients with BRAF and MAP2K1 mutations was approximately twice as high compared to those with MAP2K2 variants (30%) [8]. A significant observation is the presence of pulmonary artery stenosis in 50% of individuals with CFC syndrome carrying a BRAF mutation. Studies have shown that BRAF mutations are often associated with hypertrophic cardiomyopathy, interatrial septal defects, intellectual disabilities, and feeding difficulties [4, 9].

Recommended Evaluations Following Initial Diagnosis

Advancements in molecular diagnostics have considerably enhanced the differentiation between syndromes within the RASopathy spectrum, which present with overlapping clinical manifestations that often evolve gradually with age [11]. Many patients and their caregivers have previously experienced prolonged and burdensome diagnostic processes, frequently involving misdiagnoses prior to establishing an accurate diagnosis [12]. To determine the extent of organ involvement, a comprehensive multidisciplinary approach to care should be implemented [6].

Neurological Consultation and Imaging

Neurological consultation, accompanied by magnetic resonance imaging (MRI) of the brain, is recommended for patients exhibiting rapid head circumference growth, regression of acquired developmental skills, seizures, abnormal neurological findings, or suspicion of optic nerve hypoplasia identified during ophthalmological assessment [1]. MRI imaging may reveal characteristic structural changes, including Chiari malformation type I, ventricular system enlargement, hydrocephalus, enlarged Virchow-Robin spaces, myelination disorders, and other developmental abnormalities of the central nervous system [1, 6]. The most frequently reported finding is ventriculomegaly (43.9%), which in some cases may necessitate neurosurgical intervention, such as ventriculoperitoneal shunting [6]. In cases where seizures are suspected, electroencephalography (EEG) should be performed to assess the brain's bioelectrical activity [1]. Furthermore, patient families should be informed of the potential risk of seizures and provided with instructions on appropriate management in the event of their occurrence [2]. If peripheral nervous system damage is clinically suspected, diagnostic workup should include nerve conduction velocity (NCV) assessment and electromyography (EMG) to detect possible neuropathy [1, 2].

Developmental and Behavioral Screening in Children

For children over the age of twelve months, it is recommended to conduct routine screening for neurodevelopmental and behavioral disorders, including sleep difficulties, symptoms of attention-deficit hyperactivity disorder (ADHD), anxiety disorders, and features suggestive of autism spectrum disorder (ASD) [1]. A detailed evaluation of speech and language development is indicated, encompassing the analysis of motor functions of the articulatory apparatus, articulation precision and language competencies in terms of speech expression and comprehension [2]. Depending on the identified difficulties, behavioral therapy, mental health interventions, and alternative therapies supporting sensory, motor, social, emotional, and communicative functioning may be considered. Once formal schooling begins, close collaboration between educational specialists and the child's family is recommended to develop an Individualized Education Plan (IEP) or other support plans. It is also crucial to formally confirm the medical diagnosis and assess eligibility for special education services [2]. Upon the commencement of formal education, it is essential for educational professionals and the family to collaborate closely in order to develop an Individualized Education Plan (IEP) or another support plan. Additionally, confirming the medical diagnosis and assessing eligibility for special education services is crucial [2].

Gastroenterological and Nutritional Evaluation

A gastroenterological and nutritional assessment should be conducted to monitor nutritional status and evaluate growth parameters and body weight. Consultation with a multidisciplinary team is recommended in cases of feeding difficulties, to consider the introduction of nasogastric feeding or gastrostomy. Additionally, diagnostic workup and treatment of gastroesophageal reflux and constipation may be required, as well as consideration for upper gastrointestinal endoscopy in the presence of clinical indications [1,2]. Abdominal and pelvic ultrasonography is recommended for screening potential abnormalities in the kidneys and internal reproductive organs, including the uterus [1].

Endocrinological Consultation

An endocrinological consultation is recommended for a comprehensive evaluation of hormonal axis disorders. This includes regular monitoring of growth rate, assessment of thyroid function (TSH, FT4), screening for celiac disease (e.g., anti-TG2 antibodies), diagnosis of potential growth hormone (GH) deficiency, and observation of the progression of sexual maturation for signs of precocious or delayed onset [2].

Ophthalmological Consultation

An ophthalmological consultation is indicated due to the increased risk of various ocular pathologies, including ptosis, amblyopia, refractive errors (myopia, hyperopia, astigmatism), strabismus, cataracts, optic nerve hypoplasia or atrophy, cortical visual disturbances, and deficits in depth perception and delayed maturation of visual functions. Regular ophthalmic follow-up every 6–12 months, or more frequently depending on individual clinical needs, is recommended [1,2].

Otorhinolaryngological Consultation

An otolaryngological consultation is recommended due to the increased risk of anomalies in the auditory system and upper respiratory tract, including external auditory canal stenosis, wax accumulation, conductive or sensorineural hearing loss, and laryngomalacia. Regular audiological assessments every 2–3 years are recommended, with increased frequency in the presence of concerning symptoms. In clinically justified cases, the use of hearing aids should be considered. Middle ear infections should be promptly diagnosed and treated to minimize the risk of permanent hearing loss [1,2].

Cardiological Assessment

A comprehensive cardiological assessment should include blood pressure measurement, echocardiography (ECHO), and electrocardiography (ECG), with particular emphasis on the detection of potential structural abnormalities such as pulmonary valve stenosis, hypertrophic cardiomyopathy, or defects in the interatrial or interventricular septa. In cases of suspected arrhythmias, 24-hour Holter ECG monitoring is recommended for continuous evaluation. If a cardiac defect is diagnosed, further specialist care under the guidance of a cardiologist is required. The cardiologist, based on clinical findings and diagnostic results, will determine the necessity for pharmacological intervention, surgical procedures, or other appropriate therapeutic measures [1,2].

Dermatological Consultation

A dermatological consultation should involve the evaluation of existing skin lesions, such as hemangiomas or pigmented nevi. Regular dermatological visits are essential for the management of skin dryness, excessive keratinization, eczema, and for monitoring lymphatic edema. Additionally, proper skin care, including the use of sun protection, should be emphasized to prevent further complications [1,2].

Musculoskeletal System Assessment

A comprehensive musculoskeletal evaluation should be conducted by an orthopedist and physical therapist to identify any abnormalities early and develop an appropriate therapeutic plan, which may include rehabilitation. Particular attention should be paid to the development of motor skills, both in terms of gross and fine motor abilities, as well as the presence of contractures, hip joint dysplasia, and kyphoscoliosis. During the assessment, it is also important to evaluate the level of mobility, the ability to perform daily activities, and the potential need for adaptive devices to support functionality. Based on the clinical examination findings, radiographic imaging of the thoracolumbar spine, pelvis, and, if indicated, lateral cervical spine images should be performed. For individuals with disabilities, it is recommended to conduct pelvic X-rays in the anteroposterior (AP) view every two years to monitor the progression of hip joint dysplasia. Additionally, regular monitoring of spinal deformities is advised, and in young adults, bone mineral density testing should be considered to assess the risk of osteopenia or osteoporosis [2].

Cancer risk

Mutations responsible for CFCS affect the RAS/MAPK pathway, a signaling cascade extensively implicated in oncogenesis. Despite this, the association between CFC and an increased risk of malignant tumor development remains unclear. The BRAF gene, a proto-oncogene, undergoes somatic mutations in approximately 7% of cancer cases, including melanoma, thyroid, ovarian, and colorectal cancers. Nevertheless, reports of malignancies in patients with CFC remain very limited [3]. Most mutations observed in RASopathies, including CFC, are activating in nature, but their impact on the RAS/MAPK pathway is generally weaker than that of typical oncogenic mutations found in cancers. For example, the BRAF p.V600E mutation, a potent activator of this pathway and commonly observed in malignant tumors, has never been detected in individuals with CFC syndrome [12,21]. The identification of mutations in the MEK1/2 genes in patients with Cardiofaciocutaneous Syndrome (CFC) has significantly advanced our understanding of oncogenesis. These mutations, previously unreported in the context of cancer, were first observed as germline mutations in CFC, thereby stimulating further investigation into their role in oncogenic mechanisms. It is now established that activating mutations in the MEK genes are implicated in a variety of malignancies [12,21].

Treatment

There is no specific treatment for CFCS. Appropriate multidisciplinary care, based on monitoring the patient's health status and symptomatic treatment [4,6]. Neurological care involves monitoring the child's developmental progress and implementing supportive therapies, such as physical rehabilitation, speech therapy, and occupational therapy. Patients with CFC often require the use of orthoses and postural/mobility devices to improve posture and facilitate the achievement of developmental milestones. Increased use of wheelchairs and braces is also commonly needed [10]. An interesting finding comes from two independent studies that suggest the potential effectiveness of MEK inhibitors in treating hypertrophic cardiomyopathy in CFC patients. The therapeutic effect was particularly evident in cases where treatment was initiated before the onset of irreversible structural changes in the heart muscle. This opens new avenues for molecularly targeted therapy in this patient population, although further clinical studies are necessary to confirm the safety and efficacy of this therapeutic strategy [6].

Conclusions

Cardiofaciocutaneous (CFC) syndrome is a rare multisystem genetic disorder within the group of RASopathies. It is characterized by developmental delays, distinctive facial dysmorphisms, congenital heart defects, dermatological abnormalities, and neurological manifestations. The molecular basis of CFC has been well elucidated, and advances in genetic diagnostics have enabled increasingly rapid and accurate identification of this condition. Diagnosis is primarily based on a characteristic clinical presentation combined with the identification of pathogenic variants in relevant genes. Timely recognition of syndrome-specific complications enables the initiation of targeted medical management. Treatment of individual manifestations follows protocols similar to those used for corresponding isolated conditions. However, due to the complexity and variability of clinical presentations, optimal care requires a multidisciplinary approach involving cardiology, neurology, gastroenterology, rehabilitation medicine and clinical genetics.

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