Manifestations multisystémiques et analyse génétique chez un enfant atteint du syndrome cardio-facio-cutané

Multisystemic Features and Genetic Analysis in a Child with Cardiofaciocutaneous Syndrome

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RESUME

Introduction : Le syndrome cardio-facio-cutané (CFC) est une RASopathie rare caractérisée par une grande hétérogénéité clinique, associant retard du développement, dysmorphie faciale, anomalies cutanées et parfois cardiopathies congénitales.

Observation : Nous rapportons le cas d'un garçon de 6 ans présentant un retard psychomoteur global, une dysmorphie faciale caractéristique, une xérose cutanée et une épilepsie débutée à l'âge de 5 ans, contrôlée par monothérapie. L'imagerie cérébrale a révélé une hypotrophie diffuse du corps calleux. L'analyse génétique par séquençage de l'exome a identifié une mutation faux-sens hétérozygote du gène MAP2K1, compatible avec un CFC de type 3. Le patient bénéficie d'un suivi pluridisciplinaire (neurologique, dermatologique, endocrinien et pédopsychiatrique.

Conclusion : Ce cas illustre un phénotype typique de CFC, souligne l'importance d'une reconnaissance précoce des signes cliniques et de la confirmation génétique, et met en évidence la nécessité d'une prise en charge multidisciplinaire adaptée.

Mots clés : syndrome cardio-facio-cutané, RASopathie, retard du développement, dysmorphie faciale, mutation MAP2K1, épilepsie

ABSTRACT

Introduction : Cardiofaciocutaneous (CFC) syndrome is a rare RASopathy with marked clinical heterogeneity, characterized by developmental delay, facial dysmorphism, cutaneous anomalies, and occasionally congenital heart defects.

Case report : We report the case of a 6-year-old boy presenting with global psychomotor delay, characteristic facial dysmorphism, cutaneous xerosis, and epilepsy onset at 5 years, currently well controlled with monotherapy. Brain imaging revealed diffuse hypoplasia of the corpus callosum. Whole-exome sequencing identified a heterozygous missense mutation in the MAP2K1 gene, consistent with CFC type 3. The patient benefits from multidisciplinary follow-up (neurological, dermatological, endocrinological, and child psychiatric).

Conclusion : This case illustrates a typical CFC phenotype, highlights the importance of early recognition of clinical signs and genetic confirmation, and emphasizes the need for a comprehensive multidisciplinary management plan.

Keywords: cardiofaciocutaneous syndrome, RASopathy, developmental delay, facial dysmorphism, MAP2K1 mutation, epilepsy

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INTRODUCTION

Cardiofaciocutaneous (CFC) syndrome is a rare genetic disorder belonging to the group of RASopathies, which encompass a spectrum of developmental conditions caused by dysregulation of the RAS/MAPK signaling pathway [1]. RASopathies are characterized by multisystem congenital anomalies, commonly involving the cardiovascular system, craniofacial development, skin, nervous system, and skeletal structures. This group includes Noonan syndrome, Costello syndrome, LEOPARD syndrome, and CFC syndrome, which share overlapping clinical features while also exhibiting distinct manifestations [2]. RASopathies typically result from heterozygous de novo mutations in genes regulating the RAS/MAPK pathway, such as BRAF, MAP2K1, MAP2K2, KRAS, PTPN11, and others. This signaling pathway plays a crucial role in cell proliferation, differentiation, and survival; its disruption leads to a broad clinical spectrum ranging from congenital heart defects and characteristic facial features to cutaneous and hair abnormalities, as well as psychomotor and cognitive developmental delays [3]. Clinically, CFC syndrome is characterized by distinctive craniofacial features, including a broad forehead, hypertelorism, ptosis, a short and broad nose, and retrognathia, in association with congenital heart disease - most commonly pulmonary valve stenosis, ventricular septal defect, atrial septal defect, and valvular abnormalities - along with dermatological and hair manifestations such as dry skin, palmoplantar keratoderma, and sparse, fine hair. Growth retardation and neurodevelopmental delay, including motor delay, language impairment, and variable degrees of intellectual disability, are also frequently observed. Owing to the significant phenotypic overlap with other RASopathies, the clinical diagnosis of CFC syndrome remains challenging [4]. Precise identification of the causative mutation through targeted or whole-exome sequencing is therefore essential to confirm the diagnosis, guide treatment, and offer appropriate genetic counseling.

In this context, we report the case of a patient with CFC syndrome, aiming to describe the clinical manifestations and genetic findings and to contribute to a better understanding of this rare disorder within the RASopathy spectrum.

CASE REPORT

We report the case of Mohamed, a 6-year-old boy, followed up for global psychomotor developmental delay associated with craniofacial dysmorphism. He is the only child in the family, born to non-consanguineous parents, with good adaptation to extrauterine life and no notable family history. Developmental delay was characterized by independent walking acquired at 24 months and delayed speech development until the age of 3 years.

Clinical examination revealed macrocephaly with a head circumference at +3 standard deviations (SD) and short stature with height at -2.2 SD. Craniofacial dysmorphism included a prominent forehead, hypertelorism, a broad nose with a flat nasal bridge, a wide mouth with thin lips, and low-set ears. The systemic examination was otherwise unremarkable, except for bilateral genu valgum.

As part of the etiological work-up, brain magnetic resonance imaging demonstrated diffuse hypoplasia of the corpus callosum. Given this clinical and radiological presentation, genetic testing was subsequently performed, and whole-exome sequencing (WES) identified a heterozygous missense variant in the MAP2K1 gene (15q22.33), which encodes the mitogen-activated protein kinase kinase 1 (MEK1), consistent with cardiofaciocutaneous syndrome type 3. A comprehensive multisystem evaluation was then undertaken. Echocardiography and audiological assessment were normal. The patient has been followed by dermatology for cutaneous xerosis and treated with emollients. Additional endocrine investigations and child psychiatry follow-up confirmed severe intellectual disability.

At the age of 5 years, two years after the genetic diagnosis, the patient developed generalized tonic-clonic seizures. Electroencephalography revealed pathological findings with frontal epileptiform discharges, and he was started on antiepileptic therapy. Epilepsy is currently well controlled with antiepileptic monotherapy.

DISCUSSION

Cardiofaciocutaneous syndrome is a rare RASopathy characterized by a variable combination of craniofacial, cutaneous, cardiac anomalies, and developmental delay. The clinical features observed in our patient- including global developmental delay, suggestive facial dysmorphism, and cutaneous anomalies- fall within the spectrum classically described for CFC syndrome. This case adds value as an illustrative example of a MAP2K1-associated CFC phenotype, highlighting the diagnostic and clinical relevance of WES in guiding management.

1. Phenotypic comparison with the literature

Developmental delay, particularly of motor and language milestones, has been reported in more than 80–90% of patients with CFC syndrome [4]. Our patient exhibits a similar profile, with markedly delayed motor and speech acquisition. However, emerging evidence suggests that MAP2K1-associated cases may show a broader range of neurodevelopmental outcomes compared to BRAF-associated CFC, including variability in cognitive and motor impairment. This emphasizes the need for individualized prognostic assessment and early, tailored intervention [5,6].

Neurological involvement, mainly epilepsy as observed in this case, requires regular monitoring, with generally good response to antiepileptic therapy [4]. The onset of seizures two years after the genetic diagnosis underscores the importance of long-term neurolo-

gical surveillance in MAP2K1 cases, even in the absence of early epilepsy.
Facial dysmorphism is a major criterion of the syndrome; the features observed in our patient support the initial clinical suspicion. While these traits are not exclusive to CFC, they are frequently observed across RASopathies [7]. Cutaneous anomalies, particularly xerosis, keratosis pilaris, and hair abnormalities, remain more characteristic of MAP2K1-associated CFC and can assist in differential diagnosis [8].

2. Genotype–phenotype correlation

CFC syndrome is most commonly associated with variants in BRAF, followed by MAP2K1, MAP2K2, and, more rarely, KRAS [5]. While phenotypic overlap exists, specific MAP2K1 variants may be associated with less severe neurodevelopmental impairment than BRAF variants, though intellectual disability can still be significant. Detailed variant annotation, including amino acid change and functional studies, is crucial to refine prognostic predictions [5,6]. Our patient harbors a heterozygous missense variant in MAP2K1, with global developmental delay, facial dysmorphism, and cutaneous anomalies consistent with reported MAP2K1-associated phenotypes. This emphasizes the value of molecular confirmation for individualized prognosis, anticipatory guidance, and informed genetic counseling [9].

3. Differential diagnosis

To contextualize this case, it is important to critically compare CFC syndrome with other clinically similar RASopathies (table 1). CFC shares features with Noonan and Costello syndromes. Noonan syndrome typically presents milder dysmorphic features and less prominent skin anomalies, whereas Costello syndrome often manifests with thickened skin, papillomas, and severe hypotonia [7]. A careful evaluation of subtle differences is essential in clinical practice, as misclassification may lead to suboptimal surveillance and management. This highlights the practical relevance of integrating molecular findings with clinical assessment.

Table 1 : Comparative Clinical Features of Selected RASopathies

Feature	Cardiofaciocutaneous syndrome	Noonan Syndrome	Costello Syndrome
Frequency	Very rare	Most common RASopathy	Rare
Psychomotor Development	Moderate to severe developmental delay	Often mild developmental delay	Marked delay with severe hypotonia
Walking Acquisition	Frequently delayed	Possible delay, usually mild	Significant delay; unsteady gait
Facial Features	Broad forehead, ptosis, hypertelorism, low-set ears	Triangular face, ptosis, low-set ears	Coarse facial features, macroglossia, wide mouth
Cardiac Involvement	Pulmonary stenosis, atrial septal defect ventricular septal defect	Hypertrophic cardiomyopathy, pulmonary stenosis	Frequent hypertrophic cardiomyopathy
Skin Abnormalities	Dry skin, keratosis, fine and sparse hair	Soft skin, variable pigmentation	Thick skin, deep folds, papillomas
Growth	Frequent growth retardation	Short stature is common	Severe short stature
Neurological System	Hypotonia, moderate intellectual disability, seizures	Borderline intellectual functioning	Moderate intellectual disability
Tumor Risk	Very rare	Slightly increased (myelodysplastic disorders)	High risk: rhabdomyosarcoma, neuroblastoma

4. Genotype–phenotype correlation

Optimal care for CFC syndrome requires coordinated follow-up across multiple specialties [10], tailored to each patient's manifestations:

- Pediatric neurology and psychomotor follow-up, particularly in cases with developmental delay and epilepsy;
- Cardiology monitoring, even if no major anomalies are present;
- Dermatological care to manage xerosis and other skin abnormalities;
- Regular ophthalmologic and ENT evaluations;
- Individualized educational and child psychiatry support.

A precise genetic diagnosis not only confirms the clinical suspicion but also informs prognosis, guides surveillance strategies, and allows anticipatory management of potential complications. In MAP2K1-associated cases, knowledge of the specific variant can influence monitoring priorities and therapeutic planning.

CONCUSION

Cardiofaciocutaneous syndrome is a rare RASopathy with marked clinical heterogeneity, which can complicate diagnosis without molecular testing. This case illustrates a typical phenotype, including global developmental delay, characteristic facial dysmorphism, epilepsy, and cutaneous anomalies, emphasizing the need for early recognition. Multidisciplinary care and genetic confirmation are essential to guide management and provide appropriate counseling. This report highlights the value of combining clinical expertise with molecular analysis to improve diagnosis and follow-up in patients with RASopathies.

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