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CASE REPORT

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Cantú syndrome: A new case and evolution of clinical conditions during first 2-year follow-up

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Abstract

Cantú syndrome, or hypertrichotic osteochondrodysplasia, is a rare autosomal dominant disease characterized by congenital hypertrichosis, characteristic dysmorphisms, skeletal abnormalities and cardiomegaly. We report on a 7-year-old girl with congenital generalized hypertrichosis, coarse facial appearance and cardiac involvement, with a de novo heterozygous mutation (c.3461G > A) in the ABCC9 gene. During the annual cardiac follow-up at the age of nine the echocardiogram showed mild left ventricular dilatation in consideration of which she started ramipril treatment. The progression of the clinical manifestations of Cantú syndrome highlights the relevance of an early diagnosis, including genetic analysis, and a multidisciplinary approach with long-term follow-up.

KEYWORDS

ABCC9 gene, Cantú syndrome, congenital hypertrichosis, hypertrichotic osteochondrodysplasia

1 | INTRODUCTION

Cantú syndrome (CS), also known as hypertrichotic osteochondrodysplasia (OMIM #239850), is a rare autosomal dominant condition distinguished for numerous different clinical manifestations. Coarse facial traits and hypertrichosis are present in all affected child and manifested from birth.[1] Hypertrichosis results in massive hair on the head that extend on the forehead with a low frontal hairline, and a widespread increment in facial and body hair. Dysmorphic facial features include flat nasal bridge, epicanthal folds, anteverted nares, long philtrum, prominent mouth, macroglossia and thick lips.[2] Many pregnancies are complicated by polyhydramnios (57%) and generalized macrosomia (38%), with greater birth weight and length. Macrocephaly, and generalized edema at birth (43%) are also commonly reported. Cardiovascular abnormalities, including cardiomegaly (64%), patent ductus arteriosus (58%), pericardial effusion (25%) and pulmonary hypertension are common.[3] Skeletal anomalies, as reported in a review of 10 patients,[4] are usually mild and asymptomatic. Hypotonia can be present and cause motor development delayed. Learning difficulties, intellectual disability or behavioral problems are reported only in few affected individuals.[3] Common finding in CS patient's neuroimaging include cerebrovascular abnormality and tortuous cerebral vessels, but also white matter changes and enduring fetal circulation.[5,6]

The underlying cellular and tissue mechanisms of CS are complicated and not entirely clarify.[7] However, a

gain-of-function variants of ABCC9 gene have been described in most cases and of KCNJ8 gene in three cases.[5,8,9] ABCC9 and KCNJ8 encodes SUR2 and $K_{IR}6.1$, located in ATP-sensitive potassium (K_{ATP}) channel in several cell types. SUR2 mutations responsible of Cantú syndrome increment channel activity, this produce a reduction in channel sensibility to changes in intracellular nucleotide concentrations, lowering cell excitability.[10] Remarkably, the majority of cases arises from de novo variants.[2]

This article describes a new case of Cantú syndrome in a girl with 2-year follow-up. The purpose of this report is to emphasize the rapid evolution of the cardiac manifestations and the importance of a multidisciplinary approach, including an early genetic diagnosis and long-term follow-up.

2 | CASE DESCRIPTION

A 7-year-old Caucasian girl was referred due to the presence of diffuse congenital hypertrichosis. Hypertrichosis at the time of visit was diffuse with abundant terminal hair in the face, trunk and limbs (Figure 1). The excessive hair growth slightly improved over the years but was still present; the facial appearance was coarse with epicanthal folds, flat broad nasal bridge, flared nares, long and flat philtrum, large mouth with thick lips (Figure 2).

She was the third-born child of non-consanguineous parents. She was born at 40 weeks' gestation by Cesarean Section. At birth, macrosomia (birth weight 5720 g) and generalized hypertrichosis were observed (Figure 3). She was of muscular build with length and weight at the 90th and > 97th centile, respectively, and head circumference (37 cm) at >97th centile.

Few hours after birth she developed cyanosis and respiratory distress not attributable to infective sources. An echocardiogram showed a patent ductus arteriosus (PDA) and an atrial septal defect, ostium secundum type complicated with pulmonary hypertension. At 10 days of life, she has been transferred to the Pediatric Intensive Care Unit in order to proceed with ligation of PDA at 14 days and reduce pulmonary hypertension with sildenafil treatment which have been carried out for 2 months. The patient had mild, axial and pelvic girdle muscle hypotonia that had resolved at the neurological follow-up 1 year later, without any consequent motor delay. She had right sensorineural retrocochlear hypoacusia. When patient was 8-month-old underwent an MR imaging of the brain that reported dilated carotid siphon and basilar artery, this one was also elongated and scoliotic.

At the age of 5 years the patient went through an extensive endocrinological assessment to detect the cause of hypertrichosis (Vitamin D, ACTH, DHEAS, cortisol, TSH, FT4, FT3, and ACTH stimulation test) that did not detect any alterations. She had recurrent episodes of tonsillitis and she underwent tonsillectomy at the age of 6.

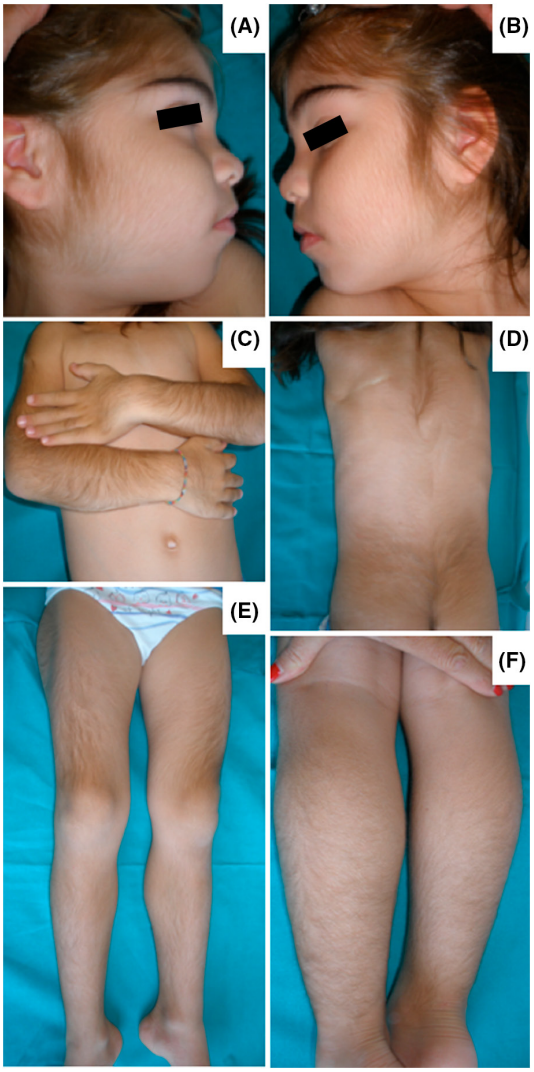

FIGURE 1 Generalized hypertrichosis of the face, back, upper and lower limbs.

Clinical presentation and medical history raised the suspicion of CS and sequencing of ABCC9 gene detected a de novo c.3461G > A p.(Arg1154Gln) heterozygous pathogenic variant (NCBI transcript reference: NM_005691.3) (Figure 4). Parents and sibs did not have any CS-related clinical features nor ABCC9 gene alterations.

Due to patient age, we decided to wait until teenager for laser hair removal. The patient is now followed up with annual orthopedic and cardiologic examinations.

At the age of 8, echocardiogram showed an asymptomatic, minimal pericardial effusion, and a mild left ventricular dilatation (LVEDV (ml): 99(z-score 2.57) LVESV (mL): 42.5 (z-score 2.9), EF (%):57) without hemodynamic repercussion. The following year the echocardiogram showed a worsening of left ventricular

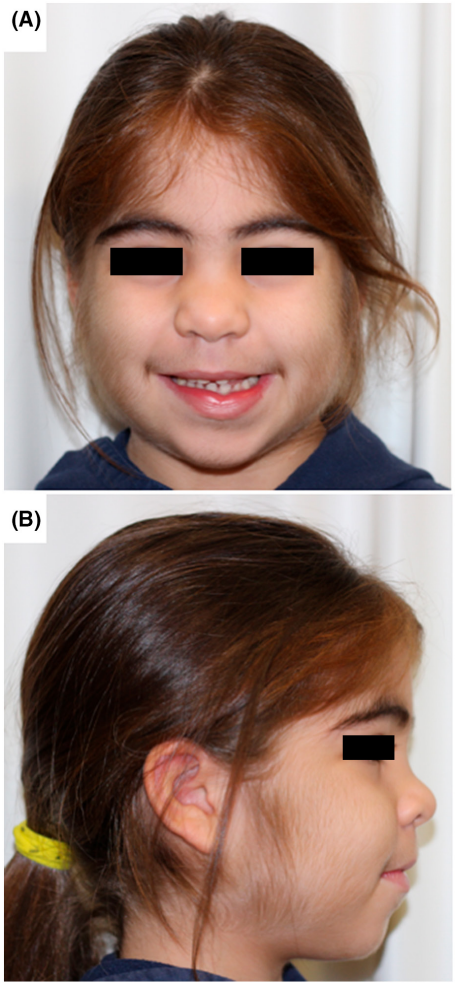

FIGURE 2 Coarse appearance with hypertelorism, epicanthal folds, flat broad nasal bridge, flared nares, long and flat philtrum, large mouth with thick lips.

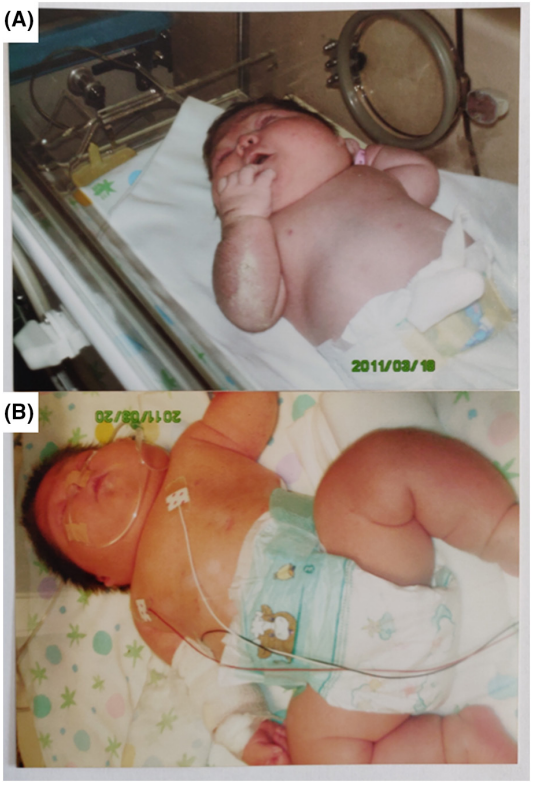

FIGURE 3 Macrosomic patient at birth with congenital generalized hypertrichosis.

dilatation (LVEDV (mL): 110(z-score 2.55), LVESV (mL): 46 (z-score 2.66) EF (%): 58) in consideration of which ramipril treatment at low dosage (1.25 mg/die) was started. Echocardiography performed after 5 months of ramipril treatment showed a reduction of both LVEDV and LVESV (LVEDV (mL): 103(z-score 1.53) LVESV (mL): 36 (z-score 1.09), EF (%):65), on the other hand no sign of hypotension has been documented. Z-score retrieved from Boston Children Hospital Heart Center (https://zscore.chboston.org/).

No anomalies have been detected at the orthopedic visits. She is currently growing up well with a BMI of 18.6 kg/m^2 (59° percentile for Cacciari standard growth curves) and she does not have cognitive impairment and is doing well at school. Despite presenting good health condition, on the last visit her mother pointed out the emerge of psychological and relational issues in relation to the persistent hypertrichosis. This clinic condition, in a 9–year-old child attending school may undoubtedly influence self-esteem and social relationships.

3 | DISCUSSION

Although our case is a single case with a well-known pathogenic variant of ABCC9, it is a typical example of diagnostic delay of CS. Despite the patient underwent through numerous medical counseling since birth and although suspicion of a genetic disorder, she did not have any formal diagnosis until the dermatological evaluation. Indeed, an overall view on the general clinical manifestations is frequently missing and this can cause diagnostic and therapeutic delays.[11–13] Furthermore, in our case, during the first 2 years of follow-up there has been a rapid progression of the cardiac conditions that required the introduction of a systemic treatment at the age of 9 years, highlighting the importance of early diagnosis and a comprehensive follow-up. Moreover, brain imaging, including evaluation of the cerebral vasculature, should be considered as an increased frequency of stroke was reported in a cohort of 74 CS patients, although long-term risk is still unclear.[1]

There are numerous different clinical manifestations in the spectrum of CS patients, even among the same family sharing the gene variant.[2] Grange et al. developed an International Cantú Syndrome Registry (ICSR) with 74 subjects enrolled to supply a comprehensive characterization of the phenotype and genetic variants of CS.[1] In this

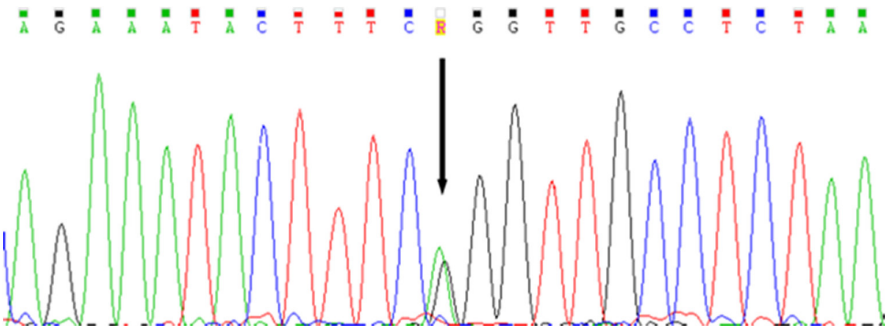

FIGURE 4 ABCC9 variant; c.3461G > A p. (Arg1154Gln).

report, the authors emphasized the width of clinical spectrum of CS, even with same gene mutation, suggesting that those patients reported having the acromegaloid facial appearance syndrome (AFA, OMIM %102,150), or the acromegaloid facial appearance (HAFF, OMIM #135400) certainly be part of the milder CS spectrum, suggesting to avoid the use of such alternatively terms. The same authors and many others suspect that there are still a large number of undiagnosed or misdiagnosed cases since the genetics of CS has been recently characterized, and not all patients may have had adequate genetic counseling. To date, about 150 individuals have been reported with CS,[3] including cases of formerly known as acromegaloid facial appearance and hypertrichosis with acromegaloid facial features.

So far, there are no target therapies for CS, and clinical management involves symptomatic treatments to address secondary complications.[1] Nevertheless, the K_{ATP} channel is a known target for which both channel blocking and opening drugs are used in the clinic,[10] with numerous studies assessing the efficacy of this drugs underway.[10,14,15] At the moment, any conclusions on clinical efficacy awaits further studies.[10] Remarkably, there is an overlapping phenotype (hypertrichosis, pericardial effusion, and edema)[16] in CS patients and people treated with minoxidil, a K_{ATP} channel opener.[17,18] Therefore, it has been speculated that K_{ATP} inhibition might mitigate hypertrichosis in individuals with CS and that topical application of K_{ATP} inhibitors may be use for hair removal.[14] In this context, glibenclamide was recently reported to be successful in one case of CS, with clinical improvement of some of the CS features such as pulmonary hypertension, but no reversion of hypertrichosis after a year of treatment.[16]

Despite phenotype changes among patients, even within the same family sharing the gene variant,[11] clinical diagnosis remains the mainstay in identifying CS patients. Most CS patients initially received other diagnoses, with mucopolysaccharidosis being the most frequent on the base of coarse facial traits.[2] Dysmorphic facial features are evident in every CS patients and are generally present at birth and plays an crucial role in the clinical diagnosis. However, the low incidence of CS restricts exposure during training and reduce the capacity of recognizing the facial features characteristic of this syndrome. A three-dimensional (3D) facial morphology study with a quantitative analysis of the described facial morphology was recently conducted. This new technology could assist in future in achieving earlier clinical suspicion.[2]

Our case was emblematic because generalized hypertrichosis represented the major clue to detect CS, suggesting that in patients with hypertrichosis it is essential to perform a thorough medical history and detect concomitant malformations. Dysmorphic facial appearance or cardiac defects can be important sign in order to suspect a genetic syndrome. In this context, dermatologists can have a leading role in the diagnosis as hypertrichosis and coarse facial appearance are clinical features common to all patients affected by CS. Moreover, this case emphasizes the importance of perform regular follow-up evaluations, especially for the cardiac complications that may be early and progressive as in our patient. Lastly, in our report we underline the need to address not only the physical health issues but also the psychological impact of this clinic condition.

AUTHOR CONTRIBUTIONS

Dr. Alessandra Mattiucci was involved in manuscript drafting and agreed upon manuscript content. Prof. Giampiero Girolomoni, Dr. Matteo Cassina, Dr. Thomas Zoller, Prof. Franco Antoniazzi, and Dr. Donatella Schena reviewed and agreed upon manuscript content.

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CONFLICT OF INTEREST STATEMENT

None.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

CONSENT

A written consent form has been signed by both parents of the patient and collected in accordance with the journal's patient consent policy. Consent for the publication of the patient photographs and medical information was obtained by the authors stating that parents of patient gave consent for photographs and medical information to be published in print and online and with the understanding that this information may be publicly available. We will retain the original written consent form and provide it to the Publisher if requested.

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