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CASE REPORT

Neonatal diagnosis of circumferential skin creases

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Abstract

Background: Circumferential skin creases is a rare and heterogeneous disorder characterized by multiple and redundant skin folds, which can present as an isolated feature or in association with other phenotypic anomalies. Here, we report the case of a newborn who immediately captured our attention because of his phenotype.

Case: A male Caucasian infant was born at 39 weeks and 4 days of gestational age with an instrumental delivery, after a pregnancy characterized by threat of preterm birth at 32 weeks. Fetal ultrasounds were reported to be normal. The patient was the first child of non-consanguineous parents. Anthropometry at birth: weight 3.590 kg (0.57 SDS); length 53 cm (1.73 SDS); cranial circumference 35.5 cm (0.83 SDS). Clinical examination soon after birth revealed multiple, asymmetric and deep skin folds involving forearms, legs and lower eyelids (right > left). These folds seemed not to cause any physical discomfort. In addition, hypertrichosis, micrognathia, low-set ears and a thin, down-turned border of upper lip were observed. Cardio-respiratory, abdominal and neurological examination was unremarkable. There was no family history of similar appearance or other physical abnormalities. Given the clinical picture, an array-CGH was performed, which was normal. A genetic counseling was requested and Circumferential Skin Creases disorder was diagnosed based on the typical cutaneous involvement and, given the absence of other clinical signs, it was supposed a benign evolution, with skin folds tending to disappear over time. In addition, the baby's DNA was requested for a targeted genetic analysis, which resulted negative.

Conclusions: This clinical case underlines the need of performing a detailed neonatal physical examination in order to realize a timely diagnostic approach. Our patient presented with multiple skin folds, facial dysmorphism but normal systemic and neurological examination. Anyways, since Circumferential Skin

Chiara Cauzzo and Valentina Chiavaroli contributed equally to this work.

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Creases may be associated with later neurological symptoms, a regular reevaluation is recommended.

KEYWORDS

circumferential skin creases, congenital disorders, newborn, skin folds

1 | INTRODUCTION

Circumferential skin creases (CSC), also known as Kunze-Riehm syndrome, is a rare and heterogeneous disorder characterized by multiple and redundant ring-like skin folds mainly involving limbs and trunk (Ramphul et al., 2018; Rothman, 2014).

This condition can be isolated or associated with other extra-cutaneous findings so that literature suggests two distinct phenotypes. Namely, the isolated type is characterized by skin creases alone, while in the other type the typical skin folds are associated with additional dysmorphic features and abnormal development of the central nervous system (Ulucan et al., 2013; Wouters et al., 2011). Therefore, it is essential for clinicians to identify promptly the phenotypic abnormalities associated with skin folds in order to recognize syndromic forms that can necessitate more cautious reevaluations and possible treatments.

Here, we report the case of a male newborn who received diagnosis of CSC because of peculiar features noted soon after birth, who turned to have the isolated type of the disorder.

2 | CASE REPORT

A male Caucasian infant was born full-term at 39 weeks and 4 days of gestational age with an instrumental delivery, after a pregnancy characterized by threat of preterm birth at 32 weeks. Fetal ultrasounds were reported to be normal. Serological tests performed during pregnancy documented previous immunization for Cytomegalovirus, Toxoplasma and Rubella and negativity for HIV, HBV and HCV infections. Maternal rectovaginal swab was negative for Group B Streptococcus. Molecular nasopharyngeal swab for SARS-CoV-2 performed at the time of delivery was also negative. The patient was the first child of non-consanguineous parents. The mother was of dominican origin while the father was Italian. Apgar score was 7/10 at 1 min and 9/10 at 5 min. Anthropometry at birth: weight 3.590 kg (0.57 SDS); length 53 cm (1.73 SDS); cranial circumference 35.5 cm (0.83 SDS).

Clinical examination performed soon after birth revealed multiple, asymmetric and deep skin folds, involving not only forearms and legs, but lower eyelids as well (right > left) (Figures 1–3). These folds seemed to be asymptomatic, not causing any physical discomfort to the child nor movement limitation. In addition, hypertrichosis, micrognathia, low-set ears and a thin, down-turned border of upper lip were observed (Figures 1 and 2). No other cutaneous or extra-cutaneous abnormalities were noted. Cardio-respiratory, abdominal and neurological examination was unremarkable. There was no family history of similar skin folds and general appearance.

Baseline laboratory investigations, including complete blood count, serum electrolytes, renal function tests and liver function tests, did not reveal any abnormal findings. No abnormality was found on ECG. Echocardiography revealed a small inter-atrial defect, in follow-up. Brain and abdominal ultrasounds were normal. Ultrasound of the right lower eyelid showed no space-occupying lesions under the skin folds. Otoacoustic emissions resulted normal, as well as the red reflex test.

Considering the clinical presentation, an array-CGH was performed, which did not show alterations. A genetic counseling was requested and CSC was diagnosed based

FIGURE 1 Multiple deep skin folds on forearms and lower eyelids.

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FIGURE 2 Hypertrichosis, mycrognathia, and low set ears.

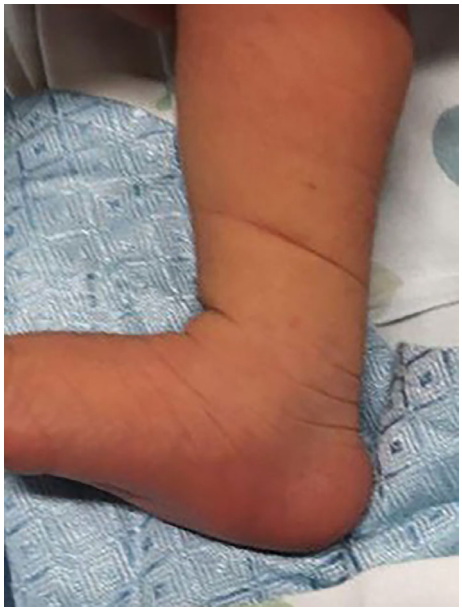

FIGURE 3 Deep skin folds in lower limb.

on the typical cutaneous involvement. Given the absence of other clinical signs, it was supposed a benign evolution, with skin folds tending to disappear over time. In addition, the baby's DNA was requested for a targeted genetic analysis (molecular sequencing of the genes *TUBB* and *MAPRE2*), which was negative.

Clinical reevaluations documented a regular physical growth and timely acquisition of the first developmental milestones: social smile at 2 months of life, neck holding at 3 months and unaided sitting at 8 months. At the 13-months follow-up visit, an initial improvement of the skin folds was observed, supporting the presumed benign evolution of the isolated form of CSC. However, regular clinical reevaluations will be performed.

3 | DISCUSSION

Ross published the first report of CSC in 1969, describing a baby girl in South Africa presenting with circumferential skin folds on the limbs, left hemi-hypertrophy and underlying nevus lipomatosis. He named his patient "Michelin Tire baby" because this child resembled the cartoon mascot of the Michelin Tire Company based in France (Malik et al., 2019; Ross et al., 1969). Approximately 30 cases have been reported since then, of which very few in the severe form characterized by multiple congenital anomalies and psychomotor retardation. Indeed, prognosis is usually benign: in the absence of other clinical signs, skin folds improve spontaneously in childhood and tend to disappear over time (Ramphul et al., 2018; Rothman, 2014).

Diagnosis is usually made based on clinical presentation. The most important features include multiple, asymptomatic, circumferential skin folds, present since birth and typically involving extremities. Trunk, palms and soles may also be involved (Al-Tayar & Al-Zaazaai, 2020; Malik et al., 2019; Uzair et al., 2015). Several congenital anomalies are associated with CSC. Namely, facial dysmorphism was reported by many authors, including bilateral epicanthic folds, hypertelorism, low set ears, cleft lip, cleft palate, hypoplastic teeth and mandible. Hypertrichosis is usually observed (Farooqi et al., 2010; Malik et al., 2019). As regards to systemic anomalies, an association with developmental delay, growth retardation, psychomotor retardation, seizures, congenital heart disease, undescended testis, joint hypermobility has been described (Uzair et al., 2015). In addition, CSC has been associated with congenital abnormalities including hypoplastic scrotum, inguinal or umbilical hernia (Malik et al., 2019; Ulucan et al., 2013).

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The combination of these associations was different in each reported case.

In children who had skin biopsies, pathology has shown two main types of underlying histological abnormalities: diffuse nevus lipomatosis in dermis or smooth muscle hamartoma. In a minority of cases fragmented elastic fibers or scarring patterns were observed. In other patients the biopsies showed normal skin or were not performed (Rothman, 2014; Schnur et al., 1993). In the present case, a skin biopsy was not performed because the dermatologist and geneticist did not propose this procedure to the parents.

There is evidence that the disorder may be familial, with an autosomal mode of inheritance, affecting several family members in successive generations (Bass et al., 1993; Farooqi et al., 2010). It is usually inherited in an autosomal dominant pattern, but recently autosomal recessive inheritance has been suggested (Kharfi et al., 2005; Ulucan et al., 2013; Wouters et al., 2011). Although the exact pathogenesis is still not properly understood, two chromosomal anomalies have been found in these patients: deletion of the long arm of chromosome 11 and balanced paracentric inversion of the long arm of chromosome 7 (Sardana et al., 2003; Ulucan et al., 2013). However, some cases have not been reported to be associated with any chromosomal abnormalities (Al-Tayar & Al-Zaazaai, 2020). Two genes are currently known to be related to the disease: *MAPRE2* (on chromosome 18, which encodes a microtubule-associated protein RP/EB family member 2), whose pathogenic variants were identified in four patients, and *TUBB* (on chromosome 6, one of the nine beta tubulin human genes), whose pathogenetic variants were found in other four patients (Dentici et al., 2018; Isrie et al., 2015). Therefore, several cases to date have not a genetic diagnosis. For this reason, diagnostic approaches such as exome sequencing could be useful to reveal the genetic etiology and pathogenesis may be clarified by biochemical and molecular analysis to delineate exact structural alterations in the mesenchymal tissue (Farooqi et al., 2010; Ulucan et al., 2013).

Differential diagnosis include Constriction Ring Syndrome and Beare-Stevenson Syndrome. In the former, the skin folds are one or few constrictions involving only the limbs and all the remaining features of CSC are absent, while in the latter dermatomegaly is limited to forehead, scalp, face and neck and it is associated with hearing impairment, undescended testes, and craniosynostosis (Malik et al., 2019).

4 | CONCLUSIONS

In this clinical case, we underline the importance of the neonatal physical examination and recognition of this peculiar disorder in order to guarantee a timely diagnostic approach. Our patient presented with multiple skin folds, facial dysmorphism but normal systemic and neurological examination, and the family history was negative. Anyways, since CSC may be part of a more complex clinical picture in which the child may manifest delayed neurological symptoms, regular clinical reevaluation is recommended (Malik et al., 2019; Ulucan et al., 2013).

AUTHOR CONTRIBUTIONS

Chiara Cauzzo and Valentina Chiavaroli wrote the manuscript. Chiara Palka Bayard de Volo, Altea Petrucci and Teresa Topazio examined the patient. Giulia Di Donato and Riccardo Fiorentino were involved in literature search and drafting the paper. Francesco Chiarelli and Susanna Di Valerio coordinated and approved the final version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

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

INFORMED CONSENT STATEMENT

Consent to publish the case report and pictures were obtained from the parents. This report does not contain any personal information that could lead to the identification of the patient.

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