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CASE REPORT

This is the case of a nineteen year-old female patient, native of Amazonas (Brazil), born from non-consanguineous parents and without family history of genetic diseases. Her mother reported polyhydramnios during pregnancy and delayed neuropsychological development. The patient presented mild mental-cognitive impairment, an outgoing personality and primary amenorrhea.

On physical examination, the patient had short stature, coarse facies, short, curly hair, thick lips, low-set ears, wide earlobes, loose and redundant skin on hands and feet, palmoplantar hyperkeratosis, accentuated palmar lines and hyperextensible fingers (Figures 1-3). Cutaneous hyperpigmentation and *acanthosis nigricans* were present since adolescence. She also presented short and webbed neck, epicanthic fold, downward slant of palpebral fissures, convergent strabismus, nystagmus, broad nose, hoarse voice, nipple hypertelorism and kyphoscoliosis. Papillomas were absent.

Cytogenetic analysis identified normal karyotype (46,XX) and echocardiography showed hypertrophic cardiomyopathy, narrowing of left ventricle, subaortic stenosis and mild mitral regurgitation.

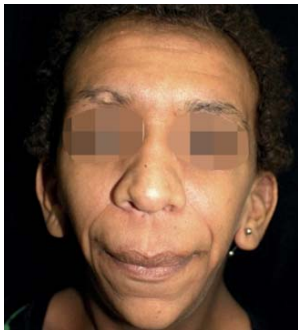

FIGURE 1: Typical facies found on the syndrome in question. Note epicanthic fold, downward slant of palpebral fissure, wide nose, thickened earlobe, large lips, marked frontal pleats with aspect of redundant skin

FIGURE 2: Deep palmar lines and skin with soft and loose aspect

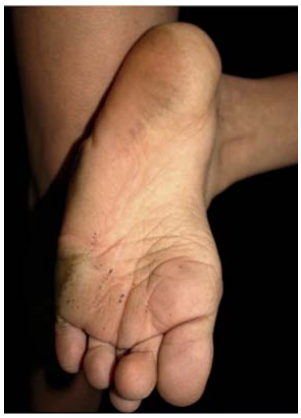

FIGURE 3: Plantar hyperkeratosis

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DISCUSSION

Costello syndrome (CS) is a rare genetic disorder, first described by Costello in 1971. Most studies support an autosomal dominant inheritance associated to germline mosaicism, with mutations in HRAS proto-oncogene. Facial dysmorphism, skin changes, cardiac and musculoskeletal defects, and cognitive impairment are characteristic of syndromes resulting from mutations in genes of the RAS family called "RASopathies"[1-3]

CS can be suspected since childhood, however the most characteristic findings appear during development. The main differential diagnoses are Noonan syndrome and cardiofaciocutaneous syndrome (CFC).[1,2] Costello proposed, in 1996 after reviewing case reports, that it would be possible to clinically diagnose SC, and differentiate it from other syndromes.[4] Findings such as low-set ears with large earlobes, large mouth and thick lips, nasal papilloma, loose skin on hands and feet, dark skin, *acanthosis nigricans*, deep palmar and plantar lines, palmar and plantar hyperkeratosis, hirsute forehead, hyperextensible fingers, and barrel chest, which correspond to the phenotype on the reported case, would be much more frequent in CS than in other syndromes.[4,5]

Other common findings in CS, also identified in our case, were: history of polyhydramnios, short stature, short curly hair, mild mental impairment, sociable personality, nystagmus, kyphoscoliosis, ulnar wrist deviation and hypertrophic cardiomyopathy. Cardiac disorders increase the morbidity and mortality of these patients, including the risk of sudden death.[1,2,3]

CS patients are predisposed to benign neoplasms, described as papillomas, and malignant ones including rhabdomyosarcoma, neuroblastoma, and transitional cell carcinoma of the bladder. This fact is explained by mutations in HRAS proto-oncogene.[2,3] There were no clinical findings suggestive of malignancy in the reported case.

Pubertal delay is reported in several cases of CS, although adolescents appear older due to kyphoscoliosis, sparse hair and premature cutaneous aging.[1]

Although the diagnosis can be suspected clinically, identification of a heterozygous mutation in HRAS proto-oncogene is necessary to confirm it.[3] Unfortunately, it was not possible to perform molecular tests in this case. However, identification of the syndrome, even clinically, is sufficient for genetic counseling and orientation regarding the increased risk of malignancy and sudden death in case of heart disease. ❑

Abstract: Costello syndrome (CS) is a rare genetic disorder, first described by Costello in 1971, caused by mutations in the HRAS proto-oncogene. Clinical findings include facial dysmorphism, skin disorders, cognitive impairment, cardiac and musculoskeletal defects. There is an increased risk of malignancies in these patients, due to the proto-oncogene mutation, and also sudden death secondary to heart disease. We report a case with characteristic phenotype, highlighting the peculiar skin changes.

Keywords: Costello syndrome; Genes, ras; Proto-oncogenes

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