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Case Report

LEOPARD Syndrome with APS-2

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Abstract:

LEOPARD syndrome is a phenotypic expression of mutations in several genes: PTPN11, RAF1 and BRAF. This rare autosomal dominant disorder is characterized by high variability of clinical manifestations. Here we report a case of LEOPARD syndrome with APS type -2. A 28 years old lady known diabetic and hypothyroidism presented with us recurrent abdominal pain and vomiting along with uncontrolled blood sugar. She is a third issue of consanguineous marriage. On query her mother gave H/O primary amenorrhea and hearing loss. On examination there is ocular hypertelorism, widely spaced nipple, loss of scalp hair, eye brow and tooth. There are multiple skin lentigines(dark skin spot), lack of secondary sexual characteristics with tanner stage-1. After evaluation she was found hypergonadotrophic hypogonadism, acute on chronic pancreatitis and dyslipidemia. Her conservative management was given for pancreatitis. Hormone replacement therapy was started and advised to continue levothyroxine and insulin. Also advised for regular follow-up on endocrine OPD of BIRDEM general hospital.

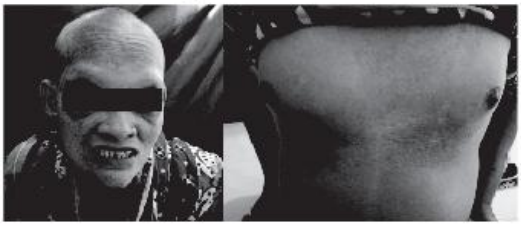
Key Words: LEOPARD syndrome, Hypertelorism, skin lentigines, APS

Introduction

LEOPARD syndrome is a phenotypic expression of PTPN11, RAF1 and BRAF gene mutations. It is an autosomal dominant disorder having high variability of clinical manifestations. These genes are responsible for Ras/MARK signaling pathway, which are important for cell cycle regulation, differentiation, growth, and aging. Mutations result in anomalies of skin, skeletal, and cardiovascular systems. The LEOPARD syndrome means lentigines, electrocardiographic conducting abnormalities, ocular hypertelorism, pulmonary stenosis, abnormal genitalia, retarded growth and deafness. Mutations affect tyrosine proteases, which are included in the signal pathway between the cell membrane and the nucleus. Usually only lentigines are common. Clinical diagnosis is based on lentigines and 2 other symptoms; in cases without lentigines – 3 symptoms and at least one affected first-line relative.[1]

Case details

Miss X 28 years Known type-1 diabetic, primary hypothyroidism and chronic pancreatitis hailing from Munshigonj, Dhaka with H/O consanguineous marriage between parents was admitted in BIRDEM general hospital on 13th May 2018 with the complains of vomiting and recurrent abdominal pain with uncontrolled blood sugar. She is primarily amenorrheoic with lack of secondary sexual characteristics. On query her mother noticed of gradual loss of hear, hair, teeth (from upper jaw) and developed characteristics skin changes from the age of fourteen. O/E her BMI is 18.2 kg/m2, MPH 148.5 cm, there is ocular hypertelorism, widely spaced nipple, multiple skin lentigines, vitiligo and tanner stage is B1 P1. Other systemic examination reveals no abnormality except NPDR on fundoscopy.



Her hormonal analysis reveals primary hypothyroidism (TSH: 8.46mIU/ml, FT4: 13.97 Pmol/L and positive anti TPO antibody) primary hypogonadism (Increased FSH: 33.49 mIU/ml, LH: 17.17 mIU/ml and decreased oestradiol: 21.80pg/ml). She was suffered from type-1 DM which was evident by C-peptide negativity (0.23 ng/ml) but antibody could not be done. ANA is negative, normal B12 assay with increased serum lipase (405 U/L). Her USG shows grade-II fatty change in liver,

small infantile uterus and ovaries could not visualized. Karyotype is 46XX (female) and echocardiography shows normal finding. Other routine examination shows normal findings except presence of normocytic normochromic anemia and high triglyceride (614mg/dl).

We advised her to follow the diet chart and to maintain regular exercise. We also gave diabetic education and counseled properly about her fertility issue. We prescribed Levothyroxine 25 mcg once daily, split mix human insulin, pancreatic enzyme and started hormone replacement therapy. We requested her to come on follow-up on BIRDEM endocrine OPD after one month with sugar profile, TSH, Lipase and CBC. Ophthalmological follow-up was scheduled every three months. Audiologist advised her to use hearing aid.

Discussion

The LEOPARD syndrome is an exceptional autosomal dominant disease.[1] The first case was described in 1936 but the LEOPARD term was first used in 1969.[2] Up to date, about 300 cases have been reported.[3] Many synonyms exist: cardiomyopathic progressive lentiginosis, multiple lentigines syndrome, cardio-cutaneous syndrome or Moynahan syndrome.[1] The LEOPARD syndrome is currently also referred to as Noonan syndrome with multiple lentigines or NSML (OMIM 151100).[3]

The penetrance is very high and the expression highly variable. In about 90% of the cases, it is linked to a germline PTPN11 missense mutation with loss of function.[1,4] The major clinical features are diffuse lentiginosis, ECG abnormalities, ocular hypertelorism, hypertrophic cardiomyopathy, pulmonary stenosis, genital anomalies, retardation of growth and deafness. Additional characteristics are a facial dysmorphism, skeletal abnormalities, and neurological troubles, hypotonia at birth, learning disabilities (present in this case) with mental retardation, oculomotor defects and EEG abnormalities.[1,5] Rare cases of cancer, including melanoma, had been reported. Nevertheless, as total case number is so low, no particular cancer susceptibility is currently established.[3] The diagnosis of a LEOPARD syndrome requires diffuse lentiginosis and two other syndrome traits. If diffuse lentigines are absent, the presence of a first degree affected relative and three other distinct features are necessary. However the diagnosis is not always obvious, especially as some signs are lacking or only appear at an advanced age. Furthermore, it shares lots of characteristics with other genetic syndromes like the Noonan syndrome, also mediated by a PTPN11 mutation but of the gain function type.[1] In atypical cases of LEOPARD syndrome, a missense PTPN11 mutation confirms the diagnosis.[4] In case of negativity, a RAF1 mutation should be searched for that is present in 1/3 of the patients without a PTPN11 mutation.[1] In less than 5%, a BRAF mutation can be associated.[6] Molecular analysis provides additional interesting clinical information helping in the long-term management and follow-up of these patients. Indeed, the prevalence of cardiac conduction disorders, ventricular or left auricular hypertrophy and familial history of sudden death is significantly higher in PTPN11 mutation negative patients. The mortality and morbidity predominantly depend on the extent of the cardiac abnormalities. A complete checkup, including rigorous clinical examination, growth parameters monitoring in children, hearing test (1/year until adulthood) and cardiological (1/year mainly when lentigines appear if none cardiac lesion was previously detected), neurological and urogenital evaluations, is highly recommended. In contrast, the management of other abnormalities does not differ from those in general population.[1]

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