LEOPARD SYNDROME. FAMILIAL CASES

Sorin Ioan Iurian[1], Han Brunner[2], Helger Yntema[2], Bogdan Mehedintu[3]
[1]Pediatric Clinic Hospital, Sibiu
[2]Departament of Metabolic and Genetic Disorders, Radboud University, Nijmegen, The Nederlands
[3]Emergency Department, Pediatric Clinic Hospital, Sibiu

ABSTRACT

LEOPARD syndrome is a complex disorder characterized by multiple dysmorphogenetic features. Both syndromes LEOPARD and Noonan are caused by different mutations in the same gene (PTPN11). Authors emphasize diagnosis peculiarities in two related cases with facial dysmorphism. Index case is represented by a 10 year-old boy admitted for evaluation because of cephalofacial dysmorphism associated with mental disabilities. Family history: non-consanguineous parents; the father's case and his sister with face dysmorphism. Clinical exam: short stature, impaired nutritional status, axillary freckles, widespread café-au-lait spots, face dysmorphism, webbed neck, skeletal anomalies and mental retardation. Blood investigations and cardiac ultrasonography: no anomalies. Differential diagnosis includes Noonan syndrome, Greig syndrome, type 1 neurofibromatosis, Albright syndrome. Regarding patient genetic evaluation: normal karyotype; DNA sequencing revealed mutation in PTPN11 gene suggestive for LEOPARD syndrome. Authors also found same mutation for probant's father.

Conclusions. Authors described two cases with dysmorphic skull, skeletal anomalies, skin pigmentation, mental disabilities and short stature, justifying further genetic evaluation that revealed a very rare disorder.

Keywords: Leopard syndrome, child

BACKGROUND

Leopard syndrome is a dismorphogenetic disorder with autosomal-dominant inheritance. The LEOPARD acronym emphasize the main syndrome features: lentigines, electrocardiographic abnormalities, ocular hypertelorism, pulmonary stenosis, genetic anomalies, growth retardation and deafness. Not all mentioned findings are fulfilled by every patient.

Noonan and Leopard syndromes are caused by different mutations of the same gene (PTPN11) located on 12q chromosome; this gene encodes the protein tyrosine phosphatase SHP-2 (1). Only 80% of cases diagnosed with Leopard syndrome could be explained by PTPN11 gene anomaly (2).

It doesn't exist solid epidemiological data (rare disease).

Clinical features. Clinical manifestations are variable and 70% of described patients are familial. Diagnostic criteria established in 1976 by Voron (3) include: multiple lentigines and minimum 2 other anomalies: other skin features (axillary freckles, cafe-au-lait spots, lack of pigmentation, skin hiperlaxity, cutaneous sindactily), electrocardiographic anomalies (cardiac arrhythmia, prolonged PR interval), hypertrophic cardiomyopathy (left ventricle or right ventricle hypertrophy with sudden cardiac death) (4), genito-urinary anomalies (cryptorchidism, hypospadias), endocrine abnormalities, cranio-facial dysmorphism (hypertelorism, mandibular prognathism, broad nasal root, low inserted ears, epichantal folds, arched palate), low stature (one third of patients) and skeletal anomalies (pectus excavatum, pectus carinatum, kyphoscoliosis).

Lentigines represents brown pigmented and irregular macules, 3-5 mm in diameter; the larger and dark-brown ones are called „cafe noir spots" by comparison with cafe-au-lait spots described in type 1 neurofibromatosis) (5); they are more

Coresponding author:
Sorin Ioan Iurian, Pediatric Clinic Hospital, Pompeiu-Onofreiu Street no. 2-4, 550166, Sibiu
e-mail: iurian_sorsab@hotmail.com

frequent localised on the neck, face and upper halg of the trunk.

The diagnosis could be established during neonatal period if the patient comprise three main features: typical cephalofacial dysmorphism, hypertrophic cardiomyopathy and lentigines (6).

Treatment. Regarding the lentigines, it has been reported the benefit not only for laser treatment and cryosurgery, but also for Tretinoin or Hydroquinone creme. For patients with cardiac anomalies it is recommended anti-arrhythmic drugs and beta-receptor blocking agents. Genetic counseling and examination of all family members is indicated in order to prevent the disease.

Echocardiography and electrocardiography should be done periodically for the patients with Leopard syndrome.

CASE PRESENTATION

The patient F.F., 10 years old male, from the countryside, is hospitalized for evaluation having facial dysmorphism and mental retardation.

Family history: healthy parents, no consanguinity.

Personal history: the first child of the family having two healthy sisters (based on genitors' declarations).

Medical record: orthopedic surgery at hallux, the left big toe; the patient presents painful walking abnormalities.

On the actual hospitalization, the clinical examination revealed a general average condition, the anthropometric indicators for weight and waist were below the 5th percentile and at the 75th percentile for head circumference; other features: cranio-facial dysmorphism (hypertelorism, broad nasal pyramid, distant ears from the skull, bilateral macrotia with posterior rotation of the ears, pterigium coli, skin pigmentation (multiple lentigines at facial / thoracic / arms level, axillary freckles – see the photos), tegument pallor, subcutaneous tissue underrepresented; without pathological adenopathy, osteoarticular system with ogival palate and mandibular prognathism, broad bilateral toe, postoperative linear scars on the left toe, deformed chest (infundibuliform sternum 1/3 inferior and barrel chest 1/3 superior), cutaneous syndactyly for I and II toes – bilateral foot, arched palate, no hepatomegaly, no splenomegaly; Central Nervous System – mental Retardation. The examination of the respiratory, cardiovascular and urogenital tracts was normal.

Investigations: Cell blood count, liver and kidney functional markers, calcium-phosphorus balance, lipid and carbohydrate: values within normal limits. The audiogram: no changes.

Psychological evaluation: mental retardation, cognitive retardation, IQ = 68.

Imagistic: the X-ray of the foot revealed bone – eroding of the distal phalanx on the right hallux and osteophytosis on the right hallux; cardiac ultrasound: no valvular pathology, normal cardiac function, normal pulmonary artery caliber, EKG unchanged.

Summarizing the clinical and laboratory data, I considered the case as dismorfic cranio-facial syndrome associated with skin pigmentation, skeletal abnormalities and mental retardation, syndromes with symptoms that do not fit the particular phenotype.

Differential diagnosis. The authors considered the following syndromes:

– ***Noonan syndrome*** was considered as differential in context of short stature, learning disabilities, pectus excavatum and characteristic facial features including webbed neck, flat nose bridge; the genetic background of Noonan syndrome consist of 4 genes mutations involved in signal transduction (PTPN11, KRAS, SOS_1, RAF_1);

– Greig syndrome was included among differential diagnosis because of its main features (wide thumb or big hallux, cutaneous syndactyly, ocular hypertelorism, macrocephaly and prominent forehead, developmental delay and intellectual disability); the pathophysiology is represented by GLI3 gene mutation (chromosome 7); lack of polydactyly (another syndrome feature) rules out Greig syndrome;

– ***type 1 neurofibromatosis*** was analyzed due to skin pigmentation anomalies (café-au-lait spots); the patient doesn't fulfilled minimum 2 diagnosis criteria necessary to confirm von Recklinghausen disease, so the authors don't consider this disorder for this case;

– ***Carney syndrome*** implies diffuse facial lentigines, multiple nevi, atrial myxomas and signs of acromegaly and Cushing syndrome and is due to gene *PRKAR1A* anomaly (17q chromosome); the patient phenotype doesn't superpose with Carney syndrome;

– ***McCune-Albright syndrome*** is a genetic disorder of bones (bone fractures, bone dysplasia, deformity of the legs, arms and skull), one-sided pigment patches on the skin and premature puberty with increased rate of growth; there was described, from genetic point of view, the anomaly of GNAS1 gene; it is unlikely in studied patient;

– ***Leopard syndrome*** could be considered in this case (see above the syndrome description); the ge-

netic background is also represented by PTPN11 gene mutation (like Noonan syndrome, but different location).

The genetic evaluation included the karyotype (normal result) and PTPN11 gene sequencing that identified mutation c.1403 C > T, p.Met 468 Thr, suggestive for LEOPARD syndrome (index case). The authors completed clinical evaluation for the other family members and there was noticed a characteristic phenotype for the father and a sister of patient. The completion of gene testing shown the same PTPN11 gene mutation also for the father. This mutation was recently (2007) described by Writzl and his teamwork in 2 family cases with Leopard syndrome (7).

It is mandatory to investigate other family members with particular phenotype.It is necesary the genetic counseling for family carriers of mutated gene and periodical assessment for audiogram, EKG, echocardiography and also neurological / psychological evaluation.

CONCLUSIONS

1. The authors described 2 familial cases with characteristic facial features, skeletal anomalies, skin pigmentation and mental disabilities justifying genetic evaluation that revealed a very rare genetic disorder.
2. The genetic diagnosis needs a multidisciplinary teamwork: pediatrician, cardiologist, specialist in medical imaging, pediatric geneticist and medical laboratory specialist.
3. Cephalofacial dysmorphism correlated with mental retardation and growth impairment justify the genetic testing.

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