

Cancer Prone Disease Section

Short Communication

Mulibrey nanism

Maria Piccione, Emanuela Salzano

Department of Sciences for Health Promotion and Mother and Child Care G. D'Alessandro,
University of Palermo, Palermo, Italy. piccionemaria@libero.it; salzanoemanuela@gmail.com

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Abstract

Mulibrey (MUScle-Liver-BRAIN-EYE) nanism is a rare autosomal recessive disorder caused by mutations in TRIM37 gene and characterized by growth failure with prenatal onset, dysmorphic features, muscular hypotonia, veins congestion secondary to constrictive pericarditis and yellowish dots in fundi. Patients present cutaneous nevi flammi, anomalies of gonadal function, type 2 diabetes, fibrous dysplasia of long bones and an increased risk for Wilms' tumor. Life expectancy depends mainly on cardiovascular complications.

Keywords Mulibrey nanism; TRIM37; dwarfism; Wilms'tumor.

Identity

Other names

Muscle-liver-brain-eye nanism
Pericardial constriction and growth failure
Perheentupa syndrome

Inheritance

115 patients described all over the world, 85 of which from Finland where it has been estimated an incidence rate of 1/37000 (Karberg et al.2004). It is an autosomal recessive disorder due to homozygous or compound heterozygous mutations in the TRIM37 gene, (605073) even if sporadic cases have been reported in several ethnic groups (Jagiello et al.2003).

Clinics

Phenotype and clinics

Growth: Short stature with prenatal onset (birth length and birth weight 1.5 – 2 SD below mean with relatively macrocephaly - occipitofrontal head circumference 0.5 below SD; adult male height 136-161 cm; adult female height 126-151 cm) (Karberg et al.2006)

Head:

- Craniofacial features: triangular face, low nasal bridge, high and broad forehead, and scaphocephaly with occipitofrontal bossing
- Eye findings: Mild hypertelorism, telecanthus, yellowish dots in fundi, decreased retinal pigmentation with dispersion, hypoplasia of choroid, astigmatism, strabismus (Karberg et al.2004)
- Mouth: relatively small tongue, dental crowding, hypodontia of second bicuspid (Myllarniemi et al. 1978)

Cardiovascular System:

Constrictive pericarditis, globular shaped heart on x-ray, congestive heart failure, myocardial fibrosis, elevated venous pressure, prominent veins in the neck, congestion in the lungs, abnormal fluid accumulation in the abdomen (ascites), swelling of the arms and/or legs (peripheral edema) (Perheentupa et al.1973; Cumming et al.1976)

Abdomen: hepatomegaly, sporadic description of urinary tract malformations

Muscle: muscular hypotonia

Central Nervous System: no intellectual disability, dysarthria

Voice: high-pitched voice

Skin: cutaneous nevi flammei

Endocrinology: delayed puberty with irregular menstrual periods, premature ovarian failure, incomplete breast development, infertility, insulin resistance type 2 diabetes, possible hypoplasia of different endocrine glands (Haraldsson 1993; Karlberg et al. 2004; Karlberg et al. 2007).

Radiological findings:

Cerebral: J-shaped sella turcica, absent or small frontal sinus, absent or small sphenoidal sinus

Skeletal: slender long bones with thick cortex and narrow medullary channel, fibrous dysplasia especially in the middle third of tibia.

Differential Diagnosis

Mulibrey nanism shares some clinical aspects mainly with two other syndromes (Silver Russell Syndrome and 3-M syndrome spectrum (OMIM 273750)) characterized by growth failure and dysmorphic features (Akawi et al. 2011).

Neoplastic risk

Benign tumors especially cystic and benign adenomatous lesions have been identified in different organs (renal cortical cysts, pancreatic cysts, thyroid lesions); the 22% of patients develop fibrous dysplasia of long bones; 6% of reported patients were diagnosed for a Wilms tumor. Female patients with premature ovarian failure are at high risk for ovarian fibrothecomas or other stromal ovarian cells tumors (Hamalainen et al., 2006;

Karlberg et al. 2009).

Treatment

Patients with constrictive pericarditis may be treated with surgery with good results, while treatment with diuretics and digoxin may be prescribed for those affected by progressive heart failure.

Hormone replacement therapy may be evaluated in children with growth hormone deficiency, delayed puberty or very irregular menstrual periods, hypothyroidism, hypoadrenocorticism and abnormal gonadal function.

All females should be monitored closely for ovarian tumors, especially in presence of premature ovarian failure (Hamalainen et al., 2006; Karlberg et al. 2006; Karlberg et al. 2009).

Evolution

Growth failure usually progresses during early infancy; after 10 years of age blood fasting glucose levels tend to increase; the diagnosis of Wilms' tumour is usually close to 1 year of age, while after puberty all female should undergo to a gynaecological follow-up; GH replacement therapy seems to have better short term effects than on the final adult stature (Karlberg et al. 2004; Karlberg et al. 2007).

Prognosis

The most life threatening complication is represented by cardiac involvement; life expectancy also depends strictly on precocious diagnosis of respiratory and feeding complications and malignancies (Balg et al. 1995; Lapunzina et al. 1995; Karlberg et al. 2006).

Major signs
<i>Growth failure (A or B or C)</i>
(A) Small for gestational age (SGA) lacking catch up growth
(B) Height in children 2.5 SDS below population mean for age
(C) Height in adults 3.0 SDS below population mean
<i>Characteristic radiological findings (A or B)</i>
(A) Slender long bones with thick cortex and narrow medullary channels
(B) Low and shallow (J-shaped) sella turcica
<i>Characteristic craniofacial features</i>
Scaphocephaly, triangular face, high and broad forehead, low nasal bridge and telecanthus
<i>Characteristic ocular findings</i>
Yellowish dots in retinal mid peripheral region
Minor signs
Peculiar high-pitched voice
Hepatomegaly
Cutaneous naevi flammei
Fibrous dysplasia of long bone

Three major signs with one minor sign or two major signs with three minor signs are required for the clinical diagnosis. SDS = standard deviation scores. Adapted by Karlberg et al. 2004.

	Mulibrey Nanism	Silver Russell Syndrome	3-M Syndrome
Head			
Relative Macrocephaly	+	+	+
Triangular face	+	+	+
Frontal Bossing	+	+	-
Hypoplastic mid-face	-	-	+
Prominent mouth and lips	-	-	+
Full eyebrows	-	-	+
Yellowish dots in fundi	+	-	-
Microgathia	+/-	+	-
Dental crowding	+	-	-
J-shaped sella turcica	+	-	-
Growth			
Short stature with prenatal onset	+	+	++
Musculoskeletal system			
Clinodactyly of 5th finger	-	+	-
Skeletal asymmetry	-	+	-
Syndactyly of 2-3 toes	-	+	-
Muscle hypotonicity	+	+	-
Thick cortex of long bone	+	-	+
Fibrous dysplasia of bone	+	-	+
Slender long bones with diaphyseal constriction and flared metaphyse	-	-	+
Anomalies in vertebral bodies	-	-	+
Thoracic kyphoscoliosis	-	-	+
Broad thorax with slender and horizontal ribs	-	-	+
Cardiovascular System			
Congestive heart failure/constrictive pericarditis	+	-	-
Hepatomegaly	+	-	-
Others			
Urogenitalia anomalies (hypogonadism)	+	+	+
Insuline Resistance type 2 diabetes	+	-	-
Cutaneous naevi flammei	+	+/-	-
Feeding difficulties	+	+/-	-
High pitched voice	+	-	-
Speech impairment	+/-	+/-	-
Neuromotor delay	+/-	+/-	-

Comparison between Mulibrey Nanism, Silver-Russell and 3-M Syndromes phenotype.

Cytogenetics

Note

The 250 Kb critical cytogenetic region for Mulibrey nanism encompasses the TRIM37 gene locus on chromosome 17q22 (Avela et al.1997).

Cytogenetics of cancer

A certain number of breast cancer cell lines show amplification of the 17q22-23 chromosome region, resulting in an overexpression of TRIM37 gene which acts as a promotor of cellular transformation by silencing onco-suppressor genes .

Genes involved and proteins

TRIM37 (tripartite motif-containing 37)

Location 17q22

DNA/RNA

Transcription

Northern blot analysis shows two transcript: the first-one, TRIM37a of about 4.5-kb and the second-one, TRIM37b of approximately 3.9 kb.

Protein

Description

This pleiotropic gene contains 4488 nucleotides from 24 exons. The encoded protein is a peroxisomal member of the tripartite motif (TRIM) family including a zinc-binding domains, a RING finger region, a B-box motif and a coiled-coil domain. TRIM37 is related to some Polycomb group (PcG) multiprotein PRC2-like complex and monoubiquitinates histone H2A, mediating an epigenetic transcriptional repression of target genes(Bhatnagar et al 2014).

Expression

The results of tissue-specific expression levels of both transcripts TRIM37a and TRIM37b measured in multiple tissue cDNA panels by qPCR also show that TRIM37a is ubiquitously expressed with higher levels in testis and brain, whereas TRIM37b is mainly expressed in testis. In addition tissue level expression is slightly higher in fetal than in adult tissue (Hämäläinen et al. 2006).

Mutations

Note

To date 23 TRIM37 gene mutations have been reported as pathogenic variants and 18 of those have

been associated to mulibrey nanism phenotype. The most common Finnish mutation is a 5 bp deletion resulting in an aberrant splicing site that causes frameshift with induction of a stop codon 10 codons downstream. Compound heterozygosity for two different mutation has also been found (<http://www.ncbi.nlm.nih.gov/clinvar>)

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