Case Report

McKusick-Kaufman or Bardet-Biedl syndrome? A new borderline case in an Italian nonconsanguineous healthy family

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McKusick-Kaufman syndrome (MKS, OMIM #236700) is a rare syndrome inherited in an autosomal recessive pattern with a phenotypic triad comprising hydrometrocolpos (HMC), postaxial polydactyly (PAP), and congenital cardiac disease (CHD). The syndrome is caused by mutations in the MKKS gene mapped onto chromosome 20p12 between D20S162 and D20S894 markers. Mutations in the same gene causes Bardet-Biedl-6 syndrome (BBS-6, OMIM #209900) inherited in an autosomal recessive pattern. BBS-6 comprises retinitis pigmentosa, polydactyly, obesity, mental retardation, renal and genital anomalies. HMC, CHD, and PAP defects can also occur in BBS-6, and there is a significant clinical overlap between MKS and BBS-6 in childhood. We describe a new borderline case of MKS and BBS syndrome and suggest insights for understanding correlation between MKKS gene mutations and clinical phenotype. Here, we report the results of molecular analysis of MKKS in a female proband born in an Italian nonconsanguineous healthy family that presents HMC and PAP. The mutational screening revealed the presence of two different heterozygous missense variants (p.242A>S in exon 3, p.339 I>V in exon 4) in the MKKS gene, and a nucleotide variation in 5'UTR region in exon 2 (-417 A>C).

Key words: Hydrometrocolpos, McKusick-Kaufman syndrome, polydactyly

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Introduction

McKusick-Kaufman and Bardet-Biedl-6 syndrome are two rare syndromes inherited in an autosomal recessive pattern caused by mutations in MKKS gene mapped onto chromosome 20p12 between D20S162-D20S894 markers.[1] The karyotypes of affected individuals have been normal. The MKKS gene has six exons and the ATG start codon is in exon 3. Two alternatively spliced 5' exons are not translated (exons 1A and 1B).[2] MKKS has been cloned and shown to encode a group II chaperonin-like protein with a wide tissue distribution involved in the folding and structural modification of numerous proteins.[2] Mutations have been identified in all of coding exons of MKKS gene. MKS syndrome was initially described by McKusick in the Amish population in 1978.

The clinical phenotype of MKS is characterized by a triad unrelated manifestations that comprises postaxial polydactyly hydrometrocolpos (HMC present in 70% of affected Amish females), (PAP present in 60% of affected Amish patients), and congenital heart disease (CHD present in 15% of Amish patients).[1,3] In MKS males subjects most commonly are glanular hypospadias, prominent scrotal raphe, cryptorchidism.[3] Cardiac malformations described in MKS individuals include atrioventricular communis with a left-sided superior vena cava, atrial or ventricular septal defect, small aorta and hypoplastic left ventricle, tetralogy of Fallot, and patent ductus arteriosus.[3]

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BBS syndrome is more genetically heterogeneous than MKS and it has been associated to at least 11 genes distributed on different chromosomes.[3] Several reports describe BBS phenotypes with three mutant alleles with at least one allele in MKKS gene. This condition generally was associated with a more severe BBS phenotype.[4] However 10% of cases remain unlinked to these loci.[5]

This syndrome is characterized by several severe clinical manifestations, including retinal dystrophy, hypogenitalism, renal malformations, PAP, central obesity, learning disability.[6] Although the hypogenitalism, PAP, and renal anomalies may be apparent at birth, the other clinical features develop and the complications are severe.[7] HMC, CHD and PAP defects are a significant clinical overlap between MKS and BBS.

We report a rare case of female neonate, born in an Italian nonconsanguineous healthy family with HMC and PAP. The association of HMC and PAP in female neonate is compatible with MKS or BBS-6 syndromes which are inherited in an autosomal recessive manner. Molecular analysis of MKKS gene identified two different sequence mutations in heterozygous, i.e. p.242A>S in exon 3 and p.339 I>V in exon 4 and a sequence variation in 5'UTR region in exon 2 (-417 A>C).

Case Report

The association of hydrometrocolpos (HMC) and postaxial polydactyly (PAP) in female neonate was compatible with McKusick-Kaufman syndrome (MKS) or Bardet-Biedl-6 syndrome (BBS-6), two rare human syndrome inherited in an autosomal recessive pattern caused by mutations in MKKS gene.

Generally, HMC and PAP are sufficient for a clinical diagnosis of MKS in a non-Amish female without evidence of overlapping syndromes.[1,2] However, the same phenotype can also be found in female infants with BBS. It is necessary to follow up the female probands until 5 years of age in order to exclude the presence of other characteristic clinical features or complications present in BBS patients. The close relationship between MKS and BBS-6 has been further complicated by the demonstration of disease-causing sequence alterations in the MKKS gene in both MKS and in an estimated 4 to 6% of unselected individuals with BBS.[3]

We report a rare case of female neonate born in an Italian nonconsanguineous healthy family with HMC and PAP. The mother (32 years) and the father (37 years), and beside mother's allergy to gramineous, other anamnestic data were negative.

Birth weight was 2 550 g with a length of 42 cm (< 3° centiles) and a head circumference of 31.3 cm (< 3° centiles). The APGAR score was 1'(7)/5' (8).

The proband presents postaxial hexadactyly [Figure 1], and a large abdominal mass displacing the intestine and elevating the diaphragms (panel A). Abdominal Magnetic Resonance Imaging (MRI) [Figure 2] revealed a large cystic mass originating from the pelvic floor and HMC, fluid-filled that compressed and displaced the urinary bladder anteriorly. With a bladder catheter about 150 cc of brown fluid accumulated was drainage. We performed complete mutation screening by sequencing six exons of MKKS gene with relative intron-exon boundary region and the alternatively spliced 5' exons.

Molecular analysis of MKKS gene identified two different sequence mutations in heterozygous, i.e., p.242Ala>Ser in exon 3 and p.339 Ile>Val in exon 4 and a sequence variation in 5'UTR region in exon 2 (-417 A>C). The A242S has been reported as a potential BBS susceptibility factor and play a major role in the pathogenesis of nonsyndromic obesity, age dependent, in combination with other obesity genes.[1,8] This mutation in heterozygote did not appear to modify the normal function

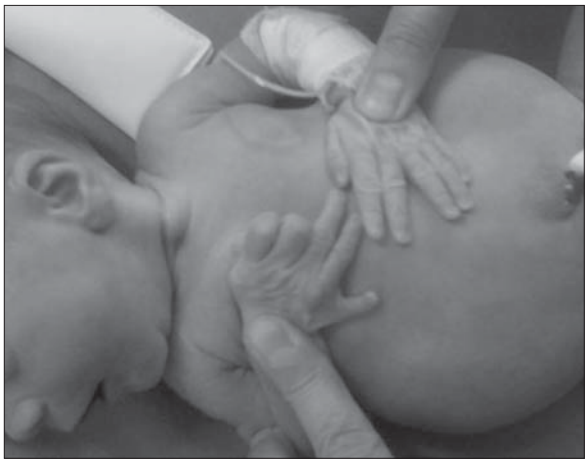

Figure 1: Photograph of the hands shows postaxial polydactyly with six digits on either hand (postaxial hexadactyly)

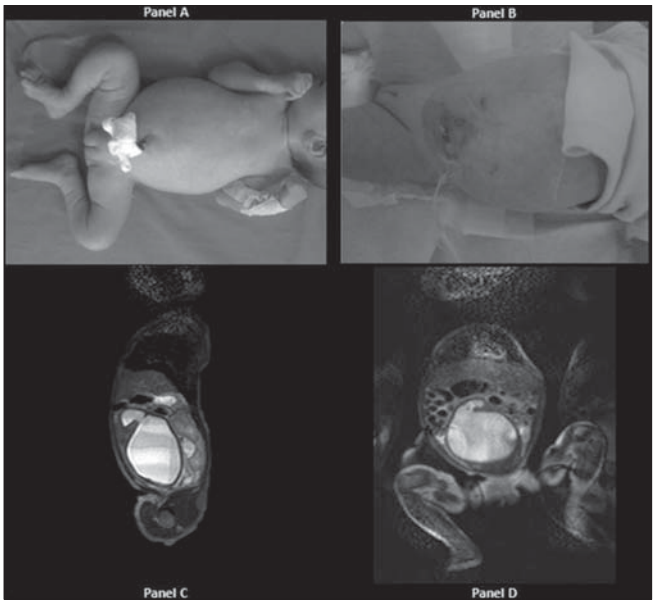

Figure 2: Panel A shows a large lower abdominal mass at birth (hydrometrocolpos). Panel B report reduction of abdominal mass after fluid drainage. Panel C and D report abdominal MRI (sag. and cor T2 w) shows large abdominal cystic mass communicating with endometrial lumen

of protein. The same mutation segregates in homozygotes with MKS syndrome in Old Order Amish population. The I339V was previously identified without other coding sequence alterations in BBS patients [Figure 3].[1,9]

The mutations identified in MKKS gene suggest strictly relationship with HMC and PAP phenotype, but the definitively diagnosis should be revaluated to exclude phenotypic BBS age-dependent features. Special attention should be paid on the organs (hart, eyes, kidneys, gonads) and age-dependent comparison of signs such as cone dystrophy, obesity, learning disability, and renal dysfunction. The above mentioned signs are characteristics of BBS, which is the final diagnosis for major number of patients even for those whose first diagnosis is MKS. The patient's follow up should be reinforced with other types of useful support such as diet and psychological.

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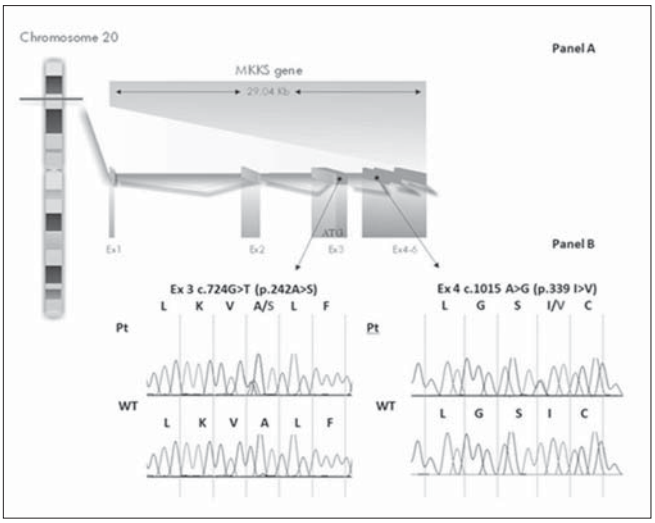

Figure 3: A schematic representation of the MKKS gene locus and mutations identified (Panel A) and chromatographs (Panel B) showing the sequence variation p.242A>S in exon 3 (left) and the sequence variation p.339I>V in exon 4 (right) in the proband (Pt) and a control subject (WT).

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