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A Review on McKusick-Kaufman Syndrome

Divya Devakumar[1], Jasmin M B[2], Reeja R[3]

[1,2]Assistant Professor, Govt. College of Nursing, Kottayam, Kerala
[3]Assistant Professor, Govt. College of Nursing, Alappuzha, Kerala

Corresponding Author: Divya Devakumar

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ABSTRACT

McKusick-Kaufman syndrome is one of the most underdiagnosed and underreported cases in the world. In family with no previous history, the condition is not at all suspected and is often diagnosed only during postnatal examination. As a cause of multiple malformations, the prognosis of which can be improved by risk assessment and genetic counselling, the condition demands early detection and identification. Also, it is vital to differentiate MKKS from Bardet- Biedl syndrome which has similar clinical presentation.

KEYWORDS: McKusick Kaufman syndrome, Bardet- Biedl Syndrome, Hydrometrocolpos, polydactyly.

INTRODUCTION

MKKS is an autosomal recessive disease, first described by McKusick et al. in 1964. It was first identified in the Amish ethnotype. Neonatal hydrometrocolpos, polydactyly, and congenital heart diseases are the cardinal features of MKKS (Yewalkar et al., 2013). Although the MKS phenotype is very rare, descriptions of hydrometrocolpos in association with polydactyly has been reported in numerous ancestries, making it a pan ethnic occurrence.

DEFINITION:

McKusick-Kaufman syndrome is an autosomal recessive disorder with human developmental anomaly syndrome(Stone et al., 1998) characterized by the combination of postaxial polydactyly (PAP), congenital heart disease (CHD), and hydrometrocolpos (HMC) in females and genital malformations in males (most commonly hypospadias, cryptorchidism, and chordee) (Slavotinek, 2020).

ETIOLOGY

Mutations in the **MKKS** gene on chromosome 20p cause McKusick-Kaufman syndrome (Stone et al., 2000). This gene provides instructions for making a protein with molecular structure similar to that of a chaperonin, which is a type of protein that helps fold other proteins in conjunction with Adenosine Triphosphate (Simpson, 2013)and thereby plays an important role in the formation of the limbs, heart, and reproductive system. The mutations that underlie McKusick-Kaufman syndrome alter the structure of the MKKS protein.

INHERITENCE

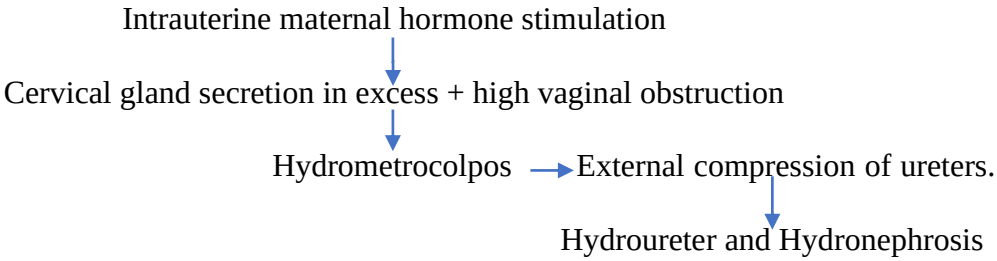
A person who has the disease receives a gene with a pathogenic variant from each of their parents. Each parent is a carrier, which means they have a pathogenic variant in only one copy of the gene, and hence will not have any symptoms of the disease. When two carriers have children, there is a 25% (1 in 4) chance to have a child who has the disease (McKusick Kaufman Syndrome - About the Disease - Genetic and Rare Diseases Information Center, n.d.).

PREVALENCE: 1-5/1000 population (Scott et al., 2017).

AGE OF ONSET: Neonatal (Birth-4 weeks).

PATHOPHYSIOLOGY

Hydrometrocolpos is seen in female fetus (McKusick-Kaufman Syndrome | Syndromes: Rapid Recognition and Perioperative Implications | Access Anesthesiology | McGraw Hill Medical, n.d.).



CLINICAL FEATURES

The symptoms can affect multiple body systems (McKusick Kaufman Syndrome - About the Disease - Genetic and Rare Diseases Information Center, n.d.).

The major symptoms are (Simpson, 2013):

Symptoms	Description
Hydrometrocolpos	an accumulation of uterine and vaginal secretions as well as menstrual blood in the uterus and vagina.
Cryptorchidism	absence of one or both testes from the scrotum owing to failure of the testis or testes to descend through the inguinal canal to the scrotum.
Glanular hypospadias	the opening of male urethra is located on the head of the penis, but not at the tip(Types of Hypospadias in Children | NYU Langone Health, n.d.)
Hydronephrosis	Severe distention of the kidney with dilation of the renal pelvis and calices.
Postaxial hand polydactyly	Supernumerary digits located at the ulnar side of the hand. (on the side of the fifth finger).
Urogenital sinus anomaly	A rare birth defect in women in which the urethra and vagina both open into a common channel.

The less frequent symptoms include (McKusick Kaufman Syndrome - About the Disease - Genetic and Rare Diseases Information Center, n.d.):

1. Abnormality of metacarpal bones.
2. Aganglionic megacolon.
3. Anal atresia
4. Atrial septal defect.
5. Brachydactyly.
6. Cleft palate.
7. Failure to thrive.
8. Ectopic anus.
9. Finger syndactyly.
10. Global developmental delay.

DIAGNOSIS

Diagnosis is made clinically and by gene mapping.

A diagnosis of McKusick-Kaufman syndrome is usually made at birth when a newborn is given a post-natal physical exam, where the birth defects are identified.

The clinical diagnosis of McKusick-Kaufman syndrome (MKS) can be established based on clinical diagnostic criteria of HMC and postaxial polydactyly provided the clinical and molecular analysis ruled out an alternative diagnosis in a child of age five years or older (Yewalkar et al., 2013).

Clinically, the patient may present with (McKusick Kaufman Syndrome - About the Disease - Genetic and Rare Diseases Information Center, n.d.)

- Large, cystic abdominal mass which can cause intestinal obstruction.
- Hydroureter and hydronephrosis caused by urinary outflow obstruction.
- Elevation of the diaphragm resulting in breathing difficulties, associated with postaxial polydactyly and congenital heart defects.
- Other cardiac malformations such as ventricular septal defect, atrial septal defect, small aorta and hypoplastic left

ventricle, tetralogy of Fallot, and patent ductus arteriosus.

A diagnosis may sometimes be confirmed with a chromosomal analysis to detect the MKKS gene with the faulty chromosome 20p. Abnormal development of the pituitary gland (pituitary dysplasia) and vertebral abnormalities can be identified in a CT or MRI scan. Ultrasonography can usually visualise confirming the presence of peritoneal cysts (Al-Salem et al., 2014).

DIFFERENTIAL DIAGNOSIS:

Bardet-Biedl syndrome (BBS) is a multisystem genetic disorder impacting multiple body systems characterised by six classical features like truncal obesity, intellectual impairment, renal anomalies, polydactyly, retinal degeneration and hypogenitalism (Slavotinek, 2020). Both MKKS and BBS are associated with mutations in the MKKS or BBS6 genes on chromosome 20p. The differentiating feature is the occurrence of ophthalmic lesions and blindness by 20 years in BBS (Forsyth & Gunay-Aygun, 2020).

MANAGEMENT

There are no approved drugs for this condition,

Treatment of manifestations: Standard surgical protocol is the repair of the obstruction causing HMC and drainage of the accumulated fluid. Treatment for the structural anomalies is standard (Yewalkar et al., 2013).

Surveillance: Watch for complications after surgery for HMC. Ongoing surveillance for manifestations including growth and developmental assessments, ophthalmologic examination, and electroretinogram (to rule out BBS), renal anomaly complications and development of severe constipation (to rule out Hirchsprung's disease) (McKusick-Kaufman Syndrome | Encyclopedia.Com, n.d.).

Genetic counselling: Clinical History of Patient who is at risk should be thoroughly collected. A Genetic Counselling session to draw a pedigree chart of family members affected with MKKS should also be drawn. Being a recessive disorder, the chances of parents being carriers should be well explained(Stone et al., 1998). Early genetic screening can detect MKKS anomalies soon as the symptoms in BBS appears late (usually after 5 yrs of age). Carrier testing for at-risk relatives, prenatal testing for pregnancies at increased risk, and preimplantation genetic testing are suggested for families known to carry the pathologic MKKS phenotype.

PROGNOSIS

Early detection with the aid of genetic counselling and risk assessment, cases can be detected at the earliest. With access to rapid surgical interventions, the prognosis improves dramatically. Sometimes multiple surgeries are required (McKusick-Kaufman Syndrome | Encyclopedia.Com, n.d.).

CONCLUSION

Being a chromosomal disorder, a genetic consultation is obligatory in cases considered to be at risk for MKKS. As the risk of recurrence is 25%, it is essential to explain this to the parents in order to offer a detailed sonographic screening during pregnancy. Patients with MKKS may present with different clinical pictures and ages. Hence the chances of misdiagnosis are high. Early diagnosis is found to offer good prognosis.

Declaration by Authors

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