MPPH Syndrome

https://pubmed.ncbi.nlm.nih.gov/27854409/

Clinical characteristics:

MPPH (

m

egalencephaly-

p

ostaxial polydactyly-

p

olymicrogyria-

h

ydrocephalus) syndrome is a developmental brain disorder characterized by megalencephaly (brain overgrowth) with the cortical malformation bilateral perisylvian polymicrogyria (BPP). At birth the occipital frontal circumference (OFC) ranges from normal to 6 standard deviations (SD) above the mean for age, sex, and gestational age; in older individuals the range is from 3 to 10 SD above the mean. A variable degree of ventriculomegaly is seen in almost all children with MPPH syndrome; nearly 50% of individuals have frank hydrocephalus. Neurologic problems associated with BPP include oromotor dysfunction (100%), epilepsy (50%), and mild-to-severe intellectual disability (100%). Postaxial hexadactyly occurs in 50% of individuals with MPPH syndrome.

Diagnosis/testing:

The clinical diagnosis of MPPH syndrome can be established in individuals with the two core features: megalencephaly and polymicrogyria (PMG). The molecular diagnosis of MPPH syndrome is established in a proband with some of the suggestive clinical and imaging features by identification of a heterozygous pathogenic variant in one of three genes:
AKT3
,
CCND2
, or
PIK3R2
. While most individuals with MPPH syndrome have a germline pathogenic variant in one of these genes, some have a somatic mosaic pathogenic variant (most commonly reported in
PIK3R2
or
AKT3
).

Management:

Treatment of manifestations:

Hydrocephalus warrants early neurosurgical intervention. Treatment per neurooncologist for those with medulloblastoma. Oromotor difficulties, epilepsy, developmental delays, intellectual disability, polydactyly, vision issues, cardiac anomalies, thyroid abnormalities, and renal anomalies are treated as per usual clinical care standards. Social worker support and care coordination for families of affected individuals.

Surveillance:

Follow up with a pediatric neurologist regularly to monitor and treat epilepsy. Brain MRI to detect hydrocephalus and/or cerebellar tonsillar ectopia is provisionally recommended every six months from birth to age two years, and yearly from age two to six years. In older individuals, the frequency should be determined based on prior brain imaging findings as well as clinical findings. Brain imaging (with particular attention to the posterior fossa) may be considered every six months to assess for medulloblastoma. Assess growth and feeding at each visit. Routine follow up with a developmental pediatrician given the high risk of developmental delays and/or intellectual disability. Ophthalmology examination annually or as needed; endocrine follow up as recommended by endocrinologist. Assess need for social work support and care coordination at each visit.

Genetic counseling:

MPPH syndrome is an autosomal dominant disorder typically caused by a de novo pathogenic variant. Almost all individuals with MPPH syndrome have the disorder as the result of a de novo germline AKT3, CCND2, or PIK3R2 pathogenic variant; somatic mosaic pathogenic variants in PIK3R2 and AKT3 have been reported in a few affected individuals. Vertical transmission of a PIK3R2 pathogenic variant from an affected heterozygous parent to several affected children has been reported in one family to date. Presumed parental germline mosaicism has been suggested in three families. Each child of an individual with a germline

AKT3

,

CCND2

, or

PIK3R2

 pathogenic variant has a 50% chance of inheriting the pathogenic variant. The risk for transmission to offspring of an individual with somatic mosaicism for an MPPH-related pathogenic variant is expected to be less than 50%. Once the MPPH syndrome-related pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing for MPPH syndrome are possible.