MPPH Syndrome

What is MPPH Syndrome?

Megalencephaly-polymicrogyria-polydactyly-hydrocephalus syndrome, also referred to as MPPH syndrome or MEG-PMG-POLY-HYD, is a rare genetic condition characterized by megalencephaly (brain overgrowth) that affects the development of the brain causing delayed development and intellectual disability. As is common with genetic conditions, each person is affected differently with symptoms ranging from mild to severe.

What caused the MPPH Syndrome?

MPPH is caused due to defects (mutations) occurring within specific genes- AKT3 (most common), CCND2 or PIK3R2. The genes associated with MPPH syndrome are located in different chromosomes, however, they play a similar role in the development and maturation of the brain.

The AKT3 gene sequence directs the production of the RAC-alpha serine/threonine protein Kinase, located on chromosome 1. Conversely, CCND2 encodes the Cyclin D2 protein, which plays a vital role in regulating the rates of cell growth and division throughout the body. The proteins produced from all these three genes play a critical role in a chemical signaling pathway called the P13K-AKT-mTOR, essential for brain and neurodevelopment. The chemical signaling influences many critical cell functions, including the creation (synthesis) of new proteins, cell growth and division (proliferation), and the survival of cells.

Defects or mutations in these genes can lead to both heightened protein activity or impaired regulation of the pathway, resulting in excessive cell growth or division in the brain before birth. The increased number of cells in the brain leads to rapid and abnormal brain growth before birth affecting both the functional and structural dynamics of the developing brain.. While changes in any of these genes can have similar effects on brain development, the specific features observed in MPPH individuals may vary depending on which gene is affected.

The syndrome name reflects its primary characteristics and features.

Megalencephaly: A developmental brain disorder due to brain overgrowth.

Polymicrogyria:- PMG is a condition characterized by abnormal development of the brain before birth. Typically, the surface of the brain has many ridges or folds called gyri. However, in children born with Polymicrogyria, an area of the brain called the perisylvian region forms an excessive number of small folds or gyri which are irregular and unusually small and prevent the normal functioning of the brain. The name of this condition means Poly (too many) micro (small) gyria (folds) in the surface of the brain.

Polydactyly: is a condition in which a person has more than 5 fingers/ hands or 5 toes per foot.

Hydrocephalus: Hydrocephalus is a condition characterized by the accumulation of cerebrospinal fluid within the brain. This excess fluid enlarges cavities known as ventricles deep within the brain, exerting pressure on surrounding brain areas.

Common Features

The majority of children diagnosed with MPPH syndrome typically exhibit:

- ☐ Development Delay
- ☐ Affected individuals are born with an unusually large brain and head size (megalencephaly).
- ☐ Recurrent seizures (epilepsy) beginning early in childhood.
- ☐ Oromotor dysfunction mostly associated with the difficulty of coordinating movements of the mouth and tongue resulting in drooling,difficulty swallowing (dysphagia) and delay in the production of speech (expressive language)
- ☐ The presence of extra Finger or toe on one of their hands or feet (polydactyly)
- ☐ Hypotonia, decreased muscle tone, usually detected during infancy and impaired vision.

Development Concerns/ Symptoms

Intellectual Development and Learning: Most children diagnosed with MPPH syndrome exhibit developmental and cognitive challenges, with the extent of intellectual disability varying from mild to severe. This variability is primarily influenced by the severity of cortical malformations and the onset and severity of epilepsy at an early age. Referral to an early

intervention program can prove particularly beneficial and formal testing to assess specific individual and educational needs is recommended.

Communication issues: The majority of children diagnosed with MPPH syndrome experience delays in speech development, with some potentially remaining non-verbal. These children may encounter challenges in coordinating the movements required for speech. Augmentative and Alternative Communication (AAC) methods such as picture-exchange communication or high-tech solutions such as voice generating devices can assist children with expressive language challenges. An evaluation by a speech-language pathologist could also prove to be beneficial in order to identify the most suitable form of communication.

Gross and Fine Motor Skills: Children with MPPH syndrome may encounter challenges in performing oromotor functions, experiencing difficulties with managing oral secretions, including excessive drooling, and dysphagia. In some cases, feeding difficulties may necessitate the placement of a gastronomy tube. Occupational therapy and feeding assessment by a specialist is advised to address fine motor skill deficits that impact activities of daily living, such as feeding, grooming, dressing, and writing.

Medical Concerns

Megalencephaly: All children diagnosed with MPPH syndrome exhibit an enlargement of the brain, known as megalencephaly, resulting in a head size larger than typical for their age, a condition referred to as macrocephaly. The head may present as large at birth or may progressively enlarge during infancy, continuing to grow at an accelerated rate.

Polymicrogyria: Most individuals diagnosed with MPPH syndrome exhibit cortical brain malformations, particularly PMG. PMG is best diagnosed through a brain MRI (Magnetic Resonance Imaging) which helps access the brain structure and provide information on the location and extent of the problem. Symptoms vary among different children based on the specific brain regions affected and the extent of deformity. Most children affected by PMG suffer from infantile spasms and develop seizures and epilepsy at some point in their life. Other common symptoms include cerebral palsy, motor delays, autism, cognitive and emotional delays, and swallowing problems. While the PMG malformation itself cannot be reversed, symptoms in both children and adults can be effectively managed and treated through various approaches such as anti-seizure medications, epilepsy surgery (when applicable), dietary interventions with a

ketogenic diet or neuromodulation techniques, such as vagus nerve stimulation (VNS), deep brain stimulation (DBS) or responsive neurostimulation (RNS). An individual with a pathogenic variant in the AKT3 gene experienced severe refractory infantile spasms, which showed a positive response to treatment with a ketogenic diet (Mirzaa 2022).

Seizures and Epilepsy: It's estimated that approximately half (50%) of children diagnosed with MPPH syndrome experience epilepsy and seizures, characterized by sudden and unforeseen alterations in brain electrical activity. Various types of seizures are observed, depending on factors such as the location, severity, and type of PMG disorder. For example: Focal seizures occur when a specific area of one brain hemisphere (side) is affected. Whereas, if these focal seizures spread to involve both sides of the brain, they may manifest as generalized tonic-clonic seizures. However, persons with bilateral polymicrogyria (BPP) suffer from atypical absence seizures and may appear confused and unresponsive. The seizure usually lasts 5 to 30 seconds, most often more than 10 seconds. EEG test is most commonly used to measure and record the electrical activity of the brain and can help to diagnose the type of seizure experienced. A regular assessment by a pediatric neurologist is also highly recommended.

Polydactyly: Approximately half of individuals with MPPH syndrome exhibit an additional finger or toe on one or more hands or feet. Polydactyly is termed postaxial as it appears on the same side as the pinky finger or little toe. The exact relationship between the mutations in the AKT, CCND2, or PIK3R2 genes, which lead to increased protein activity or disrupted pathway regulation, and polydactyly is not fully understood. However, it is possible that irregular cell proliferation during the development of hands and feet plays a role. Surgery for some may be an option to remove extra digits in cases where it enhances functionality or at the individual's request.

Ventriculomegaly and hydrocephalus: In MPPH, the enlargement of the head leads to an excess buildup of cerebrospinal fluid in the brain, causing ventriculomegaly and placing harmful pressure on the brain, a difficulty experienced in nearly 50% of individuals with MPPH syndrome. This is usually diagnosed with a brain MRI to investigate the dilation of fluid spaces within the brain (ventricles). Treatment often entails surgical intervention to insert a shunt—a

flexible yet sturdy plastic tube—to redirect cerebrospinal fluid to a different area of the body for absorption. Additionally, medications and rehabilitation therapy may provide relief and support.

Other Features: Other features have been observed in specific individuals, including vision-related issues such as cortical visual impairment (CVI) and blindness, which warrant evaluation by an ophthalmologist, low blood sugar levels (hypoglycemia), heart conditions like arrhythmia or structural anomalies, kidney abnormalities, and thyroid problems necessitating assessment by an endocrinologist.

Why did this happen?

Most cases of MPPH syndrome are a result of new gene mutations (de novo) that occur during the formation of reproductive cells (eggs or sperm) or in early embryonic development . These cases mostly occur in people with no history of the disorder in their family. This condition is considered autosomal dominant, which means one copy of the altered gene in each cell is sufficient to cause the disorder.

During conception, the genetic material of parents is replicated in the egg and sperm to create a new child. However, this biological copying process isn't flawless, leading to random alterations in the genetic code of children that aren't present in their parents' DNA. While most of these changes are harmless, some can cause health issues or developmental problems if they disrupt gene function, resulting in disorders.

In a few cases, children with MPPH syndrome inherit the changed gene from a parent who doesn't have the disorder but has a gene change only in their egg or sperm cells. This is called germline mosaicism. Parents with mosaicism may not have or show any symptoms, but they can still have a child with MPPH syndrome.

How common is MPPH syndrome?

MPPH syndrome seems to be a rare disease and is uncommon, with only 62 reported cases as of 2021.

Can it happen again?

The risk of having another child or a sibling of a proband (first person in a family who is identified as possibly having a genetic disorder) depends on the genetic code of the parents. If a parent of the proband is affected and/or is known to have the pathogenic variant identified in the proband, the risk to the sibling or another child is 50%. While the specific traits may vary among children, they are likely to exhibit features of MPPH syndrome (Mirza 2022).

However, if the AKT3, CCND2, or PIK3R2 pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent (i.e genetic testing appears normal), the risk to another child is slightly greater than the general population (but-as yet unknown) because of the parental germline mosaicism (an explanation for the inheritance pattern in cases where multiple affected offspring are born to clinically and phenotypically normal parents). However, every family's circumstances vary, and consulting with a clinical geneticist can provide tailored guidance for one's situation, including discussing options for testing related to future pregnancies, if relevant.

Can MPPH syndrome be cured?

There is no cure for MPPH since the effects of the genetic change took place during a baby's formation and development. However, knowing the diagnosis means that appropriate monitoring and interventions can be put in place.

Management Recommendations

- Follow-up with a pediatric neurologist for ongoing monitoring and treatment of epilepsy. Consider referral to a comprehensive epilepsy center if seizures persist despite trials of two or more anti-seizure medications.
- Brain imaging is recommended every six months from birth to age two years, and yearly from age two to six years. Frequency in older individuals should be determined based on prior imaging and clinical findings.
- Regular follow-up with a developmental pediatrician is advised due to the high risk of developmental delays.
- Involve appropriate social work services to connect families with special educators.

- Implement early intervention programs to stimulate visual development in cases of visual impairment.
- Educate parents and caregivers, especially regarding seizures.
- Monitor growth parameters, nutritional status, and safety of oral intake.
- Provide genetic counseling, particularly regarding family planning, to assist families in making informed medical and personal decisions.
- Regular screening for low blood sugar levels during the neonatal period, and review by an endocrinologist where hypoglycaemia is detected, is recommended.
- Echocardiogram (ECG) (to evaluate for cardiac (heart) anomalies) and renal ultrasound examination (to evaluate for structural anomalies of the kidneys, ureters and bladder) may be considered.
- Speech therapy, occupational therapy and physiotherapy often prove beneficial