DHR Proceedings

Special Edition: Junior Clinical Research (2023), Vol. 3 No. S2
https://doi.org/10.47488/dhrp.v3iS2.101

COMMENTARY

Primary Hereditary Microcephaly: A Review

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Received: November 2, 2023
Accepted for publication: November 3, 2023
Published : November 16, 2023

Introduction

Microcephaly Primary Hereditary or MCPH, is a neurological and genetic disorder that is characterized by a reduced head circumference, growth delay, and intellectual disability.[1] Microcephaly is categorized by primary and secondary microcephaly.[2] Primary is congenital, which means that the genetic disorder is present before birth and secondary is postnatal, meaning that it appears after birth or later on in life. Microcephaly is caused by a frameshift mutation, via insertion or deletion, and this mutation occurs in at least seven genes. There are a number of factors that may cause microcephaly. Microcephaly may be hereditary, with both parents being carriers of the genetic mutation and mutations causing an alteration of proteins; however, environmental factors, such as viral infections and toxins, may also play a role in the appearance of genetic mutations.[2] There are less than 5,000 people in the United States affected by microcephaly.[1] The rate of microcephaly in newborns in the United States is 8.7 in every 10,000 births, which is very low, revealing how rare microcephaly is.[2] The most obvious sign of microcephaly in newborns is the small and underdeveloped size of the cerebrum in the brain . This makes it possible for microcephaly to be diagnosed and become noticeable while the child is still developing inside the mother via ultrasound. Other forms of diagnosis include blood testing and amniocentesis. This genetic disorder is lifelong but can be treated based on the severity of the disease in a person affected. A variety of therapy techniques used for treating primary microcephaly include physical therapy, speech, alternative therapy, and a holistic therapy approach. The treatments being performed on the patients is directly proportional to their prognosis. The development of those affected by microcephaly can vary especially when considering their cognitive and social development.

Etiology

To better comprehend the etiology of MCPH, it must first be understood that MCPH is an inherited disorder that affects the autosomal chromosomes, pairs 1-22.[3] MCPH is caused by a frameshift mutation or nucleotide deletion.[4] An individual who inherits this disorder must receive a copy of the diseased gene from each of their parents. This mutation occurs in at least seven genes: ASPM, CDK5RAP, CENPJ, CEP152, KNL1, STIL, and WDR62.[5] These microcephaly associated genes are highly involved in cell-cycle related processes such as centriole biogenesis, mitotic spindle organization, cell cycle checkpoint or chromosome segregation.

The ASPM gene or abnormal spindle-like microcephaly-associated gene is located on chromosome 1.[4] It is responsible for encoding proteins that are involved in bodily functions and processes.

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Specifically speaking, the ASPM gene encodes proteins that are densely involved in brain development and the production of neural progenitor cells.[4] Neural progenitor cells are nerve cells found in the central nervous system. They are responsible for restoring damage in the brain as well as interacting with microglia cells. An abnormality in this gene can result in Microcephaly Primary Autosomal Recessive or MCPH.[5]

The CDK5RAP gene or regulatory subunit associated with protein 2, is a gene located in chromosome 9. The CDK5RAP gene allows the initiation of the cell cycle by encoding a regulator of CDK5 (cyclin-dependent kinase 5) activity.[6] This occurs in phase G1 of the cell cycle where cyclins combine with cyclin-dependent kinase for gene transcription and gene translation. Additionally, CDK5RAP is also activated during the mitotic spindle checkpoint. Before proceeding towards anaphase, the CDK5RAP gene ensures that the duplicated chromosomes are properly attached to the spindle microtubules of each kinetochore. Mutations in this gene are linked to primary microcephaly.[6]

The CENPJ or centromere protein J, is a gene located in chromosome 13.[7] It maintains centrosome activity and begins microtubule disassembly during anaphase, the separation of sister chromatids. CEP152 or centrosomal protein 152, is a gene located in chromosome 15. Similar to CENPJ, CEP152 also aids in centrosome function. Mutations in these genes are associated with Primary Microcephaly.[8]

The KNL1 or kinetochore scaffold 1 is a gene located in chromosome 15. KNL1 serves as a scaffold protein for kinetochore-microtubule attachment and chromosome segregation.[9] A scaffold protein binds with multiple proteins to relay messages between other cells at a faster rate. Its binding nature allows it to ensure that the chromosomes are correctly aligned and attached before the sister chromatids are pulled apart by the spindle microtubules (reference). Alterations in the gene are directly correlated with Primary Microcephaly and the formation of tumors.[9]

STIL Centriolar Assembly Protein located in chromosome 1 is responsible for regulating the mitotic spindle checkpoint through the process of chromosome distribution.[10] Although a mutation in this gene is associated with MCPH, more research has to be conducted for a better understanding.

WDR62 or WD Repeat Domain 62 is a gene located in chromosome 19. WDR62 or WD Repeat Domain 62 is a gene located in chromosome 19. WDR62 plays a role in the growth and development of the brain.[11] A mutation in this gene can result in delayed psychomotor development.

Risk Factors

Genetic: Protein Alteration

An alteration of proteins is a related risk factor within Primary Microcephaly. The CTNNB1 gene is responsible for producing a protein called B-catenin 1. This protein has a hand in connecting cadherins and the actin cytoskeleton in adherent junctions.[12] It has a vital function in preserving the integrity of epithelial layers and supporting adhesion, communication, and signaling between nearby cells. The Wnt signaling pathway, discovered in metazoan animals, is remarkably conserved. The term 'Wnt' originated from the fusion of 'wingless'." Drosophila segment polarity, a gene responsible for segment polarity in Drosophila, and "integrated" or 'int-1,' its vertebrate counterpart.[12] Extracellular Wnt signal triggers various intracellular signaling cascades, such as the canonical (Wnt B - Catenin dependent) pathway and the non-canonical (B Catenin- independent) pathway, which includes the Planar Cell Polarity pathway and the Wnt/Ca2+ pathway.[12].Wnt proteins are crucial regulators in a diverse array of cellular processes, including cell fate determination, motility, polarity, primary axis formation, and organ development. Furthermore, recent research has revealed their involvement in stem cell renewal within the biologic pathway, which is essential for the development of embryos and the maintenance of tissue balance in adulthood.[12] Recent studies have indicated that mutations resulting in the loss of CTNNB1 function during embryonic stages are linked to cognitive disabilities.[12] Furthermore, various syndromic phenotypic characteristics, including microcephaly, have been observed and reported in case studies and series.[12] This alteration of the CTNNB1 gene must be present within both parents for a child to be affected and develop Primary Microcephaly.

Viral Infection: Zika Virus (ZIKV)

Notably, microcephaly has been linked to various infectious agents such as *Toxoplasma gondii*, cytomegalovirus, rubella virus, syphilis, herpes simplex virus, HIV, and Zika virus in infants at birth. The extent of microcephaly is determined not only by the particular infectious agent but also significantly by the gestational age when the infection takes place.[2]

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Research has revealed that these pathogens primarily target neural progenitors.[2] However, the precise mechanisms through which most of these infections lead to microcephaly remain incompletely understood. Nevertheless, a thorough investigation in this area was sparked by the high association between the Zika virus and its connection to congenital microcephaly. Numerous studies using both in vitro and in vivo animal models have shown that Zika virus infection causes NPC cell cycle arrest or increased cell mortality. Interestingly, research data shows that the expression of several genes linked to microcephaly, including MCPH1, ASPM, Centrosomal protein, and STIL, is reduced in brain tissues removed from Zika-infected mice.[2] It indicates that the microcephaly brought on by infection may have an effect on brain development by altering the expression of different MCPH genes. Nevertheless, it is important to acknowledge the direct role that infectious agents play in the emergence of microcephaly.[2]

Signs and Symptoms: Primary Microcephaly

Autosomal Recessive Primary Microcephaly is a neurological and genetic disorder that occurs congenitally. The most common indicator of Microcephaly is the presence of an undeveloped cerebrum. Usually, symptoms start presenting themselves antepartum, which is why it can be diagnosed during pregnancy. It is vital to remember that signs are dictated by the severity and categorization of the disability.[1] Oftentimes, symptoms include poor appetite, which leads to unhealthy weight gain or weight loss. This causes deficient growth among the children. They also struggle with balance and movement. Due to joint deformities and a lack of motor skills, these kids are not able to perform tasks such as running, walking, and sitting. Seizures are very common amongst children with microcephaly as well. They develop issues such as speech delays, learning disabilities, sociability delays, and intellectual delays.[24] Their brain does not function in the way a healthy child's brain would, which is why they struggle when socializing with other kids, learning, or trying to make decisions. Lastly, they also have complications with their vision and hearing, causing them to struggle seeing things or listening. As previously stated, a small head and brain is the most common sign of microcephaly. Dwarfism is not as common but is also on the list. This is when a person has shorter stature than what would be considered typical. A sloping forehead is usual in children with microcephaly. A lot of these children also have facial deformities, which are deformities that affect the bones and face. Joint deformities are also very similar and are also recurrent in children with MCPH. These joint deformities contribute to the struggle they have when it comes to simple motor skills. The bones do not develop as they should and affect their abilities.[13]

Diagnosis

Microcephaly can be diagnosed from approximately 18 to 22 weeks of gestation and after delivery. Ultrasound and MRI testing are the primary ways to find microcephaly in newborns and fetuses.[14] Ultrasounds are the primary source to access fetal growth during pregnancies. Finding microcephaly after birth, the provider will measure the head circumference, then the provider will compare it to a standard female or male. Microcephaly is diagnosed when the infant's head circumference is more than 2 standard deviations below the average.[15]

Liquid Biopsies

Microcephaly can also be found through blood samples. The tests can be run in the early stages of pregnancy to see if the fetus has the condition. From the blood samples, the doctors can also run genetic tests to see if there is any mutation in the genes of the baby or if the condition runs in the family.[16]

Amniocentesis

An amniocentesis test can be run between 15-18 weeks of pregnancy. A small sample of amniotic fluid collected from the area surrounding the baby is collected to test for any Zika genetic material.[17] The test is recommended until after the 15th week to reduce complications that could happen if the test is done before that time.[18]

Treatment

Physical Therapy

Microcephaly is an extremely expansive disorder, each case is unique. Nevertheless, cases could have similar symptoms. Physical therapy is essential and can help a patient's condition greatly by boosting their sense of wellbeing and, ideally, restoring their ability to walk. This article discussed various physical therapy treatments to treat microcephaly caused by the Zika virus.[19] Trunk rotation techniques are the main source of therapy and are truly a game changer in a patient's lives. Please give a short explanation of trunk rotation techniques here. This treatment could be applied to primary

microcephaly exhibiting comparable symptoms.[19] Children who suffer from this condition can gain from specific exercises and programs that will improve their motor and developmental skills.[20] Trunk Rotation Techniques affect motor function, interact with other physical components and neurological systems in a mutually dependent manner, and are crucial for limb movements.[20] Lacking trunk rotation processes have a number of negative effects, including a lack of trunk stability, increased muscle tone in the upper and lower limbs, a delay or loss of the postural reaction, and weakness in the trunk muscles.[20] The main objective is to make your back muscles more flexible while also increasing the back's ability to rotate. Physical Therapy is truly an important intervention in patients with microcephaly.

Speech Therapy

Speech therapy helps individuals expand or gain a way to communicate. Individuals with microcephaly are prone to have speech delays and overall developmental delays.[21] Accordingly, speech therapy is recommended and a standard way to help people with microcephaly navigate their life on account of no known treatment.[22] Not all individuals with microcephaly are able to communicate verbally. The use of other means of communication is implemented through the use of nonverbal communication. Individuals may also use sign language to communicate. By using and learning sign language individuals possess the information to be able to express themselves.

Alternative therapies

Alternative therapies provide several benefits and do not typically follow a traditional route, such as support groups in this instance fall under alternative therapies. These groups contain a common factor where they discuss a specific topic and members help structure their day to day lives. An advantage of joining a support group essentially supplies assistance, community, and support to children and their families.[23] If local community support groups aren't available , online support groups provide options for individuals with MCPH. Online support groups tend to cater to a variety of people with different backgrounds and their respective different experiences.

Prognosis

Children affected by this condition may experience symptoms such as hindered development, intellectual disability, and mobility issues.[27] Depending on the severity of microcephaly, the prognosis of the condition can prove fatal. Head size does not always necessarily tie to prognosis.[13]
Symptoms will prove different for each case. Patients that improve do so with close monitoring and assistance through therapy, nutritional monitoring, and other supportive interventions. The physical therapies can help with their strength and maneuverability. Nutritional monitoring aids in rebuilding strength and energy levels, therefore helping microcephaly patients with growth. Prognosis for each patient differs depending on resources provided and severity of MCPH.[13]

Lifelong Development

Life Expectancy in Autosomal Recessive Primary Microcephaly

A patient's life expectancy significantly differs from person to person depending on the severity of their condition and several other factors that come into play within their diagnosis. Furthermore, not every case of primary microcephaly is entirely similar, in some occasions with the right care a patient with primary microcephaly can go on to have an ordinary life expectancy. Genetics greatly determines the expected lifetime of a patient because of the underlying conditions and complex mutations in the family's medical history, often unbeknownst to them.[15] Additionally, the symptoms vary significantly from patient to patient while at times being accompanied by a variety of developmental conditions and physical disabilities that impede basic capabilities. Consequently, the greater the gravity of this disease the higher the risk of impact to brain function is increased with the possibility of hindering lifespan.[24]. While the occurrence of microcephaly in offspring is a rather rare possibility, having the resources to provide the necessities and care a patient requires, leads to positive influences towards their life expectancy.

Cognitive Development

Primary microcephaly will be present in a patient's brain throughout their entire lifetime. In a cognitive sense, this means that their conscious intellectual activity is impaired and the afflicted individuals will face difficulties in performing tasks that those unaffected deem as basic functions. The capacity for critical thinking is altered in a patient with primary microcephaly.[5] Their lack of understanding of complex objectives and inept proficiency to use logic

sets them back from those around them. As a crucial skill for the intake of knowledge, memory execution and retainment are especially central to the cognitive development of the brain. This can be specifically troublesome during the academic years of young patients under the arduous demands of a school environment or lack thereof causing them to fall behind their peers. Moreover, in a physical aspect the mind's control over motor skills is inefficient meaning that the essential skills used in movement such as coordination and balance are limited, in turn affecting their participation in physical activities or simple tasks in daily life.[25]

Social Development

In a social environment, basic communication and interaction skills are used, but it can be strenuous for a patient with this neurodevelopmental disorder to operate as a member of society. Expression requires the right structure of words, social cues, and emotions.[21] Being able to exchange sentences in a clear and concise manner while using listening skills with the appropriate expressions to respond effectively to someone adds to the stress of having this condition making patients feel the need to be isolated from social environments due to their difficulties.[26] These barriers to socialization emphasize the need for inclusiveness and support from those around them.

Conclusion

Microcephaly Primary Hereditary otherwise known as MCPH is a genetic and hereditary condition caused by a frameshift mutation and is defined as a head more than two standard deviations below normal head circumference. The most common cause of MCPH is a mutation in the ASPM gene due to it encoding proteins involved in brain development.[4] This explains why brain development is affected. The severity of Primary Microcephaly determines the range of symptoms experienced by the afflicted. Symptoms vary from physical abnormalities deviating from what is typically seen on healthy individuals, to slowed development. Treatment plans are individualized for each patient and require constant monitoring and support in order to achieve the most positive prognosis. Life expectancy correlates to the severity of the patient's microcephaly, taking into consideration that microcephalic patients may have other comorbidities. While this condition may affect physical, cognitive, and social development, severe cases demonstrate failure to thrive.

Acknowledgements

Monica Betancourt-Garcia, MD, Program Director; Melissa Eddy, MS, Program Manager

Funding

Funded by DHR Health Institute for Research & Development; DHR Health; Region One ESC GEARUP College Ready, Career Set!; Region One ESC GEARUP College Now, Career Connected; Region One ESC PATHS; Region One ESC Upward Bound Math & Science; Benavides ISD; and Jubilee Academy-Brownsville

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