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The Role of Genetic Mutations in Gene PIK3CA in Megalencephaly-Capillary Malformation Syndrome

Shahin Asadi*, Mahsa Jamali, Soheil Nemati Arzeloo and Mohammad Hossein Moballegh Hosseini

Division of Medical Genetics and Molecular Pathology Research, Iran.

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ABSTRACT

Megalencephaly-capillary malformation syndrome (MCAP), formerly known as macrocephaly-capillary malformation, is a rare, complex disorder involving the skin, connective tissue, brain and other organs that are usually present at birth. Affected individuals usually have a disproportionately large head and capillary malformations on the skin of the midline face, trunk and limbs. These capillary malformations often show a lacy or reticulated pattern (resembling a net or web and are sometimes termed "cutis marmorata"). Most children with MCAP have an enlarged brain (or megalencephaly), in addition to other findings on brain MRI associated with neurologic problems.

Keywords: Megalencephaly-capillary malformation syndrome (MCAP), Mutation of the PIK3CA gene, Phosphatidylinositol 3 kinase (PI3K), p110α

GENERALIZATIONS OF MEGALENCEPHALY-CAPILLARY MALFORMATION SYNDROME (MCAP)

MCAP syndrome is a genetic disorder characterized by excessive growth of various tissues in the body. Its main features include the big brain (megalenpsy) and capillary malformations. Multiple terms have been used in the past for this syndrome. The earliest one was macrocephaly-cutis marmorata telangiectatica congenita (M-CMTC) because the vascular lesions were mistakenly believed to be consistent with CMTC. However, careful examination of the skin in these children revealed that the vascular lesions are not CMTC but rather capillary malformations (described below) and so the syndrome was accurately renamed to "macrocephaly-capillary malformation syndrome" (or M-CM). Recently, the name was modified from this latter term to "megalencephaly-capillary malformation" (or MCAP, in short) because the term "macrocephaly" refers to a large head due various causes, whereas "megalencephaly" is a more specific and accurate term that refers to the truly enlarged brain present in this syndrome [1,2].

SYMPTOMS AND SINGS OF MEGALENCEPHALY-CAPILLARY MALFORMATION SYNDROME (MCAP)

People with MCAP syndrome have a head that is larger than normal (macrospheric), which is commonly seen at birth. After birth, the brain and the head continue to grow fast in the first few years of life; then growth is reduced to a natural rate, although the head is larger than the average. Excessive cerebrovascular abnormalities are common in people with MCAP; this can include excess fluid in the brain (hydrocephalus) and disorders in the brain structure, such as those known as chiari and polymicrogyria abnormalities. Abnormal brain development leads to intellectual disability in most of the affected people and can also cause seizure or poor muscle tone (hypotonia). In particular, polymicrogyria is accompanied by a speech delay and difficulty in chewing and swallowing [3] **(Figure 1)**.

Corresponding author: Shahin Asadi, Director, Division of Medical Genetics and Molecular Research, Iran, E-mail: shahin.asadi1985@gmail.com

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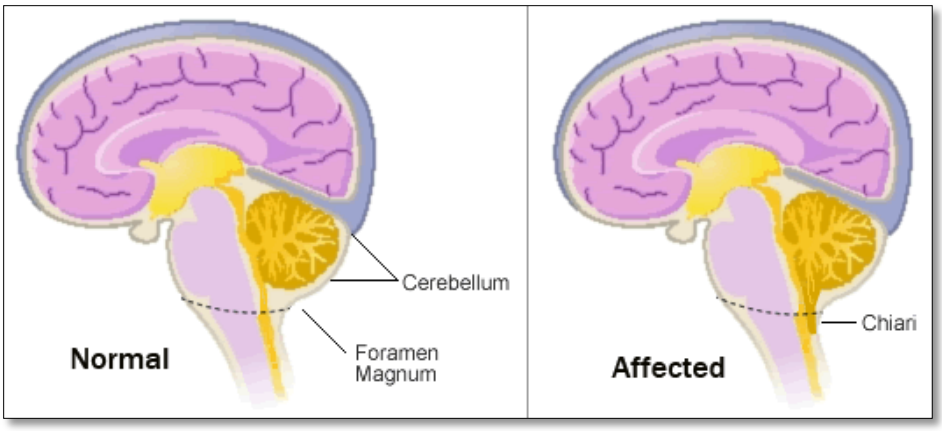

Figure 1. Schematic of the normal brain against chiari abnormalities in the brain.

Capillary abnormalities in MCAP syndrome cause large capillaries that increase blood flow near the skin surface. These abnormalities often create pink or red spots on the skin. In most cases, capillary anomalies occur on the face, especially the nose, upper lip and the space between the nose and the upper lip (philtrum). In other people with this syndrome, abnormalities develop in large parts on the body, which appear red in the skin [4] **(Figure 2)**.

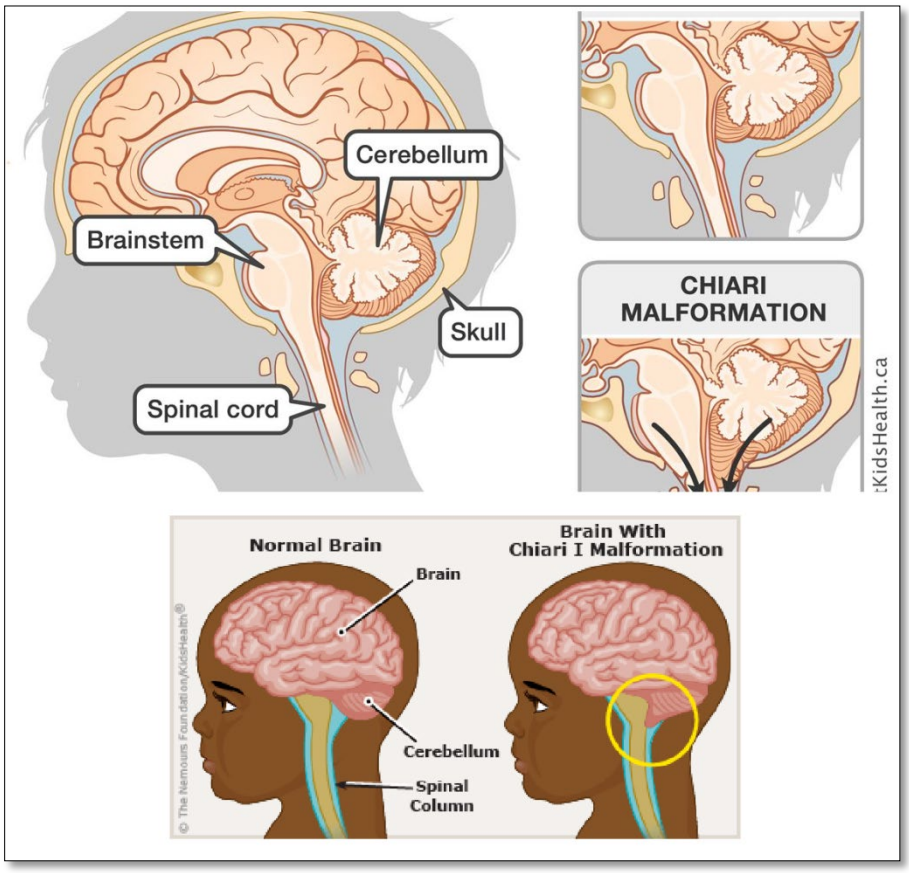

Figure 2. Another schematic of the normal brain against chiari abnormalities in the brain.

In some people with MCAP, excessive growth affects not only the brain but also the rest of the body, which is known as over-segmental growth. It can lead to an arm or leg that is larger or longer than fingers or toes or other fingers. Some people with MCAP syndrome have a fusion of fingers between two or more fingers or toes (cynadectal skin) [5].

Additional features of the MCAP syndrome include flexural joints and skin that can easily spread. Some people get

itching in the skin, because the tissue under the skin is unusually thick and soft [6] **(Figure 3)**.

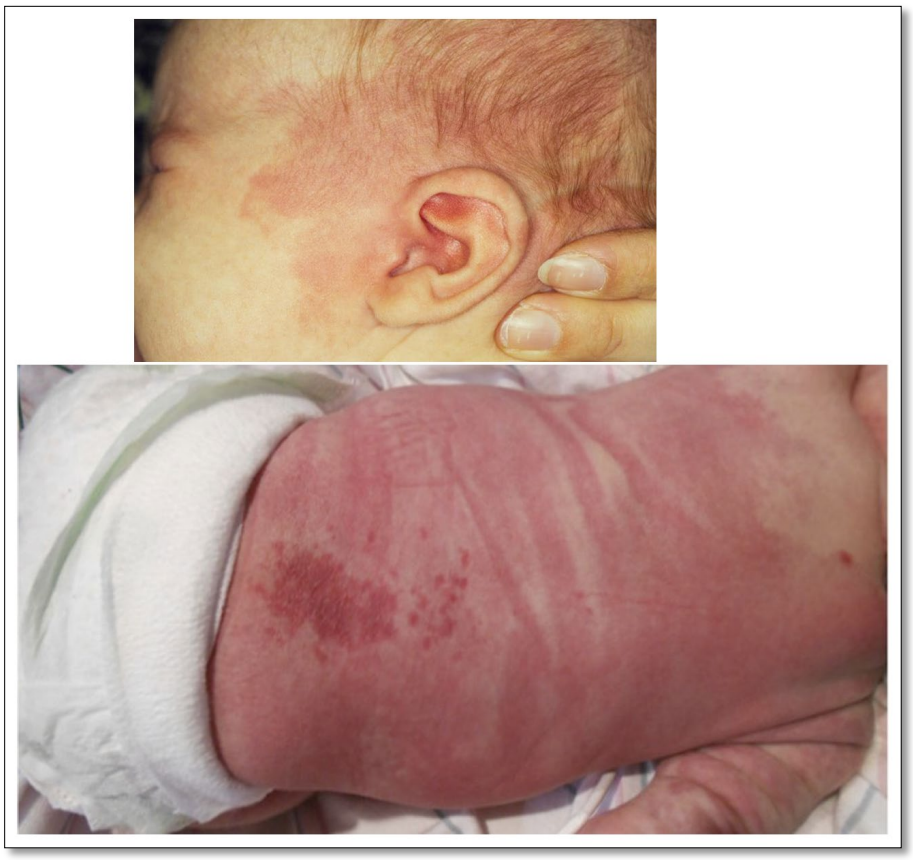

Figure 3. Images of a child with MCAP syndrome associated with dysfunction.

The gene involved in MCAP syndrome is also associated with a variety of cancers. Only a small number of people with MCAP form tumors (in particular, a type of kidney cancer called the wilms tumor and non-cancerous tumors in the nervous system known as meningium) [7] **(Figures 4 and 5)**.

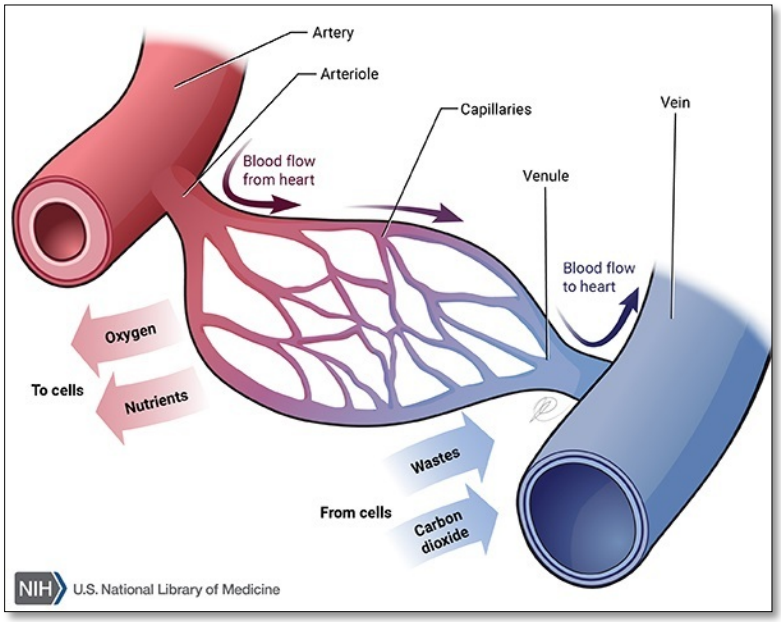

Figure 4. Schematic impairment of capillary dysfunction in MCAP syndrome.

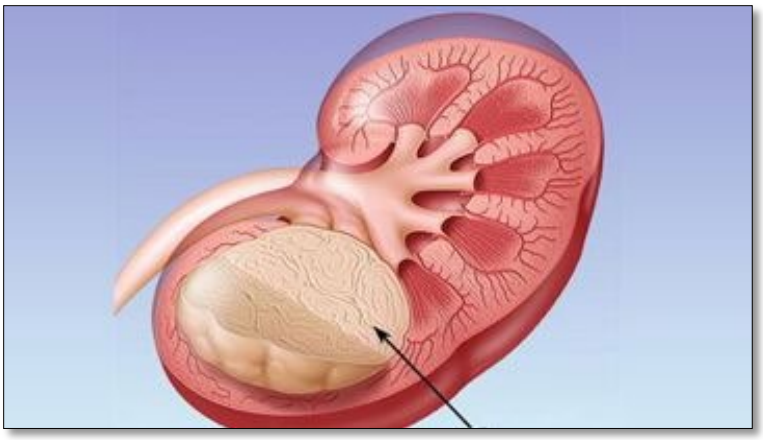

Figure 5. Schematic of the wilms tumor in the kidney.

ETIOLOGY OF MEGALENCEPHALY-CAPILLARY MALFORMATION SYNDROME (MCAP)

MCAP syndrome is caused by the mutation of the PIK3CA gene, which is based on the long arm of chromosome number 3, at 3q26.32. This gene provides instructions for protein synthesis called p110α. This protein is an enzyme subunit called phosphatidylinositol 3 kinase (PI3K), which plays an important role in intracellular biochemical signaling. Signaling PI3K is important for many cellular activities, including cell growth and division (proliferation), cell motility (cell maturity) and cell survival. These functions of the PIK3 enzyme are important for the development of tissues throughout the body, including the brain and blood vessels [8] **(Figures 6 and 7)**.

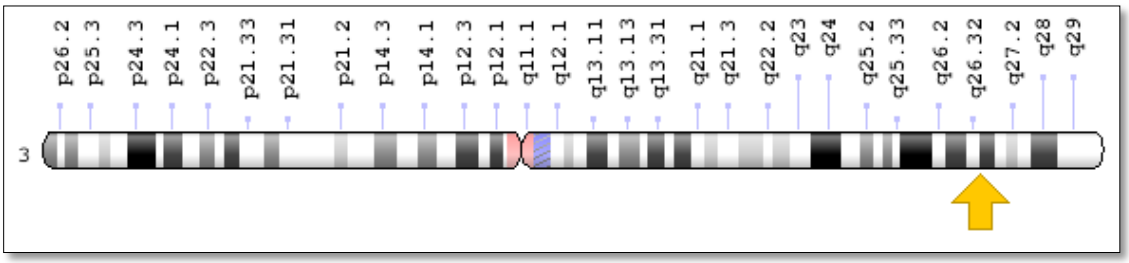

Figure 6. Schematic view of chromosome number 3 in which the PIK3CA gene is located in the long arm of this chromosome, as 3q26.32.

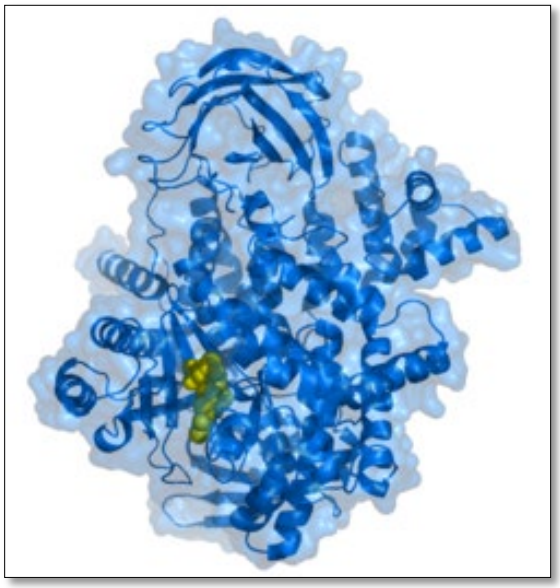

Figure 7. Schematic of the packet protein structure p110α.

The mutation in the PIK3CA gene, which causes MCAP syndrome, changes the protein p110α. The subunit of the modified PIK3 enzyme works unusually, which allows cells to grow and divide continuously. Increasing cell proliferation leads to excessive growth of the brain, blood vessels and other organs and tissues characteristic of the MCAP syndrome [8] **(Figure 8)**.

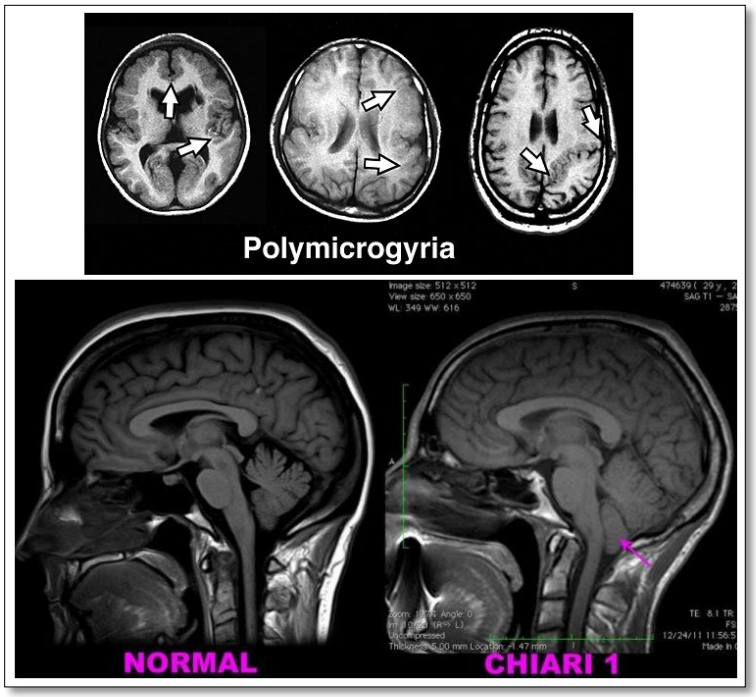

Figure 8. Radiographic images of cerebral malformations of polymicrogyria and chiari versus normal brain.

MCAP is one of the overgrowth syndromes, including the Clipple-Ternon syndrome caused by the mutation in the PIK3CA gene. These conditions are known as the PIK3CA (PROS) over growth spectrum [9].

The MCAP syndrome does not follow any inherit patterns and is caused by new mutations without family history [9] **(Figure 9)**.

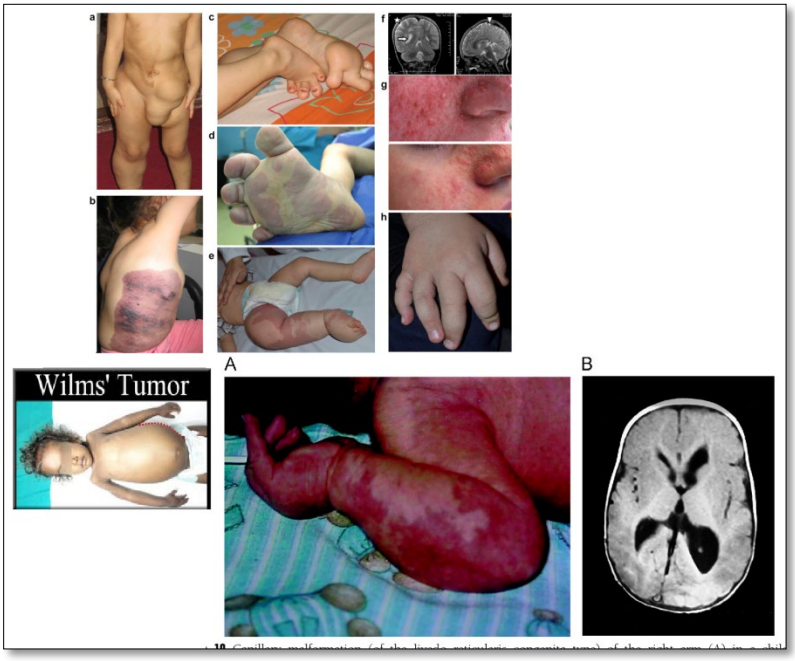

Figure 9. An overview of related disorders in the MCAP syndrome.

FREQUENCY OF MEGALENCEPHALY-CAPILLARY MALFORMATION SYNDROME (MCAP)

MCAP syndrome is a genetic disorder whose frequency is not known in the world. At least 150 cases of this syndrome have been reported in medical literature from around the world. Some patients may go unrecognized or misdiagnosed making it difficult to determine the true frequency of MCAP in the general population. Males and females appear to be affected in equal numbers [10].

DIAGNOSIS OF MEGALENCEPHALY-CAPILLARY MALFORMATION SYNDROME (MCAP)

MCAP syndrome is diagnosed based on the clinical and physical findings of the patients and some pathological tests. The most accurate method for detecting this syndrome is the molecular genetic test for the PIK3CA gene to investigate the presence of possible mutations. Brain Imaging techniques such as magnetic resonance imaging (MRI) is recommended for all children with megalencephaly overall and features of MCAP syndrome specifically. Furthermore, given the potential complications in MCAP (hydrocephalus and cerebellar tonsillar herniation), frequent MRI monitoring is recommended. While no standard recommendations exist regarding the frequency of imaging, an MRI scan every 6 month until 2-3 years of age may be reasonable. More frequent imaging maybe recommended if there are concerning signs or symptoms (such as very rapidly enlarging head size, rapidly progressive hydrocephalus and/or cerebellar tonsillar ectopia) [10] **(Figure 10)**.

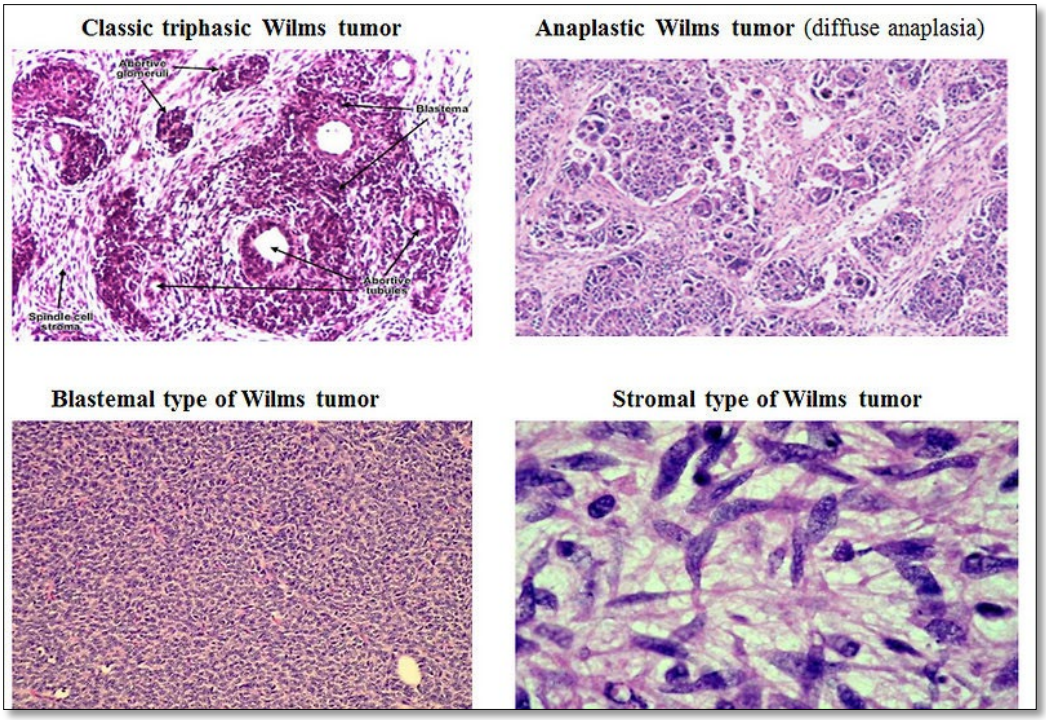

Figure 10. Microscopic images of kidney tissue cells with wilms tumor.

TREATMENT ROUTES FOR MEGALENCEPHALY-CAPILLARY MALFORMATION SYNDROME (MCAP)

The MCAP syndrome treatment and management strategy is symptomatic and supportive. Treatment may be done by a team of experts, including a neurologist, orthopedic specialist, dermatologist, cosmetologist, surgeon and other healthcare professionals. Treatment will vary depending upon many factors including the presence and severity of specific abnormalities; an individual's age and general health; and/or other elements. Decisions concerning the use of particular interventions should be made by physicians and other members of the health care team in careful consultation with the patient, based upon the specifics of his or her case; a thorough discussion of the potential benefits and risks; patient preference; and other appropriate factors. The vascular anomalies associated with MCAP, especially if few or small, may fade or disappear without treatment (i.e., undergo spontaneous remission) within the first few years of life. Some patients have undergone laser ablation therapy for lesions depending on their size, location and extent. The appropriate management of these vascular anomalies should therefore be discussed with child's caring physicians. There is no definite treatment for this syndrome and all clinical measures are needed to reduce the suffering of the sufferers. Genetic counseling is also important for all parents who want a healthy baby [11].

DISCUSSION AND CONCLUSION

Megalencephaly-capillary malformation syndrome (MCAP), formerly known as macrocephaly-capillary malformation, is a rare, complex disorder involving the skin, connective tissue, brain and other organs that are usually present at birth. The symptoms and severity of MCAP vary greatly from one person to another. Some individuals may develop milder symptoms, while others have more serious complications and it is important to note that affected individuals may not have all of the symptoms discussed below. Families of affected children should talk to their physician and medical team about their specific features, associated symptoms and discuss their medical management and overall prognosis. Most cases of MCAP are caused by mutations in the PIK3CA gene that are not inherited, but occur in the body cells as the baby develops (post-zygotic mutations). Symptoms of the following disorders can be similar to those of MCAP syndrome. Comparisons may be useful for a differential diagnosis.

Cutis marmorata telangiectatica congenita (CMTC) is a rare type of vascular malformation composed predominantly of capillary and vein-sized vessels within the skin. The skin lesions are characterized by a lace-like vascular pattern that are often pink-purple in color and may involve a limited or more widespread area of the skin surface. As a result, the skin has a purple or blue marbled or “fishnet” appearance resembling cutis marmorata. In some affected individuals, thinning of the skin (atrophy), breakdown (ulceration) or complete absence of the skin in affected areas may also be present. A diagnosis of macrocephaly-capillary malformation may be confirmed through a thorough clinical evaluation that includes a detailed history and physical examination looking for MCAP-associated features. Molecular diagnosis requires demonstration of a mosaic activating mutation in PIK3CA, which may require advanced genetic testing to be performed on affected tissues (e.g. skin fibroblasts) or samples other than blood. Different diagnostic criteria have been proposed in the medial literature. Hydrocephalus and cerebellar tonsillar ectopia warrant immediate attention and referral to a neurosurgeon. Rapidly progressive hydrocephalus may require neurosurgical shunting and experience suggests that some patients benefit from a minimally-invasive 4th ventriculostomy. The guidelines for the management of cerebellar tonsillar ectopia are less clear. However surgical management (posterior fossa decompression) should be considered on a case-by-case basis and discussed with the neurologist and neurosurgeon involved in the child’s care. Seizures, if present, should be managed by a neurologist. There is no definite treatment for this syndrome and all clinical measures are needed to reduce the suffering of the sufferers. Genetic counseling is also important for all parents who want a healthy baby [12].

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