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Café-Au-Lait Macule (CALM)

Café-au-lait macules (CALMs), also known as von Recklinghausen spots or circumscribed café-au-lait hypermelanosis, are common skin lesions characterized by well-defined, pigmented spots. These lesions are typically present at birth or during early childhood and can be indicative of both benign conditions and genetic syndromes when multiple lesions are present. CALMs are often recognized for their distinctive light to dark brown color, which resembles coffee with milk, hence the name.

Clinical Presentation

A café-au-lait macule is a flat, uniformly pigmented lesion with sharp borders. Typically, these lesions are greater than 0.5 cm in diameter and may vary in color from light brown to dark brown. They are usually well-circumscribed, with evenly distributed pigment. The size of a CALM increases as the child grows, and it stabilizes in size during adulthood. Adult CALMs usually range from 2 to 5 cm in diameter, although they can vary widely in size, ranging from less than 2 mm to more than 20 cm. CALMs are typically located on the trunk, back, and limbs, but can appear anywhere on the body except for mucous membranes, such as the mouth.

In isolation, CALMs are generally benign and do not require treatment. A single CALM is present in 10-20% of the population, and multiple CALMs may also occur without being associated with any underlying pathology. However, when multiple CALMs are present, especially when exceeding a certain number, a thorough evaluation for potential underlying genetic syndromes is recommended.

Genetic Associations

While CALMs can occur as an isolated finding, the presence of multiple macules can be associated with various genetic disorders. In particular, the number of CALMs required for suspicion of an underlying genetic condition may vary by ethnicity. For instance, the presence of more than three CALMs in a Caucasian child or more than five CALMs in an African American child warrants further investigation for genetic syndromes. The following genetic diseases have been linked to multiple CALMs:

- ***Neurofibromatosis Type 1 (NF1)***: This is the most common condition associated with multiple CALMs. NF1 is a neurocutaneous disorder caused by mutations in the NF1 gene, which encodes the neurofibromin protein. Patients with NF1 may present with a variety of additional findings, including neurofibromas, optic gliomas, and learning disabilities.
- ***Legius Syndrome***: Caused by mutations in the SPRED1 gene, Legius syndrome presents with multiple CALMs, but without the neurofibromas or other major features of NF1. Patients may also experience learning difficulties and mild intellectual disability.

- ***McCune-Albright Syndrome***: This syndrome is a genetic disorder resulting from mutations in the GNAS gene. It is characterized by the presence of multiple CALMs, polyostotic fibrous dysplasia, and endocrine abnormalities such as precocious puberty.
- ***Noonan Syndrome with Multiple Lentigines (LEOPARD Syndrome)***: LEOPARD syndrome is a rare genetic disorder caused by mutations in the PTPN11 gene. In addition to multiple CALMs, it can present with lentigines, facial dysmorphisms, cardiac malformations, and other systemic features.
- ***Watson Syndrome***: Characterized by multiple CALMs, this rare syndrome is caused by mutations in the BRCA1 gene and often involves other features such as developmental delay, learning difficulties, and the development of tumors.
- ***Bloom Syndrome***: This is a rare genetic disorder that causes a high predisposition to cancer, immunodeficiency, and growth delays. Multiple CALMs are often present from early childhood.
- ***Silver-Russell Syndrome***: This growth disorder is characterized by a small birth size and failure to thrive, and may be associated with multiple CALMs in some cases.

Given these associations, genetic counseling and genetic testing may be recommended for individuals with multiple CALMs, especially when additional clinical features suggest a genetic syndrome.

Diagnosis and Workup

The diagnosis of CALMs is primarily clinical, based on the characteristic appearance of the macules. The presence of multiple macules, particularly when they exceed the threshold number for the patient's ethnicity, should prompt further investigation for associated genetic disorders. Genetic testing and family history review are crucial in diagnosing potential underlying conditions. For example, molecular genetic testing for mutations in the NF1 gene can confirm a diagnosis of neurofibromatosis type 1. Imaging studies, such as MRI or CT scans, may be necessary if other features of a syndrome (e.g., neurofibromas, optic gliomas) are present.

Treatment and Management

In most cases, café-au-lait macules do not require treatment, as they are benign and do not pose a risk of malignancy. CALMs are permanent lesions, and there are no widely recommended interventions for their removal. Topical treatments such as hydroquinone, which is used for hyperpigmentation in other contexts, have not been proven effective for CALMs. Similarly, laser treatments have variable outcomes and generally require multiple sessions for minimal improvement. Laser therapy may help lighten the lesions but is not a cure and does not guarantee complete resolution.

For individuals with multiple CALMs who are diagnosed with a genetic syndrome, management typically focuses on addressing the associated systemic features rather than the skin lesions themselves. For example, in NF1, regular monitoring for the development of neurofibromas, optic gliomas, and other complications is essential.

Conclusion

Café-au-lait macules are common skin lesions that are often benign, especially when they occur in isolation. However, the presence of multiple CALMs can be indicative of various genetic syndromes, and their detection should prompt further investigation. Genetic disorders such as neurofibromatosis, McCune-Albright syndrome, and LEOPARD syndrome are commonly associated with multiple CALMs, and a thorough clinical evaluation is warranted in such cases. While treatment for CALMs is generally not necessary, management should focus on the underlying condition when applicable.

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