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Congenital melanocytic nevi – a literature review

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Abstract

Introduction: Congenital melanocytic nevi (CMN) are small, congenital pigmented moles on the skin that may appear after or shortly after the birth of a child (up to 12–24 months of age). CMN usually increases proportionately with the baby's physical development and occupies the same area of skin as at birth. The incidence of CMN among newborns is relatively low and ranges from 0.2% to 6%.

Purpose of work: To collect information on the congenital melanocytic nevi.

Summary: The initial step in caring for a patient with CMN involves obtaining a history and conducting a physical examination. We are able to examine the CMN using dermatoscopy, confocal microscopy, and histopathological examination. Melanoma is not common in people with CMN, but it can develop, so it is worth maintaining oncological vigilance and checking them regularly. In our literature review, we reviewed the clinical presentation of CMN and the dermatoscopic image, as well as the light microscopic and confocal microscopic picture of congenital melanocytic nevi.

Key-words: pigmented nevi, melanoma, dermoscopy, confocal microscopy

Introduction

Congenital melanocytic nevi (CMN) are melanocytic nevi that appear on the skin at the birth of a child or appear shortly afterward (up to 12–24 months of age) (1, 2). CMN, that arise later are called "late" nevi (tardive CMN). CMNs are a relatively uncommon occurrence among newborns, ranging in frequency from 0.2% to 6%. Birthmarks appear with an estimated incidence of 0.0005% (3). CMN is caused by mutations in the cellular DNA that usually appear within the first 12 weeks of pregnancy (4). The most common cause is a mutation in the NRAS gene, accounting for over 70% of the moles (5). It is estimated that mutations in the BRAF gene are the second most common cause of CMN. The NRAS gene encodes the NRAS protein for being active after binding to guanosine triphosphate (GTP) and in the inactive state bound to guanosine diphosphate (GDP). The BRAF gene encodes a protein called serine/threonine-specific protein kinase. Both are proto-oncogenes and form the Ras-Raf-MEK-ERK kinase

pathway, which transduces a signal from a receptor on the cell surface to the cell nucleus (6-10).

Clinical Presentation

Congenital pigmented moles almost always increase proportionally to the child's body growth, occupying the same area of skin as at birth. Congenital moles can be classified according to their adult size or projected adult size as small - less than 1.5 cm in diameter (projected adult size), medium (M) are divided into two groups - M1 (1.5 to 10 cm) and M2 (>10 to 20 cm), large (L) - L1 (>20 to 30 cm) and L2 (>30 to 40 cm). Finally, giant (G) are classified as G1 (>40 to 60 cm) and G2 (>60 cm) (Table 1.). This classification also assesses the number of satellite moles (S1: <20, S2: >20-50, S3: >50) (1, 11-14) (Table 2.).

Groups of congenital nevi	**Size of congenital nevi (adult size or projected adult size)**
Small (S)	Less than 1.5 cm in diameter
Medium (M)	M1 (1.5 to 10 cm)
	M2 (>10 to 20 cm)
Large (L)	L1 (>20 to 30 cm)
	L2 (>30 to 40 cm)
Giant (G)	G1 (>40 to 60 cm)
	G2 (>60 cm)

Table 1. Clasification of congenital nevi according to their adult size or projected adult size.

Groups of congenital nevi according the number of satellite nevi	**The number of satellite nevi**
S1	<20
S2	>20-50
S3	>50

Table 2. Clasification of congenital nevi according to the number of satellite moles.

Additionally, it is important to estimate the number of birthmarks in the child. CMN are most commonly found on the trunk, limbs, and scalp. At birth, CMN typically exhibits a dark purple or red hue. Nonetheless, usually, CMN exhibits various shades of brown or multiple shades within a single mole. The hair typically develops from the CMN in a shade darker than the color of the hair on your head. Occasionally, they are completely hairless (11).
Small pigmented moles may be virtually indistinguishable from ordinary acquired moles, and medical documentation is the sole means to verify the congenital origin of birthmarks. The CMN of small and medium size are well-circumscribed, round, oblong, or oval. CMN may be flat (spotty), raised (lumpy), papillary, or rarely with a structure resembling the folding of hemispheres cerebriform (15).

Larger, numerous, or changing nevi may require dermatological visits every three months for the first year of life and then annually thereafter. The frequency of monitoring depends on individual factors related to nevus appearance (7). In case of pain, ulceration, bleeding, and growth, a diagnostic biopsy should be considered (16).

Melanoma malignant (MM) remains one of the two most devastating complications, next to the neurologic involvement. MM is currently estimated to occur in approximately 1% of all patients with CMN (17) and 2% of patients with large CMN (18). It is difficult to determine the potential risk of developing melanoma related to CMN. The risk is related to the size of the CMN. The larger the mole, the greater the risk. A person with a large mole is approximately 5-10% more

likely to develop melanoma during their lifetime (19). The peak of the disease occurs between the ages of 20 and 60. Melanoma frequently arises on the peripheral margin of an existing cutaneous mammary node and is of intraepidermal origin. It has a distinctive appearance from the surrounding normal moles. In the skin, division figures are formed by groups of melanocytes that exhibit marked nuclear pleomorphism and increased cellularity. Melanoma cells may be epithelioid, spindle-shaped, or small but tall nuclear/cytoplasmic ratio. It is difficult to assess such an altered CMN, and it is not always possible to make a final diagnosis of malignancy (20, 21). Removal of CMN theoretically reduces the risk by eliminating nevus cells that could undergo malignant transformation. However, the theoretical reduction has not been confirmed in the literature, and there are reports of melanoma occurring in patients with CMN who undergo a procedure that is extensive (22-25).

A related disease with a high incidence of CMN on the skin is neurocutaneous melanosis. It manifests itself in a diffuse manner, proliferation of melanocytes in the skin and pia mater. The syndrome is most likely caused by a disorder in the morphogenesis of embryonic neuroectoemra. In over 60% of people with neurocutaneous melanosis, large, congenital melanocytic nevi, and in the remaining CMN they are numerous but small. Additionally, there are symptoms neurological, hydrocephalus, due to disturbances in the circulation of cerebrospinal fluid or the presence of tumors cancerous. Patients usually die within 3 years of the onset of neurological symptoms (1).

Dermatoscopy image

On dermatoscopic examination, the features of CMN are varied. CMN may have the following patterns: reticulated, spherical, homogeneous, paving stones, or a combination of the previously mentioned patterns. Visible by dermatoscopy dysplastic changes may have features of CMN nevi, so it is important to obtain information about the time of occurrence of lesions. There may be significant variability in pigmentation and structure in large-diameter CMN, and melanoma may develop in the deep component of the mole (1, 26).

Features of concern include an outgrowth of the mole located peripherally to the main part of the CMN or in a vertical position as a palpable lump. CMN border not clearly defined, merging

with surrounding skin. A focus of hypo- or hyperpigmentation that deviates from the overall uniform color of the rest birthmark (1, 27).

Light microscopy findings

When assessed microscopically, CMN can also be classified according to the location of the hyperplasia melanocytic: junctional, compound, or intradermal. The main features of histopathological findings of congenital pigmented nevi include symmetrical proliferation of melanocytes with a V-shaped or plate-like growth into the dermis. Well-circumscribed, regularly spaced, and relatively monomorphic nests of melanocytes. The mole cells may extend into the reticular part of the dermis or subcutaneous tissue. Melanocytes mature properly and have a normal course around the skin appendages, blood vessels, and nerves. Collagen bundles arranged in single rows or cords are also visible (27).

The histological characteristics of the nevus are primarily related to the size of the CMN. Small CMN commonly show junctional melanocytic hyperplasia. Many small CMNs extend to a depth of no more than the upper half of the dermis. In a compound nevus, melanocytes are located in the dermis, and they tend to come together in nests. Melanocytes are larger in the superficial part and show maturation from the deep to the superficial part of the middle CMN. The deeper the layer of the mole, the less crowding melanocytes and more collagen strands. Occasional mitotic figures are visible in the more superficial part of complex, congenital-pigmented nevus. As the diameter of the CMN increases, the mole's melanocytes occupy more and more space in the deeper layer of the dermis. In large CMN, melanocyte proliferation is diffusely reticular part of the dermis to the subcutaneous tissue. Sometimes they can infiltrate fatty tissue, but more often they stretch along the fibrous partitions of adipose tissue. Clusters of large CMN melanocytes tend to form around the sebaceous and sweat glands, nerves, blood vessels, and hair muscles. Large CMN can contain spindle-shaped cells or neuronally differentiated cells with a wavy arrangement, resembling the histological picture of neurofibroma (28).

Confocal microscopy

Confocal microscopy is a type of light microscopy with improved resolution and contrast obtained images. This imaging technique also allows for the reconstruction of virtual, three-dimensional images. The most frequently used method in dermatological tests for in vitro or ex vivo tests seems to be lasered, fluorescence confocal microscopy. The illumination of objects with their own light when it falls on them in external radiation is divided into two categories. When the glow occurs over a short period of time (approx 10^−8 – 10^−4 s) we talk about fluorescence, while when this time is longer, we talk about phosphorescence. Light is delivered by a laser in the microscope at a wavelength that excites a specific fluorochrome. Both laser light (and the resultant fluorescence emission pass through a beam splitter, usually it is a dichroic mirror that transmits fluorescence light from the tested material and reflects laser light, which separates these two beams of light. The fluorescence light then passes through a confocal diaphragm, which acts of a function as a spatial filter and only allows light coming from the lens's focal plane to pass through (elimination of light with worse optical parameters). By changing the plane of focus of the preparation, it is created in optical sections (29).

Confocal laser microscopy is therefore an innovative, non-invasive imaging tool. It enables in vivo assessment of skin lesions with almost histological resolution. This technique represents a promising non-invasive method tool for screening skin lesions. In the pediatric patient population, it may be particularly relevant in terms of minimizing the risk of unnecessary biopsy (30).

Odorici et. al. revealed that reflectance confocal microscopy (RCM) features closely correspond with histological counterparts of CMN and can be used as an assisting diagnostic tool to monitor age-related changes in the nevus (31). The image of CMN in RCM varies depending on the depth of the lesion's location in the dermis. A typical honeycomb pattern of dermatoglyphs might be observed in CMN in the spinous-granular layer of the epidermis. In the basal layer of the epidermis, it is possible to find basal keratinocytes pigmentation with hyperrefractile bright dots. CMN at the level of the dermal-epidermal junction shows a varied image on confocal microscopy. Imaging of small-sized CMN is characterized by an annular pattern, which is a dark papilla outlined by light-pigmented epidermal basal cells. A meshwork pattern is also described. A meshwork pattern is a distinctive mesh characterized by small dark holes

surrounded by markedly thickened inter-papillary spaces. RCM image of a medium-sized CMN at the level of dermo-epidermal junction showing a clod pattern, which shows numerous densely packed, well-demarcated refractile clusters of melanocytes, usually within dermal papillae. A multicomponent clod and meshwork pattern is also possible. In CMN localized in the stratum granulosum, corneal cysts are described, which are large, highly refractive intraepidermal structures that correlate with milia-like cysts in dermatoscopy (32). Importantly, the pagetoid spread of melanocytes with chaotic growth patterns, as well as atypical single cells in nests and dendritic processes of large melanocytic cells may indicate the diagnosis of melanoma arising on the CMN (33).

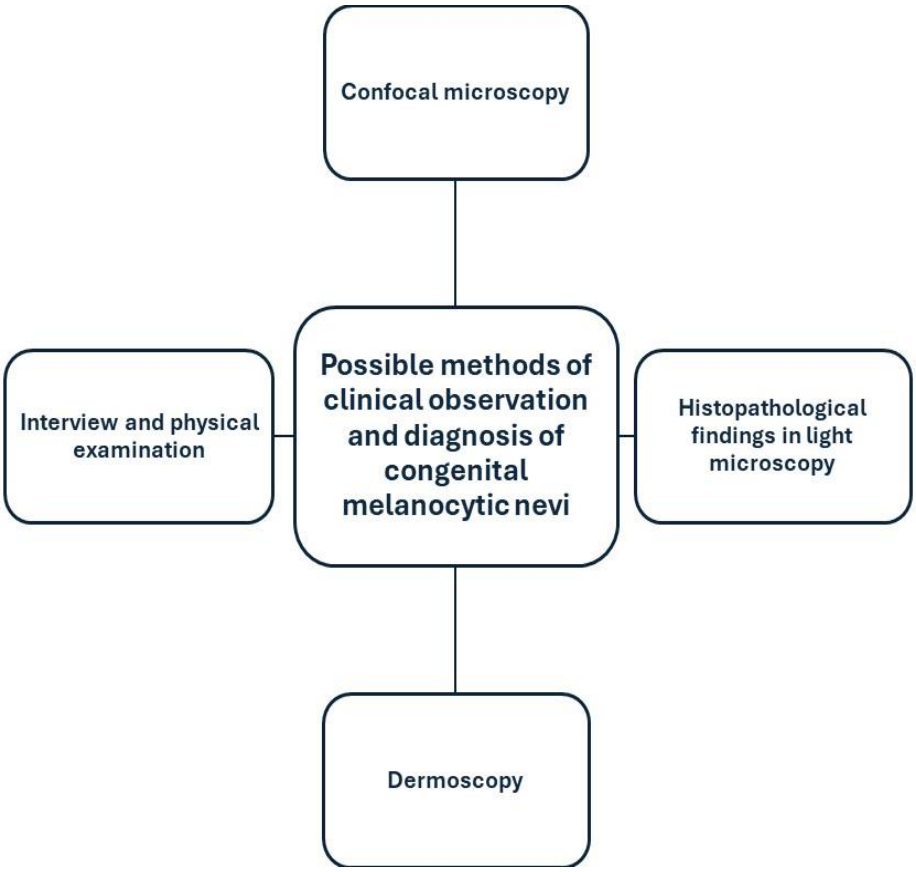

Figure 1. Possible methods of clinical observation and diagnosis of congenital melanocytic nevi.

Conclusions

Despite the rarity of CMN, their recognition and the ability to accurately diagnose them are crucial for both parents and children. By utilizing a precise diagnosis, we can establish the appropriate strategy for managing CMN. By acquiring knowledge about the characteristics that arouse concern regarding the appearance of congenital moles, we can respond earlier in the event of a potential cancer development threat. It is also important to consider CMNs connection to melanocytotic neurofibrosis.

DISCLOSURE

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Conceptualization: Izabela Staniszewska, Milena Baran
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