Addressing Frequently Asked Questions and Dispelling Myths About Melanocytic Nevi in Children

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KEYWORDS

• Congenital melanocytic nevus • Acquired melanocytic nevus • Melanoma • Sunscreen • Sun protection • Children

KEY POINTS

- The risk of malignancy of an isolated CMN is very low regardless of its size and location.
- The number of acquired congenital melanocytic nevus increases with age and is higher in children with lower phototypes and intense sun exposure.
- MN may clear in color and acquire volume with age, but this morphological change does not indicate malignant transformation.
- Information such as family history of melanoma or personal history of repeated sunburns can help identify which patients are at increased risk for melanoma.
- Sunscreens must be applied to the entire skin surface exposed to the sun and not only and specifically to melanocytic nevus.

INTRODUCTION

Melanocytic nevi (MN) are congenital (CMN) or acquired (AMN) benign melanocytic neoplasms. CMN are present from birth, although depending on their size and color, they may not become clinically evident until the first months of life. The incidence of CMN is estimated between 0.2% and 2.1% of newborns.[1,2] Classically, they have been divided according to the size of their diameter into small (<1.5 cm), medium (1.5–20 cm), and large (>20 cm).[3] In 2004, the giant CMN category was added to designate nevi with a diameter exceeding 40 cm.[4] CMN can present as single or multiple lesions. In the latter, there may be a larger nevus accompanied by other smaller ones (satellite CMN) or multiple lesions of similar size (multiple CMN).

AMN develop throughout time, predominantly during the first two decades of life.[5] The most common AMN are small, pigmented lesions (1–5 mm), homogeneous in color, with well-defined and regular borders. In some cases, color may be heterogeneous, but symmetry is present, and there are no additional clinical or dermoscopic concerning signs. Depending on their clinical and histologic appearance, specific subtypes are distinguished, among which are Spitz nevus and Reed nevus, typically presenting in children. Spitz nevus prevalence varies between 1.4 and 7 cases per 100,000 inhabitants, and it is characteristically a nonpigmented AMN with a reddish hue (**Fig. 1**).[6] From a histologic point of view, it is distinguished by the presence of theca of melanocytic cells of epithelioid or spindle morphology. The pigmented variant is called Reed nevus and is defined by dark-brown pigmentation and a dermoscopic starburst pattern (**Figs. 2** and **3**).[7] Another subtype of AMN is called atypical or dysplastic nevus, which, despite its benign biologic behavior, presents an alarming appearance because of its heterogeneous tone, size, and irregularity of its edges.[8] In

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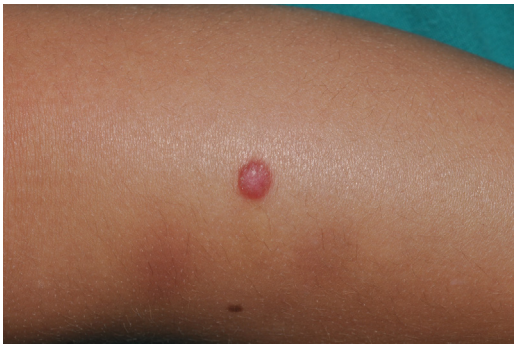

Fig. 1. Spitz nevus. Red dome-shaped papule on the lower limb of a 3-year-old boy.

general, dysplastic nevi are rare in childhood except in the context of dysplastic nevus syndrome, defined by the existence of a history of melanoma in one or more first- or second-degree relatives, the presence of 50 or more MN with the aforementioned "atypical" clinical appearance, and their distinctive histologic characteristics. Despite their low frequency, patients with atypical or dysplastic nevi compose a particular subgroup to consider because of their increased likelihood of developing melanoma.[9]

The reason for the appearance of MN is not precisely known. Molecular studies indicate that CMN appear as a result of somatic mutations in *NRAS* and *BRAF* genes,[10,11] whereas AMN would be mainly conditioned by mutations in *BRAF*.[12–14] Despite CMN having a similar mutational profile as melanoma,[15–17] only a tiny proportion of nevi ultimately give rise to melanoma. It is estimated that any single nevus's annual transformation rate ranges from approximately 1 in 200,000 in individuals younger than 40 years of age to approximately 1 in 33,000 if they are older than 60 years.[18]

MN appear mainly in childhood and are a cause for concern in parents and caregivers, because of the aesthetic consequences and the risk of malignant transformation, and other uncertainties based

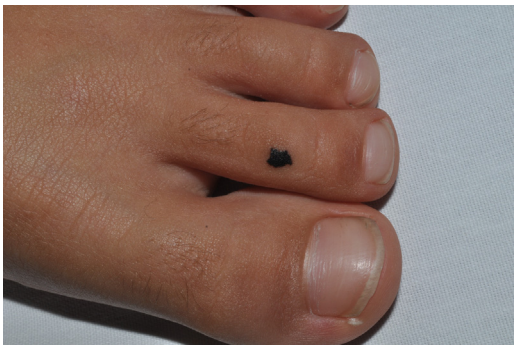

Fig. 2. Reed nevus. Hyperpigmented irregularly bordered lesion on dorsum of toe.

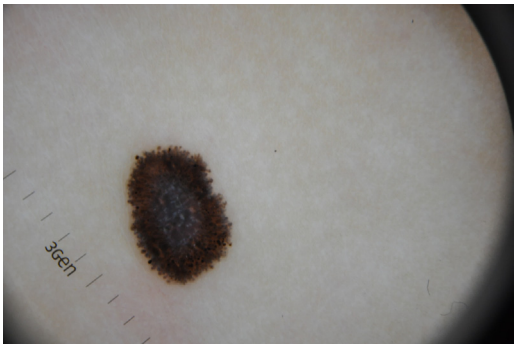

Fig. 3. Reed nevus. Dermoscopy of Reed nevus showing the classical starburst pattern.

more on beliefs than on proper scientific evidence. In this review, we answer the most frequently asked questions posed by parents and caregivers, basing our responses on scientific evidence.

DO CONGENITAL MELANOCYTIC NEVI HAVE A HIGH RISK OF MALIGNANT TRANSFORMATION?

Although classically it has been considered that CMN had a high risk of malignant transformation, this view has largely changed over the years. In the 1970s and 1980s, it was considered that the risk of developing melanoma within a CMN was about 20%, but estimates were imprecise because of small study sizes and selection bias, which overestimated the risk.[19–21] However, subsequent series that included a more significant number of patients observed a markedly lower risk. A systematic review published in 2006 with data from 6571 patients[19] determined that the incidence varied widely depending on the sample size, ranging between 0.05% in the largest sample of 3922 cases,[1] and 10.7% in a sample of 56 cases.[20] According to this systematic review, the overall incidence of melanoma is much higher in large or giant CMN, whereas melanoma seems to be exceptional in small CMN.[19] More recently, a prospective study conducted in the United Kingdom with a cohort of 448 patients observed an overall incidence of 2.2%.[22] These authors found that the 10 patients in the study who developed melanoma had more than one CMN, whereas no patient with a single CMN, regardless of size and location, presented this outcome. However, 7 of the 10 patients who developed melanoma had a giant CMN as one of the lesions. Hence, if we exclusively consider this group of patients, melanoma incidence rises to 8%. Likewise, although there is extensive literature highlighting an elevated risk of malignant transformation of large lesions located on the central area of the

back,[19,23,24] the authors found that the factor with the highest statistical power for predicting melanoma in the context of a CMN was not the size or location of the lesion, but rather the detection of a concomitant morphologic alteration in the central nervous system (CNS).[22] In turn, the latter is more likely in newborns with two or more CMN regardless of their size and location. Consequently, these authors recommend a screening MRI study of the CNS for all newborns with more than one CMN, especially if one of them is giant.[22]

The risk of malignancy of an isolated CMN is very low no matter the size or location. If the newborn has multiple CMN, and, in particular, if one of them is larger than the rest, close dermatologic and neurologic follow-up is recommended. Performing an MRI of the CNS within the first 6 months of life must be considered.

WHY DOES MY CHILD HAVE MORE AND MORE MOLES?

Patients may acquire an increasing number of MN throughout childhood, and in some patients this increase is particularly striking (**Fig. 4**). The prevalence of AMN is related to various factors including age, sex, phototype, and intensity of sunlight exposure. Concerning age, few nevi are present in early childhood, but their number increases with time, especially from 12 years of age on, reaching a peak in the third decade of life.[25,26] The difference in prevalence by sex is controversial,[27,28] but it seems the number of AMN is higher in adolescent men than in women after menarche.[29] As for skin type, individuals with a lower phototype (red hair, blue eyes, easy sunburning) tend to have a higher number of MN than individuals of darker skin phototype.[26,29]

Regarding sun exposure, it seems that the intensity of sun exposure is proportional to the number of AMN,[30,31] whether it is intermittent or continuous.[32] The beneficial effect of sunscreens during childhood in reducing the appearance of MN is controversial. A meta-analysis of the literature published in 2013 found no evidence that the use of sunscreens in childhood prevented the appearance of MN,[33] but another more recent study observed this beneficial effect if the sun protection factor (SPF) is higher than 30.[29] On the contrary, the use of sunscreens with an SPF less than 30 is related to a tendency to develop a vaster number of nevi, probably caused by the combination of insufficient protection and a false sense of security.[29]

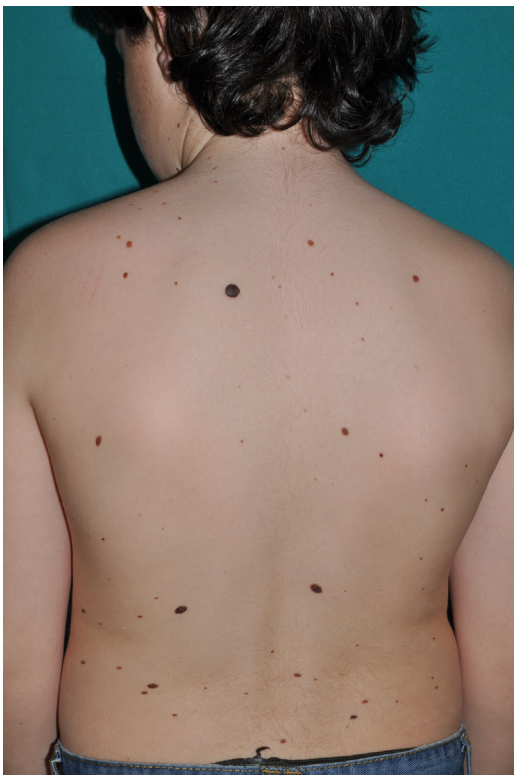

Fig. 4. Acquired melanocytic nevus. Twelve-year-old boy showing numerous acquired melanocytic nevi on the back. Note the different size, morphology, and color.

An increasing number of AMN can develop throughout childhood, especially in children with fair skin/lower phototypes and frequent or intense sun exposure.

WHAT ARE THE WARNING SIGNS THAT A MOLE IS BECOMING MALIGNANT?

The incidence of melanoma in children is much lower than in adults, and exceedingly rare in children younger than 10 years of age, so melanoma is not usually included among the main differential diagnoses in younger children. Complicating matters more, the clinical warning signs are also different, making it challenging to identify. Thus, the classic warning signs included in the acronym "ABCDE" (asymmetry, border irregularity, color variation, diameter $\geq$6 mm, evolution) may be absent in up to 60% of preadolescents and 40% of adolescents. In addition, because 76% of melanoma in children are amelanotic (nonpigmented) and develop as red or pink lesions, "modified ABCD" criteria have been proposed: *A* for amelanotic (red or pink lesion, and therefore not necessarily dark); *B* for "bleeding, bump" (ulceration

and bulging are indicative clinical data); *C* for color uniformity (and not heterogeneous, as classically occurs in adult melanoma); and *D* for "de novo, any diameter" (without preceding lesion, of any size) (**Table 1**).[34] Another additional criterion for melanoma suspicion is the acronym EFR (elevated, firm, and growing), regarding the appearance of an elevated, firm, and growing lesion persisting for more than 1 month. The EFR rule helps exclude inflammatory lesions, such as insect bites or folliculitis, common in the pediatric population, that are usually stable and tend to resolve in less than 1 month. Unlike in adult melanoma, the lesion diameter (D of the ABCDE rule) is not a valid discrimination factor for pediatric melanoma, so the D of the modified ABCD rule for children includes lesions of any diameter.[34] Some series observed that about 50% of pediatric deaths caused by melanoma had lesions of 5 mm or less in diameter,[34–36] so the size of lesions in children does not serve to discriminate between benign and malignant neoplasms. Finally, interpreting evolution, or the E of the classic rule, is challenging in children because morphologic changes of MN throughout childhood are frequent and lack prognostic significance (**Fig. 5**).

Despite the extremely low incidence of melanoma in children, it must be kept in mind that specific subgroups of pediatric patients are at a higher risk, such as fair-skinned, blue-eyed, red-haired individuals; children with poor tanning ability and prone to sunburn; or those with a genetic predisposition (familial melanoma, xeroderma pigmentosum, or immunodeficiencies).[37]

Table 1
Conventional ABCDE melanoma detection criteria and additional ABCD criteria for children

Conventional Criteria	Additional Criteria for Children
A **A**symmetry	**A**melanotic
B **B**order irregularity	**B**leeding, **B**ump
C **C**olor variation	**C**olor uniformity
D **D**iameter ≥6 mm	**D**e novo, any **D**iameter
E **E**volution	EFG[a] rule

[a] Elevated, firm, and growing.

The classical "ABCDE" criteria are not sensitive enough in children and must be accompanied by additional clinical data adapted to the pediatric age (modified ABCD criteria). Melanomas in children younger than 10 years of age usually manifest as elevated, firm, and growing red bumps, whereas clinical signs of malignant transformation in adolescents are more likely to adapt to classical ABCDE rules. Simple information, such as a family history of melanoma or personal history of repeated sunburns, can help identify which patients are at increased risk for melanoma.

IS IT NECESSARY THAT A DERMATOLOGIST REVIEW ALL MELANOCYTIC NEVI IN CHILDREN (CONGENITAL AND ACQUIRED)?

Although it is difficult to calculate because of the high prevalence of MN in a healthy population, the estimated risk of MN becoming malignant is low, ranging from 0.0005% (or <1 in 200,000) before the age of 40 years, to 0.003% (1 in 33,000).[18] In addition, melanoma arises as a de novo lesion in 70% of cases,[38,39] so it does not seem necessary to refer all patients with benign-looking MN to specialized care.

Despite this, and although the risk of melanoma within MN in the general pediatric population is low, we should not exclude beforehand such diagnostic possibility. Therefore, the previously mentioned groups at high risk of developing melanoma (ie, family history of melanoma, repeated sunburns, or immunodeficiency), any clinically suspicious lesion (according to ABCDE rules in different ages), or even one with an apparently benign morphology but that raises personal concerns about its biologic behavior, should be referred to a dermatologist.

Likewise, MN with potential relevant aesthetic impact may need a referral for a multidisciplinary approach. In particular, the deterioration in patients' quality of life because of facial skin lesions has been well studied.[40,41] Keep in mind that a significant portion of CMN undergo marked lightning throughout childhood,[42] and a "wait and see" approach may be reasonable. Nor should it be forgotten that surgical interventions, especially when the benefit is not entirely clear, can entail considerable emotional stress for the patient and parents and caregivers, and pose a risk associated with repeated surgical interventions under general anesthesia.[43,44] However, it is essential to assess each case individually, paying attention to the patients' and their parents' and caregivers' expectations, because hopes frequently do not correspond with reality, and the scar may not be as satisfactory as expected or may even be unaesthetic.[45] Along with other authors,[46] we recommend addressing surgically those facial nevi in which a potential disfiguring surgical sequelae is less than the original lesion.

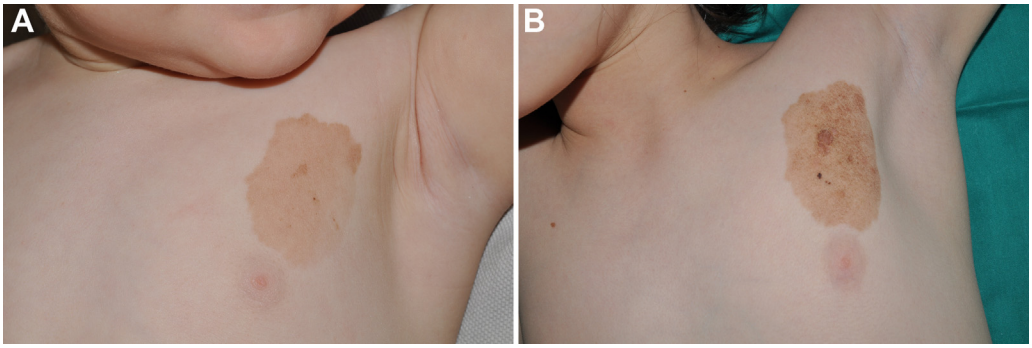

Fig. 5. Congenital melanocytic nevus. Changing appearance with time of a congenital melanocytic nevus of small-to-medium size on the trunk when the patient was 9 months old (*A*) and 10 years old (*B*).

Children with benign-looking MN do not require routine referral to the dermatologist unless the patient is at risk of developing melanoma for any reason; has atypical-appearing, rapidly evolving, or symptomatic nevi; or has a nevus requiring a multidisciplinary approach because of its aesthetic impact.

ARE MELANOCYTIC NEVI ON THE PALMS AND SOLES MORE DANGEROUS THAN THOSE IN OTHER LOCATIONS?

There is a widely held belief that MN in palms and soles have a higher risk of malignant transformation than those in other parts of the body, but current evidence does not support this. Acral melanomas are the least common type in the United States, representing 2% to 3% of all melanomas.[47] Acral melanomas are the most prevalent group in Japan, where they account for 47% of all melanomas.[48] Although in the White population the risk of suffering a melanoma is directly proportional to the total number of AMN, the number of AMN present in Japanese individuals' soles does not seem to be a risk factor for suffering acral melanoma.[49] Hence, in a study of 104 Japanese patients with acral melanoma, not only did less than 11% of patients have a previous MN at that location, but the number of acral MN was not higher in people with acral melanoma than the rest of the population.[50] Another study compared the topographic distribution of acral MN with melanomas at this location, finding a different distribution of the locations of MN and acral melanomas.[48] Acral melanomas in the Japanese population appear de novo, without preceding MN, in almost 90% of cases and arise in a different location from where acral MN usually appear.[48] In addition, the mutational profile of palmar and plantar MN is similar to MN located elsewhere on the body,[48,50] whereas the mutations of acral melanomas are different from those of acral nevi, ruling out a potential association.[51,52]

There is no current evidence to support the belief that acral MN have a more aggressive biologic behavior than MN in other locations, so their diagnosis, management, and monitoring should be similar to that of lesions in other locations.

HOW OFTEN SHOULD MELANOCYTIC NEVI BE CHECKED?

Patients with increased risk of melanoma should be reviewed periodically, along with clinical and dermoscopic follow-up of doubtful lesions, but it is uncertain what approach to take for children with CMN and AMN in the absence of warning signs. Many experts recommend an annual check-up of MN, whereas others suggest that patients request a follow-up visit only if they observe morphologic changes or discomfort in any of the lesions. Nevertheless, there is no scientific evidence to support the former, nor does self-examination seem reliable enough.[53] Traditionally, the classic ABCDE rule has been emphasized to teach how to detect worrisome MN,[54] but these warning signs may have limited utility in the pediatric age.[34] In our practice, we do not routinely review CMN or AMN when their clinical and dermoscopic characteristics are banal, but we recommend a follow-up visit in the event of any morphologic change or new-onset symptoms.

There is no well-defined universal strategy with sufficient evidence to make recommendations on the specific need to review MN with benign characteristics in children with no risk factors for melanoma or on the ideal timing of such reviews.

IS IT BETTER TO BE "SAFE THAN SORRY"? (IS IT ADVISABLE TO REMOVE AS MANY NEVI AS POSSIBLE AS SOON AS POSSIBLE?)

There is strong evidence that the number of AMN is a significant risk factor for the development of melanoma,[27,28] but the effectiveness of surgical excision as a preventive measure is more than doubtful. It is logical to think that the greater the number of melanocytes, the greater the risk of malignant transformation of these cells, and therefore, the prophylactic surgical removal of MN would, in theory, have a potential therapeutic value. However, the question is whether this attitude is cost-effective, something that has not been proved useful in young individuals so far.[55]

The risk of malignancy in solitary CMN is low, regardless of their size and location. Moreover, a substantial number of patients develop melanoma outside of CMN,[19] so theoretically, complete removal of the lesion would not eliminate the risk. Besides, there are cases where melanoma appeared where a CMN had previously been partially or entirely removed.[56] Consequently, the excision of CMN does not eliminate the risk of melanoma.[19] Regarding the theoretic possibility of malignancy of AMN, calculating the percentage of malignancy is complex because of the latter's high prevalence; however, only 30% of melanomas appear on previous AMN.[38,39] Accordingly, most of them would be de novo lesions, and prophylactic removal of AMN would not be beneficial.

> There is no scientific evidence to support prophylactic removal of either AMN or CMN, and therefore, surgery would only be advocated if there are clinical findings to advise it.

ARE NEVI THAT BULGE WORRISOME?

Often, patients come to our office expressing their desire to remove exophytic lesions on the body, mostly on their trunk or scalp. The motivations are diverse, but in general, aesthetic criteria prevail and, secondarily, the discomfort caused by rubbing against clothing or during hairstyling. Descriptions of the natural progression of AMN pointing to their natural evolution toward elevation date back to the nineteenth century.[57] This slow elevation from a nearly flat to raised lesion occurs because of the migration of melanocytes to deeper regions of the dermis, "lifting" the overlying tissue and producing a color lightning, which can become pink without evidence of pigmentation (**Fig. 6**).[57–59] Importantly, in most cases, this slow progression is not worrisome. Unless the lesion is symptomatic or subject to repeated trauma by brushes or clothing, otherwise banal-appearing lesions that are raised do not require removal.

> MN are changing lesions in changing individuals, and not all morphologic changes reflect malignant transformation. MN may clear in color and acquire volume with age, but this morphologic change does not indicate malignant transformation.

HOW CAN I PREVENT MALIGNANT TRANSFORMATION OF MOLES?

Intense sun exposure is a well-known risk factor for developing skin cancer. In particular, melanoma development is strongly related to repeated sunburns during childhood and adolescence, and therefore, implementing the appropriate strategies for sun protection is essential. However, a study performed in 2013 demonstrated that only 10% of students between 14 and 17 years of age applied sunscreen with an SPF greater than or equal to 15 while performing outdoor activities.[60] Younger children are prone to use sunscreens properly because their parents and caregivers take on the responsibility to apply them regularly. However, the adherence to sun protection diminishes noticeably with age. For example, a study performed in the United States observed that 69% of adolescents aged between 11 and 18 years had experienced sunburn the previous summer.[61]

Physicians and school policies play a crucial role in educational interventions to promote sun-protective behaviors, but, most interestingly, only 44% of adolescents and their parents reported receiving advice on photoprotection from their physicians, whereas only 22% of physicians acknowledged giving recommendations on the subject to their patients.[62] A recent survey among pediatricians showed that sun protection ranked low among preventive topics

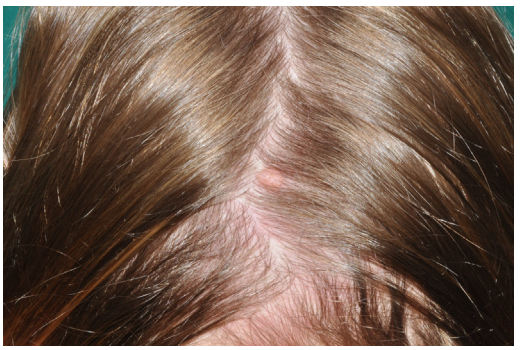

Fig. 6. Raised acquired pink melanocytic nevus on the scalp in a 14-year-old girl. The lesion was excised because of repeated traumatization of the lesion during hair styling.

and that only a minority of them offered to counsel about sun protection and indoor tanning.[63]

These data show that educational interventions in sun protection behaviors have ample room for improvement.[64]

Although the risk of malignant transformation of an individual MN is low, appropriate sun protection from an early age is important in minimizing this risk. Caregivers and parents play a pivotal role, and improvement of educational interventions carried out by physicians and health care providers is needed.

WHICH IS THE BEST SUNSCREEN?

The importance of proper use of topical sunscreens in childhood to prevent the cumulative effect of solar radiation (UVA and UVB) on the skin is well known to parents and caregivers and raises a recurring question about the ideal product. Sunscreens contain chemical (organic) or physical (inorganic) compounds that block ultraviolet radiation. In general, physical or inorganic sunscreens are preferred in children to minimize the risks of sensitization and toxicity.[65] The SPF, broad-spectrum activity against UVA and UVB, the amount of sunscreen applied, and the regularity of application are essential factors determining the usefulness of a sunscreen's protective effects.

The SPF only measures UVB protection (not UVA) and is not a measure of time but a measure of the fraction of sunburn-producing UV rays that reach the skin. For example, "SPF 20" means that one-twentieth of the burning radiation will reach the skin.[66] The American Academy of Dermatology recommends using SPF sunscreens equal to or greater than 30 regardless of skin type.[67] It is important to use sunscreen with broad-spectrum activity. The amount of protective cream is another element that determines its effectiveness, which is proportional to the amount applied. A study carried out with primary school children aged 5 to 12 years who applied the sunscreen themselves found that they used less than half of the recommended 2 g/cm^2.[68] Finally, regular reapplication of the sun protection cream, especially after bathing and physical exercise, optimizes its sustained effect throughout the photo-exposure period. The American Academy of Dermatology recommends reapplying sunscreen approximately every 2 hours, or after swimming or sweating, according to the directions on the bottle.[67] Sun protection strategies in addition to the correct use of sunscreens include photoprotective clothing and sunglasses, and avoiding intense sunlight at peak hours of UV radiation.

The best sunscreen is the one that you apply in enough quantity and frequency (again and again). Ensure your sunscreen offers broad-spectrum protection (blocks UVA and UVB radiation) and has a minimum SPF of 30.

CLINICS CARE POINTS

- The risk of malignancy of a solitary congenital melanocytic nevus is low, regardless of its size and location.
- The number of acquired melanocytic nevi increases throughout childhood, especially in children with lower phototypes and those who are more exposed to the sun, particularly if repeated sunburns.
- Surgical management of melanocytic nevi does not prevent melanoma and must be discussed individually.
- Melanoma is extremely rare in children younger than 10 years of age and may be challenging to recognize. The classic "ABCDE" alarm criteria for early detection of melanoma are not sensitive enough in children and must be accompanied by additional clinical information and pediatric-related criteria.
- Sunscreens must be applied to the entire skin surface exposed to the sun and not only and specifically to melanocytic nevi. Clothing, hats, and sunglasses offer additional protection.
- Physicians and school policies play a key role in educational interventions to promote sun-protective behaviors to prevent skin cancer.

DISCLOSURE

Dr J. Anderson-Vildósola has no conflict of interest to declare. Dr A. Hernández-Martín has conducted clinical trials for Mayne Pharma and Celgene; and has received honoraria for academic lectures from Viatrix, Leti Pharma, Pierre Fabre, and Beiersdorf Laboratories.

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