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ARTICLE

Neonatal Blue-Light Phototherapy Does Not Increase Nevus Count in 9-Year-Old Children

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What's Known on This Subject

One of the most important risk factors for melanoma is the number of acquired nevi in childhood. The role played by NNPT in the increasing incidence of melanocytic nevi in childhood or adolescence has been discussed recently with discordant results.

What This Study Adds

Our study underlines the dominant effect of phototype characteristics and history of sunburn in childhood on the early development of melanocytic nevi and shows no effect of NNPT in 9-year-old children.

ABSTRACT

OBJECTIVE. One of the most important risk factors for melanoma is the number of acquired common and atypical nevi in childhood. The role played by neonatal blue-light phototherapy in the increasing incidence of common and atypical melanocytic nevi in childhood or adolescence has been discussed recently with discordant results.

PATIENTS AND METHODS. We designed a multicenter study to assess the effects of neonatal blue-light phototherapy on nevus count in a cohort of 9-year-old children. We counted back and arm nevi as a function of size in 828 children included in a French photoprotection educational campaign. History of neonatal phototherapy, phototype, skin, hair and eye color, and sunburn were assessed through questionnaires to which both parents and children responded, and a nevus count was performed by trained nurses blinded to phototherapy history.

RESULTS. Mean nevus count was 16.7 per child. Twenty-two percent of the children had received neonatal blue-light phototherapy. Neonatal phototherapy had no effect on the nevus count irrespective of nevi location, nevi size, or phototype of the children. A light phototype, skin, and hair color; blue/green eyes; and history of sunburn were closely correlated with an increase in nevus count.

CONCLUSIONS. This study found no evidence for a major role of blue-light phototherapy on nevus count in 9-year-old children. It underlines the dominant effect of phototype characteristics and history of sunburn in childhood on the early development of melanocytic nevi. *Pediatrics* 2009;123:e896–e900

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Key Words
neonatal blue-light phototherapy, melanocytic nevus, melanoma

Abbreviation
NNPT—neonatal blue-light phototherapy

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ONCE IT HAS metastasized, melanoma is a life-threatening cancer. Its incidence has increased in the Western hemisphere, and it affects more young adults than most other forms of cancer.[1] In the United States, the probability of developing melanoma between birth and the age of 39 is 0.13% for males, second only to hematologic cancers, and 0.21% for females, second only to breast cancer in young women.[1] Two major risk factors for developing cutaneous melanoma are a high number of common melanocytic nevi and a high number of atypical nevi.[2] Risk factors for the development of melanocytic nevi in childhood have been clearly established as fair skin complexion, high level of sun exposure, and history of sunburn during childhood.[3]

For the past 2 years, the role played by neonatal blue-light phototherapy (NNPT) in the increasing incidence of melanocytic nevi in childhood and adolescence has been discussed with discordant results.[4–8] NNPT (wavelength focused at 460 nm) is the gold standard used to treat neonatal hyperbilirubinemia and prevent kernicterus. Its efficacy depends on type of light source, phototherapy dose, distance between light and infant, and area of body exposed.[9,10] Method design, age of children, melanocytic lesions assessed, identification of cofactors, and quantification of blue-light exposure differ from one study to another. We designed a blind, multicenter study to assess the effects of NNPT on the melanocytic nevus count in a large cohort of 9-year-old children.

PATIENTS AND METHODS

In May to June 2007, we performed a multicenter, cluster-randomized study to assess the effectiveness of several photoprotection educational programs in children attending primary schools in 2 departments (Hauts-de-Seines and

Yvelines) of the greater Paris, France, suburban area. Schools were stratified according to mean socioeconomic status and living conditions, rural versus urban zones. The schools were then randomly selected for the different campaigns. Finally, 52 French primary schools, including a total of 961 nine-year-old children, participated in the study. One class (third year of primary school: 8- to 9-year-old children) per school was included in the study to avoid experimental contamination. The sample was calculated for the photoprotection educational programs to detect a 20% increase in healthy behavior in the group with educational programs versus 5% in the control group.

Information was gathered from parents and children via standardized questionnaires validated previously in nonrandomized preliminary studies (data not shown). This included phototype (Fitzpatrick's classification),[11] behavior in the sun, sun protection policy, and past history of NNPT for neonatal jaundice. A melanocytic nevus count was performed by 2 nurses on the children present on the day of the evaluation and whose parents had given their written informed consent. The nurses had been trained by a dermatologist (Dr Mahé) in the identification of pigmented lesions. Freckles and café-au-lait spots were excluded. The count was performed blinded to history of NNPT. The size of nevi on exposed body parts, the arm, and back was recorded (<2 mm, 2–5 mm, and >5 mm). Hereafter we report the influence of NNPT, phototype, and sunburn history on melanocytic nevus count.

Data were collected in a case report form created with Sphinx software 5 (www.lesphinx-developpement.fr, Sphinx Développement, Chavanod, France), filled out by parents, and finally scanned with Sphinx software. Quantitative data were expressed as the means ± SDs and qualitative data as frequency and percentage. Means were compared by using Student's *t* test and analysis of variance; in the event of significant results, multiple comparison tests using the contrast method were performed. Incidences were compared via the χ^2 test. A *P* value of <.05 was considered statistically significant. Statistical analyses were performed by using SAS software 8.2 (SAS Institute, Inc, Cary, NC).

RESULTS

Of the 961 children enrolled in the study, 828 children (86%) were at school on the day of the evaluation and had obtained written informed consent from their parents to participate. A total of 180 (22%) of them had received NNPT. Characteristics of the children are shown in Table 1. The groups of children were homogenous in terms of age; skin phototype; skin, hair, and eye color; and sunburn episodes according to NNPT exposure. There was a higher number of girls in the unexposed group ($P = .03$).

Mean common melanocytic nevus count, all sizes included, was 16.7 per child on the arms and back. The mean melanocytic nevi count was 10.3 on the arms and 6.3 on the back; a mean of 13.1 measured <2 mm, 2.9 measured from 2 to 5 mm, and 0.3 measured >5 mm (Table 2). No atypical nevi were observed.

TABLE 1 Characteristics of the Children

Characteristic	Total	Neonatal Blue-Light Phototherapy		*P*
		Children Exposed	Children Unexposed	
No. (%)	828 (100)	180 (22)	648 (78)	NA
Gender, boy/girl	415/413	103/77	312/336	.03
Mean age, y	9	9	9	.47
Skin phototype, *n* (%)[a]				.93
I	25	5 (3)	20 (3)	
II	149	36 (22)	113 (19)	
III	120	24 (14)	96 (16)	
IV	283	61 (37)	222 (37)	
V	195	41 (24)	154 (25)	
Skin color, *n* (%)				.40
Fair/pale	566	117 (66)	449 (70)	
Medium	232	57 (32)	175 (27)	
Dark	24	4 (2)	20 (3)	
Hair color, *n* (%)				.29
Blond	170	28 (16)	142 (22)	
Light brown	353	86 (48)	267 (41)	
Red/auburn	19	5 (3)	14 (2)	
Dark brown/black	281	59 (33)	222 (35)	
Eye color, *n* (%)				.32
Blue/gray	210	52 (29)	158 (25)	
Hazel/green	122	26 (16)	96 (15)	
Brown/black	485	100 (55)	385 (60)	
Sunburn episodes, *n* (%)				.93
0	377	81 (45)	296 (46)	
1	214	46 (25)	168 (26)	
≥2	238	53 (30)	185 (29)	

NA indicates not applicable.

[a] Skin phototype was chosen by Fitzpatrick's classification: I: very white or freckled, always burns, never tans; II: white, always burns, then tans; III: white to olive, sometimes burns, always tans; IV: brown, always tans, rarely burns; and V: black, always tans, never burns.

There were no differences in nevus count as a function of NNPT exposure whatever the location or size of nevi (Table 2). Similarly, no differences were observed after adjustment for skin, eye, and hair color, as well as skin type. Nevi were more numerous on the backs of boys and arms of girls ($P < .01$). Pale phototype ($P < .0001$), skin ($P < .0001$), and hair ($P < .0001$) color; blue/green eye color ($P < .0001$); and history of sunburn ($P < .0001$) were strongly correlated with an increase in the nevus count. This was highly significant for nevi <5 mm and for all of the locations. Nevi >5 mm were more numerous ($P < .05$) in blond children and in children with pale skin or blue/gray eyes.

DISCUSSION

In this large, multicenter study of a homogenous population of 9-year-old children evaluating the number of melanocytic nevi with the evaluation blinded for a history of NNPT, NNPT was not associated with an increase in the number of nevi, irrespective of their location or size. Our study showed that skin characteristics and history of sunburn in childhood were determining factors for the early development of nevi. As in a previous study, we demonstrated that nevi were more numerous on boys' backs and girls' arms.[12,13] Dressing habits could explain these differences, because girls have a tendency

TABLE 2 Parameters Influencing Number of Melanocytic Nevi in Children According to Location and Size of the Nevi

Variable	Location of the Nevus, Mean ± SD		Size of the Nevus, Mean ± SD			Total, Mean ± SD
	Arm	Back	≤2 mm	2–5 mm	>5 mm	
Total, 828 children	10.3 ± 6.6	6.3 ± 5.0	13.5 ± 7.6	3.0 ± 3.8	0.3 ± 0.9	16.7 ± 10.3
Phototherapy						
Yes	10.2 ± 5.9	6.7 ± 5.1	14.0 ± 7.6	2.8 ± 3.5	0.2 ± 0.7	16.8 ± 9.8
No	10.4 ± 6.7	6.2 ± 4.9	13.4 ± 7.6	3.0 ± 3.8	0.3 ± 0.9	16.7 ± 10.5
Gender						
Boy	9.7 ± 6.1[a]	6.8 ± 5.2[a]	13.5 ± 7.6	2.8 ± 3.5	0.2 ± 0.6	16.6 ± 10.1
Girl	11.0 ± 6.9	5.9 ± 4.7	13.5 ± 7.5	3.1 ± 4.0	0.3 ± 1.1	16.9 ± 10.6
Skin phototype						
I	12.5 ± 8.2[b]	6.3 ± 6.3[b]	14.2 ± 8.9[b]	4.4 ± 5.5[b]	0.4 ± 1.1	18.8 ± 13.1[b]
II	12.8 ± 6.6	6.8 ± 4.9	15.2 ± 7.0	4.3 ± 4.6	0.3 ± 0.6	19.7 ± 10.2
III	11.4 ± 6.1	6.6 ± 5.2	14.7 ± 7.2	3.2 ± 3.6	0.4 ± 1.2	17.9 ± 9.9
IV	10.0 ± 5.8	6.7 ± 4.5	13.8 ± 6.9	2.8 ± 3.1	0.3 ± 0.9	16.8 ± 9.0
V	7.2 ± 6.1	4.6 ± 4.6	9.9 ± 7.7	1.8 ± 3.1	0.16 ± 0.5	11.7 ± 10.0
Skin color						
Fair/pale	12.0 ± 6.1[b]	7.1 ± 5.0[b]	15.3 ± 6.9[b]	3.6 ± 4.1[b]	0.3 ± 1.0[c]	19.2 ± 9.9[b]
Medium	7.3 ± 4.4	4.0 ± 4.4	10.4 ± 7.5	1.9 ± 2.7	0.2 ± 0.4	12.4 ± 9.2
Dark	1.2 ± 1.7	0.6 ± 0.7	1.7 ± 1.7	0.3 ± 0.6	0.04 ± 0.2	2.0 ± 1.8
Eye color						
Blue/gray	12.5 ± 6.3[b]	7.3 ± 5.2[b]	15.7 ± 6.7[b]	3.8 ± 4.4[b]	0.5 ± 1.3[d]	19.9 ± 10.1[b]
Hazel/green	12.3 ± 6.3	8.1 ± 5.2	16.4 ± 7.2	3.9 ± 4.2	0.3 ± 0.7	20.6 ± 10.0
Brown/black	9.2 ± 6.2	5.8 ± 4.7	12.3 ± 7.4	2.5 ± 3.2	0.2 ± 0.6	15.0 ± 9.8
Sunburn episodes						
0	9.0 ± 6.4[b]	5.3 ± 4.7[b]	11.7 ± 7.5[b]	2.4 ± 3.2[b]	0.2 ± 0.6	14.4 ± 10.0[b]
1	10.3 ± 6.5	6.5 ± 5.3	13.7 ± 7.9	3.0 ± 4.1	0.2 ± 0.6	16.7 ± 10.4
≥2	11.6 ± 6.5	7.2 ± 4.9	15.1 ± 7.0	3.5 ± 3.9	0.4 ± 1.1	18.9 ± 10.3

[a] $P \leq .01$.
[b] $P \leq .0001$.
[c] $P < .05$.
[d] $P \leq .001$.

to wear short sleeves, whereas boys more often strip to the waist.

Five studies have evaluated the risk of developing benign or malignant melanocytic lesions after NNPT with contradictory results (Table 3). Three studies performed by 2 groups have shown the following: (1) an increase in the number of nevi measuring >2 mm in 8- to 9-year-old children who were exposed to intensive NNPT (>30 μW/cm^2 per nm)[6]; (2) an increase in atypical nevi but not of common nevi in 14- to 18-year-old children who were exposed to NNPT[7]; (3) and an increase in atypical and common nevi in 6- to 30-year-old monozygotic twins exposed to NNPT compared with unexposed twins.[8] Two previous studies suggested no link between NNPT exposure and melanoma before the age of 18 years[4] and nevi count in 2- to 7-year-old children.[5]

There were a few limits to these studies. These included disparities in the ages of the populations enrolled[4,8]; the fact that the evaluation was not blinded, which is particularly important for small groups where there is a high risk of bias[6,8]; lack of statistical power of the studies[4,6,8]; the absence of evaluation of blue-light irradiance,[4,5,7,8] when only children exposed to intensive therapy were evaluated; the fact that the number of cycles was not specified[6]; and problems linked to the

TABLE 3 Results of 5 Previous Studies on the Link Between NNPT and Melanocytic Skin Lesion Development in Children

Source	Skin Melanocytic Lesions Evaluated	Population	Link Between NNPT and Melanocytic Lesions
Berg and Lindelhöf,[4] Sweden (1997)	Melanoma	30 children with melanoma/120 control subjects	No
Bauer et al,[5] Germany (2004)	Common nevus	1872 children, 2- to 7-y-old children, 18.4% NNPT	No
Matichard et al,[6] France (2006)	Common nevus	8- to 9-y-old children, 18 children with intensive NNPT, 40 control subjects	Increase of >2-mm nevus in children with intensive NNPT
Csoma et al,[7] Hungary (2007)	Common nevus, atypical nevus	14- to 18-y-old children, 740 children, 44.6% NNPT	Increase in dysplastic nevus; no impact of NNPT on typical nevus
Csoma et al,[8] Hungry (2008)	Common nevus, atypical nevus	11 twin pairs (1 exposed and 1 unexposed)	Increase in common and atypical melanocytic nevi in exposed twins

accuracy of NNPT exposure history when evaluated through parent interview.[4,5,7]

Our study has the following advantages: our population was homogenous with respect to age, the study was statistically powerful, and it was performed on the same date before summer sun exposure. However, there was no retrospective documentation about irradiance of blue-light phototherapy, there was no information about prematurity, and nevi were only counted on the back and arms. Nonetheless, there is a good correlation ($r = 0.88$) between the whole body and the upper limb in terms of the number of nevi >2 mm.[14]

Areas of darkness still exist even after our study. No studies have taken into account term of pregnancy. Immaturity of the skin in premature infants could increase the risk of developing NNPT-related nevi. This parameter is very important, because premature newborn infants have a higher risk of jaundice and, thus, are more liable to receive NNPT.[10]

Clinical data cannot, therefore, demonstrate with any degree of certainty that blue-light therapy plays a role in the development of melanocytic lesions. This is further confirmed by the fact that no increase in nevus formation is reported in patients with Crigler-Najjar syndrome, who receive daily blue-light phototherapy. Nevertheless, there is some physical and biological evidence to suggest that the lights used for neonatal phototherapy may have carcinogenic potential; the safety of NNPT should, therefore, be approached with caution. First, a blue-light wavelength of 460 nm is used in neonatal phototherapy, but it can overflow into the UV-A region (320–400 nm),[7] which plays a role in skin carcinogenesis.[15] The American Academy of Pediatrics currently recommends special blue fluorescent lamps or light-emitting diode lights when total serum bilirubin levels approach the range at which intensive phototherapy is recommended.[16] However, phototherapy units may commonly contain daylight and white or blue fluorescent tubes. However, if the phototherapy lights are standard fluorescent lamps and have a Plexiglas cover, no measurable ultraviolet should reach the infant. Second, by generating reactive oxygen species, blue light can induce indirect DNA damage.[17,18] Third, whereas blue light suppresses the growth of B16 melanoma cell line cells, exposure of uveal melanoma cell lines to blue light boosts cell proliferation.[19,20] Fourth, the blue spectral band is responsible for DNA breaks and sister chromatid exchanges in Chinese hamster cells.[21] Fifth, prolonged exposure to arc welding, which has high blue-light radiance, is an important risk factor for uveal melanoma.[22] Finally, veterinarians have recently reported a uveal melanoma induced by prolonged exposure to blue light in a rat.[23]

CONCLUSIONS

We found no evidence indicating that NNPT influenced the melanocytic nevus count in 9-year-old children. However, the results underline the importance of phototype characteristics and history of sunburn in childhood on the early development of nevi. Prospective studies, taking into account preterm neonates, seem necessary to confirm whether NNPT plays a role in the development of melanocytic lesions before systematic screening for exposed children is proposed.

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