

Nevus Depigmentosus in Infancy: Modified Classification and Diagnostic Criteria

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Abstract

Background:

Nevus depigmentosus (ND) is a common cause of hypopigmentation in infants. Coup's criteria are the original diagnostic criteria. It was classified into localized, segmental, and systemized. However, the current classification lacks detailed description of the different patterns.

Objective:

This study focused on the diagnosis, patterns and classification of ND in infants.

Methods:

All infants with ND presenting to paediatric dermatology outpatient clinic at a tertiary care center were recruited. A stepwise approach was applied including thorough history, clinical assessment, Wood's light & dermoscopy examination and Excimer Stamp test. Skin biopsy was only resorted to in non-conclusive cases.

Results:

A total of 107 infants were recruited. Adding Wood's light, dermoscopy examination and excimer stamp test as well as hinting an initial progressive course in infancy are suggested modifications to the original Coup's criteria.

A number of modifications to the original classification have been suggested to allow for more accurate and thorough inclusion of the different patterns that were observed.

Non-systematized blaschkoid ND was proposed as a more descriptive nomenclature for segmental pattern, which was taking either a single broadband pattern or a single patchy pattern.

Systematized ND was further classified according to archetypical patterns of cutaneous mosaicism. As for *localized ND*, it was further classified into single or multiple, which were either multiple scattered or multiple in a blaschkoid distribution, which is a newly recognized pattern for clinically depigmented ND that can be easily misdiagnosed as vitiligo.

Conclusion:

This work represents a broader detailed description of ND upon which a modified classification and diagnostic criteria were proposed.

Highlights

- Diagnostic dilemma for Nevus Depigmentosus was tackled with further suggested modifications for Coupe's diagnostic criteria.
- An updated descriptive classification for Nevus Depigmentosus has been proposed
- Multiple focal pattern restricted to one dermatome is a newly recognized entity that is easily misdiagnosed as vitiligo

Introduction

Hypopigmentation is a common challenging presentation in the age of infancy, with different underlying causes that vary from reassuring common conditions such as nevus depigmentosus and post inflammatory hypopigmentation to more serious, though less common causes as vitiligo and syndromic causes of hypopigmentation (1, 2).

Nevus depigmentosus is one of the most common causes of hypopigmentation in the age of infancy (1). It is due to cutaneous mosaicism affecting the pigmentary genes resulting in functional impairment of the melanocytes and in particular defective transfer of melanosomes from the melanocytes to the keratinocytes (3, 4).

Coupe's criteria, which are the classic diagnostic criteria, define nevus depigmentosus as stationary leukoderma dating since birth or early infancy with no alteration in sensation and skin texture or hyperpigmented borders (5). No or slight decrease in the melanocytes on microscopic examination as well as aggregated melanosomes in the keratinocytes under electron microscopy were suggested as further modifications to Coup's criteria (6). Nevus depigmentosus is classically classified as isolated/ localized, segmental and systematized (7–9).

Given its high frequency in the age of infancy (10, 11) and the related diagnostic challenge (12, 13), revision of the diagnostic criteria along with an updated classification that would help encompass the different patterns, is expected to increase the diagnostic accuracy and lower the chances of misdiagnosis. While ND is quite reassuring, other causes of hypopigmentation such as tuberous sclerosis and early vitiligo might prompt initiating treatment. Unless we are aware of the different clinical manifestations and different patterns, confusion would be likely and sequelae might be debilitating on the parents and the infants who might be started on unnecessary treatment in consequence to a wrong diagnosis.

To the best of our knowledge, none of the previously conducted studies have focused on meticulously describing the different clinical patterns. All the studies have followed the original classification without attempting to further highlight the different patterns that can be clinically encountered and might be confused with other causes of hypo/depigmentation such as vitiligo.

In this work, we aimed to evaluate every infant presenting with ND in our tertiary care pediatric dermatology center. We focused on the different clinical patterns and suggested some modifications to

the original classification along with revisiting the diagnostic criteria and tackling the related diagnostic challenges.

Patient and Methods

This is a cross-sectional study that was conducted in the outpatient dermatology clinic, Abu El-Reesh university hospital (tertiary pediatric center), Cairo University. It has been approved by the scientific committee and Research Ethics Committee, Faculty of Medicine, Cairo University. An informed written consent for participation and photography was signed by the parents/ guardians of all infants.

All infants (≤ 2 years old) having ND who presented to the dermatology clinic were recruited between January 2023 and January 2024. Coupe's diagnostic criteria and suggested modifications by Xu et al., 2008 were relied upon (5, 6). Children aging > 2 years old, having other hypopigmented skin lesions and those with systemic disorders contributing to the hypopigmentation such as tuberous sclerosis and hypomelanosis of Ito were excluded.

Thorough history including age of onset, duration and course was taken. Examination was done both in daylight and Wood's light. Day light and UV photographs in a dark room were captured using Samsung GW3 smartphone (64 megapixels and aperture f/1.79) mounted to a CuTechs BLB-202 Wood's lamp (Cutechs LLC, Cairo, Egypt). In addition, dermoscopic examination using 3 Gen Dermlite HUD dermoscope was done. Diascopy and friction were done to exclude cases of nevus anemicus which show lack of erythema on friction and become indistinguishable from surrounding skin on diascopy (14).

Excimer stamp test was offered to all the parents'/ guardians as a confirmatory safe test. Excimer light (MEL@308 nm, Excilite μ , DEKA, Italy) delivering 308-nm excimer laser (EL) energies of 150, 300, 450, 600 mJ to the hypo/depigmented lesions was used. One week later, the irradiated sites were evaluated for pigmentation. The test was considered positive if skin pigmentation occurred at any of the above-mentioned doses (15).

If diagnosis remained doubtful in spite of all the above-mentioned diagnostic tools, a skin biopsy was resorted to after taking consent from the parent/ guardian. H&E staining and immunohistochemistry (Sox-10/ Melan A) were done to determine whether melanocytes were present or absent and confirm the diagnosis.

Thorough pediatric assessment by a consultant Pediatrician was done for infants having 3 or more hypopigmented lesions (16) or those with ash leaf like macules even if single to rule out tuberous sclerosis (9). Infants with hypopigmentation involving one or more body segments, whether patchy or whorly were thoroughly assessed to rule out hypo melanosis of Ito and other syndromic causes of hypopigmentation (17). Further investigations such as MRI Brain, echo cardiography and skeletal survey were done whenever a systemic cause was clinically suspected.

Infants were initially classified according to the original classification of ND into localized/ focal, segmental and systematized (7–9).

Statistical analysis

Data were coded and entered using the statistical package for the Social Sciences (SPSS) version 28 (IBM Corp., Armonk, NY, USA). Data was summarized using mean, standard deviation in quantitative data and using frequency (count) and relative frequency (percentage) for categorical data.

Results

A total of 107 infants were recruited over a total duration of 12 months. The mean age of onset of ND was 2.77 ± 4.57 months (IQR= 3). Fifty five percent of the infants (59/107) were females. A stationary course was reported in (43/107) (40.2%) infants, while the majority of the infants were reported to have a progressive course in the form of expansion or development of new lesions (62/107) (57.9%). A regressive course with partial repigmentation was reported in only one infant and in one infant, the parent was not sure regarding the course of the lesion.

According to Fitzpatrick skin phototype, 23 infants (21.5%) had skin phototype III, 83 infants (77.5%) had photo type IV, and 1 infant had phototype V. Infants were thoroughly assessed for the involved anatomical sites. The trunk was the most involved site (72/107) (67.3%) followed by the flexures (42/107) (39.3%) and lower extremities (30/107) (28%). Head and neck were involved in 19 infants (17.8%) and upper extremities in 16 infants (15%). Acral sites were involved in 7 infants (6.5 %).

Regarding Wood's light examination, the majority (80/107) (74.8%) showed off white accentuation, while 22.4% (24/107) showed more bright accentuation on Wood's light examination. Three infants showed bright white fluorescence mimicking vitiligo (2.8%) (**Figure I**). Expectedly, 97.2% of the infants (104/107) showed reduced pigment network on examination by 3 Gen Dermlite HUD dermoscope.

Excimer stamp test was done in 93 infants, 87 showed positive test (93.5%) and 6 (6.5%) showed a negative test. Fourteen infants were lost for follow up. Of the different delivered doses, 12.6% (11/87) of the nevoid lesions were positive at 150 mJ, while 71.3% (62/87) were positive at a dose of 300 mJ and negative at 150 mJ. Thirteen lesions (14.9%) (13/87) were positive only at a higher dose of 450 mJ and one lesion responded only to the highest dose of 600 mJ (1.1%) (1/87).

The different patterns of ND were thoroughly assessed and classified according to the original classification into localized/focal, systematized and segmental. However, further modifications were made, opting for a more thorough detailed description of the different patterns of involvement with ND (**Figure II**) (**Table II**).

I. Focal ND was further classified into either single or multiple (**Figure III**). The multiple focal ND was either:

- a. Multiple scattered in different body areas
 - b. Multiple following a blaschkoid distribution.
- II. Segmental ND, which were all following a blaschkoid distribution were named as non-systematized blaschkoid ND (**Figure IV**). These were taking either:
- a. Single broad band pattern
 - b. Single patchy pattern which was further classified according to the pattern of depigmentation into
 - i. Diffuse
 - ii. Mottled with areas of pigmentation.
 - iii. Interrupted by islands of normal skin.
- III. Systematized Blaschkoid ND was further classified according to the archetypical patterns of cutaneous mosaicism (**Figure V**) (18) into:
- a. Narrow Band
 - b. Broad Band
 - c. Phylloid
 - d. Checkerboard
 - e. Patchy pattern with lateralization
 - f. Patchy pattern without midline separation

The multiple focal ND in a blaschkoid distribution were showing white fluorescence on Wood's light examination and skin biopsy, and immunohistochemistry were done to confirm presence of melanocytes (**Figures I & III**).

Only one infant was classified as having more than one pattern: namely, single focal ND along with non-systematized single patchy interrupted ND (**Figure VI**). The rest of the examined infants were fitting into only one of the above-described patterns.

Discussion

Nevus Depigmentosus is one of the most common causes of hypopigmentation in infants (1). Proper recognition of the different patterns of nevus depigmentosus is of utmost importance to avoid misdiagnosis and be in a better position of reassuring the parents.

Initially, we were faced with the diagnostic challenge. Thorough pediatric assessment was done for infants with ash leaf macules or ≥ 3 hypopigmented lesions to rule out tuberous sclerosis (TS) (17). In addition, systematized hypopigmentation involving 2 or more body segments necessitated pediatric assessment to rule out hypo melanosis of Ito and other syndromic causes (18).

Diagnosis of ND was based on the original Coupe's criteria and the suggested modification (5, 6). As regards the course of the lesions, given that we were focusing on the age of infancy, it was noted that more than half of the parents/ guardians would give a progressive history in the form of initial expansion or development of new lesions, which is against what was stated by Coupe in 1967. This is probably related to possible initial progression in this age group. In a study on a Korean population that involved 60 cases aged between 3 months to 35 years, a progressive course was reported in 7% (3). A regressive course was reported in only one infant, which was also reported by Sharquie et al., 2021 (9).

The trunk was the most involved site in agreement with Lee et al., 1999 (19) and acral sites were the least involved. However, in one infant, it was taking a stock like pattern that we believe might have been previously misdiagnosed as spontaneously regressing acral leukoderma in an infant (20). Another had hypopigmented fingers with islands of pigmentation in similar pattern to the case reported by Kambhampati et al., 2016 as congenital vitiligo (21). The other 5 had partial asymmetrical hypopigmentation involving the hand and feet along with nevus depigmentosus elsewhere. Our cases were not fluorescent on wood's light examination and were dating since birth in 4 infants and since the first month of life in the other 3 with no further progression or development of lesions elsewhere throughout the study duration. Thus, we propose that the previously reported acral leukoderma is a variant of patchy blaschkoid nevus depigmentosus, which is a manifestation of cutaneous mosaicism that was previously misdiagnosed as congenital vitiligo by Kambhampati et al., 2016.

Wood's light examination would classically reveal off white accentuation. However, clinically depigmented ND was noted in three infants who had surprisingly shown white florescence, confusing it with vitiligo. Those patients showed a negative excimer stamp test and absent pigment network on dermoscopic examination. Thus, a skin biopsy was arranged, when we were astonished to detect melanocytes on H&E, which were further highlighted by immunohistochemistry. One of these patients was non-systematized blaschkoid ND patchy pattern with mottled pigmentation. The other 2 were having multiple focal ND in a blaschkoid distribution.

In the light of the met diagnostic challenge, updating Coupe's criteria and its suggested modifications by Xu et al. deemed necessary (Table I). Hinting a possible initial progression of ND in the age of infancy, off- white accentuation on Wood's light examination, preserved pigmented network and serrated edges on dermoscopy examination and a positive excimer stamp test are among the suggested updates to the diagnostic criteria. Nonetheless, given that 3 cases showed white fluorescence and absent pigment network on dermoscopy, skin biopsy can occasionally be needed to confirm presence of melanocytes, which we propose to name clinically depigmented ND.

All the confirmed cases were then evaluated in the light of the original classification for ND into localized/ focal, segmental and systematized. Under each class, we recognized different patterns, which we attempted to describe and classify. We believe this would eventually help diagnose ND more confidently and lower the chances of misdiagnosis.

In this regard, the **focal ND** was recognized as either a **single** patch, which was most commonly well-defined but in a minority of the cases ill-defined, or multiple patches. The **multiple focal ND** were either **scattered** lesions in different body sites or well-defined small patches **in a blaschkoid distribution**, which was observed in 2 cases. Astonishingly, the latter 2 cases showed white fluorescence and melanocyte presence was confirmed by skin biopsy and immunohistochemistry. This in turn highlights this pattern as a distinguished newly recognized entity of clinically depigmented ND that to the best of our knowledge was not previously described in the literature. It can be very easily confused with vitiligo and can only be differentiated by skin biopsy and unless this pattern of ND is put into consideration, those infants would be misdiagnosed as vitiligo.

Regarding the segmental ND, they were all following a blaschkoid distribution; thus, **non-systematized blaschkoid ND** was favored as a nomenclature. Those were recognized as either taking a patchy pattern, which was more likely or a **single broad band pattern**. The **patchy pattern** was either **diffusely hypopigmented** or showing **mottled pigmentation** or less likely **interrupted by islands of normal skin**. Serrated borders, truncal involvement, which was the most involved site in our study cohort, absence of poliosis and young age of onset were suggested as differentiating points between segmental vitiligo and ND (24). Nonetheless, role of Wood's light and dermoscopic examination should never be underestimated in differentiating this pattern of ND from segmental vitiligo.

As for the **systematized ND**, that was classified according to the archetypical patterns of cutaneous mosaicism. Astonishingly, there were cases fitting into each type of cutaneous mosaicism. The **patchy with lateralization pattern** with patches on either side but strictly respecting the midline was the most common followed by the **patchy without midline separation**. More than one pattern can be encountered, which was found in only one infant in our cohort.

The suggested classification aligns with recent advances in cutaneous mosaicism highlighting possibility of different melanocyte precursors that might explain the large noted variable presentations (23, 24). However, this requires genetic tracing to define the affected precursor melanocyte cells for each of the clinically noted patterns.

In our study cohort, which is to the best of our knowledge, the largest, focal ND was the most common (36%). However, there was no significant difference in prevalence of the 3 different classes. Another study involving 60 patients reported close prevalence for both segmental and localized but none of the patients had whorly pattern (4). This denotes that, at this point, systematized ND was underdiagnosed as it was not yet linked to the archetypical patterns of cutaneous mosaicism. In another study that involved 15 patients, segmental ND was more common (60%) (8). However, classically, focal/ localized ND is cited as the most common in literature (19, 25).

In conclusion, we believe that ND is underdiagnosed and sometimes misdiagnosed; however, stepwise diagnostic approach together with proper recognition of the different patterns would ease the diagnostic challenge.

Declarations

Funding: Cairo University Hospitals resources

Conflict of interest: None

Availability of data and material (data transparency): Upon request

Authors' contributions:

- **Rania M Mogawer, Sarah Elsayed, Kariman El Hamamsy:** had shared in clinical work; literature search; data acquisition and interpretation; statistical analysis; manuscript preparation, editing and review.
- **Samia M Esmat:** had shared in the study design; data analysis; statistical analysis; manuscript preparation, editing and review.

IRB approval status: Reviewed and approved by:

- Medical ethics committee of the Faculty of Medicine, Cairo University.
- Scientific committee of Dermatology Department, Cairo University, Cairo, Egypt.

Consent to participate: Informed consent was signed by all parents/ guardians prior to participation in the study.

Consent for publication: Informed consent for publication of data anonymously was given by all participants.

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Tables

Table 1 and 2 are available in the Supplementary Files section.

Figures

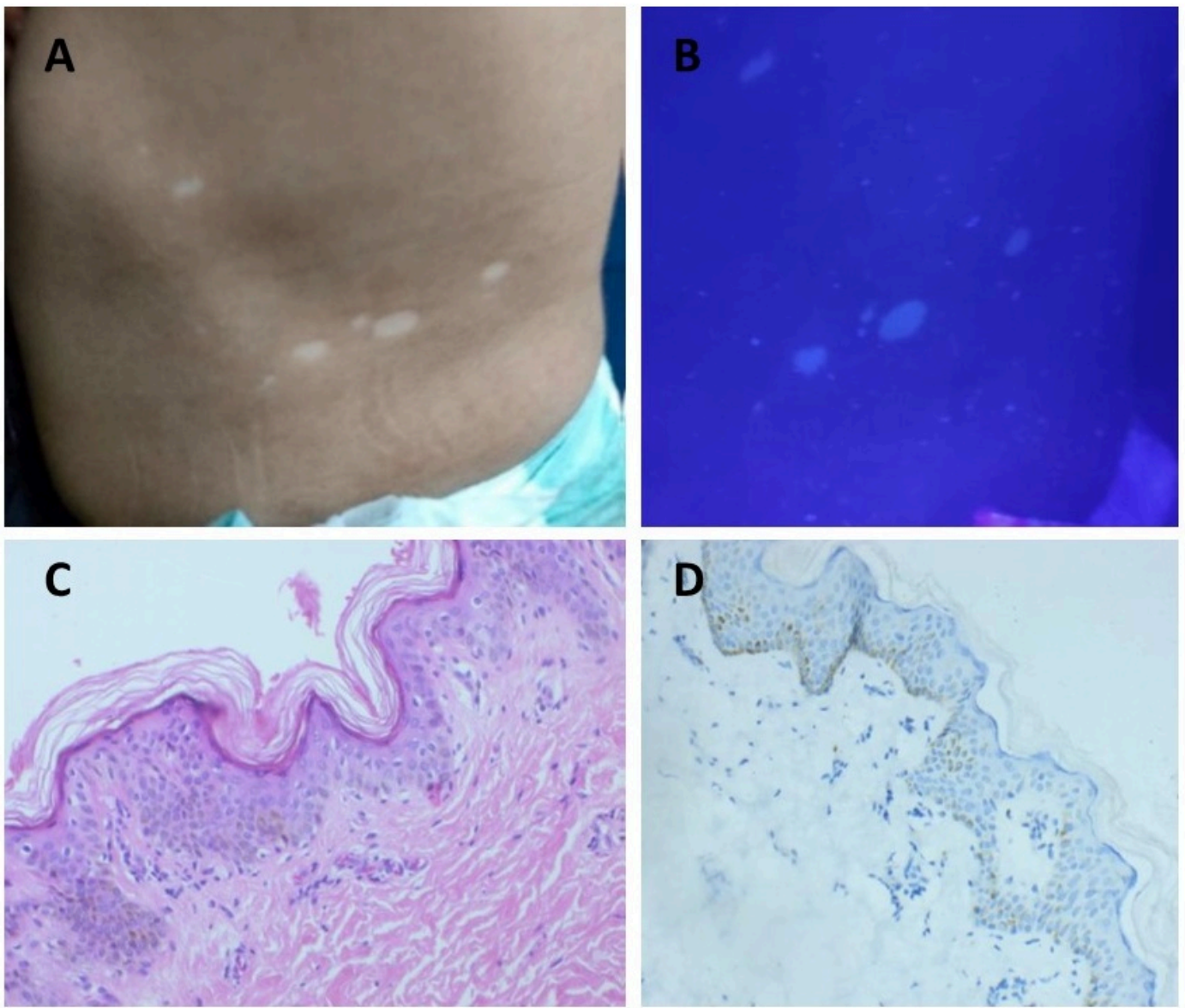


Figure 1

A- An infant with focal Nevus Depigmentosus, multiple in a blaschkoid distribution.

B- Wood's light examination showing white fluorescence.

C- Histological examination with haematoxylin and eosin showing melanocytes.

D- Sox-10 immunohistochemistry confirming presence of melanocytes.

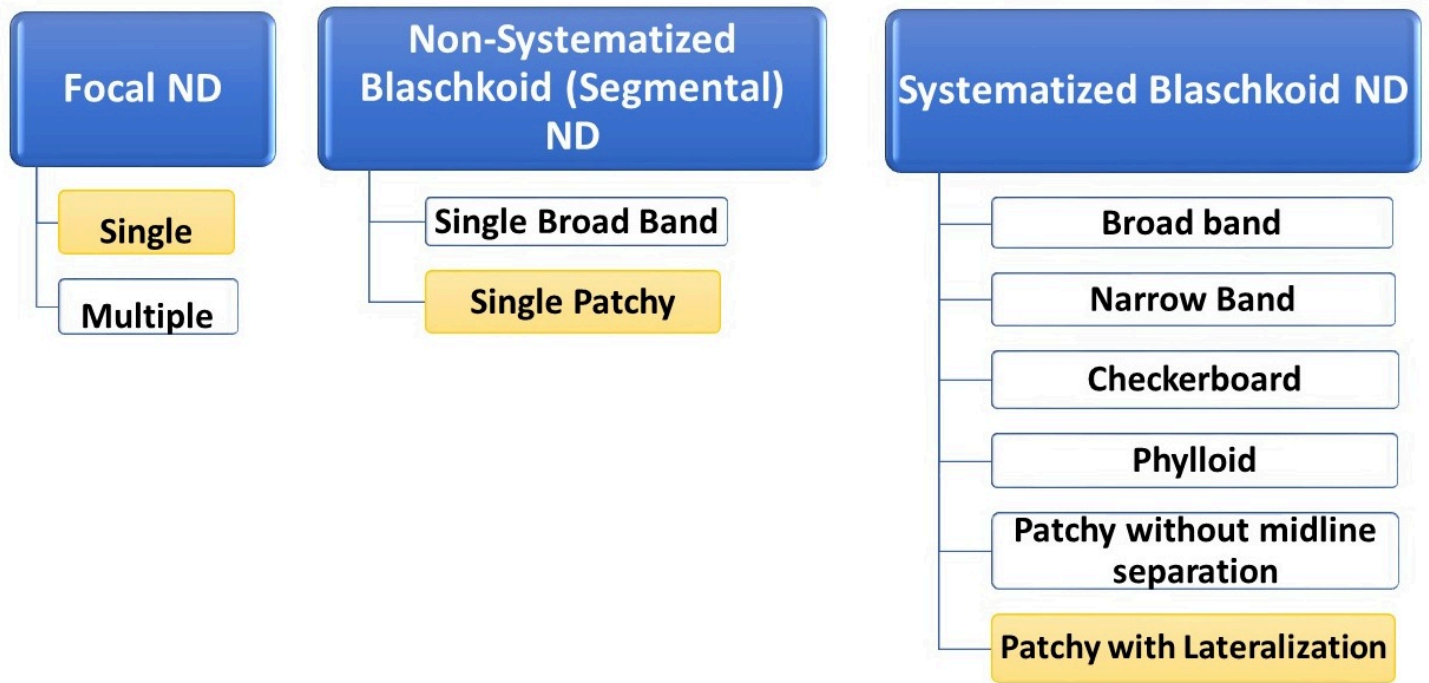


Figure 2

Modified Classification for Nevus Depigmentosus (ND). Highlighted in yellow are the most common patterns within each entity.

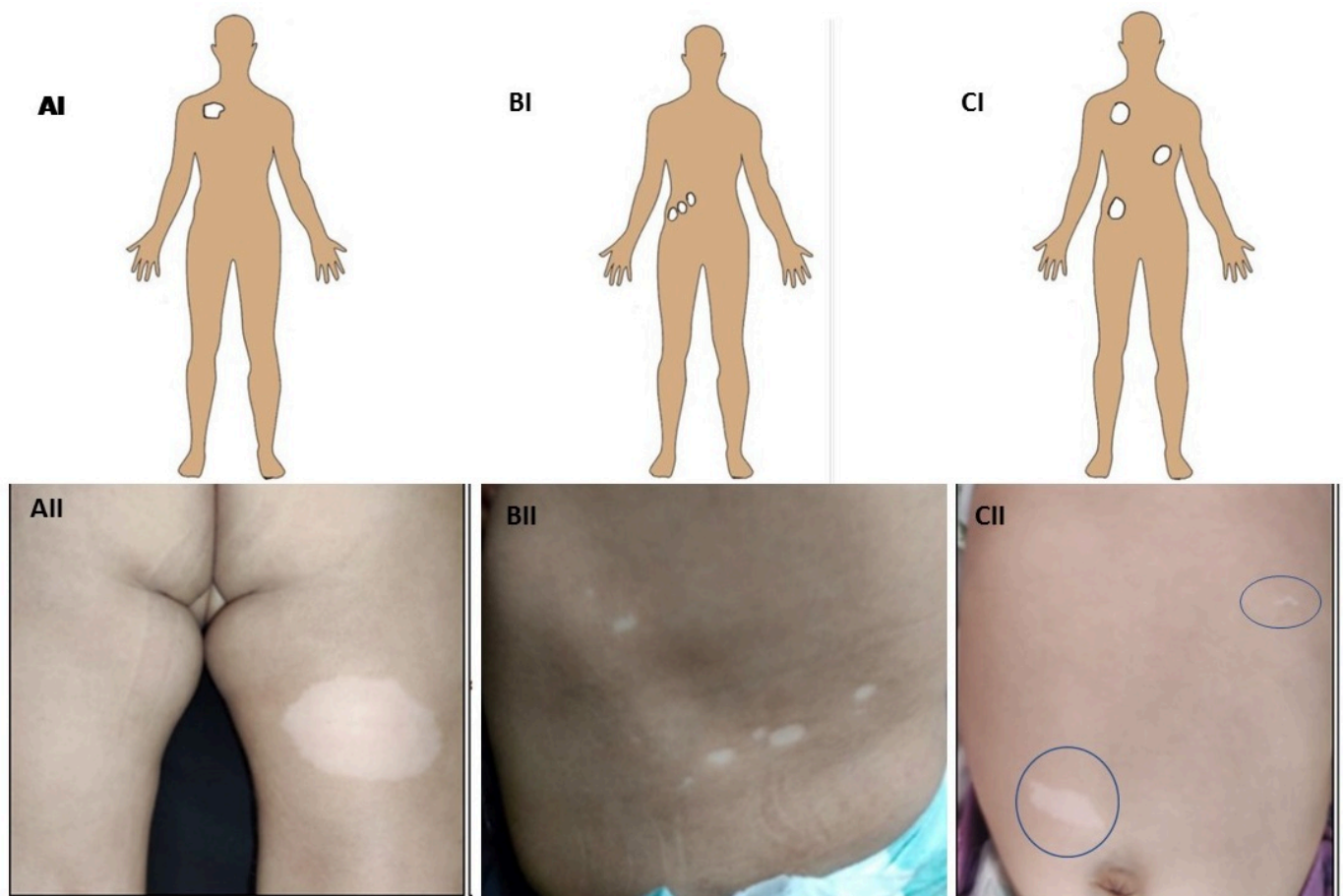


Figure 3

Focal Nevus Depigmentosis

AI: Illustrative figure showing single focal Nevus Depigmentosus (ND).

AII: An infant with single focal ND.

BI: Illustrative figure showing multiple focal ND in a blaschkoid distribution.

BII: An infant with multiple focal ND in a blaschkoid distribution.

CI: Illustrative figure showing multiple scattered focal ND.

CII: An infant with showing multiple scattered focal ND.

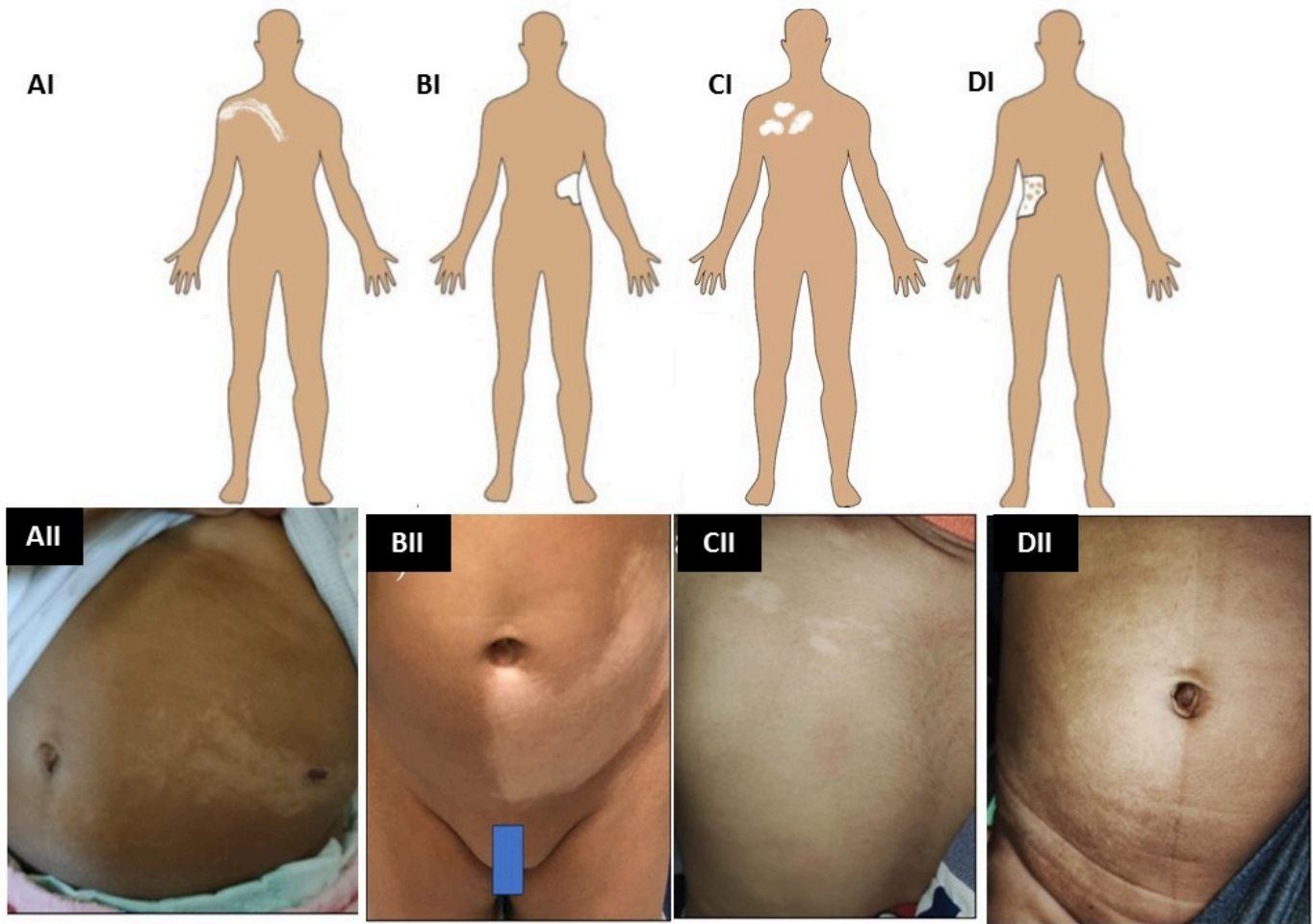


Figure 4

Non-systematized Blaschkoid nevus depigmentosus (ND)

AI: Illustrative figure showing non-systematized blaschkoid ND- single broad band pattern.

AII: An infant with non-systematized blaschkoid ND- single broad band pattern.

BI: Illustrative figure showing non-systematized blaschkoid ND- single patchy pattern with diffuse hypopigmentation.

BII: An infant with non-systematized blaschkoid ND- single patchy pattern with diffuse hypopigmentation.

CI: Illustrative figure showing non-systematized blaschkoid ND- single patchy pattern, interrupted by islands of normal skin.

CII: An infant with non-systematized blaschkoid ND- single patchy pattern, interrupted by islands of normal skin.

DI: Illustrative figure showing non-systematized blaschkoid ND- single patchy pattern, with mottled pigmentation.

DII: An infant with non-systematized blaschkoid ND- single patchy pattern, with mottled pigmentation.

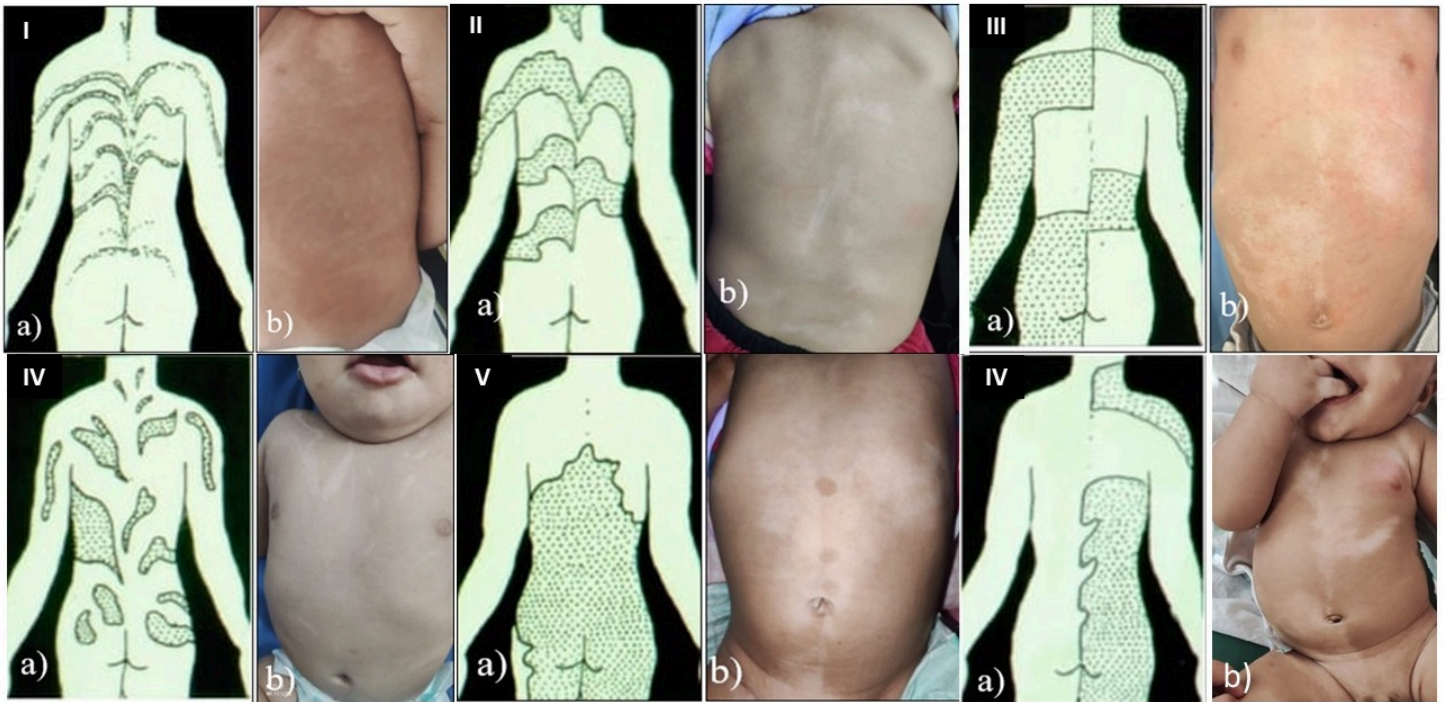


Figure 5

Systematized blaschkoid nevus depigmentosus (ND) (adapted from Happle, 2006)

I: a- Illustrative figure showing narrow band pattern; b- An infant with systematized blaschkoid ND – narrow band pattern.

II: a- Illustrative figure showing broad band pattern; b- An infant with systematized blaschkoid ND – broad band pattern.

III: a- Illustrative figure showing checkerboard pattern; b- An infant with systematized blaschkoid ND – checkerboard pattern.

IV: a- Illustrative figure showing narrow band pattern; b- An infant with systematized blaschkoid ND – narrow band pattern.

V: a- Illustrative figure showing patchy without midline separation pattern; b- An infant with systematized blaschkoid ND – patchy without midline separation pattern.

VI: a- Illustrative figure showing patchy with lateralization pattern; b- An infant with systematized blaschkoid ND – patchy with lateralization pattern.

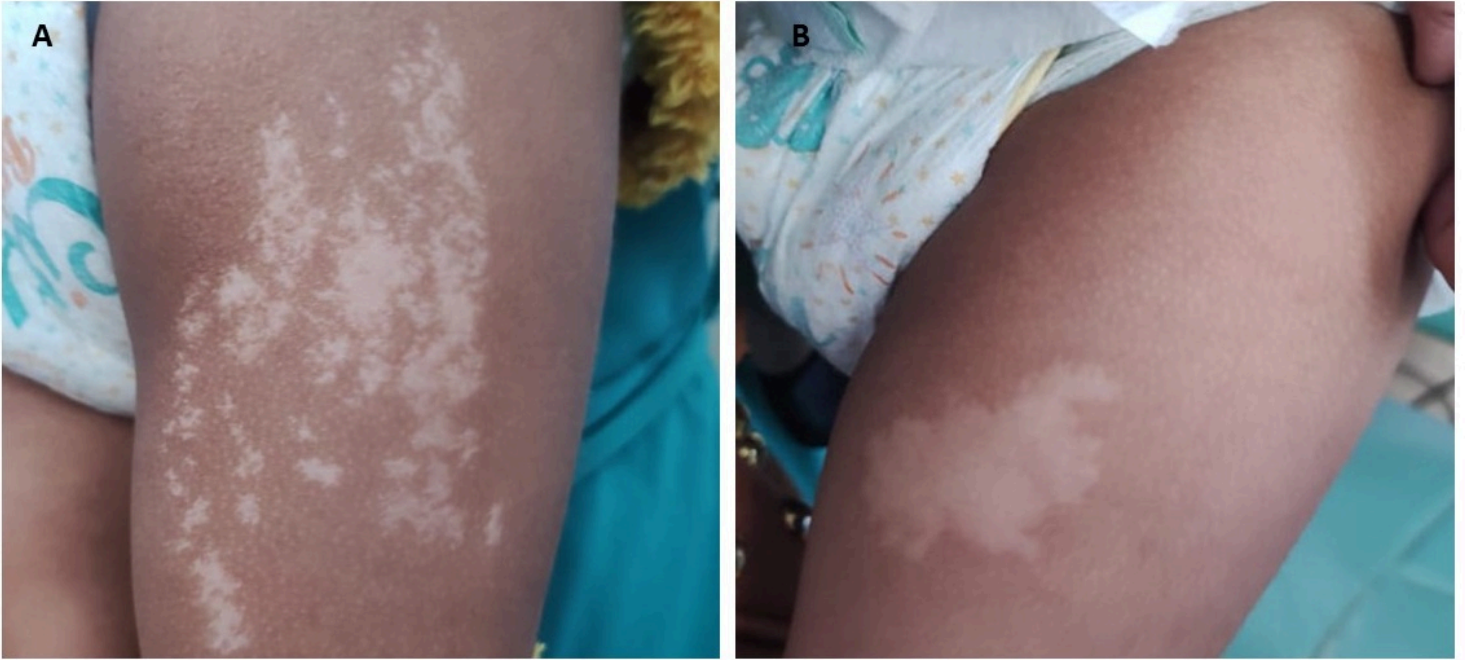


Figure 6

An infant with combined patterns of nevus depigmentosus (ND) (focal ND and non-systematized blaschkoid ND- patchy interrupted pattern)

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Table1.docx](#)
- [Table2.docx](#)