Cutaneous lesions and disorders in healthy neonates and their relationships with maternal-neonatal factors: a cross-sectional study

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Background: **Cutaneous lesions are very common in neonates. Although a number of studies have reported on their incidence, very little is known about the factors that influence them. We set out to investigate a large population of neonates with the aims of achieving an overall picture of neonatal skin manifestations, and examining their relationships with various maternal, neonatal and perinatal factors.**

Methods: **This study was conducted on neonates born at the Department of Obstetrics and Gynaecology at the University of Szeged between June 2013 and July 2015. A total of 4658 consecutive infants underwent a whole-body skin examination within the first 72 hours of extrauterine life. The official neonatal medical charts were used to collect data on the history of the participating neonates and on maternal factors.**

Results: **74.35% of the neonates exhibited at least one skin manifestation. The major diagnosis groups were transient, benign cutaneous lesions; vascular lesions; traumatic, iatrogenic, congenital or acquired disorders with skin injuries; pigmented lesions; and developmental abnormalities or benign skin tumours. The relationships between the skin findings and six neonatal or maternal factors were examined: gender, gestational age and birth weight of the neonates; maternal age and the number of previous pregnancies of the mothers, and mode and circumstances of the delivery.**

Conclusions: **We found several significant correlations between the examined maternal/neonatal factors and the occurrence of birthmarks and neonatal skin disorders. Of course, further studies are required to confirm and better understand these associations.**

World J Pediatr 2017;13(6):571-576

Key words: **cutaneous lesions; dermatology; epidemiology; neonates**

Original article

Introduction

The skin of a mature neonate is not immaculate in every case; cutaneous lesions are relatively common in the neonatal period. The delivery, the intrapartal traumas, the first encounter with the extrauterine world, the microbial colonization and the anatomical and physiological adaptations of the skin all leave their marks on the integument. Fortunately, the majority of these cutaneous conditions are physiological, reversible and spontaneously regressing lesions that require no therapy; nevertheless, inexperienced, concerned parents frequently need reassurance of the benign nature of these lesions.

Although there have been a small number of epidemiological studies on the frequency of neonatal skin conditions, only limited and controversial data are available on the factors that influence the appearance of birthmarks.[1-11] Mostly, these studies included the examination of 500-1000 neonates, and were conducted in Asia;[1-3,5-9] few studies on neonatal skin manifestations have been reported in Europe.[4] Some reports detected all the skin manifestations found, whereas others examined only some specific condition, such as erythema toxicum neonatorum (ETN).[10,11] In certain studies, the correlations between skin disorders and neonatal factors (gender, gestational age, birth weight and Apgar score) were examined, while some authors[3,4,6-9] also studied the associations with such maternal factors as age, parity, toxic habits and maternal diseases.

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doi: 10.1007/s12519-017-0063-0

The aims of this cross-sectional study were to determine the incidence of cutaneous findings in a large group of essentially healthy, term or late preterm Caucasian Hungarian neonates, within the first 72 hours after birth; the associations between various maternal and neonatal factors and the appearance of birthmarks were examined. The results were compared with those studies in the literature.

Methods

The study was conducted between June 2013 and July 2015, after approval and permission had been obtained from the Institutional Review Board of Albert Szent-Györgyi Medical Center at the University of Szeged. The neonates were examined in the Department of Obstetrics and Gynaecology at the University of Szeged, a unit that provides observation and attendance of healthy, mature neonates.

The examinations were performed three times a week by two dermatologists experienced in paediatric dermatology, and a medical student who had acquired appropriate skills in examining neonates, in the presence of the neonatologists working in the Neonatal Care Unit. The average length of hospital stay is 3 days, therefore all consecutive neonates in a stable condition after their first bath were examined (during the first 3 days after birth). The entire skin surface was examined carefully, under good illumination, including the scalp, palms, soles, nails and genitalia. All skin manifestations and disorders were registered; the diagnoses were made on the basis of clinical and morphologic features, no skin biopsy was performed. In the event of diagnoses requiring observation or therapy, the further tasks were shared with the parents. Data relating to the neonatal history of the participating neonates (gestational age, mode and circumstances of delivery, birth weight and length), and information on maternal factors (age and parity) were obtained from the official neonatal medical charts.

Statistical analysis

Data were collected and documented through the use of Excel tables and SPSS 22.0 were used for statistical analysis. The relationships between skin lesions and different maternal or neonatal aspects were calculated by using the Pearson Chi-squared test and Fischer's exact test; Continuous variables were compared using binary logistic regression and Poisson regression; $P \leq 0.05$ was considered statistically significant.

Results

A total of 4658 Caucasian neonates, 2261 (48.54%) females and 2397 (51.46%) males, were examined. Their gestational age ranged between 34 and 42 weeks (mean gestational age: 38.9±1.2 weeks). The mean birth weight was 3373.7±469.1 g; 156 (3.35%) weighed less than 2500 g, 4095 (87.91%) weighed between 2500 and 4000 g, and 407 (8.74%) weighed more than 4000 g. The mean birth length was 49.7±2.0 cm. The mean birth weight (3437.5±477.4 g) and birth length (50.07±2.03 cm) of the males were significantly higher than those of the females (3306.1±450.6 g and 49.29±1.96 cm, respectively) (P=0.000). The number of vaginal deliveries was 2625 (56.35%); the use of a vacuum extractor or forceps was needed in 86 (1.85%) cases. A total of 2033 (43.65%) children were born by cesarean section. The average maternal age was 30.9±5.3 (13-48) years. The mothers had been pregnant 2.2±1.4 times, from which pregnancies 1.8±0.97 children were born. Meconium-stained amniotic fluid was observed in 169 (3.6%) cases.

Three thousand four hundred and sixty-three neonates (74.35%) exhibited at least one skin manifestation. The cutaneous findings were assigned to five categories: transient, benign cutaneous lesions (52.5%), vascular lesions (34.1%), traumatic, iatrogenic, congenital or acquired disorders with skin injuries (7.9%), pigmented lesions (4.3%) and developmental abnormalities, benign tumours and cysts (1.2%) (Table 1).

In our study, the relationships between the skin findings and six different factors were also examined: the gender, gestational age and birth weight of the neonate, the maternal age, the number of previous pregnancies, and the mode and circumstances of the delivery. The significant correlations are shown in Table 2.

Correlation of the incidence of cutaneous findings and gender

We found a significantly higher incidence of transient, benign cutaneous lesions, sebaceous gland hyperplasia (SGH) (P<0.001), congenital or acquired disorders with skin injuries (P=0.050) and (within the latter diagnostic group) erosion (P=0.010), in the males. Vascular lesions (P<0.001), naevus simplex (NS) (P<0.001) and Hemangioma precursor lesions (P=0.031) occurred significantly more commonly among the females. The most frequent sites of NS were the occipital region (41.9%), the upper eyelids (29.4%) and the glabella (14.8%); Hemangiomas were mainly localized on the face (23.3%), on the trunk (20%) and on the buttocks (20%).

Correlation of the incidence of cutaneous findings and gestational age

The presence of ETN (P<0.001), dry, desquamating skin (P<0.001), milia (P<0.001), vascular lesions (P=0.010) and NS (P=0.020) correlated significantly with a higher gestational age; whereas the incidence of SGH (P<0.001), cutis marmorata (CM) (P<0.001)

Table 1. The frequency of cutaneous lesions seen in 4658 neonates in the first 72 hours of extrauterine life, and their distribution according to gender, *n* (%)

Cutaneous lesions	Total	Female	Male	*P* value
Transient, benign skin lesions*	2428 (52.13)	1113 (49.23)	1315 (54.86)	<0.001*
Sebaceous gland hyperplasia*	1365 (29.30)	613 (27.11)	752 (31.37)	0.001*
Erythema toxicum neonatorum	1060 (22.76)	487 (21.54)	573 (23.90)	0.054
Dry, desquamating skin	353 (7.58)	160 (7.08)	193 (8.05)	0.209
Milia	126 (2.71)	57 (2.52)	69 (2.88)	0.452
Miliaria crystallina	53 (1.14)	24 (1.06)	29 (1.21)	0.633
Cutis marmorata	30 (0.64)	17 (0.75)	13 (0.54)	0.372
Neonatal cephalic pustulosis	22 (0.47)	10 (0.44)	12 (0.50)	0.772
Acrocyanosis	8 (0.17)	3 (0.13)	5 (0.21)	0.727
Transient neonatal pustular melanosis	4 (0.09)	0 (0.00)	4 (0.17)	0.125
Vascular lesions*	1895 (40.68)	1030 (45.56)	865 (36.09)	<0.001*
Naevus simplex*	1796 (38.56)	977 (43.21)	819 (34.17)	<0.001*
Hemangioma precursor lesion*	109 (2.34)	64 (2.83)	45 (1.88)	0.031*
Hemangioma	30 (0.64)	15 (0.66)	15 (0.63)	0.872
Port-wine stain	30 (0.64)	17 (0.75)	13 (0.54)	0.372
Traumatic, iatrogenic, congenital or acquired disorders with skin injuries*	427 (9.17)	188 (8.31)	239 (9.97)	0.050*
Hematoma, purpura, petechiae	266 (5.71)	116 (5.13)	150 (6.26)	0.097
Laceration	74 (1.59)	41 (1.81)	33 (1.38)	0.234
Caput succedaneum	65 (1.40)	25 (1.11)	40 (1.67)	0.102
Erosion*	20 (0.43)	4 (0.18)	16 (0.67)	0.010*
Diaper dermatitis	14 (0.30)	9 (0.40)	5 (0.21)	0.238
Aplasia cutis congenita	5 (0.11)	2 (0.09)	3 (0.13)	1.000
Intrauterine scar	3 (0.06)	1 (0.04)	2 (0.08)	1.000
Vesiculae, bullae	3 (0.06)	0 (0.00)	3 (0.13)	0.250
Transient neonatal bullous dermolysis	1 (0.02)	0 (0.00)	1 (0.04)	1.000
Epidermolysis bullosa	1 (0.02)	0 (0.00)	1 (0.04)	1.000
Enterovirus infection-induced skin lesions	1 (0.02)	0 (0.00)	1 (0.04)	1.000
Pigmented lesions	232 (4.98)	117 (5.17)	115 (4.80)	0.554
Mongolian spots	144 (3.09)	73 (3.23)	71 (2.96)	0.599
Congenital melanocytic naevus	73 (1.57)	41 (1.81)	32 (1.34)	0.189
Café-au-lait macule	20 (0.43)	6 (0.27)	14 (0.58)	0.096
Blue naevus	6 (0.13)	3 (0.13)	3 (0.13)	1.000
Lentigo	1 (0.02)	0 (0.00)	1 (0.04)	1.000
Linear naevoid hypermelanosis	1 (0.02)	1 (0.04)	0 (0.00)	0.485
Developmental abnormalities, benign skin tumours and cysts	70 (1.50)	31 (1.37)	39 (1.63)	0.473
Benign skin tumours and cysts	42 (0.90)	18 (0.80)	24 (1.00)	0.459
Accessory tragus	14 (0.30)	7 (0.31)	7 (0.29)	0.913
Supernumerary nipple	10 (0.21)	4 (0.18)	6 (0.25)	0.755
Tooth	1 (0.02)	0 (0.00)	1 (0.04)	1.000
Naevus sebaceus	1 (0.02)	1 (0.04)	0 (0.00)	0.485
Congenital lymphoedema	1 (0.02)	0 (0.00)	1 (0.04)	1.000
Minor anomalies	1 (0.02)	1 (0.04)	0 (0.00)	0.485

Pearson's Chi-squared test and Fischer's exact test were used. *: $P \leq 0.05$.

and diaper dermatitis (P=0.006) decreased significantly with increasing maturity.

Correlation of the incidence of cutaneous findings and birth weight

ETN (P<0.001), dry, desquamating skin (P=0.024) and milia (P<0.001) occurred significantly more often in neonates with higher birth weight. Congenital or acquired disorders with skin injuries (P<0.001), and hematoma, petechiae and purpura (P<0.001) also proved to be significantly associated with a higher birth weight, whereas the incidence of CM (P<0.001) decreased with increasing birth weight. Since the birth length correlated closely with the birth weight, this factor was not examined separately.

Table 2. Significant correlations between the incidence of cutaneous findings, neonatal, maternal and perinatal factors

Cutaneous lesions	Related parameters	*P* value	OR (95% CI)
Transient, benign skin lesions	Males	<0.001	-
	Higher gestational age	0.021	1.057 (1.009-1.108)
Sebaceous gland hyperplasia	Males	0.001	-
	Lower gestational age	<0.001	0.899 (0.855-0.946)
	Higher maternal age	0.005	1.018 (1.005-1.030)
Erythema toxicum neonatorum	Higher gestational age	<0.001	1.224 (1.153-1.299)
	Higher birth weight	<0.001	1.000 (1.000-1.001)
Dry, desquamating skin	Higher gestational age	<0.001	1.351 (1.223-1.492)
	Higher birth weight	0.024	1.000 (0.999-1.000)
	Meconium-stained amniotic fluid	<0.001	-
Milia	Higher gestational age	<0.001	1.435 (1.214-1.697)
	Higher birth weight	<0.001	1.001 (1.000-1.001)
Cutis marmorata	Lower gestational age	<0.001	0.531 (0.416-0.678)
	Lower birth weight	<0.001	0.998 (0.997-0.999)
	Cesarean section	0.003	-
Vascular lesions	Females	<0.001	-
	Higher gestational age	0.010	1.065 (1.015-1.118)
Naevus simplex	Females	<0.001	-
	Higher gestational age	0.020	1.059 (1.009-1.112)
Hemangioma precursor lesions	Females	0.031	-
Traumatic, iatrogenic, congenital or acquired disorders with skin injuries	Males	0.050	-
	Higher birth weight	<0.001	1.000 (1.000-1.001)
	Primiparity	<0.001	-
	Vaginal delivery	<0.001	-
	Assisted delivery	<0.001	-
Hematoma, petechiae, purpura	Higher birth weight	<0.001	1.001 (1.000-1.001)
	Primiparity	0.001	-
	Vaginal delivery	<0.001	-
	Assisted delivery	<0.001	-
Caput succedaneum	Primiparity	<0.001	-
	Vaginal delivery	0.001	-
	Assisted delivery	0.009	-
Erosion	Males	0.010	-
Diaper dermatitis	Lower gestational age	0.006	0.604 (0.421-0.868)
Pigmented lesions	Lower maternal age	<0.001	0.957 (0.933-0.980)
Mongolian spots	Lower maternal age	0.001	0.947 (0.918-0.977)

Pearson's Chi-squared test, Fischer's exact test and binary logistic regression were used, significance level: $P \leq 0.05$. OR: odds ratio; CI: confidence interval; "-": no data.

Correlation of the incidence of cutaneous findings and the route/circumstances of delivery

Cutaneous conditions were significantly more frequent in vaginally born infants, as were traumatic, iatrogenic, congenital or acquired disorders with skin injuries (P<0.001), hematoma, petechiae and purpura (P<0.001), and caput succedaneum (CS) (P<0.001). CM proved to be significantly associated with cesarean section (P=0.003). There was a significantly higher incidence of traumatic skin lesions (P<0.001), hematoma, purpura, petechiae (P<0.001) and CS (P=0.009) following the use of a vacuum extractor or forceps. In the event of meconium-stained amniotic fluid, the frequency of dry, desquamating skin was significantly higher (P<0.001).

Correlation of the incidence of cutaneous findings and maternal age

The frequency of SGH (P=0.005) increased, whereas those of pigmented lesions (P<0.001) and Mongolian

spots (MSs) (P<0.001) decreased with increasing maternal age. No other significant correlations were found between the incidence of cutaneous findings and maternal age.

Correlation of the incidence of cutaneous findings and parity

Traumatic, iatrogenic, congenital or acquired disorders with skin injuries (P<0.001), hematoma, purpura, petechiae (P<0.001) and CS (P<0.001) were significantly more prevalent among first-born neonates.

Discussion

The majority of neonatal skin conditions are physiological, reversible and spontaneously regressing lesions requiring no therapy; however, a few initially unspecific and minor lesions may draw attention to significant disorders affecting the internal organs. In this cross-sectional study, the vast majority of the neonates presented some kind of cutaneous lesions.

52.5% of the skin findings comprised transient, benign lesions. In this group, SGH was observed most commonly in 29.30% of the neonates. This transient lesion, a manifestation of maternal androgen stimulation, appears in the form of white or yellow follicular papules, mainly over the nose.[1,2,12-15] There was a significantly higher incidence of the lesion in males; in agreement with Nanda et al,[1] we found that SGH was significantly more common in neonates of a lower gestational age.

ETN (Fig. A) presents as erythematous macules, papules or pustules resembling flea bites. In previous reports,[1-9,13,15-18] the frequency of ETN varied widely between 1.3% and 40.8%; the incidence in our study population was 22.76%. There are conflicting results conserning the predisposing factors. Some studies[10,11] found a significant correlation between the frequency of the lesion and vaginal delivery, whereas another[6] revealed a higher incidence in neonates born by cesarean section. Liu et al[10] and Sadana et al[9] observed an association with primiparity, whereas others[6,7] detected a higher frequency in cases of multiparity. The data relating to the frequency according to gender were also contradictory. Liu et al[10] reported a higher occurrence in males, whereas Sadana et al[9] demonstrated a correlation with female gender. In our study, ETN occured more frequently in males (23.9%) than in females (21.54%), but the difference was not significant. In accordance with several previous studies,[2-5,7,9-11,15,16] we found a significant correlation between the occurrence of ETN and a higher gestational age or birth weight. These latter findings correlated well with the most generally accepted view that ETN is a result of the immunological response of the skin to microbiological colonization, a condition which presupposes a certain degree of maturity of the immune system.

Dry skin with desquamation was seen in 7.58% of the neonates. Consistent with other reports,[2,3,7-9,15] we detected a significant correlation between the incidence of this transient skin finding and a higher gestational age; moreover, there was a significant association with meconium-stained amniotic fluid. Milia are considered to be more common in infants of higher birth weight,[3,7,9] our results confirmed this observation. In our study, physiological CM resulting

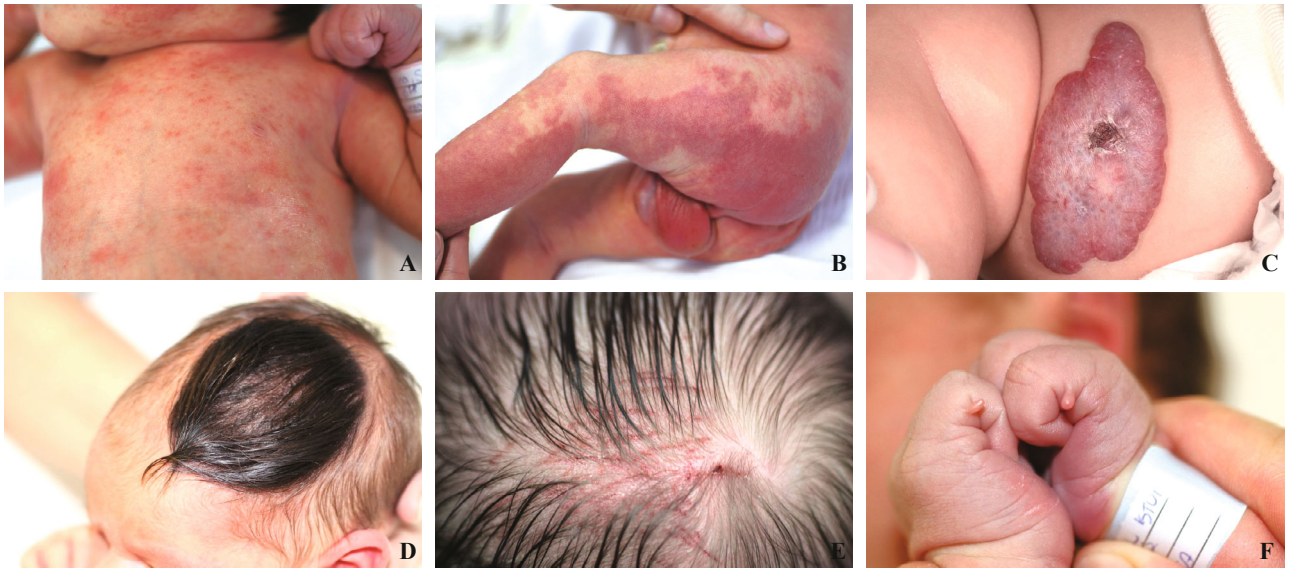

Fig. Skin lesions. **A:** Erythema toxicum neonatorum; **B:** Port-wine stain; **C:** Ulcerated Hemangioma; **D:** Congenital melanocytic naevus on the scalp; **E:** Lacerations on the scalp after cesarean section; **F:** Bilateral supernumerary digits.

from vasomotor instability was more common in neonates born by cesarean section than in those born vaginally; additionally, we observed a correlation between the presence of the phenomenom and a lower gestational age and birth weight. This association may reflect the greater vulnerability of these neonates, who are therefore more likely to present with adaptation disorders and vasomotor instability.

NS affected 1796 neonates. It is not a true vascular malformation, but is presumed to appear as a result of transient immaturity of the vascular innervation and the persistence of the local fetal circulation.[12,14,19-23] Previous studies relating to different countries and ethnic groups[1-9,13,15-18,24-26] reported widely varying incidences of the lesion (1.3%-83%). In agreement with other reports,[5,17] we detected a significantly higher incidence in females. Whereas El Moneim et al[3] reported a relationship between NS and a low birth weight, we did not detect a significant correlation between them. However, like others,[2,16] we found a higher incidence in neonates with a higher gestational age.

In contrast with NS, naevus flammeus (or port-wine stain) (Fig. B) is a true capillary vascular malformation that ordinarily presents as a unilateral, often segmental, red or livid macule. The lesions persist throughout life, becoming darker, more raised, infiltrated and nodular over time. Its prevalence in neonates was earlier reported as 0.04%-3.3%.[1,3-5,9,13,16-18,24-26] The rate in our study was 0.64%.

Hemangiomas typically appear shortly after birth (infantile Hemangiomas), though in 1.1%-2.6% of the neonates they are already present at birth (congenital Hemangiomas) (Fig. C). After birth, the sites of the subsequent Hemangiomas are often indicated only by a teleangiectic patch surrounded by a pale halo. Our survey revealed Hemangioma in 0.64% of the neonates, while a further 2.34% exhibited teleangiectic macules possibly corresponding to an incipient Hemangioma. Although Hemangiomas are often considered to be more common in preterm infants,[5,6,14,15,17-22,24-30] we did not detect such an association; however, it is important to mention that the number of preterm infants in our study was very low.

Pigmented lesions were seen in 232 neonates, of which MSs were the most frequent. MSs are bluish-grey macules that evolve in consequence of the residual melanocytes trapped in the dermis in the course of embryonal migration. Their prevalence varies widely among different racial and ethnic groups: they are much more common in the black, native American, Asian and Hispanic populations (60%-90%).[1-9,13,15-18,24-26] The incidence in our study was much lower: we observed MSs in 144 cases. In disagreement with some previous reports,[2,7,9] the gestational age and birth weight did not correlate with the incidence of MSs, but the frequency of MSs decreased with increasing maternal age.[14,31,32] The reported incidence of congenital melanocytic naevi (Fig. D) is 0.15%-2.7%,[1-9,13,15-18,24-26] and it was 1.57% in our studied neonates. Some hypopigmented disorders, such as albinism, piebaldism, naevus depigmentosus and naevus anaemicus may rarely also be seen in newborns.

Congenital or acquired disorders with skin injuries (Fig. E) affected 9.17% of our neonates. We detected significant correlations between primiparity, vaginal delivery, a higher birth weight and the incidence of traumatic lesions. This can be explained in that the larger size of the neonate, the more rigid the pelvic structures and the tighter the birth canal of primiparous mothers make the passage through the birth canal more difficult. Traumatic lesions were also significantly more frequent in males than in females, which may account for the significantly higher birth weight and birth length of male infants. In agreement with Ekiz et al,[6] our survey revealed significant associations between primiparity, vaginal delivery and CS. This is suggestive of the role of trauma in the aetiology of CS: during delivery, the foetal skull and the cervix tighten each other, resulting in serosanguinous, subcutaneous oedema that is generally absorbed spontaneously in several days. Moreover, a significantly higher proportion of the neonates born vaginally or with a higher birth weight exhibited hematoma, purpura or petechiae. Following the use of a vacuum extractor or forceps, the incidence of traumatic skin lesions, hematoma, purpura or petechiae and CS was also significantly higher; Nanda et al[1] reported similar results. However, we observed no case of incontinentia pigmenti, this disorder is also important to be mentioned, regarding the fact, that the skin manifestations usually appear during the neonatal period. It is an X-linked dominant neuroutaneous syndrome including cutaneous, neurologic, ophtalmologic and dental abnormalities. Typically, the cutaneous lesions follow the Blaschko lines, and progress through 4 stages (vesicular, verrucous, hyperpigmented and hypopigmented or atrophic). We observed developmental abnormalities and benign skin tumours in only 1.5% of the neonates (Fig. F).

Our report provides new epidemiological data on the incidence of neonatal skin conditions in the Caucasian race. As far as we know, this is the largest and most detailed descriptive study conducted to date in Europe, and at the same time it includes a detailed analysis of various maternal and neonatal factors.

A relevant limitation of our study is the potentially missed observation of transient benign neonatal skin conditions, i.e., ETN. The individual lesions of ETN disappear rapidly, usually within a few hours or days; the rapid and spontaneous regression of the lesions does not facilitate the determination of the exact incidence of the skin condition. Other benign conditions, such as

NS, infantile Hemangioma, or Hemangioma precursor lesions cannot be recognized in the first few days of life, and in these cases re-examination of the infants is therefore recommended.

In conclusion, significant differences in incidence are principally observed as concerns common skin conditions such as NS, ETN, SGH and MS. Such differences may be due in part to geographical and climatic factors. The frequency of some cutaneous lesions (e.g., MSs) differs significantly as a function of the skin type and skin pigmentation in the various ethnic groups. In our study, it emerged that the gender, gestational age and birth weight of the neonates, the maternal age, the parity, and the mode and circumstances of the delivery may all have a significant influence on the occurrence of neonatal cutaneous lesions. Of course, further studies are necessary to acquire more exact knowledge of the factors influencing the development of neonatal skin conditions.

Funding: Csoma Z is supported by the János Bolyai Research Scholarship from the Hungarian Academy of Sciences (2015-2018).
Ethical approval: The study was approved by the Institutional Review Board of Albert Szent-Györgyi Medical Center at the University of Szeged.
Competing interest: None declared.
Contributors: Ábrahám R participated in the skin examinations, collected and analyzed data and wrote the main manuscript. Meszes A participated in the skin examinations and contributed to the acquisition of data. Gyurkovits Z and Bakki J contributed to the acquisition of data. Orvos H designed the study and was responsible for attaining data relating to the neonatal and maternal factors. Csoma ZR designed and organized the study, participated in the skin examinations, contributed to the interpretation of data, and wrote the manuscript. All authors revised the manuscript and approved the final version to be published. Ábrahám R is the guarantor.

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Received December 22, 2015
Accepted after revision July 15, 2016