CASE REPORT

Erythrokeratodermia variabilis – variant with circumscribed variable erythema and periorificial fixed Bazex Dupré erythema

LIGIA STĂNESCU[1)], CLAUDIA VALENTINA GEORGESCU[2)], ANA CLAUDIA GEORGESCU[3)], IULIANA GEORGESCU[4)], G. CĂLIN[1)]

[1)]*Department of Pediatry, "Filantropia" University Hospital of Craiova,*
[2)]*Department of Internal Medicine*
[3)]*Department of Internal Medicine, Medical Clinic II, Emergency Departmental University Hospital of Craiova*
[4)]*Dermatologic Service, "Buna Vestire" Policlinic, Craiova*
University of Medicine and Pharmacy of Craiova

Abstract

Erythrokeratodermia represents a group of rare genetic diseases characterized through disorders of keratinization. Clinically, they are presenting themselves with erythematous and hyperkeratosic lesions that can be persistent or variable as to their aspect and localization. They were classified in erythrokeratodermia variabilis (EKV) and erythrokeratodermia symmetric progressive (EKSP). We are presenting the case of a 9-years-old child which presents from birth facial and perioral erythema; erythematous and hyperkeratosic lesions with circinate character, extremely variable, localized especially on the anterior thorax (on the chest and in the axillar and inguinal folds). The neonatal debut, the clinical and histological aspect are suggestive elements for the EKV. In addition, the child has a plan frontal angioma and a congenital horizontal nistagmus. We realized a review of a literature data being different clinical variants of presentation of EKV and the eventual possible associations. It is considered the fact that the clinical presentation in the presented case corresponds to the variant of EKV with variable circinate erythema described by Bazex and Dupré. The case is also particular through the association of a plan frontal angioma, particularly of a congenital horizontal nistagmus, associations that we could not find in the literature.

***Keywords*:** erythrokeratodermia, dermatosis, erythema.

Introduction

The term of erythrokeratodermia refers to the association of erythema and hyperkeratosis in the circumscribed lesions, persistent even though sometimes variable [1]. It is a group of rare dermatosis, clinically heterogeneous, due to a disorder of keratinizes with autosomal dominant transmission with variable penetrance. At present they are classified in: erythrokeratodermia variabilis (EKV) and erythro-keratodermia symmetrically progressive (EKSP) [1–3]. Both forms can have more clinical variants.

Patient and methods

A 9-years-old patient is admitted for round erythematosquamous plaques with anterior axillaries and inguinal localization; perioral and perinasal erythema, palmoplantar hyperkeratosis.

From personal antecedents we retain a plan horizontal angioma and congenital nistagmus.

From heredo-collateral antecedents we are discovering the presence of a generalized xerodermia associated to palmar hyperkeratosis at an 18-years-old girl, his unique sister.

From mother's affirmations results that the child at birth presented a red spot in the frontal region, an easy facial erythema, and also an erythema in the subombilical region, extended on the abdomen, the last one disappeared after 2 months. In the following months, the facial erythema ameliorated, but soon appeared red spots around the eyes, nose and mouth. It was at the same time that red spots appeared in the axillar and inguinal regions, spots that after a while disappeared and reappeared at regular periods of time. Around the age of 3, at the palmar and plantar level started to become obvious red spots that covered themselves of squama. The child has tried treatments in more clinics of dermatology, the case has been interpreted, most of the time as a cutaneous mycosis, but only passing ameliorating results were obtained.

The dermatologic exam finds out at the face, perinasal, perioral and periorbital level a diffuse erythema covered with a fine squama. In the frontal region, we could observe a plan angioma, with a

triangle aspect having the peak in the intereyebrow region and the base in the hairy limit (Figure 1).

Superiorly, on the anterior thorax, in the axillary and inguinal folds, an erythemato-squamous exanthema with circinate elements which realized a true lace trough the marginal confluence. The elementary lesion is a keratosic medallion perfectly limited, traced with the compass, which realizes polycyclic images. On the lesion, the skin is red with hyperkeratosis exaggerating the normal fold. The margin of these elements is more accentuated as compared to healthy skin and goes down in a very smooth slope to the interior of the lesion (Figure 2). At the level of palm and planta, accentuated erythema covered by hyperkeratosic squama (Figure 3).

The well-defined and round contour designs medallion net circinations, which show the fusion of the many medallions, the aspect being similar to the one, observed in the axillary and inguinal folds.

Paraclinic:

▪ Bioumoral we find no modification.

▪ Histopatologically, it was evidentiated a hyperkeratosis with focal parakeratosis and akantosis, diluted capillaries, presenting stases in the derma, the images being though nonspecific (Figures 4–7).

▪ Mycologically, the exam has excluded the eventuality of a mycosis.

The complementary clinical exams:

▪ Ophthalmologic exam notes the presence of the congenital horizontal nistagmus and a grade II hypermetropia.

▪ The neuropsychiatric exam discovers, additionally to the nistagmus, a liminal intellect probably because of "the deficit of intake" and of a mixed nevrosis. EEG has been suggestive in this case, presenting pathological grapho-elements of a mixed type with the predominance of the irritant ones, with a maxim of incidence in bilateral parietal records and relative symmetric increase by hyperventilation.

The genetic tests, the only ones who could certify the supposed diagnosis of erythrokeratodermia variabilis, could not be performed. We retain however from the anamnesis the presence of the lesions from birth and the fact that he has a sister with generalized xerodermia and plantar keratosis.

Evolutively, it is important to note that during the admission, while some lesions disappeared for a while, new identical lesions were appearing in other places attesting the variable aspect of the affection.

The clinical aspect, the anamnesis, the histopathological exam, the evolutive character conducted us to the establishment of the diagnosis of erythrokeratodermia variabilis.

Therapeutically, the administration of the emollient and cortisone keratolitics proved to be beneficial. Considering the fact that the dose of oral retinoids for children has not been yet well established, we did not use this therapeutic option.

Discussions

Erythrokeratodermia variabilis or the Mendes da Costa syndrome is a determined genetically cutaneous disease, clinically characterized by two distinctive morphological aspects: hyperkeratosis and the transient erythema. The first case has been signalized by de Buy Wenninger in Holland in 1907 [4], but Mendes da Costa S is the one who in 1925 realized the first detailed description of the disease at a mother and her daughter giving the name of "erythro- et keratodermia variabilis" [5]. Later, multiple cases have been described in Europe, and in 1964, Barsky S and Bernstein G reported the first case in America [6].

Physiopathologically, EKV is a disturbance of keratinization associated with a non-inflammatory erythema. A marked hyperkeratosis is present, probably because of an augmentation of proliferation and the perturbated differentiation of keratinocytes. There have been identified mutations of the genes GJB3 and GJB4, on the chromosome 1p35 [7].

These genes encoding the gap junction of the protein b3 and b4 are from the connexin family (c respectively, connexin 31 and 30.3). Connexins are part from the group of trans-membranary proteins that participate in the formation of intercellular channels. The performed studies have proved that these mutations determine the apparition of the intercellular signalization and communication defects with the alteration of the normal differentiation of the epidermis. In addition, it was observed a high interfamilial phenotypical variability, suggesting a tight connection of the genetically and epigenetically modifying factors. It has been confirmed the genetically heterogeneity in EKV and it has been underlined that the epidermical differentiation is significantly affected by intercellular communication mediated by Cx31 and Cx 30.3 [2, 3].

Morphopathologically, the modifications are not specific. Irregular hyperkeratosis and acanthosis most often at a very high degree are associated with dermical variable edema and cellular infiltrate. The studies with tritiated thymidine in the affected skin have shown a normal dimension [8]. In the electronic microscopy, it was observed an important reduction of keratinosomes [9].

Clinically, the manifestations are extremely variable in a single family and at the same individual. The lesions that are of two types, erythema and hyperkeratosis are usually present at birth or in the first months of life or towards the third year life, but occasionally they can develop later. The erythema in EKV appears like well-limited spots of variable intensity, sometimes surrounded by an anemic halo. These can enter in coalescence making big figurate plaques or with circinate aspect. They can appear in the healthy skin and in the hyperkeratosis plaque. Every erythematous lesion is temporary, persisting minutes to hours, though sometimes they can persist for days.

In almost 35% of the cases, the erythema can be preceded or accompanied by a sensation of burn causing a discomfort state to the patient. The most frequent are the buttocks and the face, the late appeared colored in red. The remarkable variability of the spots in number, dimension, form, localization and duration is the typical aspect for EKV reflected in his name [10–12].

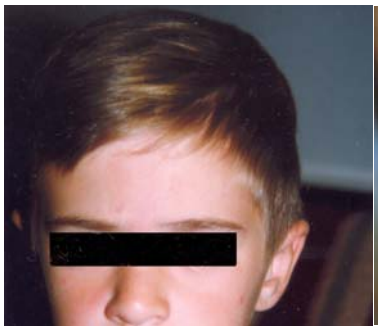

Figure 1 – ***Vascular rectangular spot having the peak in the inter eyebrow region (plan angioma)***

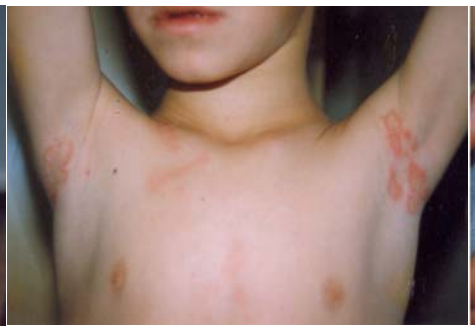

Figure 2 – ***Erythematosquamous cincinate lesions, well delimited, realizing through confluence poly-clinical images***

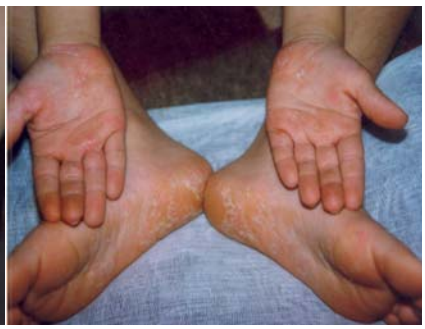

Figure 3 – ***Erythema, covered by hyperkeratosic squama at the level of palms and planta***

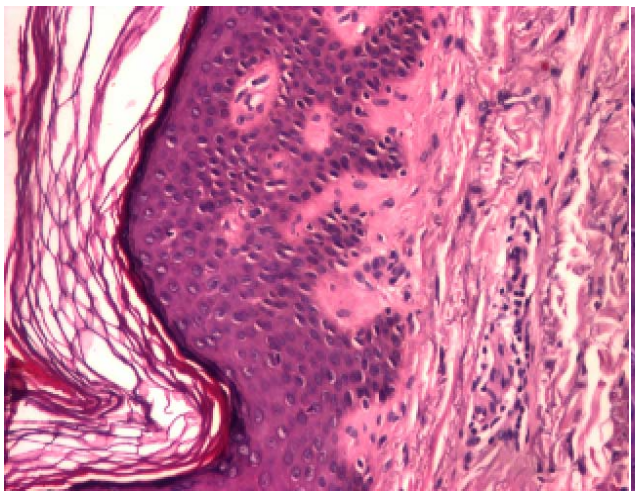

Figure 4 – ***Hyperkeratosis, akantosis and papillomatosis***

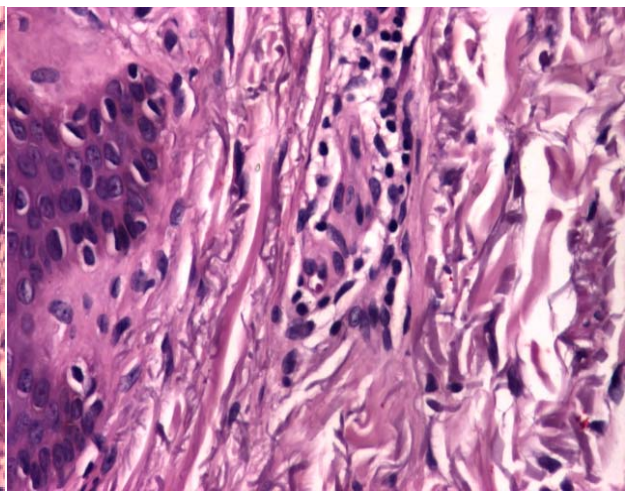

Figure 5 – ***Dilated capillaries with stasis in dermis***

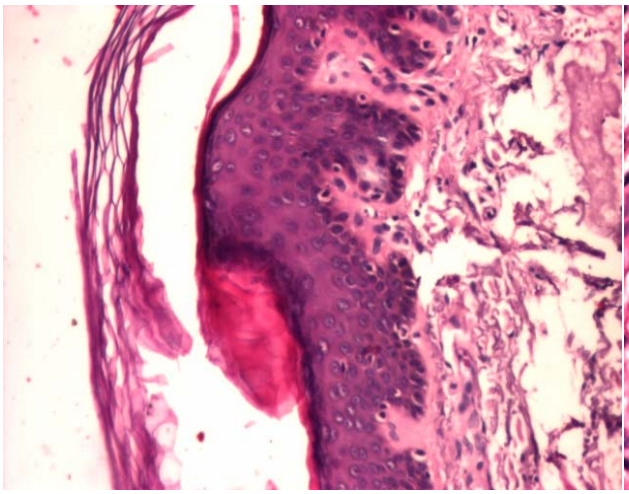

Figure 6 – ***Hyperkeratosis orthokeratosis with focal parakeratosis and papillomatosis in the papillary dermis and perivascular edema***

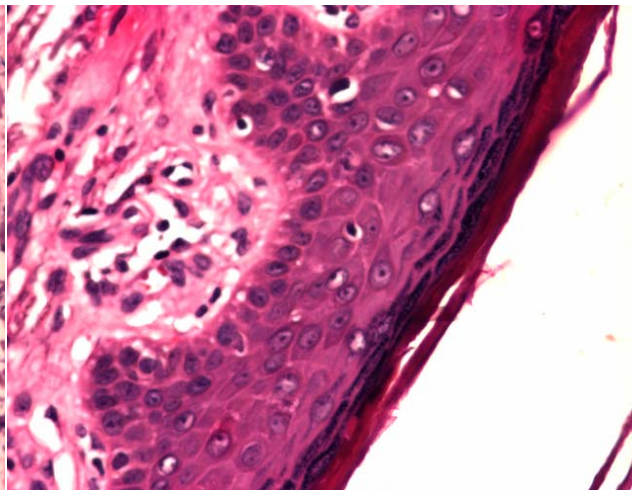

Figure 7 – ***Conservation of 2–3 granular cell layers in epidermis and discrete edema with some dilated capillaries in dermis***

Hyperkeratosis can be localized or generalized. The generalized form of hyperkeratosis appears like a yellow-brown-gray thickening of the skin with accentuation of the skin markings. Fine squama can also be present. The localized form is characterized through brown hyperkeratosis plaque with the outlined, figurate margins. Their surface can be crossed and mucous or squamous. They are distributed almost symmetrically on shank, buttocks and trunk. Often, the folds, face and the head skin are unaffected. The form and dimension of the hyperkeratosis lesions can be modified. These lesions can regress leaving healthy skin in their place.

Over the distal joints, the surface of these plaques may become velvety or have a cobblestone pattern. In almost half the affected families, hyperkeratosis involves hands and in a form of circumscribed diffuse keratodermia. In about half of the affected families, hyperkeratosis involves the palms and soles of the feet as a patchy or diffuse palmoplantar keratodermia. Often, this palmoplantar hyperkeratosis is associated with peeling. Hair, nails, teeth, and mucous membranes are not involved.

Evolutively, the disease can persist the whole life but the general aspect is not affected. After progressing at new born and little children, EKV stabilizes after puberty but regresses slowly at elderly people. The improvement and the periodical remission are is not unusual. Cutaneous lesions can be induced by internal and external factors. These factors include stress, temperature changing, cold and rarely sun exposure.

There have been described many types of erythrokeratodermia. They have been researched by Bazex and Dupré who in order to put together all the reported observations have proposed in 1956 the term of "genodermatosis with variable erythema", making a classification of the clinical forms [10]. Besides the variable erythrokeratodermia Mendes da Costa they found:

▪ Genodermatosis en cocarde Degos with round erythematous plaques of large dimension whose centre is covered by large squamas giving to the element the aspect en cocarde. These lesions disappear in three weeks and reappear in attacks. They are being associated to zones of regional hyperkeratosis (especially on the knee) more stable. The debut is early in the childhood and the buttocks and the shank are the most involved.

▪ Variable figurate Miescher Staeli keratodermia, described at two sisters with yellowish placard, peeled, on vast segments of the body, more powerful from a keratosic point of view are progressing eccentrically, with seasonal evolution.

▪ The cases with variable circumscribed erythema, with fixed periorificial erythema and congenital hypotrichosis described by Bazex şi Dupré [13].

Follow a unique conception, there has been brought as a solid argument, Sommacal-Schopf D and Schynder UW [12], after a study on 14 cases brought solid arguments showing that in the same family the existence of cases where the erithema and the keratosis found on the same plaques, while in others the erythema and the keratosis are very distinct [10].

Trying to precise the nosological limits of these affections, Leclercq MR (1962) attributed this group the following characters [14]:

▪ Hereditary character;

▪ Appearance at birth or often in the first weeks of life;

▪ Erithematous areas usually associated to distinct keratosic areas and without erythema (aspect described by Mendes da Costa);

▪ Erythrokeratosic areas that can have four aspects (or clinical forms), and can coexist at the same patient or to follow:

– The cocarde aspect (described by Degos R) with frequent central squamas and erythematous circle;

– The prominent aspect on the shanks and upper arms in the case of verrucous erythrokeratodermia in symmetrical positive surfaces (Hudelo, Boulanger, Pilet and Caillon) case in which it is not mentioned any variability but a progression of the lesion with age that makes it reserve a particular nosological part in treaties;

– The verrucous aspect that at axilla and neck can remember acanthosis nigricans (cases of Jeanselme, Nicolas, Mischer şi Staheli) or the aspect of seborrheic verruca of the face (case of Sidi);

– The pseudomycosis with periphery peeling collar is particular in the case of Burreau, Jarry and Barriere and in the case of Bazex and Dupré. The latest accompanies with unusual characters (hypotrichosis and periorificial erythemas).

The differential diagnosis is made with progressive symmetrical erythrokeratodermia, a disease inherited with autosomal dominant transmission and incomplete penetrance and variable expressivity. EKSP has a clinical presentation little well defined that EKV. It is manifesting through the presence of hyperkeratosis plaques well delimited, fixed, symmetrical, gently progressive on the body, predominant on the extension surfaces of the limbs, trunk, but on the face as well. Palmoplantar keratodermia is often present. The main distinction between EKV and EKSP is the presence of variable erythema in EKV.

Pathogenically, the proliferation of the epidermic cells is increased in EKSP [15], while is normal in EKV. This difference is produced by the different physiopathology of the two conditions – excess of production of horny cells while in EKSP and anomalies in the cohesion of the cells in the corneum stratum [16] in EKV.

Histopathologically, the aspects are similar in both conditions, but electron microscopy reveals anomalies in the cohesion of keratinocytes in the corneum stratum in EKV and without edematization of the mitochondria or an increase in their number in EKSP [16].

In the literature have been reported two sisters with erythrokeratodermia, at the little one the clinical aspect corresponds to EKV while at the oldest one the clinical aspect is relevant for EKSV, the ultrastructural aspects being identical in both cases [17].

The authors suggest that EKV and EKSP are different manifestation of one single disease. Recently, it has been identified a new locus for EKSP at 21q11.2–q21.2 [18].

Therapeutically, the oral retinoids represent the therapeutically alternative for progressive erythrodermia variabilis [19], with some reserve in children. The use of emollients and keratolytics, such as salicylic acid and topical retinoid preparations, may be beneficial.

As to the case that we have reported, this corresponds to the clinical aspect and their variability and to the neonatal debut of EKV. With the pseudomycosis aspect of the lesions and the presence of periorificial erythema, it appeared to be closer to the variant described by Bazex A and Dupré A, than the classical variant of Mendes da Costa S.

Conclusions

The particularity of the case is the association with a plan angioma, congenital horizontal nistagmus. In the literature, we can find EKV cases associated to chronic keratoconjunctivitis, with urogenital anomaly, with deafness or pachydermatoglyphs, but not with nistagmus and angioma.

References

[1] GRIFFITHS W. A. D., JUDGE M. R., LEIGH I. M., Disorders of keratinization. In: CHAMPION R. H., BURTON J. L., BURNS D. A., BREATHNACH S. M. (eds), *Textbook of Dermatology*, Blackwell Scientific Publications, Oxford, 1998, 1483–1588.

[2] RICHARD G., BROWN N., SMITH L. E., TERRINONI A., MELINO G., MACKIE R. M., BALE S. J., UITTO J., *The spectrum of mutations in erythrokeratodermias – novel and de novo mutations in GJB3*, Hum Genet, 2000, 106(3):321–329.

[3] RICHARD G., BROWN N., ROUAN F., VAN DER SCHROEFF J. G., BIJLSMA E., EICHENFIELD L. F., SYBERT V. P., GREER K. E., HOGAN P., CAMPANELLI C., COMPTON J. G., BALE S. J., DIGIOVANNA J. J., UITTO J., *Genetic heterogeneity in erythrokeratodermia variabilis: novel mutations in the connexin gene GJB4 (Cx30.3) and genotype–phenotype correlations*, J Invest Dermatol, 2003, 120(4):601–609.

[4] DE BUY WENNINGER L. M., Erythrokeratodermie congenitale ichthyosiforme avec hyperepidermotrophie. In: *Verslagen van vereeningingene*, Nederl Tijdschr Geneesk, 1907, 1A:510–515.

[5] MENDES DA COSTA S., *Erythro- et keratodermia variabilis in a mother and a daughter*, Acta Derm Venerol (Stockh), 1925, 6:255–261.

[6] BARSKY S., BERNSTEIN G., *Keratosis Rubra Figurata*, Arch Dermatol, 1964, 90:373–374.

[7] RICHARD G., SMITH L. E., BAILEY R. A., ITIN P., HOHL D., EPSTEIN E. H. JR., DIGIOVANNA J. J., COMPTON J. G., BALE S. J., *Mutations in the human connexin gene GJB3 cause erythrokeratodermia variabilis*, Nat Genet, 1998, 20(4):366–369.

[8] EBLING F. J., ROOK A., Disorders of keratinisation. In: ROOK A., WILKINSON D. S., EBLING E. J., *Textbook of Dermatology*, Blackwell Scientific Publications, London, 1982, 1285–1287.

[9] VANDERSTEEN P. R., MULLER S. A., *Erythrokeratodermia variabilis. An enzyme histochemical and ultrastructural study*, Arch Dermatol, 1971, 103(4):362–370.

[10] BAZEX A., DUPRÉ A., *Génodermatose à érythèmes circinés variables*, Ann Dermatol Syphiligr (Paris), 1956, 83(6):612–617.

[11] BROWN J., KIERLAND R. R., *Erythrokeratodermia variabilis: report of three cases and review of the literature*, Arch Dermatol, 1966, 93(2):194–201.

[12] SCHNYDER U. W., SOMMACAL-SCHOPF D., *Fourteen cases of erythro-keratodermia figurata variabilis within one family*, Acta Genet Stat Med, 1957, 7(1):204–206.

[13] DEGOS R., *Dermatologie*, Edition Flammarion, Paris, 1972, 651–655.

[14] LECLERCQ M. R., *Génodermatose en cocarde. La suite d'une observation princeps. Atteinte de deux descendantes directes*, Bull Soc Fr Dermatol Syphiligr, 1962, 69:855–860.

[15] HOPSU-HAVU V. K., TUOHIMAA P., *Erythrokeratodermia congenitalis progressiva symmetrica (Gottron). II. An analysis of kinetics of epidermal cell proliferation*, Dermatologica, 1971, 142(3):137–144.

[16] DAL MAGRO C., PELLENZ C., BAKOS L., *Symmetrical progressive erythrokeratodermia: a case report*, An Bras Dermatol (Rio de Janeiro), 2003, 78(5):587–591.

[17] MACFARLANE A. W., CHAPMAN S. J., VERBOV J. L., *Is erythrokeratoderma one disorder? A clinical and ultrastructural study of two siblings*, Br J Dermatol, 1991, 124(5):487–491.

[18] CUI Y., YANG S., GAO M., ZHOU W. M., LI M., WANG Y., CHEN J. J., YAN K. L., NIU Z. M., WANG P. G., XIAO F. L., LIANG Y. H., SUN L. D., FAN X., HUANG W., ZHANG X. J., *Identification of a novel locus for progressive symmetric erythrokeratodermia to a 19.02-cM interval at 21q11.2–21q21.2*, J Invest Dermatol, 2006, 126(9):2136–2139.

[19] VAN DER WATEREN A. R., CORMANE R. H., *Oral retinoic acid as therapy for erythrokeratoderma variabilis*, Br J Dermatol, 1977, 97(1):83–85.

Corresponding author

Ligia Stănescu, Assistant Professor, MD, PhD, Department of Pediatry, "Filantropia" University Hospital of Craiova, University of Medicine and Pharmacy, 2–4 Petru Rareş Street, 200349 Craiova, Romania; Phone +40740–182 404, E-mail: ligstanescu@yahoo.com

Received: September 15th, 2007

Accepted: October 20th, 2007