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Review Article

Etiology, prevalence and clinical signs of erythema toxicum neonatorum

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ABSTRACT

Evidence shows that Erythema toxicum neonatorum (ETN) has been described in the literature since the 15th decade as a primarily rash in pediatric patients. Clinical studies show that the lesion of ETN is mainly characterized by the presence of minute yellowish papules and pustules that are usually surrounded by an irregular reddish wheal. It should be noted that evidence also demonstrated the pathology of these lesions is temporary and usually disappears within a few hours. In the present literature review, we discussed the etiology, prevalence, risk factors, and clinical signs of ETN based on findings from relevant research. The etiology of ETN is not clear among the different studies. However, some studies show involvement of immune and potential allergic reactions. The prevalence of the condition among infants is also remarkably variable among the relevant studies worldwide. There is also inconsistency in reporting the significance of the risk factors related to the prevalence and severity of the condition. On the other hand, the clinical signs among studies seem to be consistent and easily detected except when evaluating dark-skinned infants. Further studies are needed better to understand the etiology and epidemiology of the condition.

Keywords: Erythema toxicum neonatorum, Risk factors, Etiology, Clinical manifestations, Cutaneous lesions, Pediatrics

INTRODUCTION

Evidence shows that Erythema toxicum neonatorum (ETN) has been described in the literature since the 15th decade as a primarily rash in pediatric patients.[1] It has been shown that the condition mainly develops secondary to an abnormal reaction between the affected baby's skin and meconium. Over time, studies reported that the nomination of the condition has changed over the past decades from erythema populated to erythema dyspepsia and erythema neonatorum allergicum.[1,2] Finally, another investigation was published by Leiner and suggested that the condition should be termed erythema toxicum neonatorum, which

has been used subsequently in the current literature since 1912.[3]

Clinical studies show that the lesion of ETN is mainly characterized by the presence of minute yellowish papules and pustules that are usually surrounded by an irregular reddish wheal. It should be noted that evidence also demonstrated the pathology of these lesions is temporary and usually disappears within a few hours. Moreover, evidence indicates that the affected children usually recover within a week or two, and most children usually present within the 1st week since birth. However, it has been noted that other similar lesions usually develop in another area in the body.[4] In addition, it has been shown that the lesion can affect any part of the affected patient's body except for the palms and soles. In the present literature review study, we aim to discuss the etiology, epidemiology, and clinical manifestations of ETN based on evidence from the present studies in the literature.

METHODS

This literature review is based on an extensive literature search in Medline, Cochrane, and EMBASE databases which was performed on 27th November 2021 using the Medical subject headings (MeSH) or a combination of all possible related terms, according to the database. To avoid missing potential studies, a further manual search for papers was done through Google Scholar while the reference lists of the initially included papers. Papers discussing etiology, prevalence and clinical signs of erythema toxicum neonatorum were screened for useful information. No limitations were posed on date, language, age of participants, or publication type.

DISCUSSION

Etiology

Among the different relevant studies in the literature, there is no clear evidence regarding the exact etiology of the condition. However, it has been proposed that the underlying pathophysiology is initiated and mediated by a graft-versus-host reaction against maternal lymphocytes. However, it should be noted that among more recent studies, there are no apparent guidelines or evidence events regarding this mechanism and the presence of such maternal cells within the corresponding lesions.[2] On the other hand, it has been suggested that within the first hours since birth, an abnormal immunological reaction usually develops against the underlying microbes within the hair follicles of the affected children. In the lesions of ETN, previous immunohistochemical studies of 1-day-old infants suffering from the condition indicate that relevant immune reactions are noticed with abnormal accumulation and accumulation of immune cells in the lesions of the condition.[5] The immunohistochemical evidence furtherly demonstrated that ETN lesions are usually associated with various immune mediators and cells. These include High mobility group box protein 1 ($HMGB_1$), nitric oxide synthetases 1, 2, and 3, psoriasin, aquaporins 1 and 3, eotaxin, interleukin (IL)-8, IL-1β, and IL-α. Moreover, it has been shown that tryptase-expressing mast cells are abundantly present in ETN lesions based on immunohistochemical analysis. On the other hand, such evidence indicates that cathelicidin antimicrobial peptide LL-37 is not usually detected in these lesions.[6,7] The presence of an allergic reaction might also attribute to the pathogenesis of the condition in the affected infants. In this context, it has been demonstrated that ETN lesions contained extensive amounts of eosinophils.

Prevalence and risk factors

Studies show that ETN is a condition that is usually self-limited, benign, with evanescent eruption, and transient. However, epidemiological studies indicate that the condition is common among full-term infants. The estimated prevalence of the condition in this population has been reported to range between 48% and 72%.[8] In 1986, a previous Japanese investigation included 5387 infants that were followed up for ten years to investigate the characteristics of skin lesions and the epidemiology of ETN in these infants. The authors reported that the prevalence of ETN among these infants was 40.8%. Furthermore, the authors reported that the most significant risk factor for developing the condition was found to be being a preterm infant (birth weight <2500 g).[9,10] Further epidemiological data show that the condition is not usually confined to a certain race. However, evidence indicates that the condition is more common among males.

Another Spanish investigation which included 356 newborns, aimed to estimate the prevalence and other epidemiological parameters of ETN among these infants. It has been reported that the estimated prevalence of ETN among the included infants was found to be 25.3%. Moreover, it has been indicated that the prevalence was significantly higher in males than in female patients (61.9% versus 38.1%, respectively). Some reports show that recurrence might occur in previously recovered children. However, overall evidence indicates that such events are rare in this context. Many other investigations were also published reporting epidemiological data of ETN patients. Budair et al conducted a prospective cross-sectional study in Saudi Arabia to find which cutaneous lesions are the most common among included newborns.[11] Among 313 newborns included in this study, the authors reported that all of them had skin lesions. ETN was prevalent in 24.92% of these children accounting for the third commonest skin lesion after Mongolian spot and milia and followed by physiological scaling (63.07%, 61.34%, and 18.01%, respectively). The authors also reported that the condition was more prevalent among female than male Saudi patients (51.2% versus 35.8%). In comparison, non-Saudi male patients with ETN were more frequent than non-Saudi female patients (7.6% versus 5.1%, respectively). Other similar investigations also demonstrated that the prevalence of ETN among their population is hugely variable, being 7% in some and 68%

in others.[12,13] The study by Budair et al suggested that gender is not a significant indicator of the prevalence and epidemiology of the condition.[11] However, other studies reported that gender and mode of delivery were both significant risk factors associated with the prevalence of ETN.[14,15] Another Saudi investigation was also conducted by Alakloby et al to assess the epidemiological data of acne neonatorum across the eastern region.[16] The authors reported that they managed to identify 26 infants with these lesions and were included in the study for further evaluation. It is worth mentioning that the diagnosis of acne neonatorum is widely variable and includes different conditions, including a variety of fungal, viral, and bacterial infections. ETN is one of these conditions. Other disorders might also include acneiform reactions to drugs such as phenytoin or lithium, acne venenata infantum, acne infantum, and neonatal sebaceous gland hyperplasia.[17-22] Accordingly, it has been demonstrated that proper management of these patients is required after establishing an appropriate evaluation of their conditions.

In China, Liu et al also reported that the incidence of ETN in their included infants was 43.68%.[23] The authors furtherly aimed to find the most significant risk factors that were associated with the development and severity of ETN in their population. The authors reported that many risk factors could predict the development of ETN. These include vaginal delivery, being fed with a mixed diet or milk powder substitute, birth season, first-pregnancy birth, and gender. On the other hand, the severity of ETN can be predicted by the total length of labor among infants born with vaginal deliveries. Another investigation by Monteagudo et al was also conducted in Spain to assess the epidemiological and clinical characteristics of ETN in their infants.[24] In this context, the prevalence of ETN has been estimated to be 16.7%. Moreover, it has been shown that higher prevalence rates were reported among Caucasian newborns and those with <two previous pregnancies, maternal age of <30 years, vaginal delivery, increased gestational age, and higher birth weight (p value=0.01, 0.12, 0.28, <0.05, <0.05, and <0.05, respectively).

Another cross-sectional investigation was also conducted in Brazil by Reginatto et al to assess the epidemiological and clinical findings for patients with ETN.[3] The authors reported that the prevalence of the condition among 2831 included infants in their multicenter investigation was 21.3%. The authors reported that the prevalence of ETN was significantly correlated with the birth season, birthweight, gestational age, is never admitted to the neonatal intensive care unit, with no gestational risk factors, with 1 min Apgar scores from 8 to 10, being male, and Caucasian. Another similar study was also conducted in Brazil to assess the cutaneous findings among neonates within the first three days of life. The authors reported that the prevalence of ETN was 23%. Many lesions were more prevalent in this study than ETN, including sebaceous hyperplasia, dermal melanocytosis, and skin desquamation (35%, 24.61%, and 23.3%, respectively). On the other hand, many lesions were less common than ETN, including salmon patch, skin erythema, genital hyperpigmentation, eyelid edema, milia, genital hypertrophy, and skin xerosis (20.4%, 19%, 18.4%, 17.4%, 17.3%, 12%, and 10.9%, respectively).[25,26]

Clinical signs

Two variations were reported for ETN, including pustular or an erythematous papular variant. Evidence shows that an erythematous irregular base surrounds a 1-3 mm in size, yellow-white, and firm pustules or papules is the observed lesion for patients with ETN (Figure 1).

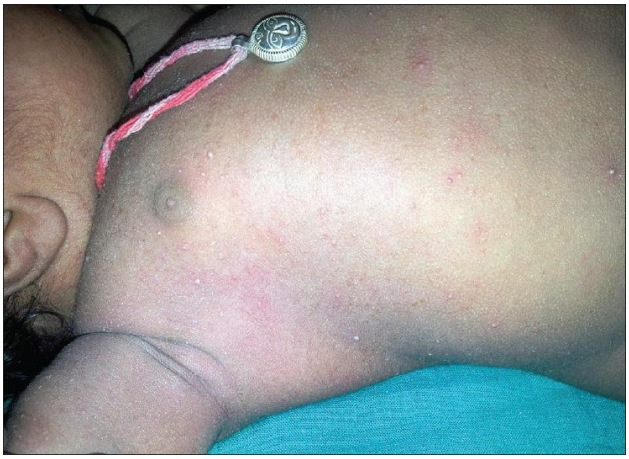

Figure 1: An infant with erythema toxicum neonatorum showed a trunk-related distribution of tiny, discrete, multiple pustules with an erythematous base.[32]

It has been furtherly reported that the lesion can be observed as a see of erythema surrounding a papule or as having a characteristic flea-bitten appearance. Evidence furtherly indicates that these lesions can be found in clusters scattered at different body parts or confined to a single area. Besides, they can be found multiple or single lesions as observed in the affected patients. Splotchy erythema has also been reported as a single potential manifestation of the condition in some patients.[27,28] Macules are usually found outside the erythematous lesions during the first days of presentation. They are usually observed during the first days on the cheeks and spread to different body parts later on. In this context, the rest of the forehead is usually involved together with other parts, including the extremities, trunk, and chest. However, it should be noted that further investigations demonstrated that the skin of the scrotum could also be involved in these events. Accordingly, an extensive body workup should be conducted for these patients to detect these lesions adequately.[29]

It is worth mentioning that clinicians report that it is difficult to examine infants with dark skins for ETN. Accordingly, it has been reported that identifying the lesions in these children might be challenging in these settings. Papules tend to appear when the persistence of the

erythematous macules occurs. However, it has been reported that the latter lesions are usually evanescent, and the papules might be detected as sole lesions. Urticarial lesions on the trunk should be differentiated from these macules, which are confluent and give a blotchy appearance in affected patients. As previously reported that soles and palms are not usually impacted. This indicates the theory suggesting that the pathology of ETN is correlated with the distribution of hair follicles.

Papules are usually superficial, particularly when noticed over the skin of the abdomen and back. Secondary infection was also reported to affect pustules. However, this is not very common. The 2nd day of life is when the incidence of ETN is highest, and the estimated incidence of recurrence is 11%. It should furtherly be noted that the pathology of ETN can be delayed in some infants as evidence shows that some affected infants might present after days to weeks following premature birth. In addition, eosinophilia might be observed in some patients, and estimates show that it might be up to 18%.[30] However, no systemic manifestations usually develop, and the prognosis of the condition is generally good.[25,31]

CONCLUSION

The etiology of ETN is not clear among the different studies. However, some studies show involvement of immune and potential allergic reactions. The prevalence of the condition among infants is also remarkably variable among the relevant studies worldwide. There is also inconsistency in reporting the significance of the risk factors related to the prevalence and severity of the condition. On the other hand, the clinical signs among studies seem to be consistent and easily detected except when evaluating dark-skinned infants. Further studies are needed better to understand the etiology and epidemiology of the condition.

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