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THE ETIOLOGY AND CLINICAL MANIFESTATION OF ERYTHEMA NODOSUM IN HOSPITALIZED CHILDREN – ANALYSIS OF 12 CASES. PRELIMINARY REPORT

ETIOLOGIA I OBRAZ KLINICZNY RUMIENIA GUZOWATEGO U HOSPITALIZOWANYCH DZIECI – ANALIZA 12 PRZYPADKÓW. DONIESIENIE WSTĘPNE

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Abstract

Aim: To analyse etiologic factors and the clinical course of erythema nodosum in hospitalized children.

Material and methods: A retrospective study of 12 children and young people (7 girls and 5 boys) admitted to the Paediatric Clinic in Zabrze with erythema nodosum was performed from January 2004 to February 2014. The patients' mean age on admission was 11.9 years (2-16).

Results: In ten of the 12 patients elevated CRP was identified – from 10 mg/L to 131.5 mg/L, which is proof of an ongoing inflammatory process. Only two patients had a CRP level below 5 mg/L. Three of the 12 patients were diagnosed with Crohn's Disease, one with diarrhoea (*Salmonella* was cultured and antigen Rotavirus was found), one with arthritis, one with bilateral cervical lymphadenopathy, three with Streptococcal infection, two had elevated anti-streptolysin O level (ASO).

Conclusion: The present research may confirm the hypothesis that EN could be the first sign of systemic diseases. However, it requires further studies because of the limited number of patients.

Key words: erythema nodosum, panniculitis, child

Streszczenie

Cel: Analiza czynników etiologicznych i przebiegu klinicznego rumienia guzowatego u hospitalizowanych dzieci.

Material i metody: Badanie retrospektywne objęło 12 dzieci i młodzieży (w tym 7 dziewcząt i 5 chłopców), hospitalizowanych w Klinice Pediatrii w Zabrze od stycznia 2004 do lutego 2014, u których przy przyjęciu rozpoznano rumień guzowaty. Średni wiek pacjentów w chwili rozpoznania wynosił 11,9 lat (2-16).

Wyniki: U 10 na 12 pacjentów stwierdzono podwyższenie CRP – od 10 mg/l do 131,5 mg/l, co świadczyło o toczącym się procesie zapalnym. Tylko u dwojga pacjentów CRP było poniżej 5 mg/l. U 3/12 pacjentów rozpoznano chorobę Leśniowskiego-Crohna, u jednego biegunkę (wyhodowano *Salmonella* i stwierdzono antygen Rotawirusa), u jednego zapalenie stawów, również u jednego obustronną limfadenopatię szyjną, u trojga zakażenie paciorkowcowe, u dwojga stwierdzono podwyższony poziom antystreptolizyny O (ASO).

Wnioski: Nasze badania mogą potwierdzać hipotezę, że rumień guzowaty może być pierwszym sygnałem chorób o charakterze systemowym, jednak zbyt mała liczba naszych pacjentów wymaga prowadzenia dalszych badań

Słowa kluczowe: rumień guzowaty, zapalenie tkanki podskórnej, dziecko

INTRODUCTION

Erythema nodosum (EN) is the most common type of panniculitis in children (1). The nodules are described as red, tender, painful and nonulcerating, they usually affect lower limbs and resolve completely without scarring (2).

According to some investigations, in EN there is an involvement of a type IV delayed hypersensitivity response to different antigens. EN can be the first sign of a systemic disease, such as tuberculosis, bacterial infection, sarcoidosis, inflammatory bowel disease or cancer (4).

The histopathological picture of EN is septal panniculitis with no signs of vasculitis (3). However, the clinical presentation of EN is usually clear and since biopsy is an invasive procedure, it is a rare approach in children.

The estimated prevalence of EN is reported as 1 to 5 per 100 000 people. Its frequency in children has not yet been proven (4). The prevalence of underlying conditions varies between studies and depends on age, geographical and racial factors (1). Furthermore, the relative frequency of conditions associated with EN fluctuates, as some of them become more common and others are better controlled (2).

There are no recent studies of EN in children among the Polish population that could reflect possible changes and differences between populations.

AIM

To analyse etiologic factors and the clinical course of EN in hospitalized children who derive from the Polish population.

MATERIAL AND METHODS

Among over 30 thousand admissions to the Paediatric Clinic at the Department of Medical University in Zabrze between January 2004 and February 2014 only 12 patients (pt) (7 girls and 5 boys) were admitted with EN. Their mean age on admission was 11.9 years (from 2 to 16 years old). A retrospective review of medical records of all 12 pt with EN was performed. The localisation of lesions, accompanying signs and symptoms, past medical history, demographic data, diagnostic test results and the clinical course of EN were analysed.

RESULTS

In ten of the 12 patients elevated CRP was identified – from 10 mg/L to 131.5 mg/L, as proof of the ongoing inflammatory process. Only two patients had CRP level below 5 mg/L. Three of the 12 patients were diagnosed with Crohn's Disease, one with diarrhoea (*Salmonella* was cultured and a Rotavirus antigen was found), one with arthritis, one with bilateral cervical lymphadenopathy, three with Streptococcal infection, two had elevated anti-streptolysin O level. For full details see Table I.

Antibiotic therapy was administered to all the pt before or during hospitalization. In most of the children (10 pt;

83%) skin lesions occurred once and disappeared by the end of hospitalization. Two children had recurrent EN. In one of them lesions recurred repeatedly over 4 years and the underlying cause was not explained.

Our data indicate that the most commonly identified etiological factors of EN in children are infections and inflammatory diseases. The most widespread infectious agent remains *Streptococcus* sp. and the most frequent inflammatory bowel disease – CD. Tuberculosis is not a common disease nowadays in our country.

DISCUSSION

EN is a rare disease in childhood and its etiology has a wide scope. The prevalence of underlying conditions varies between paediatric and adult population. In adults the most common causes of EN are streptococcal infections and sarcoidosis (5). In all the reviewed EN series in children only one case of sarcoidosis associated with EN was described (1). We did not find any case of sarcoidosis among the group examined, either.

Moreover, Inflammatory Bowel Diseases (IBD) are rarely described as causes of EN in adults. In 1998 Cribier et al. described 1 case of CD and 1 of Colitis Ulcerosa (CU) in a series of 128 adult patients with EN (5). In another study García-Porrúa et al. found 2 cases of CD and 1 of CU among 102 patients (all over 14 years old). The relative frequency of IBD in children with EN varies between studies. Hassink et al. reported 3 cases of CD and 3 cases of CU in a group of 36 pt (6 pt; 17%) and Garty et al. described 3 cases of IBD among 28 paediatric pt (3 pt; 11%) (6, 1). However, Kakourou et al. diagnosed only 1 case of IBD in 35 children with EN (1 pt, 3%) (7). The relatively high prevalence of CD in our data (3 pt; 25%) seems to be consistent with the hypothesis that IBD associated with EN is more common in children. However, there is a possible bias resulting from the specificity of our Clinic. The Clinic consists of five Departments; one of them is the Paediatric Gastroenterology Department, which is a reference centre for children with IBD from the Silesian region. It should be considered that the prevalence of IBD varies between ethnic groups (8). Karolewska-Bochenek et al. reported IBD incidence among Polish children to be lower than in Western countries, suggesting under- or misdiagnosing at the same time (9). Anyway, the reported prevalence of EN in IBD is similar in adults (3-8%) and children (5,4%) (10,11). Jose et al. described the cumulative incidence of EN in IBD among the paediatric population as 0.4; 1.1; 1.6 on examination 1, 5, and 10 years after the initial diagnosis of IBD respectively (10). The following predictive factors for the main cutaneous manifestations (EN and pyoderma gangrenosum) in IBD were identified in the adult population: female, CD, young age at diagnosis of IBD, and presence of other extraintestinal manifestations (eye and joint disorders, stomatitis). Moreover, it was reported that early therapies in cases with manifested predictive factors may prevent the development of cutaneous manifestations in this population (12). Further study to determine the prevalence of CD as an etiologic factor of EN in children among the Polish population and the predictive factors of its occurrence is necessary.

Table I. Signs, symptoms, test results, clinical course.
Tabela I. Objawy i badanie przedmiotowe, wyniki badań, przebieg kliniczny.

Patient number Numer pacjenta	Age wiek (years/lat) Gender płeć	Comorbidities Choroby towarzyszące	Signs and symptoms Objawy i badanie przedmiotowe	Test results/ Wyniki badań	Clinical course Przebieg kliniczny
1. W. K. 1068/05	14 years/lat Girl Dziewczynka		Tender, red, warm nodules on both shins, fever Tkliwe, czerwone, ucieplone, guzy na obu podudziach, gorączka	CRP-11 mg/l, ESR-70/115 WBC-13,5 G/L ASO-23 IU/ml Waaler-Rose test <6 IU/ml Throat/nose swab-normal flora. Wymaz z gardła/nosa-prawidłowa flora Chest X-ray-negative Rtg płuc prawidłowe MTX test-negative/ujemny	EN and fever occurred 5 days before hospital admission, resolved completely after antibiotic treatment within 2 weeks. RG pojawił się 5 dni przed hospitalizacją, ustąpił całkowicie po antybiotykoterapii w ciągu 2 tygodni.
2. M. A. 1249/04	10 years/lat Girl Dziewczynka		Tender, red, warm nodules on both shins, tonsillitis Tkliwe, czerwone, ucieplone guzy na obu podudziach, zapalenie migdałków	CRP-90 mg/l, ESR-68/108 WBC-9,4 G/l ASO-10 IU/ml ANA-0.91 index pANCA-1,7 U/ml cANCA-20 U/ml M. pneumoniae-negative/ujemne Yersinia enterocolica<1:20 negative/ujemne Throat/nose swab-normal flora Wymaz z gardła/nosa- prawidłowa flora Chest X-ray negative Rtg płuc prawidłowe MTX test-negative/ujemny	EN during upper respiratory infection occurred 4 days before hospital admission, resolved completely after antibiotic treatment within 2 weeks. RG pojawił się w trakcie infekcji górnych dróg oddechowych 4 dni przed hospitalizacją, ustąpił całkowicie po antybiotykoterapii w ciągu 2 tygodni.
3. K. A. 4427/09	16 years/lat Girl Dziewczynka		Tender, red, warm nodules on both shins, Tkliwe, czerwone, ucieplone guzy na obu podudziach	CRP-17 mg/l WBC-6,9 G/l ASO-57 IU/ml RFII-5,14 IU/ml IgA-4,28g/l IgM-0,7 g/l IgG-11,1 g/l Borrelia burgdorferi-IgM-0,25 index IgG-7,7 U/ml Throat/nose swab-normal flora Wymaz z gardła/nosa-prawidłowa flora Chest CT negative TK klatki piersiowej prawidłowe MTX test-negative/ujemny	Recurrent EN during 2 months before hospital admission, sarcoidosis suspicion. EN resolved completely after antibiotic treatment within 5 weeks. Sarcoidosis was excluded. Rumień nawracający przez 2 miesiące, podejrzenie sarkoidozy. RG ustąpił całkowicie po antybiotykoterapii w ciągu 5 tygodni. Sarkoidozę wykluczono

Table I. Cont.
Tabela I. Cd.

4. B.A 3466/08	16 years/lat Girl/ Dziewczynka		Tender, warm, red nodules on both shins Tkliwe, ucieplone guzki na obu podudziach	CRP-4 mg/l WBC-5,8 G/L ASO-264 IU/ml Throat/nose swab-normal flora Wymaz z gardła/nosa-prawidłowa flora Chest X-ray negative Rtg płuc prawidłowe MTX test negative/ujemny	EN preceded pharyngitis occurred 5 days before hospital admission, resolved completely after antibiotic treatment within 2 weeks. RG poprzedzony zapaleniem gardła pojawił się 5 dni przed hospitalizacją, ustąpił całkowicie po antybiotykoterapii w ciągu 2 tygodni.
5. U.D. 3331/11	10 years/lat Boy/Chłopiec	Atopic dermatitis Atopowe zapalenie skóry	Tender, warm, red nodules on both shins Tkliwe, ucieplone guzki na obu podudziach	CPR-20 mg/l, ESR-30 WBC-5,2 G/L ASO-937 IU/ml Waaler-Rose test <0,6U/ml IgA-3,12g/l IgG-12,35 g/l, IgM-1,11g/l, IgE-342 IU/ml Borrelia burgdorferi- IgM-0,9 index IgG-89 U/ml pANCA-1,0 U/ml cANCA-19 U/ml Throat/nose swab-normal flora Wymaz z gardła/nosa-prawidłowa flora	Tonsillitis and EN occurred 14 days before hospital admission, resolved completely after antibiotic treatment within 3 weeks. Zapalenie migdałków i RG pojawiły się 14 dni przed hospitalizacją, RG ustąpił całkowicie po antybiotykoterapii w ciągu 3 tygodni.
6. 732/14 M.A	2 years/lat Girl/ Dziewczynka	Diarrhea (Salmonellosis D Rotavirus)/ Biegunka (Salmonellosis D, Rotavirus)	Tender, warm, red nodules on both shins, fever, bloody diarrhea Tkliwe, ucieplone czerwone guzy na podudziach, gorączka, wymioty, krwista biegunka	CRP-13,89 mg/l, ESR-38/72 WBC-8,4 G/L ASO-1 IU/ml stool examination/badanie kału – Salmonella enteritidis D, Rotavirus	Fever, upper respiratory tract infection and antibiotic therapy 2 weeks before hospital admission. After 7 days occurred EN. EN resolved completely within 2 weeks. Gorączka, infekcja górnych dróg oddechowych antybiotykoterapia 2 tygodnie przed hospitalizacją. Po 7 dniach pojawił się RG RG ustąpił całkowicie po 2 tygodniach.
7. J.M. 635/09	12 years/lat Boy/Chłopiec	Obesity Otyłość	Tender, warm, red nodules and rash on both shins Tkliwe, czerwone, ucieplone guzy oraz wysypka na obu podudziach	CRP 0,93 mg/l, ESR-7 WBC-5,0 G/l ASO-260 IU/ml Waaler-Rose test <6 IU ANA-25,51 U/ml pANCA-0,96U/ml, cANCA-10 U/ml Yersinia enterocolica- IgA-0,4, IgG -0,11, IgM-0,31 index Throat/nose swab-normal flora Wymaz z gardła/nosa-prawidłowa flora	Recurrent EN (three episodes of EN). Biopsy of skin lesion 4 years ago: panniculitis. EN recovered completely after antibiotic and NSIDs treatment within 3 weeks. Referred to rheumatologist. Nawroty RG (3 epizody). Biopsja zmian skórnych sprzed 4 lat: panniculitis. RG ustąpił całkowicie po antybiotykoterapii i NZL w ciągu 3 tygodni. Skierowany do reumatologa.

Table I. Cont.
Tabela I. Cd.

8. G..D. 6893/13	13 years/lat Boy/Chłopiec	Atopic asthma Chronic sinusitis Neutropenia, IgM-deficiency Asthma atopowa Przewlekłe zapalenie zatok Neutropenia, Niedobór IgM	Tender, red, warm nodules and rash on both shins and , hips joint pain Tkliwe, czerwone, ucieplone, guzy i wysypka obu na podudziach, ból stawów biodrowych	CRP-10 mg/l WBC-3,4 G/L ASO-203 IU/ml IgA-0,93 g/ IgM-0,2g/l IgG-6,4g/l ANA-0,5 index, cANCA-20 U/ml, pANCA-0,8U/ml MTX-negative/ ujemny Throat/nose swab-normal flora Wymaz z gardła/nosa-prawidłowa flora Chest X- ray and hips negative Rtg płuc i stawów biodrowych prawidłowe	Recurrent EN (three episodes EN during 2 years. ENs resolved completely after antibiotic and NAIDs treatment within 3-5 weeks. Referred to immunologist, haematologist, allergist. Nawroty RG (3 epizody w ciągu 3 lat), RG ustąpił całkowicie po antybiotykoterapii i NLPZ w ciągu 3-5 tygodni. Skierowany do immunologa, hematologa, alergologa.
9. H.A. 6836/13; 6946/13;	12 years/lat Girl/ Dziewczynka	Scheurmann Disease/ Choroba Scheurmana	Red, painful nodules on both shins, cervical lymphadenopathy, fever Czerwone, bolesne guzy na obu podudziach na obu podudziach, limfadenopatia szyjna, gorączka	CRP-33 mg/l, ESR-126 WBC-8,8 G/l ASO-904 IU/ml ANA,-08 index cANCA-20U/m pANCA-1,8 U/ml Yersina enterocolica- IgG-0,1 index, IgM-0,9 index Bartonella henselae and quitana IgM-negative/ujemne Throat/nose swab-normal flora Wymaz z gardła/nosa- prawidłowa flora MTX-negative/ujemny CT chest-feature of Scheurmann Disease TK klatki piersiowej-cechy choroby Scheurmana	Fever, cervical lymphadenopathy for 2 weeks. EN resolved completely after antibiotic treatment within 6 weeks. Gorączka, limfadenopatia szyjna od 2 tygodni. RG ustąpił całkowicie po antybiotykoterapii w ciągu 6 tygodni.
10. K.K. 6512/13	14 years/lat Boy/ Chłopiec	CD (since 6 years) Choroba L-C (od 6 lat)	Painful, red, warm nodules on both shins on bloody diarrhea Bolesne, czerwone, ucieplone guzy na obu podudziach, biegunka z krwią	ESR-50/100, CRP-13,1 mg/l WBC-8,0 G/L Hb-8,2 g% Quantiferon test-negative/ujemny	EN occurred during CD exacerbation. EN recovered completely after treatment including antibiotic, PRBCs, GCs, AZA within 2 weeks. Currently CD treatment No EN relapses. RG pojawił się w trakcie zaostrzenia choroby L-C. RG ustąpił po leczeniu antybiotykami, KKCZ, GKS, AZA. W ciągu 2 tygodni Nadal leczenie choroby L-C. Nawrotów RG nie było.

Table 1. Cont.
Tabela 1. Cd.

11. N.L. 3544/2011	11 years/lat Girl/ Dziewczynka	CD/Choroba L-C	Fever, skin pale, painful, red, warm nodules on both shins, bloody diarrhea, abdominal pain <i>Gorączka, bladość, bolesne, czerwone, ucieplone guzy na obu podudziach, biegunka z krwią, bóle brzucha</i>	ESR-30/60 CRP-131,5 mg/l/, PCT-21,8 pg/ml L-14 G/l HB-5,7 g %, Fe-3,2 umol/l WBC-15 G/l TP-4,3 g/l Albumin-2,6 g/l IgA-2,6 g/l, IgM-0,96 g/l, IgG-11,96 g/l ASCA-positive/dodatnie ANCA-0,4 index Chest X- ray negative <i>Rtg płuc prawidłowe</i> MTX-negative/ujemny Stool exam-negative <i>Badanie kału-ujemne</i> Colonoscopy and biopsy confirm CD diagnosis <i>Kolonoskopia i biopsja potwierdziły chorobę L-C</i>	EN proceeded by diarrhea of 2 months' duration and weight loss. CD diagnosis was confirmed. EN resolved completely after treatment including antibiotic, GCs, PRBCs within 5 weeks. Currently CD treatment No EN relapses. <i>RG poprzedzony 2 miesięczną biegunką z krwią i utratą masy ciała. Rozpoznano chorobę L-C. RG ustąpił po leczeniu m.in. antybiotykami i GKS w ciągu 5 tygodni. Nadal leczenie choroby L-C. Nawrotów RG nie było.</i>
12. K.K 6365/2011	13 years/lat Boy/Chłopiec	CD (since 2 years)/ <i>Choroba L-C (od 2 lat)</i>	Painful, red, warm nodules on shins, nodules and rash on upper limbs, perianal fistulae <i>Bolesne, czerwone, ucieplone guzy na podudziach, guzy i wysypka na kończynach górnych, przetoki okołoodbytnicze</i>	CRP-14,93 mg/l L-11,0 G/L MTX-negative/ujemny Chest X- ray negative <i>Rtg płuc prawidłowe</i>	EN occurred after GCs reduction 2 weeks before hospital admission. After antibiotic therapy and continuation of CD treatment (e.g. GCs, AZA) EN resolved completely within 3 weeks. Currently CD treatment. No EN relapses. <i>Zmiany skórne pojawiły się w trakcie redukcji dawki GKS 2 tygodnie przed hospitalizacją</i> <i>Po leczeniu:antybiotyk, + leczenie choroby L-C (GKS, AZA) ustąpiły całkowicie w ciągu 3 tygodni.</i> <i>Nadal leczenie choroby L-C. Nawrotów RG nie było.</i>

Tuberculosis, which was a common cause of EN in the past is rare nowadays, both among young and adult pt (1, 5, 13). In all the reviewed EN series in children (126 pt in total) only 2 cases of tuberculosis associated with EN were diagnosed (1, 6, 7, 13). We did not diagnose tuberculosis in our group, either. However, tuberculosis remains a feasible threat and we confirm the necessity of tuberculosis testing in pt with EN.

Lymphomas, Behçet disease, autoimmune hepatitis, cat scratch disease and viral infections associated with EN in children were occasionally reported in the literature (1, 6, 7, 13, 14). As the frequency of EN is low, we did not manage to gather a group numerous enough to estimate the frequency of rare EN aetiology factors.

The data collected confirm that there is not a huge difference between the frequency of EN in male and female children, as opposed to the adult population (1, 2, 5, 6, 7, 13).

The clinical course of EN in children is benign and rarely recurrent. The most common trigger of EN seems to remain *Streptococcus* sp. infections. Thus, initial antibiotic therapy could be considered as the first option in children with EN and without symptoms suggesting different underlying causes of lesions. In the case of an atypical clinical course or recurrence of EN, an extensive diagnostic approach should be applied.

Our retrospective data could be influenced by some biases. We included only inpatient data and some of the children admitted had received antibiotic therapy before admission. However, we give a new insight in the field, as there are not any recent studies of EN in children among the Polish population that could reflect the current aetiology and clinical course.

CONCLUSION

Our research may confirm the hypothesis that EN could be the first sign of systemic diseases. However, it requires further studies, because of the limited number of patients.

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Conflicts of interest/Konflikt interesu

The Authors declare no conflict of interest.

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