Jankowska Paula, Jankowski Krzysztof, Kamiński Piotr, Rudnicka-Drożak Ewa. Generalized infection with unknown starting point in children hospitalized in a district hospital. Journal of Education, Health and Sport. 2019;9(7):742-747. eISSN 2391-8306. DOI http://dx.doi.org/10.5281/zenodo.3357156
http://ojs.ukw.edu.pl/index.php/johs/article/view/7200

The journal has had 7 points in Ministry of Science and Higher Education parametric evaluation. Part B item 1223 (26/01/2017).
1223 Journal of Education, Health and Sport eISSN 2391-8306 7

The authors declare that there is no conflict of interests regarding the publication of this paper.

Received: 01.07.2019. Revised: 05.07.2019. Accepted: 01.08.2019.

Generalized infection with unknown starting point in children hospitalized in a district hospital

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ABSTRACT
Introduction
Infection is the most common cause of children medical consultations. Often the clinical picture of the patient is disproportionate to the results of laboratory tests which may indicate for generalized infection.
Case reports
Case 1: A 4-year-old patient admitted to the Department due to a fever 39˚C lasting from 2 days and periodic abdominal pain. Good general condition, throat slightly red. In laboratory studies, procalcitonin 44.5 ng/ml, CRP 121.5 mg/dl, WBC 15.32 ths/ul. Empirical treatment with ceftriaxone and vancomycin was included. Blood cultures, Staphylococcus hominis MLSB, MRCNS.
Case 2: A patient nearly 5 years old admitted to the Department due to a fever 39.5˚C. In outpatient examinations CRP 41 mg/dl, WBC 39 ths/ul. Physical examination: reddening of throat mucosa, palatine tonsils slightly enlarged, reddish, without rash. In laboratory tests CRP 95 mg/dl, WBC 41.95 ths/ul, PCT 1.19 ng/ml. On the second day of hospitalization, an increase in inflammatory markers was observed (PCT 1.47 ng/ml, CRP 235.7 mg/dl). Vancomycin was added.
Case3: 18-month-old boy admitted to the Department due to fever 40.5˚C. Good general condition, throat slightly reddened, occasional cough. In laboratory tests PCT 8.07 ng/ml. Empirical antibiotic therapy with ceftriaxone was implemented. Due to persistence of fever up to 39.5˚C - control tests of PCT 10.03 ng / ml. Vancomycin was implemented. Urine culture negative, in blood culture the present growth of Staphylococcus warneri.
Conclusions
It is extremely important to be vigilant in case of feverish children. Sometimes, despite a good general condition and no significant abnormalities in a physical examination, we can deal with generalized infection.

Keywords: Infection, Children, Pharyngeal Tonsil

INTRODUCTION

Infection is the most common cause of children medical consultations. Thus, it is one of the most important concerns of Primary Health Care and hospital-working doctors. Upper respiratory tract infections (known in literature as *rhinopharyngitis*) are mainly associated with viruses as etiological factor [1,2]. Bacterial infections have some characteristic features. According to recommendations rhinosinusitis of bacterial etiology can be diagnosed when there is presence of at least three of the following symptoms: purulent rhinorrhea (mainly unilateral) or purulent secretion in the nasal passages, severe local pain (with a predominance of one side), fever (>39.5˚C), increased CRP, worsening of symptoms after the initial milder period of the disease [3]. In turn, plausibility of bacterial tonsillitis is assessed according to Centor Scale in modification of McIsaac, when fever >38˚C, no cough, enlarged frontal cervical lymph nodes, fibrinopurulent coat on tonsills, and age of 3-14 years may indicate for bacterial infection [4]. Careful physical examination in many cases is a clue to proper diagnosis. Although, occasionally the clinical picture of the patient is disproportionate to the results of laboratory tests which may indicate for generalized infection.

CASE REPORTS

Case No. 1:

4-year-old patient reported to the Paediatric Ward Admissions on 14.01.2019r. due to the fever up to 39˚C lasting from 2 days and periodically occurring abdominal pain in the periumbilical area. Without any features of gastrointestinal infection. She had been given antipyretic drugs twice a day, and there was an effective reaction. At admission, good general condition, conscious, cardiovascularly and respiratorily stable, body temperature 36.9 Celsius degrees, clean skin, posterior pharyngeal wall and palatine arches red, with vesicles, angular lymph nodes bilaterally enlarged to 1.5 cm. Auscultation over pulmonary fields-alveolar murmur, heart rate, approx. 120 /min. Soft abdomen, painless during palpation, liver, spleen not enlarged, no pathological resistance, negative peritoneal symptoms, intestinal motility accelerated, negative meningeal symptoms. In laboratory tests high levels of inflammatory process parameters - procalcitonin 44.44 ng/ml, CRP 121.5 mg/L, WBC 15.32 ths/ul. Diagnostics were extended by gasometry (correct result), coagulation assessment (APTT 62.2 s, INR 1.4, fibrinogen 478 mg/dl), blood culture, urine culture, culture of rectal and pharyngeal swab were collected. Urinalysis without the characteristics of infection in the urinary system. Electrolyte level, transaminase and renal parameters were within normal limit. Latex test for CNS infections negative. Empiric treatment with ceftriaxone, vancomycin and fluconazole was implemented. Chest X-ray performed - without any abnormalities. In ultrasound of the abdominal cavity presence of additional spleen (size 9mm), free liquid in the abdominal cavity up to max. 16 mm were revealed. On the second day of hospitalization, inflammation parameters were monitored (procalcitonin 33.29 ng/ml, CRP 83.2 mg/dl, WBC 12.67 ths/ul) and the coagulation system (APTT 51.1 s, INR1,3, fibrinogen 365 mg/dl). Due to the good response to the included empirical treatment, antibiotic therapy was maintained. In-depth interview showed symptoms associated with hypertrophy of the pharyngeal tonsil in the form of snoring during sleep, breathing through open mouth, recurrent impairment of the nasal patency. In the ward, the patient did not get feverish, her condition was good, she did not report any symptoms. The urine culture obtained growth of E. coli titer 10 ^ 3, blood culture contamination - Staphylococcus hominis MLSB, MRCNS, pharyngeal swab culture - Staphylococcus aureus and Streptococcus pyogenes, feces in the direction of Salmonella, Shigella, EPEC, EHEC, EIEC, and Yersinia negative. In control laboratory tests taken on the seventh day of antibiotic therapy, normalization of inflammation parameters was observed (procalcitonin 0.66 ng/ml, CRP 5.8 mg/dl, WBC 6.91 ths/ul). The APTT index (58.9-69.1s) was consistently maintained in laboratory studies. The patient was discharged from the ward and referred to the Otolaryngological Outpatient Clinic for Children and Hematology Outpatient Clinic for Children.

Case report No. 2: A patient less than 5 years old, referred on 26.01.2019. to the Paediatrics Department due to fever from the previous day to 39.5 Celsius degrees and abnormalities in the results of laboratory tests performed in outpatient settings - WBC 39 ths/ul, CRP 41 mg/dl. In medical history of the patient about 2 weeks earlier, antibiotic therapy with intramuscular lincomycin due to pharyngitis and tonsillitis. Good general condition, conscious patient, cardiovascularly and respiratorily stable, clean skin, posterior throat wall and palatal arches reddish, palatine tonsils enlarged, red, peripheral lymph nodes not enlarged. Auscultation above pulmonary fields - alveolar murmur, heart rate approx. 100/min. Soft abdomen, painless during palpation, liver, spleen not enlarged, no pathological resistance, negative peritoneal symptoms, negative meningeal symptoms. Blood culture, urine collection, laboratory tests were taken and empiric antibiotic therapy with ceftriaxone and fluconazole was immediately started. Obtained

results: procalcitonin 1.19 ng/ml, CRP 95 mg/dl, WBC 41.5 ths/ul. Chest X-ray was performed - without any abnormality and abdominal ultrasound – within normal limits. Urinalysis without the characteristics of infection in the urinary system. Latex test for CNS infections negative. Renal and hepatic parameters below upper normal range. Coagulation system: APTT 31 s, INR 1,4, fibrinogen 430 mg/dl. On the second day of stay in the ward, a laboratory control was carried out, revealing an increase in inflammatory markers - procalcitonin 1.47 ng/ml, CRP 235.7 mg/dl and a significant decrease in leukocyte levels - up to 23.03 ths/ul. Microscopic blood smear: 89% divided leukocytes, 1% eosinophils, 2% monocytes, 8% lymphocytes, no visible atypical lymphocytes. Vancomycin was added to empiric antibiotic therapy. The general condition of the patient did not raise any objections, she did not report any symptoms nor had a fever. On the third day, the parametres of inflammatory process were again assessed - procalcitonin 1.01 ng/ml, CRP 102.9 mg/dl, WBC 8.26 ths/ul. Antibiotic therapy was maintained. In the blood and urine culture, there was no growth of the bacterial flora. Due to symptoms of hypertrophy of the pharyngeal tonsil in the form of numerous recurrent infections of the upper respiratory tract and snoring at night, the patient was consulted otolaryngologically - qualified for adenotomy. On the sixth day of hospitalization, laboratory tests were carried out - procalcytonin 0.241 ng/ml, CRP 14.1 mg/dl, WBC 6.44 ths/ul. In good condition, the patient was discharged home with a referral to the Allergology and Otolaryngology Outpatient Clinic.

Case report No. 3: 18-month-old boy admitted to the Children's Department on 12.02.2019. due to fever up to 40.9˚C during the course of upper respiratory tract infections. At admission, general condition quite good, conscious, cardiovascularly and respiratorily stable, body temperature 37.4 Celsius degrees, clean skin, in nose mucopurulent secretion, posterior throat wall and palatine arches reddened, palatine tonsils swollen, slightly red. Auscultation over the pulmonary fields, alveolar murmur, heart rate approx. 140/min. soft abdomen, liver, spleen not enlarged. Negative meningeal symptoms, child's behavior appropriate to age. In laboratory tests, the level of procalcitonin 8,07 ng ml, CRP <1mg/dl, WBC 16.32/ul. Normal renal parameters, elevated transaminases (ALT 64U/l, ASAT 142 U/l). Coagulation: APTT 22.9 s, INR 1.3, fibrinogen 247 mg/dl. Blood and urine culture were performed. Empirical antibiotic therapy with ceftriaxone and vancomycin was implemented. In the ward, the boy presented a fever up to 39.5 Celsius degrees until the third day of hospitalization. Sporadic cough appeared, mucopurulent secretion in the nasal passages and single bronchial inflammatory changes in the bronchi. The swelling of the face was also temporarily observed, mainly in the area of the orbital cavities. Attention was drawn by breathing through the mouth during the child's sleep and snoring. Mother of the patient also reported recurrent infections of the upper respiratory tract. The control laboratory tests were carried out on the third day of the stay in the ward - procalcitonin 10.03 ng/ml, CRP <1 mg/dl, WBC 9.55 thousand/ul. Empirical antibiotic therapy was maintained and the level of procalcitonin was checked on the following day - 4.91 ng/ml. Chest X-ray performed - without any abnormalities, abdominal ultrasound without visible pathologies. After the fever subsided, the child's condition improved, the rhinitis and cough decreased, the bronchial inflammatory lesions subsided. Blood culture revealed Staphylococcus warneri contamination, culture of urine - negative. On the fifth and sixth day of hospitalization, symptoms of gastrointestinal infection appeared in the form of numerous loose stools and vomiting. Symptomatic treatment was applied. On the seventh day of the stay in the ward, laboratory parameters were controlled - procalcitonin 0.448 ng/ml, WBC 5.72 ths/ul. The patient was discharged home with recommendations for continuing treatment and referred to the Otolaryngological Outpatient Clinic for Children.

DICSUSSION AND CONCLUSIONS

Presented cases of children reporting themselves on Paediatric Ward Emergency in winter time show patients with features of generalized infection. The leading cause of visiting Paediatric Emergency was high body temperature exceeding 39˚C. General condition of patients was good. None of them presented alarming symptoms. The main deviation in physical examination were symptoms of pharyngotonsillitis, however with low score in Centor/McIsaac Scale. Other not disquieting manifestations were nasal mucopurulent discharge and not extensive auscultation changes over pulmonary fields. There was not any other findings suggesting generalization of infection and its bacterial background like tachycardia or bradycardia, tachypnoe, hypotension, petechiae or clinical signs of poor perfusion. Notwithstanding, according to the best clinical algorithms laboratory test were performed. Laboratory findings were disproportionate to clinical picture of patients. In all three cases, inflammation indicators were several times higher than normal limits (for procalcitonin it was 0,5 ng/ml, CRP - 5mg/dl). Leukocytosis was also seriously higher than normal limits.

Procalcitonin is synthesized in neuroendocrine cells of many organs: lungs, intestines, liver, pancreas, brain, kidneys and blood cells [5]. IL-1β, TNF-α and other inflammation mediators as well as bacterial toxins may induce CALC-1 gene expression. In course of viral infection INF-γ is produced in significant amounts. It blocks the activity of IL-1 and attenuates expression of CALC-1 gene [6]. Thus, procalcitonin may be read as bacterial infection marker, as its level remains low in viral infection.

C-Reactive Protein (CRP), an acute phase protein synthesized in the liver is also a good marker of inflammation. Although it has lower sensitivity and specificity than procalcitonin an slower kinetics which is relatively important in diagnosing children in conditions of Emergency Department [7].

Leukocytosis is not correlated with the severity of inflammation, moreover shows low specificity for bacterial infection. Although in clinical practice seriously high levels of leukocytosis are considered to be helpful in making diagnosis of infection, but the rise of WBC levels may be gradual and not specific.

In delineated patients inflammation parameters were high, especially procalcitonin concentration. High values of procalcitonin were the reason for empirical implementation of intravenous antibiotics implementation. These were ceftriaxone and vancomycin. Blood, urine and local swab cultures were performed. Only in case no. 1 it was positive (E. coli titer 10 ^ 3 in urine culture, pharyngeal swab culture - Staphylococcus aureus and Streptococcus pyogenes, making probable thesis that bacterial infection of upper respiratory tract (i.e. tonsills and pharynx) was a source of infection. In other described cases origin of infection stayed unclear. However, it is absorbing that all patients presented symptoms of pharyngeal tonsil hypertrophy. This overgrowth of pharyngeal lymphoid tissue may result from infectious etiology (viruses – commonly adenovirus, coronavirus or rhinovirus, bacteria – Streptococcus spp., Staphylococcus aureus, Moraxella catarrhalis) as well as other causes like allergies or gastrointestinal reflux [8, 9].

The final diagnosis in all three patients was generalized infection without diacrisis of sepsis. Sepsis in pediatric age is life-threatening organ (or multiorgan) dysfunction caused by a detrimental organism response to infection [10]. Sepsis in children is a serious illness associated with noticeable mortality [11]. It is associated with being more prone to rapid fluid losses due to vasodilatation. Moreover heart rate elevation to maintain higher cardiac output providing proper perfusion is a leading compensatory mechanism in children. It is considered as increase in myocadium contractions meets a ceiling effect on a certain level. Thus, early diagnosis of sepsis

and proper management is utterly important. Further, rapid recognition of generalized infection still without manifestations of organ failure is focal point in prevention of sepsis development.
In conclusion, it worth to emphasize again that it is extremely important to be vigilant in case of feverish children. Sometimes, despite a good general condition and no significant abnormalities in a physical examination, we can deal with generalized infection.

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