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Regular paper

Evaluation of clinical usefulness of serum neopterin determination in children with bacterial infections

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Neopterin (NPT) (6-D-erythro-trihydroxypropyl pteridin) is one of the indicators of the immune system activity. Elevated neopterin concentration occurs in diseases mostly involving stimulation of cellular immunity. The determination of neopterin concentration, usually in blood serum and urine but also in many other bodily fluids, has already been applied in many areas of medicine, such as transfusiology, transplantology, oncology, infectious diseases and autoimmunological diseases. Objective. The aim of this work is to evaluate clinical usefulness of serum neopterin determination in children with urinary tract infections of confirmed bacterial etiology. Material. The study involved 56 children with bacterial urinary tract infections — patients of the Clinic of Paediatrics, Paediatric Gastroenterology, Hepatology & Paediatric Nutrition of Medical University of Gdańsk in the years 2012–2013. The control group included 105 healthy children. Results. The values of NPT concentration in blood serum obtained in the group of children with urinary tract infections did not significantly differ from the values obtained in the control group. Conclusions. The determination of neopterin concentration in children with bacterial urinary tract infections is not a clinically useful parameter.

Key words: neopterin, children, urinary tract infections

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INTRODUCTION

Evaluation of clinical usefulness of determining immune system activity indicators is still a debatable issue. One of many such markers is neopterin (NPT) (6-D-erythro-trihydroxypropyl pteridin). Transformation of guanosine triphosphate (GTP) into neopterin starts in macrophages as a result of stimulation with interferon-γ (IFN-γ) produced by T lymphocytes, hence elevated neopterin concentration occurs in diseases which mostly involve stimulation of cellular immunity (Huber *et al*., 1984; Fuchs *et al.,* 1988). Monitoring changes taking place in the immune system during a disease with a quick and sensitive method helps to explain the etiopathogenesis of a disease and makes it possible to introduce appropriate treatment early on. The determination of neopterin concentration, usually in blood serum and urine but also in many other bodily fluids, has already been applied in many areas of medicine, such as transfusiology, transplantology, oncology, infectious diseases and autoimmunological diseases (Fuchs, 1998; Hamerlinck, 1999; Murr *et al.,* 2002; Plata-Nazar *et al*., 2011).

First observations concerning increased secretion of neopterin in people with diagnosed viral infections were made by Wachter and coworkers in 1979 (Wachter *et al*., 1979). A number of other studies indicates that determination of neopterin concentration is a useful parameter in differentiating between viral and bacterial infections (Fuchs, 1998; Wiedermann *et al*., 1999; Murr *et al.,* 2002).

However, results of many published research projects indicate that determination of neopterin concentration cannot be considered useful in differential diagnosis of the etiological factor of infection (Niederwieser *et al*., 1986; Greassl *et al.,* 2001; Pourakbari *et al*., 2010).

Therefore, the authors of this work have attempted to evaluate clinical usefulness of determination of neopterin concentration in children with bacterial urinary tract infections.

Urinary tract infections (UTI) are a significant clinical problem occurring in children. They are the second most frequent type of child infections (while respiratory tract infections are the most frequent). These are mostly bacterial infections.

The most common pathogen are Gram-negative bacteria from the gastrointestinal tract, usually *E. coli*, responsible for 80–90% of the first UTI episodes. Other bacteria, e.g. *Klebsiella, Proteus* or *Staphylococcus*, can also be the etiological factor (Ziolkowska, 2014).

Aim of the work: To evaluate clinical usefulness of serum neopterin determination in children with urinary tract infections of confirmed bacterial etiology.

MATERIALS AND METHODS

Material. The participants were patients of the Clinic of Paediatrics, Gastroenterology, Hepatology & Paediatric Nutrition of Medical University of Gdańsk in the years 2012–2013.

The group of children with urinary tract infections (UTI) was composed of 56 patients, including 36 girls (64.3%) and 20 boys (35.7%) aged between one month

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Abbreviations: COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; GLDH, glutamate dehydrogenase; GTP, guanosine triphosphate; HIV, Human Immunodeficiency Virus; IFN-γ, interferon-γ; NPT, neopterin; UTI, urinary tract infections

Table 1. NPT concentrations in blood serum of children from the UTI group compared to the control group

Group	Number of children	NPT concentration (nmol/l)				
		Median	Minimum	Maximum	Lower quartile	Upper quartile
Control	105	4.734	2.872	14.779	4.050	5.292
UTI	56	4.717	3.158	17.256	4.109	9.118

and 17.5 years (mean 4.0±4.9; S.D.) years, median 1.9 years).

They were patients with urinary tract infections of extrinsic origin — children without any anatomic abnormalities of urinary tract.

The biological material (blood and urine) was obtained on the day of admission to the Clinic. Most of the children had had clinical symptoms for 2–3 days before admission to the hospital.

Exclusion criteria: children vaccinated within 6 months before the study, children who had undergone antibiotic therapy or immunomodulation therapy within 3 months before the study, children with eating disorders (above the 97th percentile and below 3rd percentile).

The control group was comprised of healthy children without the symptoms of an acute or chronic infection history, physical examination or additional examinations. 105 children were included in this group: 47 girls (44.8%) and 58 boys (55.2%) agd between one month and 17.99 years (mean 7.6±5.7; S.D. years, median 7.2 years).

Method. All children qualified for the study had a paediatric assessment conducted, medical history taken, physical examination performed, temperature measured and additional laboratory tests done.

Additional laboratory tests included:

— complete blood count,

— determination of C-reactive protein (CRP) concentration,

— evaluation of erythrocyte sedimentation rate (ESR),

— evaluation of urea and creatinine concentrations in serum,

— measurement of procalcitonin concentration in serum,

— measurement of neopterin concentration in serum,

— urinalysis,

— microbiological tests (urine cultures).

Complete blood count with a differential white cell count and the ESR test were carried out with traditional methods.

The measurement of CRP concentration was done with the latex immunoturbidimetric assay.

Urea was determined with the GLDH-urease method, and creatinine with the Jaffe method, which allowed to assess renal function of all the children as normal.

Neopterin concentration was determined with the enzyme-linked immunosorbent assay (ELISA), using the Brahms ELItest Neopterin kit for quantitative determination of neopterin concentration in blood serum and plasma (catalogue no. 99.1). This assay involves the coated plates technique.

Measurement of procalcitonin concentration in children qualified for the study was done using the quantitative method, with LIA PCT assay from Brahms (catalogue no. 54.1). This test is based on the immunoluminometric method. All children had microbiological urine tests (cultures) performed.

In all children qualified for the study, a urinary tract infection was diagnosed on the basis of medical history, physical examination and abnormalities in urinalysis (leukocituria), and significant bacteriuria was found in all the participants. The positive result threshold was 10^5 CFU/ml in a midstream specimen of urine.

The results obtained were subject to statistical analysis. The Mann–Whitney test and Spearman's rank correlation test were used to evaluate the quantitative parameters. The Pearson χ^2 (chi-square) test was used to evaluate the qualitative parameters. Values of $p < 0.05$ were regarded as statistically significant.

The study obtained the consent of the Independent Research Bioethics Committee of the Medical University of Gdańsk (NKEBN/942/2004).

RESULTS

Neopterin concentrations in blood serum of children from the control group ranged between 2.872 and 14.779 nmol/l (Table 1).

The determined neopterin concentrations in blood serum of children from this group were used to establish reference values. The cut-off point of serum neopterin concentration, irrespective of children's age or sex, was 11 nmol/l (Plata-Nazar e*t al*., 2007).

In the study group, the urinary tract infections had 100% bacterial etiology. The following strains were found: *Escherichia coli* — in 51 children (91%), *Klebsiella pneumoniae* — 4 children (7%), *Morganella morganii* — 1 child (2%).

Neopterin concentrations in blood serum of children from the UTI group ranged between 3.158 and 17.256 nmol/l (Table 1).

Values of NPT concentration in blood serum obtained in the group of children with UTI did not significantly differ from the values obtained in the control group.

Table 2. Occurrence of positive NPT concentrations in blood serum of children with UTI

Group	NPT concentration (nmol/l)		Number of children
	below 11 years old	over 11 years old	
Control	99 (94.3%)	6 (5.7%)	105
UTI	46 (82.1%)	10 (17.9%)	56
No. of children (total)	145	16	161

No statistically significant correlations were found between NPT concentration in blood serum and: body temperature (N=56; Rs=-0.03; p=0.88), ESR (N=56; Rs=-0.21; *p*=0.64), CRP concentration (N=56; Rs=-0.17; *p*=0.39), number of leukocytes (N=56; Rs=–0.14; *p*=0.48), or PCT concentration (N=56; Rs=-0.10; *p*=0.60).

There was no statistically significant difference between these two groups either regarding the occurrence of positive results, i.e. ones which are higher than the cut-off point: 11 nmol/l of serum NPT concentration (p=0.09) (Table 2).

DISCUSSION

In the group of participants with bacterial urinary tract infections, no statistically significant difference was found between neopterin concentration in the serum of ill and healthy children. The diagnosed urinary tract infections were acute. Material for examination was always taken on the day of admission (within the first hours after the admission), and the history of the disease had not been longer than 3 days in any of the children. Children with other diseases apart from UTI were excluded from the study. Therefore, the analyzed group is homogenous.

Since the peak incidence of UTI occurs between 2 and 6 years of age, the mean age of children in the studied group — 4.0±4.9; S.D. (median 1.9) — seems to be appropriate.

The risk of infection is 10–30 times higher in girls than in boys (except in the neonatal period), as a result of girls' shorter urethra, meaning a shorter route for pathogens. Girls also dominated in the study group.

Literature on the clinical usefulness of the determination of neopterin concentration discusses the usefulness of determining this parameter in differential diagnosis of the etiological factor.

Cellular immunity is activated in the organism's response to infections caused by viruses, intracellular bacteria, parasites or fungi. Then, we can expect high NPT concentrations in different body fluids such as serum, urine, cerebrospinal fluid, saliva and synovial fluid.

In such infections, the assessment of neopterin concentration can serve not only as a differential parameter but also as a monitoring and prognostic one (Fuchs, 1998; Hamerlinck, 1999; Murr *et al.,* 2002; Plata-Nazar *et al.*, 2011).

The usefulness of determining NPT concentration in viral infections has been studied by many researchers.

Increase in neopterin concentration depending on the disease progression was observed in patients with acute hepatitis, rubella, morbilli, epidemic parotitis, varicella, influenza, as well as in the course of cytomegaly, mononucleosis and viral digestive tract infections (Griffin e*t al.*, 1990; Zaknun *et al.*, 1993; Fuchs, 1998; Jungraithmayr e*t al.,* 2001; Murr *et al.,* 2002; Okumura e*t al.*, 2003; Plata- Nazar e*t al.*, 2010).

Determination of neopterin concentration in the course of viral infections proved to be the most useful as a monitoring and prognostic parameter in the case of HIV (*Human Immunodeficiency Virus*) infections (Murr *et al.,* 2002; Kiepiela *et al.,* 2005).

During an acute viral infection, neopterin concentration increases even before the first clinical symptoms appear, reaching the highest values before the increase of antibodies, up to the limit of quantification. After seroconversion, neopterin concentration returns to normal within a few days (between two and four weeks) of the achievement of the maximum value (Fuchs, 1998; Murr *et al.,* 2002).

Intracellular bacteria activate a cellular response in the body. The bacteria are e.g.: *Mycobacterium tuberculosis, Mycobacterium leprae, Listeria monocytogenes, Salmonella* and *Brucella.*

Research concerning patients (adults and children) with pulmonary tuberculosis showed that neopterin concentration is commensurate to the progression and activity of the disease (Fuchs *et al.*, 1984).

Research projects to evaluate clinical usefulness of neopterin in the course of parasitic diseases have also been conducted (Fuchs, 1998; Murr *et al.,* 2002). Neopterin concentration proved to be elevated even in a mild course of malaria (Reibnegger *et al.*, 1984). In patients with the highest neopterin concentrations, the most clinically severe course of the disease was observed. Among those infected with *Plasmodium falciparum*, in 94% of patients the course of the disease and treatment could be monitored using urine NPT concentration (Brown *et al.,* 1990). So as to emphasize the usefulness of NPT determination, it is worth mentioning that *Plasmodium falciparum* infection is the first cause of children's deaths in international statistics.

A number of reports prove that elevated NPT concentration may also occur in patients with chronic bacterial infections (Denz *et al.,* 1990; Fuchs, 1998).

Denz *et al.* (1990) describe extremely high neopterin concentrations in all the patients (17 persons) suffering from an acute viral infection (hepatitis A, respiratory tract infections, diarrhoea). In patients with a bacterial infection (52 persons), with diagnosed pneumonia (43 persons), urine neopterin concentration was low. In the other patients (9 persons), a urinary tract infection was diagnosed and an elevated neopterin concentration in urine was found (Denz *et al.,* 1990).

In patients with pneumonia, an acute infection was diagnosed, and in those with urinary tract infections, the symptoms lasted over 5 days and the infections were rather protracted or chronic. There was also an age difference between the patients. In the case of UTI, the patients were elderly (53–81 years old), which also seems important (Denz *et al.,* 1990).

Local neopterin production in urinary tract is still unexplained (Denz *et al.,* 1990; Eisenhut *et al.*, 2013).

In order to confirm the observed elevation of NPT concentration in chronic infections and to exclude the local origin of NPT (local activation of the immune system), NPT and interferon-γ concentrations in the serum were also analyzed in work the presented by Denz and coworkers (1990), which gave increased values of both studied parameters too (Denz *et al.,* 1990).

The increase of NPT concentration in chronic bacterial infections is probably connected with the participation of various cytokines, e.g. IL-1 or TNF-alfa, which cause the increase of IFN-gamma concentration (Plata-Nazar *et al.*, 2011).

Strohmaier *et al.* (1987) associate the higher neopterin concentrations in blood serum of a patient suffering from a longer bacterial infection with the occurrence of septic complications, which they proved in their research (Strohmaier *et al.,* 1987).

The clinical usefulness of NPT concentration was also evaluated by Lacoma *et al.* (2011) in patients with chronic obstructive pulmonary disease (COPD). He found statistically significant differences in NPT concentrations depending on the etiological factor causing the exacerbation of a chronic disease. In patients with a disease of a proven bacterial etiology, serum NPT concentrations were low (Lacoma *et al.*, 2011).

Other researchers think that the inflammatory process caused by endotoxins of Gram-negative bacteria may cause activation of T lymphocytes and trigger interferon-γ production. This issue is still a matter of discussion (Denz *et al.,* 1990; Fuchs 1998). This hypoth-

esis may be confirmed by the findings of research by Bloom *et al.* (1990). They observed a two- or four-fold increase of NPT concentration within 24 hours of intravenous administration of endotoxins to healthy volunteers (Bloom *et al.*, 1990).

Niederwieser and coworkers (1986) observed extremely high values of urinary neopterin in 7 out of 10 adult patients with staphylococcal pneumonia and in 4 out of 7 children with bacterial infections (pneumonia, cerebrospinal meningitis). The authors present the opinion that NPT concentration is not useful in differential diagnosis of infection etiology. It must be noted that the studied patient groups are small, so there is no basis for drawing general conclusions (Niederwieser e*t al.*, 1986).

Similar observations were made by Graessl *et al.* (2001) who determined urine neopterin concentration in 45 children with asthma, 29 children with rotavirus diarrhoea, 5 children with bacterial infections and 6 children with infections of mixed etiology (viral and bacterial), as well as 29 healthy children (without the signs of infection). Neopterin concentration in urine of children with asthma was low, comparable to NPT concentrations in the healthy children group. In all the children with infections, significantly higher NPT concentrations were observed. The concentration was clearly the highest in the group of children with rotavirus diarrhoea (Greassl *et al.,* 2001).

Pourakbariet *et al.* (2010) examined 158 children aged between 2 months and 10 years with diagnosed infections (bacterial *vs.* non-bacterial).

The mean neopterin level was 44.43 nmol/L in bacterial infections and 42.93 nmol/L in nonbacterial (viral or fungal) infections, which was not statistically significant (p=0.88)

It was found that the determination of NPT concentration in serum of those patients is not a parameter useful in differential diagnosis of infection etiology (Pourakbari e*t al.*, 2010).

Ip *et al.* (2007) highlights the usefulness of simultaneous determination of a few inflammation parameters. They analyzed a group of patients with lower respiratory tract infections (139 persons with bacterial infections and 128, with viral infections) and 146 healthy persons. In the group of ill persons, serum concentrations of CRP, NPT and PCT were determined within the first day of hospitalization. The median NPT concentration in patients with viral infections was almost twice as high as in patients with bacterial infections. Analyzing various combinations of the determined parameters, the authors of this work suggest that determining two or three inflammatory markers greatly facilitates the differential diagnosis of infection etiology (Ip *et al.*, 2007).

Also, Shaw *et al.* (1991) claim that none of the nonspecific inflammatory parameters determined in isolation is sufficient for differential diagnosis of infection etiology.

On the basis of evaluation of CRP and NPT concentrations in the serum of patients with bacterial and viral infections, they found that the determination of neopterin concentration cannot be seen as a parameter which allows for differentiation between the studied groups. Besides, they are of the opinion that only the CRP/NPT ratio is useful in differential diagnosis. The ratio of CRP concentration (mg/l) to NPT concentration (nmol/l) below 1 is characteristic of a viral infection, whereas the value above 1 proves the bacterial etiology of the infection (Shaw *et al.,* 1991).

A similar opinion is presented in the work by Rainer *et al.* (2009). They assessed the usefulness of determination of CRP and NPT concentrations in blood serum for the purpose of differentiation between the infection etiology in 561 patients with acute respiratory infections who were admitted to the emergency department. It was proved that the CRP/NPT ratio is a very useful, quick and cheap indicator to differentiate between bacterial and viral infections (Rainer *et al.*, 2009).

In most publications, neopterin was described as a parameter useful in the differential diagnosis allowing to differentiate acute bacterial infections from viral infections involving high neopterin concentrations in different bodily fluids tested.

Some researchers think that acute local bacterial infections, regardless of the etiology, do not lead to increased levels of neopterin. This is confirmed by our research. Children with acute urinary tract infections caused by bacteria alone had low NPT concentrations in blood serum.

CONCLUSIONS

The determination of neopterin concentration in children with bacterial urinary tract infections is not a clinically useful parameter.

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