Pericardial Effusion in Childhood Nephrotic Syndrome

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Background: *Nephrotic syndrome (NS) is one of the most common renal diseases in children, which is defined as idiopathic NS and secondary NS. Current data on adult showed that pericardial effusion was related only to SLE, but not to non-SLE nephrotic patients. Until now there were no studies about children.*
Objective: *To compare the frequency and clinical manifestations of pericardial effusion in childhood NS with SLE and non-SLE patients.*
Material and Method: *Consecutive cases of NS at Queen Sirikit National Institute of Child Health (QSNICH) from June 2004 to May 2005 were prospectively studied. Information concerning the following: gender, age, clinical manifestations, laboratory investigation and echocardiogram in each patient were obtained.*
Results: *A total of 37 cases were included, 13 with SLE and 24 with idiopathic cause. Pericardial effusion was found without any symptoms and signs of pericardial disease in both groups; 9 cases (69.2%) of SLE and 2 cases (8.3%) of non-SLE patients. Statistically significant differences were demonstrated between two groups (p = 0.001).*
Conclusion*: Pericardial effusion in childhood NS was more frequent in SLE than non-SLE nephrotic patients statistically significant. This result was different from previous study in adult which revealed no pericardial effusion in non-SLE group.*

Keywords: *Pericardial effusion, Nephrotic syndrome, NS, Systemic lupus erythematosus, SLE*

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Pericardium is composed of visceral and parietal components which encloses a potential space (pericardial cavity) between these two serosal layers. This cavity is normally lubricated by a very small amount of serous fluid, 15-35 mL in adults. Inflammation of the pericardium or obstruction of lymphatic drainage from the pericardium of any etiologies cause an increase in fluid volume, referred to as a pericardial effusion. Excess of effusion may accommulate in acute pericarditis, post-pericardiotomy syndrome, connective tissue diseases, tuberculosis, uremia, chronic dialysis and myxedema[1,2].

Nephrotic syndrome (NS) is clinical entity characterized by heavy proteinuria resulting in hypoalbuminemia and edema formation which is divided into 2 groups as idiopathic and secondary NS. Many factors are commonly cited as possible 'causes' or temporally associated conditions for idiopathic NS which include infectious diseases, drugs, allergies, vaccinations, and some malignancies. It is not at all clear what final common pathway permits these differing factors to result in the common clinical and pathological outcome of minimal change NS, or less commonly focal and segmental glomerulosclerosis (FSGS), or how this relates to ideas on pathogenesis[3]. The data indicated that approximately 80% of children with renal disease had idiopathic NS, as opposed to only 25% of adults. Chronic glomerulonephritis was responsible for about 50% of the cases of NS in adults but only 10% to 15% of childhood cases. These glomerulonephritides may result from a systemic disease, such as systemic lupus erythematosus (SLE)[4].

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General systemic symptoms such as fever, malaise, and weight loss; and evidence of diffuse inflammation as demonstrated by lymphadenopathy and hepatosplenomegaly are common in SLE. This is true both at diagnosis and throughout the course of the disease. Nephropathy, fever, lymphadenopathy, and the requirement for the use of corticosteroids have been reported to be more common in children than in adults. Involvement of the heart in SLE has been recognized for approximately a century which may cause a pancarditis with abnormalities of pericardium, myocardium and coronary arteries. The incidence of pericardial effusion in this condition occurs more than 50% of the patients with active disease. The results of pericardial fluid analyses may mimic those seen in bacterial pericarditis, and on occasions this latter diagnosis is difficult to distinguish. Studies of pericardial fluid have shown the presence of an antinuclear antibody (ANA), LE cells, and even hypocomplementemia[5].

Previous data in adult showed no pericardial effusion in non-SLE nephrotic patients but there were 8 cases with pericardial effusion in 40 SLE associated with NS[6]. The objective of the present study was to compare the incidence and clinical manifestations of pericardial effusion in childhood NS with SLE to non-SLE patients.

Material and Method

Study population

The study population consisted of all pediatric inpatients and outpatients diagnosed as active NS at Queen Sirikit National Institute of Child Health (QSNICH) from June 2004 to May 2005. The patients were divided into 2 groups: SLE and non-SLE nephrotic patients. The criteria used for the diagnosis of SLE were those purposed by American Rheumatism Association (ARA) in 1982 and 1997[7,8]. The inclusion criteria were nephrotic range proteinuria and hypoalbuminemia with edema. Nephrotic range proteinuria was defined as (1) urine protein more than 50 mg/kg/day or 40 mg/m^2/hr and/or (2) urine protein to creatinine ratio more than 3. Hypoalbuminemia was defined as serum albumin level less than 2.5 g/dL. Exclusion criteria, the patients were excluded from the study if they had (1) hemodynamic instability (2) cardiovascular anomaly and/or post cardiothoracic surgery (3) infection, sepsis and/or septicemia. Demographic data such as gender, age, clinical manifestations of SLE, complete blood count, serum cholesterol, creatinine, albumin, complement, antinuclear antibody, anti-dsDNA, urine for protein and creatinine in each patient were prospectively collected. Echocardiography was performed in a standard fashion by the only pediatric cardiologist who was blinded to the underlying diagnosis. The study was approved by the institutional ethics committee.

Statistical analysis

Data were expressed as percentage and mean $\pm$ SD. Statistical analysis were conducted using SPSS. All p-value presented as two tailed, $p < 0.05$ was considered statistically significant.

Results

The 37 pediatrics patients with active NS were included which consisted of 13 with SLE and 24 with non-SLE. The demographic characteristics and overall data were revealed in Table 1. The patients in

Table 1. Demographic data and laboratory finding in SLE and non-SLE nephrotic syndrome

	SLE (n = 13)	Non-SLE (n = 24)	p-value
Age (years)	12.20 $\pm$ 2.40	5.7 $\pm$ 3.1	0.01
Sex: Male	3 (23.1%)	14 (58.3%)	0.04
Laboratory			
Hb (g/dL)	9.75 $\pm$ 2.17	13.34 $\pm$ 2.49	0.01
Cholesterol (mg/dL)	319.40 $\pm$ 271.00	537.00 $\pm$ 169.00	0.004
Serum creatinine (mg/dL)	1.42 $\pm$ 2.00	0.47 $\pm$ 0.20	0.001
Serum albumin (g/dL)	1.97 $\pm$ 0.55	1.51 $\pm$ 0.34	0.001
C3 (IU/ml)	48.40 $\pm$ 30.20	113.40 $\pm$ 57.90	0.001
Low C3 (< 50 IU/ml)	9 (69.2%)	0	<0.001
ANA positive	13 (100%)	0	<0.001
anti-dsDNA positive	9 (69.2%)	0	<0.001
Pleural effusion	9 (69.2%)	6 (25.0%)	0.02
Pericardial effusion	9 (69.2%)	2 (8.3%)	0.001

SLE groups were older (mean age: 12.2 $\pm$ 2.4 in SLE versus 5.7 $\pm$ 3.1 in non-SLE, p = 0.001) and had higher ratio between female to male (4.7:1 in SLE versus 1:1.4 in non-SLE). The mean values of hemoglobin (p = 0.01), serum cholesterol (p = 0.004) and complement (p = 0.001) were significantly lower in the nephrotic patients with SLE. The pericardial effusion was found in SLE more frequently than non SLE-nephrotic patients (p = 0.001), so as pleural effusion from chest x-ray (p = 0.02). None of the patients had signs or symptoms of pericardial disease.

Discussion

The result of this present study showed the significant differences of age, hemoglobin, serum albumin, cholesterol and creatinine level between the groups. In general, age group of SLE is not the same as NS. Most cases of SLE occur after age 5, with a peak incidence in late childhood or adolescent while childhood NS is common in 1-6 years old[9,10].

Anemia is one of the most common manifestations of SLE which may be due to chronic disease, iron deficiency, autoimmune hemolytic, blood loss (from gastrointestinal tract or other organs), chronic renal insufficiency and suppression of the bone marrow by drugs (such as azathioprine or cyclophosphamide)[11,12]. But minimal change NS might present with hemo concentration because hypoalbuminemia induces falling of oncotic pressure and intravascular depletion respectively. In this present data revealed 6 cases of polycythemia in 24 non-SLE nephrotic patients but no polycythemia was found in SLE group (p = 0.04).

Low albumin level is included in the definition of NS and severe hypoalbuminemia with concentration below 1 g/dL occurs in approximately 25% of the patients with minimal change NS; in about two-thirds the concentration is between 1 and 2 g/dL. An elevation of serum cholesterol is almost a constant finding in patients with minimal change NS which is considered to be a consequence of hypoalbuminemia also with decreased clearance of cholesterol and triglyceride. Serum cholesterol exceeded 400 mg/dL was found in approximately two-thirds of patients from the report of the International Study of Kidney Disease in Children (ISKDC)[13,14].

Renal involvement is the major cause of mortality in patients with SLE. Lupus nephritis has been reported in 29% to 80% of pediatric cases depending on whether the reporting investigators are rheumatologists or nephrologists. In approximately 90% of patients with renal lupus, the nephritis is manifested within the first year after diagnosis of SLE. When the kidney becomes involved in lupus, there are many symptoms which range from none, to mild hematuria, proteinuria and cellular casts to a clinical picture of nephritic syndrome with hypertension, edema and renal failure. Up to 50% of children with childhood lupus nephritis have a decreased glomerular filtration rate (GFR)[9,15,16]. Compare with NS, renal function is usually normal. Some patients have a reduction of GFR attributed to hypovolemia, with complete return to normal after remission. A reduced GFR may also be found despite normal effective plasma flow which revealed a close relationship between the degree of foot-process effacement and both the GFR and the filtration fraction, suggesting that foot process effacement leads to a reduction of the glomerular filtering area and/or of permeability to water and small solutes. This reduction is also transitory, with rapid return to normal after remission[3,17].

There are two distinct renal mechanisms of edema formation. In the first, characteristic of the acute nephritic syndrome and renal failure, a primary failure to excrete salt and water results in expansion of intravascular volume, hypertension and pulmonary congestion. In the second, as in nephrotic syndrome, edema results from hypoalbuminemia, the diminished colloid osmotic pressure of plasma leading to seepage of fluid from intravascular into interstitial compartment, with contraction of plasma volume secondarily causing salt and water retention. On the other hand, there is also evidence for a primary increase in distal tubular reabsorption in nephrotic patients[18,19]. In minimal change NS, the most consistent change apparent from the renal hemodynamic studies was a low filtration fraction. Also with other nephrotic lesions such as Heymann nephritis, filtration fraction is also low associated with high tubular sodium reabsorption and absence of signs of a decreased effective circulating volume. The pathogenesis of the increased tubular reabsorption in humans is still incompletely understood; however, until now the data in nephrotic children do not suggest a fundamental difference between minimal change and non-minimal change nephrotic pattern[20- 25].

Due to fluid retention, nephrotic patients could present with peripheral edema, ascites, pleural effusion and also with pericardial effusion. But on the previous data documented that there was no association of pericardial effusion and NS except for the report case of a 67-year-old man with NS attributed to long-standing diabetic mellitus, his echocardiography

showed a moderate to large pericardial effusion with right atrial collapse[26]. Gobel U et al[6], compared 20 nephrotic patients with SLE to 20 nephrotic patients with other causes; revealed 8 SLE-nephrotic patients had pericardial effusion while none of the non-SLE nephritic patients developed pericardial effusion. They described that the appearance of pericardial fluid in nephrotic patients strongly suggested a diagnosis of SLE or perhaps other secondary causes and pericardial effusion did not appear to be a benign accompaniment of extra-cellular volume expansion related to NS, at least in adult. Interestingly, in this present data showed not only pleural effusion but also pericardial effusion in both groups. Pleural and pericardial effusion occurred in nephrotic patients associated with SLE more frequently than non-SLE. The cause of pleural and pericardial effusion in non-SLE nephrotic patient might be from abnormal leakage of fluid from the plasma to the interstitial space across the capillaries[27], but nephritis and serositis might be included in the etiology of SLE[28]. All patients who had pericardial effusion were clinically silent; neither of them had signs or symptoms of cardiovascular compromise nor pericardial disease.

From the present data, there did not perform pericardiocenthesis on all patients, so we could not identify the etiology of the fluid accumulation to determine if it was transudate or exudate. None of our patients had cardiovascular sequelae after treatment.

In conclusion, this is the report of a prospective study about the occurrence and clinical manifestations of pericardial effusion in childhood NS which demonstrated that pericardial effusion was more common in SLE-nephrotic patients but it could happen in NS with other causes. The result of this data was different from previous study in adult which revealed no pericardial effusion in non-SLE nephrotic patients.

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ภาวะน้ำในช่องเยื่อหุ้มหัวใจในผู้ป่วยเด็กกลุ่มอาการเนโฟรติก

ชูเกียรติ เกียรติขจรกุล, อรุณี กลิ่นกล่อม, ธวัชชัย กิระวิทยา

ภูมิหลัง: *กลุ่มอาการเนโฟรติกพบได้บ่อยในผู้ป่วยเด็ก สาเหตุที่ก่อให้เกิดกลุ่มอาการนี้อาจเป็นผลจากปฐมภูมิ หรือทุติยภูมิ เคยมีการศึกษาเปรียบเทียบภาวะน้ำในช่องเยื่อหุ้มหัวใจระหว่างผู้ป่วยกลุ่มอาการเนโฟรติกที่พบร่วมกับภาวะ systemic lupus erythematosus (SLE) และผู้ป่วยกลุ่มอาการเนโฟรติกที่ไม่ได้พบร่วมกับภาวะ SLE ในผู้ใหญ่ แต่ยังไม่เคยมีการศึกษาในเด็ก*

วัตถุประสงค์: *เพื่อเปรียบเทียบอุบัติการณ์และอาการแสดงทางคลินิกของภาวะน้ำในช่องเยื่อหุ้มหัวใจระหว่างผู้ป่วยกลุ่มอาการเนโฟรติกที่พบร่วมกับภาวะ SLE และผู้ป่วยกลุ่มอาการเนโฟรติกที่ไม่ได้พบร่วมกับภาวะ SLE ในเด็ก*

วัสดุและวิธีการ: *ศึกษาแบบ prospective ในกลุ่มผู้ป่วยเด็กที่รับการวินิจฉัยว่าเป็นเนโฟรติกที่เข้ามารับการตรวจรักษาในสถาบันสุขภาพเด็กแห่งชาติมหาราชินี ระหว่างเดือนมิถุนายน พ.ศ. 2547 ถึงเดือนพฤษภาคม พ.ศ. 2548 โดยบันทึกข้อมูลเกี่ยวกับ เพศ, อายุ, อาการแสดงทางคลินิก, ผลตรวจทางห้องปฏิบัติการ และผลการตรวจคลื่นเสียงสะท้อนหัวใจ*

ผลการศึกษา: *ผู้ป่วยกลุ่มอาการเนโฟรติก 37 รายแบ่งเป็นกลุ่มที่พบร่วมกับภาวะ SLE 13 ราย และไม่ได้พบร่วมกับภาวะ SLE 24 ราย พบภาวะน้ำในช่องเยื่อหุ้มหัวใจผู้ป่วยกลุ่มอาการเนโฟรติกทั้ง 2 กลุ่มโดยที่ไม่มีอาการแสดงทางคลินิก พบน้ำในช่องเยื่อหุ้มหัวใจร่วมกับภาวะ SLE 9 ราย (ร้อยละ 69.2) และกลุ่มที่ไม่ได้พบร่วมกับภาวะ SLE 2 ราย (ร้อยละ 8.3) เมื่อเปรียบเทียบอุบัติการณ์การเกิดภาวะน้ำในช่องเยื่อหุ้มหัวใจระหว่างผู้ป่วยทั้งสองกลุ่มจะพบว่ามีความแตกต่างกันอย่างมีนัยสำคัญ (p = 0.001)*

สรุป: *สามารถพบภาวะน้ำในช่องเยื่อหุ้มหัวใจได้ทั้งในผู้ป่วยกลุ่มอาการเนโฟรติกในเด็กที่พบร่วมกับภาวะ SLE มากกว่ากลุ่มที่ไม่ได้พบร่วมกับภาวะ SLE อย่างมีนัยสำคัญ แตกต่างกับการศึกษาในผู้ใหญ่ที่พบภาวะน้ำในช่องเยื่อหุ้มหัวใจเฉพาะในผู้ป่วยกลุ่มอาการเนโฟรติกที่พบร่วมกับภาวะ SLE เท่านั้น*